

REVIEW

Complications of obesity

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Summary

Global obesity rates have increased exponentially in recent decades. People are becoming obese younger, morbid obesity is increasing and the full health implications are only beginning to be seen. This article discusses the latest epidemiological data on obesity in adults and children, and systemically reviews the complications associated with the condition.

Introduction

The prevalence of overweight and obesity has increased dramatically in recent decades.^{1,2} From 1975 to 2014, global rates of obesity (body mass index ≥ 30 kg/m²) increased from 3.2 to 10.8% in men and from 6.4 to 14.9% in women.² In England, the numbers of overweight/obese adults increased from 36% to 62% between 1980 and 2013.³ If trends continue, it is estimated that by 2025, 18% of men and 21% of women worldwide will be obese.²

Since 2006, the increase in obesity in developed countries has slowed down.¹ In the USA, the rate of adult obesity remained steady at 35% between 2003 and 2004 and 2011 and 2012,⁴ although rates of morbid obesity (BMI > 40) continued to rise.⁵

As rates of obesity rise, so has interest in its associated complications and there is greater understanding of the role it plays in many diseases. This has led to fears that obesity-related complications such as diabetes, heart disease, dementia and cancer threaten to slow or even reverse the improvements in life expectancy seen over the past several decades.⁶

The worldwide economic burden of managing obesity and its complications has been estimated at roughly \$2 trillion annually or 2.8% of global GDP—nearly as much as smoking,

armed conflict and terrorism combined.⁷ In the UK, the health-care cost associated with obesity is forecast to increase by £1.9–2 billion per year by 2030.⁸

Obesity in childhood

Obesity in children has mirrored the trends in adults; there were massive increases from the 1980s but this has slowed down in the developed world in the past decade.⁹ In the USA, the rates of obesity in children has remained steady at 17% from 2003–04 to 2011–12.⁴ A review of rates of obesity in 11- to 15-year olds across 25 European and North American countries from 2002 to 2010 found no change in over half the countries, with the remaining countries showing increases.¹⁰

Within individual countries, the improvements have not been shared out evenly. In England, childhood obesity and overweight prevalence has stabilized in higher but not lower socio-economic groups.¹¹ In Ireland, the numbers of obese 7-year olds decreased from 6.3% in 2008 to 3.9% in 2015, but the divide between advantaged and disadvantaged areas widened.¹²

The risks of childhood obesity are not to be underestimated. Obese children are at least twice as likely to become obese as adults¹³ and have an increased risk of cancer,¹⁴ premature

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death and disability in adulthood.¹⁵ In addition to the long-term risk, obese children have increased risk of fractures, hypertension, markers of cardiovascular disease (CVD), insulin resistance and psychological issues.¹⁵

Measuring obesity

Adults

The World Health Organization uses BMI to define obesity in adults.¹⁵ It uses the following classes:

The advantages of BMI are that it is simple to assess and is the most widely used measure in population-based studies.¹⁶ However, the accuracy of BMI at an individual level, for predicting health has rightly been called into question. BMI will continue to be used as the best population measure but increasingly, other measures such as waist circumference and waist-to-hip ratio will be used to assess an individual's obesity-related risk.¹⁷ Several studies have suggested these are better predictors of mortality and morbidity than BMI.^{18–21}

Children

In children, BMI is adjusted for age and gender. The WHO use standard deviations of BMI from mean,²² while the CDC use BMI percentiles (Tables 1 and 2).²³

Obesity and mortality

Although it is well established that obese people have higher rates of mortality from heart disease, stroke and many cancers,²⁴ studies have suggested obesity improves survival in certain conditions such as heart failure.^{25–27} More recently, large reviews have been published which confirm a direct relationship between BMI and mortality.

The Global BMI Mortality Collaboration published results in 2016 from the largest ever dataset examining the relationship between BMI and mortality.²⁸ They looked at 10.6 million participants in 239 prospective studies from Asia, Europe and North America and found that all-cause mortality was lowest in the 20–25 BMI range. Mortality increased significantly just below this range and throughout the overweight/obese range.

Table 1. WHO adult BMI classification

Classification	BMI (kg/m ²)
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obese Class I	30.0–34.9
Obese Class II	35.0–39.9
Obese Class III	≥ 40

Table 2. Weight status categories in children

Classification	WHO definition ²²	CDC definition ²³
	BMI Standard Deviations (SDs)	BMI percentile
Underweight	<2 SD below mean	<5th
Normal weight	2 SD below to 1 above mean	5th–85th
Overweight	>1 SD above mean	85th–95th
Obese	>2 SD above mean	> 95th

Mechanism of complications of obesity

There are numerous mechanisms underlying the complications of obesity. We will look at two of the more prominent players; inflammation and the gut microbiome.

Inflammation

Obesity is associated with a state of chronic low-level inflammation, orchestrated by metabolic cells in response to excess nutrients.^{29,30} This inflammatory state is present in organs such as the liver, brain, pancreas and adipose tissue and has been implicated in immuno-metabolic disease.³¹

Immune cells are abundant in adipose tissue and obesity-induced activation of their inflammatory response causes changes in their number and activity.³² This leads to inflammation and a dysregulated immune system, with changes seen as early as in childhood.³³ This has been proposed as the central mechanism connecting obesity to its metabolic and vascular complications.³² It also helps explain the increased risk of cancer³⁴ and infectious disease.³⁵

Gut microbiome

Increasing attention is being paid to the role of the microbiome in the development of obesity-related complications. Gut microbes impact host metabolism through signalling pathways, with effects on inflammation, fat deposition and insulin resistance.³⁶ It has been demonstrated that obesity is associated with profound microbial changes.³⁷ Studies transplanting lean faecal microbiota into obese individuals have demonstrated improved insulin sensitivity and microbial diversity.³⁸

Diabetes

Currently over 12% of adults in the US have diabetes³⁹ and this is projected to rise to 21–33% by 2050.⁴⁰ Most patients with type 2 diabetes are obese and the global epidemic of obesity largely explains the explosion in cases of T2DM over the past two decades.⁴¹ The risk of T2DM rises with increasing body weight; a study of over 21 000 adults in the National Health and Nutrition Examination Survey (NHANES) found the risk rising from 8% in normal weight people to 43% in individuals with morbid obesity.⁴² A study in the NHS in the UK showed a 100-fold increased risk of diabetes over 14 years in nurses with a BMI > 35 compared with those with BMI < 22.⁴³

Cardiovascular disease

Hypertension

Obese children are approximately three times likelier to have hypertension than non-obese children.⁴⁴ In adults, there is a nearly linear relationship between BMI and blood pressure (BP) and weight loss reduces BP in most hypertensive individuals.⁴⁵

Dyslipidaemia

The effects of obesity on lipid metabolism include high low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, triglycerides and low levels of the protective high-density lipoprotein cholesterol.⁴⁶

Coronary heart disease

One study found that for every 4 kg/m² increase in BMI there is a 26% increase in odds for coronary heart disease (CHD).⁴⁷ Data from the NHANES study including death information for 2.3 million American adults showed that obesity was associated with significantly increased mortality from both CHD and other forms of CVD.⁴⁸ Although BMI may also affect CHD risk through intermediate factors such as hypertension, dyslipidaemia and diabetes, recent studies have shown obesity is an independent risk factor.^{47,49}

Heart failure

Obesity has been shown to effect the heart as early as in childhood, with obese children having significantly higher left ventricular mass.⁵⁰ The Framingham Heart Study, which followed 6000 adult subjects without a history of heart failure for a mean of 14 years, found that the risk of heart failure was doubled in obesity.⁵¹ After adjusting for established risk factors, the risk of heart failure increased 5% in men and 7% in women for each extra 1 kg/m² in BMI. A review of 28 studies found that both overweight and obesity are associated with increased risk of heart failure.⁵²

However, in people with established heart failure, several studies have observed better outcomes in obese compared with lean individuals.⁵³ This has been termed the obesity paradox, and proposed explanations have included that obesity is associated with less cardiac cachexia, earlier presentation due to more impaired quality of life, greater metabolic reserves and protective adipokines.⁵⁴

Stroke

Obese individuals have been shown to be twice as likely to have a stroke, either ischaemic or haemorrhagic, than people with a BMI of < 23.⁵⁵ Even after adjusting for other risk factors, excess weight was still associated with increased risk.

Neurological disease

Vascular risk factors such as hypertension, dyslipidaemia and diabetes are all associated with increased risk of dementia and Alzheimer's disease.⁵⁶ Although a raised BMI contributes to each of these factors, the independent relationship between obesity and dementia is a little more complicated. A review article found that five out of nine studies reported an independent association between high BMI and risk of dementia.⁵⁶ It appears that being obese in midlife is what conveys the risk; studies measuring BMI at midlife had a more consistent association, while the four studies that did not find a link all measured BMI after the age of 75 years.

Cancer

It is estimated that obesity accounts for ~20% of all cancer cases.⁵⁷ A large-scale review by the International Agency for Research on Cancer concluded that obesity was the cause of a quarter to one-third of cancers of the colon, breast, endometrium, kidney and oesophagus.⁵⁸ It is also associated with increased risk of gastric, pancreatic and gallbladder cancer, as well as leukaemia.⁵⁹

Furthermore, prognosis is poorer in obese individuals who develop some cancer types. One study found obese women with breast cancer were found to be 46% more likely to develop distant metastases and 38% more likely to die than lean

counterparts.⁶⁰ Chemotherapy and radiotherapy dosing is more difficult with up to 40% of obese patients receiving limited chemotherapy doses that are not based on their body weight.⁶¹ Weight loss has been shown to reduce the risk of some cancers; it has been shown to lessen the risk of breast cancer, particularly among postmenopausal women.⁵⁷

Respiratory

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) adversely affects multiple systems and is associated with hypertension, insulin resistance, liver dysfunction, systemic inflammation and dyslipidaemia.^{62,63} In children, it can lead to failure to thrive, behavioural problems, decreased intellectual function and a higher risk of cardiovascular morbidity.⁶⁴

Obesity has long been known to be a major pathogenic factor in OSA in adults. A study of 4000 US adults found prevalence was 12% in obese vs. 3% in lean subjects.⁶⁵ In children, OSA was primarily felt to be due to adeno-tonsillar hypertrophy.⁶⁴ However, with increasing levels of childhood obesity, this has changed. Whereas < 15% of all habitually snoring children were obese in the early 1990s, by 2006, this figure had risen to >50%.⁶⁶

Asthma

Rates of asthma and obesity in childhood have increased in parallel over the last 40 years, with asthma prevalence doubling between 1980 and 1994.⁶⁷ It has been well established that obesity increases the risk of asthma^{68,69} but the mechanism underlying this is not fully understood.⁶⁹ Inflammatory, mechanical, immunological, hormonal and genetic causes have all been postulated.^{67,68} Obese people are also more likely to have severe asthma and are more likely to have their asthma misdiagnosed.⁷⁰ Weight loss has been shown to be an effective treatment for asthma in obese patients.⁷¹

Immune system

Obesity induces a dysregulated immune system which can be seen from childhood.³³ It is associated with increased susceptibility to infections of numerous types, including surgical-site,⁷² urinary tract,⁷³ nosocomial⁷⁴ and skin.⁷⁵ Furthermore, obese individuals don't respond as well to vaccines^{76,77} and were found to be at greater risk of death during the H1N1 influenza pandemic in 2009.⁷⁸

It has been suggested that the parallel rise in autoimmune disease and obesity seen in the past few decades are causally linked.⁷⁹ There is strong evidence supporting obesity driving an increased risk of rheumatoid arthritis (RA) (OR = 1.2–3.4), Multiple Sclerosis (OR = 2), Psoriasis and Psoriatic Arthritis (OR = 1.48–6.46).⁷⁹

Gastrointestinal

Non-alcoholic fatty liver disease (NAFLD) is now the commonest cause of chronic liver disease worldwide, estimated to be present in 20–35% of adults in the developed world.⁸⁰ One-third of these cases progress to non-alcoholic steatohepatitis (NASH), characterized by liver inflammation and injury, which can lead to cirrhosis and hepatocellular carcinoma.^{81,82} NAFLD is considered the hepatic manifestation of metabolic syndrome and its risk is strongly correlated with BMI.⁸³ One study found rates of steatosis

to be 15% in non-obese persons, 65% in people with Class I or II obesity and 85% in Class III obesity.⁸³ Weight loss is the best treatment for NAFLD with studies showing bariatric surgery-induced weight loss leading to resolution of NASH in 80% of cases.⁸⁴

Obesity is also a risk factor for gallbladder disease. A meta-analysis of 17 prospective studies covering nearly 2 million participants found a relative risk of 1.63 for a 5 unit increment in BMI.⁸⁵ The risk of gallbladder disease doubled from lower to upper limit of the normal BMI range, suggesting even moderate weight gain increases risk. Rapid weight loss also increases the risk of gallstone formation with ursodeoxycholic acid and/or higher dietary fat content being protective in this instance.⁸⁶

Obesity is associated with greater risk of pancreatitis⁸⁷ and is a poor prognostic factor in the disease.⁸⁸ It is also considered a major reason for the 2-fold increase in incidence of gastroesophageal reflux disease and its associated conditions Barrett's oesophagus and oesophageal adenocarcinoma.⁸⁹ Weight loss has been found to be the most effective way to treat reflux.⁹⁰

Kidney disease

Overweight and obesity are risk factors for hypertension, diabetes, and other conditions associated with impaired renal function. A study following up over 8 million person-years found that, compared with lean people, the relative risk for End-Stage Renal Failure (ESRF) was 1.87 for overweight individuals, 3.57 for those with class I obesity, 6.12 for those with class II obesity, and 7.07 for those with class III obesity.⁹¹ After

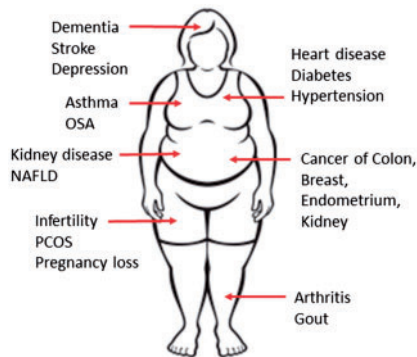


Figure 1. Complications of obesity.

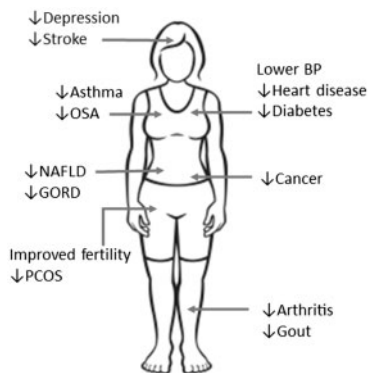


Figure 2. Benefits of weight loss.

adjusting for other risk factors, higher BMI remained an independent predictor of ESRF.

Obesity is also associated with greater risk of kidney stones⁹² and urinary incontinence in women,⁹³ while obesity-related glomerulopathy has increased in prevalence in parallel with obesity.⁹⁴

Fertility

In men, obesity is associated with reduced sperm count⁹⁵ and increased rates of erectile dysfunction.⁹⁶ In women, it also leads to reduced fertility, poorer outcomes after fertility treatment and more pregnancy loss.⁹⁷ Polycystic Ovarian Syndrome (PCOS) is the primary cause of female infertility and increases the rate of pregnancy complications.⁹⁸ The risk of PCOS is slightly increased with obesity⁹⁹ and obese women with PCOS often have a more serious phenotype (Figures 1 and 2).⁹⁸

Musculoskeletal

Obesity is associated with significant reductions in physical activity levels and is one of the main risk factors for osteoarthritis.¹⁰⁰ The greatest impact is on the knee, but there is also increased risk in hand joints, suggesting an inflammatory as well as a mechanical cause.^{100,101} Radiating lower back pain is increased in obesity, as well as in those with low levels of physical activity.¹⁰² Furthermore, a long-term follow-up of over one hundred thousand nurses in the UK found that RA was increased in obesity; 10 years of being obese conferred a 37% increased risk of RA.¹⁰³

Obesity is the strongest modifiable risk factor for gout, with obese men having a relative risk of 2–3 compared with lean subjects.¹⁰⁴ Weight loss has been found to decrease the risk of recurrent gout attacks, while weight gain makes it more likely.¹⁰⁵

Psychosocial

Obese individuals are often exposed to public disapproval and stigma due to their weight,¹⁰⁶ with women experiencing more discrimination.¹⁰⁷ This takes place in employment,¹⁰⁷ health-care,¹⁰⁸ education¹⁰⁹ and other areas. Depression is more common in obesity, particularly in women and younger people, while weight loss is associated with improved mood.¹¹⁰ Adolescents who are obese or overweight, or perceive themselves as such, are more likely to engage in risk behaviour than those of normal weight.¹¹¹ This can involve substance abuse, risky sexual behaviour or violence.

Conclusion

Global obesity rates have increased exponentially in recent decades. This represents an enormous and growing health and financial burden. People are becoming obese younger, morbid obesity is increasing and the full health implications of this are only beginning to be seen.

Research shows that obesity is associated with increased mortality and numerous complications including diabetes, heart disease, dementia and cancer. Even low levels of overweight are associated with increased risk and weight loss remains the best way to tackle the complications. Without more urgent action, the obesity crisis already overwhelming our health services will also cripple our economy.

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