The Journal of Nutrition, Health & Aging©
Volume 12, Number 9, 2008

MANAGEMENT OF OBESITY IN THE ELDERLY: TOO MUCH AND TOO LATE?

R.L. KENNEDY, U. MALABU, M. KAZI, V. SHAHSIDHAR

James Cook University School of Medicine, Queensland, Australia. Address for correspondence: Professor R.L. Kennedy. Department of MedicineJames Cook University; The Townsville Hospital, 100 Angus Smith Drive, Douglas, Queensland QLD 4814, Australia, Tel: 07-4796-1265, Fax: 07-4796-1271, Email: lee.kennedy@jcu.edu.au

Introduction

The prevalence of obesity is increasing globally. This with the aging population structure accounts for the increased prevalence of chronic diseases associated with obesity. For example, the number of people with diabetes in the world is projected to reach 300 million before 2025. Through childhood, adolescence, and adult life, obesity prevalence increases with age. However, the elderly (aged 60 plus), have a lower prevalence and in the extreme elderly (aged 80 plus), it is only a third of that in middle life. Obesity in the elderly presents a distinct problem. As at younger ages, it is associated with chronic diseases, and with functional and cognitive decline. However, the prevalence of being underweight is also a high and is itself a marker for poor health and functional decline. The ideal body weight and composition for elderly populations has yet to be defined. Weight management should be a target for certain elderly individuals whose health is at risk. However, in the elderly is important to maintain an optimal body composition as well as weight. Elderly individuals with weight-related diseases such as type 2 diabetes represent an obvious target for weight management. It is, in practice, difficult to identify elderly patients who would benefit from weight management programmes. The various components of the metabolic syndrome (MS) become more common with aging. Drugs to decrease cardiovascular risk and to treat diabetes and the other chronic diseases of aging have improved in recent years. The elderly are frequently prescribed complex drug regimens with which they often comply poorly, derive little benefit, and experience a high risk of adverse reactions and drug interactions. Although it is clear that obesity should be treated in high-risk elderly patients, pharmacotherapy and surgery do not have an evidence base specific to the elderly. There is emerging evidence to guide us with dietary and exercise therapy (1, 2). This review attempts to define the situations in which management of obesity is indicated, and to summarise what is known, and what is emerging, about the various treatment options.

The Scope of the Problem

The projected increased prevalence of overweight and obesity in the elderly (60 plus) in the United States between 2000 and 2010 is from 32.0% to 37.4%, reflecting an increase from 14.6 million to 20.9 million (3). The general prevalence of obesity, particularly abdominal obesity, has increased steadily in recent years – Figure 1 (4). Obesity is the most important modifiable risk factor after smoking, and may be overtaking smoking as a determinant of poor health. It is said that over 300,000 deaths annually in the United States are directly attributable to obesity. The impact of obesity on health and mortality risk is hard to estimate precisely because of the complex interplay with other factors, the lack of definition as to what constitutes obesity in the elderly, and the fact that most studies focus on BMI as an index of excess weight (5). Being either underweight or obese increases risk of death, but being modestly overweight may not increase risk for the elderly (6).

Evidence suggests that obesity prevalence continues to increase in the young and in men, although it may have reached a plateau in women (7). At least 32% of adults in the United States are obese, with extreme obesity (BMI $\geq$ 40 kg/m^2) affecting 2.8% of men and 6.9% of women. Obesity affects 30% of white non-Hispanic US citizens, 37% of Hispanic subjects and 45% of the black population (7). Diabetes is more than twice as likely to occur in Hispanic or Black Americans compared with Caucasians. The prevalence of diagnosed diabetes has increased from 5.1% to 6.5% (8). Prevalence of undiagnosed diabetes (2.8%) and impaired fasting glucose have remained static.

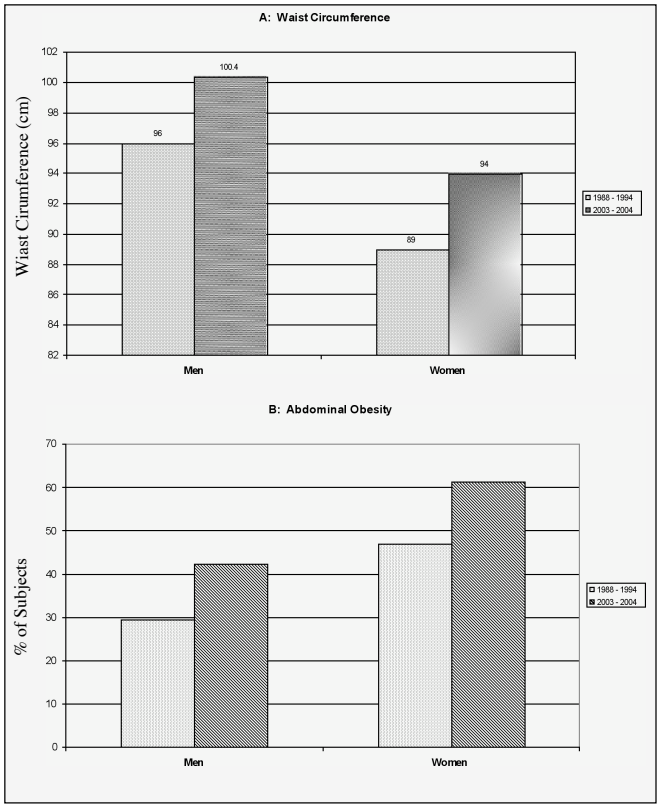
Expenditure on healthcare for obese individuals is likely to increase markedly. Costs are difficult to estimate for a number of reasons: The relative contributions of obesity and aging are hard to gauge; Expenditure on healthcare is increasing as new treatments become available, the evidence base favouring their use expands, and public expectations increase; it is not clear what the most appropriate clinical measures and reference ranges are for the elderly. The direct costs of managing people with obesity are particularly high in those with severe obesity (BMI $\geq$ 40 kg/m^2), accounting for over $11 billion annually in the US (9).

There is strong evidence that increased BMI is associated with risk of death. However, low BMI is also a risk, presumably because of the association with diseases which influence life expectancy (10-12). Both decreased energy expenditure (13) and increased body mass (10, 12) have been correlated with increased mortality. In the Physicians' Health Study, (10) over 85,000 males were followed up for five years, during which there were 2,856 deaths. Those who never

Received October 8, 2007
Accepted for publication October 13, 2007

smoked but had BMI > 30 kg/m^2 were at 70% increased risk of death. Both all-cause and cardiovascular mortality showed a clear relationship with BMI. Similarly, in a study of over 1.2 million Koreans, increased BMI was linked with increased mortality (12). Janssen and Mark (14) performed a meta-analysis of 28 studies and reported that overweight (but not obese) elderly subjects were not at increased risk, and that those who were only modestly obese had only slightly increased risk.

Figure 1
Increasing Prevalence of Abdominal Obesity



Data are from the National Health and Nutrition Examination Survey (NHANES) (4). A shows the increase in waist circumference from 1988-1994 to 2003-2004. B shows the increase in the prevalence of abdominal obesity.

Metabolic Syndrome (MS), Diabetes and Cardiovascular Risk

The precise definition of MS has been controversial. Currently, two definitions are widely used: The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) definition (2001) defines MS as any three from abdominal obesity (waist circumference $\geq$ 102 cm for men or $\geq$ 88 cm for women), increased triglycerides, decreased HDL-cholesterol, hypertension, or fasting plasma glucose $\geq$ 6.1 mmol/l. The International Diabetes Federation (IDF) definition (2005) is based on waist circumference $\geq$ 94 cm for men or $\geq$ 80 cm for women, plus any two of increased triglycerides, decreased HDL-cholesterol, hypertension, or fasting plasma glucose $\geq$ 5.6 mmol/l. However defined, MS is highly prevalent among the elderly (15-17). He et al. (15) reported a prevalence of 19.6% among men and 39.2% among women using the ATPIII. The corresponding figures using the IDF definition were 34.8% and 54.1%. Similar high prevalence has been reported in recent Swedish (18) and Italian (16) studies. As expected, the prevalence of MS factors is higher amongst those with diabetes (16).

MS is strongly associated with cardiovascular (CV) disease, (19, 20) including stroke (21) and peripheral vascular disease (22) in the elderly. Not surprisingly, MS predicts death, (23) although mortality prediction may not be so reliable in the elderly unless combined with other biological markers (e.g.cytokines) (24). Obesity itself is strongly correlated with decreased physical activity and function, with both increased fat and decreased muscle (sarcopenia) making independent contributions (25-28). Chronic inflammation and changes in adipokines may mediate the link between increased fat and functional decline (29). Higher CV risk profile is itself a predictor of functional decline (30, 31). The relationship between MS and impaired function may be apparent from early old age with simple measures such as gait speed, (32, 33) even in the absence of vascular events (34).

Increased body mass, particularly fat, strongly correlates with decreased quality of life in elderly men (35) and elderly women, (36) even after correcting for co-morbidities (37). Physical variables are particularly affected (38). There is a strong relationship between impaired quality of life and the functional decline (28, 34). The prevalence of MS components, except diabetes has decreased in the past four decades (39). MS variables are strongly predictive of type 2 diabetes in the elderly, (40) with both body mass and insulin resistance exerting overlapping but also independent influences (40, 41) Diabetes, diagnosed and undiagnosed, affects 9.3% of the US adult population and is a major determinant of quality of life (42) and disability (43). It seems self evident that prevention and effective management of diabetes should be one of the major goals of managing obesity.

Other Consequences of Obesity in the Elderly

Predisposition to a wide range of disease states is increased in the overweight or obese – Table 1. These should not be neglected when assessing the impact of obesity, and in planning social and medical management. After CV disease, cancer is the most common cause of death. Mortality from cancer increases with BMI (12, 44). It was estimated that the equivalent of 14% of cancers in men and 20% in women in the US could be attributed to obesity (44). A particular link between obesity and colorectal neoplasia has been documented in recent years (45). Obesity and diabetes are independent risk

factors, (46) and the inflammation and other metabolic changes may contribute. Low levels of exercise may also directly contribute: In the study by Larsson et al., (46) the hazard ratio for colorectal cancer was 0.57, comparing those who exercised for > 60 minutes per day with those who exercised for < 10 minutes.

Loss of muscle mass directly contributes to impaired function and mobility, (47) but through loss of muscle tone and joint protection, may also directly contribute to development of osteoarthritis (OA). Knee OA is more strongly associated with obesity than is hip OA (48, 49). In the Rotterdam study, (49) BMI of $\geq$ 27 kg/m^2 was associated with odds ratio of 3.3 for development of knee OA, and odds ratio of 3.2 for its progression. Decreased respiratory function also accompanies obesity, and is related to total BMI and abdominal obesity, (50) as well as with inflammatory markers (51). There is also a high incidence of obstructive sleep apnoea hypopnoea syndrome (OSAHS) in the elderly. Obesity and diabetes are contributory factors in many patients with OSAHS (52). Urinary symptoms are also very common in obese subjects, even without diabetes. In the Health, Aging and Body Composition study (53) urge and stress incontinence were increased in obese subjects. Nocturia may predispose to decreased quality of life through loss of sleep, and also to worsening obesity through increased nocturnal and daytime eating (54).

Dental disease is often overlooked as a cause of morbidity. Tooth loss, periodontal disease and poor masticatory performance can all cause under-nutrition, and attenuate the relationship between previous obesity and chronic disease. Tooth loss and periodontal disease, through low-grade systemic inflammation, have been linked with diabetes and CV risk. Gastro-oesophageal reflux disease (GORD) is common generally, and more likely to occur in the overweight or obese. Rey et al. (55) reported that a weight gain of < 5 kg increased OR of GORD by 1.5, while an weight increase > 5 kg was associated with an OR of 3.0. Non-alcoholic fatty liver disease (NAFLD) is increasingly recognised with obesity. This is often asymptomatic, and may only be recognised because of increased liver enzymes (56). NAFLD is, however, an important condition as it may lead to cirrhosis and hepatocellular carcinoma. Also, there is a strong association between NAFLD and the risk factors that constitute MS (57). Weight loss, however achieved, improves biochemical and histological features of NAFLD and consequently improves insulin resistance and dyslipidaemia. Specific trial data with NAFLD as a therapeutic target are somewhat lacking (58).

Table 1
Health Consequences of Obesity in the Elderly

Metabolic syndrome	Ischaemic heart disease
Type 2 diabetes	Stroke
	Peripheral vascular disease
Increased cancer risk	
Visual failure – diabetic retinopathy, cataract, macular degeneration	
Functional decline	Impaired quality of life
Cognitive decline	Social isolation
Anxiety, depression	
Poor respiratory function	Obstructive sleep apnoea
Osteoarthritis	
Gastro-oesophageal reflux	Non-alcoholic fatty liver disease
Urinary symptoms	Endocrine disorders

Age-related macular degeneration (AMD) is an important cause of visual deterioration with aging. AMD may not be more common in overweight or obese subjects, but progression of the condition is more rapid in those with higher body mass (59, 60). A recent study from the Women's Health Initiative (61) has demonstrated that high CV risk is associated with advanced AMD, with smoking, high BMI and hypertension being particularly important. There may be an interaction between obesity and genetic factors, including variations in the complement factor H (CFH) in determining susceptibility to progression of AMD (62, 63) Systemic inflammation (increased levels of IL-6 and CRP) is also related both to obesity and progression of AMD (64). Extreme obesity has also been identified as a possible risk factor for cataract (65).

MS is a recognised risk factor for cognitive decline and dementia, particularly in elderly women (66, 67). This risk extends to patients with diabetes (68) where both hypo- and hyper- glycaemia may contribute to impaired mental functioning. Cognitive decline is highly predicative of functional decline (69). The Health, Aging and Body Composition study (70) confirmed a strong association between mental and physical decline. A recent meta-analysis (71) suggested that high BMI was an independent risk factor for dementia, although other authors (72) have proposed a protective effect of obesity because of increased exposure to endogenous oestrogen.

In relatively low-risk and independently functioning individuals, primary management of obesity seems reasonable, particularly if there is potential for favourable change in diet and exercise. In patients at moderate to high risk e.g. those with poorly controlled diabetes or established vascular disease, specific management of their disease states is appropriate with weight management as a secondary goal. At the extreme end of the aging spectrum, frailty syndrome (not always directly related to chronological age) is characterised by weakness, exhaustion, slowness, and low levels of activity. Development of this syndrome is accelerated in subjects with pre-existing obesity (73, 74) It may be difficult to offer anything more than supportive care in such cases.

Body Composition and Biochemical Changes with Aging

Obesity in aging is accompanied by increasing mass and altered distribution of fat, along with decreased muscle mass and function. Sarcopenia predisposes to decreased performance in activities of daily living, (75) increased physical disability, (47) and development of the frailty syndrome (76). Loss of muscle mass also correlates with decreased bone quality, presumably because of decreased mechanical stresses (77). On the other hand, loss of muscle mass may protect against development of CV risk factors in elderly obese subjects (78). The issue is not simply loss of muscle tissue with consequent weakness of muscle groups, but other qualities of muscle such as fatigability may be affected, and may not be entirely reversed by treatments which preserve or restore muscle mass (79, 80). It is clearly important that measures to treat obesity in the elderly decrease fat mass while preserving muscle mass. Skeletal muscle mass is an important determinant of basal metabolic rate. Resting energy expenditure of typically 3.5 ml/min/kg may overestimate the energy expenditure of elderly subjects, irrespective of body composition (81, 82).

Fat mass not only increases with age but the distribution changes with increased accumulation in the abdominal and subscapular depots (83). Increased abdominal fat correlates strongly with MS and other CV risk factors, while peripheral adiposity in the typical female distribution may be protective (84). General adiposity of the elderly population has increased in recent years because of social changes and differences in dietary and other habits (85). Nonetheless, the level of adiposity associated with increased risk to health may be higher in the elderly than in younger age groups (86). Along with increased fat deposition in traditional fat depots, those with obesity develop ectopic fat deposition in including in the liver leading to NAFLD and within muscle leading to insulin resistance (87).

Adipokines are hormones produced in adipose tissue, and which mediate interactions with other tissues. Adipokine measurements have not, to date, proved useful in routine clinical practice. As with younger subjects, circulating leptin levels increase in the elderly in relation to fat mass, and increased levels correlate with the presence of MS (88). Leptin is involved in regulating appetite but also in other processes including inflammation and bone turnover (89). Resistin is also increased in obesity, including in the elderly, and correlates with MS (90). In younger subjects ghrelin, an orexigenic mediator, levels decrease with obesity. This relationship is attenuated in the elderly (91). Low levels of adiponectin occur in elderly obese subjects (92, 93) and are associated with risk of diabetes and CV disease. Higher levels in the extreme elderly have suggested that the hormone may have a role in regulating longevity (94). While the association of low adiponectin with CV risk is established, (95) its role as an independent predictor of events has been questioned (96). Leptin and adiponectin levels return towards normal when elderly obese subjects undergo exercise training, (97) suggesting that they could be used as surrogate markers for treatment response.

Many chronic disease states are accelerated by low-grade inflammation. In the elderly, inflammatory markers are increased with abdominal obesity, (98) metabolic syndrome, (99) or type 2 diabetes (100). In these high-risk groups, increased inflammatory markers (e.g. C-reactive protein or interleukin-6) are highly predictive of functional decline (100, 101). The association with other disease states make it not surprising that inflammatory markers are often increased in those who are nearing the end of life (102). As with adipokines, inflammatory markers have not yet been used routinely to indicate high-risk from obesity or to monitor treatment response.

Hormonal Changes and the Prospects for Endocrine Treatment

A number of endocrine changes take place in midlife and the ensuing years. Many of these tend to occur at an earlier age in the obese and may be more exaggerated. Collectively, we term these changes Obesity-related Endocrinopathy (ORE) - Table 1. Important alterations occur in secretion of sex steroids, the growth hormone/IGF-I axis, thyroid hormones, cortisol and in the regulation of calcium.

The most obvious endocrine change is the female menopause, which typically occurs around age 52. Women now spend up to 40% of their life in an oestrogen deficient state. It should not be assumed that all hormone changes around the menopause are related to oestrogen withdrawal and could, therefore, be reversed by oestrogen replacement. A number of recent sequential studies have clarified the changes in body composition and metabolism which accompany the menopause, but the influence of hormone replacement therapy has varied in different studies (103, 104). Following menopause there is an increase in fat mass with a shift towards upper body obesity, a decrease in lean body mass and skeletal mass. The Study of Women's Health across the Nation (SWAN) has documented changes in body composition over six years in the absence of hormone replacement therapy (HRT) (105). Total fat mass increased by 6.0 kg with a 5.7 cm increase in waist circumference, while skeletal mass decreased by 0.23 kg. Average weight gain was 9.0 kg, corresponding to a 1.2 kg/m^2 increase in BMI. Decreased muscle mass may be an important determinant of skeletal loss while increased central obesity leads to increased leptin and free androgen index (77, 106-108). Increased fat and loss of muscle, along with co-morbidities associated with obesity, are strong markers for disability and diminished quality of life (28, 36). Increased central fat mass may make an important contribution to oestrogen status by conversion from circulating androgens, and that this may protect against cognitive decline (109). Eating frequency is a determinant of overall energy intake but appears not to greatly influence adiposity in pre-menopausal women but correlates with adiposity in post-menopausal women (110).

Table 2
Obesity-related Endocrinopathy (ORE)

Decreased oestrogen (women)	Decreased testosterone (men)
Low SHBG	Decreased DHEA (men and women)
Low growth hormone (GH)	Low insulin-like growth factor-1 (IGF-1)
Increased prolactin	
Changes in thyroid hormones (see text)	
Low vitamin D	Secondary hyperparathyroidism
High Cortisol	

HRT protects from loss of skeletal mass following the menopause for as long as it is taken. However, concerns about the increased breast cancer risk, and doubts about benefit in CV protection have led to recommendations that HRT is limited to those experiencing menopausal symptoms and that prolonged use be avoided where possible. Data from the Women's Health Initiative study suggested that combined HRT protected from loss of lean body mass following menopause, although it was doubtful whether the magnitude of this protection was likely to be of major significance (111). This confirms another recent report (112) that HRT did not protect against menopause-induced changes in body composition or muscle function. Additionally, it is likely that HRT leads to a slight, but significant, decrease in insulin sensitivity (113, 114).

Recent studies confirm that aging men have gradually decreasing levels of free and total testosterone, and that these changes relate to altered health, functioning, and quality of life (115, 116). Decreasing levels of testosterone with aging coincide with increasing fat mass (particularly abdominal) in aging men (117, 118). Changes in leptin and adiponectin levels with obesity correlate strongly with decreased testosterone levels, particularly in men (93, 119-121). Overall, androgens tend to be associated with predominantly lipolytic states while the effect of oestrogen on adipose tissue is mainly lipogenic. For both men and women, the ratio of androgen to oestrogen relates more closely to adiposity than levels of the individual hormones (120). Loss of muscle with aging also correlates with decreasing testosterone, but this is not the sole determinant (122). Low androgen status, which may be a consequence, as well as a cause, of obesity increases risk of developing MS or type 2 diabetes (119, 123).

The relationship between obesity and androgen status in aging women is not so clear cut. While total testosterone tends to decrease with age, this may be due to decreased SHBG secondary to oestrogen withdrawal, and free testosterone may remain relatively stable (124). Testosterone levels are lower in individuals who have undergone oophorectomy and in those taking pharmacological doses of steroids. The significance of decreasing testosterone as a determinant of changes in body composition with aging has been questioned (28, 122, 124). Testosterone level is probably only a weak determinant of physical functioning in elderly women (125). There is a clear relationship between low testosterone status and decreased libido and sexual function in women. SHBG is lower, and free testosterone higher, in women with abdominal obesity, insulin resistance and metabolic syndrome (106, 126, 127). As in men, this may be effect rather than a causative relationship.

Androgen replacement prevents or reverses some of the changes in body composition and features of MS that develop with aging in men (128). Although some studies support the benefits of low-dose testosterone, most have been fairly limited and of short duration. A more prolonged and extensive study, (129) did not show any benefit. Potential side effects include increased risk of breast cancer, prostatic disorders and altered liver function. At present, androgen replacement should be reserved for those with clear-cut symptoms of hypogonadism, preferably with an established diagnosis, and the treatment should be carefully monitored (130). Some of this variability in symptoms and treatment response may relate to the CAG repeat polymorphism in the androgen receptor (AR) gene (131). Androgen replacement is more beneficial when combined with other treatments: Exercise not only increases the testosterone level achieved with replacement, but the combination but also enhances physical and social functioning (132). The combination of testosterone and growth hormone replacement has been reported to have beneficial effects on protein turnover, lipid profile, and fat mass (133, 134).

Dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) are the most abundant circulating adrenal steroids in humans, and levels decline progressively with age. DHEA exerts peripheral effects through conversion in tissues to either androgens or oestrogens, and may also have direct effects. The decline in DHEA with aging has been related to increased risk of obesity, type 2 diabetes, CV disease, neurodegenerative diseases, as well as to general physical and cognitive decline. Relative androgen deficiency contributes to sarcopenia, and may limit the response to exercise programmes. Villareal et al. (135) found no effect of six months of DHEA supplementation on muscle performance or on muscle bulk assessed by MRI. However, in a subsequent four months of treatment where DHEA was continued along with a muscle-building exercise programme, both performance and muscle bulk were increased. These improvements were accompanied by increased IGF-I levels. Decreases in both circulating DHEA and IGF-I have been reported in frail elderly individuals, (136) and decreases in these two hormones may correlate with low grade inflammation as evidenced by increased IL-6.

The Massachusetts Male Aging Study (MMAS) examined the relationship between measures of obesity and sex steroid levels in 942 men examined in 1985 – 1987, and during follow-up until 1995 – 1997 (117). Obesity was defined as BMI greater than 30 kg/m^2, waist circumference greater than 100 cm, or waist-hip ratio greater than 0.95. All three measures were associated with progressive decrease in testosterone (total and free) and SHBG. Central adiposity was particularly related to decreased DHEAS. The relationship between the latter and

risk of MS is uncertain (119). A recent two-year trial of DHEA supplementation (137) in elderly men and women failed to show any improvements in insulin secretion or sensitivity or in postprandial glucose. Increased fat mass, decreased muscle mass and performance, as well as the presence of co-morbidities are undoubtedly associated with decreased quality of life, but recent studies suggest that levels of DHEA(S) or IGF-1 may not be determinants (36, 129). In the study by Nair et al., (129) there was no beneficial effect of DHEA replacement on body composition, aerobic performance, muscle strength or insulin sensitivity in either men or women. Recent studies, therefore, suggest that routine supplementation of DHEA is not warranted even though many of the changes in body composition and other parameters that accompany aging are paralleled by declining levels of DHEA.

SHBG is down-regulated by insulin, and low levels in hyperinsulinaemic states may be useful marker for MS, (138) and increasing SHBG levels could be a useful therapeutic target (127). Low SHBG is strongly associated with MS variables in older men, (117, 119, 123) as well as in younger, non-obese men (139). Low SHBG occurs in women with polycystic ovarian syndrome (PCOS) and in those with isolated MS (140, 141). A number of studies have documented the inverse relationship between circulating SHBG and obesity/MS in post-menopausal women (106, 125, 126, 142). The relationship between SHBG and features of MS holds good in cohorts from different ethnic groups (143, 144). SHBG levels are partly genetically determined. The (TAAAA)n polymorphism in the SHBG gene has been linked with PCOS, (145) women with PCOS having a larger number of repeats and lower SHBG. More recently, the Pro12Ala polymorphism in the PPAR-γ2 gene has been linked with susceptibility to MS as well as with SHBG levels (146). Individuals with the Ala12 Ala genotype had higher SHBG and lower incidence of MS compared with those with Pro12Ala or Pro12Pro genotypes. Furthermore, amongst those with the latter two genotypes, SHBG was particularly low in those who had MS.

The gradual decline in activity of the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis with aging has been termed the somatopause. It is physiological and does not indicate development of clinical hypopituitarism. Symptoms include decreased muscle strength, decreased cardiovascular performance, impaired sense of well being, and decreased cognition. Numerous relatively short term studies have demonstrated improvement in these symptoms with GH. However, recombinant human GH is expensive and can cause side effects (peripheral oedema, joint pains, carpal tunnel syndrome) and theoretically might accelerate development of malignancies. It is not, therefore, recommended for routine use, (147-149) except in patients with proven hypopituitarism where there is sustained benefit (150). Low-dose GH has been advocated, particularly with testosterone treatment, to improve protein metabolism (133) and body composition (134) in the elderly. Studies with positron emission tomography (PET) and functional MRI have respectively shown improved cerebral blood flow (151) and cerebral function (152) with GH replacement. A recent meta-analysis (153) of 13 studies confirmed the association between low IGF-1 and cognitive impairment. Low IGF-1 is also involved in loss of lean body mass (121) and development of frailty, (136) but not with features of MS (127).

Increased circulating prolactin has been correlated with high BMI, (126) abdominal obesity, (154) and insulin resistance (155). High prolactin may help explain the relationship between obesity and breast cancer. The metabolic effects may be mediated through prolactin receptors on adipocytes, leading to decreased adiponectin (156, 157). Increased platelet aggregation (158) and increased inflammation (159) in obesity may also be related to hyperprolactinaemia. Levels of prolactin decrease with weight loss, (160) and preliminary data suggest that lowering prolactin with dopamine agonists leads to lower levels of inflammation (159) and weight loss (161). Increased free thyroxine (fT4) and reverse triiodothyronine (rT3) with decreased triiodothyronine (T3) may occur with decreased physical functioning during aging, while lower fT4 correlates with longer survival (162). These differences almost certainly reflect changes in thyroid hormone metabolism, perhaps mediated by TNF-α, rather than changes in underlying thyroid status. They do not therefore merit treatment to alter circulating thyroid hormone changes. The decrease in metabolic rate with aging is not mediated by changes in thyroid hormones (163). Hyperparathyroidism has been shown to be associated with increased body weight and fat mass (164). Low vitamin D status is also common, (165) and could contribute to development of secondary hyperparathyroidism. It is not clear whether hyperparathyroidism leads to obesity or vice versa and these changes are only partially reversed if the patients lose weight (86). Renal impairment is common with aging, especially with diabetes, and may contribute to low vitamin D and high PTH. Bone changes secondary to renal disease with increased calcium mobilisation contribute to vascular calcification which is a marker for developing atherosclerosis (72, 166)

Increased circulating cortisol occurs in patients with central obesity, insulin resistance and MS (167, 168). This may due to increased activity of the pituitary adrenal axis because of stress or to increased generation of cortisol from the biologically inactive hormone cortisone by 11-β-hydroysteroid dehydrogenase type 1 (11-beta-HSD1). Cortisol levels are particularly high in patients with diabetes, where there is a correlation with the presence of vascular complications (169). High cortisol has been linked with cognitive decline, (170) and with the development of dementia (171). Inhibitors of 11-beta-HSD1 have been developed and may assist with the management of obesity and insulin resistance by decreasing bioavailable glucocorticoid (172, 173)

Activity and Exercise

Sarcopenic obesity leads to functional decline and is related to co-morbidites and decreased life expectancy. The Health, Aging and Body Composition Study (174) investigated > 3,000 subjects aged 70 – 79 years, and showed that habitual activity was a major determinant of physical functioning. In young and old subjects, obesity is more common in those who have lower levels of habitual activity. Obesity is 2-3 times more common in elderly people who walk < 30 minutes per day compared with those who have a higher level of regular activity (175). Additionally, low levels of exercise strongly correlate with impaired performance in activities of daily living. By contrast, elderly subjects who perform high-intensity exercise have decreased fat mass, increased skeletal mass, and perform better in activities of daily living (175). Relationship between energy expenditure during the active period of the day and fat mass has been confirmed recently (176). Muscle fat oxidation is increased during exercise, leading to mobilisation of fat. Sequential changes in body composition of elderly subjects over a three-year period have been studied by Raguso et al. (177). Even when total body weight is unchanged, fat-free soft tissue and skeletal mass characteristically decrease, and individuals with high in leisure time activity are not protected. Activity level is lower in those with lower life expectancy. Menini et al. (13) studied 302 subjects aged 70 - 82 years followed for six years, measuring total energy expenditure (TEE, with doubly labelled water), resting metabolic rate and diet-induced thermogenesis (RMR and DIT, by indirect calorimetry). Free-living energy expenditure (FLEE) was calculated from TEE and RMR, and reported to be higher in patients still living at the end of the follow-up period. The presence of chronic diseases such as diabetes and cardiovascular disease may themselves influence activity level, energy expenditure, and life expectancy.

Although metabolic changes of aging and obesity relate to low levels of habitual activity, a higher intensity of activity than that typified by activities of daily living is required to reverse the changes. In elderly subjects, exercise interventions increased expression of skeletal muscle glucose transporter (GLUT4) and decreased intramuscular triglyceride; (178) Muscular strength, energy expenditure (resting and during exercise), and maximal oxygen consumption, along with flexibility and range of movement of various joints are all increased my programmes of exercise (97, 179). At the same time, leptin levels decrease, and adiponectin levels increase. These changes may contribute to altered feeding behaviour and decreased risk of diabetes. The low-grade inflammatory changes which accompany obesity are also reversed: Bautmans et al. (180) reported decreased circulating TNF-α and IL-6 and decreased expression of heat shock protein-70 (Hsp-70) in circulating monocytes. Exercise induces oxidative stress in muscle. This stress is decreased and circulating homocysteine increased with exercise training (181).

Short-term exercise interventions in the elderly have benefits including increasing lean body mass; and decreasing fat mass; decreasing waist circumference, insulin resistance, circulating triglycerides, and blood pressure (182-184). Weight loss induced by regular exercise has also been linked with functional improvement in frail elderly subjects (185). In a small trial conducted by Weiss et al., (186) weight loss by either calorie restriction or by exercise improved insulin sensitivity, while a control group who were simply given healthy living advice showed no change. Recent work confirms that exercise interventions have to be of relatively high intensity to improve insulin sensitivity and glucose disposal (187, 188). For example, in the study by Thomas et al., (187) Tai Chi did not lead to improved insulin sensitivity. That is not to say that relatively low intensity (in terms of energy expenditure) regimens such as yoga and Tai Chi do not have health benefits, which include effects on mood and mental function, improved sense of well-being, increased suppleness and improved muscle tone. The interventions which are most likely to increase energy expenditure, improve physical performance, and to enhance insulin sensitivity are those that increase muscle mass (189). Skeletal muscle has a metabolic rate which is approximately eight times that of other lean tissues in the body. Even a modest increase in muscle mass can improve energy expenditure. Furthermore, endurance or resistance exercises can improve metabolic status without influencing overall body weight. This may be due to improved insulin action and decreased systemic inflammation, perhaps related to lower intramuscular levels of triglyceride. Interventions should target the major muscle groups of the body and perhaps a combination of endurance exercise for lower limbs and resistance exercise for upper limbs is ideal (184).

The regimen used has be tailored to the ability and preference of the patient while being of sufficient intensity for benefit to accrue. In practice, this balance is hard to gauge. Evans et al. (190) suggest that increasing energy expenditure by 400 kcal per day leads to decreased fat mass and improved insulin sensitivity in subjects aged 77 – 87 years. An increase in energy expenditure of this order is often hard to achieve, particularly in very elderly subjects. Another issue is compliance and the duration of treatment. While the benefits of exercise on energy expenditure and body composition in the elderly have been demonstrated, it is equally apparent that these are rapidly lost when the subject becomes detrained (97, 179, 191). Longer term strategies are required. Translating the findings of short-term intervention studies into long-term programmes is difficult practically and likely to be costly. Successful and economically viable programmes are likely to be delivered to groups of subjects and to be community-based. More intensive short programmes to induce weight loss or to improve glucose tolerance or CV risk profile may need to be interspersed. As with pharmacological interventions, we need to consider weight loss and weight maintenance phases separately.

Improved compliance will involve provision of a variety of interventions. For example, aquatic training provides a good mixture of resistance and aerobic exercise and increases muscular performance, lean body mass, and exercise capacity (192). The aim of short-term interventions should be to improve the mass and function of key muscle groups, and to promote loss of fat, particularly from abdominal depots. Where possible, simple measures of success of these interventions should be employed (fasting glucose and lipids, inflammatory markers, anthropomorphic measures, and measures of performance and well-being). Maintenance of benefit requires encouragement of habitual activity and energy expenditure. Use of biofeedback devices such as a pedometer may help. Design of living environments to encourage walking activity within the individual's capabilities may also be important (193). Activity and exercise are of central importance in managing the high-risk overweight or obese elderly patient. Assessment of current exercise and planning increased exercise should never be neglected. As well as improving measures of health, the patient may benefit from improved sense of well-being and decreased reliance on drugs. Ideally, tailored programmes of exercise should be designed with a qualified and suitably experienced exercise physiologist.

Diet

While the role of nutrition therapy in weight management in the elderly is paramount, the optimum approach or approaches have yet to be determined, and there is little in the way of supporting evidence. Even modest weight loss may improve body fat content, fat distribution, adipokine profile, and MS variables (194, 195). However, severe calorie restriction, or repeated attempts at dieting with weight regain, may worsen muscle loss and thus hasten functional decline (196). Concurrent exercise will help to preserve muscle mass. Ideally, a calorie deficit of 200 – 500 kcal per day should be achieved by a combination of diet and exercise. Restriction of calorie intake should focus on the fat and carbohydrate components of the diet. The effectiveness of very low fat diets has been questioned in recent years, partly because they are poorly tolerated. Moderate restriction of carbohydrate is reasonable in patients who are hyperglycaemic. A tailored approach taking into account the patient's preferences and eating habits is needed, (197) and more likely to achieve realistic outcomes. Severe dietary restriction is stressful, increases cortisol secretion and may thus worsen some of the features of the features of the obesity/sarcopenia syndrome (198).

Many elderly patients consume less than the recommended daily protein intake of 0.8 grams/kilogram body weight per day. Poor appetite, dental problems and economic considerations may contribute. As in younger subjects (199), the response to exercise in the elderly may be optimal with increased protein intake above the recommended daily intake (200). Endurance exercise increases the need for dietary protein while muscle gain with resistance exercise is increased with higher protein intake. Daily protein intake of up to 1.6 grams/kilogram body weight is reasonable. Improved insulin sensitivity with exercise inhibits protein breakdown. Decreased protein breakdown has been documented with amino acid supplementation, (201, 202) and this should be considered in stressful situations which might lead to a catabolic state such as surgery on intercurrent illness (203). Wholegrain foods improve insulin sensitivity and cardiovascular risk profile, and elderly subjects should be encouraged to consume these foods regularly as part of a controlled diet (203). The importance of micronutrient components of the diet should not be underestimated. Deficiency of vitamins B6 and B12 as well as selenium have been associated with functional decline, (204) and low levels of magnesium increase risk of insulin resistance and cardiac disease.

Drugs and Bariatric Surgery

While pharmacotherapy is never the first line treatment for obesity, modern drugs have a place in some elderly patients with obesity. Available agents are summarised in Table 3. Orlistat, sibutramine and rimonabant are now widely used and considered safe. The amphetamine derivative phentermine is still used in some countries. Its use should be short-term (up to three months) and under close supervision. Interaction with other centrally-acting drugs, central side effects and adverse effects on pulse rate and blood pressure limit its use in the elderly. Greater understanding of adipocyte biology and the pathways that regulate food intake is leading to development of novel approaches (205). An example is inhibition of the renin angiotensin system, widely used in CV event protection. Angiotensin converting enzyme inhibitors may improve body composition and retard functional decline in the elderly (206, 207). With current evidence examining endpoints such as diabetes prevention, lifestyle interventions are at least as effective as drug treatments (208).

Orlistat, a derivative of a bacterial product (lipstatin), inhibits multiple gastrointestinal lipases, thus decreasing dietary fat absorption by up to one third. Very little is absorbed systemically, and side effects are limited to the gastrointestinal tract (oily stool, flatulence, increased defecation, faecal incontinence). Use is not necessarily confined to the short term but long-term effects can be modest. The recent study by Richelsen et al. (209) perhaps points the way to optimal use of orlistat. Patients who successfully lost weight with a very low calorie diet were randomised to either orlsitat or placebo. Those taking orlistat were more likely to maintain their weight, and there was a lower incidence of diabetes in the treated group. Weight loss with orlistat has been associated with lower levels of inflammatory and oxidative markers, and improved features of non-alcoholic fatty liver disease (210, 211). Because of the theoretical risk of fat-soluble vitamin malabsorption, patients taking orlistat are often recommended to take a multivitamin

supplement. This seems prudent in the elderly.

Sibutramine is a centrally-acting inhibitor of serotonin and noradrenaline reuptake. It increases satiety and decreases food intake. Side effects occur in up to 10% of patients and include headache, insomnia, dry mouth, rhinitis and constipation. Use for up to one year is recommended and, like orlistat, the optimal use may be in weight maintenance after initial weight loss. When used for three months or twelve months, typical weight loss in around 3 kg and 4.5 kg respectively (212). Use beyond one year is not generally recommended, particularly in the elderly. Both orlistat and sibutramine are effective but, predictably, there is often rebound weight gain when they are discontinued (213). The effects of sibutramine on cardiovascular risk profile are mixed with modest improvements in lipids and insulin sensitivity but increased pulse rate and blood pressure (up to 5 mm systolic). It should not be used in patients with uncontrolled hypertension. The recent Hypertension Obesity Sibutramine (HOS) study has shown that hypertension management with ACE inhibitors $\pm$ calcium channel blockers is preferable to a regimen based on beta-blockers and diuretics (214). Recent studies suggest that weight loss with sibutramine improves quality of life, (215) and decreases symptoms of sleep apnoea (216).

Table 3
Drug Treatments for Obesity

	Orlistat	Sibutramine	Rimonabant
Mechanism	Lipase inhibitor	5-HT and N Reuptake inhibitor	CB-1 antagonist
Action	Peripheral	Central	Central + Peripheral
Recommended Duration *	Up to 4 years	Up to 1 year	1 year
Dose	120 mg TDS	10 or 125 mg OD	20 mg OD
Side effects	> 30% Oily stool Faecal incontinence Flatulence ⇑ Defecation	10% Headache Insomnia Rhinitis Constipation Dry mouth	5% Depression Anxiety Nausea Dizziness
Drug interactions	+	+++	++
Lipids	⇓	⇓⇓	⇓⇓⇓
Diabetes	⇓⇓	⇔	⇓⇓
Blood pressure	⇓	⇑	⇔
Suitable for the elderly	++	+	Probably

* Duration of treatment based on available evidence.

Rimonabant is an antagonist at the cannabinoid-1 (CB-1) receptor. Agonists to this receptor (e.g. cannabis) commonly stimulate appetite. Endogenous cannabinoids are involved in regulation of appetite and CB-1 antagonists decrease appetite. Large studies in Europe (217) and in North America (218) confirm that the drug used over one year decreases body weight and waist circumference, improves dyslipidaemia and insulin sensitivity, but has limited effect on blood pressure. Typical weight loss over one year is 3.4 kg with the 5 mg dose and 6.6 kg with the 20 mg dose. The latter is now used in clinical practice. Side effects are relatively common (up to 5%) and include depression, anxiety, nausea and dizziness. More recent trials confirm significant improvements in lipid profile (219), and in glycaemic control in patients with diabetes (220). Some of these improvements may be due to peripheral as well as central effects of the drug. CB-1 receptors have recently been demonstrated on adipocytes and may mediate some of the effects of a high-fat diet inducing adipocyte hypertrophy (221). Rimonabant has only recently become available in many countries, and clinical experience with the drug is limited. The balance of evidence suggests that, like other anti-obesity drugs, it is moderately effective when combined with a hypocaloric diet, although the drop-out rate in studies is a cause for concern (222).

The utility of drug treatments for obesity in the elderly is limited by the efficacy of available treatments, the fact that they are only recommended for short to medium term use after which there may be rebound weight gain, and the lack of specific evidence relating to the elderly. There are only limited data to suggest that they improve overall body composition and protect against adverse clinical outcomes. Bariatric surgery is becoming safer and more widely available, and is indicated for patients who do not necessarily have morbid obesity but are otherwise at risk from their excess body weight (223). It is undoubtedly more effective than available medical treatments in decreasing body weight. Other reported benefits include improvements in sleep disturbances, gastro-oesophageal symptoms, diabetes and other MS variables, respiratory function, mobility and quality of life. There is growing experience of bariatric surgery in the elderly and clear evidence that it may be of benefit for carefully selected patients (224, 225).

Conclusions

Obesity, insulin resistance and metabolic syndrome are common in the elderly and influence health status and life expectancy. These are targets for clinical intervention, as in the younger age group, but care needs to be taken as over-enthusiastic attempts by medical practitioners to regulate body weight of their patients in later life are not always welcome and do not always improve function or outcome. For some patients, monitoring and vigorous management of individual conditions associated with obesity is appropriate. For others, management of the underlying problem – excess body fat with decreased muscle mass – is more appropriate. Inflammatory markers, endocrine changes and adipokines may all be useful in identifying high-risk individuals and in monitoring the effect of interventions.

It should go without saying that diet and exercise are the cornerstones of management. Lack of evidence precludes firm

and proscriptive dietary recommendations. Modest restriction of calories from fat and carbohydrate seems appropriate, along with ensuring that there is adequate protein intake. The latter may enhance the benefits of exercise which go beyond simple weight management and include improved functional status. A combination of lower body endurance and upper body resistance training appears to be particularly beneficial for the elderly. Among potential hormonal treatments, current evidence does not favour routine growth hormone, IGF-1, androgen or oestrogen replacement, except in proven clinical deficiency states. However, endocrine treatment may augment the response to exercise. Lowering prolactin and decreasing glucocorticoid excess are manoeuvres with therapeutic potential. Drug treatments and surgery for obesity should rarely be in the first line of management, but there is every reason to believe, and emerging evidence, that they are as effective in the elderly. Demographic changes along with the complexity of disease states and physiological changes with aging and obesity are opening up a new area of medicine which transcends current specialty and professional boundaries. Appropriate and effective management of obesity and its complications in the elderly has considerable potential to improve the quantity and quality of life for many people.

References

1. Kennedy RL, Chokkalingham K, Srinivasan R. Obesity in the elderly: who should we be treating, and why, and how? Current Opinion in Clinical Nutrition & Metabolic Care 2004;7(1):3-9.
2. McTigue KM, Hess R, Ziouras J. Obesity in older adults: a systematic review of the evidence for diagnosis and treatment. Obesity 2006;14(9):1485-97.
3. Arterburn DE, Crane PK, Sullivan SD. The coming epidemic of obesity in elderly Americans. Journal of the American Geriatrics Society 2004;52(11):1907-12.
4. Li C, Ford ES, McGuire LC, Mokdad AH. Increasing trends in waist circumference and abdominal obesity among US adults. Obesity 2007;15(1):216-24.
5. Flegal KM, Williamson DF, Pamuk ER, Rosenberg HM. Estimating deaths attributable to obesity in the United States.[see comment]. American Journal of Public Health 2004;94(9):1486-9.
6. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity.[see comment]. JAMA 2005;293(15):1861-7.
7. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295(13):1549-55.
8. Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. Diabetes Care 2006;29(6):1263-8.
9. Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. International Journal of Obesity 2005;29(3):334-9.
10. Ajani UA, Lotufo PA, Gaziano JM, Lee IM, Spelsberg A, Buring JE, et al. Body mass index and mortality among US male physicians. Annals of Epidemiology 2004;14(10):731-9.
11. Nyholm M, Merlo J, Rastam L, Lindblad U. Overweight and all-cause mortality in a Swedish rural population: Skaraborg Hypertension and Diabetes Project. Scandinavian Journal of Public Health 2005;33(6):478-86.
12. Jee SH, Sull JW, Park J, Lee SY, Ohrr H, Guallar E, et al. Body mass index and mortality in Korean men and women. New England Journal of Medicine 2006;355(8):779-87.
13. Manini TM, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M, et al. Daily activity energy expenditure and mortality among older adults.[see comment]. JAMA 2006;296(2):171-9.
14. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. Obesity Reviews 2007;8(1):41-59.
15. He Y, Jiang B, Wang J, Feng K, Chang Q, Fan L, et al. Prevalence of the metabolic syndrome and its relation to cardiovascular disease in an elderly Chinese population. Journal of the American College of Cardiology 2006;47(8):1588-94.
16. Maggi S, Noale M, Gallina P, Bianchi D, Marzari C, Limongi F, et al. Metabolic syndrome, diabetes, and cardiovascular disease in an elderly Caucasian cohort: the Italian Longitudinal Study on Aging. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2006;61(5):505-10.
17. Park HS, Kim SM, Lee JS, Lee J, Han JH, Yoon DK, et al. Prevalence and trends of metabolic syndrome in Korea: Korean National Health and Nutrition Survey 1998-2001. Diabetes, Obesity & Metabolism 2007;9(1):50-8.
18. Gause-Nilsson I, Gherman S, Kumar Dey D, Kennerfalk A, Steen B. Prevalence of metabolic syndrome in an elderly Swedish population. Acta Diabetologica 2006;43(4):120-6.
19. Kasai T, Miyauchi K, Kurata T, Ohta H, Okazaki S, Miyazaki T, et al. Prognostic value of the metabolic syndrome for long-term outcomes in patients undergoing percutaneous coronary intervention. Circulation Journal 2006;70(12):1531-7.
20. Cabrera MAS, Gebara OCE, Diament J, Nussbacher A, Rosano G, Wajngarten M. Metabolic syndrome, abdominal obesity, and cardiovascular risk in elderly women. International Journal of Cardiology 2007;114(2):224-9.
21. Milionis HJ, Rizos E, Goudevenos J, Seferiadis K, Mikhailidis DP, Elisaf MS. Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. Stroke 2005;36(7):1372-6.
22. Golledge J, Leicht A, Crowther RG, Clancy P, Spinks WL, Quigley F. Association of obesity and metabolic syndrome with the severity and outcome of intermittent claudication. Journal of Vascular Surgery 2007;45(1):40-6.
23. Otiniano ME, Du XL, Maldonado MR, Ray L, Markides K. Effect of metabolic syndrome on heart attack and mortality in Mexican-American elderly persons: findings of 7-year follow-up from the Hispanic established population for the epidemiological study of the elderly. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2005;60(4):466-70.
24. Ravaglia G, Forti P, Maioli F, Bastagli L, Chiappelli M, Montesi F, et al. Metabolic Syndrome: prevalence and prediction of mortality in elderly individuals. Diabetes Care 2006;29(11):2471-6.
25. Lee JS, Kritchevsky SB, Tylavsky F, Harris T, Simonsick EM, Rubin SM, et al. Weight change, weight change intention, and the incidence of mobility limitation in well-functioning community-dwelling older adults. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2005;60(8):1007-12.
26. Bohannon RW, Brennan PJ, Pescatello LS, Marschke L, Hasson S, Murphy M. Adiposity of elderly women and its relationship with self-reported and observed physical performance. Journal of Geriatric Physical Therapy 2005;28(1):10-3.
27. Jensen GL. Obesity and functional decline: epidemiology and geriatric consequences. Clinics in Geriatric Medicine;21(4):677-87.
28. Lebrun CEI, van der Schouw YT, de Jong FH, Grobbee DE, Lamberts SW. Fat mass rather than muscle strength is the major determinant of physical function and disability in postmenopausal women younger than 75 years of age. Menopause 2006;13(3):474-81.
29. Cankurtaran M, Halil M, Yavuz BB, Dagli N, Oyan B, Ariogul S. Prevalence and correlates of metabolic syndrome (MS) in older adults. Archives of Gerontology & Geriatrics 2006;42(1):35-45.
30. Ramsay SE, Whincup PH, Shaper AG, Wannamethee SG. The relations of body composition and adiposity measures to ill health and physical disability in elderly men. American Journal of Epidemiology 2006;164(5):459-69.
31. Lafortuna CL, Agosti F, Proietti M, Adorni F, Sartorio A. The combined effect of adiposity, fat distribution and age on cardiovascular risk factors and motor disability in a cohort of obese women (aged 18-83). Journal of Endocrinological Investigation 2006;29(10):905-12.
32. Okoro CA, Zhong Y, Ford ES, Balluz LS, Strine TW, Mokdad AH. Association between the metabolic syndrome and its components and gait speed among U.S. adults aged 50 years and older: a cross-sectional analysis. BMC Public Health 2006;6:282.
33. Blazer DG, Hybels CF, Fillenbaum GG. Metabolic syndrome predicts mobility decline in a community-based sample of older adults. Journal of the American Geriatrics Society 2006;54(3):502-6.
34. Roriz-Cruz M, Rosset I, Wada T, Sakagami T, Ishine M, Roriz-Filho JS, et al. Stroke-independent association between metabolic syndrome and functional dependence, depression, and low quality of life in elderly community-dwelling Brazilian people. Journal of the American Geriatrics Society 2007;55(3):374-82.
35. Arterburn DE, McDonell MB, Hedrick SC, Diehr P, Fihn SD. Association of body weight with condition-specific quality of life in male veterans. American Journal of Medicine 2004;117(10):738-46.
36. Lebrun CEI, van der Schouw YT, de Jong FH, Pols HAP, Grobbee DE, Lamberts SWJ. Relations between body composition, functional and hormonal parameters and quality of life in healthy postmenopausal women. Maturitas 2006;55(1):82-92.
37. Sach TH, Barton GR, Doherty M, Muir KR, Jenkinson C, Avery AJ. The relationship between body mass index and health-related quality of life: comparing the EQ-5D, EuroQol VAS and SF-6D. International Journal of Obesity 2007;31(1):189-96.
38. Huang IC, Frangakis C, Wu AW. The relationship of excess body weight and health-related quality of life: evidence from a population study in Taiwan. International Journal of Obesity 2006;30(8):1250-9.
39. Gregg EW, Cheng YJ, Cadwell BL, Imperatore G, Williams DE, Flegal KM, et al.

Secular trends in cardiovascular disease risk factors according to body mass index in US adults.[see comment][erratum appears in JAMA. 2005 Jul 13;294(2):182]. JAMA 2005;293(15):1868-74.
40. Noale M, Maggi S, Marzari C, Limongi F, Gallina P, Bianchi D, et al. Components of the metabolic syndrome and incidence of diabetes in elderly Italians: the Italian Longitudinal Study on Aging. Atherosclerosis 2006;187(2):385-92.
41. Onat A, Hergenc G, Turkmen S, Yazici M, Sari I, Can G. Discordance between insulin resistance and metabolic syndrome: features and associated cardiovascular risk in adults with normal glucose regulation. Metabolism: Clinical & Experimental 2006;55(4):445-52.
42. Wexler DJ, Grant RW, Wittenberg E, Bosch JL, Cagliero E, Delahanty L, et al. Correlates of health-related quality of life in type 2 diabetes. Diabetologia 2006;49(7):1489-97.
43. Wray LA, Ofstedal MB, Langa KM, Blaum CS. The effect of diabetes on disability in middle-aged and older adults. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2005;60(9):1206-11.
44. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity and mortality from cancer in a prospectively studied cohort of US adults. New England Journal of Medicine 2003;348(17):1625-38.
45. Sedjo RL, Byers T, Levin TR, Haffner SM, Saad MF, Tooze JA, et al. Change in body size and the risk of colorectal adenomas. Cancer Epidemiology, Biomarkers & Prevention 2007;16(3):526-31.
46. Sturmer T, Buring JE, Lee IM, Gaziano JM, Glynn RJ. Metabolic abnormalities and risk for colorectal cancer in the physicians' health study. Cancer Epidemiology, Biomarkers & Prevention 2006;15(12):2391-7.
47. Janssen I. Influence of sarcopenia on the development of physical disability: the Cardiovascular Health Study. Journal of the American Geriatrics Society 2006;54(1):56-62.
48. Jinks C, Jordan K, Croft P. Disabling knee pain--another consequence of obesity: results from a prospective cohort study. BMC Public Health 2006;6:258.
49. Reijman M, Pols HAP, Bergink AP, Hazes JMW, Belo JN, Lievense AM, et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study.[see comment]. Annals of the Rheumatic Diseases 2007;66(2):158-62.
50. Wannamethee SG, Shaper AG, Whincup PH. Body fat distribution, body composition, and respiratory function in elderly men. American Journal of Clinical Nutrition 2005;82(5):996-1003.
51. Yende S, Waterer GW, Tolley EA, Newman AB, Bauer DC, Taaffe DR, et al. Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects.[see comment]. Thorax 2006;61(1):10-6.
52. Ocasio-Tascon ME, Alicea-Colon E, Torres-Palacios A, Rodriguez-Cintron W. The veteran population: one at high risk for sleep-disordered breathing. Sleep & Breathing 2006;10(2):70-5.
53. Jackson RA, Vittinghoff E, Kanaya AM, Miles TP, Resnick HE, Kritchevsky SB, et al. Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study. Obstetrics & Gynecology 2004;104(2):301-7.
54. Asplund R. Obesity in elderly people with nocturia: cause or consequence? Canadian Journal of Urology 2007;14(1):3424-8.
55. Rey E, Moreno-Elola-Olaso C, Artalejo FR, Locke GR, 3rd, Diaz-Rubio M. Association between weight gain and symptoms of gastroesophageal reflux in the general population. American Journal of Gastroenterology 2006;101(2):229-33.
56. Oh S-Y, Cho Y-K, Kang M-S, Yoo T-W, Park J-H, Kim H-J, et al. The association between increased alanine aminotransferase activity and metabolic factors in nonalcoholic fatty liver disease. Metabolism: Clinical & Experimental 2006;55(12):1604-9.
57. Onat A, Hergenc G, Karabulut A, Turkmen S, Doan Y, Uyarel H, et al. Serum gamma glutamyltransferase as a marker of metabolic syndrome and coronary disease likelihood in nondiabetic middle-aged and elderly adults. Preventive Medicine 2006;43(2):136-9.
58. Clark JM. Weight loss as a treatment for nonalcoholic fatty liver disease. Journal of Clinical Gastroenterology 2006;40(3 Suppl 1):S39-43.
59. Seddon JM, Cote J, Davis N, Rosner B. Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio. Archives of Ophthalmology 2003;121(6):785-92.
60. Moeini HA, Masoudpour H, Ghanbari H. A study of the relation between body mass index and the incidence of age related macular degeneration. British Journal of Ophthalmology 2005;89(8):964-6.
61. Klein R, Deng Y, Klein BEK, Hyman L, Seddon J, Frank RN, et al. Cardiovascular disease, its risk factors and treatment, and age-related macular degeneration: Women's Health Initiative Sight Exam ancillary study. American Journal of Ophthalmology 2007;143(3):473-83.
62. Seddon JM, George S, Rosner B, Klein ML. CFH gene variant, Y402H, and smoking, body mass index, environmental associations with advanced age-related macular degeneration. Human Heredity 2006;61(3):157-65.
63. Schaumberg DA, Hankinson SE, Guo Q, Rimm E, Hunter DJ. A prospective study of 2 major age-related macular degeneration susceptibility alleles and interactions with modifiable risk factors.[see comment]. Archives of Ophthalmology 2007;125(1):55-62.
64. Seddon JM, George S, Rosner B, Rifai N. Progression of age-related macular degeneration: prospective assessment of C-reactive protein, interleukin 6, and other cardiovascular biomarkers. Archives of Ophthalmology 2005;123(6):774-82.
65. Navarro Esteban JJ, Gutierrez Leiva JA, Valero Caracena N, Buendia Bermejo J, Calle Puron ME, Martinez Vizcaino VJ. Prevalence and risk factors of lens opacities in the elderly in Cuenca, Spain. European Journal of Ophthalmology 2007;17(1):29-37.
66. Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hanninen T, Soininen H, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. Neurology 2006;67(5):843-7.
67. Komulainen P, Lakka TA, Kivipelto M, Hassinen M, Helkala E-L, Haapala I, et al. Metabolic syndrome and cognitive function: a population-based follow-up study in elderly women. Dementia & Geriatric Cognitive Disorders 2007;23(1):29-34.
68. Xiong GL, Plassman BL, Helms MJ, Steffens DC. Vascular risk factors and cognitive decline among elderly male twins. Neurology 2006;67(9):1586-91.
69. McGuire LC, Ford ES, Ajani UA. Cognitive functioning as a predictor of functional disability in later life. American Journal of Geriatric Psychiatry 2006;14(1):36-42.
70. Rosano C, Simonsick EM, Harris TB, Kritchevsky SB, Brach J, Visser M, et al. Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. Neuroepidemiology 2005;24(1-2):8-14.
71. Gorospe EC, Dave JK. The risk of dementia with increased body mass index. Age & Ageing 2007;36(1):23-9.
72. Alexandersen P, Tanko LB, Bagger YZ, Jespersen J, Skouby SO, Christiansen C. Associations between aortic calcification and components of body composition in elderly men. Obesity 2006;14(9):1571-8.
73. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies.[see comment]. Journal of the American Geriatrics Society 2005;53(6):927-34.
74. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study.[see comment]. Journal of the American Geriatrics Society 2005;53(8):1321-30.
75. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obesity Research 2004;12(12):1995-2004.
76. Cesari M, Leeuwenburgh C, Lauretani F, Onder G, Bandinelli S, Maraldi C, et al. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. American Journal of Clinical Nutrition 2006;83(5):1142-8.
77. Liu-Ambrose T, Kravetsky L, Bailey D, Sherar L, Mundt C, Baxter-Jones A, et al. Change in lean body mass is a major determinant of change in areal bone mineral density of the proximal femur: a 12-year observational study. Calcified Tissue International 2006;79(3):145-51.
78. Aubertin-Leheudre M, Lord C, Goulet EDB, Khalil A, Dionne IJ. Effect of sarcopenia on cardiovascular disease risk factors in obese postmenopausal women. Obesity 2006;14(12):2277-83.
79. Katsiaras A, Newman AB, Kriska A, Brach J, Krishnaswami S, Feingold E, et al. Skeletal muscle fatigue, strength, and quality in the elderly: the Health ABC Study. Journal of Applied Physiology 2005;99(1):210-6.
80. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2006;61(10):1059-64.
81. Kwan M, Woo J, Kwok T. The standard oxygen consumption value equivalent to one metabolic equivalent (3.5 ml/min/kg) is not appropriate for elderly people. International Journal of Food Sciences & Nutrition 2004;55(3):179-82.
82. Krems C, Luhrmann PM, Strassburg A, Hartmann B, Neuhauser-Berthold M. Lower resting metabolic rate in the elderly may not be entirely due to changes in body composition. European Journal of Clinical Nutrition 2005;59(2):255-62.
83. Tyagi R, Kapoor S, Kapoor AK. Body composition and fat distribution pattern of urban elderly females, Delhi, India. Collegium Antropologicum 2005;29(2):493-8.
84. Tanko LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women.[see comment]. Circulation 2003;107(12):1626-31.
85. Ding J, Kritchevsky SB, Newman AB, Taaffe DR, Nicklas BJ, Visser M, et al. Effects of birth cohort and age on body composition in a sample of community-based elderly. American Journal of Clinical Nutrition 2007;85(2):405-10.
86. Sanchez-Garcia S, Garcia-Pena C, Duque-Lopez MX, Juarez-Cedillo T, Cortes-Nunez AR, Reyes-Beaman S. Anthropometric measures and nutritional status in a healthy elderly population. BMC Public Health 2007;7:2.
87. Goodpaster BH, Brown NF. Skeletal muscle lipid and its association with insulin resistance: what is the role for exercise? Exercise & Sport Sciences Reviews 2005;33(3):150-4.
88. Zamboni M, Zoico E, Fantin F, Panourgia MP, Di Francesco V, Tosoni P, et al. Relation between leptin and the metabolic syndrome in elderly women. Journals of

Gerontology Series A-Biological Sciences & Medical Sciences 2004;59(4):396-400.
89. Crabbe P, Goemaere S, Zmierczak H, Van Pottelbergh I, De Bacquer D, Kaufman J-M. Are serum leptin and the Gln223Arg polymorphism of the leptin receptor determinants of bone homeostasis in elderly men? European Journal of Endocrinology 2006;154(5):707-14.
90. Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L, Catapano AL. Plasma resistin levels correlate with determinants of the metabolic syndrome. European Journal of Endocrinology 2007;156(2):279-84.
91. Schutte AE, Huisman HW, Schutte R, van Rooyen JM, Malan L, Malan NT. Aging influences the level and functions of fasting plasma ghrelin levels: the POWIRS-Study. Regulatory Peptides 2007;139(1-3):65-71.
92. Zoico E, Di Francesco V, Mazzali G, Vettor R, Fantin F, Bissoli L, et al. Adipocytokines, fat distribution, and insulin resistance in elderly men and women. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2004;59(9):M935-9.
93. Gannage-Yared M-H, Khalife S, Semaan M, Fares F, Jambart S, Halaby G. Serum adiponectin and leptin levels in relation to the metabolic syndrome, androgenic profile and somatotropic axis in healthy non-diabetic elderly men. European Journal of Endocrinology 2006;155(1):167-76.
94. Bik W, Baranowska-Bik A, Wolinska-Witort E, Martynska L, Chmielowska M, Szybinska A, et al. The relationship between adiponectin levels and metabolic status in centenarian, early elderly, young and obese women. Neuroendocrinology Letters 2006;27(4):493-500.
95. Frystyk J, Berne C, Berglund L, Jensevik K, Flyvbjerg A, Zethelius B. Serum adiponectin is a predictor of coronary heart disease: a population-based 10-year follow-up study in elderly men. Journal of Clinical Endocrinology & Metabolism 2007;92(2):571-6.
96. Laughlin GA, Barrett-Connor E, May S, Langenberg C. Association of adiponectin with coronary heart disease and mortality: the Rancho Bernardo study. American Journal of Epidemiology 2007;165(2):164-74.
97. Fatouros IG, Tournis S, Leontsini D, Jamurtas AZ, Sxina M, Thomakos P, et al. Leptin and adiponectin responses in overweight inactive elderly following resistance training and detraining are intensity related. Journal of Clinical Endocrinology & Metabolism 2005;90(11):5970-7.
98. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, et al. Sarcopenic obesity and inflammation in the InCHIANTI study. Journal of Applied Physiology 2007;102(3):919-25.
99. Hoekstra T, Geleijnse JM, Schouten EG, Kok FJ, Kluft C. Relationship of C-reactive protein with components of the metabolic syndrome in normal-weight and overweight elderly. Nutrition Metabolism & Cardiovascular Diseases 2005;15(4):270-8.
100. Figaro MK, Kritchevsky SB, Resnick HE, Shorr RI, Butler J, Shintani A, et al. Diabetes, inflammation, and functional decline in older adults: findings from the Health, Aging and Body Composition (ABC) study. Diabetes Care 2006;29(9):2039-45.
101. Penninx BWJH, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, et al. Inflammatory markers and incident mobility limitation in the elderly. Journal of the American Geriatrics Society 2004;52(7):1105-13.
102. Jenny NS, Yanez ND, Psaty BM, Kuller LH, Hirsch CH, Tracy RP. Inflammation biomarkers and near-term death in older men. American Journal of Epidemiology 2007;165(6):684-95.
103. Sipila S. Body composition and muscle performance during menopause and hormone replacement therapy. Journal of Endocrinological Investigation 2003;26(9):893-901.
104. Augoulea A, Mastorakos G, Lambrinoudaki I, Christodoulakos G, Creatsas G. Role of postmenopausal hormone replacement therapy on body fat gain and leptin levels. Gynecological Endocrinology 2005;20(4):227-35.
105. Sowers M, Zheng H, Tomey K, Karvonen-Gutierrez C, Jannausch M, Li X, et al. Changes in body composition in women over six years at midlife: ovarian and chronological aging. Journal of Clinical Endocrinology & Metabolism 2007;92(3):895-901.
106. Tufano A, Marzo P, Enrini R, Morricone L, Caviezel F, Ambrosi B. Anthropometric, hormonal and biochemical differences in lean and obese women before and after menopause. Journal of Endocrinological Investigation 2004;27(7):648-53.
107. Morita Y, Iwamoto I, Mizuma N, Kuwahata T, Matsuo T, Yoshinaga M, et al. Precedence of the shift of body-fat distribution over the change in body composition after menopause. Journal of Obstetrics & Gynaecology Research 2006;32(5):513-6.
108. Li S, Wagner R, Holm K, Lehotsky J, Zinaman MJ. Relationship between soft tissue body composition and bone mass in perimenopausal women. Maturitas 2004;47(2):99-105.
109. Bagger YZ, Tanko LB, Alexandersen P, Qin G, Christiansen C. The implications of body fat mass and fat distribution for cognitive function in elderly women. Obesity Research 2004;12(9):1519-26.
110. Yannakoulia M, Melistas L, Solomou E, Yiannakouris N. Association of eating frequency with body fatness in pre- and postmenopausal women. Obesity 2007;15(1):100-6.
111. Chen Z, Bassford T, Green SB, Cauley JA, Jackson RD, LaCroix AZ, et al. Postmenopausal hormone therapy and body composition--a substudy of the estrogen plus progestin trial of the Women's Health Initiative. American Journal of Clinical Nutrition 2005;82(3):651-6.
112. Maddalozzo GF, Cardinal BJ, Li F, Snow CM. The association between hormone therapy use and changes in strength and body composition in early postmenopausal women. Menopause 2004;11(4):438-46.
113. Sites CK, L'Hommedieu GD, Toth MJ, Brochu M, Cooper BC, Fairhurst PA. The effect of hormone replacement therapy on body composition, body fat distribution, and insulin sensitivity in menopausal women: a randomized, double-blind, placebo-controlled trial. Journal of Clinical Endocrinology & Metabolism 2005;90(5):2701-7.
114. Goodrow GJ, L'Hommedieu GD, Gannon B, Sites CK. Predictors of worsening insulin sensitivity in postmenopausal women. American Journal of Obstetrics & Gynecology 2006;194(2):355-61.
115. Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI. The association between obesity and the diagnosis of androgen deficiency in symptomatic ageing men. Medical Journal of Australia 2006;185(8):424-7.
116. Travison TG, Araujo AB, O'Donnell AB, Kupelian V, McKinlay JB. A population-level decline in serum testosterone levels in American men.[see comment]. Journal of Clinical Endocrinology & Metabolism 2007;92(1):196-202.
117. Derby CA, Zilber S, Brambilla D, Morales KH, McKinlay JB. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. Clinical Endocrinology 2006;65(1):125-31.
118. Chen RYT, Wittert GA, Andrews GR. Relative androgen deficiency in relation to obesity and metabolic status in older men. Diabetes, Obesity & Metabolism 2006;8(4):429-35.
119. Maggio M, Lauretani F, Ceda GP, Bandinelli S, Basaria S, Ble A, et al. Association between hormones and metabolic syndrome in older Italian men. Journal of the American Geriatrics Society 2006;54(12):1832-8.
120. Laughlin GA, Barrett-Connor E, May S. Sex-specific association of the androgen to oestrogen ratio with adipocytokine levels in older adults: the Rancho Bernardo Study. Clinical Endocrinology 2006;65(4):506-13.
121. Carraro R, Ruiz-Torres A. Relationship of serum leptin concentration with age, gender, and biomedical parameters in healthy, non-obese subjects. Archives of Gerontology & Geriatrics 2006;43(3):301-12.
122. Zamboni M, Zoico E, Scartezzini T, Mazzali G, Tosoni P, Zivelonghi A, et al. Body composition changes in stable-weight elderly subjects: the effect of sex. Aging-Clinical & Experimental Research 2003;15(4):321-7.
123. Muller M, Grobbee DE, den Tonkelaar I, Lamberts SWJ, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men.[see comment]. Journal of Clinical Endocrinology & Metabolism 2005;90(5):2618-23.
124. Cappola AR, Ratcliffe SJ, Bhasin S, Blackman MR, Cauley J, Robbins J, et al. Determinants of serum total and free testosterone levels in women over the age of 65 years. Journal of Clinical Endocrinology & Metabolism 2007;92(2):509-16.
125. Santoro N, Torrens J, Crawford S, Allsworth JE, Finkelstein JS, Gold EB, et al. Correlates of circulating androgens in mid-life women: the study of women's health across the nation.[see comment]. Journal of Clinical Endocrinology & Metabolism 2005;90(8):4836-45.
126. McTiernan A, Wu L, Chen C, Chlebowski R, Mossavar-Rahmani Y, Modugno F, et al. Relation of BMI and physical activity to sex hormones in postmenopausal women. Obesity 2006;14(9):1662-77.
127. Maggio M, Lauretani F, Ceda GP, Bandinelli S, Basaria S, Paolisso G, et al. Association of hormonal dysregulation with metabolic syndrome in older women: data from the InCHIANTI study. American Journal of Physiology - Endocrinology & Metabolism 2007;292(1):E353-8.
128. Gould DC, Kirby RS, Amoroso P. Hypoandrogen-metabolic syndrome: a potentially common and underdiagnosed condition in men. International Journal of Clinical Practice 2007;61(2):341-4.
129. Nair KS, Rizza RA, O'Brien P, Dhatariya K, Short KR, Nehra A, et al. DHEA in elderly women and DHEA or testosterone in elderly men.[see comment]. New England Journal of Medicine 2006;355(16):1647-59.
130. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocrine Reviews 2005;26(6):833-76.
131. Lapauw B, Goemaere S, Crabbe P, Kaufman JM, Ruige JB. Is the effect of testosterone on body composition modulated by the androgen receptor gene CAG repeat polymorphism in elderly men? European Journal of Endocrinology 2007;156(3):395-401.
132. Katznelson L, Robinson MW, Coyle CL, Lee H, Farrell CE. Effects of modest testosterone supplementation and exercise for 12 weeks on body composition and quality of life in elderly men. European Journal of Endocrinology 2006;155(6):867-75.
133. Huang X, Blackman MR, Herreman K, Pabst KM, Harman SM, Caballero B. Effects of growth hormone and/or sex steroid administration on whole-body protein turnover in healthy aged women and men. Metabolism: Clinical & Experimental 2005;54(9):1162-7.
134. Giannoulis MG, Jackson N, Shojaee-Moradie F, Sonksen PH, Martin FC, Umpleby AM. Effects of growth hormone and/or testosterone on very low density lipoprotein apolipoprotein B100 kinetics and plasma lipids in healthy elderly men: a randomised controlled trial. Growth Hormone & Igf Research 2006;16(5-6):308-17.

135. Villareal DT, Holloszy JO. DHEA enhances effects of weight training on muscle mass and strength in elderly women and men. American Journal of Physiology - Endocrinology & Metabolism 2006;291(5):E1003-8.
136. Leng SX, Cappola AR, Andersen RE, Blackman MR, Koenig K, Blair M, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. Aging-Clinical & Experimental Research 2004;16(2):153-7.
137. Basu R, Man CD, Campioni M, Basu A, Nair KS, Jensen MD, et al. Two years of treatment with dehydroepiandrosterone does not improve insulin secretion, insulin action, or postprandial glucose turnover in elderly men or women. Diabetes 2007;56(3):753-66.
138. Kalme T, Seppala M, Qiao Q, Koistinen R, Nissinen A, Harrela M, et al. Sex hormone-binding globulin and insulin-like growth factor-binding protein-1 as indicators of metabolic syndrome, cardiovascular risk, and mortality in elderly men. Journal of Clinical Endocrinology & Metabolism 2005;90(3):1550-6.
139. Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. Journal of Clinical Endocrinology & Metabolism 2006;91(3):843-50.
140. Cikim AS, Ozbey N, Sencer E, Molvalilar S, Orhan Y. Associations among sex hormone binding globulin concentrations and characteristics of the metabolic syndrome in obese women. Diabetes, Nutrition & Metabolism - Clinical & Experimental 2004;17(5):290-5.
141. Chen M-J, Yang W-S, Yang J-H, Hsiao CK, Yang Y-S, Ho H-N. Low sex hormone-binding globulin is associated with low high-density lipoprotein cholesterol and metabolic syndrome in women with PCOS. Human Reproduction 2006;21(9):2266-71.
142. Weinberg ME, Manson JE, Buring JE, Cook NR, Seely EW, Ridker PM, et al. Low sex hormone-binding globulin is associated with the metabolic syndrome in postmenopausal women. Metabolism: Clinical & Experimental 2006;55(11):1473-80.
143. Heald AH, Anderson SG, Ivison F, Riste L, Laing I, Cruickshank JK, et al. Low sex hormone binding globulin is a potential marker for the metabolic syndrome in different ethnic groups. Experimental & Clinical Endocrinology & Diabetes 2005;113(9):522-8.
144. Sutton-Tyrrell K, Wildman RP, Matthews KA, Chae C, Lasley BL, Brockwell S, et al. Sex-hormone-binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the Study of Women Across the Nation (SWAN). Circulation 2005;111(10):1242-9.
145. Xita N, Tsatsoulis A, Chatzikyriakidou A, Georgiou I. Association of the (TAAAA)n repeat polymorphism in the sex hormone-binding globulin (SHBG) gene with polycystic ovary syndrome and relation to SHBG serum levels. Journal of Clinical Endocrinology & Metabolism 2003;88(12):5976-80.
146. Mousavinasab F, Tahtinen T, Jokelainen J, Koskela P, Vanhala M, Oikarinen J, et al. The Pro12Ala polymorphism of the PPAR gamma 2 gene influences sex hormone-binding globulin level and its relationship to the development of the metabolic syndrome in young Finnish men. Endocrine 2006;30(2):185-90.
147. Toogood AA. The somatopause: an indication for growth hormone therapy? Treatments in Endocrinology 2004;3(4):201-9.
148. Lombardi G, Tauchmanova L, Di Somma C, Musella T, Rota F, Savanelli MC, et al. Somatopause: dismetabolic and bone effects. Journal of Endocrinological Investigation 2005;28(10 Suppl):36-42.
149. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Annals of Internal Medicine 2007;146(2):104-15.
150. Gotherstrom G, Bengtsson B-A, Sunnerhagen KS, Johannsson G, Svensson J. The effects of five-year growth hormone replacement therapy on muscle strength in elderly hypopituitary patients. Clinical Endocrinology 2005;62(1):105-13.
151. Arwert LI, Veltman DJ, Deijen JB, Lammertsma AA, Jonker C, Drent ML. Memory performance and the growth hormone/insulin-like growth factor axis in elderly: a positron emission tomography study. Neuroendocrinology 2005;81(1):31-40.
152. Arwert LI, Veltman DJ, Deijen JB, van Dam PS, Drent ML. Effects of growth hormone substitution therapy on cognitive functioning in growth hormone deficient patients: a functional MRI study. Neuroendocrinology 2006;83(1):12-9.
153. Arwert LI, Deijen JB, Drent ML. The relation between insulin-like growth factor I levels and cognition in healthy elderly: a meta-analysis. Growth Hormone & Igf Research 2005;15(6):416-22.
154. Kok P, Roelfsema F, Frolich M, Meinders AE, Pijl H. Prolactin release is enhanced in proportion to excess visceral fat in obese women. Journal of Clinical Endocrinology & Metabolism 2004;89(9):4445-9.
155. Tuzcu A, Bahceci M, Dursun M, Turgut C, Bahceci S. Insulin sensitivity and hyperprolactinemia. Journal of Endocrinological Investigation 2003;26(4):341-6.
156. Nilsson L, Binart N, Bohlooly-Y M, Bramnert M, Egecioglu E, Kindblom J, et al. Prolactin and growth hormone regulate adiponectin secretion and receptor expression in adipose tissue. Biochemical & Biophysical Research Communications 2005;331(4):1120-6.
157. Asai-Sato M, Okamoto M, Endo M, Yoshida H, Murase M, Ikeda M, et al. Hypoadiponectinemia in lean lactating women: Prolactin inhibits adiponectin secretion from human adipocytes. Endocrine Journal 2006;53(4):555-62.
158. Wallaschofski H, Kobsar A, Sokolova O, Siegemund A, Stepan H, Faber R, et al. Differences in platelet activation by prolactin and leptin. Hormone & Metabolic Research 2004;36(7):453-7.
159. Serri O, Li L, Mamputu J-C, Beauchamp M-C, Maingrette F, Renier G. The influences of hyperprolactinemia and obesity on cardiovascular risk markers: effects of cabergoline therapy. Clinical Endocrinology 2006;64(4):366-70.
160. Kok P, Roelfsema F, Langendonk JG, de Wit CC, Frolich M, Burggraaf J, et al. Increased circadian prolactin release is blunted after body weight loss in obese premenopausal women. American Journal of Physiology - Endocrinology & Metabolism 2006;290(2):E218-24.
161. Galluzzi F, Salti R, Stagi S, La Cauza F, Chiarelli F. Reversible weight gain and prolactin levels--long-term follow-up in childhood. Journal of Pediatric Endocrinology 2005;18(9):921-4.
162. van den Beld AW, Visser TJ, Feelders RA, Grobbee DE, Lamberts SWJ. Thyroid hormone concentrations, disease, physical function, and mortality in elderly men.[see comment]. Journal of Clinical Endocrinology & Metabolism 2005;90(12):6403-9.
166. Katz R, Wong ND, Kronmal R, Takasu J, Shavelle DM, Probstfield JL, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. Circulation 2006;113(17):2113-9.
167. Purnell JQ, Brandon DD, Isabelle LM, Loriaux DL, Samuels MH. Association of 24-hour cortisol production rates, cortisol-binding globulin, and plasma-free cortisol levels with body composition, leptin levels, and aging in adult men and women. Journal of Clinical Endocrinology & Metabolism 2004;89(1):281-7.
168. Walker BR. Cortisol--cause and cure for metabolic syndrome? Diabetic Medicine 2006;23(12):1281-8.
169. Chiodini I, Adda G, Scillitani A, Coletti F, Morelli V, Di Lembo S, et al. Cortisol secretion in patients with type 2 diabetes: relationship with chronic complications. Diabetes Care 2007;30(1):83-8.
170. Fiocco AJ, Wan N, Weekes N, Pim H, Lupien SJ. Diurnal cycle of salivary cortisol in older adult men and women with subjective complaints of memory deficits and/or depressive symptoms: relation to cognitive functioning. Stress 2006;9(3):143-52.
171. Csernansky JG, Dong H, Fagan AM, Wang L, Xiong C, Holtzman DM, et al. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. American Journal of Psychiatry 2006;163(12):2164-9.
172. Tomlinson JW, Sherlock M, Hughes B, Hughes SV, Kilvington F, Bartlett W, et al. Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 activity in vivo limits glucocorticoid exposure to human adipose tissue and decreases lipolysis. Journal of Clinical Endocrinology & Metabolism 2007;92(3):857-64.
173. Walker BR. Extra-adrenal regeneration of glucocorticoids by 11beta-hydroxysteroid dehydrogenase type 1: physiological regulator and pharmacological target for energy partitioning. Proceedings of the Nutrition Society 2007;66(1):1-8.
174. Brach JS, Simonsick EM, Kritchevsky S, Yaffe K, Newman AB, Health AaBCSRG. The association between physical function and lifestyle activity and exercise in the health, aging and body composition study. Journal of the American Geriatrics Society 2004;52(4):502-9.
175. Di Francesco V, Zamboni M, Zoico E, Bortolani A, Maggi S, Bissoli L, et al. Relationships between leisure-time physical activity, obesity and disability in elderly men. Aging-Clinical & Experimental Research 2005;17(3):201-6.
176. Rimbert V, Montaurier C, Bedu M, Boirie Y, Morio B. Behavioral and physiological regulation of body fatness: a cross-sectional study in elderly men. International Journal of Obesity 2006;30(2):322-30.
177. Raguso CA, Kyle U, Kossovsky MP, Roynette C, Paoloni-Giacobino A, Hans D, et al. A 3-year longitudinal study on body composition changes in the elderly: role of physical exercise. Clinical Nutrition 2006;25(4):573-80.
178. Kim HJ, Lee JS, Kim CK. Effect of exercise training on muscle glucose transporter 4 protein and intramuscular lipid content in elderly men with impaired glucose tolerance. European Journal of Applied Physiology 2004;93(3):353-8.
179. Fatouros IG, Kambas A, Katrabasas I, Leontsini D, Chatzinikolaou A, Jamurtas AZ, et al. Resistance training and detraining effects on flexibility performance in the elderly are intensity-dependent. Journal of Strength & Conditioning Research 2006;20(3):634-42.
180. Bautmans I, Njemini R, Vasseur S, Chabert H, Moens L, Demanet C, et al. Biochemical changes in response to intensive resistance exercise training in the elderly. Gerontology 2005;51(4):253-65.
181. Vincent HK, Bourguignon C, Vincent KR. Resistance training lowers exercise-induced oxidative stress and homocysteine levels in overweight and obese older adults. Obesity 2006;14(11):1921-30.
182. Villareal DT, Miller BV, 3rd, Banks M, Fontana L, Sinacore DR, Klein S. Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults.[see comment]. American Journal of Clinical Nutrition 2006;84(6):1317-23.
183. Tsuzuku S, Kajioka T, Endo H, Abbott RD, Curb JD, Yano K. Favorable effects of non-instrumental resistance training on fat distribution and metabolic profiles in healthy elderly people. European Journal of Applied Physiology 2007;99(5):549-55.
184. Verney J, Kadi F, Saafi MA, Piehl-Aulin K, Denis C. Combined lower body

endurance and upper body resistance training improves performance and health parameters in healthy active elderly. European Journal of Applied Physiology 2006;97(3):288-97.
185. Villareal DT, Banks M, Sinacore DR, Siener C, Klein S. Effect of weight loss and exercise on frailty in obese older adults. Archives of Internal Medicine 2006;166(8):860-6.
186. Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, et al. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. American Journal of Clinical Nutrition 2006;84(5):1033-42.
187. Thomas GN, Hong AWL, Tomlinson B, Lau E, Lam CWK, Sanderson JE, et al. Effects of Tai Chi and resistance training on cardiovascular risk factors in elderly Chinese subjects: a 12-month longitudinal, randomized, controlled intervention study. Clinical Endocrinology 2005;63(6):663-9.
188. Coker RH, Hays NP, Williams RH, Brown AD, Freeling SA, Kortebein PM, et al. Exercise-induced changes in insulin action and glycogen metabolism in elderly adults. Medicine & Science in Sports & Exercise 2006;38(3):433-8.
189. Binder EF, Yarasheski KE, Steger-May K, Sinacore DR, Brown M, Schechtman KB, et al. Effects of progressive resistance training on body composition in frail older adults: results of a randomized, controlled trial. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2005;60(11):1425-31.
190. Evans EM, Racette SB, Peterson LR, Villareal DT, Greiwe JS, Holloszy JO. Aerobic power and insulin action improve in response to endurance exercise training in healthy 77-87 yr olds. Journal of Applied Physiology 2005;98(1):40-5.
191. Toraman NF, Ayceman N. Effects of six weeks of detraining on retention of functional fitness of old people after nine weeks of multicomponent training. British Journal of Sports Medicine 2005;39(8):565-8; discussion 568.
192. Tsourlou T, Benik A, Dipla K, Zafeiridis A, Kellis S. The effects of a twenty-four-week aquatic training program on muscular strength performance in healthy elderly women. Journal of Strength & Conditioning Research 2006;20(4):811-8.
193. Berke EM, Koepsell TD, Moudon AV, Hoskins RE, Larson EB. Association of the built environment with physical activity and obesity in older persons. American Journal of Public Health 2007;97(3):486-92.
194. Mazzali G, Di Francesco V, Zoico E, Fantin F, Zamboni G, Benati C, et al. Interrelations between fat distribution, muscle lipid content, adipocytokines, and insulin resistance: effect of moderate weight loss in older women. American Journal of Clinical Nutrition 2006;84(5):1193-9.
195. Wannamethee SG, Shaper AG, Whincup PH. Modifiable lifestyle factors and the metabolic syndrome in older men: Effects of lifestyle changes. Journal of the American Geriatrics Society 2006;54(12):1909-14.
196. Newman AB, Lee JS, Visser M, Goodpaster BH, Kritchevsky SB, Tylavsky FA, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. American Journal of Clinical Nutrition 2005;82(4):872-8; quiz 915-6.
197. van Strien T, van de Laar FA, van Leeuwe JFJ, Lucassen PLBJ, van den Hoogen HJM, Rutten GEHM, et al. The dieting dilemma in patients with newly diagnosed type 2 diabetes: does dietary restraint predict weight gain 4 years after diagnosis? Health Psychology 2007;26(1):105-12.
198. Rideout CA, Linden W, Barr SI. High cognitive dietary restraint is associated with increased cortisol excretion in postmenopausal women. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2006;61(6):628-33.
199. Phillips SM, Hartman JW, Wilkinson SB. Dietary protein to support anabolism with resistance exercise in young men. Journal of the American College of Nutrition 2005;24(2):134S-139S.
200. Evans WJ. Protein nutrition, exercise and aging. Journal of the American College of Nutrition 2004;23(6 Suppl):601S-609S.
201. Guillet C, Zangarelli A, Gachon P, Morio B, Giraudet C, Rousset P, et al. Whole body protein breakdown is less inhibited by insulin, but still responsive to amino acid, in nondiabetic elderly subjects. Journal of Clinical Endocrinology & Metabolism 2004;89(12):6017-24.
202. Flakoll P, Sharp R, Baier S, Levenhagen D, Carr C, Nissen S. Effect of beta-hydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. Nutrition 2004;20(5):445-51.
203. Tidermark J, Ponzer S, Carlsson P, Soderqvist A, Brismar K, Tengstrand B, et al. Effects of protein-rich supplementation and nandrolone in lean elderly women with femoral neck fractures. Clinical Nutrition 2004;23(4):587-96.
204. Bartali B, Semba RD, Frongillo EA, Varadhan R, Ricks MO, Blaum CS, et al. Low micronutrient levels as a predictor of incident disability in older women. Archives of Internal Medicine 2006;166(21):2335-40.
205. Hofbauer KG, Nicholson JR, Boss O. The obesity epidemic: current and future pharmacological treatments. Annual Review of Pharmacology & Toxicology 2007;47:565-92.
206. Carter CS, Onder G, Kritchevsky SB, Pahor M. Angiotensin-converting enzyme inhibition intervention in elderly persons: effects on body composition and physical performance. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2005;60(11):1437-46.
207. Cesari M, Kritchevsky SB, Baumgartner RN, Atkinson HH, Penninx BWHJ, Lenchik L, et al. Sarcopenia, obesity, and inflammation--results from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study. American Journal of Clinical Nutrition 2005;82(2):428-34.
208. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007;334(7588):299.
209. Richelsen B, Tonstad S, Rossner S, Toubro S, Niskanen L, Madsbad S, et al. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. Diabetes Care 2007;30(1):27-32.
210. Bougoulia M, Triantos A, Koliakos G. Effect of weight loss with or without orlistat treatment on adipocytokines, inflammation, and oxidative markers in obese women. Hormones 2006;5(4):259-69.
211. Zelber-Sagi S, Kessler A, Brazowsky E, Webb M, Lurie Y, Santo M, et al. A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. Clinical Gastroenterology & Hepatology 2006;4(5):639-44.
212. Arterburn DE, Crane PK, Veenstra DL. The efficacy and safety of sibutramine for weight loss: a systematic review. Archives of Internal Medicine 2004;164(9):994-1003.
213. Gursoy A, Erdogan MF, Cin MO, Cesur M, Baskal N. Comparison of orlistat and sibutramine in an obesity management program: efficacy, compliance, and weight regain after noncompliance. Eating & Weight Disorders: EWD 2006;11(4):e127-32.
214. Scholze J, Grimm E, Herrmann D, Unger T, Kintscher U. Optimal treatment of obesity-related hypertension: the Hypertension-Obesity-Sibutramine (HOS) study.[see comment]. Circulation 2007;115(15):1991-8.
215. Di Francesco V, Sacco T, Zamboni M, Bissoli L, Zoico E, Mazzali G, et al. Weight loss and quality of life improvement in obese subjects treated with sibutramine: a double-blind randomized multicenter study. Annals of Nutrition & Metabolism 2007;51(1):75-81.
216. Yee BJ, Phillips CL, Banerjee D, Caterson I, Hedner JA, Grunstein RR. The effect of sibutramine-assisted weight loss in men with obstructive sleep apnoea. International Journal of Obesity 2007;31(1):161-8.
217. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S, Group RI-ES. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study.[see comment][erratum appears in Lancet. 2005 Jul 30-Aug 5;366(9483):370]. Lancet 2005;365(9468):1389-97.
218. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, Group RI-NAS. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial.[see comment][erratum appears in JAMA. 2006 Mar 15;295(11):1252]. JAMA 2006;295(7):761-75.
219. Despres J-P, Golay A, Sjostrom L, Rimonabant in Obesity-Lipids Study G. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia.[see comment]. New England Journal of Medicine 2005;353(20):2121-34.
220. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF, Group RI-DS. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study.[see comment][erratum appears in Lancet. 2006 Nov 11;368(9548):1650]. Lancet 2006;368(9548):1660-72.
221. Yan ZC, Liu DY, Zhang LL, Shen CY, Ma QL, Cao TB, et al. Exercise reduces adipose tissue via cannabinoid receptor type 1 which is regulated by peroxisome proliferator-activated receptor-delta. Biochemical & Biophysical Research Communications 2007;354(2):427-33.
222. Curioni C, Andre C. Rimonabant for overweight or obesity. Cochrane Database of Systematic Reviews 2006(4):CD006162.
223. O'Brien PE, Dixon JB, Laurie C, Skinner S, Proietto J, McNeil J, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial.[see comment][summary for patients in Ann Intern Med. 2006 May 2;144(9):I12; PMID: 16670127]. Annals of Internal Medicine 2006;144(9):625-33.
224. Fatima J, Houghton SG, Iqbal CW, Thompson GB, Que FL, Kendrick ML, et al. Bariatric surgery at the extremes of age. Journal of Gastrointestinal Surgery 2006;10(10):1392-6.
225. Taylor CJ, Layani L. Laparoscopic adjustable gastric banding in patients > or =60 years old: is it worthwhile? Obesity Surgery 2006;16(12):1579-83.