

## Review

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# The medical complications of obesity

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## Introduction

The prevalence of overweight and obesity is increasing worldwide.<sup>1</sup> A comparison of data from 1976–80<sup>2</sup> with that from 1999–2000 shows that the prevalence of overweight (defined as body mass index, BMI, of 25–29.9 kg/m<sup>2</sup>) increased from 46% to 64.5%, and the prevalence of obesity (BMI  $\geq$  30 kg/m<sup>2</sup>) doubled to 30.5%. The epidemic of obesity is not just isolated to the US, but is worldwide,<sup>3,4</sup> including less affluent countries.<sup>4</sup>

Obesity and overweight have many causes, including genetic, metabolic, behavioural and environmental. The rapid increase in prevalence suggests that behavioural and environmental influences predominate, rather than biological changes.

We summarize data from many studies evaluating the impact of obesity on mortality and morbidity, discuss some controversies and provide practical guidelines for managing obese patients.

## Relation between body weight and mortality

Direct associations between obesity and several diseases, including diabetes mellitus, hypertension, dyslipidaemia and ischaemic heart disease, are well recognized. Despite this, the relationship between body weight and all-cause mortality is more controversial. A very high degree of obesity (BMI  $\geq$  35 kg/m<sup>2</sup>) seems to be linked to higher mortality rates,<sup>5</sup> but the relationship between more modest degrees of overweight and mortality is unclear.

Initial data from actuarial studies of more than 4 million men and women showed a direct positive association between body weight and overall mortality rates.<sup>6</sup> Subsequent studies confirmed increased mortality risk above a certain threshold, but found a U-shaped association between weight and mortality.<sup>7,8</sup> In the Build study,<sup>9</sup> there was a higher mortality in lean subjects, but there was no adjustment for smoking. The American Cancer Society found a much stronger association between leanness and mortality, specifically cancer mortality, in the group of smokers compared to non-smokers.<sup>10</sup>

The Harvard Alumni Study<sup>11</sup> was a prospective cohort study of more than 19 000 middle-aged men. It also noted a U-shaped relation between BMI and mortality after adjustment for age, cigarette smoking and physical activity. However, after excluding those who had ever smoked and those who died within the first 5 years of follow-up, there was no evidence for increased mortality in those with a BMI <22.5 kg/m<sup>2</sup> and the lowest mortality was noted in those who weighed 20% below the average.

A direct relationship between BMI and mortality was also described in a cohort of more than 8000 Seventh Day Adventists, with the lowest mortality rate found in men with a BMI <22.3 kg/m<sup>2</sup>.<sup>12</sup> This group is usually lean by choice, and therefore their leanness is less likely to be the result of cigarette smoking or underlying illness.

Obesity has also been associated with an increased risk of mortality in women. There have

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been some reports that did not find a relationship between BMI and mortality in women,<sup>13–15</sup> but due to the small number of endpoints occurring in these cohorts, these studies lacked sufficient power. Several larger studies showed a significant association between body weight<sup>8–10</sup> or BMI and mortality.<sup>16</sup> Notably, the Nurses' Health Study, showed a U-shaped relationship between BMI and all-cause mortality.<sup>16</sup> Another recent study found a U-shaped association between weight and mortality in a large cohort of Chinese men and women.<sup>17</sup>

There are several explanations for the discrepancies observed in the above epidemiological studies. There may be an adverse effect of leanness and leanness can be a surrogate marker of underlying diseases.<sup>18</sup> The possibility that there may be some beneficial effect of mild degree of excess body weight on overall survival, also cannot be entirely ruled out. For example, in the INTERHEART study, high hip circumference had a negative predictive value for myocardial infarction, while high waist circumference was associated with high rates of myocardial infarction, implying that considering only the BMI and ignoring fat distribution may be misleading.<sup>19</sup>

Weight or BMI may be relatively low in an elderly person with little lean body mass relative to adipose tissue. The correlations between BMI and more direct measures of adiposity (e.g. underwater weighing) range between 0.6 and 0.8.<sup>20,21</sup> Furthermore, reported correlations between waist-hip ratios and visceral adipose tissue volume (as assessed by CT) are imperfect.<sup>22</sup>

Other limitations of several epidemiological studies are: partial adjustment for confounding factors (such as physical fitness, type of diet, family history, weight cycling, use of diet drugs, economic status), inclusion of self-reported data, not taking into account the age of onset of obesity and not estimating the obesity-attributable mortality. It has been estimated that the excess mortality associated with obesity in the Framingham study is due to the effect of weight cycling, and that participants with stable body weights were not at increased risk.<sup>23</sup> A similar finding has been reported in the National Health and Nutrition Examination Survey (NHANES).<sup>24</sup>

Flegal *et al.* recently made an estimation of relative risks of mortality associated with different levels of BMI from the nationally representative NHANES I, II and III, and applied these relative risks to the distribution of BMI and other covariates from NHANES 1999–2002 data to estimate attributable fractions and number of excess deaths related to obesity.<sup>25</sup> After adjusting for confounding factors

and for effect modification by age, they found an increased mortality associated both with being underweight and with being obese. Notably, the increased mortality was found in subjects with a BMI  $\geq 35$  kg/m<sup>2</sup>, but there was no increase in mortality in the less obese groups. In addition, there was a decline in the relative risk of mortality according to BMI categories from NHANES I to NHANES III.

This finding suggests that the attenuation in the strength of the association between obesity and mortality is related to the improvement in the standard medical care that has resulted in reduced cardiovascular mortality in recent years. Age-adjusted death rates from heart disease (per 100 000 population) declined from 412.1 in 1980 to 240.8 in 2002.<sup>26</sup> In addition, there was a decrease in the prevalence of hypercholesterolemia and smoking, but not of diabetes, between 1960–62 and 1999–2000.<sup>27</sup> These changes occurred despite the marked increase in the prevalence of obesity during this time period.

## Morbidity associated with obesity

### Diabetes mellitus

There is a strong association between obesity and type 2 diabetes mellitus, in both genders and all ethnic groups. Data from the Nurses' Health Study showed an age-adjusted relative risk of 40 for diabetes in women with a BMI  $\geq 31$  kg/m<sup>2</sup>, compared with women with a BMI  $< 22$  kg/m<sup>2</sup>.<sup>28</sup> A similar risk was shown for men in the Health Professionals Follow-up Study: a BMI of  $\geq 35$  kg/m<sup>2</sup> was associated with an age-adjusted relative risk for diabetes of 60.9, compared with a BMI of  $< 23$  kg/m<sup>2</sup>.<sup>29</sup> In addition, weight gain appears to precede the development of diabetes. In the Pima Indians, a group with a high incidence of type 2 diabetes, body weight was shown to increase by 30 kg from a mean of 60 kg to a mean of 90 kg in the years prior to the diagnosis of diabetes.<sup>30</sup> The importance of obesity as a risk factor for diabetes in the presence of other risk factors is underlined by a recent report from Israel. In a cohort of relatively young men in the Israel Defence Forces who were subjected to regular physical examinations, the combination of a fasting plasma glucose in the high-normal range (91–99 mg/dl) and a BMI of  $> 30$  kg/m<sup>2</sup> was associated with a hazard ratio of 8.29 for developing diabetes, compared to those men with a BMI  $< 25$  kg/m<sup>2</sup> and a fasting plasma glucose  $< 86$  mg/dl.<sup>31</sup>

## Hypertension

Hypertension is strongly linked to obesity. The Swedish Obesity Study showed hypertension to be present at baseline in 44–51% of obese subjects.<sup>32,33</sup> In the Nurses' Health Study, BMI at age 18 years and in mid-life were both positively associated with the occurrence of hypertension.<sup>34,35</sup> Furthermore, weight gain was also associated with an increased risk. The relative risk for developing hypertension in women who gained 5–9.9 kg was 1.7, and in those who gained >25 kg, the relative risk was 5.2.<sup>34</sup> Similar findings in men were apparent in the Health Professionals Study.<sup>29</sup> It has been estimated from the Framingham Health Study that excess body weight may account for up to 26% of cases of hypertension in men and 28% in women.<sup>36</sup>

Not only is obesity linked with hypertension, but weight loss in obese subjects is associated with a decline in blood pressure.<sup>35</sup> In a 4-year follow-up of 181 overweight hypertensive patients, a 10% weight loss was independently associated with a 4.3/3.8 mmHg decrease in 24-h ambulatory blood pressure monitoring.<sup>37</sup> A meta-analysis of 25 randomized controlled trials that enrolled nearly 5000 participants found that both systolic and diastolic blood pressures fell by approximately 1 mmHg for each kg weight loss.<sup>38</sup> The anti-hypertensive effect of weight loss is independent of race or gender.<sup>39</sup> Furthermore, chronic obesity reduces the efficacy of anti-hypertensive medication.<sup>40</sup>

## Dyslipidaemia

Obesity is associated with an unfavourable lipid profile. Lipid abnormalities related to obesity include an elevated serum concentration of cholesterol, low-density-lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, triglycerides and apolipoprotein B, as well as a reduction in serum high-density-lipoprotein (HDL) cholesterol.<sup>41</sup> The mechanism(s) underlying this dyslipidaemia are not fully understood but involve the combination of insulin resistance and hyperinsulinaemia stimulating hepatic triglyceride synthesis from an increased adipose tissue undergoing enhanced lipolysis. This leads to postprandial hypertriglyceridaemia, smaller and denser LDL particles, and reduced HDL cholesterol concentrations.

In a comprehensive meta-analysis, weight loss of 1 kg decreased serum total cholesterol by 0.05 mmol/l and LDL cholesterol by 0.02 mmol/l, and increased HDL cholesterol by 0.009 mmol/l.<sup>42</sup>

## Heart disease

In addition to the link between obesity and mortality from cardiovascular disease, obesity is associated with increased risks of coronary artery disease, heart failure and atrial fibrillation.

### Coronary artery disease

An increased risk of coronary artery disease (CAD) in the overweight was apparent in both the Framingham Heart Study and the Nurses Health Study.<sup>6,34,36,43,44</sup> In the Nurses Health Study, the adjusted relative risk for CAD (taking BMI of 21 kg/m<sup>2</sup> as a reference value) increased from 1.19 at a BMI of 21–22.9 kg/m<sup>2</sup> to 3.56 at a BMI >29 kg/m<sup>2</sup>.<sup>33,45</sup> The Asia-Pacific Cohort Collaboration Study, involving >300 000 adults followed up for almost 7 years, found a 9% increase in ischaemic-heart disease events for each unit change in BMI.<sup>46</sup> In addition, obesity was associated with both fatty streaks and raised atherosclerotic lesions in the right coronary and left anterior descending coronary arteries in young men, although not in women.<sup>47</sup>

In patients with pre-existing heart disease, however, the relationship between obesity and cardiovascular mortality is not as strong. A subgroup analysis from the Physicians Health Study comparing cardiovascular mortality in men with a BMI of 22.0–24.9 kg/m<sup>2</sup> vs. those with a BMI >28 kg/m<sup>2</sup>, did not find a significant increase on multivariate analysis.<sup>48</sup>

### Heart failure

The relationship between obesity and heart failure is complex. In the Framingham Study, almost 6000 individuals without a history of heart failure (mean age 55 years) were followed for a mean of 14 years. The risk of developing heart failure was two-fold higher in obese individuals, compared with subjects with a normal body-mass index.<sup>45</sup> On multivariate analysis adjusting for risk factors including hypertension, coronary artery disease and left ventricular hypertrophy, there was an excess risk of 5% in men and 7% in women for each 1 point increase in BMI. It was estimated that 11% of the cases of heart failure in men and 14% in women could be attributed to obesity alone.

Individuals with obesity have a form of cardiomyopathy attributed to chronic volume overload, characterized by left ventricular dilatation, increased left ventricular wall stress and compensatory left ventricular hypertrophy.<sup>49</sup> Most studies have reported abnormal diastolic function<sup>50,51</sup> without abnormal systolic function.<sup>52,53</sup>

Recently, however, in a study comparing the transthoracic echocardiography findings of the heart of overweight or obese subjects with non-obese controls, subtle changes in systolic function were observed in parameters such as myocardial velocity and strain index even when conventional 2D echo found a normal ejection fraction.<sup>54</sup> These changes were more prominent in the patients who had a BMI  $>35 \text{ kg/m}^2$ , compared to the less obese patients. Similar findings have been reported in obese young women (21–37 years of age).<sup>55</sup>

Elevated BMI, however, appears to be associated with an improved survival in patients with congestive heart failure (CHF).<sup>56</sup> In the large Digitalis Intervention Group trial, patients who were overweight (BMI 25.0–29.9  $\text{kg/m}^2$ ) and obese (BMI  $>30 \text{ kg/m}^2$ ) had a mortality hazards ratio of 0.88 compared to a control group of BMI 18.5–24.9 on multivariate analysis. This has been termed the obesity paradox.

### *Atrial fibrillation*

As noted above, obesity is linked to hypertension, coronary artery disease, diabetes mellitus, left ventricular hypertrophy, left atrial enlargement and CHF. Hypertension, left atrial enlargement and congestive heart failure are all strongly linked to atrial fibrillation (AF).<sup>57,58</sup> Despite the close relationship between obesity and several of the risk factors for AF, a clear relationship between AF and obesity has only recently been established. Previous epidemiologic studies produced conflicting results as to whether AF is linked to obesity. This may be due to short-term follow-up, failure to account for interim cardiovascular events and/or lack of echocardiographic data.<sup>58–61</sup>

Data from the Framingham Heart Study<sup>62</sup> show a correlation between the risk of developing AF and BMI. In multivariate analysis, adjusting for interim myocardial infarction or heart failure, every increase of 1 point in BMI was associated with a 4% increase in the risk of AF. In addition, there was a gradual increase in left atrial size as BMI increased. The relationship between BMI and AF was not significant after adjusting for left atrial diameter, suggesting a physiological link between obesity and left atrial diameter. In addition there is an association between obstructive sleep apnoea and AF,<sup>63</sup> and as will be discussed below, obesity and obstructive sleep apnoea are closely linked.

### **Cerebrovascular disease**

Obesity is linked to an increased risk of stroke in both men and women.<sup>64–69</sup> In a study of 234 863 Korean men aged 40–64 years, an adjusted hazard

of 11% for ischaemic stroke was found for each 1 point increase in BMI.<sup>69</sup> In the Physicians Health Study of 21 414 US physicians, those with a BMI  $\geq 30 \text{ kg/m}^2$  had a relative risk of 1.95 for an ischaemic stroke and 2.25 for a haemorrhagic stroke. Each 1 point increase in BMI resulted in a 6% increase in the relative risk for total stroke.<sup>65</sup> In a study from Sweden of 7402 apparently healthy men aged 47–55 years, followed up over a 28-year period, BMI  $>30 \text{ kg/m}^2$  resulted in a hazard ratio of 1.78 for ischaemic stroke, but not haemorrhagic stroke.<sup>64</sup> In these studies, the increased risk for stroke persisted, although attenuated, after adjusting for concomitant risk factors such as hypertension, diabetes and hypercholesterolaemia.

Obese women also have an increased risk for stroke. Data from the Women's Health Study of 39 053 women with self-reported weight and height, found a hazards ratio of 1.72 for ischaemic stroke in women with BMI  $>30 \text{ kg/m}^2$  compared to those with BMI  $<25 \text{ kg/m}^2$ .<sup>70</sup> There was no significant relationship between BMI and haemorrhagic stroke. Similar results were found in 116 759 women in the Nurses' Health Study.<sup>67</sup> In this study there was a non-significant inverse relationship between obesity and haemorrhagic stroke. It is unclear why there is no relationship between haemorrhagic stroke and obesity, but it may be linked to the lower number of cases in each of the trials, compared to ischaemic stroke.

However, not all studies have shown an association between BMI and stroke,<sup>71,72</sup> and recent data suggest that central fat accumulation is a stronger risk factor for stroke than overall obesity. In a report from the Israeli Ischemic Heart Disease Study of 9151 male civil servants, trunk body fat was a predictor of stroke mortality, independent of BMI, blood pressure, smoking, socioeconomic status and diabetes mellitus.<sup>73</sup>

### **Respiratory disease**

#### *Obstructive sleep apnoea*

Obesity is a major risk factor for obstructive sleep apnoea (OSA). Over 75% of patients with OSA are reported to be  $>120\%$  of ideal body weight.<sup>74</sup> Epidemiological evidence from the Wisconsin Sleep Cohort Study showed that sleep apnoea risk increased significantly with obesity.<sup>75</sup> A neck circumference  $>17$  inches, which is correlated with obesity, has also been highly correlated with OSA.<sup>76,77</sup> In addition, mild-to-moderate weight loss can substantially improve sleep apnoea.<sup>79</sup> Obesity probably contributes to OSA via multiple mechanisms. Increased fat deposits in tissues surrounding the upper airway in obese patients

may directly impinge on the airway lumen.<sup>80</sup> Upper-body fat deposits may increase airway collapsibility and interfere with the function of the inspiratory and expiratory muscles that maintain airway calibre. Upper airway collapsibility also decreases after weight loss in obese patients with OSA.<sup>81</sup>

### *Asthma*

The prevalence of asthma is increased in overweight subjects,<sup>82</sup> and obese or overweight subjects account for 75% of emergency department visits for asthma.<sup>83</sup> Longitudinal studies indicate that obesity antedates asthma, and that the relative risk of incident asthma increases with increasing obesity.<sup>84,85</sup> In addition, morbidly obese asthmatic subjects studied after weight loss demonstrate decreased severity of asthma symptoms.<sup>85</sup> Obesity also appears to be a risk factor for airway hyper-responsiveness.<sup>86</sup> The relationship between obesity and asthma is underlined by the finding that obesity is a strong predictor of the persistence of childhood asthma into adolescence.<sup>5</sup> Potential mechanisms for this relationship include obesity-related changes in lung volumes, systemic inflammation and other adipocyte-derived factors that might alter airway smooth muscle function and promote airway narrowing.<sup>87</sup>

Recently, the relationship between respiratory function and obesity has been examined in the EPIC-Norfolk cohort in Norfolk, UK.<sup>88</sup> This group included 9674 men and 11 876 women aged 45–79 years. FEV<sub>1</sub> and FVC were linearly and inversely correlated across the entire spectrum of the waist-hip ratio in both men and women, and this relation persisted after adjustment for BMI. This suggests that abdominal obesity may impair respiratory function, and more so than generalized obesity. Furthermore, a *post-hoc* analysis of a database of four previous placebo-controlled studies of monteleukast or inhaled beclomethasone, showed a lower placebo response and also a lower response to inhaled corticosteroid, with increasing BMI, whereas response to monteleukast was not affected by BMI.<sup>89</sup>

## **Gastrointestinal system**

### *Gastroesophageal reflux*

Gastroesophageal reflux disease (GORD) is a common disorder that has been linked to obesity. Most population-based studies supported this association in studies conducted in the US, UK, Norwegian and Spanish populations,<sup>90–95</sup> and two of these studies showed a gradual increase in GORD symptoms as BMI increased.<sup>90,91</sup> However, two

large population-based studies did not find any association.<sup>96,97</sup>

Several studies have examined the relationship between GORD and oesophageal erosions. Three reported a moderate positive association,<sup>98–100</sup> one reported no association,<sup>101</sup> and one found a positive association in women but not in men.<sup>102</sup> In a recent study in 453 patients, obese patients were 2.5 times as likely as patients with a BMI <25 kg/m<sup>2</sup> to have either reflux symptoms or oesophageal erosions.<sup>103</sup> Since there is a link between GORD and oesophageal adenocarcinoma, the connection between GORD and obesity deserves further investigation. A recent meta-analysis found a significant association between obesity and the risk for GORD symptoms, erosive oesophagitis and oesophageal adenocarcinoma.<sup>104</sup>

### *Hepatobiliary disease*

Obesity is associated with cholelithiasis. In the Nurses' Health Study, women with BMI <24 kg/m<sup>2</sup> had an incidence of symptomatic gallstones of approximately 250 per 100 000 person-years of follow-up.<sup>105</sup> Women with BMI >45 kg/m<sup>2</sup> had a seven-fold increase in risk for gallstones compared to women with BMI <24 kg/m<sup>2</sup>. Women with BMI >30 kg/m<sup>2</sup> had a yearly gallstone incidence of >1% and those with BMI ≥45 kg/m<sup>2</sup> had a rate of approximately 2% per year. Similar data were found in men in the Health Professionals Study.<sup>34</sup>

Notably however, there is an increased risk for cholelithiasis in patients who lose weight rapidly. Gallstone formation after bariatric surgery has been reported to affect about 38% of patients.<sup>106</sup>

### *Non-alcoholic fatty liver disease (NAFLD)*

NAFLD is increasing in prevalence in developed countries, and is one of the most common causes of cryptogenic cirrhosis. It is strongly linked to the metabolic syndrome, of which obesity is a central component, and is in fact regarded as the hepatic manifestation of the metabolic syndrome.<sup>107,108</sup> NAFLD is a spectrum of diseases ranging from simple steatosis to steatohepatitis and cirrhosis, with all of its concomitant complications. Patients with NAFLD especially those with mainly steatosis, respond favourably to weight reduction, and a recent large study showed that achieving ≥5% weight reduction by lifestyle modifications was associated with improvement and even normalization of liver enzymes in subjects with impaired liver function tests.<sup>109</sup>

Interestingly, waist-hip ratio is an independent predictor of advanced fibrosis at liver biopsy.<sup>110</sup>

## Osteoarthritis

There is a marked increase in osteoarthritis in the obese. It is most common in the knees and the ankles, which may be a consequence of trauma related to the excess body weight. In a study of over 1000 women, the age-adjusted odds ratio of unilateral and bilateral osteoarthritis of the knee, as determined by X-ray, was 6.2 for BMI <23.4 kg/m<sup>2</sup> and 18 for BMI >26.4 kg/m<sup>2</sup>. When BMI <23.4 kg/m<sup>2</sup> was compared to BMI 23.4–26.4 kg/m<sup>2</sup>, the odds ratios for osteoarthritis were increased: 2.9 fold for the knee, 1.7 fold for carpometacarpal joint, 1.5 fold for the distal interphalangeal joint, and 1.2 fold for the proximal interphalangeal joint.<sup>111</sup> A co-twin control study noted that each one kg increase in weight was associated with an increased risk of radiographic features of osteoarthritis at the knee and carpometacarpal joint.<sup>112</sup>

Not only is obesity associated with osteoarthritis, but weight loss is associated with a decreased risk of osteoarthritis. A study of 800 women showed that a decrease in BMI of 2 kg/m<sup>2</sup> or more in the preceding 10 years decreased the odds for developing osteoarthritis by >50%.<sup>113</sup> This benefit was also present in those women with a BMI >25 kg/m<sup>2</sup> and thus at high risk of osteoarthritis.

The fact that osteoarthritis occurs more frequently in non-weight-bearing joints suggests there are components of the obesity syndrome that alter cartilage and bone metabolism independent of weight bearing.

## Cancer

The WHO International Agency for Research on Cancer has estimated that overweight and inactivity account for from a quarter to a third of all cancers of the breast, colon, endometrium, kidney and oesophagus.<sup>114</sup>

Obesity also increases the likelihood of dying from cancer. A 16-year prospective study of >900 000 men and women in the US found a relative risk of death from cancer of 1.5 for men and 1.6 for women in the group with BMI >40 kg/m<sup>2</sup> vs. BMI 18.5–24.9 kg/m<sup>2</sup>.<sup>115</sup> For both men and women, increasing BMI was associated with higher death rates due to cancers of the oesophagus, colon and rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin's lymphoma and multiple myeloma. Men were also at increased risk for death from stomach and prostate cancer, while women were at increased risk of death from cancers of the breast, cervix, uterus and ovary. On the basis of these data, the authors estimated that overweight and obesity

in the USA could account for 14% of all cancer deaths in men and 20% in women.

In a systematic review and meta-analysis from the Comparative Risk Assessment Project evaluating data on 7 million deaths from cancer, 2.43 million were attributable to potentially modifiable risk factors, including overweight and obesity. For every risk factor, they calculated the population attributable fraction (PAF), estimating the proportional reduction in cancer death if the risk factor was reduced. The corresponding PAF for over-weight and obesity was: 11% for colon and rectum cancers; 5% for breast cancer; 40% for uterine cancer.<sup>116</sup>

In the Nurses' Health Study, obesity and weight gain had differing effects on the risk of breast cancer in premenopausal and postmenopausal women.<sup>117</sup> Premenopausal women with BMI >26 kg/m<sup>2</sup> had lower mortality from breast cancer. In addition, weight gain after the age of 18 years was not associated with increased risk of breast cancer before menopause, but was a risk factor after menopause. In postmenopausal women who had never taken oestrogen hormone replacement therapy, the relative risk of developing breast cancer was 1.6 if they had gained 10–20 kg and 2.0 if they had gained >20 kg, compared to women with minimal weight gain. Women who were taking oestrogen, however, did not have an increased risk of breast cancer associated with weight gain.

The data suggesting that obesity is one of the causes for cancer are derived mainly from epidemiological studies, which cannot prove cause-effect relationship, and may be confounded by selection bias. There are also limited data clarifying the underlying mechanisms for this association. It is possible that the increased production of oestrogens by adipose tissue stromal cells, together with the decrease of sex-steroid-binding globulin, is responsible for the increased risk of endometrial and perhaps breast cancer. Insulin resistance and increased levels of insulin-like growth factor-I (IGF-I) may play a role in colon neoplasm.<sup>118–120</sup> Further studies evaluating the possible interaction between genetic background and obesity in the development of specific type of cancers, are needed.

Obesity may also unfavourably influence the diagnosis of cancer and the response to therapy. The commonly accepted dose reduction of chemotherapy in the obese may be deleterious. A review of four trials of treatment for breast cancer with a total of 2443 patients in whom the BMI was known, showed that obese patients received a lower dose of chemotherapy and had a worse outcome in the group with oestrogen-receptor-negative tumours but not in the group with oestrogen-receptor-positive tumours.<sup>121</sup>

## Psychosocial function

Obesity in the past was seen as a sign of wealth and wellbeing. This remains the case in many parts of Africa, partly as a result of the HIV epidemic and its associated wasting. However, in affluent countries there is a stigma associated with obesity in areas such as education, employment and health care. A survey of more than 10 000 adolescents found that women with a BMI above the 95th percentile for age and sex completed fewer years of school (0.3 years), were 20% less likely to be married, had lower household incomes and higher rates of household poverty compared to women who had not been overweight, independent of their baseline socioeconomic status and aptitude test scores.<sup>122</sup> Men who had been overweight were less likely to be married.

In a group of 294 patients seeking consultation for bariatric surgery, half the patients had a psychiatric disorder and 29% had comorbidity. The highest prevalence rates were 29% for somatization, 18% for social phobia, 15% for hypochondriasis and 14% for obsessive-compulsive disorder.<sup>123</sup>

In addition, eating disorders such as binge eating disorder and night eating syndrome have been linked with depression and obesity.<sup>124</sup>

## Gynaecological and obstetric complications

Obesity during pregnancy is associated with an increased risk of complications, including gestational diabetes, pre-eclampsia, and delivery complications such as macrosomia, shoulder dystocia and higher rates of caesarean sections and infections. Maternal obesity may also be an independent risk factor for neural tube defects and fetal mortality. This subject has been reviewed recently.<sup>125</sup>

Obesity is now estimated to be responsible for 6% of primary infertility.<sup>126</sup> In men, there is a link between impotence and increasing infertility, with abdominal obesity a particular risk.<sup>127,128</sup>

Polycystic ovary syndrome (PCOS), the most common endocrine disorder in women of reproductive age, is characterized by a combination of chronic anovulation, polycystic ovary morphology and hyperandrogenism.<sup>129</sup> Obesity and insulin resistance are closely related with PCOS, and insulin resistance has a pivotal role in the pathogenesis of this syndrome. Women with PCOS respond favourably to weight loss, as well as to pharmacological treatment of insulin resistance, with decrease in androgen levels and ovulation.<sup>130</sup>

## Surgical and anaesthetic complications

In the light of the previously mentioned pulmonary changes associated with obesity, one might expect obesity to be a risk factor for post-operative pulmonary complications, but the data are inconsistent. A review of ten series of obese patients undergoing gastric bypass operations showed a similar 3.9% rate of post-operative pneumonia and atelectasis to that in the general population.<sup>131</sup> In a prospective study of 117 patients undergoing thoracic surgery, there was no difference in the rate of pulmonary complications when the patients were stratified by BMI.<sup>132</sup> Contrasting findings were found in a prospective study of 1000 patients undergoing laparotomy, in which BMI >25 kg/m<sup>2</sup> was an independent risk factor for postoperative pulmonary complications.<sup>133</sup> Furthermore, in a prospective study of 400 patients undergoing abdominal surgery, BMI >27 kg/m<sup>2</sup> was one of six independent factors for pulmonary complications.<sup>134</sup> One possible explanation for the differences between these reports may be failure to distinguish between obesity and other comorbid conditions. In a prospective study of 272 patients referred for medical evaluation prior to non-thoracic surgery, using explicit criteria for postoperative pulmonary complications, the odds ratio was 4.1 for patients with BMI >30 kg/m<sup>2</sup>, but this was no longer significant under multivariate analysis.<sup>135</sup> A review of six studies encompassing a total of 4536 patients found a similar risk of pulmonary complications for both obese and non-obese patients.<sup>136</sup>

## Chronic kidney disease

The epidemic of obesity in the developed world has been associated with an increase in the prevalence of chronic kidney disease. It is however, unclear whether obesity is a risk factor independent of diabetes and hypertension.<sup>137</sup>

Among NHANES III participants, the risk of either incident end-stage renal disease or kidney-related death was independently associated with a BMI >35 kg/m<sup>2</sup>, with a relative risk of 2.3 among those morbidly obese compared with normal weight persons, but risk was not increased for those classified as overweight or obese.<sup>138</sup> In the Framingham study, patients who were obese at baseline were more likely to have a decrease in estimated glomerular filtration rate (GFR).<sup>139</sup> Under multivariate analysis, increased baseline BMI was significantly associated with progression to chronic kidney disease, with an odds ratio of 1.23 for each standard deviation.

Notably, weight loss may preserve renal function. In a study of 24 type 1 and type 2 diabetics with nephropathy, a reduction in BMI from 33 to 26 kg/m<sup>2</sup> was associated with a decrease in proteinuria from 1.3 to 0.623 g per 24 h, and an improvement in GFR from 66 to 81 ml/min/1.73m<sup>2</sup>.<sup>140</sup>

## Are all obese patients at increased risk?

Despite the mortality and morbidity associated with obesity described in previous sections, clinicians are well aware of the phenomenon of the healthy obese individual. Therefore, further characteristics that will identify subsets of obese high-risk patients vs. obese non high-risk patients are needed.

### Physical fitness and activity

Several studies have shown that low physical fitness and physical activity are independent predictors for all-cause mortality, CVD mortality and cardiovascular events in lean and obese men and women.<sup>141–144</sup> In the Aerobics Center Longitudinal Study, unfit lean men had a higher risk for all-cause and CVD mortality than men who were fit and obese.<sup>142</sup> In a long-term prospective study of Finnish men and women, low leisure time physical activity and physical fitness, but not high BMI, were predictors of all-cause and CVD mortality.<sup>145</sup> However in another study conducted in men and women, physical fitness, although associated with reduced mortality from CVD, did not completely reverse the increased risk associated with obesity.<sup>146</sup> One of the mechanisms by which increased physical activity and fitness can reduce CVD risk and all-cause mortality is by modulating insulin sensitivity. In both Caucasians and Pima Indians, maximal aerobic capacity is positively correlated with insulin action.<sup>147</sup> Other protective mechanisms of physical activity include: improvement of blood pressure, atherogenic dyslipidaemia and inflammation, increased fibrinolytic and endothelial function.<sup>148</sup> The protective role of physical exercise and fitness implies that physicians should at least obtain a self-record of physical activity and fitness as part of assessing the risks associated with obesity.

### Insulin resistance and the metabolic syndrome

Insulin resistance and the compensatory hyperinsulinemia, are strongly associated with increased risk for type 2 diabetes, CVD and CHD mortality in large epidemiological studies.<sup>149–152</sup> The metabolic

syndrome, a cluster of abnormalities related to insulin resistance,<sup>153</sup> was also associated with increased risk of developing type 2DM and CVD in large prospective studies.<sup>154–156</sup> Population-attributable risk estimates associated with the metabolic syndrome were 34%, 29% and 62% in men, and 16%, 8% and 47% in women, for CVD, CHD, and type 2DM, respectively.<sup>157</sup> The metabolic syndrome includes known risk factors for CVD such as abdominal obesity, hypertension, glucose intolerance, high triglycerides and low HDL-cholesterol. In addition, some data suggest that even after adjusting for these known risk factors, the metabolic syndrome remains an independent risk factor for CVD.<sup>158,159</sup> Obese and overweight people tend to be more insulin-resistant, yet only about half have significant insulin resistance.<sup>160</sup> Identifying obese insulin-resistant individuals in daily practice is of great importance, since weight reduction is especially beneficial in reducing CVD risk factors in this sub-group.<sup>160,161</sup> Fortunately, insulin resistance can be identified by relatively simple measures such as high fasting serum insulin levels or by high triglycerides and low HDL-cholesterol levels.<sup>160</sup>

Obesity has been associated with increased risk of several types of commonly occurring cancer, as noted above. In addition, obesity is associated with both a higher rate of recurrence of breast cancer and a worse prognosis.<sup>161</sup> Interestingly, abdominal obesity and insulin resistance were shown to be associated with some types of cancer such as colon and breast neoplasia, suggesting that one of the mechanisms linking obesity and cancer is related to insulin-like growth factors.<sup>118–120</sup>

### Fat distribution

The recently published INTERHEART study examined the predictive value for myocardial infarction of different obesity markers in >27 000 subjects from different ethnic groups, in 52 countries.<sup>162</sup> It found that waist-hip ratio was superior to BMI, having a graded and significant association with myocardial infarction that persisted after adjusting for the other known risk factors. BMI, in contrast, showed only a modest association, in some but not all populations, and the association was not significant after further adjustments. This study confirms (and extends to different populations) the results of previous studies, showing that simple measures of waist or waist-hip ratio are closely related with CVD risk.<sup>163–165</sup> Increased waist-hip ratio is a surrogate of increased visceral adipose tissue known to be more metabolically active, releasing free fatty acids, adipokines and cytokines, all leading



to insulin resistance.<sup>166</sup> In a study comparing removal of 1 kg visceral fat at bariatric surgery with bariatric surgery alone, there was a significant improvement in insulin sensitivity in those patients who underwent the combined procedure,<sup>167</sup> while removal of subcutaneous tissue had no effect on insulin sensitivity.<sup>168</sup> Therefore, assessment of visceral fat accumulation by measuring waist–hip ratio should be part of the routine assessment of the obese individual.

## Genetics

The gene-environment interaction is known to play a role in multiple diseases. Obesity is associated with many comorbidities, and an interaction between obesity and a positive family history has been shown in several of these associated illnesses. In individuals with a strong family history of diabetes and increased BMI, reduced beta-cell compensation to the insulin resistance associated with obesity was found, increasing the risk for developing type 2 diabetes.<sup>169</sup> BMI was strongly associated with breast cancer risk among women with a strong family history of breast cancer, but only weakly associated in those women without a family history.<sup>170</sup> In women with a family history of premature coronary artery disease, BMI was an independent predictor of coronary artery calcification.<sup>171</sup> Further studies are needed to elucidate the possible interactions between obesity and genetic background, but obtaining a family history may be helpful in assessing the risk of the individual obese patient.

## Conclusions

Obesity is linked with a large range of medical complications. There is evidence that obesity is not only related to conditions such as diabetes, hypertension, heart disease, obstructive sleep apnoea, asthma, non-alcoholic fatty liver disease, osteoarthritis and polycystic ovary syndrome, but also that weight reduction has beneficial effects and therefore is an integral part of treating these morbidities (Table 1). Although there is a significant association between certain types of cancer and obesity, the inherent limitation of epidemiological studies in establishing causality, together with the lack of intervention studies, underline the need for further studies before the role of obesity in cancer is established.

Another controversial issue is the association between obesity and mortality. While some researchers believe that obesity will shorten the life expectancy of obese populations, there are other

**Table 1** Obesity-associated complications that respond to weight reduction

Complication	References
Type 2 diabetes	174, 176, 177
Hypertension	35, 37, 38, 39
Dyslipidaemia	42
Obstructive sleep apnoea	78
Asthma	85
Coronary heart disease	178
Obesity-related cardiomyopathy	179
NAFLD	109
Osteoarthritis	180, 181
Polycystic ovary syndrome	130

NAFLD, non-alcoholic fatty liver disease.

data describing a U-shaped association, with excess mortality in both under-weight and severe obesity, while milder degrees of overweight do not show increased rates. In addition, improved standards of medical care may attenuate the effect of obesity on life expectancy. The economic burden of providing this medical care to increasing numbers of obese subjects cannot however be dismissed.

Not all obese patients will develop complications. Further characterization of physical activity and fitness, fat distribution, insulin resistance and family history of obesity-related diseases, can identify the obese person who is at increased risk. The age of onset of obesity also needs to be taken into account, as the life-long risk of developing obesity-related complications is higher in early-onset compared with late-onset obesity.

We suggest the following scheme for the management of the patient with obesity. Firstly, for patients who suffer from obesity-related complications listed in Table 1 that have been shown to respond favourably to weight loss, we recommend that dietary consultation be part of the treatment plan.

Secondly, since not all obese subjects will develop associated morbidities, we list clinical characteristics that are of assistance in identifying those asymptomatic obese people who have a particularly high risk for developing obesity-related complications (Table 2). The rationale of focusing the effort to achieve weight reduction in this high-risk group, is based on data from studies such as the large Diabetes Prevention Program, in which 3234 non-diabetic overweight or obese patients with elevated glucose levels were randomized to placebo, lifestyle modification program or metformin. The lifestyle modification program was aimed at achieving 7% weight loss and 150 min of physical activity per week. This program lasted for

**Table 2** Clinical characteristics of the 'high-risk' obese patient

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Abdominal obesity (increased waist-hip ratio)
Low physical fitness
High triglycerides and low HDL-cholesterol levels
High fasting insulin levels
High fasting glucose levels
Family history:
Diabetes
Hypertension
Dyslipidaemia
Coronary heart disease

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3 years, and resulted in a 58% reduction in diabetes incidence.<sup>172</sup>

For morbidly obese persons with a high-risk profile or the above-mentioned complications, who fail to lose weight, pharmacological adjunct therapy and bariatric surgery should be considered. This is supported by the results of two large intervention studies with a relatively long-term follow up. In the first, a randomized trial comparing combined dietary intervention with orlistat (lipase inhibitor) and dietary intervention to dietary intervention alone, the combined therapy given for 4-year period, resulted in a 37% reduction in the incidence of diabetes due to the effect in a subgroup of patients with impaired glucose tolerance.<sup>173</sup> In the second large study, 1703 obese patients who underwent bariatric surgery were followed for 10 years, and compared to conventionally treated obese subjects. The surgery group lost significantly more weight and maintained the weight loss throughout the follow-up period and this weight loss was accompanied by a significantly lower incidence of diabetes and hypertriglyceridemia.<sup>174</sup>

The issues of safety, cost-effectiveness and quality of life, related to pharmacological and surgical therapies for obesity, are still debated, and an individual approach has been suggested.<sup>175</sup> Before establishing definite treatment guidelines, more large intervention studies, focusing on different age groups and obesity-related comorbidities are needed to address the long-term cost-effectiveness and quality of life associated with various treatment modalities.

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