Health risks associated with obesity

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Obesity is defined clinically as a state of increased body weight, more specifically of increased fat tissue mass. It is associated with increased fat cell size and number, and is usually followed by serious health consequences if not controlled. Body weight and the storage of energy as triglyceride in adipose tissue are determined by the interaction between genetic, metabolic, environmental, and psychological factors. These influences ultimately act by changing the balance between energy intake and expenditure.[1]

Obesity is a prevalent health hazard, both in developed and developing countries, and is associated with a number of pathological disorders, including hypertension, type 2 diabetes mellitus, cardiovascular disease (CVD), cancer, gallstones, respiratory system problems, and sleep apnoea. The degree of health impairment is determined by three factors: first is the amount of fat, second is the distribution of fat and third is the presence of other risk factors. The fat deposition may be generalised, or may occur preferentially in different adipose tissue compartments. Two major variants of obesity are distinguished for their differential impact on morbidity, viz. truncal and peripheral obesity.[2]

Predominant accumulation of fat in the truncal area, which includes subcutaneous and visceral fat divisions, is the main feature of android obesity. This form of obesity is more often found in men and is associated with high risk of CVD, independent of generalised adiposity. Accumulation of fat in the gluteofemoral area is the main feature of gynoid obesity, which is more frequently found in premenopausal women and apparently is not associated with increased risk of CVD.[2]

Hypertension

According to the World Health Organization (WHO), up to 20% of the population in developed countries may suffer from obesity-associated hypertension.[3] Obesity alone possibly accounts for 78% and 65% of essential hypertension in men and women respectively.[4] The prevalence of high blood pressure in obese adults is 38.4% for men and 32.2% for women, compared with 18.2% for men and 16.5% for women with a body mass index (BMI) less than 25 kg/m^2.[5]

Some of the major characteristics associated with obesity-associated hypertension in humans are activation of the renin-angiotensin system,[6-8] high levels of circulating leptin[5, 9] and activation of the sympathetic nervous system.[6, 9] Leptin may be an important factor in the aetiology of obesity-associated hypertension as it increases sympathetic activity and may mediate increases in catecholamines and activation of the renin-angiotensin system. Angiotensin II levels are high in obesity, which may result from the secretion of angiotensinogen from adipocytes[10] and the presence of increased glomerular pressures suggest activation of the renin-angiotensin system.[11]

Studies have shown that losing weight leads to decreased blood pressure. Weight loss is associated with reductions in vascular resistance, total blood volume and cardiac output, improvement in insulin resistance, reduction in sympathetic nervous system activity, and suppression of the activity of the renin-angiotensin-aldosterone system.[9]

Diabetes mellitus

The association between obesity and type 2 diabetes mellitus is well recognised.[12] A majority of patients with type 2 diabetes are obese, approximately 85 - 95% in most population studies.[13] However only 10% of obese patients are diabetic,[14] suggesting that obesity alone is not sufficient to cause type 2 diabetes. Other factors are also required, most especially islet beta-cell dysfunction.[15]

The risk of developing diabetes increases by approximately 25% for each additional unit of BMI over 22 kg/m^2.[16] It has been found that weight gain is responsible for 27% of new cases of type 2 diabetes in the USA[17] and that the prevalence of type 2 diabetes correlates strongly (r = 0.64) with the prevalence of obesity.[18] Both cross-sectional[19-21] and longitudinal studies[22] have indicated that central obesity is a strong risk factor for type 2 diabetes.[21, 22]

Obesity increases insulin resistance and glucose intolerance and via these metabolic effects plays a major role in the pathophysiology of type 2 diabetes. Insulin resistance may present 10 - 20 years before onset of the disease, and is considered to be the best predictor of whether or not an individual will later become diabetic.[23] The mechanism by which obesity leads to insulin resistance is uncertain. However, much experimental evidence exists to demonstrate that adipocytes secrete a number of factors that may play a role in the control of

insulin sensitivity. These include adiponectin, interleukin-6 (IL-6), tumour necrosis factor α (TNF-α), resistin, free fatty acids and cortisol.[24] It has also been demonstrated that obesity leads to increased deposition of triglycerides within skeletal muscle and that the level of intramuscular triglyceride correlates negatively with insulin sensitivity.[25]

Obesity not only increases the risk of developing type 2 diabetes but also complicates its management. The presence of obesity exacerbates metabolic abnormalities of type 2 diabetes, including hyperglycaemia, hyperinsulinaemia and dyslipidaemia. Obesity may contribute to excessive morbidity in type 2 diabetics as the risk of developing hypertension and cardiovascular disease increase with the coexistence of obesity and diabetes.[13]

Coronary heart disease (CHD)

The negative effects of obesity on health and cardiovascular disease are well documented.[26-29] Body weight independent of traditional risk factors is directly related to the development of CHD. A study by Willett *et al*.[30] showed that overweight and obese women have an increased risk of CHD of 2- and 3.6-fold respectively. An increase in weight of up to 11 kg increases the risk of disease 1.6-fold, while an increase in weight of 11 - 19 kg increases the risk 1.9-fold. The risk of CHD increases 3-fold when the BMI passes 29 kg/m^2 compared with the risk in lean subjects.[30]

The nature of the postulated association between insulin resistance and CHD remains obscure. It has been suggested that tissue insulin resistance is the primary initiating defect that leads to compensatory hyperinsulinaemia and an increase in atherogenic risk factors.[31] Also, visceral adipose tissue, which has been shown to be associated with increased insulin resistance, is the strongest predictor of cardiovascular disease in white and African-American women.[29]

Increased body mass also has mechanical effects on the cardiovascular system. Total body oxygen consumption is increased as a result of expanded tissue mass and the oxidative demands of metabolically active adipose tissue, and this is associated with an absolute increase in cardiac output. Total blood volume is increased in proportion to body weight, and this will contribute to an increase in the left ventricular preload and an increase in resting cardiac output.[32] Increased cardiac output is achieved by an increase in stroke volume while the heart rate remains comparatively unchanged. The obesity-related increase in stroke volume results from an increase in diastolic filling of the left ventricle.[26] The volume expansion and increase in cardiac output leads to structural changes of the heart, and the increase in left ventricular filling results in an increase in the left ventricular cavity dimension and an increase in wall stress.[26]

Observational studies[33] have shown that obesity and excess abdominal fat are directly related to cardiovascular risk factors, including high levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, blood pressure, fibrinogen and insulin and low levels of high-density lipoprotein (HDL) cholesterol. It has also been suggested that both obesity and CHD are proinflammatory states and that adipose tissue secretes a number of proinflammatory cytokines that may be involved in the aetiology of CHD.[34]

Cancer

Breast cancer accounts for approximately 20% of all female cancers, with 80% of cases occurring in postmenopausal women.[35] More than 100 epidemiological studies have examined the relationship between breast cancer and BMI, fat distribution, and weight gain at different ages.[36] These studies have shown that women who were overweight or obese had a 30 - 50% greater risk of postmenopausal breast cancer development than leaner women. In contrast, overweight and obesity are associated with a lower risk of breast cancer developing during the premenopausal years. The International Agency for Research on Cancer (IARC) estimates that 25% of breast cancer cases worldwide are the result of obesity and a sedentary lifestyle.[37]

The Women's Health Initiative (WHI) Observational Study[38] is a multi-ethnic, multisite cohort study of women aged 50 - 79 years at study entry. Women underwent several measures of adiposity on entering the study. Analysis of these data showed that anthropometric factors were associated with breast cancer risk, but only among those women who had never used hormone replacement therapy (HRT).[38] The risk of developing breast cancer in obese women with BMIs above 31.1 kg/m^2 was 2.5 times higher than in women with BMIs less than 22.6 kg/m^2. Similarly, the Nurses Health Study[39] found a 60% greater risk of postmenopausal breast cancer associated with overweight and obesity in women who had never used HRT.

Data from cohort studies[38-40] demonstrate that abdominal obesity is associated with an approximate doubling of breast cancer risk among postmenopausal women, independent of BMI. In the WHI study,[38] a statistically significant trend of increasing breast cancer risk with increasing waist circumference, but not waist-hip ratio, was observed. This finding was limited to women who had never used HRT.[38]

Obese men and women have a much higher risk of developing colon cancer. Studies have shown that when the BMI is greater than 24 kg/m^2 the chances of developing colon cancer double and triple when the BMI passes 30 kg/m^2.[41] Colon cancer in men is positively associated with obesity, while in women this relationship is weaker.[42] Studies have shown that increased consumption of dietary fat, especially animal fat, is associated with the development of colon[43, 44] and colorectal cancer.[45]

A number of other cancer types have been found to be more prevalent in obese subjects. Obese women have a risk of endometrial cancer three times greater than women with normal weight.[46] Studies have also shown a positive association between prostate cancer and BMI,[47, 48] and body weight.[49] A Swedish study[50] detected a relationship between obesity and a number of different cancer types. The researchers detected a 33% excess incidence of cancer among the obese subjects (25% more among men and 37% more among women). The obese patients had an increased risk of Hodgkin's disease and cancers of the endometrium, kidney, gallbladder, colon, pancreas, bladder, cervix, ovary and brain.

The mechanism by which obesity may give rise to an increased risk of cancer is not known. However, it has been suggested that in the case of breast cancer the higher level of bioavailable oestrogen in obese subjects may play some role.[51]

Gallstones

Gallstones are concretions in the gallbladder or bile duct and are composed chiefly of a mixture of cholesterol, calcium bilirubinate and calcium carbonate; occasionally there are pure stones composed of just one of these substances. The prevalence of gallstones has been found to be high in obese subjects. The probability of gallstone formation increased 2.7-fold in women with BMIs above 40 kg/m^2 compared with women with BMIs less than 24.9 kg/m^2, while in men the probability increased 2.3-fold for the same categories.[52] The process by which obesity may lead to gallstone formation is not fully understood; however, it is known that precipitation of cholesterol within the bile is involved. This precipitation may be induced by a number of factors, including a cholesterol solubility defect, the presence of nucleating factors and increased residence time of bile within the gallbladder because of reduced mobility.[53] Gallstone formation is also associated with weight loss. The risk of gallstone formation increased from 44% when obese women lost 4 - 10 kg, to 94% when they lost more than 10 kg.[28] However, it has been suggested that it is the underlying obesity rather than the weight loss that is the predominant cause of gallstone formation.

Osteoarthritis

Osteoarthritis is characterised by erosion of articular cartilage, either primary or secondary to trauma or other conditions. The cartilage becomes soft, frayed, and thinned with eburnation of the subchondral bone and outgrowths of marginal osteophytes, pain and loss of function. This mainly affects weight-bearing joints, and is

more common in older people. Overweight or obese people are at high risk of developing osteoarthritis.[54-57] In a study[54] of twin, middle-aged women, it was estimated that for every kilogram increase in weight the risk of developing osteoarthritis increased by 9 - 13%, while another study[58] demonstrated that at least two-thirds of osteoarthritis patients were overweight at the time of their surgery.

Sleep apnoea and other respiratory system problems

Obesity has a negative effect on lung function. However, this effect differs according to the degree of obesity, the kind of obesity (abdominal or peripheral) and age. Studies on animals have shown that obesity affects the respiratory system by reducing total lung volume and functional residual capacity. Abdominal obesity causes pressure on the diaphragm, decreasing the ability of the lung to expand during inspiration, while accumulation of fat on the chest reduces the chest cavity space.[59, 60]

Sleep apnoea is characterised by recurrent episodes of cessation of respiratory airflow caused by occlusion in the upper airway during sleep, with a consequent decrease in oxygen saturation. Obesity is considered to be a very important factor affecting sleep apnoea. Many cross-sectional studies have confirmed the relationship between increased body weight and the risk of sleep apnoea.[61] Significant sleep apnoea is present in about 40% of obese individuals[62] and 70% of sleep apnoea patients are obese. In one study[63] a 10% increase in body weight was associated with a 6-fold increase in the risk of developing sleep apnoea. Health consequences such as arterial hypoxia, increased sympathetic tone, and pulmonary and systemic hypertension are usually associated with severe cases.[64]

The exact mechanisms underlying the relationship between obesity and sleep apnoea are still unclear. It may be related to the effect of fat deposition on airway anatomy or changes in upper airway function.[62] Weight loss has been shown to be associated with a decrease in upper airway collapsibility in obstructive sleep apnoea.[65]

A number of studies have demonstrated a relationship between BMI and the prevalence and severity of asthma in children and adults.[66] In the American Nurses Health Study II[67] BMI was found to be a positive predictor of asthma development, while a study from Finland[68] has shown that weight reduction in obese asthmatics leads to improvements in both lung function and asthma symptoms. However the role played by obesity in the aetiology of asthma is not known.

Obesity and reproductive function

Obesity is related to menstrual abnormalities, infertility and miscarriage. Obesity is associated with menstrual abnormalities including cycles longer than 36 days, irregular cycles, and virile hair growth with facial hair.[69] It has also been shown that the risk of subsequent ovulatory infertility is increased by elevated BMI at the age of 18 years, even in women who are not considered obese.[70]

Studies have reported that obesity during pregnancy is accompanied by increased hypertension, gestational diabetes, congenital malformations, and morbidity of both mother and child.[71, 72] Furthermore, induction of labour, delivery by emergency caesarean section, and postpartum haemorrhage are reported to be more common in obese pregnant women than in their normal counterparts.[72, 73] Spontaneous abortion is more common in pregnancies complicated by obesity, and can occur in pregnancies resulting from natural conception and from treatment with assisted reproductive technology (ART).[74] Obesity has also been demonstrated to reduce fertility substantially in the general population, and to reduce pregnancy rates greatly when using ART.[75, 76]

Polycystic ovary syndrome (PCOS) is the association of hyperandrogenism with chronic anovulation in women without specific underlying diseases of the adrenal or pituitary glands. PCOS is associated with obesity, particularly abdominal obesity.[77] Two important factors contribute to PCOS in obese women – the high production of oestrogen compared with their lean counterparts, and the low production of sex hormone-binding globulin (SHBG), which is accompanied by an elevated free biologically active fraction of oestradiol.[78] Insulin resistance is considered to be pivotal in the expression of PCOS, and is highly associated with abdominal obesity. Direct or indirect reduction in insulin concentrations increase ovarian activity[78] and the treatment of PCOS patients with insulin-sensitising agents leads to a reduction in androgen levels and improved ovulatory function.[79] Reduction in weight has been found to improve outcomes significantly for obese subjects. In one study[80] of obese infertile women who lost an average of 10.2 kg on a 6-month exercise and diet programme the majority resumed spontaneous ovulation and achieved pregnancy.

Obesity in South Africa

The prevalence of obesity is increasing worldwide, particularly in developing countries such as South Africa. This will inevitably lead to an increased prevalence of the diseases associated with obesity. Indeed, it has been shown that between the years 2000 and 2010, based on current trends, the prevalence of type 2 diabetes within Africa will increase by 50%.[81] This will put an increased financial burden on already overstretched health services. This can be illustrated by data from the USA showing that in 1998 overweight- and obesity-attributable medical spending accounted for 9.1% (equivalent to $78.5 billion) of total annual USA medical expenditure.[82] The prevalence of obesity in South Africa, as estimated using data collected in 1998,[83] was 10% for males and 30% for females, compared with data from the USA for the period 1999 - 2000 where the prevalence was 27.6% for men and 33.2% for women.[84] Therefore, the prevalence of obesity in South Africa is reaching a level similar to that in the USA, which has one of the highest prevalences of obesity in the world. Data also demonstrate that the prevalence of obesity-related disorders is high in South Africa. Metabolic syndrome, which is the grouping together of dyslipidaemia, insulin resistance, hypertension and abdominal obesity within the same individual, was found to be prevalent in 9.1% of black, 10.2% of white and 18.3% of Indian subjects resident in Johannesburg, and the prevalence increased with increasing BMI (N H Naran, N Chetty – unpublished data, 2005). The Medical Research Council[85] has also published data showing that cardiovascular disease and diabetes mellitus are the second and tenth leading causes of death in South Africa, respectively. Obesity-related diseases are therefore a prime cause of morbidity and mortality in South Africa and their contribution to the national burden of disease cannot be ignored.

1. Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. *Cell* 2001; **104:** 531-543.
2. Bray GA. Risks of obesity. *Endocrinol Metab Clin North Am* 2003; **32:** 787-804.
3. Baynes J, Dominiczak MH. *Medical Biochemistry*. London: Mosby, 2003.
4. Garrison RJ, Kannel WB, Stokes J, *et al.* Incidence and precursors of hypertension in young adults: the Framingham Offspring study. *Prev Med* 1987; **16:** 234-251.
5. Hirose H, Saito I, Tsujioka M, Mori M, Kawabe H, Saruta T. The obese gene product, leptin: possible role in obesity-related hypertension in adolescents. *J Hypertens* 1998; **16:** 2007-2012.
6. Hall JE, Hildebrandt DA, Kuo J. Obesity hypertension: role of leptin and sympathetic nervous system. *Am J Hypertens* 2001; **14:** 103S-115S.
7. Hall JE, Louis K. Dahl Memorial lecture: Renal and cardiovascular mechanisms of hypertension in obesity. *Hypertension* 1994; **23:** 381-394.
8. Domfeld LP, Maxwell MH, Waks A, Tuck M. Mechanisms of hypertension in obesity. *Kidney Int Suppl* 1987; **22:** S254-S258.
9. Hall JE, Crook ED, Jones DW, *et al.* Mechanisms of obesity-associated cardiovascular and renal disease. *Am J Med Sci* 2002; **324:** 127-137.
10. Engeli S, Schling P, Gorzelniak K, *et al.* The adipose-tissue renin-angiotensin-aldosterone system: role in the metabolic syndrome? *Int J Biochem Cell Biol* 2003; **35:** 807-825.
11. Reaven G. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. *Circulation* 2002; **106:** 286-288.
12. Björntorp P. Regional obesity and NIDDM. *Adv Exp Med Biol* 1993; **334:** 279-285.
13. Maggio CA, Pi-Sunyer FX. Obesity and type 2 diabetes. *Endocrinol Metab Clin North Am* 2003; **32:** 805-822.
14. Nadler ST, Stoehr JP, Schueler KL, Tanimoto G, Yandell BS, Attie AD. The expression of adipogenic genes is decreased in obesity and diabetes mellitus. *Proc Natl Acad Sci USA* 2000; **97:** 11371-11376.
15. Bell GI, Polonsky KS. Diabetes mellitus and genetically programmed defects in b-cell function. *Nature* 2001; **414:** 788-791.
16. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995; **122:** 481-486.
17. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol* 1997; **146:** 214-222.
18. Mokdad AH, Ford ES, Bowman BA, *et al.* Diabetes trends in the US 1990 - 1998. *Diabetes Care* 2000; **23:** 1278-1283.
19. Despres JP, Nadeau A, Tremblay A, *et al.* Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. *Diabetes* 1989; **38:** 304-309.
20. Haffner SM, Mitchell BD, Hazuda HP, Stern MP. Greater influence of central distribution of adipose tissue on incidence of non-insulin-dependent diabetes in women than men. *J Clin Nutr* 1991; **53:** 1312-1317.
21. Sparrow D, Borkan GA, Gerzof SG, Wisniewski C, Silbert CK. Relationship of fat distribution to glucose tolerance. Results of computed tomography in male participants of the Normative Aging Study. *Diabetes* 1986; **35:** 411-415.
22. Chan JM, Rimm EB, Colditz GA, Stamfer MJ, Willett WC. Obesity, fat distribution, and weight gain as a risk factor for clinical diabetes in men. *Diabetes Care* 1994; **17:** 961-969.
23. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type 2 diabetes in the offspring of diabetic patients. *Ann Intern Med* 1990; **113:** 909-915.

24. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000; **11:** 327-331.
25. Sinha R, Dufour S, Petersen KF, *et al.* Assessment of skeletal muscle triglyceride content by (1)H nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insulin sensitivity, total body fat, and central adiposity. *Diabetes* 2002; **51:** 1022-1027.
26. Wikstrand J, Pettersson P, Björntorp P. Body fat distribution and left ventricular morphology and function in obese females. *J Hypertens* 1993; **11:** 1259-1266.
27. Lovejoy JC, de la Bretonne JA, Klemperer M, Tulley R. Abdominal fat distribution and metabolic risk factors: effects of race. *Metabolism* 1996; **45:** 1119-1124.
28. Jung RT. Obesity as a disease. *Br Med Bull* 1997; **53:** 307-321.
29. Lovejoy JC, Smith SR, Rood JC. Comparison of regional fat distribution and health risk factors in middle-aged white and African American women: the healthy transition study. *Obes Res* 2001; **9:** 10-16.
30. Willett WC, Manson JE, Stampfer MJ, *et al.* Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. *JAMA* 1995; **273:** 461-465.
31. Laws A, Reaven GM. Insulin resistance and risk factors for coronary heart disease. *Baillieres Clin Endocrinol Metab* 1993; **7:** 1063-1078.
32. de Divitiis O, Fazio S, Petitto M, Maddalena G, Contaldo F, Mancini M. Obesity and cardiac function. *Circulation* 1981; **64:** 477-482.
33. Klein S, Burke LE, Bray GA, *et al.* American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American College of Cardiology Foundation. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation* 2004; **110:** 2952-2967.
34. Poirier P, Eckel RH. Obesity and cardiovascular disease. *Curr Atheroscl Rep* 2002; **4:** 448-453.
35. Pharoah PD, Stratton JF, Mackay J. Screening for breast and ovarian cancer: the relevance of family history. *Br Med Bull* 1998; **54:** 823-838.
36. Friedenreich CM. Review of anthropometric factors and breast cancer. *Eur J Cancer Prev* 2001; **10:** 15-32.
37. International Agency for Research on Cancer Working Group on the Evaluation of Cancer-Preventive Agents, Weight Control and Physical Activity. *IARC Handbooks of Cancer Prevention*. Vol. 6. Lyon, France: IARC, 2002.
38. Morimoto LM, White E, Chen Z, *et al.* Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control* 2002; **13:** 741-751.
39. Huang Z, Hankinson SE, Colditz GA, *et al.* Dual effects of weight and weight gain on breast cancer risk. *JAMA* 1997; **278:** 1407-1411.
40. Sellers TA, Kushi LH, Potter JD, *et al.* Effect of family history, body fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. *N Engl J Med* 1992; **326:** 1323-1329.
41. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin* 2003; **53:** 5-26.
42. Lew EA, Garfinkel L. Variations in mortality by weight among 750 000 men and women. *J Chronic Dis* 1979; **32:** 563-576.
43. Tavani A, Pelucchi C, Parpinel M, *et al.* n-3 polyunsaturated fatty acid intake and cancer risk in Italy and Switzerland. *Int J Cancer* 2003; **105:** 113-116.
44. Reddy BS. Novel approaches to the prevention of colon cancer by nutritional manipulation and chemoprevention. *Cancer Epidemiol Biomarkers Prev* 2000; **9:** 239-247.
45. Lin J, Zhang SM, Cook NR, Lee IM, Buring JE. Dietary fat and fatty acids and risk of colorectal cancer in women. *Am J Epidemiol* 2004; **160:** 1011-1022.
46. Schottenfeld D, Fraumeni JF. *Cancer Epidemiology and Prevention*. New York: Oxford University Press, 1996.
47. Andersson SO, Wolk A, Bergstrom R, *et al.* Body size and prostate cancer: a 20-year follow-up study among 135 006 Swedish construction workers. *J Natl Cancer Inst* 1997; **89:** 385-389.
48. Talamini R, La Vecchia C, Decarli A, Negri E, Franceschi S. Nutrition, social factors and prostate cancer in a northern Italian population. *Br J Cancer* 1986; **53:** 817-821.
49. Snowdon DA, Philips RL, Choi W. Diet, obesity, and risk of fatal prostate cancer. *Am J Epidemiol* 1984; **120:** 244-250.
50. Wolk A, Gridley G, Svensson M, *et al.* A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* 2001; **12:** 13-21.
51. Hulka B, Liu E, Lininger R. Steroid hormones and risk of breast cancer. *Cancer* 1994; **74:** 1111-1124.
52. Everhart JE, Khare M, Hill MC, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology* 1999; **117:** 632-639.
53. Busch N, Matern S. Current concepts in cholesterol gallstone pathogenesis. *Eur J Clin Invest* 1991; **21:** 453-460.
54. Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and the knee in women: a twin study. *J Rheumatol* 1996; **23:** 1221-1226.
55. Hochberg MC, Lethbridge-Cejku M, Scott WW jun., Reichle R, Plato CC, Tobin JD. The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: data from the Baltimore Longitudinal Study of Aging. *J Rheumatol* 1995; **22:** 488-493.
56. Carman WJ, Sowers M, Hawthorne VM, Weissfeld LA. Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. *Am J Epidemiol* 1994; **139:** 119-129.
57. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med* 1988; **109:** 18-24.
58. Marks R, Allegrante JP. Comorbid disease profiles of adults with end-stage hip osteoarthritis. *Med Sci Monit* 2002; **8:** CR305-309.
59. Ray C, Sue D, Bray G, *et al.* Effect of obesity on respiratory function. *Am Rev Respir Dis* 1983; **128:** 501-506.
60. Lazarus R, Sparrow D, Weiss ST. Effects of obesity and fat distribution on ventilatory function: the normative aging study. *Chest* 1997; **111:** 891-898.
61. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep disordered breathing among middle aged adults. *N Engl J Med* 1993; **328:** 1230-1235.
62. Vgontazas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. Sleep apnea and sleep disruption in obese patients. *Arch Intern Med* 1994; **154:** 1705-1711.
63. Peppard PE, Young T, Palta M, Dempsy J, Skaturd J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000; **284:** 3015-3021.
64. Millman RP, Carlisle CC, McGarvey ST, Eveloff SE, Levinson PD. Body fat distribution and sleep apnea severity in women. *Chest* 1995; **107:** 362-366.
65. Schwartz AR, Gold AR, Schubert N, *et al.* Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991; **144:** 494-498.
66. Motala A, Omar M, Pirie F. Epidemiology of type 1 and type 2 diabetes in Africa. *J Cardiovasc Risk* 2003; **10:** 77-83.
67. Camargo CA jun., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999; **159:** 2582-2588.
68. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000; **320:** 827-832.
69. Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA. The association of obesity with infertility and related menstrual abnormalities in women. *Int J Obes* 1979; **3:** 57-73.
70. Rich-Edwards JW, Goldman MB, Willett WC, *et al.* Adolescent body mass index and infertility caused by ovulatory disorder. *Am J Obestet Gynecol* 1994; **171:** 171-177.
71. Johnson SR, Kolberg BH, Varner MW, Railsback LD. Maternal obesity and pregnancy. *Surg Gynecol Obstet* 1987; **164:** 431-437.
72. Prentice A, Goldberg G. Maternal obesity increases congenital malformations. *Nutr Rev* 1996; **54:** 146-152.
73. Sebire NJ, Jolly M, Harris JP, *et al.* Maternal obesity and pregnancy outcome: a study of 287 213 pregnancies in London. *Int J Obesity* 2001; **25:** 1175-1182.
74. FIVNAT (French In Vitro National). Pregnancies and births resulting from *in vitro* fertilization: French national registry, analysis of data 1986 to 1990. FIVNAT (French In Vitro National). *Fertil Steril* 1995; **64:** 746-756.
75. Norman RJ, Clark AM. Obesity and reproductive disorders: a review. *Reprod Fertil Dev* 1998; **10:** 55-63.
76. Wang JX, Davies M, Norman RJ. Body mass and probability of pregnancy during assisted reproduction treatment: a retrospective study. *BMJ* 2000; **321:** 1320-1321.
77. Franks S. Polycystic ovary syndrome. *N Engl J Med* 1995; **333:** 853-861.
78. Pettigrew R, Hamilton-Fairley D. Obesity and female reproductive function. *Br Med Bull* 1997; **53:** 341-358.
79. Seli E, Duleba AJ. Treatment of PCOS with metformin and other insulin-sensitizing agents. *Curr Diab Rep* 2004; **4:** 69-75.
80. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998; **13:** 1502-1505.
81. Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; **414:** 782-787.
82. Finkelstein EA, Fiebelkorn IC, Wang G. National medical spending attributable to overweight and obesity: how much, and who's paying? *Health Aff* 2003; **W3:** 219-226.
83. Puoane T, Steyn K, Bradshaw D, *et al.* Obesity in South Africa: The South African demographic and health survey. *Obes Res* 2002; **10:** 1038-1048.
84. Baskin ML, Ard J, Franklin F, Allison DB. Prevalence of obesity in the United States. *Obes Rev* 2005; **6:** 5-7.
85. Bradshaw D, Groenewald P, Laubscher R, *et al. Initial Burden of Disease Estimates For South Africa*, 2000. Cape Town: South African Medical Research Council, 2003.