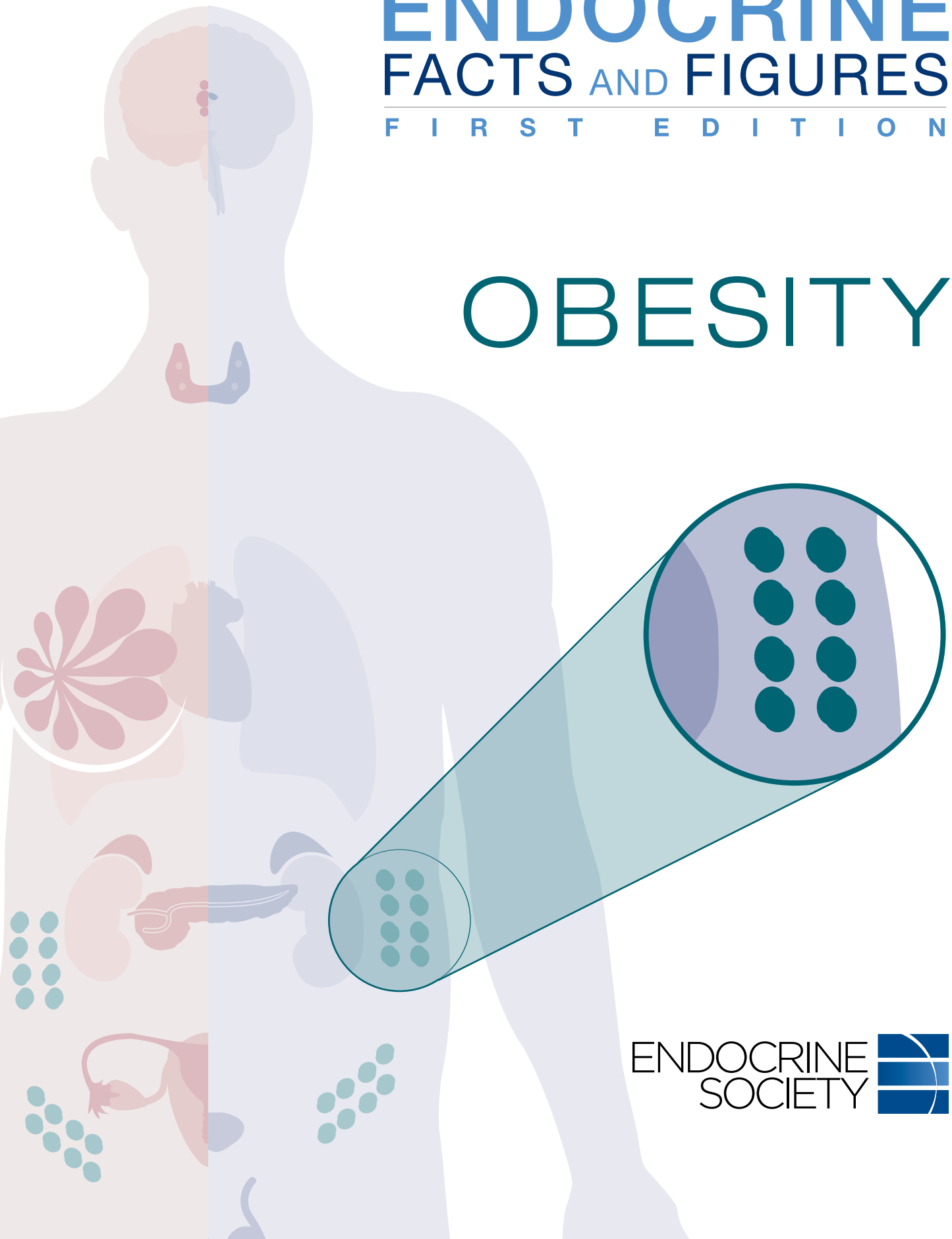
ENDOCRINE FACTS AND FIGURES

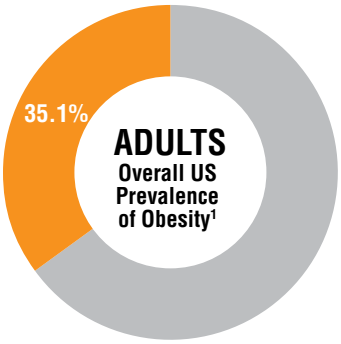
FIRST EDITION

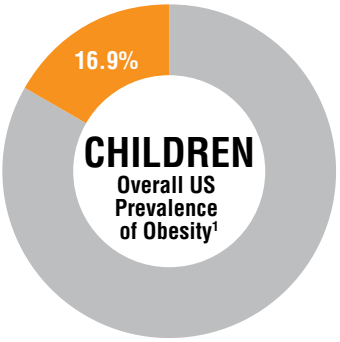
OBESITY

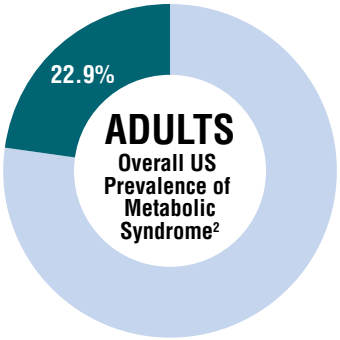


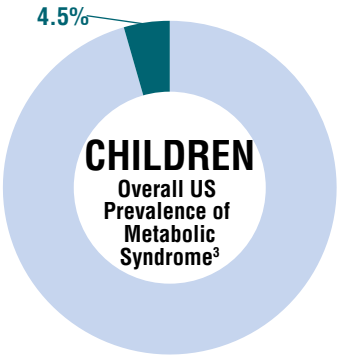
ENDOCRINE SOCIETY

PREVALENCE









SEX DIFFERENCES IN ADULTS AGED 20+ YEARS

Obesity
BMI ≥ 30 kg/m^2

Metabolic Syndrome
with abdominal obesity

COST BURDEN

$3,976 PER ADULT WITH OBESITY
ANNUAL MEDICAL SPENDING PER CAPITA[4]

MEAN 10-YEAR TOTAL MEDICAL COSTS FOR US ADULTS[5]

$40,873 vs. **$33,010**

WITH METABOLIC SYNDROME

NO METABOLIC SYNDROME

1 Source: NHANES 2011-2012
2 Source: NHANES 2009-2010
3 Source: NHANES 1999-2004
4 Source: Medical Expenditure Panel Survey, 2001
5 Source: Curtis et al., 2007

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Mission Statement of the Endocrine Society

The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

About Endocrine Facts and Figures

Endocrine Facts and Figures is a compendium of epidemiological data and trends related to a spectrum of endocrine diseases. The data is organized into nine chapters covering the breadth of endocrinology: Adrenal, Bone and Calcium, Cancers and Neoplasias, Cardiovascular and Lipids, Diabetes, Hypothalamic-Pituitary, Obesity, Thyroid, and Reproduction and Development.

All data is sourced from peer-reviewed publications, with an additional round of review by a group of world-renowned experts in the field. Additional oversight from the Endocrine Facts and Figures Advisory Panel ensured fair and balanced coverage of data across the therapeutic areas.

The first edition of **Endocrine Facts and Figures** emphasizes data on the United States. Future updates to the report will include additional data for other countries.

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For More Information

For more information, updates, and the online version of this report, visit: endocrinefacts.org

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Disclaimer

This publication summarizes current scientific information about epidemiology and trends data related to a spectrum of endocrine diseases. It is not a practice guideline or systematic review. Except when specified, this publication does not represent the official policy of the Endocrine Society.

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I OVERVIEW

Obesity is a complex disease that is associated with a number of comorbidities, increased mortality, and reduced quality of life. Abdominal obesity is one of the components of metabolic syndrome (MetS), a cluster of risk factors that increases an individual's risk for chronic conditions such as cardiovascular disease and diabetes. This chapter details the epidemiology of obesity and MetS by age, race, and geographic location and includes data on the direct costs associated with obesity and MetS.

1.1 EPIDEMIOLOGY

The following tables summarize the most recently published data on the prevalence of obesity in US adults and children, and MetS in US adults. In all cases, data from the National Health and Nutrition Examination Survey (NHANES) was used.

MetS in adults is defined as abnormal values for three or more of the harmonized criteria, including waist circumference, triglycerides, HDL-cholesterol, blood pressure or glucose, as outlined in the 2009 Joint Interim Statement of the International Diabetes Federation Task force on Epidemiology; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.[4]

MetS in adolescents was defined using the International Diabetes Federation's 2007 definition for use in children and adolescents.[6]

1.2 COST BURDEN OF DISEASE

The direct costs associated with obesity and MetS are for the most part estimated through services rendered, i.e., the costs of treating the attributable consequences of illnesses and comorbidities, as well as those costs recorded by healthcare and insurance providers. Importantly, there are additional costs that are more difficult to estimate, such as absenteeism and lost productivity.

Table 1

Prevalence of adult overweight and obesity in the United States.

SOURCE	POPULATION	OVERWEIGHT BMI ≥ 25 KG/M^2	OBESITY BMI ≥ 30 KG/M^2	EXTREME OBESITY BMI ≥ 40 KG/M^2
NHANES 2011-2012	Age 20+ years	33.9%	35.1%	6.4%

Source: Fryar et al. 2014[1]

Table 2

Prevalence of childhood overweight and obesity in the United States.

SOURCE	POPULATION	OVERWEIGHT BMI FOR AGE ≥ 85TH PERCENTILE	OBESITY BMI FOR AGE ≥ 95TH PERCENTILE
NHANES 2011-2012	Age 2-19 years	31.8%	16.9%

Source: Ogden et al. 2014[2]

Table 3

Prevalence of metabolic syndrome in adults in the United States.

SOURCE	POPULATION	METABOLIC SYNDROME
NHANES 2009-2010	Age 20+ years	22.9%

Source: Beltran-Sanchez et al. 2013[3]

Table 4

Prevalence of metabolic syndrome in adolescents in the United States.

SOURCE	POPULATION	METABOLIC SYNDROME
NHANES 1999-2004	Age 12-19 years	4.5%

Source: Ford et al. 2008[5]

1.2.1

Cost of Obesity in Adults

Patients with obesity are more susceptible to chronic illnesses, thus contributing to increases in medical spending. While the available estimates of cost burden vary based on data sources used, assumptions made, and mathematical methods applied[7], the vast majority of studies agree that patients with obesity spend more on medical care than their normal weight counterparts.

Thorpe et al. reported that 27% of the overall growth in per-capita spending between 1987-2001 was attributable to increases in the prevalence of obesity (Table 5).[8] Alternative estimates have been posited by others, such as the incremental cost of overweight and obesity based on a systematic review of over thirty studies of US populations (Table 6).[7]

It has been suggested that the Medical Expenditure Panel Surveys (MEPS) underestimate spending due to their reliance on self-reporting by survey respondents.[9] For comparison, an analysis of actual costs in the Medicare population is provided in Table 7.

With the rise in obesity among the older adult population, the cost burden is predicted to increase substantially: the combined medical costs associated with treatment of obesity-related diseases, cardiovascular diseases, and diabetes in the US alone have been estimated to increase by $48-66 billion/year from 2010 through 2030.[11] Apart from medical costs, the associated losses in productivity need to be accounted for. According to a cross-sectional analysis of the Agency for Healthcare Research and Quality's 2006 MEPS and the 2008 Health and Wellness Survey that calculated the annual cost attributable to obesity among full-time employees, the cost of obesity in the workplace is estimated to be $73.1 billion.[12] That increase in cost is attributed to increased health-related work limitations: the time needed to complete tasks and an inability to perform physical job demands.[13] As a result,

Table 5

Annual medical spending per capita in adults who are overweight or have obesity.

		ANNUAL MEDICAL SPENDING PER CAPITA		
DATA SOURCE	POPULATION	NORMAL	OVERWEIGHT	OBESITY
National Medical Expenditure Survey, 1987	US adults age 19+ years	$2,117	$2,154	$2,438
Medical Expenditure Panel Survey-Household Component, 2001	US adults age 19+ years	$2,907	$3,247	$3,976

Source: Thorpe et al. 2004[8]

Table 6

Estimated incremental cost of obesity in US adults (in 2008 US dollars).

		INCREMENTAL COST	
DATA SOURCE	POPULATION	OVERWEIGHT	OBESITY
Systematic review of 33 US-based studies published between 1992-2008	US adults age 18+ years	$266-$498	$1,630-1,723

Source: Tsai et al. 2011[7]

Table 7

Excess annual expenditures by US Medicare beneficiaries with overweight or obesity.

		ANNUAL INCREMENTAL MEDICARE EXPENDITURES COMPARED TO NORMAL-WEIGHT BENEFICIARIES	
DATA SOURCE	POPULATION	OVERWEIGHT	OBESITY
Medicare Current Beneficiary Survey, 1997-2006	US adults 65 years and older	$108	$149

Source: Alley et al. 2012[10]

workers with obesity experienced a 4.2% health-related loss in productivity, 1.2% more than all other employees.

1.2.2

Cost of Obesity in Children

Using these cost estimates multiplied by the number of 10-year-old children with obesity in May 2013, Finkelstein et al. proposed a total direct medical cost of obesity of $14 billion for this age group alone.

Extrapolated to the nation, elevated BMI in childhood was associated with $14.1 billion in additional prescription drug, emergency room, and outpatient visit costs annually.[15]

1.2.3

Cost of Metabolic Syndrome

Due to the complex nature of MetS, treatment costs attributable to any one of its components are difficult to quantify. Recent data suggest, however, that the presence of MetS adds to the cost of treating specific comorbidities. Table 10 presents comparative data on medical costs among patients over the age of 65 with and without MetS for 10 years starting in 1992.

Table 8

Incremental lifetime direct medical cost for a 10-year-old child with obesity, relative to a normal weight child, in two scenarios.

DATA SOURCE	ASSUMPTION	INCREMENTAL LIFETIME DIRECT MEDICAL COST FOR A 10-YEAR-OLD CHILD WITH OBESITY
Systematic review of 6 papers estimating cost of obesity	Relative to normal weight child who maintains normal weight in adulthood	$16,310-19,350
	Relative to normal weight child who becomes overweight in adulthood	$12,660-19,630

Source: Finkelstein et al. 2014[14]

Table 9

Incremental cost by type of medical expenditure for overweight children and children with obesity compared to children with normal or underweight BMI.

			INCREMENTAL COST COMPARED TO CHILDREN WITH UNDERWEIGHT OR NORMAL BMI	
DATA SOURCE	POPULATION	TYPE OF EXPENDITURE	OVERWEIGHT CHILDREN	CHILDREN WITH OBESITY
Medical Expenditure Panel Survey, 2002-2005	US children age 6-19 years	Outpatient visits	$79 (+13.1%)	$194 (+32.2%)
		Prescription drugs	$64 (+19.5%)	$114 (+35.0%)
		Emergency room visits	$25 (+19.9%)	$12 (+9.6)

Source: Trasande and Chatterjee. 2009[15]

Table 10

Mean 10-year hospital resource use and medical costs, per patient (ages 65 years and older).

	NO METABOLIC SYNDROME	METABOLIC SYNDROME
Total costs to Medicare	$33,010	$40,873
Medicare Part A Inpatient	$18,806	$24,414
Medicare Part B Physician	$10,779	$12,299
Medicare Part B Institutional	$3,425	$4,359

Source: Curtis et al. 2007[16]

1.3

SCIENTIFIC BREAKTHROUGHS

The following section highlights notable scientific discoveries and innovations identified by the expert reviewers at the time of publication.

1.3.1

The Role of Brown Fat

Brown fat has been seen as a possible target for obesity therapy since the earliest animal studies in the 1970s.[17] The physiological mechanisms that point to possible therapeutic targets have been increasingly explored in the past two years after interest was reawakened by finding brown fat scattered along the vertebrae and in the neck of adult human beings. The effects of exercise on muscle stimulate increased expression of a membrane protein that is cleaved and secreted as a newly discovered hormone, irisin. Irisin in turn stimulates the conversion (or "browning") of white adipose cells into brown adipose tissue (BAT).[18]

In laboratory experiments using mouse models, hemodynamic responses in BAT metabolism to pharmacological agents, *in vivo*, revealed the physiological role of fibroblast growth factor 21 (FGF21): it can induce thermogenic gene expression and augmentation of a brown fat-like phenotype in white adipocytes, so called "beige" cells. This beneficial effect of FGF21 suggests it as a potential treatment for obesity.[19] Another study presented MRI imaging related to BAT volume, distribution, and metabolic function in both resting and active states in pharmacologically induced responses to a beta3-andrenergic receptor agonist.[20]

In vitro MRI imaging of adipose tissue samples from mice and post-mortem humans aged 3 days to 18 years showed close similarity of mouse to human BAT in beige/brite cells.[21] Another study using mouse models suggested a possible genetic link to obesity: a mitochondrial dysfunction that can lead to obesity, and a possible way that this phenotype lacking in Atg7 was protective against diet-induced obesity by increasing the browning of white adipose tissue through the promotion of FGF21.[22]

These and other studies have provided greater understanding of brown/beige fat, its mechanisms in mammals and the human body, and possibilities for new anti-obesity therapies.

1.3.2

The Role of the Gut Microbiome

A landmark study by Ley et al in 2005[23], built on work by Bäckhed[24], introduced the notion that the bacterial population of the gut, the "microbiome," might play a significant role in the development of obesity. The study by Ley and colleagues, which used mice as the animal model, showed that the gut and its microbial population constituted a host-microbe relationship that allowed extracted energy to be stored in adipocytes. Moreover, it was shown that this pathway involved microbial regulation of the intestinal epithelial expression of fasting-induced adipocyte protein (Fiaf), a circulating inhibitor of lipoprotein lipase.

A 2006 study comparing gut microbiota between genetically altered obese mice and lean littermates showed that obesity is associated with changes in the relative abundance of the two dominant bacterial divisions, the Bacteroidetes and the Firmicutes.[25]

In a human study of the host-microbe relationship, sequencing human fecal matter identified levels of differing bacterial populations that are predictive of obesity.[26] Comparing individuals with lean (BMI < 25 kg/m^2) to overweight (BMI 25–30 kg/m^2) and obese (BMI > 30 kg/m^2) BMI levels, the authors postulated that differences in a very few groups of bacterial species predispose progression to comorbidities such as type 2 diabetes mellitus (T2DM).

In a 2013 study, human fecal microbiota from adult female twin pairs, where one had obesity and one was normal weight, were transplanted into germ-free mice. The co-housing of mice harboring an obese twin's microbiota with mice containing the lean co-twin's microbiota prevented the development of increased body mass and obesity-associated metabolic phenotypes in obese cage mates.[27]

In 2014, news broke that using artificial "non-caloric" sweeteners (NAS) to avoid intake of calories might actually be detrimental. Suez and colleagues[28] showed that consumption of commonly used NAS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota.

Thus, the understanding of how alterations in the microbiome of the human gut, as well as alterations in human dietary habits, might provide the therapeutic means to reduce or prevent obesity.

1.3.3

The Role of Circadian Rhythm and Sleep Deprivation

One of the first studies exploring the relationship between sleep deprivation and obesity was published in 2004.[29] That study reported a U-shaped curvilinear association between sleep duration and BMI. In subjects sleeping fewer than 8 hours (74.4% of the 1024 person sample), increased BMI was proportional to decreased sleep. Short sleep (habitual sleep of 5 h vs 8 h) was associated with 15.5% lower leptin and 19.9% higher ghrelin, independent of BMI. The authors noted that these differences are likely to increase appetite; however, the study population was too nonselective to enable a definitive statement about a causative correlation with obesity and MetS.

An analysis of the 2004-2005 US National Health Interview Survey for adults aged 18 to 85 noted that sleep duration was frequently more strongly associated with risk of chronic disease than demographic characteristics, geographic region, and other health behaviors such as smoking. Both short and long sleep duration were significantly associated with obesity, relative to sleeping 7 to 8h.[30]

A 2010 review found that after correcting for obesity and other covariates, both quantity and quality of sleep predicted the risk of development of T2DM.[31] In 2012, a more specific investigation at the cellular level revealed a role for the adipocyte clock in the temporal organization of energy regulation. This study highlighted timing as a modulator of the adipocyte-hypothalamic axis and showed the impact of timing of food intake on body weight.[32]

In a comparison using functional MRI to study volunteer participants' brain responses to food and non-food stimuli under differing sleep conditions, restricted sleep increased overall neuronal activity, which in turn led to a greater propensity to overeat.[33] In another study, a definite role was shown for circadian rhythm in maintaining weight loss: circadian rhythms at the beginning of a weight loss program were predictive of the success of future weight loss.[34]

Finally, a recent review concluded that optimum sleep duration of 7–8 hours per night avoids disturbance of circadian rhythm and the concomitant risks for MetS.[35] However, understanding of the specific pathophysiological pathways remains incomplete.

1.3.4

The Role of Appetite and Food Intake

Factors underlying the difficulty of maintaining weight loss have been examined at the physiological and behavioral levels. A 2011 study enrolled 50 overweight patients or patients with obesity, of whom 36 completed the protocol. Before starting a 10-week very-low-energy diet, baseline levels of leptin, ghrelin, peptide YY, gastric inhibitory polypeptide (GIP), glucagon-like peptide 1 (GLP-1), amylin, pancreatic polypeptide, cholecystokinin, and insulin were measured, and a subjective rating of appetite was obtained from all participants.[36]

Upon completion of the 10-week regimen, the mean weight loss was 13.5 kg, 14% of the net weight at baseline levels. Significant reductions in levels of leptin, peptide YY, cholecystokinin, insulin, and amylin were found at the 10-week point. However, from baseline to week 62, the net percent weight loss was down to 8.2%. Levels of leptin and other hormonal regulators of appetite remained significantly elevated as compared with the 10-week values. The increase of leptin level and weight regained was linear, indicating that these compensatory responses to caloric restriction could help provide a physiological basis for weight regain after the initial loss from changed dietary intake.

Recent obesity studies have utilized advanced radiological techniques and gene sequencing, resulting in a deeper understanding of physiological mechanisms and cell structures that influence obesity. Prenatal exposures to obesogens[37], tobacco use during pregnancy[38], and endocrine-disrupting chemicals[39] have been cited as contributors to epigenetic changes that promote obesity through changes to the satiety response.

1.3.5

Transgenerational Inheritance of Obesity

Epigenetics involves heritable alterations in gene expression or cellular phenotypes that are not encoded on the DNA sequence itself. Major epigenetic mechanisms include modifications of histone proteins in chromatin and DNA methylation (which does not alter the DNA sequence). Changes that impact the memory of previous events, which can affect even a fetus in utero, can result in pathologies when exposed to a hostile environment. Association of lower birth weight with increased risk of cardiovascular diseases later in life reflects developmental responses of the fetus and/or infant to environmental conditions.[38]

Studies of the transgenerational inheritance of metabolic disorders have suggested that, in specific instances, certain obesogens act through the peroxisome proliferator activated receptor (PPAR), the master regulator of adipogenesis, whereas others act through currently unidentified pathways.[37,40] Generations of mice exposed to DDT showed that the generation exposed to DDT and its progeny did not suffer any obvious changes; however, the next (F1) generation developed a host of serious diseases, and by F3, over 50% of the animals developed obesity.[41]

A 38-year prospective longitudinal study of a representative birth cohort in New Zealand used gene sequencing for genome-wide association studies of obesity-related phenotypes.[42] After birth, children at higher genetic risk gained weight more rapidly and reached adiposity rebound earlier and at a higher BMI. In turn, these developmental phenotypes predicted adult obesity, mediating about half the genetic effect on adult obesity risk. Plastics-derived compounds, BPA and phthalates have also been shown to promote transgenerational changes.[43]

1.3.6
Skeletal Muscle as Secretory Organ

There is evidence that skeletal muscle is actually a secretory organ; the muscle secretome has been found to consist of several hundred secreted peptides. This provides a conceptual basis and a new paradigm for understanding how muscles communicate with other organs, including adipose tissue.[44] Myokines may exert their influence within the muscle itself, providing a potential mechanism for the association between sedentary behavior and chronic disease, including obesity.

II OBESITY

Obesity is defined according to the body mass index (BMI), calculated by dividing weight in kilograms by height in meters squared. When this number is 30 or higher, an individual is considered to have obesity (Table 11). A number of organizations have supported the classification of obesity as a disease[45-47] and in June 2013, an American Medical Association (AMA) policy resolution recognizing obesity as a disease requiring a range of medical interventions was officially adopted.[48]

In children older than 2 years of age, obesity is defined as a BMI at or above the 95th percentile of the 2000 CDC sex-specific BMI-for-age growth charts.[51,52] While there is no standard definition of obesity for children younger than age 2 years, recent analyses have used weight for recumbent length at or above the 95th percentile on the CDC sex-specific weight for recumbent length growth charts (Table 12).[2,53]

Table 11

Adult obesity classifications and risk of comorbidities.

CLASSIFICATION	BMI, KG/M^2	RISK OF COMORBIDITIES
Underweight	<18.5	Low, but increased risk of other clinical problems
Normal weight	18.5–24.9	Average
Overweight	25–29.9	Increased
Obesity (Grade 1)	30–34.9	Moderate
Obesity (Grade 2)	35–39.9	Severe
Obesity (Grade 3)	≥40	Very severe

Source: Flegal et al. 2010[49]; NHLBI 2013[50]

It is recognized that universal BMI values used to define obesity may not be appropriate for all populations based on factors such as age, sex, race and ethnicity.[54] For example, persons of Asian descent may have different body fat levels at the same BMI. Although a technical review by the World Health Organization and the joint American College of Cardiology, American Heart Association, and The Obesity Society (ACC/AHA/TOS) Guidelines both recommended that universal BMI ranges be retained as an international classification, they suggested the possibility of revised thresholds for Asian populations as trigger points for public health action.[55] Additional measures such as waist circumference may also offer better indicators of morbidity and mortality risk in such populations.[56]

2.1

OBESITY: PREVALENCE AND INCIDENCE

The latest US prevalence data shows that over one in three adults has obesity. Among the various age groups, prevalence is highest among those 40-59 years of age (Table 13).

The NHANES dataset spanning 1960 to 2012 clearly illustrates a steady rise in the prevalence of obesity among US adults (Table 14).

Among all US children aged 2-19 years, the overall prevalence of overweight is 31.8% and obesity 16.9% (Table 15). Cunningham et al. have shown that young overweight children are more likely to have obesity later in life: their prospective study of 7,738 children demonstrated that overweight 5-year-olds were 4 times

Table 12

Childhood obesity classifications.	
CLASSIFICATION	WEIGHT AS A PERCENTILE OF HEIGHT
Underweight	<5th percentile
Normal weight	5th to 85th percentile
Overweight	85th to 95th percentile
Obesity	>95th percentile

Source: Ogden and Flegal, 2010[52]

Table 13

Age-adjusted prevalence of obesity in US adults, by sex and age group, among adults aged 20 and over, 2011-2012.			
AGE GROUP	OVERALL	MEN	WOMEN
All ages 20 and older	34.9%	33.5%	36.1%
20-39 years	30.3%	29.0%	31.8%
40-59 years	39.5%	39.4%	39.5%
60 years and older	35.4%	32.0%	38.1%

Source: Ogden et al. 2013[54]

Table 14

Trends in overweight and obesity prevalence in the US adult population (age 20-79 years), 1960-2012.			
	OVERWEIGHT	OBESE	EXTREMELY OBESE
1960-1962	31.5%	13.4%	0.9%
1971-1974	32.7%	14.5%	1.3%
1976-1980	32.1%	15.0%	1.4%
1988-1994	32.6%	23.2%	3.0%
1999-2000	33.6%	30.9%	5.0%
2001-2002	34.4%	31.2%	5.4%
2003-2004	33.4%	32.9%	5.1%
2005-2006	32.2%	35.1%	6.2%
2007-2008	33.6%	34.3%	6.0%
2009-2010	32.7%	36.1%	6.6%
2011-2012	33.3%	35.5%	6.6%

Source: Fryar et al. 2014[1]

Table 15

Age-adjusted prevalence of obesity by sex and age group in US children age 2-19 years, 2011-2012.			
AGE GROUP	OVERALL	BOYS	GIRLS
2-5 years	8.4%	9.5%	7.2%
6-11 years	17.7%	16.4%	19.1%
12-19 years	20.5%	20.3%	20.7%

Source: Ogden et al. 2014[2]

as likely as normal-weight children to have obesity by age 14.[57]

2.2 DEMOGRAPHIC DIFFERENCES

There are notable differences in obesity prevalence and risk for comorbidities based on factors that include age, sex, race, ethnicity, and geographic location.[58] Differences in obesity prevalence among major ethnic/racial groups in the US are summarized below (Table 16).

According to a recent meta-synthesis, obesity disproportionally affects Spanish-speaking women of Central American, South American and Caribbean descent living in the United States.[59] In addition, a recent study of patients treated for overweight or obesity in US federally supported health centers reported that overweight patients or patients with obesity were over 2.5 times more likely to be told they had a weight problem if they were Hispanic or Latino.[60]

Obesity prevalence has also tripled among Asian/Pacific Islander (API) populations over the last two decades, from 3.7% in 1992 to 13.3% in 2010 for all API subgroups (Table 17). Though the overall prevalence remains lower in API populations than non-Hispanic whites, the estimated annual rate of increase in prevalence is higher for APIs: 6.2% versus 4.0% for non-Hispanic whites.[61]

The risk for overweight and obesity appears to augment among immigrants, with increasing duration of residence in the United States (Table 18).[62] In 2003–2008, obesity prevalence ranged from 2.3% for recent Chinese immigrants to 31%–39% for Native Americans, US-born

Table 16

Obesity in US adults by race and ethnicity, 2011-2012.

	NON-HISPANIC WHITE	NON-HISPANIC BLACK	ASIAN	HISPANIC
Total[a]	32.6%	47.8%	10.8%	42.5%
Men[b]	32.4%	37.1%	10.0%	40.1%
Women[b]	32.8%	56.6%	11.4%	44.4%

Source: a, Ogden et al. 2013[54]; b, Fryar et al. 2014[1]

Table 17

Obesity in Asian/Pacific Islander subgroups in the United States, 1992-2011.

RACE/ETHNICITY	PREVALENCE, 1992-1995	PREVALENCE, 2006-2011
Non-Hispanic white	13.9%	25.5%
Chinese	3.3%	7.1%
Asian Indian	6.8%	19.0%
Filipino	6.9%	22.0%
Korean	3.2%	ND
Vietnamese	1.1%	ND
Japanese	6.1%	ND
Hawaiian/Pacific Islander	25.7%	43.5%
Other APIs	11.4%	11.5%

Source: Singh and Lin. 2013[61]
ND = no data available

Table 18

Increase in prevalence of obesity among immigrants to the United States, 1992-2008.

DURATION OF RESIDENCE IN US (YEARS)	PREVALENCE, 1992-1995	PREVALENCE, 2003-2008
<1	5.7%	8.1%
1–5	7.9%	10.8%
5–9	7.6%	14.6%
10–14	9.7%	16.4%
15+	13.1%	22.0%
US-born	15.6%	26.5%

Source: Singh et al. 2011[62]

blacks, Mexicans, and Puerto Ricans, and long-term Mexican and Puerto Rican immigrants, as summarized in Table 19. Obesity prevalence for US-born adults increased from 13.9% to 28.7%, whereas prevalence for immigrants increased from 9.5% to 20.7%. The prevalence of obesity among Native American/Alaska Native people was very high, at 39.2%, in 2003-2008.

Among children in the United States, like the adult population, prevalence of obesity is highest among Hispanic and non-Hispanic black populations (Table 20).

These results are corroborated by an observational study conducted by Kaiser Permanente Northern California (KPNC) on obesity prevalence among KPNC members 2–5, 6–11, and 12–19 years of age (Table 21). Prevalence of obesity (BMI ≥ 95th percentile) at 2003–2005 and 2009–2010 was highest among Hispanics/Latinos across all age groups and lowest among Asians at both time points.[63]

As the BRFSS data is self-reported, the actual state-level prevalence of obesity is likely underestimated, because people tend to overestimate their height and underestimate their weight.

Table 19

Prevalence of obesity among recent immigrants by race and country of origin, 2003-2008.

US IMMIGRANTS BY RACIAL GROUP	PREVALENCE, 2003–2008
Non-Hispanic White	10.5%
Non-Hispanic Black	17.3%
US IMMIGRANTS BY COUNTRY OF ORIGIN	
Chinese	2.3%
Filipino	7.6%
Asian Indian	5.7%
Other Asian and Pacific Islanders	4.0%
Mexican	18.9%
Puerto Rican	27.6%
Cuban	22.0%
Central, South American, other Hispanics	14.6%

Source: Singh et al. 2011[62]

Table 20

Obesity in US children by race and ethnicity, 2011-2012.

	NON-HISPANIC WHITE	NON-HISPANIC BLACK	ASIAN	HISPANIC
All	14.1%	20.2%	8.6%	22.4%
Boys	12.6%	19.9%	11.5%	24.1%
Girls	15.6%	20.5%	5.6%	20.6%

Source: Ogden et al. 2014[2]

Table 21

Age, sex, and race/ethnicity distributions at each time period.

KAISER PERMANENTE NORTHERN CALIFORNIA MEMBERS	2003-2005 N (%)	2009-2010 N (%)
Ages, years		
02–05	85,804 (33.8%)	137,479 (32.2%)
06–11	82,464 (32.5%)	140,815 (33.0%)
12–19	85,739 (33.7%)	148,383 (34.8%)
Sex		
Male	128,598 (50.6%)	218,249 (51.1%)
Female	125,404 (49.4%)	208,423 (48.9%)
Race/ethnicity		
Asian	34,413 (13.6%)	63,947 (15.0%)
Black	23,179 (9.1%)	34,175 (8.0%)
Hispanic/Latino	25,959 (10.2%)	55,977 (13.1%)
White	98,449 (38.8%)	153,714 (36.3%)
Other	21,660 (8.5%)	40,918 (9.6%)
Unknown	50,342 (19.8%)	76,941 (18.0%)
Total	254,007	426,677

Source: Gee et al. 2013[63]

2.3 LIFE EXPECTANCY AND MORTALITY

2.3.1 Life Expectancy

The combined negative effects of increasing obesity are projected to reduce mean life expectancy at age 40 (for both men and women) by 0.28 years by 2020, 0.55 years by 2030, and 0.78 years by 2040.[66]

Among the high-income countries, the US has one of the highest prevalence rates of obesity and one of the lowest life expectancies.[67] According to a study that projected the fraction of deaths attributable to obesity, obesity reduced US life expectancy at age 50 years in 2006 by 1.54 years for women and by 1.85 years for men.[67] The differences between the population attributable fraction of deaths from obesity in the US was typically greatest at ages 50 to 59 years for both men and women, reflecting the large proportion of US residents with obesity in this age group. For women, the greatest effects were found between 60 and 69 years of age, whereas for men, the impact of obesity was highest at ages 50 to 59 years. At age 50 years, obesity has reduced life expectancy from between 0.88 and 1.54 years for women, and 0.62 to 1.85 years for men.[66] Patterns of socioeconomic disparity have been found to relate to 11 health indicators, including life expectancy at age 25 and obesity: across all racial groups, it has been argued that the health problems that accompany obesity are exacerbated by low income and educational level.[68]

According to a study based on the 1997-2000 National Health Interview Survey of non-smoking US women, women with obesity who have breast cancer stand to lose 1 to 12 years of life, depending on their age, race, and obesity status. The relative risk for death in this population increases with the degree of obesity. Among women with obesity who have breast cancer, those under age 50 across all racial groups were predicted to lose the most life years; racial groups other than whites and blacks lost the most life years (11.9 years), followed by whites (9.8 years) and blacks (9.2 years).[69] However, this conclusion may need to be re-evaluated. A recent study of physical activity levels by race, age, and obesity indicates that fewer African-American patients met American Cancer Society guidelines. The authors suggest that disparities in survival among breast cancer patients with obesity correlates with average physical activity levels.[70]

In 2008, a systematic review of literature from 1966 through 2007 showed a small but significant increase (risk ratio, 1.12) in postmenopausal breast cancer in women with obesity.[71] It is hypothesized that in these women, the increase in white adipose tissue allows for increased production of estrogen as compared with women of normal weight. Conversely, a 2012 analysis of the Study of Tamoxifen and Raloxifene (STAR) trial and the Breast Cancer Prevention Trial (BCPT) showed only a modest, statistically non-significant increase in risk for postmenopausal breast cancer correlated with BMI. The authors of that analysis point out that there are other factors besides BMI that might explain the discrepancies, including detection bias. Addressing this conundrum, a recent study applied systems analysis to the variables that possibly affect the prevalence of breast cancer—age, race/ethnicity, age at menarche, age at first birth, age at menopause, obesity, alcohol consumption, income, tobacco use, use of hormone therapy (HT), and BRCA1/2 genotype. The authors applied their analysis to women in the state of California; a 50% decrease in excess BMI would reduce the incidence of invasive breast cancer by 384 cases per 100,000 women over 55 years of age. A 100% decrease in excess BMI would produce a reduction of 375 cases per 100,000.[72]

2.3.2 Mortality

Mortality risk

According to a 2013 study[73], in the year 2000, obesity was associated with nearly 112,000 excess deaths relative to normal weight. In a meta-analysis of white women throughout the world, including the US, grade 1 obesity (BMI 30 to <35) was associated with ~30,000 excess deaths and grades 2 to 3 (BMI ≥35) with more than 82,000 deaths.[73] Compared with normal-weight adults, adults with obesity had at least a 20% significantly higher rate of dying of all-cause or cardiovascular disease (CVD). These rates advanced death by 3.7 years (grades 2 and 3) for all-cause mortality and between 1.6 (grade 1) and 5.0 years (grade 3) for CVD-specific mortality. The burden of obesity was greatest among adults aged 45 to 64 years for all-cause and CVD-specific mortality and among women for all-cause mortality.

Using waist circumference as a metric in a pooled study of 650,386 white adults aged 20 to 83 years, a strong positive linear association of waist circumference (WC) with all-cause mortality was observed for men (hazard ratio 1.52 for WC ≥110 vs <90 cm) and women (hazard

ratio 1.80 for WC ≥95 vs <70 cm).[74] A meta-analysis using more recent data from adequately adjusted studies found that obesity was associated with significantly higher all-cause mortality, with a summary hazard ratio of 1.21 for all grades of obesity combined, 0.97 for grade 1, and 1.34 for grades 2 and 3. Relative to the normal weight category, the hazard ratio for obesity estimated from pooled studies was 1.20 for men and 1.28 for women.[75]

Overall influence on life expectancy: Obesity as comorbidity

Studies that look at the relationship between increased mortality risks for persons with specific illnesses provide further evidence that obesity is a disease. In a population-based case-control study of men who underwent radical prostatectomy, men with obesity overall experienced greater than 50% increase in prostate cancer mortality, with the strongest effect for men having the most aggressive forms of cancer (Gleason score 8 and higher, adjusted odds ratio 2.37).[76]

Similarly, a large study that pooled five-year follow-up data for African Americans who died from pancreatic cancer, relative to a BMI 18.5–24.9, those with BMI of 30.0 to 34.9 had an HR of 1.25, and those with BMI ≥35.0 had an HR of 1.31.[77] For women who underwent surgery for advanced epithelial ovarian cancer, the obese group (BMI ≥40.0) had a higher adjusted odds ratio for severe complications and a 90-day mortality rate of 15.7%, higher than both underweight and normal to patients with grade 2 obesity.[78] Finally, a study that pooled information in 20 prospective studies of adults with obesity, grade 3 obesity was associated with substantially elevated HRs of death and major reductions in life expectancy compared with normal weight: BMI of 40–44.9, 45–49.9, 50–54.9, and 55–59.9 kg/m2 was associated with an estimated 6.5, 8.9, 9.8, and 13.7 years of life lost, respectively.[79]

2.4

DIAGNOSIS, TREATMENT, AND PRESCRIPTION TRENDS

2.4.1

Anti-Obesity Drugs

During the period 1991–1996, the outpatient use of anti-obesity drugs, mostly phentermine or fenfluramine, in the United States peaked at 8,529 anti-obesity drug prescriptions filled per 100,000 US population. Starting in 1997, prescription rates decreased dramatically when fenfluramine and dexfenfluramine were voluntarily withdrawn from the market due to their association with valvular heart disorders. Whereas the use of phentermine started to increase in 2004 after an earlier decline, this drug has remained the leading prescription weight-loss drug throughout the study period. In 2011, 2,554 anti-obesity drug prescriptions were filled per 100,000 US population, of which 86.6% were for phentermine.[80] Table 23 summarizes the distribution of all patients using anti-obesity medication between 2008-2011. Notably, these data are prior to the most recent FDA approvals.

Table 22

US states with the highest and lowest prevalence of obesity.

STATE	PREVALENCE, 2011-2013	STATE	PREVALENCE, 2011-2013
Mississippi	35.1%	Colorado	21.3%
West Virginia	35.1%	Hawaii	21.8%
Arkansas	34.6%	Massachusetts	23.6%
Tennessee	33.7%	Utah	24.1%
Kentucky	33.2%	California	24.1%
Louisiana	33.1%	Montana	24.6%
		Vermont	24.7%

Source: Behavioral Risk Factor Surveillance Survey, 2011-2013[65]

Table 23

The distribution of all anti-obesity drug users by age and BMI range (2008-2011).

AGE	0–16	17–44	45–64	65 +
% distribution	0.5%	62.3%	35.55%	3.6%
BMI RANGE	≤ 24.9	25–26.9	27–29.9	≥ 30
% distribution	4.5%	6.0%	12.7%	65.7%

Source: Hampp et al. 2013[80]

Orlistat, a pancreatic lipase inhibitor, was approved in 1999 by the FDA. Until 2012, orlistat was the only anti-obesity drug approved by the FDA for long-term use.[22] A number of new pharmacotherapies for obesity management have since come to market, including lorcaserin and phentermine/topiramate in 2012, and most recently naltrexone/bupropion in 2014 and liraglutide in 2015, as treatment options for chronic weight management supplemental to diet and exercise.[81] Preliminary studies suggest that naltrexone and buproprion affect two separate areas of the brain that are in involved in food intake.[82] Liraglutide, a GLP-1 inhibitor, at 3 milligrams per day was recently approved by the US FDA and has been approved for anti-obesity use in the EU.[83] In a clinical trial [ClinicalTrials.gov ID:NCT01272219], as reported at the 96th annual meeting, of the Endocrine Society, liraglutide induced greater mean weight loss (8.0%) than placebo (2.6%) after 56 weeks; the adverse events were mild and transient. It reduced blood pressure and improved glycemic control.[84,85] In existing studies, phentermine/topiramate had a superior weight loss profile to lorcaserin, but the incidence of adverse effects was lower with lorcaserin. Both drugs were well-tolerated, and adverse events were modest in intensity, dose dependent, mild, resolved quickly,[86] and tended to decrease with the duration of treatment.[87]

2.4.2
Surgical Procedures

As shown in Table 24, the rate of bariatric surgery per 100,000 adults increased more than 4-fold between 1998 and 2002; the population-based rate continued to increase to 63.9 in 2004 but plateaued at 54.2 procedures in 2008.

Over 10 years, the number of adolescent inpatient bariatric procedures increased from 328 in 2000 to 1009 in 2009. Adolescent bariatric surgery trends mirror those observed in the adult population, with a plateau in volume during the mid-2000s and a shift toward less invasive procedures.[88] One such innovation, sleeve gastrectomy, has been shown effective in producing weight loss.

In 117 patients with a starting mean BMI of 46.6 ± 6.0 kg/m2, laparoscopic gastric band significantly lowered the BMI to 30.3 ± 5.9 kg/m2 and 30.6 ± 5.6 kg/m2 at 12 and 24 months respectively, and resolved obesity-related diseases; at two years, the remission-rate for type 2 diabetes mellitus was 80.7%, hypertension 63.9%. However, there were some complications, including an increase of GERD, from 12.8% prior to the operation to 27.4% at 2 years post-operative.[89]

2.5
HEALTH OUTCOME MEASURES

2.5.1
Diet-Related Outcomes

One of the first studies to provide a comprehensive comparison of diets randomly assigned 811 overweight adults to diets with four different percentages of fat, protein, and carbohydrates. All participants were offered group and individual instructional sessions for 2 years. Among the 80% of participants who completed the trial, the average weight loss was 4 kg and 14% to 15% of the participants had a reduction of at least 10% of their initial body weight. Satiety, hunger, satisfaction with the diet, and attendance at group sessions were similar for all diets; attendance was strongly associated with weight loss (0.2 kg per session attended). The diets improved lipid-related risk factors and fasting insulin levels. The end result was that clinically meaningful weight loss resulted from reduced-calorie diets, no matter which macronutrient was emphasized.[90,91]

A recent meta-analysis reviewed sources that make claims for superiority of one diet over others for inducing weight loss (Table 25). Among 59 eligible articles reporting 48 unique randomized trials (including 7,286 individuals) as compared with no diet, the largest weight loss was associated with low-carbohydrate diets and low-fat diets and there was no difference between the effectiveness of these diet categories.

In the analysis adjusted for diet class, all treatments were superior to no diet at 6-month follow-up. Significant weight loss was observed with any low-carbohydrate or low-fat diet. Behavioral support and exercise as an add-on to diet appeared to modestly enhance the weight loss effects at the 6-month follow-up, though this association was nonsignificant for behavioural support at 12 months. Overall, the authors concluded that although weight loss differences between individual named diets were small, all treatments were superior to no diet. This supports the practice of recommending any diet that a patient will adhere to in order to lose weight.[92]

Table 24

Use of bariatric surgery among US adults, 1998–2008.				
	1998	2002	2007	2008
Procedures				
Total number	12,775	70,256	84,129	124,838
Gastric bypass (Roux-en-Y)	78%	92%	72%	69%
Gastroplasty	22%	8%	4%	2%
Laparoscopic gastric band	n/a	n/a	24%	29%
Overall annual rate/100,000 adults[a]	6.3	32.7	36.9	54.2
Laparoscopy rate	2.1%	17.9%	87.5%	90.2%
Patient Characteristics				
Median age, years	39	42	44	45
Female, %	82%	84%	80%	79%
Caucasians, %	81%	81%	71%	74%
Comorbidity				
Diabetes, %	14%	21%	30%	33%
Hypertension, %	35%	44%	52%	56%
Hyperlipidemia, %	5%	7%	33%	20%
Chronic liver disease, %	11%	9%	7%	10%
Sleep apnea, %	19%	26%	13%	14%
Outcome				
In-hospital mortality, %	0.80%	0.50%	0.12%	0.10%
Median length of stay, days	4	3	2	2

Source: Nguyen et al. 2013[88]

Table 25

Difference in average weight loss for four diet classes versus no diet.		
DIET TYPE	WEIGHT LOSS AT 6 MONTHS	WEIGHT LOSS AT 12 MONTHS
Low-carbohydrate	8.73 kg	7.25 kg
Low-fat	7.99 kg	7.27 kg
Moderate macronutrients	6.78 kg	5.70 kg
Lifestyle, Exercise, Attitudes, Relationships, and Nutrition (LEARN)	6.07 kg	5.16 kg

Source: Johnston et al. 2014[92]

The aforementioned studies also suggest that dietary advice needs to be backed up by ongoing support, and that differences in various dietary approaches might be successful for different persons. Facing that challenge, representatives from the American College of Cardiology, American Heart Association, and The Obesity Society published an extensive evaluation of the components of weight-loss management (hereinafter "the ACC/AHA/TOS guidelines"). The conclusion of the AHA/ACC/TOS guidelines was that caloric restriction is the key mechanism driving weight loss, and in agreement with the results of the two studies mentioned above, acknowledgement of minimal distinction between diets based on different proportions of macronutrients. The panel recommended future research to further examine application of dietary guidelines to specific patient populations according to demographic influences, degree of obesity, diet as a preventive strategy, and baseline co-morbid conditions.[47] On the basis of the panel's meta-analyses, the following table illustrates interventions deemed effective according to studies where strength of evidence was rated as high.

Lesser improvements were found in health profiles where the strength of evidence was moderate. In those overweight and adults with obesity and T2D managed only with a comprehensive lifestyle treatment, there was some weight gain over 4 years. This weight gain resulted in an increase in HbA1c below pre-intervention, but at clinically meaningful levels. In observational cohort studies, showing low strength of evidence, there was a 25% decrease in mortality rate among overweight and adults with obesity and T2D who intentionally lost 9–13 kg compared with weight-stable controls.[47]

2.5.2

Exercise-Related Outcomes

A systematic review of randomized clinical trials showed that exercise alone as a means of weight loss only produced small mean weight loss compared to no treatment. However, when combined with diet, increasing exercise intensity not only increased the weight loss but also resulted in significant positive changes in other metabolic outcome measures: reduced diastolic blood pressure, triglycerides, and fasting glucose.[93] Furthermore, the response to exercise, like other weight loss interventions, is highly variable with some individuals losing significant amounts of weight while whereas others do not.

A recent review based on NHANES data in US adults has shown that average caloric intake did not change significantly over the period 1988 to 2010; instead, the main determinant for increasing obesity was a decline in physical activity level.[94] The proportion of adults who reported no leisure-time physical activity increased over the period from 19.1% to 51.7% in women, and from 11.4% to 43.5% in men.

Studies have differed in their emphasis on weight loss versus physical activity as being primarily responsible for improvements in lipid profile and overall health.[95,96]

2.5.3

Pharmacotherapy

Successful pharmacotherapy as an adjunct to diet and exercise provides an additional tool for those persons who are not able to lose weight, or for those in whom obesity has reached a critical stage.[46] Drugs to treat obesity can be divided into three groups: those that reduce food intake; those that alter metabolism; and those that increase thermogenesis.[97] There is general consensus that weight loss of 5% or more, achieved through intensive lifestyle intervention, is clinically meaningful: it reduces cardiovascular risk factors, prevents or delays development of T2DM, and ameliorates other health consequences of obesity. Based on available evidence to date, the US Preventive Services Task Force (USPSTF) recommends that patients with a BMI of 30 kg/m^2 or higher be offered or referred to intensive behavioral interventions.[98]

Five drugs are currently approved by the US Food and Drug Administration for long-term management of obesity. Outcomes associated with each pharmacotherapy are highlighted below and discussed in greater detail by Apovian et al.[46]:

Orlistat, approved in 1999 as a prescription drug and for over-the-counter sale in 2007, partially blocks absorption of fats. In trials, the mean body weight loss was 3% greater than placebo, and patients experienced less weight gain after 2 years.[22] The weight loss in a 3 year study was 11% at 1 year compared to 7% for the placebo and after 3 years, the loss was 6.5% in patients as compared with 4.1% for the placebo.[86] Side effects can include an increased number of bowel movements and potential changes in the bowel function and microbiota.[22]

Lorcaserin, a serotonin, dopamine and norepinephrine reuptake inhibitor, was approved by the FDA in 2012. The mean body weight loss for lorcaserin was 5.8 kg vs 2.2 kg for placebo. Side effects include a possible concern for cancer risk.[22]

Naltrexone/buproprion, approved in 2014, is intended for patients with a BMI of 30 kg/m^2 or above, or 27 kg/m^2 or greater in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes, dyslipidemia.[82]

Phentermine, an appetite suppressant, was approved for short-term use in 1959; weight loss for patients using this drug was 3.6 kg greater than those treated with a placebo. However, phentermine is approved only for short-term use[86], and discontinuation of this drug involves withdrawal symptoms.[22]

Phentermine/topiramate, a combination of phentermine with topiramate, involves a synergistic action. It was approved in 2012. Using a dosage of 7.5 mg phentermine with 46 mg topiramate produced a reduction in weight of 9.3% versus the placebo at -2.2%. For the combination 15 mg phentermine and 92 mg topiramate, the reduction was as high as 10.75%.[22] The most commonly observed side effects in clinical trials were those of the constituent drugs: phentermine causes insomnia and dry mouth early in treatment, but these resolved. Topiramate, a carbonic anhydrase inhibitor, is associated with altered taste for carbonated beverages and tingling in fingers, toes, and perioral areas, and may lead to mild metabolic acidosis.[86]

Liraglutide, FDA approved in December 2014, is a GLP-receptor agonist. In a European study, the weight loss, depending on a dosage ranging from 1.2 to 3.0 mg, was 4.8 to 7.2kg, versus the placebo at 2.8 kg and 4.1 kg in the orlistat-treated comparator group. Liraglutide remains the only anti-obesity medication approved by the European Medicines Agency.[86]

2.5.4
Bariatric Procedures

A review of nearly 30 long-term studies comparing bariatric procedures showed that gastric bypass surgery had better outcomes than gastric banding for long-term weight loss, controlling T2DM and high blood pressure, and lowering cholesterol levels.[99]

The authors of the review found that those undergoing gastric bypass operations lost more weight—an average of 66% of their excess weight (which translates to about a 30% loss of body weight)—compared with a 45% average excess weight loss for those undergoing gastric banding procedures (about 22% loss of body weight). In a study of 208 patients with clinically severe obesity (BMI ≤50 kg/m^2) who underwent sleeve gastrectomy as a sole procedure at a bariatric referral center, a mean excess weight loss of 71.1% (about 35% weight loss) was documented in 90 (89.4%) of 106 patients, available for follow-up after 3 years. The excess weight loss slowly declined to 57.6% (about 28% weight loss) in 21 (77.7%) of 27 patients at 5 years of follow-up. No deaths were recorded. Early morbidity (≤30 d) was 9.6%, chiefly owing to staple line closure leaks, and late morbidity was 4.8%. The excess weight loss slowly declined to 57.6% in 21 (77.7%) of 27 patients after 5 years of follow-up. No major metabolic deficiencies were apparent. Statistically significant improvements in pre-existing hypertension, diabetes mellitus, and dyslipidemia were achieved. GERD symptoms developed in 9.8% of patients within the first postoperative year but lessened over time to 7.4% at the 5-year mark.[100]

III METABOLIC SYNDROME

On the basis of NHANES 2003–2006 data, the age-adjusted prevalence of MetS, a cluster of major cardiovascular risk factors with increased waist circumference and insulin resistance, is 34% (35.1% among men and 32.6% among women).[101] MetS components as detailed in the 2001 Adult Treatment Panel (ATP) III report and updated by a joint statement in 2009 are:

- Elevated waist circumference with population and country-specific definitions (ranging from 85 to 102 cm in men and 80 to 90 cm in women);
- Elevated fasting triglycerides ≥150 mg/dL;
- Reduced HDL cholesterol <40 mg/dL in men and <50 mg/dL in women;
- Elevated blood pressure ≥130/85 mmHg or treatment for hypertension; and

- Fasting glucose ≥100 mg/dL or use of antidiabetic medication.[4,102]

Three abnormal findings out of these five qualify an adult for MetS. Modified criteria for children and adolescents have been published by a panel of the International Diabetes Federation (IDF).[6] These are as follows:

Age 6 to <10 years
- Obesity ≥ 90th percentile as assessed by waist circumference
- MetS cannot be diagnosed, but further measurements should be made if family history of MetS, type 2 diabetes mellitus, dyslipidaemia, cardiovascular disease, hypertension, or obesity

Age 10 to <16 years
- Obesity ≥ 90th percentile (or adult cutoff if lower) as assessed by waist circumference
- Triglycerides ≥ 1.7 mmol/L
- HDL-cholesterol <1.03 mmol/L
- Blood pressure ≥ 130 mmHg systolic or ≥85 mmHg diastolic
- Glucose ≥ 5.6 mmol/L (oral glucose tolerance test recommended) or known type 2 diabetes mellitus

Age ≥ 16 years
- Use existing criteria for adults

Jolliffe and Janssen have also proposed age-specific MetS criteria for adolescents (age 12 to 19) that are linked to both the National Cholesterol Education Program Adult Treatment Panel III (ATP) and IDF adult MetS criteria.[103]

3.1

METABOLIC SYNDROME: PREVALENCE AND INCIDENCE

Tables 26 and 27 present the estimated prevalence of MetS in a study based on the results of the NHANES 1999-2000 and biannually through 2009-2010.[3]

3.1.1

Trends

The decrease in age-adjusted prevalence of MetS between 1999-2000 and 2009-2010 may be explained by an improved treatment of the underlying risk factors. During that period, prevalence of hypertriglyceridemia decreased (33.5% to 24.3%), as did elevated blood pressure (32.3% to 24.0%). The prevalence of hyperglycemia increased, as did elevated waist circumference (45.4% to 56.1%). These trends varied considerably by gender and race/ethnicity groups. Decreases in elevated blood pressure, suboptimal triglycerides, and HDL-C prevalence have corresponded

Table 26

Age-standardized prevalence of MetS as estimated by the diagnostic criteria.

YEARS	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010
Total Population	25.54%	27.37%	25.76%	23.18%	24.94%	22.90%
Males	23.35%	27.45%	25.26%	24.57%	26.54%	23.69%
Females	27.50%	26.98%	26.20%	22.10%	23.54%	21.80%

Source: Beltrán-Sánchez et al. 2013[3]

Table 27

Age-standardized prevalence of MetS as estimated for persons with abdominal obesity.

YEARS	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010
Total Population	43.45%	48.96%	55.35%	54.24%	53.78%	56.07%
Males	36.48%	39.82%	46.02%	46.41%	45.44%	46.44%
Females	53.53%	57.67%	64.41%	61.70%	61.93%	65.38%

Source: Beltrán-Sánchez et al. 2013[3]

with increases in antihypertensive and lipid-modifying drugs. The increase in elevated waist circumference parallels the increase in obesity in the US over this time period.[3]

3.2

DEMOGRAPHIC DIFFERENCES

The recently published cross-sectional cohort, interview-administered Hispanic Community Health Study/Study of Latinos (HCHS/SOL) tested theoretically driven hypotheses concerning psychosocial factors in CVD and was primarily focused on the high prevalence of diabetes among Latinos.[104] In general, there was a higher rate of MetS among Latinos than among non-Hispanic whites, but the incidence of MetS differed among different Hispanic/Latino groups. It was highest among Puerto Ricans (37%) and lowest among South Americans (27%). The prevalence of MetS was significantly higher among Puerto Rican women (40.9%) than Puerto Rican men (32.6%) and paralleled the presence of diabetes.[105]

In a 2011 study of 300 Filipino-Americans, representative of the second largest Asian subgroup in the United States, a modified definition of MetS was used to take account of the ethnic-specific body structure: elevated waist circumference was defined as ≥90 cm in men and ≥88 cm in women. In participants 35 to 75 years of age, 18.3% of the participants (21.1% of males and 15.7% of females) met the threshold for MetS. The prevalence of MetS was considerably lower than the NHANES values for 2009-2010.[106]

Another study examining NHANES 2003-2006 found that non-Hispanic black males were about one-half as likely as non-Hispanic white males to meet the criteria for MetS, whereas non-Hispanic black and Mexican-American females were about 1.5 times as likely as non-Hispanic white females to meet the criteria. Further, MetS increased with age but even more dramatically as BMI increased.[107]

A more recent study taking account of both the WHO and Adult Treatment Panel III criteria for MetS found that rates for racial/ethnic minority groups are higher than those for adults overall. The modest decrease in MetS from 1999-2000 to 2009-2010 among US adults noted previously was not shared by racial/ethnic minorities: there was little change in prevalence among blacks (22.0% vs 22.71%) or Hispanics (32.9% vs 31.9%).[108]

The pediatric and adolescent prevalence of MetS, on the basis of NHANES 1999-2002 data, is summarized in Table 28. The prevalence of MetS in adolescents 12 to 19 years of age was 9.4%, which represents about 2.9 million people.

In 1999 to 2004, about 4.5% of US adolescents 12 to 17 years of age had MetS, according to the definition developed by the International Diabetes Federation. In 2006, this prevalence would have represented about 1.1 million adolescents aged 12 to 17. Prevalence increased from 1.2% among those 12 to 13 years of age to 7.1% among those 14 to 15 years of age, and was higher among boys (6.7%) than girls (2.1%). Furthermore, 4.5% of white adolescents, 3.0% of black adolescents, and 7.1% of Mexican American adolescents had MetS. The prevalence of MetS remained relatively stable during successive 2-year periods: 4.5% for 1999 to 2000, 4.4% to 4.5% for 2001-2002, and 3.7% to 3.9% for 2003-2004. Between 1999 and 2002, 44% of overweight adolescents or adolescents with obesity had MetS. From 1988 to 1994, two-thirds of all adolescents had at least 1 metabolic abnormality.[73]

3.3

HEALTH OUTCOMES

Presence of MetS has health consequences beyond cardiovascular risk. A recent study using the ATPIII definition of MetS found a borderline-significant (P=0.06) relationship between MetS and glaucoma. In a sample of 3026 adult men and women from the 2005-2008 NHANES (weighted mean age: 57.0 years), the prevalence of glaucoma in patients with and without MetS was 5.3% and 3.6%, respectively.[102] In a retrospective cohort study of 4216 women enrolled in an integrated

Table 28

Prevalence of MetS in US adolescents 12 years of age.

ADOLESCENT DEMOGRAPHIC	METS PREVALENCE (%)
Boys	13.2
Girls	5.3
White	10.7
Black	5.2
Mexican American	11.1
Overall	9.4

Source: Beltrán-Sánchez et al. 2013[3]; Falkner et al. 2014[108]

health plan who were diagnosed with incident early-stage breast cancer between 1990 and 2008, 26% had at least 3 MetS components. Compared with women with no MetS components, presence of at least 3 MetS components was associated with an increased risk of second breast cancer events (hazard ratio, 1.50) and breast-cancer specific mortality (hazard ratio, 1.65).[109] In a study of a large cohort (40,977 men; 21,277 women) in France using the NCEP-ATP criteria to define MetS, the following clinical and biological parameters were significantly associated with MetS in men and women, after adjustment for age: lower physical activity, lower vital capacity ratio, higher pulse pressure and heart rate, higher gamma-glutamyl transpeptidase, ASA and ALA transaminase and alkaline phosphatase levels, higher uricemia, leukocyte and globulin levels, dental and gingival inflammation, and higher stress and depression scores. After adjustment for age, the excess risk of all-cause mortality in subjects with MetS compared to subjects without MetS was 1.82 in men and 1.80 in women. After adjustment for age and gender, the risk of death associated with each MetS component was 2.36 for high waist circumference, 2.08 for elevated triglyceride levels, 1.71 for low HDL-cholesterol levels, 1.75 for elevated arterial pressure, and 2.93 for elevated glucose level.[109]

3.4 LIFE EXPECTANCY AND MORTALITY

3.4.1 Death from Cardiovascular Disease

A prospective cohort study used data from 6255 adult participants in the NHANES II (30 to 74 years of age, 54% female) weighted to 63.9, representative of 64 million adults in the US All subjects had mortality information, and were followed for a mean of 13.3 years. MetS was defined by modified National Cholesterol Education Program criteria. From sample-weighted multivariable Cox proportional-hazards regression, compared with those with neither MetS nor prior cardiovascular disease (CVD), age-, gender-, and risk factor-adjusted hazard ratios (HRs) for congestive heart disease (CHD) mortality were 2.02 for those with MetS and 4.19 for those with pre-existing CVD. For CVD mortality, HRs were 1.82 and 3.14, respectively; for overall mortality, HRs were 1.40 and 1.87, respectively. In persons with MetS but without diabetes, risks of CVD and CHD mortality remained elevated. Diabetes predicted all mortality end points. Those with even 1 to 2 MetS risk factors were at increased risk for mortality from CHD and CVD. Furthermore, MetS more strongly predicted CHD, CVD, and total mortality than did its individual components.[110]

In a 2014 study, the age-adjusted prevalence of MetS was 26.7% in the US Of the five MetS components, obesity significantly predicted CVD mortality in the US In that study, after a median follow-up of 13.8 years in the US, based on NHANES III for patients 30 year of age and older, 1,683 patients died from CVD (11.75 per 1,000 person-years).[111]

3.5 DIAGNOSIS, TREATMENT, AND PRESCRIPTION TRENDS

3.5.1 Treatment

The primary approaches for management of the individual components of MetS range from bariatric surgery to pharmaceutical intervention to behavioral modification. These treatments target the individual risk factors of MetS or obesity/insulin resistance. Because it results in weight loss, bariatric surgery significantly reduces prevalence. For instance, increased weight among breast cancer patients with MetS was the major factor in increased risk for a second breast cancer occurrence.[109]

Bariatric Surgery

A population-based, retrospective study of patients who had MetS as defined by the American Heart Association/National Heart, Lung, and Blood Institute were evaluated for bariatric surgery between January 1, 1990, and December 31, 2003. 180 underwent Roux-en-Y gastric bypass, and 157 were assessed in a weight-reduction program but did not undergo surgery. In the surgical group, all MetS components improved and medication use decreased. Nonsurgical patients showed improvements in high-density lipoprotein cholesterol levels. After bariatric surgery, the number of patients with MetS decreased from 156 (87%) of 180 patients to 53 (29%); of the 157 nonsurgical patients, MetS prevalence decreased from 133 patients (85%) to 117 (75%). A relative risk reduction of 0.59 was observed in patients who underwent bariatric surgery and had MetS at follow-up. Results were similar after excluding patients with diabetes or cardiovascular disease or after using diagnostic criteria other than body mass index for MetS. Significant predictors of MetS resolution included a

5% loss in excess weight; the reversibility of MetS depended more on the amount of excess weight loss than on other parameters.[112]

Bariatric surgery brings serious risks along with possibility of improvement. Among 186,576 bariatric surgery patients drawn from the Bariatric Outcomes Longitudinal Database between 2007 and 2010, 23,106 met the criteria for MetS. Among those patients, 62% underwent gastric bypass, 32% gastric banding, and 4.5% sleeve gastrectomy. MetS patients had an increase in serious complications compared with those without MetS (2.4% vs 1.0%), readmissions (6.2% vs 4.7%) and mortality (0.3% vs 0.1%) within 90 days of surgery. In 12,144 (53%) of the MetS patients, remission of hypertension, diabetes, and dyslipidemia occurred in 6%, 50%, and 35% of patients, respectively; 76% of MetS patients with sleep apnea went off all forms of treatment 12 months after the bariatric operation. Among procedures, adjustable gastric banding had a lower 12-month rate of remission of MetS compared with Roux-en-Y gastric bypass, sleeve gastrectomy, and biliopancreatic diversion with duodenal switch.[113]

Pharmaceutical Intervention

A direct pharmaceutical intervention has been the subject of investigation since the discovery in 2003 that it was possible to lower MetS through a combination of drugs—statin, aspirin, and folic acid—termed the "polypill" or "polycap." In 2009, a group in India had some success in a clinical trial using 3 different statins with aspirin and folic acid to reduce cardiovascular risk factors.[114]

In a study based on 10-year longitudinal observations in an Australian population, in 1,991 cases classified as MetS in individuals free of existing diabetes mellitus or CVD, treatment with the polypill (or its components) was shown by mathematical analysis to be effective at reducing cardiovascular events. In 1,000 individuals, statin use alone could reduce MetS in 171 patients; aspirin (acetylsalicylic acid), in 201; and an antihypertensive in 186. The more drug therapies employed, the greater the reduction, with the polypill reducing up to 351 cardiovascular events per 10,000 individuals. Although not cost-effective compared with aspirin alone in the general population, in a high-risk population, among whom combination therapy is often prescribed, the polypill is likely to be more cost-effective than antihypertensive therapy alone or dual therapy with a statin and antihypertensive combination.[115]

Recently, interest in possible intervention has focused on the presence of reactive oxygen species as initiators of a vicious cycle activating an inflammatory response, ultimately contributing to diabetes, cardiovascular diseases, and steatosis. It is known that MetS is associated with oxidative stress and mitochondrial dysfunction.[116] Recent evidence suggests that because Co-enzyme Q10 (Co-Q10), is an essential component of mitochondrial electron transport, Co-Q10 supplementation may be useful in MetS therapy. The anti-inflammatory response and lipid metabolizing effect of Co-Q10 is probably mediated by transcriptional regulation of inflammation and lipid metabolism.[117] A study of obesogenic mice indicated that the mitochondria-targeted antioxidant MitoQ, a ubiquinone compound with the same antioxidant component as Coenzyme Q, had potential as a helpful therapy for MetS components.[118] However, a recent study that investigated levels of Co-Q10, vitamin E, and antioxidant status in subjects with MetS concluded that only a higher level of antioxidant enzyme activities was significantly associated with a reduction in the risk of MetS independent of the levels of Co-Q10 and vitamin E.[119]

Behavioral modification

Behavioral modification as a way to reduce obesity and MetS seems to have a higher success rate in studies of pediatric populations, perhaps because adults were able to enforce changes in behavior among the children. 457 Singaporean children and adolescents (age 2-18 years) with obesity were guided through a 24-week lifestyle modification trial with components of exercise, diet education, and behavior modification. Among the 98% of the children who completed the trial, prevalence of MetS decreased from 20.8% to 1.8%.[120]

In a family-based approach, Swedish tutors guided 26 children with obesity aged 8 to 12 years and their parents through a study of eating habits, physical and sedentary activity, meeting every 3 months for a period of 2 years. For most of the participants, the favorable changes were in the increased amount of physical activity; eating habits according to the children's self-reports improved after the intervention, whereas parental reports showed only a decrease in binge eating.[121] A similar program among families of 423 children ages 2 to 5 years in preschool centers showed significant improvements in the rate of obesity and favorable trends in the BMI z-score.

Another approach used a combination of pharmaceuticals and behavioral modification. In a Diabetes Prevention Program randomized trial involving community volunteers having 3 or more MetS characteristics (waist circumference; blood pressure; and levels of high-density lipoprotein cholesterol, triglycerides, and fasting plasma glucose) that met criteria from the National Cholesterol Education Program Adult Treatment Panel II, 3 groups were compared. One group received metformin, 850 mg, twice daily; a second group received a placebo in place of metformin, and a third group underwent intensive lifestyle intervention designed to achieve and maintain a 7% weight loss and 150 minutes of exercise per week. Incidence of the MetS was reduced by 41% in the lifestyle group and by 17% in the metformin group compared with placebo.[122]

Finally, dietary changes have been shown to reduce MetS. In 2008, a one-year trial showed that in a cohort where 61.4% of the participants met criteria for MetS, a Mediterranean diet supplemented with nuts reduced the prevalence of MetS in 13.7% of the participants originally presenting with MetS.[123]

Further corroboration of the Mediterranean diet's effectiveness came in a secondary analysis of the multicenter, randomized PREDIMED trial conducted between 2003 and 2010. In a group of participants at high risk for CVD, MetS developed in 50.0%; reversion occurred in 28.2% of the participants who followed either the Mediterranean diet supplemented with nuts (HR, 1.10) or olive oil (HR, 1.35) as opposed to a control group who had received only advice to follow a low-fat diet. There was a significant reduction in both central obesity and high fasting glucose in the group supplemented with olive oil, and a significant decrease in central obesity in the group supplemented with nuts.[124]

REFERENCES

1. Fryar CD, Carroll MD, Ogden CL. Prevalence of overweight, obesity, and extreme obesity among adults: United States, 1960-1962 through 2011-2012. Atlanta: National Center for Health Statistics; 2014.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. The Journal of the American Medical Association. 2014;311(8):806-814.
3. Beltran-Sanchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult US population, 1999-2010. Journal of the American College of Cardiology. 2013;62(8):697-703.
4. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr. 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.
5. Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Prevalence of the metabolic syndrome among US adolescents using the definition from the International Diabetes Federation. Diabetes Care. 2008;31(3):587-589.
6. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S, International Diabetes Federation Task Force on Epidemiology and Prevention of Diabetes. The metabolic syndrome in children and adolescents. Lancet. 2007;369(9579):2059-2061.
7. Tsai AG, Williamson DF, Glick HA. Direct medical cost of overweight and obesity in the USA: a quantitative systematic review. Obesity Reviews. 2011;12(1):50-61.
8. Thorpe KE, Florence CS, Howard DH, Joski P. The impact of obesity on rising medical spending. Health Affairs (Millwood). 2004;Suppl Web Exclusives:W4-480-486.
9. Sing M, Banthin JS, Selden TM, Cowan CA, Keehan SP. Reconciling medical expenditure estimates from the MEPS and NHEA, 2002. Health Care Financing Review. 2006;28(1):25-40.
10. Alley D, Lloyd J, Shaffer T, Stuart B. Changes in the association between body mass index and Medicare costs, 1997-2006. Archives of Internal Medicine. 2012;172(3):277-278.
11. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet. 2011;378(9793):815-825.
12. Finkelstein EA, DiBonaventura M, Burgess SM, Hale BC. The costs of obesity in the workplace. Journal of Occupational and Environmental Medicine/American College of Occupational and Environmental Medicine. 2010;52(10):971-976.
13. Gates DM, Succop P, Brehm BJ, Gillespie GL, Sommers BD. Obesity and presenteeism: the impact of body mass index on workplace productivity. Journal of Occupational and Environmental Medicine/American College of Occupational and Environmental Medicine. 2008;50(1):39-45.
14. Finkelstein EA, Graham WC, Malhotra R. Lifetime direct medical costs of childhood obesity. Pediatrics. 2014;133(5):854-862.
15. Trasande L, Chatterjee S. The impact of obesity on health service utilization and costs in childhood. Obesity (Silver Spring). 2009;17(9):1749-1754.
16. Curtis LH, Hammill BG, Bethel MA, Anstrom KJ, Gottdiener JS, Schulman KA. Costs of the metabolic syndrome in elderly individuals: findings from the Cardiovascular Health Study. Diabetes Care. 2007;30(10):2553-2558.
17. Dulloo AG. Translational issues in targeting brown adipose tissue thermogenesis for human obesity management. Annals of the New York Academy of Sciences. 2013;1302:1-10.
18. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Bostrom EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Hojlund K, Gygi SP, Spiegelman BM. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012;481(7382):463-468.
19. Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdeguer F, Wu J, Kharitonenkov A, Flier JS, Maratos-Flier E, Spiegelman BM. FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis. Genes & Development. 2012;26(3):271-281.

20. Chen YI, Cypess AM, Sass CA, Brownell AL, Jokivarsi KT, Kahn CR, Kwong KK. Anatomical and functional assessment of brown adipose tissue by magnetic resonance imaging. Obesity (Silver Spring). 2012;20(7):1519-1526.
21. Sharp LZ, Shinoda K, Ohno H, Scheel DW, Tomoda E, Ruiz L, Hu H, Wang L, Pavlova Z, Gilsanz V, Kajimura S. Human BAT possesses molecular signatures that resemble beige/brite cells. PLoS One. 2012;7(11):e49452.
22. Kim GW, Lin JE, Blomain ES, Waldman SA. Antiobesity pharmacotherapy: new drugs and emerging targets. Clinical Pharmacology and Therapeutics. 2014;95(1):53-66.
23. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(31):11070-11075.
24. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(44):15718-15723.
25. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027-1031.
26. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto J-M, Kennedy S, Leonard P, Li J, Burgdorf K, Grarup N, Jorgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clement K, Dore J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Ponten T, de Vos WM, Zucker J-D, Raes J, Hansen T, Meta HITc, Bork P, Wang J, Ehrlich SD, Pedersen O, Meta HITcam. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013;500(7464):541-546.
27. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150):1241214.
28. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, Kuperman Y, Harmelin A, Kolodkin-Gal I, Shapiro H, Halpern Z, Segal E, Elinav E. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014.
29. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Medicine. 2004;1(3):e62.
30. Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. Social Science & Medicine. 2010;71(5):1027-1036.
31. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010;33(2):414-420.
32. Paschos GK, Ibrahim S, Song WL, Kunieda T, Grant G, Reyes TM, Bradfield CA, Vaughan CH, Eiden M, Masoodi M, Griffin JL, Wang F, Lawson JA, Fitzgerald GA. Obesity in mice with adipocyte-specific deletion of clock component Arntl. Nature Medicine. 2012;18(12):1768-1777.
33. St-Onge MP, McReynolds A, Trivedi ZB, Roberts AL, Sy M, Hirsch J. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. The American Journal of Clinical Nutrition. 2012;95(4):818-824.
34. Bandin C, Martinez-Nicolas A, Ordovas JM, Madrid JA, Garaulet M. Circadian rhythmicity as a predictor of weight-loss effectiveness. International Journal of Obesity. 2014;38(8):1083-1088.
35. Sheikh-Ali M, Maharaj J. Circadian clock desynchronisation and metabolic syndrome. Postgraduate Medical Journal. 2014;90(1066):461-466.
36. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, Proietto J. Long-term persistence of hormonal adaptations to weight loss. The New England Journal of Medicine. 2011;365(17):1597-1604.
37. Janesick AS, Shioda T, Blumberg B. Transgenerational inheritance of prenatal obesogen exposure. Molecular and Cellular Endocrinology. 2014.
38. Whayne TF. Epigenetics in the development, modification, and prevention of cardiovascular disease. Molecular Biology Reports. 2014.

39. Burgio E, Lopomo A, Migliore L. Obesity and diabetes: from genetics to epigenetics. Molecular Biology Reports. 2014.
40. Bastos Sales L, Kamstra JH, Cenijn PH, van Rijt LS, Hamers T, Legler J. Effects of endocrine disrupting chemicals on in vitro global DNA methylation and adipocyte differentiation. Toxicology in vitro. 2013;27(6):1634-1643.
41. Skinner AC, Foster EM. Systems science and childhood obesity: a systematic review and new directions. Journal of Obesity. 2013;2013.
42. Belsky DW, Moffitt TE, Houts R, Bennett GG, Biddle AK, Blumenthal JA, Evans JP, Harrington H, Sugden K, Williams B, Poulton R, Caspi A. Polygenic risk, rapid childhood growth, and the development of obesity: evidence from a 4-decade longitudinal study. Archives of Pediatrics & Adolescent Medicine. 2012;166(6):515-521.
43. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS One. 2013;8(1):e55387.
44. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nature Reviews Endocrinology. 2012;8(8):457-465.
45. Allison DB, Downey M, Atkinson RL, Billington CJ, Bray GA, Eckel RH, Finkelstein EA, Jensen MD, Tremblay A, Grp TODW. Obesity as a disease: A white paper on evidence and arguments commissioned by the Council of the Obesity Society. Obesity. 2008;16(6):1161-1177.
46. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2015;100(2):342-62.
47. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Journal of the American College of Cardiology. 2014;63(25 Pt B):2985-3023.
48. American Medical Association. Recognition of obesity as a disease. Policy H-440.8422013.
49. Flegal KM, Ogden CL, Yanovski JA, Freedman DS, Shepherd JA, Graubard BI, Borrud LG. High adiposity and high body mass index-for-age in US children and adolescents overall and by race-ethnic group. The American Journal of Clinical Nutrition. 2010;91(4):1020-1026.
50. National Heart, Lung, and Blood Institute. Managing overweight and obesity in adults: Systematic Evidence Review From the Obesity Expert Panel, 2013. 2013.
51. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC growth charts for the United States: methods and development. Vital and Health Statistics. Series 11, Data from the National Health Survey. 2002:1-190.
52. Ogden CL, Flegal KM. Changes in terminology for childhood overweight and obesity. National Health Statistics Report. 2010(25):1-5.
53. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. The Journal of the American Medical Association. 2012;307(5):483-490.
54. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among adults: United States, 2011-2012. NCHS Data Brief. 2013(131):1-8.
55. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-163.
56. Fujimoto WY, Newell-Morris LL, Grote M, Bergstrom RW, Shuman WP. Visceral fat obesity and morbidity: NIDDM and atherogenic risk in Japanese American men and women. International Journal of Obesity. 1991;15 Suppl 2:41-44.
57. Cunningham SA, Kramer MR, Narayan KMV. Incidence of childhood obesity in the United States. The New England Journal of Medicine. 2014;370(5):403-411.
58. Zeigler-Johnson C, Weber A, Glanz K, Spangler E, Rebbeck TR. Gender- and ethnic-specific associations with obesity: individual and neighborhood-level factors. Journal of the National Medical Association. 2013;105(2):173-182.

59. Gerchow L, Tagliaferro B, Squires A, Nicholson J, Savarimuthu SM, Gutnick D, Jay M. Latina food patterns in the United States: a qualitative metasynthesis. Nursing Research. 2014;63(3):182-193.
60. Lebrun LA, Chowdhury J, Sripipatana A, Nair S, Tomoyasu N, Ngo-Metzger Q. Overweight/obesity and weight-related treatment among patients in US federally supported health centers. Obesity Research and Clinical Practice. 2013;7(5):e377-390.
61. Singh GK, Lin SC. Dramatic increases in obesity and overweight prevalence among asian subgroups in the United States, 1992-2011. ISRN Preventive Medicine. 2013;2013:898691.
62. Singh GK, Siahpush M, Hiatt RA, Timsina LR. Dramatic increases in obesity and overweight prevalence and body mass index among ethnic-immigrant and social class groups in the United States, 1976-2008. Journal of Community Health. 2011;36(1):94-110.
63. Gee S, Chin D, Ackerson L, Woo D, Howell A. Prevalence of childhood and adolescent overweight and obesity from 2003 to 2010 in an integrated health care delivery system. Journal of Obesity. 2013;2013:417907.
64. Centers for Disease Control and Prevention. Vital signs: obesity among low-income, preschool-aged children-United States, 2008-2011.MMWR. Morbidity and Mortality Weekly Report. 2013;62(31):629-34.
65. Centers for Disease Control and Prevention. Prevalence of self-reported obesity among US adults, by state and territory. 9 September 2014. Available at: http://www.cdc.gov/obesity/data/table-adults.html.
66. Preston SH, Stokes A, Mehta NK, Cao B. Projecting the effect of changes in smoking and obesity on future life expectancy in the United States. Demography. 2014;51(1):27-49.
67. Preston SH, Stokes A. Contribution of obesity to international differences in life expectancy. American Journal of Public Health. 2011;101(11):2137-2143.
68. Braveman PA, Cubbin C, Egerter S, Williams DR, Pamuk E. Socioeconomic disparities in health in the United States: what the patterns tell us. American Journal of Public Health. 2010;100 Suppl 1:S186-196.
69. Chang SH, Pollack LM, Colditz GA. Obesity, mortality, and life years lost associated with breast cancer in nonsmoking US Women, National Health Interview Survey, 1997-2000. Preventing Chronic Disease. 2013;10:E186.
70. Thompson CL, Owusu C, Nock NL, Li L, Berger NA. Race, age, and obesity disparities in adult physical activity levels in breast cancer patients and controls. Frontiers in Public Health. 2014;2:150.
71. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569-578.
72. Hiatt RA, Porco TC, Liu F, Balke K, Balmain A, Barlow J, Braithwaite D, Diez-Roux AV, Kushi LH, Moasser MM, Werb Z, Windham GC, Rehkopf DH. A multilevel model of postmenopausal breast cancer incidence. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2014;23(10):2078-2092.
73. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics-2013 update: a report from the American Heart Association. Circulation. 2013;127(1):143-152.
74. Cerhan JR, Moore SC, Jacobs EJ, Kitahara CM, Rosenberg PS, Adami H-O, Ebbert JO, English DR, Gapstur SM, Giles GG, Horn-Ross PL, Park Y, Patel AV, Robien K, Weiderpass E, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hartge P, Bernstein L, Berrington de Gonzalez A. A pooled analysis of waist circumference and mortality in 650,000 adults. Mayo Clinic Proceedings. 2014;89(3):335-345.
75. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. The Journal of the American Medical Association. 2013;309(1):71-82.
76. Haque R, Van Den Eeden SK, Wallner LP, Richert-Boe K, Kallakury B, Wang R, Weinmann S. Association of body mass index and prostate cancer mortality. Obesity Research & Clinical Practice. 2014;8(4):e374-381.

77. Bethea TN, Kitahara CM, Sonderman J, Patel AV, Harvey C, Knutsen SF, Park Y, Park SY, Fraser GE, Jacobs EJ, Purdue MP, Stolzenberg-Solomon RZ, Gillanders EM, Blot WJ, Palmer JR, Kolonel LN. A pooled analysis of body mass index and pancreatic cancer mortality in african americans. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2014.
78. Kumar A, Bakkum-Gamez JN, Weaver AL, McGree ME, Cliby WA. Impact of obesity on surgical and oncologic outcomes in ovarian cancer. Gynecologic Oncology. 2014.
79. Kitahara CM, Flint AJ, Berrington de Gonzalez A, Bernstein L, Brotzman M, MacInnis RJ, Moore SC, Robien K, Rosenberg PS, Singh PN, Weiderpass E, Adami HO, Anton-Culver H, Ballard-Barbash R, Buring JE, Freedman DM, Fraser GE, Beane Freeman LE, Gapstur SM, Gaziano JM, Giles GG, Hakansson N, Hoppin JA, Hu FB, Koenig K, Linet MS, Park Y, Patel AV, Purdue MP, Schairer C, Sesso HD, Visvanathan K, White E, Wolk A, Zeleniuch-Jacquotte A, Hartge P. Association between class III obesity (BMI of 40-59 kg/m2) and mortality: a pooled analysis of 20 prospective studies. PLoS Medicine. 2014;11(7):e1001673.
80. Hampp C, Kang EM, Borders-Hemphill V. Use of prescription antiobesity drugs in the United States. Pharmacotherapy. 2013;33(12):1299-1307.
81. Food and Drug Administration. FDA approves weight-management drug Contrave. 10 September 2014. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm413896.htm.
82. Gohil K. Pharmaceutical approval update. P & T. 2014;39(11):746-772.
83. Iepsen EW, Lundgren J, Dirksen C, Jensen JE, Pedersen O, Hansen T, Madsbad S, Holst JJ, Torekov SS. Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. International Journal of Obesity (London). 2014.
84. Ng SY, Wilding JP. Liraglutide in the treatment of obesity. Expert Opinion on Biological Therapy. 2014;14(8):1215-1224.
85. Lau D, Astrup A, Fujioka K, Greenway FL, Halpern A, Krempf M, Roux CL, Ortiz RV, Wilding J, Jensen CB, Pi-Sunyer FX. Safety and tolerability of Liraglutide 3.0 mg in overweight and obese adults: the scale obesity and prediabetes randomized, double-blind, placebo-controlled 56-week trial. Human Obesity: Targets and Therapies: SAT-0929-SAT-0929.
86. Bray GA, Ryan DH. Update on obesity pharmacotherapy. Annals of the New York Academy of Sciences. 2014;1311:1-13.
87. Hainer V, Aldhoon-Hainerova I. Tolerability and safety of the new anti-obesity medications. Drug Safety. 2014;37(9):693-702.
88. Nguyen NT, Masoomi H, Magno CP, Nguyen XM, Laugenour K, Lane J. Trends in use of bariatric surgery, 2003-2008. Journal of the American College of Surgeons. 2011;213(2):261-266.
89. Vage V, Sande VA, Mellgren G, Laukeland C, Behme J, Andersen JR. Changes in obesity-related diseases and biochemical variables after laparoscopic sleeve gastrectomy: a two-year follow-up study. BMC Surgery. 2014;14:8.
90. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. The New England Journal of Medicine. 2009;360(9):859-873.
91. Centers for Disease Control and Prevention. Vital signs: state-specific obesity prevalence among adults - United States, 2009. MMWR. Morbidity and Mortality Weekly Report. 2010;59(30):951-955.
92. Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, Ball GD, Busse JW, Thorlund K, Guyatt G, Jansen JP, Mills EJ. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. The Journal of the American Medical Association. 2014;312(9):923-933.
93. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. The Cochrane Database of Systematic Reviews. 2006(4):Cd003817.
94. Ladabaum U, Mannalithara A, Myer PA, Singh G. Obesity, abdominal obesity, physical activity, and caloric intake in US adults: 1988 to 2010. The American Journal of Medicine. 2014;127(8):717-727.e712.

95. Beavers KM, Ambrosius WT, Nicklas BJ, Rejeski WJ. Independent and combined effects of physical activity and weight loss on inflammatory biomarkers in overweight and obese older adults. Journal of the American Geriatrics Society. 2013;61(7):1089-1094.
96. Baillot A, Audet M, Baillargeon JP, Dionne IJ, Valiquette L, Rosa-Fortin MM, Abou Chakra CN, Comeau E, Langlois MF. Impact of physical activity and fitness in class II and III obese individuals: a systematic review. Obesity Reviews. 2014;15(9):721-739.
97. Bray GA. A concise review on the therapeutics of obesity. Nutrition. 2000;16(10):953-960.
98. Moyer VA. Screening for and management of obesity in adults: US Preventive Services Task Force recommendation statement. Annals of Internal Medicine. 2012;157(5):373-378.
99. Puzziferri N, Roshek TB, 3rd, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. The Journal of the American Medical Association. 2014;312(9):934-942.
100. Kehagias I, Spyropoulos C, Karamanakos S, Kalfarentzos F. Efficacy of sleeve gastrectomy as sole procedure in patients with clinically severe obesity. Surgery for Obesity and Related Diseases. 2013;9(3):363-369.
101. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics - 2012 update: a report from the American Heart Association. Circulation. 2012;125(1):188-197.
102. Zhao D, Cho J, Kim MH, Friedman D, Guallar E. Diabetes, glucose metabolism, and glaucoma: the 2005-2008 national health and nutrition examination survey. PLoS One. 2014;9(11):e112460.
103. Jolliffe CJ, Janssen I. Development of age-specific adolescent metabolic syndrome criteria that are linked to the Adult Treatment Panel III and International Diabetes Federation criteria. Journal of the American College of Cardiology. 2007;49(8):891-898.
104. Gallo LC, Penedo FJ, Carnethon M, Isasi CR, Sotres-Alvarez D, Malcarne VL, Roesch SC, Youngblood ME, Daviglus ML, Gonzalez P, Talavera GT. The hispanic community health study/study of latinos sociocultural ancillary study: sample, design, and procedures. Ethnicity & Disease. 2014;24(1):77-83.
105. Schneiderman N, Chirinos DA, Aviles-Santa ML, Heiss G. Challenges in preventing heart disease in hispanics: early lessons learned from the hispanic community health study/study of latinos (HCHS/SOL). Progress in Cardiovascular Diseases. 2014.
106. Dalusung-Angosta A, Gutierrez A. Prevalence of metabolic syndrome among Filipino-Americans: a cross-sectional study. Applied Nursing Research. 2013;26(4):192-197.
107. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. National Health Statistics Report. 2009(13):1-7.
108. Falkner B, Cossrow NDFH. Prevalence of metabolic syndrome and obesity-associated hypertension in the racial ethnic minorities of the United States. Current Hypertension Reports. 2014;16(7):449.
109. Calip GS, Malone KE, Gralow JR, Stergachis A, Hubbard RA, Boudreau DM. Metabolic syndrome and outcomes following early-stage breast cancer. Breast Cancer Research and Treatment. 2014;148(2):363-377.
110. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation. 2004;110(10):1245-1250.
111. Liu L, Miura K, Fujiyoshi A, Kadota A, Miyagawa N, Nakamura Y, Ohkubo T, Okayama A, Okamura T, Ueshima H. Impact of metabolic syndrome on the risk of cardiovascular disease mortality in the United States and in Japan. American Journal of Cardiology. 2014;113(1):84-89.
112. Batsis JA, Romero-Corral A, Collazo-Clavell ML, Sarr MG, Somers VK, Lopez-Jimenez F. Effect of bariatric surgery on the metabolic syndrome: a population-based, long-term controlled study. Mayo Clinic Proceedings. 2008;83(8):897-907.

113. Inabnet WB, 3rd, Winegar DA, Sherif B, Sarr MG. Early outcomes of bariatric surgery in patients with metabolic syndrome: an analysis of the bariatric outcomes longitudinal database. Journal of the American College of Surgeons. 2012;214(4):550-556; discussion 556-557.
114. Yusuf S, Pais P, Afzal R, Xavier D, Teo K, Eikelboom J, Sigamani A, Mohan V, Gupta R, Thomas N. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet. 2009;373(9672):1341-1351.
115. Zomer E, Owen A, Magliano DJ, Ademi Z, Reid CM, Liew D. Predicting the impact of polypill use in a metabolic syndrome population: an effectiveness and cost-effectiveness analysis. American Journal of Cardiovascular Drugs. 2013;13(2):121-128.
116. Mitchell T, Darley-Usmar V. Metabolic syndrome and mitochondrial dysfunction: insights from preclinical studies with a mitochondrially targeted antioxidant. Free Radical Biology & Medicine. 2012;52(5):838-840.
117. Alam MA, Rahman MM. Mitochondrial dysfunction in obesity: potential benefit and mechanism of Co-enzyme Q10 supplementation in metabolic syndrome. Journal of Diabetes and Metabolic Disorders. 2014;13:60.
118. Feillet-Coudray C, Fouret G, Ebabe Elle R, Rieusset J, Bonafos B, Chabi B, Crouzier D, Zarkovic K, Zarkovic N, Ramos J, Badia E, Murphy MP, Cristol JP, Coudray C. The mitochondrial-targeted antioxidant MitoQ ameliorates metabolic syndrome features in obesogenic diet-fed rats better than Apocynin or Allopurinol. Free Radical Research. 2014;48(10):1232-1246.
119. Yen CH, Yang NC, Lee BJ, Lin JY, Hsia S, Lin PT. The antioxidant status and concentrations of coenzyme Q10 and vitamin E in metabolic syndrome. TheScientificWorldJournal. 2013;2013:767968.
120. Memtsoudis SG, Kirksey M, Ma Y, Chiu YL, Mazumdar M, Pumberger M, Girardi FP. Metabolic syndrome and lumbar spine fusion surgery: epidemiology and perioperative outcomes. Spine. 2012;37(11):989-995.
121. Teder M, Morelius E, Nordwall M, Bolme P, Ekberg J, Wilhelm E, Timpka T. Family-based behavioural intervention program for obese children: an observational study of child and parent lifestyle interpretations. PLoS One. 2013;8(8).
122. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Annals of Internal Medicine. 2005;142(8):611-619.
123. Salas-Salvado J, Fernandez-Ballart J, Ros E, Martinez-Gonzalez MA, Fito M, Estruch R, Corella D, Fiol M, Gomez-Gracia E, Aros F, Flores G, Lapetra J, Lamuela-Raventos R, Ruiz-Gutierrez V, Bullo M, Basora J, Covas MI. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. Archives of Internal Medicine. 2008;168(22):2449-2458.
124. Babio N TE, Estruch R, Ros E, Martinez-Gonzalez M, Castañer O, Bulló M, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Sorlí JV, Salas-Salvadó J; PREDIMED Study Investigators. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. Canadian Medical Association Journal. 2014;186(17):E649-57.

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