Public Health Nutrition: 10(10A), 1156–1163 DOI: 10.1017/S1368980007000651

Obesity and cardiovascular disease

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Submitted December 2006: Accepted April 2007

Abstract

Background: The prevalence of obesity has reached epidemic proportions, and in terms of the extent of its negative impact on the health has been compared to those of tobacco and alcohol. One of the first medical consequences of obesity to be recognised was cardiovascular disease (CVD). Obesity, particularly abdominal obesity, predisposes a person to a number of other cardiovascular risk factors, and is an independent predictor of clinical CVD including coronary death, coronary heart disease, heart failure and stroke.

Materials and methods: A Medline search using the following keywords (obesity, cardiovascular disease, body mass index, cardiovascular risk factors, type 2 diabetes, metabolic syndrome) was performed looking for high impact factor English-written references.

Results: Ninety-nine ($N = 99$) relevant articles published in the last 15 years were selected and commented. As detailed throughout the text, current therapies available for weight management can improve or prevent many of these obesity-related risk factors for CVD. However, there is some controversy as to whether weight loss is beneficial for health, and large clinical outcome trials such as the Look-AHEAD (Action for Health in Diabetes) trial or the SCOUT (Sibutramine Cardiovascular Outcomes Trial) study are currently ongoing.

Discussion: In the present review, we summarise the effects of obesity as well as the efficacy of weight-loss interventions on cardiovascular risk factors and CVD.

Keywords
Obesity
Cardiovascular disease
Body mass index
Cardiovascular risk factors
type 2 diabetes
Metabolic syndrome

The increased prevalence of obesity in the past few years has been the focus of literally thousands of articles in the scientific and lay press as well as in the newspapers. The problem has been called an epidemic and compared to the harmful effects of tobacco and alcohol in terms of the extent of its negative impact on the health of the population[1–9]. Furthermore, as the full extent of the relatively rapid increase in weight in the population has been recognised, the significant involvement of children and adolescents in this change has become obvious. It is interesting to consider why the increase in obesity in the population over the past two decades has suddenly been recognised as so potentially harmful. The publication of the National Health and Nutrition Examination Survey (NHANES) data from 1999–2000[2] was key in bringing this problem to the attention of health professionals and the public. In addition, the excellent review by Kopelman[3] published in 2000 highlighted many aspects about obesity that were underappreciated, and also stressed obesity as a medical problem with deleterious effects on health. Overweight and obesity are associated with the morbidity and mortality of many health conditions, such as coronary heart disease (CHD), type 2 diabetes, gall bladder disease, ischaemic stroke, osteoporosis, sleep apnoea and some types of cancers[1,6–9]. Obesity is also associated with a substantial reduction in life expectancy. Recent data from the United States suggest that a severe level of obesity (body mass index (BMI) $> 45\,kg\,m^{-2}$) during early adulthood (aged 20–30 years) may reduce a man's life expectancy by up to 13 years and a woman's by up to 8 years[9].

The objectives of this review are to summarise the effects of obesity and the effects of weight-loss interventions on cardiovascular risk factors and cardiovascular disease (CVD).

Classification and prevalence of obesity

Obesity is characterised by an excess of adipose tissue. There are, however, different types of fat and different locations for fat in the body[3,10–13]. Visceral fat has been shown to be a better indicator of obesity-associated disorders than the amount of total fat. The most commonly used measurement for determining obesity is the BMI, which is calculated as the weight (kg)/height (m^2) or as the weight (lb)/height (in^2) $\times$ 703. Although there are

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some limitations to measuring obesity by the BMI, it is an index that provides a measurable estimate of body fat and is related to the risk of complications associated with obesity[11]. According to the National Institute of Health (NIH)[14] and the World Health Organisation (WHO) documents, the normal range for the BMI is 18.5–24.9 kg m^{-2}, while 25.0–29.9 kg m^{-2} is class (or grade) 1 overweight, 30.0–39.9 kg m^{-2} is class (or grade) 2 overweight and ≥40.0 kg m^{-2} is class (or grade) 3 overweight. There are alternative measurements of obesity that are useful[12]. Waist circumference alone has been shown to correlate with obesity-related disorders. In fact, this measurement relates closely to the BMI and does reasonably accurately reflect the proportion of intra-abdominal body fat compared to subcutaneous fat and its disease implications[10]. Other methods include underwater weighing (hydrodensitometry), dilution methods (hydrometry), dual energy X-ray absorptiometry (DXA), skin fold measurements by calipers, bioimpedance analysis and imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI). However, they are too costly and complex to use for individual patient's assessment or large-scale epidemiologic studies[13].

Applying the BMI to epidemiological surveys[2] has indicated that approximately 65% of US adults are overweight (35%) (BMI ≥ 25 kg m^{-2}) or obese (BMI ≥ 30 kg m^{-2}) (30%). The greatest increases in the past two decades have been in the highest BMI category (extreme or morbid obesity) i.e. BMI ≥ 40 kg m^{-2}. The prevalence of extreme obesity is approximately 4.7% of US adults (up from 0.8% in 1960). When one translates these percentages to absolute numbers the scope of the problem becomes obvious[15]. The prevalence and trends in overweight and obesity among US children and adolescents were measured in 1976–1980, 1988–1994 and 1999–2000 and were updated between 1999 and 2002[16,17]. The prevalence of overweight was 15–16% among 6 to 19-year-olds in 1999–2000, which represented a marked increase compared to similar measurements made in 1988–1994 (10.5–11.3%). Among the youngest group (2 to 5 years old) the overweight prevalence increased from 7.2% to 10.4% over the decade. Finally, it is worth noting that data from the Behavioural Risk Factor Surveillance System (BRFSS), which is a cross-sectional telephone survey of non-institutionalised adults, conducted between the years 1986 to 2000, indicated that the prevalence of a BMI of 40 kg m^{-2} or greater quadrupled and the prevalence of a BMI of 50 kg m^{-2} or greater increased five-fold in adults[5,12].

Health consequences of obesity

The health consequences of obesity are many and there is a dose–response relationship between the degree of obesity and the risk of morbidity and mortality from CVD and other conditions. Although there have been studies indicating that increasing body weight is associated with a higher mortality[13–15,18,19], this relationship remained controversial until relatively recently. The excellent study by Calle *et al.*[19] has reinforced the conclusions reached in many earlier analyses that indicate that there is a curvilinear relationship in which the risk of death is increased among those with the highest or lowest weights. The same study showed that the lowest rates of death from all causes were found at BMI's between 23.5 and 24.9 kg m^{-2} in men and between 22.0 and 23.4 in women. Death rates from all causes (cardiovascular, cancer or other diseases) increased throughout the range of moderate and severe overweight for both men and women in all age groups. It is of interest that the risk was greater for whites than for blacks, particularly black women[19]. According to recent NIH statistics, obese individuals have a 50% to 100% increased risk of death from all causes compared to normal weight individuals (BMI 20–25 kg m^{-2}). Most of the increased risk is due to CVDs. Life expectancy of a moderately obese person could be shortened by 2–5 years, while morbidly obese men could reduce their life expectancy by almost 13 years[15].

Obesity and other cardiovascular risk factors

Obesity predisposes a person to a number of cardiovascular risk factors, including impaired glucose tolerance and type 2 diabetes, hypertension, dyslipidaemia and sleep apnoea.

There is good evidence of an association between excess body weight, especially when located in the abdominal region, and type 2 diabetes. The high prevalence of diabetes in overweight or obese individuals is of particular concern, especially in young adults. As examples, among patients diagnosed with type 2 (non-insulin-dependent) diabetes, 67% have a BMI ≥ 27 kg m^{-2}, and 46% have a BMI ≥ 30 kg m^{-2}[15]. About 70% of diabetes risk in the US can be attributed to excess weight. In the Nurses Cohort Study, the risk of diabetes increased five-fold for those with a BMI of 25 kg m^{-2}, 28-fold for those with a BMI of 30 kg m^{-2} and 93-fold for those with a BMI of 35 kg m^{-2} or greater compared with women with a BMI of less than 21 kg m^{-2} [20,21]. Similar patterns of increasing prevalence of diabetes with increasing weight have been noted in men. As was mentioned earlier, a waist circumference of >40 in increases the risk of diabetes 3–5-fold even after controlling for BMI. In children and adolescents type 2 diabetes has been estimated to account for between 8% and 45% of all new cases of diabetes[22]. Moreover, the potential for the development of renal failure, impaired vision, cardiovascular and cerebrovascular disease and the neurological complications of diabetes after 15–20 years, when these individuals are young adults, indicates the incredibly serious implications of this epidemic.

There is good evidence of an association between excess body weight and high blood pressure. The age-adjusted prevalence of hypertension in overweight US adults is 22.1% for men with BMI 25–27 kg m^{-2}, 27% for men with BMI 27–30 kg m^{-2}, 27.7% for women with BMI 25–27 kg m^{-2} and 32.7% for women with BMI 27–30 kg m^{-2}. These compare with the prevalence of hypertension of approximately 15% in normal weight men and women[15]. The effect of hypertension together with other deleterious haemodynamic effects on the heart has resulted in an increase in the development of congestive cardiac failure (CCF) best documented in the Framingham Heart Study. It is of interest that body weight was directly related to the development of CCF independent of other traditional risk factors[23].

Obesity has a strong effect on lipoprotein metabolism, regardless of ethnic groups[24–26]. Increased weight is a determinant of higher levels of triglycerides, elevated LDL-C, and low HDL-C. Conversely, weight loss is associated with a healthier lipoprotein profile in both genders. There is evidence that central adiposity compared with total adiposity is more positively associated with increased triglyceride level, lower HDL cholesterol and less positively associated with LDL cholesterol. Total adiposity is more strongly associated with LDL cholesterol.

Breathing problems during sleep are a common consequence of obesity. For example, it is not uncommon for some obese men to have low oxygen saturation during REM sleep while their awake arterial gases are normal[27]. A minority of individuals progress to the sleep apnoea syndrome[28]. In the Swedish Obesity Study, over 50% of the men and 33% of the women with a BMI $>$ 35 kg m^{-2} reported snoring and sleep apnoea[29]. These changes during sleep seem to carry an increased risk of myocardial infarction and stroke[30].

Obesity and CVD

Prospective studies that have reported follow-up data over 2–4 decades have documented that obesity is an independent predictor of clinical CVD, including coronary death, CHD, heart failure and stroke in white and non-white populations[23,31–53]. One of the earliest analyses of the Framingham Heart Study was reported by Hubert *et al.*[23] After 26 years of follow-up, they concluded that obesity, measured as the ratio of actual weight to desirable weight (MRW), was a significant independent predictor of CVD, including CHD, coronary death and congestive heart failure in both men and women, and stroke in women after adjustment for risk factors. After 44 years of follow-up, Wilson *et al.*[31] showed that CVD risk (including angina, myocardial infarction, CHD or stroke) was higher among overweight obese men and obese women after adjustment for age, smoking, high blood pressure, high cholesterol and diabetes. The association was not significant among overweight women. In the Nurses' Health Study,[32] after 16 years of follow-up, the risk of death from CVD was significantly greater among women with a BMI $\geq$ 27 kg m^{-2} compared with the risk among women with a BMI $<$ 19 kg m^{-2}. Analysis of results from the American Cancer Society's Cancer Prevention Study I[34] involving 324 135 participants showed that excess body weight increased the risk of death from CVD in healthy white adults aged 30–74 years followed up over a period of 12 years. Above 74 years, however, the risk of death was not significant for either men or women. Similar results were obtained by Baik *et al.*[35] in the Health Professionals Follow-up Study. CVD mortality among obese (BMI $\geq$ 30 kg m^{-2}) men aged less than 65 years was significantly greater after accounting for other risk factors including smoking compared with those with a BMI $<$ 23 kg m^{-2}. Among men 65 years or older, there was no significant relationship between BMI and risk of CVD mortality. Thus, there is good evidence of an association between overweight and obesity and CVD incidence among young to middle-aged men and women but not among older people. The reduced risk at older ages may, however, be mediated by the duration of excess bodyweight[23,37,38]. Finally, there is moderate evidence of an association between abdominal obesity and risk of CVD, particularly among older men[46–51].

Abdominal obesity and CVD: the metabolic syndrome

The presence of abdominal obesity, due to excess visceral fat, is associated with both an increased risk of developing CVD[54,55] and an increased risk of metabolic syndrome, which includes a greater risk of developing type 2 diabetes[56] and attendant cardiometabolic disturbances[57].

Metabolic syndrome has been widely studied in adults. Its prevalence in adults is approximately 20% of individuals $\geq$20 years of age and 40% of the population $>$40 years of age[58]. Taking into account its high predictive value for the development of type 2 diabetes and CVD, it is of great concern that this syndrome is being diagnosed in adolescents in increasing numbers. Thus Duncan *et al.*[59] have shown a significant increase in this syndrome in adolescents over the past decade (4.2% in 1988–1992 to 6.4% in 1999–2000). Moreover, the syndrome was found in 32.1% of overweight adolescents (BMI $\geq$ 95th percentile for age and sex).

There is ongoing debate regarding the acceptance of the various metabolic syndrome definitions and guidelines worldwide[60], but the other definitions of metabolic syndrome are very similar[61,62]. In the clinical setting, waist circumference is commonly used as a surrogate marker of abdominal fat[63], since measurement of waist circumference is more practical than BMI and has been found to correlate closely with total abdominal fat mass[64].

In addition, waist circumference is strongly associated with all-cause mortality in middle-aged adults[65].

In the Nurses' Health Study, Rexrode *et al.*[51] concluded that the waist-to-hip ratio (WHR) and waist circumference are independently associated with CHD risk after controlling for BMI and other cardiac risk factors. Women in the highest quintile of WHR or waist circumference were about 2.5 times more likely to develop CHD than women in the lowest quintile and the association was more pronounced in women younger than 60 years. Accordingly, results from case–control studies showed that abdominal fat was associated with an increased risk of stroke. In the Northern Manhattan Stroke Study, involving 576 stroke cases, those with a WHR greater than or equal to the median had an OR of 3.0 for ischaemic stroke[48]. The association occurred in men and women and in all race–ethnic groups; it was a stronger predictor of stroke than BMI, and had a greater effect among younger persons. In a British case–control study involving men and women aged 35–74 years, Shinton *et al.*[49] found that excess body fat, in particular abdominal fat, increased the risk of stroke, although cigarette smoking presented a greater risk than abdominal fat alone. In a large study by Rimm *et al.*[50] involving 29 122 men aged 40–75 years, it was found that BMI and WHR were associated with an increased risk of CHD. Among younger men, obesity is a strong risk factor for CHD, independent of fat distribution, whereas for older men, measures of fat distribution may be a better predictor of coronary disease. Finally, the INTERHEART study was designed to assess the importance of nine risk factors on CHD risk, as measured by a first episode of myocardial infarction[66]. These factors were current or former smoking, history of diabetes or hypertension, abdominal obesity, combined psychosocial stressors, irregular consumption of fruits and vegetables, no alcohol intake, avoidance of any regular exercise and raised plasma lipids. All nine risk factors represented a population attributable risk (PAR) of 90.4%, accounting for most of the risk of acute myocardial infarction in the study population. After adjustment for age, sex and geographic region, abnormal lipids had the highest PAR in men (49.5%) and women (47.1%). Abdominal obesity contributed 19.7% (men) and 18.7% (women) to this risk, and had a similar odds ratio to hypertension, especially in men (odds ratios of 2.24 and 2.32, respectively).

Although there is evidence of an association between abdominal obesity and increased risk of CVD, current debate concerns how visceral adiposity contributes to the development of CVD. Although the main function of adipocytes is regarded as storage and release of energy, several factors secreted by adipocytes have regulatory roles in metabolism and exert vascular effects[67]. The possibility of a direct link between endothelial dysfunction and insulin resistance, mediated via adipokine action on the vascular endothelium, is a topical issue[68]. The role of these adipokines in the pathogenesis of obesity, particularly abdominal obesity and insulin resistance, has created much controversy[69–72]. In summary, pro-inflammatory adipokines play a causal role in the development of insulin resistance and pathologies associated with increased cardiovascular risk[73]. Obesity has also been linked with chronic low-grade inflammation[67,73], as mediated by interleukin (IL)-6 and tumour necrosis factor-α, which may also contribute to the atherosclerotic process[74]. Furthermore, IL-6 has been suggested to increase hepatic triglyceride secretion, which in turn may lead to insulin resistance[71].

Effects of weight loss on CVD

Obesity predisposes a person to a number of cardiovascular risk factors, including hypertension, dyslipidaemia and impaired glucose tolerance and, in overweight and obese subjects, weight loss can improve or prevent many of these obesity-related risk factors for CVD[75,76]. However, there is some controversy as to whether weight loss is beneficial for health.

Effective treatments exist for overweight/obese patients and a combination of therapies provides the best results. Current therapies available for weight management include lifestyle intervention, physical activity, pharmacotherapy and surgery.

Both clinical prospective and intervention studies have shown that sustained moderate weight loss (10%) achieved through lifestyle intervention are effective for the prevention/treatment of hypertension, diabetes and dyslipidaemia[75,76]. In a recent systematic review, weight loss of 10 kg was associated with a fall in diastolic blood pressure of 3.6 mmHg, and a weight loss of 10% was associated with a fall in systolic blood pressure of 6.1 mmHg[77,78]. The benefit of modest weight loss achieved by lifestyle intervention on diabetes prevention was demonstrated in the Diabetes Prevention Program[79]. After an average of 3.2 years, lifestyle intervention reduced the incidence of diabetes by 58% and Metformin reduced the incidence by 31% when compared with placebo. In addition, lifestyle intervention was accompanied by an important reduction in other traditional cardiovascular risk factors (reduction in hypertension, triglycerides, atherogenic LDL particles, and an elevation in HDL-cholesterol concentration) and non-traditional cardiovascular risk factors relative to both placebo and to a lesser degree to Metformin[80,81]. Similar findings were reported in the Chinese Da Qing IGT and Diabetes Study[82] and the Finnish Diabetes Prevention Study[83]. In addition, in patients with type 2 diabetes modest weight loss is associated with reductions in HbA1c of 1.1%, fasting blood glucose of 1.6 mmol l^{-1}, triglycerides of 0.5 mmol l^{-1} and with an increase in HDL-cholesterol of 0.1 mmol l^{-1}[84].

Weight management is also associated with an improvement of the lipid profile of obese subjects. In general, a 5–10% weight loss can produce a reduction in

https://doi.org/10.1017/S1368980007000651 Published online by Cambridge University Press

LDL cholesterol of 15% and triglycerides of 20–30% with an increase in HDL cholesterol of 8–10%[76]. Furthermore, a systematic review has shown that a fall of 0.23 mmol l^{-1} in total cholesterol may be expected for a weight loss of 10 kg in a person suffering from obesity or overweight[85]. Finally, there is evidence that modest weight loss decreases levels of several haemostatic factors associated with obesity and the development of CVD, and markers of vascular inflammation, such as C-reactive protein and ILs 6, 7 and 18[86,87]. Overall, these findings suggest that even moderate weight loss with lifestyle intervention can improve risk factors for CVD in overweight and obese subjects.

The two drugs currently approved for obesity treatment (sibutramine and orlistat), and the new class of drugs that antagonise central and peripheral CB1 cannabinoid receptors (rimonabant), produce similar degrees of weight loss and weight loss maintenance. In placebo-controlled studies, the percentage of patients achieving 5% weight loss at 1 year is broadly similar to sibutramine, orlistat0 and rimonabant[88–92].

Pharmacologically induced weight loss has a beneficial impact on a number of cardiovascular risk factors, such as diabetes, blood pressure and dyslipidaemia, and in some cases these effects appear to be over and above that explained by weight loss. Repeated observations have suggested that weight loss with sibutramine is associated with a specific increase in HDL-cholesterol. A meta-analysis of studies in which patients received long-term sibutramine treatment show that, regardless of the degree of weight loss, there is a marked increased effect on raising HDL-cholesterol, suggesting that there may be an independent effect, while the effects of orlistat are most marked with regard to LDL-cholesterol[93]. Similarly, in type 2 diabetes patients, at equivalent weight loss, the use of orlistat resulted in greater improvement in free fatty acids levels and insulin sensitivity than placebo[94]. Finally, results from the RIO-Europe study suggest that about half of the rise in HDL-cholesterol and about half of the fall in triglycerides cannot be accounted for by weight loss alone, suggesting possible independent effects[90].

Weight-loss surgery is the most effective therapy available for people who are extremely obese. It reverses, ameliorates or eliminates major cardiovascular risk factors, including diabetes, hyperlipidaemia, hypertension and other lipid disturbances[95].

Despite the risks of overweight and obesity are being generally well accepted and the beneficial effects of weight loss on a number of cardiovascular risk factors being proved, there is some controversy as to whether weight loss is beneficial because some observational epidemiological studies have associated weight loss with increased mortality[96]. A likely explanation lies in the fact that the studies did not distinguish between intentional and unintentional weight loss. Interestingly, the few studies that have addressed this issue show benefit from weight loss on mortality[97]. Other difficulty surrounding the relationship between intentional weight loss and mortality is that success with behaviour modification and currently available medications in achieving sustained weight loss is quite limited and surgical procedures, such as gastric bypass, are effective for sustained weight loss, but are used as a last resort for patients with a BMI >40 kg m^{-2} and those with multiple obesity-related complications.

Thus, longer term, well-controlled studies are needed to define accurately the benefits of weight loss on mortality and other 'hard' clinical endpoints. Two large-scale randomised clinical trials are now under way and should provide important information on the effects of non-surgical obesity treatment on cardiovascular morbidity and mortality. Look AHEAD (Action for Health in Diabetes)[98] is a large outcome study that is currently assessing the effect of weight loss produced by an intensive lifestyle intervention delivered over 4 years on cardiovascular events and mortality in obese diabetic patients. This programme is compared to a control condition involving a program of diabetes support and education. The primary basis for the comparison is the incidence of serious cardiovascular events. Other outcomes, including CVD risk factors, diabetes-related metabolic factors and complications, and the cost-effectiveness of the intensive intervention are also studied. The other trial is the SCOUT trial (Sibutramine Cardiovascular Outcomes Trial)[99]. This is a double-blinded, randomised, placebo-controlled, parallel group, global multi-centre study with a single-blinded sibutramine lead-in period. It involves a large group of overweight and obese subjects at high risk for CVD and has been designed to determine the impact of weight loss with sibutramine on cardiovascular endpoints. The primary endpoint of the trial will include a composite of myocardial infarction, stroke, resuscitated cardiac arrest and cardiovascular death.

Acknowledgements

Sources of funding: ISCIII-RETIC RD06, PI052099 and PI051540 funded this work.

Conflict of interest declaration: None of the authors had any conflict of interest.

Authorship contributions: All the authors (A.P.P., J.Y.M., V.B.C., P.P.V.) declare that they participated sufficiently in the work to take full and public responsibility for its content.

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