Obesity and the lung: 1 · Epidemiology

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Received 19 December 2007
Accepted 14 January 2008

ABSTRACT

Obesity is the most common metabolic disease in the world and its prevalence has been increasing over several decades. The World Health Organization (WHO) predicts that, by 2015, around 700 million adults will be obese (at least 10% of the projected global population). This will be a huge health and economic burden with associated increases in diabetes, cardiovascular and musculoskeletal disease, and malignancy. While there has been little focus on the impact of obesity on respiratory disease, there are clear effects on pulmonary function and inflammation which will increase the prevalence and morbidity of lung disease. There is an inverse relationship between body mass index and forced expiratory volume in 1 s. Increases in body weight lead to worsening of pulmonary function. The reasons for this include the mechanical effects of truncal obesity and the metabolic effects of adipose tissue. Obesity is linked to a wide range of respiratory conditions including chronic obstructive pulmonary disease, asthma, obstructive sleep apnoea, pulmonary embolic disease and aspiration pneumonia. It is important for those providing care for people with respiratory disease to appreciate the impact of obesity and to provide appropriate advice for weight reduction. Healthcare planners should consider the impact of obesity for future resources in respiratory care.

Obesity is the most common metabolic disease in the world[1] and its prevention has become one of the leading priorities for the World Health Organization (WHO).[2] Obesity is defined as "abnormal or excessive fat accumulation that may impair health".[3] It is categorised by body mass index (BMI, kg/m^2), which is highly correlated with body fat and is therefore a useful measure in clinical assessment and epidemiological studies.[1] A BMI of 18.5–24.9 kg/m^2 is healthy in adults and a BMI of >30 kg/m^2 is classed as obesity (table 1). However, epidemiologists agree that precise thresholds carry little biological meaning, given the continuous gradient of risk.

The BMI index was originally eponymously named the "Quetelet Index". It was devised in 1835 by Lambert Adolphe Quetelet (1796–1874), a Belgian astronomer and mathematician.[4] He was one of the first to apply statistics to social phenomena and is famous for developing the concept of the "average man" (fig 1).

The prevalence of obesity has been increasing over several decades,[5] and recent figures estimate that there are over 1.6 billion overweight adults worldwide (BMI ⩾25 kg/m^2). Of these, at least 400 million are obese.[3] The WHO further predicts that, by 2015, around 2.3 billion adults will be overweight and more than 700 million will be obese.

Obesity was previously thought to be a problem of high-income societies, but it is now globally one of the most significant contributors to morbidity and mortality among virtually all ages and socioeconomic groups.[3] Weight gain leads to greater adverse metabolic changes in all ethnic groups, although there has been some controversy over whether the BMI cut-off values for obesity should vary between racial groups. At the same BMI, Asians have a higher percentage of body fat and a more central distribution of adipose tissue than Caucasians and African-Americans.[6] Consequently, this group are often considered obese at BMI levels of <30 kg/m^2.

The worldwide prevalence of obesity ranges from <5% in China, Japan and some African nations to >75% in some of the Polynesian islands (fig 2). In Europe the prevalence of obesity has tripled in the last two decades. Between 30% and 80% of adults are overweight in most European countries, the average BMI being almost 26.5 kg/m^2.[2] The National Health and Nutrition Examination Survey (NHANES) shows that, between the early 1960s and 2000, the mean BMI for men aged 20–74 years in the USA increased from just over 25 kg/m^2 to almost 28 kg/m^2 (fig 3).[7] The pattern was similar for women.[5] Cultural differences in the acceptability and perception of obesity vary from country to country. Obesity is seen as a sign of wealth, fertility or status in some countries while in others it is becoming increasingly socially unacceptable.

The rates of childhood obesity are particularly alarming as being overweight is the most common childhood disorder in the European region.[8] One in 10 children in this area are expected to be obese by 2010. These children will be at much greater risk of developing obesity-related diseases such as type 2 diabetes, hypertension and psychosocial problems. Childhood obesity is a strong risk factor for adult obesity and is associated with a higher chance of premature death and disability in adulthood.[3] Patterns of diet and exercise developed in childhood are difficult to change. By 2050 the average life expectancy for men in the UK is likely to be 5 years lower than currently.[8] The Framingham Heart Study showed a significant reduction in life expectancy among non-smoking obese people compared with non-smokers with a healthy BMI. At 40 years, life expectancy in women was reduced by 7.1 years and in males by 5.9 years.[9] The relative risk associated with greater BMI declines with age.[10]

Obesity is a chronic disease and is associated with increased mortality.[7] It can affect almost every organ and tissue of the body. Multiple health problems are common among the obese and include cardiovascular and metabolic disturbances (eg, non-insulin dependent diabetes, ischaemic heart disease, stroke and dyslipidaemia). Obese individuals are also at greater risk of accidents,[11]

Table 1 Classification of body mass index in adults

Body mass index (kg/m^2)	Classification in adults
<18.5	Underweight
18.5–24.9	Healthy
25–29.9	Overweight
30–34.9	Obesity class I
35–39.9	Obesity class II
⩾40	Obesity class III (morbid obesity)

psychosocial problems, hypercoagulability, gallstones, osteoarthritis, back pain, complications of pregnancy and cancer (endometrial, ovarian , breast, cervical, prostate, colorectal, gallbladder, pancreatic, hepatic and renal).[12 13] In the respiratory system, obesity is linked to a wide range of conditions including chronic obstructive pulmonary disease (COPD), asthma, obesity hypoventilation syndrome, pulmonary embolism, aspiration pneumonia and obstructive sleep apnoea.[14]

Obesity is a significant health and economic burden and social class differentials are often apparent. It is responsible for a large percentage of healthcare expenditure and may consume up to 9% of a country's health service.[2] Obesity costs the UK economy £3.5bn every year and contributes to 30 000 deaths and 18 million days of absence from work.[15] In Europe as a whole, obesity is responsible for 2–8% of health costs and 10–13% of deaths.[3 8] The indirect costs of loss of lives, productivity and income are in addition to this. The WHO states that, in the USA, annual healthcare costs are 36% higher for obese individuals than for those with a healthy BMI. The associated secondary health costs are often greater in more socially deprived areas. Obesity "reflects and compounds" social inequalities.[3] Those with lower incomes may find it more difficult to access fitness facilities and to buy fresh fruit and vegetables, choosing to buy cheaper, energy-dense, less healthy foods.[2]

PATHOPHYSIOLOGY OF OBESITY AND LINK WITH RESPIRATORY DISEASE

Obesity may affect respiratory function in a number of ways. Multiple cross-sectional studies have demonstrated an inverse relationship between forced expiratory volume in 1 s (FEV_1) and BMI.[16] This is of particular importance since FEV_1 is an independent predictor of all-cause mortality[17–20] and a strong risk factor for cardiovascular disease, stroke and lung cancer.[21]

Several longitudinal studies have shown that increases in body weight can lead to a reduction in pulmonary function.[22 23] In an 8-year Italian longitudinal study of BMI, spirometry and transfer factor in over 1000 subjects from a general population (aged >24 years), Bottai *et al* observed that most of those who lost weight improved their lung function and those who gained weight reduced their lung function.[24] This suggests that the detrimental effects of gaining weight may be reversible for some people.[25 26] Those who had higher baseline BMI values tended to have greater reductions in lung function.

A 10-year longitudinal study of middle-aged men in Northern Ireland showed that the decline in lung function was greater in those who had the largest increases in BMI over the study period. The rate of decline in FEV_1 increased by 2.9 ml per year per unit increase in BMI over 10 years ($p<0.001$).[27]

Several studies agree that the effect of weight gain on lung function is greater in men than in women, probably due to gender-related differences in fat distribution (ie, the mechanical effect of central fat distribution on the diaphragm in men).[28 29] The mechanical effects of truncal obesity partly explain the reductions in chest wall compliance, respiratory muscle strength and function, lung volumes and peripheral airway size found in obese individuals.[30 31] Obesity has a modest effect on conventional respiratory function tests until the BMI is ⩾40 kg/m^2.[32] Abdominal fat may alter the pressure-volume characteristics of the thorax and restrict the descent of the diaphragm, thereby limiting lung expansion. This reduced ventilation at the lung bases can lead to the closure of peripheral lung units, ventilation to perfusion ratio abnormalities and arterial hypoxaemia, especially in the supine position.[33] The expiratory reserve volume is also reduced and the work of breathing is increased.[34] These changes can also lead to lower forced vital capacity (FVC) measurements. Obesity can lead to respiratory muscle inefficiency and creates a heightened demand for ventilation.[32]

Figure 1 Lambert Adolphe Quetelet (1796–1874). This image is taken from a Belgian stamp issued in his honour in 1974.

Body fat distribution is an important predictor of adverse health events such as diabetes, hypertension, hyperlipidaemia and coronary events.[35] The two main types of fat distribution are central and peripheral. In central obesity most of the fat deposits are in the abdominal area, both subcutaneous and visceral. These visceral fat deposits are highly correlated with cardiovascular risk.[1] In peripheral obesity the fat deposits are mainly located subcutaneously in the lower body. BMI is easily calculated from weight and height measurements but it does not give information on body fat distribution. Waist circumference and waist-hip ratio are also easy to measure and add vital information about the pattern of obesity. Waist circumference is a better assessor of metabolic risk than BMI because it is more directly proportional to total body fat and the amount of metabolically active visceral fat.[15] In a cross-sectional study of 1674 adults, waist circumference was negatively associated with FEV_1 and FVC. On average, an increase in waist circumference of 1 cm was associated with a 13 ml reduction in FEV_1 and an 11 ml reduction in FVC.[29] Abdominal adiposity—as measured by abdominal height, waist circumference and waist/hip ratio—is a better predictor of pulmonary function than weight

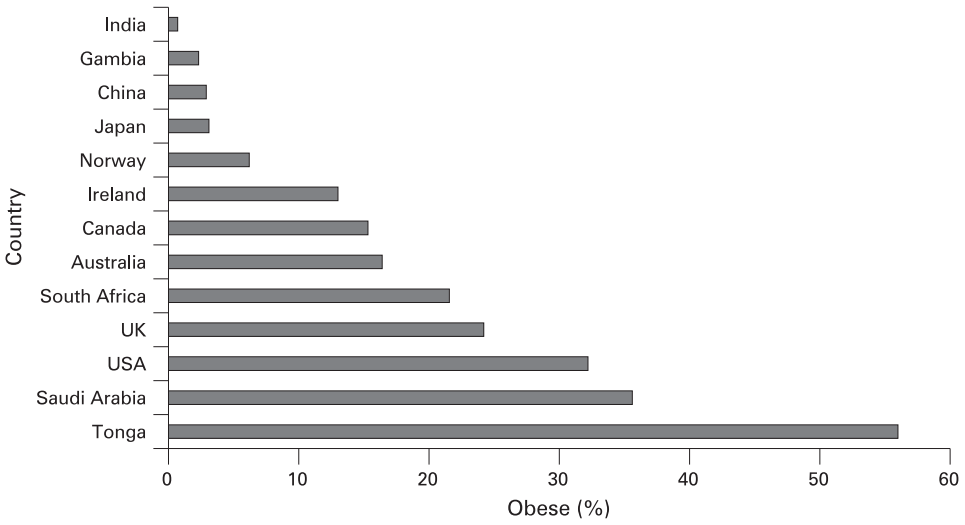

Figure 2 Prevalence of obesity in different countries. Graph adapted from the World Health Organization global database on body mass index (BMI) (most recent figures). The national BMI data displayed in this graph are empirical and have been verified. They apply internationally recommended BMI cut-off points. However, it is important to note that the data presented are not directly comparable since they vary in terms of sampling procedures, age ranges and the year(s) of data collection.

or BMI. Inverse associations between abdominal height and waist circumference and pulmonary function in men and women with BMI values of >25 kg/m^2 were also demonstrated.[36] A larger waist-hip ratio is more detrimental in men than in women.[37] Total body fat and central adiposity are inversely associated with lung function, but the amount of fat-free mass correlates positively with lung function with reduced odds of a low FEV_1:FVC ratio.[38 39]

Body fat distribution is linked to the metabolic effects of obesity. Adiposity is a low-grade inflammatory condition and is linked to insulin resistance.[40] Fat cells have been shown to act as a type of endocrine cell, and adipose tissue can be thought of as an endocrine organ. Central type obesity can lead to an imbalance in the production of several metabolic products, adipokines and cytokines, with a variety of local and peripheral effects.[41] It has been suggested that visceral adipose tissue influences circulating concentrations of interleukin-6, tumour necrosis factor-α, resistin, free fatty acids, leptin and adiponectin (fat cell-derived products). These cytokines may cause systemic inflammation which is thought to be involved in the association between reduced pulmonary function and cardiovascular mortality as well as all-cause mortality.[36]

Obese individuals have a tendency towards increased dyspnoea, decreased exercise capacity, decreased muscle mass, increased joint pain and skin friction.[32] These problems make physical exercise more difficult and uncomfortable, thus creating a vicious circle of inactivity and weight gain leading to further deconditioning.

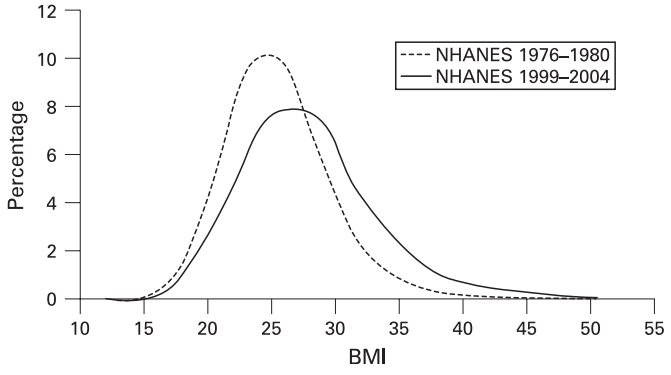

Figure 3 Change in the distribution of BMI between 1976–1980 and 1999–2004 for adults aged 20–74 years in the USA.[7]

IMPACT OF OBESITY ON RESPIRATORY DISEASE

Epidemiological studies of obesity usually rely on self-reported weight and height measurements. This risks inaccurate results due to under or overestimation.[42] Consistent methods of measurement can be difficult to achieve, particularly in longitudinal studies. Mortality statistics in the elderly may underestimate the effect of obesity as individuals may lose weight due to chronic illness as they get older and the effects of obesity during a lifetime may be underestimated.

Obesity and asthma

Obesity may increase the prevalence, incidence and severity of asthma, while weight loss in obese individuals improves asthma outcomes.[43 44] A meta-analysis of seven prospective epidemiological studies in which BMI was self-reported showed that the incidence of asthma increased by 50% in overweight/obese individuals. There was a dose-response relationship between body weight and asthma, with no significant gender disparity in the obesity-asthma relationship.[45] It has also been suggested, however, that this may be because obesity decreases lung volumes and increases airway resistance leading to symptoms that could mimic asthma.[46] Pooled data from three large epidemiological studies showed that subjects with severe obesity reported more wheeze and shortness of breath, suggesting a diagnosis of asthma. In contrast, levels of atopy, airway hyperresponsiveness and airway obstruction did not support a higher prevalence of asthma in this group.[47] The increase in breathlessness in obese individuals may be due to deconditioning or the increased work of breathing.[48] It is possible that changes in compliance or elastic recoil resulting from low lung volumes could decrease the tidal fluctuations of airway smooth muscle and enhance contractility.[49] In a study of randomly selected subjects aged 28–30 years, King *et al* reported that, with increasing BMI, airways were narrower than expected on the basis of the reduction in lung volume, suggesting that there were structural or functional changes in the airways that were specifically associated with this increase.[50] Less controversial is the possibility that asthma may lead to obesity because of fear of exercise or the inability to exercise regularly. Long-term steroids increase appetite and may lead to weight gain which may worsen already established asthma.[51] This treatment, which clearly improves asthma in the short term, can lead to a reduction in lung function in the long term secondary to weight gain.

There are cross-sectional associations between indices of self-reported physical activity and FEV_1 independent of age, height and BMI.[52]

Obesity and COPD

Respiratory muscle strength and lung function are closely associated with body weight and lean body mass in patients with COPD.[23] Nishimura *et al* also reported an association between weight gain and increasing rate of decline of FEV_1. However, patients with COPD have significantly less muscle mass than healthy controls, suggesting that BMI alone is insufficient to assess nutritional status in these individuals. It is possible that malnutrition may exist despite a normal BMI.[53] BMI tends to be lower in patients with COPD than in normal controls, particularly in those who still smoke. It must be noted that there is a tendency towards increased mortality in patients with COPD who are underweight. BMI tends to decrease as stage of disease increases.[54] These factors emphasise the importance of keeping BMI in the normal range in the COPD population.[55]

Obesity and sleep-disordered breathing

Obesity is the major risk factor for obstructive sleep apnoea (OSA) and around 50–70% of those with OSA are obese.[56] The prevalence of OSA among obese individuals is approximately 40%.[56] Increased fat tissue deposition in the pharyngeal region and reduced operating lung volumes in obesity act together to reduce the upper airway calibre, modify airway configuration and increase their collapsibility. Airways are thus predisposed to repetitive closures during sleep.[57] BMI, neck circumference and the size of the retroglossal space are the main determinants of OSA. Individuals with OSA are at greater risk of hypertension, stroke and other cardiovascular diseases. Symptoms of snoring, daytime somnolence, headaches and restless sleep can lead to occupational and social problems.

Upper airway neuromuscular activity decreases with sleep, and in patients with OSA this decrease may be more pronounced and lead to upper airway obstruction, particularly if the patient has an upper airway predisposed to collapse for anatomical reasons. Obesity hypoventilation syndrome (OHS) consists of a combination of obesity and chronic hypercapnia accompanied by sleep-disordered breathing.[58] Compared with patients with OSA, patients with OHS have a lower quality of life, higher healthcare expenses and a greater risk of pulmonary hypertension.

Obesity and perioperative complications

As obesity increases in prevalence, more obese patients will require surgical care of all descriptions. Some postoperative complications are more frequent among the obese (eg, surgical site infection and atelectasis).[59 60] This may be secondary to tension and secondary ischaemia along suture lines, immune impairment[61] and decreased oxygen tension.[62] Specialised beds and equipment are often needed to accommodate the extra body weight.[63] The use of some new technologies is restricted by the physical size of some patients.

Obesity is associated with a hypercoagulable state as there are increased levels of fibrinogen, factor VIII and von Willebrand factor.[64] Along with increased intra-abdominal pressure and venous stasis in obese individuals, this contributes to a link between perioperative deep venous thrombosis, pulmonary embolism and obesity. Surgical procedures which involve prolonged immobility are associated with greater risk.[59] Difficulties with endotracheal intubation and airway management are more common in obese individuals. A large neck predicts problematic intubation.[65] Larger anaesthetic doses are often needed to combat a greater volume of distribution and various ventilator techniques may be employed to improve oxygenation (eg, positive end-expiratory pressure).

Abdominal or thoracic operations are a significant risk to obese patients. Atelectasis has been found in up to 45% of obese patients following upper abdominal surgery.[66] Obesity affects the pharmacokinetics and pharmacodynamics of many drugs due to changes in tissue distribution, haemodynamics and blood flow to adipose, splanchnic and other tissues. Plasma composition and liver and kidney function are also altered.[67] In patients with OSA, preoperative initiation and perioperative use of continuous airway pressure can reduce hypercarbia, hypoxaemia, and pulmonary artery vasoconstriction to decrease the incidence of pulmonary complications.[59]

Obese patients with diabetes should have strict perioperative glycaemic control.[68] Early ambulation is vital in all obese patients to reduce the risk of thrombosis and pulmonary dysfunction.

Obesity and smoking cessation

Lung function after smoking cessation is significantly influenced by weight gain, an effect more marked in men than in women. This may be because men tend to preferentially increase abdominal fat compared with women when they gain weight.[69] In a study by Williamson *et al*, black patients, those under the age of 55 and people who smoked 15 cigarettes or more per day were at higher risk of major weight gain after quitting smoking.[70] Data from the third NHANES showed that weight gain associated with the cessation of smoking over a 10-year period was 4.4 kg for men and 5.0 kg for women.[71] The deleterious effects of weight gain are small, however, in comparison with the beneficial effects of smoking cessation.[72] Nevertheless, fear of weight gain may contribute to reluctance to quit smoking and the issue should therefore be addressed in smoking cessation programmes.

MANAGEMENT OF OBESITY

Individuals

The NICE guidelines on obesity emphasise that energy intake from food should not exceed the energy expended through everyday activities and exercise.[73] An ideal diet should include low-fat and fibre-rich foods, breakfast and at least five portions of fruit and vegetables each day. Calories from alcohol should be minimised and portion sizes controlled. It is recommended that activity should be built into the working day and that sedentary activities should be curtailed. Counselling and peer support groups are encouraged. New behaviour patterns must be established to achieve sustained weight loss. Self-monitoring, identifying internal triggers for eating and the creation of coping strategies are possible behaviour modification techniques. Drug treatments such as orlistat and sibutramine may be useful in some cases.

Bariatric surgery is only recommended if the individual has a BMI of 40 kg/m^2 or more (or 35 kg/m^2 or higher in a patient with a high-risk condition such as sleep apnoea) and other strict suitability criteria are fulfilled. These include previous attempts to lose weight and the absence of medical and psychological contraindications.[73] Given the significant improvements in sleep apnoea, hypertension, hyperlipidaemia and diabetes which have been reported 2 years after surgery, perhaps we are not

considering this option in enough patients.[74] A multidisciplinary environment with medical, surgical, nutritional and psychological input is essential to achieve success.[75]

Population

National policies are required to provide more opportunities for physical activity and greater accessibility of healthy foods. All sections of society need to be involved—the media, private businesses, food producers, supermarkets and government sectors. Local authorities are encouraged to provide play areas, cycling and walking routes. Local shops should be advised regarding the promotion of healthy foods and drinks. Schools and nurseries need to help to develop lifelong healthy eating and physical activity patterns.[73]

CONCLUSION

Obesity has multiple detrimental effects on the respiratory system. Weight loss can reverse many of these problems. Challenges in achieving weight loss include the genetic predisposition to weight gain, high fat and sugar diets and reduced physical activity. Our ''obesogenic'' environment needs to change: processed foods are cheaper and more convenient and more people live in urban areas and travel by car.

The costs of obesity prevention and treatment are high but, if action is not taken now, its prevalence will continue to rise and the morbidity and mortality costs of obesity will become even more overwhelming.

Funding: KMM is funded by the Research and Development Office.

Competing interests: None.

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Lung alert

Lysophosphatidic acid is an important mediator of fibroblast recruitment in IPF

Lysophosphatidic acid (LPA) and its G protein-coupled receptor (LPA1) play key pathogenic roles in idiopathic pulmonary fibrosis (IPF). Previous research has highlighted the importance of fibroblast chemoattractant activity in the lungs in patients with IPF. New findings suggest the LPA-LPA1 pathway has a pivotal role in mediating fibroblast migration and vascular leakage in IPF. The end result is the aberrant healing process that characterises this fibrotic condition.

Using an experimental bleomycin-induced lung injury mouse model, the investigators showed that LPA levels were high in bronchoalveolar lavage samples compared with unexposed controls. They also showed that LPA1 knockout mice were protected from fibrosis after bleomycin challenge with reduced fibroblast accumulation and vascular leakage.

Similar findings were reproduced in human subjects; nine patients with IPF had high LPA levels in bronchoalveolar lavage samples compared with seven healthy controls. Increased fibroblast chemotactic activity in these samples was inhibited by a specific LPA1 antagonist, Ki16425, suggesting that fibroblast migration is mediated by the LPA-LPA1 pathway.

These experimental and clinical findings suggest that the LPA-LPA1 pathway is crucial in fibroblast recruitment and vascular leakage in IPF. It provides a novel therapeutic target in this generally refractory disease. Only a small number of subjects were studied, so the relative importance of this pathway needs to be confirmed. As fibroblast proliferation persists in bleomycin-challenged LPA1 knockout mice, the evidence suggests that IPF is mediated by other pathogenic factors.

► Tager AM, LaCamera P, Shea BS, *et al*. The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nat Med* 2008;**14**:45–54.

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