

VU Research Portal

What aspects of body fat are particularly hazardous and how do we measure them?

Snijder, M.B.; van Dam, R.M.; Visser, M.; Seidell, J.C.

published in

International Journal of Epidemiology
2006

DOI (link to publisher)

[10.1093/ije/dyi253](https://doi.org/10.1093/ije/dyi253)

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Snijder, M. B., van Dam, R. M., Visser, M., & Seidell, J. C. (2006). What aspects of body fat are particularly hazardous and how do we measure them? *International Journal of Epidemiology*, 35(1), 83-92.
<https://doi.org/10.1093/ije/dyi253>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

REVIEWS

What aspects of body fat are particularly hazardous and how do we measure them?

MB Snijder,^{1,2*} RM van Dam,^{1,3} M Visser^{1,2} and JC Seidell^{1,2}

Introduction

There is a worldwide increase in the prevalence of obesity,¹ which contributes to a higher incidence of cardiovascular disease and type 2 diabetes mellitus.^{2,3} It has been projected that by 2020, type 2 diabetes and cardiovascular disease will account for almost three-fourth of all deaths worldwide.⁴

Since the 1950s it has been recognized that apart from overall obesity the distribution of body fat can influence disease risk.⁵ In particular an abdominal fat distribution is associated with metabolic disturbances and increased risk of cardiovascular disease and type 2 diabetes. In the present paper we will discuss different ways to measure body composition and focus on which aspects of body fatness (e.g. central vs total, subcutaneous vs visceral) are particularly hazardous in terms of morbidity and mortality.

How to measure body fat?

Body fat measurements

Numerous techniques are available to estimate body composition and fat distribution, and the method to use will depend on the aim of the study, economic resources, availability, time, and sample size.^{6–8} Multi-compartment models, such as underwater weighing, dilution techniques and dual-energy X-ray absorptiometry (DXA) are all reliable methods to obtain accurate measures of total body fat. However, because of their costs in terms of time and money, these methods are not practical in large epidemiological studies and for routine clinical use. In these situations, body mass index (BMI) is often used and assumed to represent the degree of body fat. BMI, however, does not distinguish between fat mass and lean (non-fat) mass. For example, well-trained body builders have a very low percentage of body fat, but their BMI may be in the overweight range because of their large lean (muscle) mass. In addition, in the elderly and non-Caucasian populations, the relationship between BMI and body fatness may be different as compared with younger Caucasian populations.^{9–14}

Another potential limitation of the BMI is that the distribution of fat over the body is not captured. Many studies have shown that an abdominal fat distribution, independent of overall obesity, is associated with metabolic disturbances and increased disease risk.^{15–23} An increased abdominal fat accumulation is largely caused by the accumulation of visceral (or intra-abdominal) fat (for distinction of these fat depots, see Figure 1). Owing to metabolic differences between different fat depots, they differ in their role of predicting metabolic disturbances and diseases. Table 1 summarizes the capability of the most commonly used methods to assess total adiposity and fat distribution. Abdominal obesity is usually assessed by the easily measured waist circumference, the waist-to-hip circumference ratio (WHR), or the less-commonly used sagittal abdominal diameter (SAD). By the use of sophisticated imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT), different fat depots can be distinguished at the waist level, and it has been shown that in particular the visceral fat depot is associated with metabolic disease risk.^{24–30} Because the SAD or waist circumference alone are more strongly correlated with visceral fat than the WHR,^{31–35} guidelines tend to focus on waist circumference to estimate disease risk as suggested by Lean *et al.*³⁶ These widely used cut-points (i.e. 102 cm for men and 88 cm for women) were originally based on a replacement of the classification of BMI,³⁶ but other cut-points have also been suggested on the basis of relationships with visceral fat area.³⁷

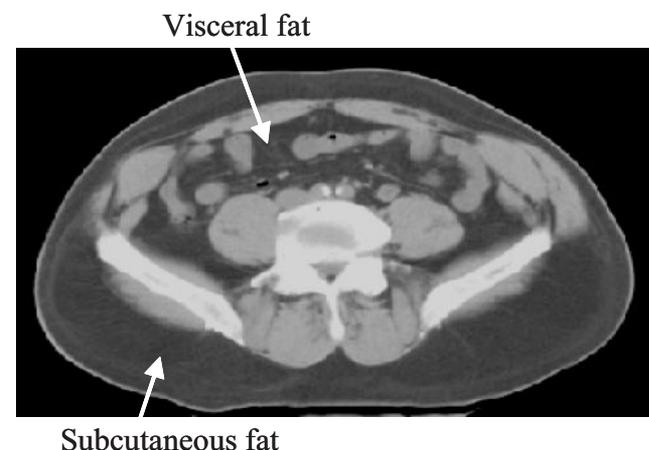


Figure 1 Cross-section of the abdomen in which subcutaneous and visceral fat can be distinguished. Lighter-coloured areas are muscles, bones, and organs

¹ Institute of Health Sciences, Faculty of Earth and Life Sciences, Vrije Universiteit Amsterdam, The Netherlands.

² Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands.

³ Department of Nutrition, Harvard School of Public Health, Boston, MA, USA.

* Corresponding author. Institute of Health Sciences, Faculty of Earth and Life Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands. E-mail: marieke.snijder@falw.vu.nl

Table 1 Capability of different body fat measurements to estimate total body fat and fat distribution

Method	Capability measuring total body fat	Capability measuring fat distribution	Applicability in large population studies
CT	Moderate	Very high	Low
MRI	High	Very high	Low
DXA	Very high	High	Moderate
Densitometry	Very high	Very low	Low
Dilution techniques	High	Very low	Moderate
BIA	Moderate	Very low	High
Anthropometry			
BMI	Moderate	Very low	Very high
WC, HC, WHR, SAD	Low	High	Very high
Skinfolds	Moderate	Moderate	High

CT, computed tomography; MRI, magnetic resonance imaging; DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; SAD, sagittal abdominal diameter.

These simple cut-points may be helpful for the classification of Caucasian adults, but they are probably less appropriate in other ethnic groups³⁸ or older age groups.³⁹ No large or consistent differences have been found between SAD and waist circumference in relation to visceral fat.^{31,33–35,40,41}

The waist circumference, however, is not always a stronger predictor of type 2 diabetes^{42,43} and other cardiovascular risk^{16,20,44–46} than the WHR. Because a higher WHR can be the result of a larger waist as well as a smaller hip, this suggests that a smaller hip (representing either lower muscle and/or fat mass at the hips) may be involved in determining the increased risk associated with an increased WHR. Hip circumference is more strongly associated with leg fat mass, but also with leg lean mass (particularly in men).⁴⁷ Indeed, WHR has been related to both a larger trunk fat mass, and a smaller leg fat mass (both sexes) and leg lean mass (men).⁴⁷ In another study, WHR has been related to both larger visceral fat and smaller leg muscle areas in men.⁴⁸ Several studies have found that a smaller hip circumference (for a given waist circumference) is associated with an increased risk.^{43,49–56}

Early studies on fat distribution often used skinfold measurements to characterize subcutaneous fat distribution.⁵⁷ Subcutaneous fat patterns were described using Z-score patterns, ratios of skinfolds (e.g. triceps/subscapular skinfold ratio and ratio of the sum of trunk skinfolds to the sum of skinfolds on extremities) and principal components analyses. The most promising and simple indicator of central fat distribution using skinfolds seems to be the subscapular skinfold. A prospective study showed that the subscapular skinfold predicted coronary heart disease in men independently of BMI and other cardiovascular risk factors⁵⁸ but studies that have compared the use of skinfold over and above the use of body circumferences or circumference ratios are rare. A few studies have compared the associations between skinfolds and circumferences in relation to components of the metabolic syndrome^{59,60} and these showed that correlations of waist circumference with risk factors were either similar or stronger compared with those of the subscapular skinfold. Misra *et al.* have proposed that the subscapular skinfold should be considered

as an indicator of central fat distribution separately of the waist circumference.⁶¹ It is, however, difficult to say with certainty that the measurements of skinfolds improve substantially the prediction of disease independently of body circumferences.

Anthropometry in specific groups: older persons

The composition of the body changes with age, and this may have serious implications for the interpretation of anthropometric data of older persons. First, older persons are generally shorter than younger persons owing to secular trends in height and owing to shrinkage of the spine because of vertebral bone loss, kyphosis, and scoliosis.^{62,63} Consequently, the BMI of older persons may be overestimated and it is, therefore, preferable to use a body height measured in early life to calculate the BMI of older persons. Second, with age the amount of lean body mass decreases, a process called sarcopenia.⁶⁴ Sarcopenia occurs even in weight stable persons owing to a concomitant increase in the amount of body fat.^{65,66} The relationship between BMI and percentage of body fatness has been shown to be dependent on age.⁹ Data from the Rosetta Study show that older adults have, on average, more fat than younger adults at any given BMI.⁶⁷ Prediction equations to estimate body composition from BMI will generally underestimate the amount of body fat in the elderly.⁶⁸ Also, a similar skinfold thickness in young and older persons represents a higher percentage of body fatness in older persons.⁶⁸ Age-specific prediction equations should be used to estimate body fatness from skinfold thickness.⁶⁹ A recent study in older men and women (mean age 60.4 years) showed that the change in skinfold thickness over time did not predict change in body fat mass, suggesting its limited use in longitudinal studies.⁷⁰ Finally, the distribution of body fat also changes with age because relatively more fat accumulates in the abdomen and less fat at the extremities.^{71,72} Waist circumference has been suggested as an indicator of overall body fatness in older persons.⁷³ Changes in waist and hip circumference were better anthropometric predictors of change in body fat mass over a 10 year period compared with changes in skinfold thickness.⁷⁰ However, in persons aged 70–79 years the explained variance in total body fat remained higher for BMI than for waist circumference.⁷⁴

The waist circumference has been shown to be similarly correlated with the amount of visceral fat in young and older persons.⁷⁵ In several studies, waist circumference was a better predictor of visceral fat in older persons compared with SAD or WHR.^{32,76} However, in very old men and women (>70 years) SAD was a better predictor of visceral fat compared with the waist circumference.⁷⁴ In that study the BMI performed as good as the waist circumference in predicting visceral fat.⁷⁴ An alternative, non-anthropometric method proposed to estimate the amount of visceral fat in older persons is subregional DXA.⁴⁰ The prediction of visceral fat by DXA was better compared with the waist circumference but was similar to the SAD.

For a given waist circumference, visceral fat has been shown to be higher in older persons compared with younger persons,⁷⁶ suggesting that absolute levels of waist circumference should be interpreted differently in younger and older persons. Prediction equations for visceral fat generally include age.⁷⁷ Whether the proposed waist circumference cut-points are useful for the prediction of cardiovascular disease risk factors in older persons is still unclear.^{78,79}

Anthropometry in specific groups: ethnicity

Several studies have shown a race difference in the association between BMI and percentage of body fat. For a given BMI, Chinese, Malay, Indian, Taiwanese, and Indonesian men and women have a higher percentage of body fat compared with Caucasians.^{10–14} Differences in trunk-to-leg-length ratio, slenderness, and muscularity may contribute to these racial differences in the percentage of body fat–BMI relationship.^{80,81} No clear differences in the relation between percentage of body fat and BMI have been observed for African-Americans vs Caucasians.⁶⁷ Based on these findings and the observed differences in the relation between BMI and disease risk, lower BMI cut-points have been suggested to define overweight and obesity for specific ethnic groups.^{10–12,82–84} However, the expert committee of the WHO has not redefined the cut-points for specific Asian populations, because available data do not necessarily indicate a clear BMI cut-off point for all Asian ethnic groups.⁸⁵

Ethnic differences in the relation between waist circumference and visceral fat have frequently been reported. Asian ethnic groups generally have a smaller waist circumference compared with Caucasians, although this is not necessarily true for Asian emigrants who are generally affluent and have more generalized and abdominal obesity.^{38,86} Despite the smaller waist circumference, the visceral fat mass is higher for Asians compared with Caucasians and African-Americans.^{87,88} Moreover, for specific Asian groups disease risks may already be increased at a lower level of waist circumference, suggesting that a lowering of the waist circumference cut-points should be considered for these ethnic groups.^{38,82,83} For a similar waist circumference (or WHR) and BMI, African-Americans have a lower visceral fat mass compared with Caucasians.^{89–91} Although a larger amount of visceral fat is associated with a higher disease risk in both African-Americans and Caucasians, similar amounts of visceral fat are associated with different levels of metabolic risk factors in these groups.⁹² The cause of the more diabetogenic profile in African-Americans as compared with Caucasians is currently unknown.⁹³

Epidemiology of body fat measures and associated disease risk

Time trends and prevalence of abdominal obesity

Secular changes in the prevalence of overweight and obesity as measured by BMI have been reported in many countries over the last decades.¹ Several studies have reported on secular changes in waist circumference and WHR. In German adults and in British adolescents, stronger increases over time in the average waist circumference than in relative weight were observed.^{94,95} A more rapid secular increase in WHR than in BMI was shown in Swedish women.⁹⁶ Lahti-Koski *et al.*⁹⁷ observed a similar secular change but did not compare this to the time trend in BMI. A more recent study from Sweden observed a significant increase in BMI but not in WHR in the period from 1985 to 2002.⁹⁸ A Dutch study showed similar secular changes in waist circumference as compared with BMI over a short period of time.⁹⁹ Large increases in the waist circumference were shown in the US adult population from 1960 to 2000 in all categories of BMI.¹⁰⁰ It has been suggested that the waist circumference is

more sensitive to changes in energy balance (e.g. decreased physical activity) than the BMI.⁹⁹ With decreasing physical activity muscle may be gradually replaced by fat mass and this may have less effect on overall body weight than on the waist circumference.

The prevalence of abdominal obesity according to these cut-points has been reported for several countries. In the US the age-adjusted prevalence of abdominal adiposity has tripled in men from ~13% in 1960–62 to 38% in 1999–2000. In women the prevalence increased from ~19 to 60% over the same period.¹⁰⁰ In The Netherlands the prevalence of abdominal obesity was ~15% in men and 21% in women in 1993–97.⁹⁹ These prevalences were similar to those of the US some 30 years earlier.

Body fat measures in relation to cardiovascular disease and type 2 diabetes

The worldwide increase in the prevalence of (abdominal) obesity is alarming because of the associated disease risk, in particular type 2 diabetes and cardiovascular diseases. Several studies were conducted to compare the contribution of measures of overall obesity (BMI) and abdominal obesity (waist circumference, WHR, SAD) with disease risk. Overall, it can be concluded that persons with a BMI in the normal weight range can still be at increased risk of metabolic disturbances if the WHR or waist circumference is increased, and that the combination of a high BMI and a high WHR results in a particularly high risk of an unfavourable metabolic profile, type 2 diabetes, and cardiovascular diseases.^{15–23}

In the elderly, few studies have directly compared BMI and waist circumference as predictors of metabolic abnormalities. The limited available data suggest that waist circumference and/or SAD are better indicators of cardiovascular risk factors in older men and women compared with BMI.^{21,101} However, in other studies waist circumference contributed little to the prediction of disease risk after BMI had been taken into account.^{102,103}

Regarding the comparison of waist circumference and WHR as predictors of metabolic disturbances and the risk of cardiovascular diseases, results have been inconsistent. Some studies have found waist circumference a stronger correlate of metabolic risk factors and cardiovascular disease than the WHR,^{31,104,105} whereas others found no difference,^{106–108} or found that the WHR was superior.^{16,20,42–46} The last observation resulted in several studies that investigated the separate contributions of waist and hip circumferences to disease risk. These studies consistently show that a smaller hip circumference, for a given waist circumference, is related to an increased risk for metabolic disturbances,^{49–51,53} type 2 diabetes,^{43,50,52,54} and cardiovascular disease and mortality.^{52,55,56} These results suggest that the measurement of hip circumference can contribute to the prediction of cardiovascular disease risk.

If waist circumference or WHR were compared with the SAD in the prediction of metabolic disturbances and disease risk, some studies found SAD a stronger correlate than waist circumference, WHR, and BMI.^{109–111} However, waist and SAD correlated similarly (but stronger than WHR) with metabolic variables in another study.³¹ In others, none of these three measures was superior in their association with metabolic disturbances or cardiovascular disease risk.¹⁰⁶

Considering more sophisticated body composition measurements, numerous studies have shown a consistent and strong association of CT-measured visceral fat area in relation to metabolic or disease risk.^{24–30} Results from the literature are not consistent on whether abdominal subcutaneous fat area contributes to an unfavourable metabolic profile and cardiovascular disease, independently of visceral fat area.¹¹² In the Health, Aging and body composition Study, a larger amount of abdominal subcutaneous fat was substantially and independently associated with higher glucose and lipid levels, although associations were stronger for visceral fat.³⁰ This independent association of subcutaneous abdominal fat with metabolic risk factors agrees with findings in earlier smaller studies.^{113,114}

Studies using DXA or CT to estimate fat and muscle content at the legs found that in particular more subcutaneous fat at the legs, and to a lesser extent muscle mass at the legs, was associated with a more favourable cardiovascular risk profile (for a given amount of abdominal fat).^{30,47,115,116} Thus, the association of a smaller hip circumference (for a given waist circumference) with increased disease risk can mostly be explained by larger peripheral fat mass.

Body fat distribution and premature mortality

Results for measures of body fatness and risk of premature mortality are more difficult to interpret than results for disease risk. First, causes of mortality can vary substantially for different populations and the effects of body fatness on these underlying causes will be different. Second, the induction time for effects of body fatness on mortality is likely to be longer than for effects on the development of diseases.¹¹⁷ Third, associations between anthropometry and mortality seem particularly prone to bias owing to ‘reverse causation’: (subclinical) diseases that are related to increased mortality can result in weight loss.^{117,118} Fourth, most studies of adiposity and mortality have used BMI as a measure of body fatness. Because BMI can reflect both fat and lean body mass, variation in lean body mass that may be associated with mortality can complicate the interpretation of results for BMI. Indeed, the U-shaped association between BMI and mortality that has been observed in some studies may reflect the opposite monotonous relations of lean mass (beneficial) and fat mass (detrimental) with risk of premature mortality.^{119,120} Overall, study findings have indicated that obesity (i.e. BMI ≥ 30 kg/m²) increases the risk of premature death.^{118,121} However, results for lower levels of BMI in relation to mortality have been less consistent, and methodological limitations of studies have undoubtedly contributed to variation in results.¹¹⁸

Studies of body fat distribution and premature mortality have been limited to studies of anthropometric measures of body fat distribution. In several studies, larger waist circumference,¹²² larger WHR,^{16,44,123} larger iliac-to-thigh circumference,¹²⁴ larger SAD,¹²⁵ and smaller hip circumference^{52,55,126} were substantially associated with risk of premature mortality after adjustment for BMI. Because BMI may also reflect variation in lean body mass, one could argue that these independent associations are owing to incomplete adjustment for overall body fatness. However, measures of central fat distribution also remained associated with premature mortality after adjustment for overall body fatness assessed by skinfold thickness^{44,127} or

bioelectrical impedance.^{128,129} These results are consistent with results for morbidity that suggest that given a certain degree of body fatness, it is preferable to have fat stored in the femoral-gluteal region instead of the abdominal region. It should be noted that studies of body fat distribution and mortality have mostly been conducted in white populations. Large waist circumference was a stronger predictor of premature mortality than BMI in black men,¹³⁰ but neither measure was clearly associated with mortality in black women¹³¹ possibly owing to the limited size of the study.

Pathophysiology

The role of free fatty acids

Although the concept that obesity, in particular abdominal obesity, is an important cause of metabolic disturbances is generally accepted, the exact pathophysiological mechanisms are not completely known. It is widely acknowledged that fatty acids play an important role in the development of type 2 diabetes.^{132–134} When free fatty acid levels in the circulation are high (as in abdominal obesity¹³⁵), glucose uptake and oxidation by muscle and other organs is inhibited through several mechanisms. The pancreas will compensate the diminished glucose uptake by increasing insulin secretion, but in many of the insulin resistant persons, the beta-cell eventually fails. In addition, free fatty acids will accumulate in organs (so-called ‘lipotoxicity’ or ‘ectopic fat storage’), particularly in the muscle and in the liver, but also in the pancreas. Accumulation of fat in non-adipose tissue may further promote insulin resistance and impair beta-cell function, which are the two key features in the development of type 2 diabetes.^{133,136}

Metabolic effects of different fat stores

Visceral fat is more sensitive to lipolytic stimuli, and less sensitive to anti-lipolytic stimuli (such as insulin), compared with subcutaneous fat. Therefore, visceral fat is more likely to release free fatty acids into the circulation causing increased free fatty acid levels, which may lead to ectopic fat storage in muscle, liver, and pancreas.^{133,137–139} It has been argued, however, that the quantitative contribution to circulating free fatty acid levels of subcutaneous fat is probably much larger because there simply is much more of it.^{112,140} However, the release of free fatty acids from visceral fat into the portal vein that directly leads to the liver, may cause reduced hepatic insulin clearance, increased gluconeogenesis and increased dyslipidaemia.^{141,142} Removal of visceral fat reversed hepatic insulin resistance and prevented age-induced insulin resistance and glucose intolerance in rats,^{143,144} whereas removal of equivalent amounts of subcutaneous fat had little effect.¹⁴⁴ And a pilot study in humans suggests that omentectomy (removal of part of visceral fat) might improve the metabolic profile.¹⁴⁵

From epidemiological studies (see above) it is unclear whether a larger abdominal subcutaneous fat mass also contributes to an increased disease risk, independently of visceral fat. In a study in six obese women, surgical removal of abdominal subcutaneous fat (55–65% of subcutaneous abdominal fat corresponding to 4.3 \pm 1.1 litres) by liposuction, led to improvement of insulin sensitivity and glucose levels after 3–4 weeks.¹⁴⁶ Long-term consequences of subcutaneous liposuction are

inconsistent, however.^{147–149} Abdominal subcutaneous fat can be further divided into deep and superficial subcutaneous adipose tissue. It was demonstrated that the amount of deep subcutaneous adipose tissue had a much stronger association with insulin resistance than superficial subcutaneous fat, which may be due to differences in lipolysis.^{150,151} This difference between different types of subcutaneous fat may have contributed to the inconsistent results regarding removal of total abdominal subcutaneous fat and changes in insulin resistance.

As also described in a previous section, recent studies suggest that more peripheral subcutaneous fat in the legs, for a given amount of abdominal fat, may be associated with a more favourable cardiovascular risk profile.^{47,115,116} It has been suggested that the femoral-gluteal fat depot plays a protective role by acting as a 'sink' for circulating FFA.¹⁵² Adipocytes in the femoral region are relatively insensitive to lipolytic stimuli and have a high sensitivity for anti-lipolytic stimuli. The enzyme lipoprotein lipase (LPL) plays an important role in the uptake of free fatty acids from the circulation, and particularly in women, the femoral fat depot has a relatively high LPL activity and relatively low rate of basal and stimulated lipolysis.^{153,154} Therefore, the femoral-gluteal region is more likely to effectively take up FFA from the circulation and is less likely to release them readily. As a result of FFA uptake in the femoral-gluteal region, detrimental ectopic fat storage in the liver, skeletal muscle, and pancreas, may be prevented.¹³⁶

In line with this potential mechanism, transplantation of subcutaneous adipose tissue in lipoatrophic animals reversed elevated glucose levels¹⁵⁵ and subcutaneous lipectomy caused metabolic disturbances in hamsters.¹⁵⁶ In humans, the critical role of subcutaneous adipose tissue is illustrated by the observation that adipose tissue deficiency (lipodystrophy or lipoatrophy) is accompanied by ectopic fat storage, insulin resistance, and type 2 diabetes.¹³⁶ No studies have been conducted that compared the effects of liposuction in the femoral-gluteal region with liposuction in the abdominal region. The medical drug thiazolidinediones increases insulin sensitivity in insulin resistant patients, while a considerable amount of total body fat is accumulated. These drugs promote preadipocyte differentiation into mature adipocytes, in particular in the gluteal regions.¹⁵⁷ These new mature adipocytes have a better capacity to store lipids, which may result in reduced ectopic fat deposition, and consequently in improved insulin resistance and beta-cell function.

Alternative or additional explanations for the associations of fat depots and disease risk

Adipose tissue secretes many signalling proteins and cytokines with broad biological activity and critical functions. Some of these adipokines may be involved in the development of insulin resistance in obesity.¹⁵⁸ The secretory functions of adipose tissue is probably also subject to regional variations.¹⁵⁹ Therefore, the different associations of abdominal and femoral-gluteal subcutaneous fat depots with metabolic risk factors may be due to differences in the secretion of adipokines between the fat depots. There are known differences in endocrine secretion of leptin, adiponectin, and IL-6 between abdominal subcutaneous fat and visceral fat,^{160–162} whereas the existence of regional

differences in the secretion of plasminogen activator inhibitor-1 (PAI-1) and TNF-alpha is controversial.¹⁵⁹ Little is known about possible differences in the secretion of these adipokines between abdominal and femoral-gluteal subcutaneous fat. In addition, there are probably many more yet undiscovered proteins, differently secreted by different fat depots, which might influence metabolic function. Clearly, more research in this area is needed.

There are several factors that may influence body fat patterning as well as the development of metabolic disturbances and may, therefore, underlie or confound the associations between these phenomena. These factors include behavioural factors (smoking, physical activity, diet), hormonal factors (disturbances in glucocorticoid metabolism, sex hormones, growth hormone), and demographic factors such as age and gender.^{163,164} Recently, it has been shown that fat depots are also innervated by the parasympathetic nervous system, in addition to the earlier finding of a sympathetic innervation, and that stimulation of the parasympathetic nervous system promotes lipid accumulation (anabolic function).¹⁶⁵ Kreier *et al.*¹⁶⁶ have proposed an unbalanced and disturbed autonomic nervous system function as a major cause of changed body fat storage and the metabolic syndrome.

Conclusions

In conclusion, it is supported by mechanistic studies, studies of metabolic risk factors, and studies of cardiovascular disease and premature mortality, that body fat distribution is relevant for the risk of cardiovascular disease and mortality. Time trend studies have shown that there is a consistent increase over time in the prevalence of obesity and, particularly, abdominal obesity, which is likely to contribute to a higher incidence of type 2 diabetes, cardiovascular disease, and mortality.

Several methods are available to measure body fatness, and the choice largely depends on the purpose. For clinical applications it should be considered that usually no information on body fatness is collected at all and the health problems of being overweight are often not discussed by clinicians with their patients.¹⁶⁷ The systematic, repeated collection of a measure of body fatness in clinical practice may already be an important step forward and the simplicity of the measurement is an important consideration. For this purpose, BMI can be an adequate measure of body fatness in adults. However, waist circumference may be a simple alternative that also captures information on abdominal fat distribution and may be less affected by variation in lean mass. The WHR is more difficult to interpret because it may reflect an effect of larger waist as well as a smaller hip circumference. The SAD can be used instead of waist circumference but has not consistently been shown to be superior for the prediction of disease risk.

For large epidemiological studies the BMI can capture most of the relevant variation in body fatness depending on the age of the study population. However, many studies have shown that the collection of information on body fat distribution (waist circumference, WHR, SAD, DXA) can provide additional insights. For mechanistic studies and intervention studies with exposures that may affect body fat distribution, accurate methodology to assess fat depots (CT, MRI, DXA) is necessary.

References

- 1 Seidell JC. Epidemiology of obesity. *Semin Vasc Med* 2005;**5**:3–14.
- 2 Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;**414**:782–87.
- 3 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;**27**:1047–53.
- 4 World Health Organization. Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation. WHO Technical report series. Geneva, Switzerland: WHO, 2002, p. 916.
- 5 Vague P. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. 1956. *Nutrition* 1999;**15**:89–90; discussion 91.
- 6 Lukaski HC. Methods for the assessment of human body composition: traditional and new. *Am J Clin Nutr* 1987;**46**:537–56.
- 7 Jebb SA, Elia M. Techniques for the measurement of body composition: a practical guide. *Int J Obes Relat Metab Disord* 1993;**17**:611–21.
- 8 van der Kooy K, Seidell JC. Techniques for the measurement of visceral fat: a practical guide. *Int J Obes Relat Metab Disord* 1993;**17**:187–96.
- 9 Jackson AS, Stanforth PR, Gagnon J *et al.* The effect of sex, age and race on estimating percentage body fat from body mass index: The Heritage Family Study. *Int J Obes Relat Metab Disord* 2002;**26**:789–96.
- 10 Deurenberg-Yap M, Chew SK, Deurenberg P. Elevated body fat percentage and cardiovascular risks at low body mass index levels among Singaporean Chinese, Malays and Indians. *Obes Rev* 2002;**3**:209–15.
- 11 Chang CJ, Wu CH, Chang CS *et al.* Low body mass index but high percent body fat in Taiwanese subjects: implications of obesity cutoffs. *Int J Obes Relat Metab Disord* 2003;**27**:253–59.
- 12 Gurruci S, Hartriyanti Y, Hautvast JG, Deurenberg P. Relationship between body fat and body mass index: differences between Indonesians and Dutch Caucasians. *Eur J Clin Nutr* 1998;**52**:779–83.
- 13 Ko GT, Tang J, Chan JC *et al.* Lower BMI cut-off value to define obesity in Hong Kong Chinese: an analysis based on body fat assessment by bioelectrical impedance. *Br J Nutr* 2001;**85**:239–42.
- 14 He M, Tan KC, Li ET, Kung AW. Body fat determination by dual energy X-ray absorptiometry and its relation to body mass index and waist circumference in Hong Kong Chinese. *Int J Obes Relat Metab Disord* 2001;**25**:748–52.
- 15 Ohlson LO, Larsson B, Svardstudd K *et al.* The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 1985;**34**:1055–58.
- 16 Folsom AR, Kushi LH, Anderson KE *et al.* Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med* 2000;**160**:2117–28.
- 17 Prineas RJ, Folsom AR, Kaye SA. Central adiposity and increased risk of coronary artery disease mortality in older women. *Ann Epidemiol* 1993;**3**:35–41.
- 18 Rimm EB, Stampfer MJ, Giovannucci E *et al.* Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol* 1995;**141**:1117–27.
- 19 Huang B, Rodriguez BL, Burchfiel CM, Chyou PH, Curb JD, Sharp DS. Associations of adiposity with prevalent coronary heart disease among elderly men: the Honolulu Heart Program. *Int J Obes Relat Metab Disord* 1997;**21**:340–48.
- 20 Rexrode KM, Carey VJ, Hennekens CH *et al.* Abdominal adiposity and coronary heart disease in women. *JAMA* 1998;**280**:1843–48.
- 21 Turcato E, Bosello O, Di Francesco V *et al.* Waist circumference and abdominal sagittal diameter as surrogates of body fat distribution in the elderly: their relation with cardiovascular risk factors. *Int J Obes Relat Metab Disord* 2000;**24**:1005–10.
- 22 Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. *Arch Intern Med* 2002;**162**:2074–79.
- 23 Lakka HM, Lakka TA, Tuomilehto J, Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. *Eur Heart J* 2002;**23**:706–13.
- 24 Fujimoto WY, Bergstrom RW, Boyko EJ *et al.* Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. *Diabetes Care* 1999;**22**:1808–12.
- 25 Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care* 2000;**23**:465–71.
- 26 Brochu M, Starling RD, Tchernof A, Matthews DE, Garcia-Rubi E, Poehlman ET. Visceral adipose tissue is an independent correlate of glucose disposal in older obese postmenopausal women. *J Clin Endocrinol Metab* 2000;**85**:2378–84.
- 27 Goodpaster BH, Krishnaswami S, Resnick H *et al.* Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care* 2003;**26**:372–79.
- 28 von Eyben FE, Mouritsen E, Holm J *et al.* Intra-abdominal obesity and metabolic risk factors: a study of young adults. *Int J Obes Relat Metab Disord* 2003;**27**:941–49.
- 29 Blackburn P, Lamarche B, Couillard C *et al.* Contribution of visceral adiposity to the exaggerated postprandial lipemia of men with impaired glucose tolerance. *Diabetes Care* 2003;**26**:3303–09.
- 30 Snijder MB, Visser M, Dekker JM *et al.* Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. *Diabetologia* 2005;**48**:301–08.
- 31 Poulit MC, Despres JP, Lemieux S *et al.* Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;**73**:460–68.
- 32 Rankinen T, Kim SY, Perusse L, Despres JP, Bouchard C. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. *Int J Obes Relat Metab Disord* 1999;**23**:801–09.
- 33 Clasey JL, Bouchard C, Teates CD *et al.* The use of anthropometric and dual-energy X-ray absorptiometry (DXA) measures to estimate total abdominal and abdominal visceral fat in men and women. *Obes Res* 1999;**7**:256–64.
- 34 Onat A, Avci GS, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. *Int J Obes Relat Metab Disord* 2004;**28**:1018–25.
- 35 Zamboni M, Turcato E, Armellini F *et al.* Sagittal abdominal diameter as a practical predictor of visceral fat. *Int J Obes Relat Metab Disord* 1998;**22**:655–60.
- 36 Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *BMJ* 1995;**311**:158–61.
- 37 Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP. A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *Am J Clin Nutr* 1996;**64**:685–93.
- 38 Misra A, Wasir JS, Vikram NK. Waist circumference criteria for the diagnosis of abdominal obesity are not applicable uniformly to all populations and ethnic groups. *Nutrition* 2005; (in press).

- ³⁹ Molarius A, Seidell JC. Selection of anthropometric indicators for classification of abdominal fatness—a critical review. *Int J Obes Relat Metab Disord* 1998;**22**:719–27.
- ⁴⁰ Snijder MB, Visser M, Dekker JM *et al*. The prediction of visceral fat by dual-energy X-ray absorptiometry in the elderly: a comparison with computed tomography and anthropometry. *Int J Obes Relat Metab Disord* 2002;**26**:984–93.
- ⁴¹ Seidell JC. Chapter 40. Are abdominal diameters abominable indicators? *Prog Obes Res* 1996;**7**:305–08.
- ⁴² de Vegt F, Dekker JM, Jager A *et al*. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. *JAMA* 2001;**285**:2109–13.
- ⁴³ Snijder MB, Dekker JM, Visser M *et al*. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. *Am J Clin Nutr* 2003;**77**:1192–97.
- ⁴⁴ Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed)* 1984;**288**:1401–04.
- ⁴⁵ Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *Br Med J (Clin Res Ed)* 1984;**289**:1257–61.
- ⁴⁶ Silventoinen K, Jousilahti P, Vartiainen E, Tuomilehto J. Appropriateness of anthropometric obesity indicators in assessment of coronary heart disease risk among Finnish men and women. *Scand J Public Health* 2003;**31**:283–90.
- ⁴⁷ Snijder MB, Dekker JM, Visser M *et al*. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. *Diabetes Care* 2004;**27**:372–77.
- ⁴⁸ Seidell JC, Bjorntorp P, Sjostrom L, Sannerstedt R, Krotkiewski M, Kvist H. Regional distribution of muscle and fat mass in men—new insight into the risk of abdominal obesity using computed tomography. *Int J Obes* 1989;**13**:289–303.
- ⁴⁹ Snijder MB, Dekker JM, Visser M *et al*. Larger thigh and hip circumferences are associated with better glucose tolerance: the Hoorn study. *Obes Res* 2003;**11**:104–11.
- ⁵⁰ Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study. *Int J Obes Relat Metab Disord* 2004;**28**:402–09.
- ⁵¹ Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent association of hip circumference with metabolic profile in different ethnic groups. *Obes Res* 2004;**12**:1370–74.
- ⁵² Lissner L, Bjorkelund C, Heitmann BL, Seidell JC, Bengtsson C. Larger hip circumference independently predicts health and longevity in a Swedish female cohort. *Obes Res* 2001;**9**:644–46.
- ⁵³ Seidell JC, Perusse L, Despres JP, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr* 2001;**74**:315–21.
- ⁵⁴ Seidell JC, Han TS, Feskens EJ, Lean ME. Narrow hips and broad waist circumferences independently contribute to increased risk of non-insulin-dependent diabetes mellitus. *J Intern Med* 1997;**242**:401–06.
- ⁵⁵ Heitmann BL, Frederiksen P, Lissner L. Hip circumference and cardiovascular morbidity and mortality in men and women. *Obes Res* 2004;**12**:482–87.
- ⁵⁶ Canoy D, Luben R, Welch A *et al*. Fat distribution, body mass index and blood pressure in 22,090 men and women in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) study. *J Hypertens* 2004;**22**:2067–74.
- ⁵⁷ Seidell JC, Deurenberg P, Hautvast JG. Obesity and fat distribution in relation to health—current insights and recommendations. *World Rev Nutr Diet* 1987;**50**:57–91.
- ⁵⁸ Donahue RP, Abbott RD, Bloom E, Reed DM, Yano K. Central obesity and coronary heart disease in men. *Lancet* 1987;**1**:821–24.
- ⁵⁹ Seidell JC, Cigolini M, Charzewska J *et al*. Indicators of fat distribution, serum lipids, and blood pressure in European women born in 1948—the European Fat Distribution Study. *Am J Epidemiol* 1989;**130**:53–65.
- ⁶⁰ Seidell JC, Cigolini M, Deslypere JP, Charzewska J, Ellsinger BM, Cruz A. Body fat distribution in relation to serum lipids and blood pressure in 38-year-old European men: the European fat distribution study. *Atherosclerosis* 1991;**86**:251–60.
- ⁶¹ Misra A, Wasir JS, Pandey RM. An evaluation of candidate definitions of the metabolic syndrome in adult Asian Indians. *Diabetes Care* 2005;**28**:398–403.
- ⁶² Noppa H, Andersson M, Bengtsson C, Bruce A, Isaksson B. Longitudinal studies of anthropometric data and body composition. The population study of women in Gotenberg, Sweden. *Am J Clin Nutr* 1980;**33**:155–62.
- ⁶³ Miller JA, Schmatz C, Schultz AB. Lumbar disc degeneration: correlation with age, sex, and spine level in 600 autopsy specimens. *Spine* 1988;**13**:173–78.
- ⁶⁴ Roubenoff R, Hughes VA. Sarcopenia: current concepts. *J Gerontol A Biol Sci Med Sci* 2000;**55**:M716–24.
- ⁶⁵ Gallagher D, Ruts E, Visser M *et al*. Weight stability masks sarcopenia in elderly men and women. *Am J Physiol Endocrinol Metab* 2000;**279**:E366–75.
- ⁶⁶ Hughes VA, Frontera WR, Roubenoff R, Evans WJ, Singh MA. Longitudinal changes in body composition in older men and women: role of body weight change and physical activity. *Am J Clin Nutr* 2002;**76**:473–81.
- ⁶⁷ Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* 1996;**143**:228–39.
- ⁶⁸ Deurenberg P, van der Kooy K, Hulshof T, Evers P. Body mass index as a measure of body fatness in the elderly. *Eur J Clin Nutr* 1989;**43**:231–36.
- ⁶⁹ Visser M, van den Heuvel E, Deurenberg P. Prediction equations for the estimation of body composition in the elderly using anthropometric data. *Br J Nutr* 1994;**71**:823–33.
- ⁷⁰ Hughes VA, Roubenoff R, Wood M, Frontera WR, Evans WJ, Fiatarone Singh MA. Anthropometric assessment of 10-y changes in body composition in the elderly. *Am J Clin Nutr* 2004;**80**:475–82.
- ⁷¹ Carmelli D, McElroy MR, Rosenman RH. Longitudinal changes in fat distribution in the Western Collaborative Group Study: a 23-year follow-up. *Int J Obes* 1991;**15**:67–74.
- ⁷² Svendsen OL, Hassager C, Christiansen C. Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. *Metabolism* 1995;**44**:369–73.
- ⁷³ Chumlea WC, Roche AF, Webb P. Body size, subcutaneous fatness and total body fat in older adults. *Int J Obes* 1984;**8**:311–17.
- ⁷⁴ Harris TB, Visser M, Everhart J *et al*. Waist circumference and sagittal diameter reflect total body fat better than visceral fat in older men and women. The Health, Aging and Body Composition Study. *Ann N Y Acad Sci* 2000;**904**:462–73.
- ⁷⁵ Seidell JC, Oosterlee A, Deurenberg P, Hautvast JG, Ruijs JH. Abdominal fat depots measured with computed tomography: effects of degree of obesity, sex, and age. *Eur J Clin Nutr* 1988;**42**:805–15.
- ⁷⁶ Han TS, McNeill G, Seidell JC, Lean ME. Predicting intra-abdominal fatness from anthropometric measures: the influence of stature. *Int J Obes Relat Metab Disord* 1997;**21**:587–93.

- 77 Stanforth PR, Jackson AS, Green JS *et al*. Generalized abdominal visceral fat prediction models for black and white adults aged 17–65 y: the HERITAGE Family Study. *Int J Obes Relat Metab Disord* 2004; **28**:925–32.
- 78 Iwao S, Iwao N, Muller DC, Elahi D, Shimokata H, Andres R. Effect of aging on the relationship between multiple risk factors and waist circumference. *J Am Geriatr Soc* 2000; **48**:788–94.
- 79 Molarius A, Seidell JC, Visscher TL, Hofman A. Misclassification of high-risk older subjects using waist action levels established for young and middle-aged adults—results from the Rotterdam Study. *J Am Geriatr Soc* 2000; **48**:1638–45.
- 80 Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev* 2002; **3**:141–46.
- 81 Rush E, Plank L, Chandu V *et al*. Body size, body composition, and fat distribution: a comparison of young New Zealand men of European, Pacific Island, and Asian Indian ethnicities. *N Z Med J* 2004; **117**:U1203.
- 82 Wildman RP, Gu D, Reynolds K, Duan X, He J. Appropriate body mass index and waist circumference cutoffs for categorization of overweight and central adiposity among Chinese adults. *Am J Clin Nutr* 2004; **80**:1129–36.
- 83 Zhou BF. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults—study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci* 2002; **15**:83–96.
- 84 Vikram NK, Misra A, Pandey RM *et al*. Anthropometry and body composition in northern Asian Indian patients with type 2 diabetes: receiver operating characteristics (ROC) curve analysis of body mass index with percentage body fat as standard. *Diabetes Nutr Metab* 2003; **16**:32–40.
- 85 World Health Organization Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; **363**:157–63.
- 86 McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991; **337**:382–86.
- 87 Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. *J Clin Endocrinol Metab* 2001; **86**:5366–71.
- 88 Banerji MA, Lebowitz J, Chaiken RL, Gordon D, Kral JG, Lebovitz HE. Relationship of visceral adipose tissue and glucose disposal is independent of sex in black NIDDM subjects. *Am J Physiol* 1997; **273**:E425–32.
- 89 Conway JM, Yanovski SZ, Avila NA, Hubbard VS. Visceral adipose tissue differences in black and white women. *Am J Clin Nutr* 1995; **61**:765–71.
- 90 Yanovski JA, Yanovski SZ, Filmer KM *et al*. Differences in body composition of black and white girls. *Am J Clin Nutr* 1996; **64**:833–39.
- 91 Hoffman DJ, Wang Z, Gallagher D, Heymsfield SB. Comparison of visceral adipose tissue mass in adult African-Americans and whites. *Obes Res* 2005; **13**:66–74.
- 92 Albu JB, Murphy L, Frager DH, Johnson JA, Pi-Sunyer FX. Visceral fat and race-dependent health risks in obese nondiabetic premenopausal women. *Diabetes* 1997; **46**:456–62.
- 93 Bacha F, Saad R, Gungor N, Janosky J, Arslanian SA. Obesity, regional fat distribution, and syndrome X in obese black versus white adolescents: race differential in diabetogenic and atherogenic risk factors. *J Clin Endocrinol Metab* 2003; **88**:2534–40.
- 94 Liese AD, Doring A, Hense HW, Keil U. Five year changes in waist circumference, body mass index and obesity in Augsburg, Germany. *Eur J Nutr* 2001; **40**:282–88.
- 95 McCarthy HD, Ellis SM, Cole TJ. Central overweight and obesity in British youth aged 11–16 years: cross sectional surveys of waist circumference. *BMJ* 2003; **326**:624.
- 96 Lissner L, Bjorkelund C, Heitmann BL, Lapidus L, Bjorntorp P, Bengtsson C. Secular increases in waist-hip ratio among Swedish women. *Int J Obes Relat Metab Disord* 1998; **22**:1116–20.
- 97 Lahti-Koski M, Pietinen P, Mannisto S, Vartiainen E. Trends in waist-to-hip ratio and its determinants in adults in Finland from 1987 to 1997. *Am J Clin Nutr* 2000; **72**:1436–44.
- 98 Berg C, Rosengren A, Aires N *et al*. Trends in overweight and obesity from 1985 to 2002 in Goteborg, West Sweden. *Int J Obes Relat Metab Disord* 2005; **29**:916–24.
- 99 Visscher TL, Seidell JC. Time trends (1993–1997) and seasonal variation in body mass index and waist circumference in the Netherlands. *Int J Obes Relat Metab Disord* 2004; **28**:1309–16.
- 100 Okosun IS, Chandra KM, Boev A *et al*. Abdominal adiposity in U.S. adults: prevalence and trends, 1960–2000. *Prev Med* 2004; **39**:197–206.
- 101 Visscher TL, Seidell JC, Molarius A, van der Kuip D, Hofman A, Witteman JC. A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. *Int J Obes Relat Metab Disord* 2001; **25**:1730–35.
- 102 Woo J, Ho SC, Yu AL, Sham A. Is waist circumference a useful measure in predicting health outcomes in the elderly? *Int J Obes Relat Metab Disord* 2002; **26**:1349–55.
- 103 Iwao S, Iwao N, Muller DC, Elahi D, Shimokata H, Andres R. Does waist circumference add to the predictive power of the body mass index for coronary risk? *Obes Res* 2001; **9**:685–95.
- 104 Reeder BA, Senthilselvan A, Despres JP *et al*. The association of cardiovascular disease risk factors with abdominal obesity in Canada. Canadian Heart Health Surveys Research Group. *Cmaj* 1997; **157** (Suppl. 1):S39–45.
- 105 Wei M, Gaskill SP, Haffner SM, Stern MP. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans—a 7-year prospective study. *Obes Res* 1997; **5**:16–23.
- 106 Rissanen P, Hamalainen P, Vanninen E, Tenhunen-Eskelinen M, Uusitupa M. Relationship of metabolic variables to abdominal adiposity measured by different anthropometric measurements and dual-energy X-ray absorptiometry in obese middle-aged women. *Int J Obes Relat Metab Disord* 1997; **21**:367–71.
- 107 Dalton M, Cameron AJ, Zimmet PZ *et al*. Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. *J Intern Med* 2003; **254**:555–63.
- 108 Rexrode KM, Buring JE, Manson JE. Abdominal and total adiposity and risk of coronary heart disease in men. *Int J Obes Relat Metab Disord* 2001; **25**:1047–56.
- 109 Riserus U, Arnlov J, Brismar K, Zethelius B, Berglund L, Vessby B. Sagittal abdominal diameter is a strong anthropometric marker of insulin resistance and hyperproinsulinemia in obese men. *Diabetes Care* 2004; **27**:2041–46.
- 110 Valsamakis G, Chetty R, Anwar A, Banerjee AK, Barnett A, Kumar S. Association of simple anthropometric measures of obesity with visceral fat and the metabolic syndrome in male Caucasian and Indo-Asian subjects. *Diabet Med* 2004; **21**:1339–45.
- 111 Ohrvall M, Berglund L, Vessby B. Sagittal abdominal diameter compared with other anthropometric measurements in relation to cardiovascular risk. *Int J Obes Relat Metab Disord* 2000; **24**:497–501.
- 112 Frayn KN. Visceral fat and insulin resistance—causative or correlative? *Br J Nutr* 2000; **83** (Suppl. 1):S71–77.

- 113 Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 1997;**46**:1579–85.
- 114 Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 1995;**96**:88–98.
- 115 Tanko LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. *Circulation* 2003;**107**:1626–31.
- 116 Van Pelt RE, Evans EM, Schechtman KB, Ehsani AA, Kohrt WM. Contributions of total and regional fat mass to risk for cardiovascular disease in older women. *Am J Physiol Endocrinol Metab* 2002;**282**:E1023–28.
- 117 Seidell JC, Visscher TL, Hoogveen RT. Overweight and obesity in the mortality rate data: current evidence and research issues. *Med Sci Sports Exerc* 1999;**31**:597–601.
- 118 Solomon CG, Manson JE. Obesity and mortality: a review of the epidemiologic data. *Am J Clin Nutr* 1997;**66**:1044S–1050S.
- 119 Allison DB, Faith MS, Heo M, Kotler DP. Hypothesis concerning the U-shaped relation between body mass index and mortality. *Am J Epidemiol* 1997;**146**:339–49.
- 120 Heitmann BL, Erikson H, Ellsinger BM, Mikkelsen KL, Larsson B. Mortality associated with body fat, fat-free mass and body mass index among 60-year-old Swedish men—a 22-year follow-up. The study of men born in 1913. *Int J Obes Relat Metab Disord* 2000;**24**:33–37.
- 121 Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;**341**:1097–105.
- 122 Bigaard J, Tjonnelland A, Thomsen BL, Overvad K, Heitmann BL, Sorensen TI. Waist circumference, BMI, smoking, and mortality in middle-aged men and women. *Obes Res* 2003;**11**:895–903.
- 123 Bengtsson C, Bjorkelund C, Lapidus L, Lissner L. Associations of serum lipid concentrations and obesity with mortality in women: 20 year follow up of participants in prospective population study in Gothenburg, Sweden. *BMJ* 1993;**307**:1385–88.
- 124 Filipovsky J, Ducimetiere P, Darne B, Richard JL. Abdominal body mass distribution and elevated blood pressure are associated with increased risk of death from cardiovascular diseases and cancer in middle-aged men. The results of a 15- to 20-year follow-up in the Paris prospective study I. *Int J Obes Relat Metab Disord* 1993;**17**:197–203.
- 125 Seidell JC, Andres R, Sorkin JD, Muller DC. The sagittal waist diameter and mortality in men: the Baltimore Longitudinal Study on Aging. *Int J Obes Relat Metab Disord* 1994;**18**:61–67.
- 126 Bigaard J, Frederiksen K, Tjonnelland A *et al*. Waist and hip circumferences and all-cause mortality: usefulness of the waist-to-hip ratio? *Int J Obes Relat Metab Disord* 2004;**28**:741–47.
- 127 Oppert JM, Charles MA, Thibault N, Guy-Grand B, Eschwege E, Ducimetiere P. Anthropometric estimates of muscle and fat mass in relation to cardiac and cancer mortality in men: the Paris Prospective Study. *Am J Clin Nutr* 2002;**75**:1107–13.
- 128 Lahmann PH, Lissner L, Gullberg B, Berglund G. A prospective study of adiposity and all-cause mortality: the Malmo Diet and Cancer Study. *Obes Res* 2002;**10**:361–69.
- 129 Bigaard J, Frederiksen K, Tjonnelland A *et al*. Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women. *Int J Obes Relat Metab Disord* 2005;**29**:778–84.
- 130 Stevens J, Keil JE, Rust PF *et al*. Body mass index and body girths as predictors of mortality in black and white men. *Am J Epidemiol* 1992;**135**:1137–46.
- 131 Stevens J, Keil JE, Rust PF, Tyroler HA, Davis CE, Gazes PC. Body mass index and body girths as predictors of mortality in black and white women. *Arch Intern Med* 1992;**152**:1257–62.
- 132 Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. *Nutrition* 1997;**13**:65; discussion 64, 66.
- 133 McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. *Diabetes* 2002;**51**:7–18.
- 134 Arner P. Insulin resistance in type 2 diabetes: role of fatty acids. *Diabetes Metab Res Rev* 2002;**18** (Suppl. 2):S5–S9.
- 135 Jensen MD, Haymond MW, Rizza RA, Cryer PE, Miles JM. Influence of body fat distribution on free fatty acid metabolism in obesity. *J Clin Invest* 1989;**83**:1168–73.
- 136 Ravussin E, Smith SR. Increased fat intake, impaired fat oxidation, and failure of fat cell proliferation result in ectopic fat storage, insulin resistance, and type 2 diabetes mellitus. *Ann N Y Acad Sci* 2002;**967**:363–78.
- 137 Tiikkainen M, Tamminen M, Hakkinen AM *et al*. Liver-fat accumulation and insulin resistance in obese women with previous gestational diabetes. *Obes Res* 2002;**10**:859–67.
- 138 Seppala-Lindroos A, Vehkavaara S, Hakkinen AM *et al*. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *J Clin Endocrinol Metab* 2002;**87**:3023–28.
- 139 Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. *Am J Clin Nutr* 2000;**71**:885–92.
- 140 Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. *J Clin Invest* 2004;**113**:1582–88.
- 141 Despres JP, Lemieux S, Lamarche B *et al*. The insulin resistance-dyslipidemic syndrome: contribution of visceral obesity and therapeutic implications. *Int J Obes Relat Metab Disord* 1995;**19** (Suppl. 1):S76–86.
- 142 Bjorntorp P. 'Portal' adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. *Arteriosclerosis* 1990;**10**:493–96.
- 143 Barzilai N, She L, Liu BQ *et al*. Surgical removal of visceral fat reverses hepatic insulin resistance. *Diabetes* 1999;**48**:94–98.
- 144 Gabrieli I, Ma XH, Yang XM *et al*. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? *Diabetes* 2002;**51**:2951–58.
- 145 Thorne A, Lonnqvist F, Apelman J, Hellers G, Arner P. A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. *Int J Obes Relat Metab Disord* 2002;**26**:193–99.
- 146 Gonzalez-Ortiz M, Robles-Cervantes JA, Cardenas-Camarena L, Bustos-Saldana R, Martinez-Abundis E. The effects of surgically removing subcutaneous fat on the metabolic profile and insulin sensitivity in obese women after large-volume liposuction treatment. *Horm Metab Res* 2002;**34**:446–49.
- 147 Giugliano G, Nicoletti G, Grella E *et al*. Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. *Br J Plast Surg* 2004;**57**:190–94.
- 148 Klein S, Fontana L, Young VL *et al*. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004;**350**:2549–57.
- 149 Esposito K, Giugliano G, Giugliano D. Metabolic effects of liposuction—yes or no? *N Engl J Med* 2004;**351**:1354–57; author reply 1354–57.
- 150 Kelley DE, Thaete FL, Troost F, Huwe T, Goodpaster BH. Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance. *Am J Physiol Endocrinol Metab* 2000;**278**:E941–48.
- 151 Monzon JR, Basile R, Heneghan S, Udupi V, Green A. Lipolysis in adipocytes isolated from deep and superficial subcutaneous adipose tissue. *Obes Res* 2002;**10**:266–69.
- 152 Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 2002;**45**:1201–10.

- ¹⁵³ Rebuffe-Scrive M, Enk L, Crona N *et al.* Fat cell metabolism in different regions in women. Effect of menstrual cycle, pregnancy, and lactation. *J Clin Invest* 1985;**75**:1973–76.
- ¹⁵⁴ Rebuffe-Scrive M, Lonnroth P, Marin P, Wesslau C, Bjorntorp P, Smith U. Regional adipose tissue metabolism in men and postmenopausal women. *Int J Obes* 1987;**11**:347–55.
- ¹⁵⁵ Gavrilova O, Marcus-Samuels B, Graham D *et al.* Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J Clin Invest* 2000;**105**:271–78.
- ¹⁵⁶ Weber RV, Buckley MC, Fried SK, Kral JG. Subcutaneous lipectomy causes a metabolic syndrome in hamsters. *Am J Physiol Regul Integr Comp Physiol* 2000;**279**:R936–43.
- ¹⁵⁷ Virtanen KA, Hallsten K, Parkkola R *et al.* Differential effects of rosiglitazone and metformin on adipose tissue distribution and glucose uptake in type 2 diabetic subjects. *Diabetes* 2003;**52**:283–90.
- ¹⁵⁸ Jazet IM, Pijl H, Meinders AE. Adipose tissue as an endocrine organ: impact on insulin resistance. *Neth J Med* 2003;**61**:194–212.
- ¹⁵⁹ Arner P. Regional differences in protein production by human adipose tissue. *Biochem Soc Trans* 2001;**29**:72–75.
- ¹⁶⁰ van Harmelen V, Dicker A, Ryden M *et al.* Increased lipolysis and decreased leptin production by human omental as compared with subcutaneous preadipocytes. *Diabetes* 2002;**51**:2029–36.
- ¹⁶¹ Eriksson P, Van Harmelen V, Hoffstedt J *et al.* Regional variation in plasminogen activator inhibitor-1 expression in adipose tissue from obese individuals. *Thromb Haemost* 2000;**83**:545–48.
- ¹⁶² Motoshima H, Wu X, Sinha MK *et al.* Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab* 2002;**87**:5662–67.
- ¹⁶³ Seidell JC, Bouchard C. Visceral fat in relation to health: is it a major culprit or simply an innocent bystander? *Int J Obes Relat Metab Disord* 1997;**21**:626–31.
- ¹⁶⁴ Bjorntorp P. Body fat distribution, insulin resistance, and metabolic diseases. *Nutrition* 1997;**13**:795–803.
- ¹⁶⁵ Kreier F, Fliers E, Voshol PJ *et al.* Selective parasympathetic innervation of subcutaneous and intra-abdominal fat—functional implications. *J Clin Invest* 2002;**110**:1243–50.
- ¹⁶⁶ Kreier F, Yilmaz A, Kalsbeek A *et al.* Hypothesis: shifting the equilibrium from activity to food leads to autonomic unbalance and the metabolic syndrome. *Diabetes* 2003;**52**:2652–56.
- ¹⁶⁷ Bramlage P, Wittchen HU, Pittrow D *et al.* Recognition and management of overweight and obesity in primary care in Germany. *Int J Obes Relat Metab Disord* 2004;**28**:1299–308.