

Chapter 6

Other beneficial effects

Weight control

Many prospective observational studies have investigated the impact of relative weight, measured as BMI, on risk of mortality and disease endpoints. Other prospective observational studies have looked at the effect of change in body weight that often occurred later in life. Relative weight has also been studied in relation to biological markers of disease and quality of life in observational and experimental settings. The results of experimental weight loss trials have often provided further evidence on effects of weight control on health.

Some major reports have summarized current evidence on the role of obesity and weight control with respect to risk for non-cancer diseases and all-cause mortality (WHO Expert Committee, 1995; National Task Force on the Prevention and Treatment of Obesity, 2000); these reports have provided the scientific background for major public health initiatives on weight control.

All-cause mortality

Weight status

The earliest data on the importance of relative weight for mortality and disease occurrence came from studies that prospectively related existing BMI to risk. This concept is straightforward because there is in general considerable variation in BMI between individuals within a study population which persists with nearly unchanged ranking for long time periods.

All-cause mortality increases with both higher and lower BMI in the general population. The association between relative weight and mortality was first demonstrated in a study of life insurance policy holders (Build and Blood Pressure

Study, 1959) and the non-linearity of this association was confirmed in a later study of volunteers in the American Cancer Society Study (Lew & Garfinkel, 1979). Most subsequent studies have documented U-, reversed J-, and J-shaped associations between BMI and mortality in men and women; see for example Waaler (1988).

The increase in risk among subjects with the lowest BMI values has attracted particular attention in recent years (Seidell *et al.*, 1999). The low BMI values in such studies were usually in the range defined as normal. Smoking was long believed to account for the excess mortality among lean individuals, and it has also been speculated that pre-existing disease is another factor. The exclusion of subjects who die during the first years of follow-up has therefore been recommended to avoid confounding. However a meta-analysis of studies specifically conducted on the relation between BMI and all-cause mortality revealed that the effect of excluding early death from the analysis was significant but of minor magnitude (Allison *et al.*, 1999a).

Some more recent prospective studies have analysed the relationship between BMI and mortality particularly among non-smokers, excluding subjects with pre-existing diseases, and ignoring mortality in the first years of follow-up. Attempts were made to adjust for direct consequences of obesity such as diabetes and hypertension and to exclude subjects with a large loss of weight. Some studies with proper control of confounding demonstrated no significant increase in risk of all-cause mortality among subjects in the lower end of the BMI range (Wannamethee & Shaper,

1989; Lee *et al.*, 1993; Sorkin *et al.*, 1994; Manson *et al.*, 1995; Stevens *et al.*, 1998; Baik *et al.*, 2000). Baik *et al.* (2000) found evidence that lean men particularly suffer from death due to respiratory diseases and that risk of mortality is particularly high among inactive lean subjects. Allison *et al.* (1997, 1999b) demonstrated that the higher mortality risk among lean subjects can be attributed to low lean body mass, whereas a low fat mass decreases mortality risk.

It appears that gender is a major modifier of the shape of the BMI–mortality association in the general population. For instance, Waaler (1988) found a U-shaped association in middle-aged men, while a reversed J-shaped association was observed in females, with the highest mortality rates among lean women. In a study of slightly younger adults in the Netherlands, a U-shaped association was seen in men but not in women (Seidell *et al.*, 1996). It has been suggested that the gender difference in obesity-related mortality can be explained in part by a greater tendency for males to develop abdominal obesity (Larsson *et al.*, 1992).

Stevens *et al.* (1998) conducted the largest recent study on a non-smoking population and showed in general a direct relationship between BMI in young age and all-cause mortality. This cohort study of the American Cancer Society also strongly indicated that age is a modifier of the effect of weight on all-cause mortality (and cardiovascular diseases). In this cohort of 62 116 men and 262 019 women, the increased relative risk of mortality with higher BMI decreased with age. The trend was similar in men and women. The modifying effect of age was

further evaluated by Stevens (2000), taking previous research into account. Baik *et al.* (2000) also recently highlighted this issue and provided further evidence that in older subjects BMI may be less important compared with direct measurements of fatness such as waist circumference. Comparative analyses of different measures of fatness in the same study population are rare, but have shown that other measures of fatness than BMI are also related to risk and add further information on the relationship between fatness and mortality (Folsom *et al.*, 2000). Seidell and Visscher (2000) considered five possible explanations for the observed modifying effect of age: (1) BMI is not a good indicator; (2) there is selective survival of only the fittest obese subjects; (3) a ceiling effect occurs because most study participants in old age groups die during follow-up; (4) cohort effects arise because of different experience in terms of development of obesity and morbidity/mortality across birth cohorts; (5) excess fat is less detrimental in older than in younger age groups. They also presented empirical data showing that ageing is associated with a change in body composition, with an increase in fat mass at the expense of lean body mass.

In a prospective study in the USA of the relationship of BMI and fitness to risk of all-cause mortality, 21 925 men, aged 30–83 years, had a body composition assessment and a maximal treadmill exercise test. The 428 deaths over the eight-year follow-up period (on average) were linked to obesity and cardiorespiratory fitness. Compared with lean fit subjects, obese fit subjects (% body fat ≥ 25) experienced a similar relative risk for all-cause mortality (RR = 0.92; 95% CI 0.65–1.3) which was lower than the relative risk of unfit subjects with normal weight (RR = 1.6; 95% CI 1.2–2.3) after adjustment for age, year of examination, smoking habits, alcohol intake and parental history of ischaemic heart disease (Lee *et al.*, 1999d). The highest

relative risk compared with lean fit subjects was found for the unfit lean subjects (RR = 2.1; 95% CI 1.2–3.7) taking the lean fit subjects as reference. However this study population was highly selective and cardiorespiratory fitness is not identical with physical activity (see Chapter 1).

Methodological issues still dominate the debate about the relation between BMI and mortality. However, the data from studies with proper control of confounding clearly indicate that risk of all-cause mortality is lower at BMI < 25 kg/m² (Wannamethee & Shaper, 1989; Lee *et al.*, 1993; Sorkin *et al.*, 1994; Manson *et al.*, 1995; Stevens *et al.*, 1998; Baik *et al.*, 2000). Ethnic differences probably exist for optimal BMI; there is evidence that the optimal BMI is higher for blacks, while in Pima Indian women no relationship between BMI and mortality was found (National Task Force on the Prevention and Treatment of Obesity, 2000).

Weight change

Weight change in the adult population is a common phenomenon often recorded in the prospective cohort studies that form the basis for the evaluation of long-term effects of weight on risk for all-cause mortality. In some studies, in addition to repeated measurements of weight and other anthropometric variables, weight histories were obtained. Subjects can also be asked about dieting behaviour, their intention to lose weight and how they lost weight. Thus it is possible to follow the development of weight over time in subjects and to compare groups with different patterns of weight development in terms of subsequent risk. In theory, data on the effect of weight change on risk in adult life may be much more relevant to weight reduction programmes focusing on change of weight in adult life than studies based on BMI at a given point in time.

The design of studies on weight change is more complex than that of

studies on BMI status. In most recent prospective studies, weight change was first measured and then the risk associated with such changes was assessed over the subsequent follow-up period. Only a few studies have incorporated data on weight changes during follow-up until end-point occurrence in their analysis (e.g., Deeg *et al.*, 1990). The effect of weight change on risk was usually controlled for initial BMI. Thus, these studies allow simultaneous investigation of both weight and weight change, and have often led to the conclusion that these two aspects act independently of each other (Mikkelsen *et al.*, 1999).

However, these studies have severe limitations. Whereas it is relative easy to record weight change over time, it is very hard to obtain information about the reason for changes. It is known that weight change in itself affects further weight development (Colditz *et al.*, 1990). For example, weight reduction is a good predictor of subsequent increase in weight. Background information relating to weight change may be less important for weight gain but is very important in the case of weight loss. Weight loss is often related to underlying chronic diseases in an early stage, not yet verified by a physician. In some studies, specific enquiry was made about reasons for weight loss. Two studies have found that among weight losers, the percentages of intentional and unintentional loss of weight were about 50 and 50% (French *et al.*, 1995) in women and about 40 and 60% in men (Wannamethee *et al.*, 2000). However, even if a person has intentionally reduced weight, the various ways of doing so may affect disease risk differently: reduction of energy intake, increase of physical activity, change of dietary pattern, use of drugs etc. A recent large study of 4713 British men shed some light on the characteristics of those who indicated that they intentionally or unintentionally lost weight as they aged (Wannamethee *et al.*, 2000). Intentional

weight loss was associated with higher BMI than in those with unintentional loss and the latter group felt more unhealthy. However, both groups clearly differed from those with stable weight in having poorer health. A group of weight cyclers comprising only 82 of the men in this study showed the highest BMI and the poorest health. In conclusion, it seems very difficult to identify subjects in a cohort who reduced their weight for preventive reasons only with no relation to acute or chronic illness. Weight loss due to health impairment, even if considered as intentional, might therefore be particularly subject to the phenomenon of reverse causation, so that available data may be misleading.

It is nevertheless worthwhile to examine the results of prospective observational cohort studies that have analysed effects of weight change on risk of all-cause mortality in more detail. In such studies, stable weight is usually the reference category. For the determination of weight variability (cycling), at least three measurement points over time per subject are needed. In most of the studies that investigated this aspect, weight variability was defined as standard deviation of the subject-specific measurements or as the variation of the measurement points along a regression line (Lissner *et al.*, 1990). The latter was considered particularly useful because weight variability could be separated from weight development over time, allowing differentiation between the two aspects of weight change.

Only a few of the studies analysing the effect of weight change on all-cause mortality investigated all aspects of weight change, including the effect of stable weight, simultaneously in one study population. It is more usual to find studies within the same cohort but looking at different time periods, specific aspects of weight change and different disease outcomes. In addition, it is nearly impossible to standardize the results of the different studies. Wide

variation exists across studies in terms of the age range of the population, the time period at which weight change was measured and the follow-up period used, as well as in the categories of weight change used. The study-specific definition of weight change has often mixed various aspects depending on the study design and the information available. For example, weight variability might be specifically measured in a study population or included in the weight change measure.

Studies of the effect of weight change on mortality were reviewed by Lee and Paffenbarger (1996) and a meta-analysis was performed by Andres *et al.* (1993). The earliest study was that of Dublin (1953), which used data from a life insurance company, and was followed by a similar study published in 1959 (Build and Blood Pressure Study), based on about five million subjects. Subsequent studies were those conducted by the American Cancer Society (Hammond & Garfinkel, 1969) and a second Build and Blood Pressure Study (1980) of members of a health insurance scheme. The first studies indicated a reduction of mortality with weight loss in both men and women. However, the detailed analysis by Hammond and Garfinkel (1969) revealed that weight loss might not only have beneficial effects by reducing the risk of mortality but also increase risk particularly for cardiovascular death in some strata. Table 51 summarizes the results of most of the subsequent studies, as far as they directly reported relative risk estimates. The relative risk estimates presented in this table refer in general to the highest or lowest weight change category if there was a linear trend. In addition to the studies reporting relative risk in Table 51, Deeg *et al.* (1990) found increased risk with increase and decrease of weight in a national sample of 604 Dutch subjects aged 65 to 99 years, particularly among males. Rhoads and Kagan (1983) reported increased risk with decreased

weight and a slight increase in risk with increased weight among Honolulu Japanese men aged 45 to 68 years.

Overall, the studies indicate excess mortality associated with both weight loss and weight gain. Significantly increased risks were often seen for weight loss and studies that investigated weight cycling usually found consistently elevated risks for all-cause mortality. In most studies, weight gain was associated with only slightly increased risk compared with stable weight, often in a non-significant manner. However, many of the studies were conducted in older age groups. Effect modification by age similar to that seen for BMI should be considered. The same applies to modifying effects of initial BMI. Data from some studies suggest that weight loss and weight cycling in obese subjects are less strongly associated with risk than in subjects of normal weight (Blair *et al.*, 1993; Pamuk *et al.*, 1993) and some studies of obese subjects have not revealed increased risk associated with weight reduction (Williamson *et al.*, 1995, 1999).

Studies that have separately investigated intentional and unintentional weight loss have failed to show reduced all-cause mortality for intentional weight loss compared with stable weight (Williamson *et al.*, 1995, 1999; French *et al.*, 1999b). However, two of these studies (Williamson *et al.*, 1995; French *et al.*, 1999b) found that the excess mortality associated with weight loss seemed to be attributable to unintentional loss. Intentional weight loss was associated with decreased premature mortality among obese women with obesity-related co-morbidities but not those without co-morbidities (Williamson *et al.*, 1995).

In conclusion, methodological problems remain serious in the area of research into weight change and all-cause mortality. The current data do not indicate that weight loss lowers the risk of all-cause mortality.

Table 51. Studies of total mortality in relation to weight gain or loss

Reference	No. of total outcome	Total number of participants	Study population	Time-scale	Effect of intentional (I) or unintentional (U) weight change on risk			Remarks
					Increase	Decrease	Cycling	
Harris <i>et al.</i> (1988)	528	1723	USA, Framingham Study, men and women, 65 y	Weight change period: 10 y Follow up period: 1 to 23 y	M: 1.5 (0.9-2.4) F: 1.1 (0.8-1.7)	M: 1.9 (1.1-3.2) F: 1.8 (1.2-1.6)	Non-smoking	
Hamm <i>et al.</i> (1989)	736	1959	USA, Western Electric Study, men, 40-56 y	Weight change period: since age 20 y Follow-up period: 25 y	1.4 (1.0-2.1)	1.5 (1.0-2.3)		
Lissner <i>et al.</i> (1991)	942	3130	USA, Framingham Study, men and women, 30-62 y	Weight change period: since age 2 y Follow-up period: 32 y		M: 1.6 (1.3-2.1) F: 1.3 (1.0-1.6)		
Parnuk <i>et al.</i> (1992)	1496	4690	NHANES I Study, men and women, 45-74 y	Weight change period: maximum change Follow-up period: 10 y		2.0 (1.5-2.8)	BMI \geq 29 kg/m ²	
Lee & Paffenbarger (1992c)	1441	11 703	USA, Harvard University alumni, men, 45-84 y	Weight change period: 11 to 15 y Follow-up period: 11 y	1.4 (first 5 y) 1.3 (second 2 y)	1.8 (first 5 y) 1.5 (second 6 y)		
Blair <i>et al.</i> (1993)	228	10 529	USA, Multiple Risk Factor Intervention Trial, men, 35-57 y	Weight change period: 6-7 y Follow-up period: 4 y	1.2 (0.86-1.7)	1.6 (1.2-2.2)	Effect of weight cycling only in normal weight men	
Higgins <i>et al.</i> (1993)	Not reported	2500	USA, Framingham Study, men and women, 35-54 y	Weight change period: 10 y Follow-up period: 20 y	M: 0.78 (0.60-1.0) F: 1.2 (0.87-1.6)	M: 1.3 (1.1-1.7) F: 1.3 (0.98-1.7)		
Paffenbarger <i>et al.</i> (1993)	476	10 269	USA, Harvard College alumni, men, 45-84 y	Weight change period: 11-15 y Follow-up period: 8 y	1.4 (non-sign.)	1.3 (non-sign.)	Recalculated: BMI <26 kg/m ² in both periods as basis	
Ho <i>et al.</i> (1994)	35	374	Hong Kong women (> 70 y)	Weight change period: 2 y Follow-up period: 2 y	1.3 (0.2-7.1)	4.8 (1.3-18.4)		

Table 51 (cont'd)

Reference	No. of total outcome	Total number of participants	Study population	Time-scale	Effect of intentional (I) or unintentional (U) weight change on risk			Remarks
					Increase	Decrease	Cycling	
Iribarren <i>et al.</i> (1995)	1217	6537	Japanese American men, 45–68 y	Weight change period: 6 y Follow-up period: 15 y	0.99 (0.79–1.3)	1.2 (1.0–1.4)	1.2 (1.0–1.5)	
Losonczy <i>et al.</i> (1995)	2650	6387	USA, whites over 70 y	Weight change period: ≥ 20 y Follow-up period: 3 and 6 y	M: 0.91 (0.76–1.1) F: 0.90 (0.90–1.1)	M: 1.7 (1.4–2.0) F: 1.6 (1.4–1.9)		Old subjects, increased risk disappeared after controlling for chronic conditions
Manson <i>et al.</i> (1995)	1059	115 195	USA, nurses, women, 30–55 y	Weight change period: since age 18 y Follow-up period: 16 y	1.6 (1.3–1.9)	0.7 (0.4–1.4)		
Peters <i>et al.</i> (1995)	1845	6441	EU, Seven Countries Study men, 40–59 y	Weight change period: 10 y Follow-up period: up to 15 y	1.0 (0.92–1.2)	1.3 (1.2–1.5)	1.2 (1.0–1.4)	
Williamson <i>et al.</i> , (1995)	1819	28 388	USA, Cancer Prevention Study, overweight men, 40–64 y	Weight change period: 22 to 46 y Follow-up period: 13 y	0.99 (0.74–1.3)	I: 0.98 (0.82–1.2) U: 1.2 (0.93–1.6)		Subjects with no preexisting illness, non-smoking
Folsom <i>et al.</i> (1996)	1068	33 760	Iowa Health Study, women, 55–69 y	Weight change period: 44 y Follow-up period: 6 y	1.20 (0.8–1.8)	2.0 (1.3–3.1)	1.8 (1.2–2.8)	
Yaari & Goldbourt (1998)	2983	9228	Israel, Ischaemic Heart Disease Study, men, 40–65 y	Weight change period: 5 y Follow-up period: 18 y	0.91 (0.80–1.0)	1.2 (1.1–1.4)		
Allison <i>et al.</i> (1999b)	321	1890	USA, Tecumseh Study, men and women	Weight change period: 4 y Follow-up period: 16 y	1.3 (1.1–1.5)			Risk per 4.6 kg weight loss, fat loss was protective
	507	2731	USA, Framingham Study, men and women	Weight change period: 14 y Follow-up period: 8 y	1.4 (1.2–1.5)			Risk per 6.7 kg weight loss, fat loss was protective

Table 51 (contd)

Reference	No. of total outcome	Total number of participants	Study population	Time-scale	Effect of intentional (I) or unintentional (U) weight change on risk		
					Increase	Decrease	Cycling
French <i>et al.</i> (1999b)	1038	25 897	Iowa Health Study, women, 55-69 y	Weight change period: 25 y Follow-up period: 3 y	I: 1.2 (0.94-1.5) U: 1.3 (1.1-1.6)		
Mikkelsen <i>et al.</i> (1999)	3160	15 113	Denmark, men and women, 20-93 y	Weight change period: 5 to 25 y Follow-up period: 10 y	1.2 (0.94-1.4)	1.6 (1.3-1.9)	Compared at initial BMI 22-24 kg/m ²
Reynolds <i>et al.</i> (1999)	106	648	Baltimore, women, 65+ y	Weight change period: 2 y Follow-up period: 6 y		3.8 (2.1-6.9)	
Williamson <i>et al.</i> (1999)	3726	36 280	USA, Cancer Prevention Study, overweight men, 40-64 y	Weight change period: 22-46 y Follow-up period: 13 y	1.1 (0.92-1.3)	I: 1.1 (0.98-1.2) U: 1.0 (0.91-1.2)	Subjects with no reported health conditions
Dyer <i>et al.</i> (2000)	686	1281	USA, Western Electric Company Study, men, 40-56 y	Weight change period: 8 y Follow-up period: 25 y			1.1 (1.0-1.2)

Cardiovascular disease

Excess body weight has been demonstrated in many studies to increase the risk for mortality from cardiovascular disease in subjects of both genders (Pi-Sunyer, 1999). Also studies on weight change have analysed, in addition to all-cause mortality, coronary heart or cardiovascular disease mortality or morbidity (e.g., Lissner *et al.*, 1991; Lee & Paffenbarger, 1992d; Blair *et al.*, 1993; Higgins *et al.*, 1993; Iribarren *et al.*, 1995; Rimm *et al.*, 1995; Willett *et al.*, 1995; Folsom *et al.*, 1996; Fulton & Shekelle, 1997; French *et al.*, 1997; Yaari & Goldbourt, 1998; Galanis *et al.*, 1998b; French *et al.*, 1999b; Dyer *et al.*, 2000). In general, weight gain seems to be more tightly linked to an increase of risk for coronary heart diseases than for all-cause mortality, while the risk in connection with weight loss was on average less elevated for coronary heart diseases than for all-cause mortality and only slightly higher compared with stable weight. The three studies that addressed the question of intentional or unintentional weight loss (Williamson *et al.*, 1995, 1999; French *et al.*, 1999b) showed similar risk associated with intentional weight loss and with stable weight, while among women, unintentional loss of weight was associated with increased risk. However, the limitations of the current studies on weight loss discussed above also apply in relation to cardiovascular diseases and therefore the evidence for an effect of weight loss on cardiovascular diseases can be considered as limited.

This conclusion has to be weighed against the benefits seen in intervention studies among high-risk subjects (see following sections). Weight reduction improved cardiovascular disease clinical measurements and symptoms (Ornish *et al.*, 1990) and decreased mortality in a secondary prevention trial (Singh *et al.*, 1992). The National Task Force on the Prevention and Treatment of Obesity (2000) pointed out that most of the

effects of weight on coronary heart diseases presumably act through its impact on other risk factors including hypertension, impaired glucose tolerance, type II diabetes mellitus and dyslipidaemia.

Hypertension

Both systolic and diastolic blood pressure increase with increasing BMI (Stamler *et al.*, 1978; Van Itallie, 1985). Observational studies on risk of hypertension in relation to weight change suggest that an increase in weight increases the risk of hypertension (e.g., Curtis *et al.*, 1998; Huang *et al.*, 1998; Field *et al.*, 1999). Weight reduction seems to decrease the risk of hypertension (Huang *et al.*, 1998). Little information is available on the effect of weight cycling on risk of hypertension and no firm conclusion can currently be drawn. However, a recent small case-control study in Italy with a group of 103 hypertensive obese women aged 25–64 years and 155 controls revealed an increased risk associated with weight cycling (Guagnano *et al.*, 2000). It was concluded that weight cycling leads to increased weight and to a larger waist-to-hip ratio, both of which are associated with increased risk for hypertension.

Prevention of hypertension in overweight normotensive individuals

Stevens *et al.* (2001) randomized 1191 overweight subjects with non-medicated diastolic blood pressure of 83 to 89 mm Hg and systolic blood pressure less than 140 mm Hg to two groups. The intervention group lost weight through a three-year programme including dietary changes, physical activity and social support. After three years, the mean weight loss in the intervention group was 0.2 kg, while the control group had gained a mean of 1.8 kg. The risk ratio for hypertension in the intervention group was 0.81 (95% CI 0.70–0.95) at three years. Subjects who had lost at least 4.5 kg at six months and maintained this

weight loss up to three years had the lowest risk ratio for hypertension, of 0.35 (95% CI 0.20–0.59).

Established hypertension

A systematic review of 18 randomized trials (Mulrow *et al.*, 2000) evaluated whether weight-loss diets are more effective than other antihypertensive therapies in controlling blood pressure in hypertensive subjects. The trials included 2611 hypertensive participants. Most studies excluded subjects with normal weight. Intervention periods with a weight-loss diet ranged from two weeks to three years. In general, participants assigned to weight-reduction groups lost weight compared with the control groups. Six trials involving 361 participants assessed a low-energy diet versus a normal diet. A 4–8% weight loss was associated with a decrease in blood pressure in the range of 3 mm Hg systolic and diastolic. The review included three trials that assessed a weight-loss diet versus treatment with antihypertensive medications and suggested that a stepped-care approach with antihypertensive medications produced greater decreases in blood pressure (6 and 5 mm Hg systolic and diastolic, respectively) than did a weight-loss diet. However, the review suggested that patients on a weight-reducing diet required less intensive antihypertensive drug therapy.

Type II diabetes

The development of type II diabetes is characterized by obesity, early insulin resistance and progressive deterioration of glucose homeostasis over several years from hyperinsulinaemia with normal fasting glucose to impaired fasting glucose ('impaired glucose tolerance') and ultimately to fasting hyperglycaemia accompanied by a cluster of other metabolic abnormalities predisposing to vascular disease (Laakso & Lehto, 1997). Excess weight, particularly abdominal obesity, has a deleterious effect on all

phases of this process. An increasing risk of diabetes with greater initial BMI and weight gain has been amply documented in prospective studies from various parts of the world (Maggio & Pi-Sunyer, 1997). The risk increases almost linearly, being 2.1 and 3.5 for BMI 22–22.9 and 23–23.9 kg/m², respectively, compared with BMI < 22 kg/m² in US women aged 30–55 years who were followed for eight years (Colditz *et al.*, 1990). The positive effects of sustained weight loss on glycaemic control and associated metabolic complications in obese type II diabetes patients can be expected to have a favourable effect on mortality and morbidity among these patients. However, some studies have reported no association or an increased risk of mortality in obese diabetic patients with weight loss (Knatterud *et al.*, 1982; Chaturvedi & Fuller, 1995; Hanson *et al.*, 1995); these studies were not able to differentiate between intentional and unintentional weight loss. Some studies suggest that weight cycling increases the risk of type II diabetes (French *et al.*, 1997; Moore *et al.*, 2000b), but this issue needs further research. In a recent re-analysis of the American Cancer Society Study (Williamson *et al.*, 2000), overweight people with type II diabetes who reported intentional weight loss had lower total mortality (RR = 0.75; 95% CI 0.67–0.84) and cardiovascular disease and diabetes mortality (RR = 0.72; 95% CI 0.63–0.82) than those not reporting such weight loss. Weight loss of 20–29 lb [9–13 kg] was associated with the greatest reductions in mortality (0.67; 95% CI 0.58–0.77).

Prevention of diabetes in non-diabetic individuals

Short-term studies have shown a significant correlation between improved insulin sensitivity and percentage decrease in fat mass, especially in visceral adiposity (Goodpaster *et al.*, 1999). Weight loss produced by a low-energy

diet reduces blood glucose and insulin levels in obese individuals (National Institutes of Health and National Heart, Lung and Blood Institute, 1998). It also reduces the risk of developing type II diabetes, but the weight loss achieved by dietary interventions is usually not maintained and the benefit is short-lived. However, the protective effect is maintained if weight loss is maintained. After a two-year programme of diet and exercise in obese (30–100% overweight) persons with a family history of diabetes (Wing *et al.*, 1998), no overall difference in weight loss between the intervention and control groups was found at the end of the trial, despite impressive results in the first six months. However, among the participants maintaining a weight loss of 4–5 kg or more, regardless of study group, the risk of developing diabetes was reduced by 30%. The protective effect of a small maintained weight loss is also illustrated by a pooled analysis of randomized placebo-controlled weight loss trials (Heymsfield *et al.*, 2000). In this study, 10.8% of the obese subjects receiving diet only (mean weight loss 3.7 kg) developed impaired glucose tolerance and 1.2% developed diabetes in two years, whereas in the group on diet plus orlistat (a gastrointestinal lipase inhibitor) (mean weight loss 6.7 kg), impaired glucose tolerance developed in 6.6% and none developed diabetes. The benefits of a modest amount of sustained weight loss is preserved for extended periods of time. In a long-term follow-up of the Framingham cohort (Moore *et al.*, 2000b), weight loss of 3.5 kg or more maintained for eight years substantially lowered the risk of diabetes (RR = 0.38; 95% CI 0.18–0.81) in subjects with BMI ≥ 29 kg/m², whereas those who regained the weight they had lost had no reduction in diabetes risk. The most impressive protective effect is seen in subjects who lose a large amount of weight by obesity surgery (Long *et al.*, 1994; Sjöström *et al.*, 1999). In the

Swedish Obese Subjects (SOS) Study, the eight-year incidence of diabetes among surgically treated morbidly obese subjects (maintained weight loss about 20 kg) was greatly reduced compared with matched controls (no weight change), with an odds ratio of 0.16 (95% CI 0.07–0.36) (Sjöström *et al.*, 2000).

Prevention of diabetes in subjects with impaired glucose tolerance (IGT)

Several studies have demonstrated the potential of modest weight loss achieved by lifestyle modification to reduce the risk of diabetes in persons with IGT (e.g., Pan *et al.*, 1997; Heymsfield *et al.*, 2000; Tuomilehto *et al.*, 2001). In Chinese subjects with IGT followed for six years after an intervention of diet or exercise or both, the conversion rate to diabetes at six years was reduced by 31% in the diet intervention group achieving permanent weight loss of 1–3 kg (Pan *et al.*, 1997b). In a pooled analysis of two-year randomized placebo-controlled weight reduction trials comparing orlistat plus diet (mean weight loss 6.7 kg) versus diet alone (3.8 kg), half as many subjects with IGT progressed to diabetic status in the orlistat group (3.0%) as those with placebo (7.6%). In a randomized trial in Finland (Tuomilehto *et al.*, 2001), a weight loss of about 3.5 kg resulting from lifestyle intervention (versus 0.9 kg in controls) reduced the incidence of diabetes by more than 50% during the first four years of follow-up.

Greater sustained weight loss appears to almost completely reverse the risk of diabetes in subjects with IGT. A randomized controlled trial by Long *et al.* (1994) examined the progression of IGT to type II diabetes in 109 morbidly obese individuals with gastric bypass and in 27 non-surgical controls. Maintenance of the weight loss, corresponding to about 50% of the excess weight in the surgery group, was associated with a more than 30-fold

decrease in the risk of developing diabetes over six years.

Established type II diabetes

The health benefits of weight loss in obese patients with type II diabetes are well documented (Maggio & Pi-Sunyer, 1997; National Institutes of Health and National Heart, Lung and Blood Institute, 1998, Williamson *et al.*, 2000). Negative energy balance results in rapid improvement of hyperglycaemia, independent of weight loss, which is followed by a more enduring improvement in glycaemic control and other metabolic risk factors with loss of (abdominal) fat (Markovic *et al.*, 1998). Several studies have reported improved metabolic control with modest short-term weight loss (Liu *et al.*, 1985; Wing *et al.*, 1987; Goldstein, 1992). A meta-analysis of 89 short-term intervention studies using diet or a behavioural approach to induce negative energy balance concluded that a low-energy diet alone (often denoting a period of very low-energy diet) had a significant impact on weight (loss of about 9 kg), glycaemic control (-2.7% in glycosylated haemoglobin) and lipids and blood pressure, whereas the effects were smaller for behavioural therapies alone (about 2.9 kg and -1.5%) and for exercise alone (1.7 kg and -0.8%) (Brown *et al.*, 1996).

The short-term reduction in fasting hyperglycaemia is usually greatest in patients who lose the most weight (UKPDS Group, 1990), but in most trials a modest weight loss of 5–15% body weight has been associated with distinct improvements in glycaemic control (e.g., Heller *et al.*, 1988; UKPDS Group, 1990; Franz *et al.*, 1995; Manning *et al.*, 1995). For instance, in the randomized controlled trial by Heller *et al.* (1988), a median weight loss of 7 kg through dietary education (versus 2 kg in controls) resulted in a significant improvement in glycaemic control (median haemoglobin A1 7.5% versus 9.5%) at six months. However, glucose control

does not always improve with weight loss (Watts *et al.*, 1990). The benefits may also depend on the type of diet, e.g., total energy content and fat and carbohydrate composition (Heilbronn *et al.*, 1999).

Unfortunately, most of the benefit of weight loss seen in the early months of an intervention is lost with the weight regain that almost invariably later occurs, especially in diabetics (Guare *et al.*, 1995). The improvement in metabolic control is sustained if weight loss is maintained, as in a 12-month trial comparing the efficacy of orlistat plus diet versus diet only in drug-treated diabetics (Hollander *et al.*, 1998). A mean weight loss of 6 kg was seen in the orlistat group versus 4 kg with placebo at 12 months, in addition to decreased haemoglobin A1c and reductions in the use of sulfo-nylurea medication and in serum lipids. One of the few reports of successful long-term weight loss with diet comes from the Diabetes Treatment Study (Hadden *et al.*, 1986), an uncontrolled prospective trial of 223 patients with recently diagnosed diabetes who were seen for up to 72 months. Average weight loss at six months was 9 kg, and this was maintained for the six years of the study. At the end, about 80% of the patients could still be managed by diet alone. Prospective studies of patients with surgically treated obesity convincingly demonstrate the benefits of sustained weight loss (Pories *et al.*, 1995; Long *et al.*, 1994; Sjöström *et al.*, 1999). Over 80% of the 146 morbidly obese diabetics followed for 14 years after a gastric bypass operation had attained normoglycaemia, although they still were considerably overweight after a sustained weight loss of about 40 kg (Pories *et al.*, 1995).

Taken together, these data indicate that maintained major weight loss results in dramatic improvement of metabolic control or even in cure of obese type II diabetics. Although successful weight

loss due to diet and lifestyle modification is difficult to achieve and even more difficult to maintain, even modest maintained weight loss offers considerable benefits. The unexplained variability of the metabolic response of type II diabetics to moderate weight loss may be due to the heterogeneity of the disease.

Other morbidity

Obesity is also associated with increased risk of gallbladder disease, liver disease, reproductive problems, sleep apnoea, poor pulmonary function and degenerative joint disease (Pi-Sunyer, 1999; National Task Force on the Prevention and Treatment of Obesity, 2000). BMI and weight gain are associated with risk of adult-onset asthma (Camargo *et al.*, 1999). Weight loss decreases symptoms of these diseases, except for gallbladder disease. Significant improvement in both symptoms and objective findings of obstructive sleep apnoea syndrome after weight loss have been demonstrated (Lojander *et al.*, 1998). In a randomized trial, weight reduction in obese patients with asthma improved their lung function, symptoms and health status (Stenius-Aarniala *et al.*, 2000). In the Framingham study (Felson *et al.*, 1992), a decrease of 2 BMI units or more during a 10-year period decreased the odds of developing knee osteoarthritis by more than 50%, while weight gain was associated with a slight increase in risk.

Effects on surrogate markers

Effects of weight on insulin resistance, IGF, sex steroids, other hormones and immune function are covered in Chapter 4. Notably, associations between obesity and blood pressure, type II diabetes, dyslipidaemia and cardiovascular disease risk differ between racial and ethnic groups (Fujimoto, 1996; Cappuccio, 1997; Zoratti, 1998; Brown *et al.*, 2000)

Visceral adipose tissue

Hormonal and metabolic disturbances observed in abdominal obesity affect cardiovascular disease risk (Després *et al.*, 1990). A weight-loss diet promotes the loss of visceral adipose tissue (VAT). A review (Smith & Zachwieja, 1999) covered only studies measuring VAT with computed tomography or magnetic resonance imaging. The 16 eligible studies comprised 399 subjects. The duration of the studies ranged from 7 days to 16 months. Reductions in body weight ranged from 3.9% to 19.8% and in VAT from 9.4% to 49.3%. Diet intervention led to a greater loss of VAT than total fat loss. Individuals with greater visceral fat mass appear to lose more visceral fat, when adjustment is made for loss of body fat.

Dyslipidaemia

A higher BMI is associated with higher plasma triglyceride levels and lower high-density lipoprotein (HDL) cholesterol level, but the association with low-density lipoprotein (LDL) cholesterol levels is inconsistent (Després *et al.*, 1990). A meta-analysis (Yu-Poth *et al.*, 1999) evaluated the effects of the National Cholesterol Education Program's Step I and Step II dietary interventions on blood lipids. The 37 eligible randomized trials included 9276 subjects in intervention groups and 2310 subjects in control groups. The duration of intervention ranged from three weeks to four years. There was no restriction as to baseline obesity. Mean baseline total and LDL cholesterol concentrations were 6.04 ± 0.53 mmol/L and 4.01 ± 0.46 mmol/L, respectively. Mean baseline HDL cholesterol concentration was 1.24 ± 0.23 mmol/L and triacylglycerol concentration was 1.67 ± 0.46 mmol/L. Reductions in dietary fat and saturated fatty acids had beneficial effects on blood lipids. Plasma total cholesterol, LDL cholesterol, and triacylglycerol concentrations and the ratio of total cholesterol to HDL cholesterol significantly

decreased after both Step I (by 10%, 12%, 8% and 10%, respectively) and Step II (by 13%, 16%, 8% and 7%, respectively) dietary interventions. In many of the studies, the subjects lost weight (mean 3.38 kg). The changes in body weight significantly affected plasma HDL cholesterol and triacylglycerol concentrations; for every 1 kg decrease in body weight, plasma triacylglycerol concentrations decreased by 0.011–0.012 mmol/L (0.77–0.87%), whereas HDL cholesterol concentrations increased by 0.011 mmol/L ($\approx 1\%$). The correlations between body weight reduction and changes in total cholesterol and LDL cholesterol were significant only when the analyses were weighted by the number of subjects in each study. Another meta-analysis found that during active weight loss, HDL cholesterol levels tend to decrease, but when reduced weight stabilizes, HDL cholesterol levels increase to above the level before weight loss (Dattilo & Kris-Etherton, 1992).

Psychosocial aspects and quality of life

There are probably ethnic and cultural differences in reactions and attitudes to overweight and obese individuals. There is an inverse association between weight and socioeconomic status, especially among women (Sobal & Stunkard, 1989). Low socioeconomic status of origin is predictive of weight gain during adulthood (Lahmann *et al.*, 2000). Obese individuals may be prone to discrimination and negative attitudes in the areas of marital, employment and educational opportunities (Wadden & Stunkard, 1993). Most of the psychological disturbances (poor mental well-being, anxiety and depressive symptoms) associated with morbid obesity are believed to be consequences rather than causes of obesity. Decreasing psychological and behavioural symptoms after weight loss support this direction of causality (Wing *et al.*, 1984; Karlsson *et al.*, 1998).

Some studies have found that overweight (measured either as BMI or waist circumference) leads to poorer physical functioning (Le Pen *et al.*, 1998; Lean *et al.*, 1998). However, mental and social dimensions of quality of life (QOL) seem to remain unchanged with overweight. Only the additional burden of other chronic conditions compromises the mental and social dimensions of QOL in persons suffering from obesity (Doll *et al.*, 2000). Compared with the general population, obese patients seeking treatment suffer impairment in all dimensions of quality of life (Fontaine *et al.*, 2000).

Most of the studies assessing the effects of weight loss on QOL (functioning and well-being) have been conducted on surgically treated morbidly obese patients. The marked weight loss achieved by surgical techniques has been shown to improve deteriorated QOL in all of its dimensions (Karlsson *et al.*, 1998; Choban *et al.*, 1999). Positive changes in QOL have been related to the magnitude of weight loss and the duration of follow-up, with some tendency for QOL scores to return to baseline levels in subjects with less than 20 kg weight loss at long term (Karlsson *et al.*, 1998). As regards non-surgical methods of weight loss, one randomized controlled trial showed that a 7-kg difference between groups in weight outcome achieved by increased physical activity, low-energy diet and group support led to improved QOL in the intervention group (Rippe *et al.*, 1998). The duration of this study was only 12 weeks; the long-term effects of non-surgical weight loss interventions on QOL remain largely unknown.

Physical activity

A large body of evidence shows that physical inactivity increases mortality and morbidity (US Department of Health and Social Services, 1996). In the following review, priority has been given to health outcomes where the effects of

physical activity have been demonstrated consistently in different populations, to studies with sound measures of physical activity or physical fitness, and—because of their relevance to developing public health recommendations for physical activity—to studies providing information on dose–response issues. The evidence discussed is derived for the most part from studies in Caucasian populations.

Total mortality

Physical activity is inversely associated with all-cause mortality rates in middle-aged and older (≥ 60 years) men and women (Table 52). The relationship with volume of physical activity (estimated energy expenditure or a proxy for this) is linear, at least up to a level of about 14.7 MJ (3500 kcal) per week (Lee *et al.*, 1995), but approaches an asymptote at higher levels. Information on independent effects of the components of volume of physical activity (intensity, duration, frequency of sessions) is sparse. Some reports suggest a benefit only from vigorous activities (≥ 6 METs) (Lee *et al.*, 1995; Lee & Paffenbarger, 2000) and others a benefit from moderately vigorous activity (≥ 4.5 METs) (Paffenbarger *et al.*, 1993). Simple, non-sporting activities such as walking and stair climbing have been associated with lower risk. Distance walked and storeys climbed were predictive of longevity, independently of other components of physical activity, among male graduates of Harvard (Lee & Paffenbarger, 2000). Bicycling to work was associated with a 40% lower risk of mortality among Danish men and women, after multivariate adjustment which included leisure-time physical activity (Andersen *et al.*, 2000). Among retired men aged 61–81 years at the start of a 12-year follow-up period, the mortality rate among those who walked less than 1.6 km per day was nearly twice the rate in those who walked more than 3.2 km per day (Hakim *et al.*, 1998).

Inverse gradients for mortality exist across categories of increasing fitness (Sandvik *et al.*, 1993; Blair *et al.*, 1996); adjusted relative risks for medium and/or high fitness vs low fitness of 0.66 (95% CI 0.55–0.78) (Blair *et al.*, 1996) and 0.54 (95% CI 0.32–0.89) (Sandvik *et al.*, 1993) for men and 0.48 (95% CI, 0.31–0.74) for women (Blair *et al.*, 1996) have been reported. The available data suggest that a fitness level (assessed as maximal oxygen uptake) below 8–9 METs in middle-aged men is associated with a significant increase in risk (Whaley & Blair, 1995). Too few data are available for women to make a comparable estimate.

Low fitness is an important determinant of mortality risk. Among North American men, individuals with none of the established risk factors for coronary heart disease (smoking, high total cholesterol, hypertension) but who were in the lowest quintile for fitness had higher death rates than men who had two or three of these factors but were in the top quintile for fitness (Blair *et al.*, 1996).

Differences in mortality associated with physical activity levels are not explained by familial factors, as shown by comparison of death rates during follow-up in physically active twins with those of their less active siblings (Kujala *et al.*, 1998). Controlling for known confounders, including BMI, had relatively little impact on the relative risks of inactivity (Lee *et al.*, 1995) or low fitness (Sandvik *et al.*, 1993; Blair *et al.*, 1996). The effect of low fitness *per se* is evident from the report that unfit (bottom quintile of population studied) but lean men had significantly higher all-cause mortality than men who were fit (top quintile) but who had a BMI > 30 kg/m² (Lee *et al.*, 1999d). The importance of physical activity, as opposed to constitutional factors, is clear from reports that men and women who take up moderately vigorous activity or who increase their fitness level between two observations separated by some years

experience substantially lower all-cause mortality rates than their peers who remain inactive or unfit (Paffenbarger *et al.*, 1993; Blair *et al.*, 1995).

Cardiovascular disease

Physical inactivity is linked to increased risk of mortality and morbidity from coronary heart disease (CHD). A meta-analysis of the findings from studies of 27 cohorts showed that the protective effect probably lies in prevention of occurrence of major events, rather than in the reduction in the severity of events which do occur (Berlin & Colditz, 1990). The relationship between level of activity and CHD risk is strong. The relative risk of inactivity varies in different studies but the median value (based on a review of 43 mainly cohort studies) is about 1.9 for CHD event or CHD death, with methodologically superior studies tending to report higher values (Powell *et al.*, 1987). The relative risk associated with low (compared with high) fitness is somewhat higher (Blair *et al.*, 1996), possibly because measuring fitness reduces misclassification. Thus the magnitude of the increase in CHD risk associated with physical inactivity and low fitness is of the same order of magnitude as that conferred by smoking, hypertension and hypercholesterolaemia (Powell *et al.*, 1987).

The relationship between activity or fitness and CHD risk is dose-related (Morris *et al.*, 1990; Blair *et al.*, 1996), has been observed in populations worldwide (for review see Morris *et al.*, 1990), is independent of other major risk factors, including BMI (Figure 30) (Morris *et al.*, 1990; Haapanen *et al.*, 1997b) and is evident among women (Lemaitre *et al.*, 1995; Manson *et al.*, 1999; Haapanen-Niemi *et al.*, 2000) as well as men. Most information, however, relates to white Europeans and North Americans.

Everyday activities such as regular walking and cycling are associated with CHD risk. Among British civil servants, those who rated their regular walking as fast (over 6.4 km/h) or who did

Table 52. Prospective studies of total mortality in relation to physical activity or fitness in men

Reference	Population	Country	Measure of activity/ fitness	Analysis	Main findings	Notes
Sandvik <i>et al.</i> (1993)	1960 men aged 40–59 y, average follow-up 16 y	Norway	Fitness, measured as total work on a cycle ergometer during symptom-limited exercise tolerance test	Adjusted relative risk, highest vs lowest quartile	RR = 0.54 (0.32–0.89); $p = 0.015$ Mortality similar in fitness quartiles 1, 2 and 3	Data adjusted for many potential confounders. Fitness measured on cycle ergometer may not relate well to day-to-day activities where body weight is supported
Lee <i>et al.</i> (1995)	17 321 men, mean age 46 y, follow-up 22–26 y	USA (Harvard Alumni Study)	Physical activity by questionnaire	Relative risk for energy expended highest (≥ 6300 kJ/week) vs lowest (< 630 kJ/week) quintile	Total activity RR = 0.91 (0.82–1.0), p for trend < 0.05 Vigorous activity RR = 0.87 (0.78–0.97), p for trend = 0.007 Non-vigorous activity RR = 0.92 (0.82–1.0), p for trend = 0.36	Activity information very detailed. Analysis for different intensities mutually adjusted
Blair <i>et al.</i> (1996)	25 341 men, 7080 women, aged 20–88 y, average follow-up 8 y	USA	Fitness, time on maximal treadmill test, i.e., surrogate for maximal oxygen uptake	Adjusted relative risk, medium and highest vs lowest quintile	Men: RR = 0.66 (0.55–0.78) Women: RR = 0.48 (0.31–0.74)	Effects of fitness held independent of smoking, high cholesterol or high systolic blood pressure. Moderate and high fitness seemed to protect against influence of these other predictors
Kampert <i>et al.</i> (1996)	25 341 men, 7080 women aged 20–88 y, average follow-up ~ 8 y	USA	Fitness, time on maximal treadmill test, and physical activity by questionnaire	Trends across quintiles	Inverse association between level of physical fitness and mortality in men and women (p for trend < 0.001) Inverse association between level of physical activity and mortality in men (p for trend 0.01), but not in women	Lack of relationship with physical activity in women may result from greater misclassification

Table 52 (contd)

Reference	Population	Country	Measure of activity/ fitness	Analysis	Main findings	Notes
Hakim <i>et al.</i> (1998)	707 men aged 61–81 y, follow-up 12 y	USA (Hawaii)	Self-reported regular walking distance	Age-adjusted mortality rate	< 1.6 km/day = 40.5% > 3.2 km/day = 23.8% <i>p</i> for trend = 0.002	One of few studies specifically in elderly
Kujala <i>et al.</i> (1998)	7925 men 7977 women aged 25–64 y, follow-up 17 y	Finland	Physical activity by questionnaire	Adjusted relative risk, compared with sedentary (no leisure activity)	Occasional exercisers RR = 0.71 (0.62–0.81) Conditioning exercisers (at least vigorous walking > 6 times/month) RR = 0.57 (0.45–0.74) (<i>p</i> for trend < 0.001)	Twin study, examining potential modification of the effects of physical activity by genetic factors
Bijnen <i>et al.</i> (1999)	472 men, mean age 75 y, follow-up 5 y.	Netherlands	Physical activity by questionnaire	Adjusted relative risk, highest vs lowest tertile	RR = 0.44 (0.25–0.80); <i>p</i> for trend = 0.004 No association with intensity or type of exercise	Time in physical activity at baseline; low tertile 20 min/day; middle tertile 60 min/day; high tertile 150 min/day Activity at baseline not related to risk

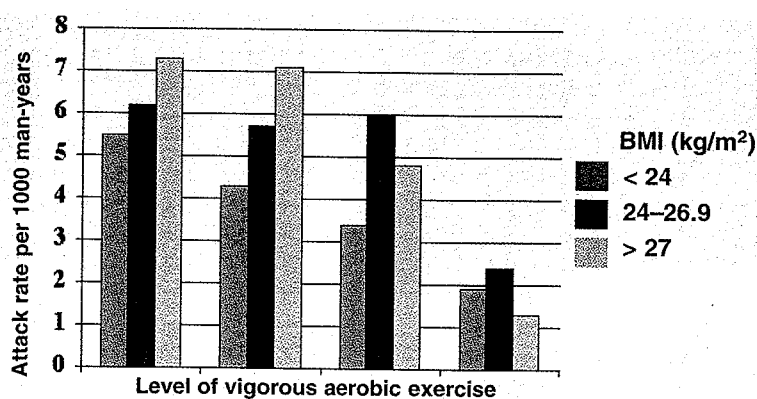


Figure 30 Rate of coronary heart disease attacks (1976–1986) in male executive-grade civil servants (rates per 1000 man-years) and levels of vigorous aerobic exercise, at different BMI (adapted from Morris *et al.*, 1990).

considerable amounts (≥ 40 km/week) of cycling experienced less than half the fatal and non-fatal CHD of the other men (Morris *et al.*, 1990). Among women who did not engage in vigorous exercise, those who walked the equivalent of three or more hours per week at a brisk pace had a multivariate relative risk of 0.65 (95% CI 0.47–0.91) compared with those who walked infrequently (Manson *et al.*, 1999).

Evidence from cohort studies, with follow-up periods of between five and 26 years, shows a lower risk of stroke in physically active men and women, but data are less extensive and less consistent than for CHD. In the US Nurses' Health Study ($n \approx 72\,500$ women), there was an inverse gradient of risk with volume of activity assessed as MET \times h per week (a measure of 'volume' of physical activity) (p for trend = 0.003) (Hu *et al.*, 2000): this was primarily due to the relation with ischaemic (thromboembolytic) stroke, women in the highest activity category exhibiting only half the risk of the least active. Among male Harvard alumni, total stroke incidence was inversely associated with energy expenditure in physical activity after adjustment for confounding factors but, as in some other studies, there was an

indication that this relationship might be U-shaped (Lee & Paffenbarger, 1998). All studies have related a single baseline measure of activity to incidence of stroke some or many years later. No studies of physical fitness are available.

Regular physical activity decreases the risk of developing hypertension. In a representative sample of the Finnish population, age-adjusted rates were 60–70% higher for sedentary men than for the most active men (estimated total energy expenditure) (Haapanen *et al.*, 1997b). Participation in vigorous sports was associated with a 35% lower risk among Harvard alumni, but chiefly among men who were overweight (Paffenbarger *et al.*, 1983). Information on women and on dose–response issues is lacking.

Intervention studies show that physical training decreases resting arterial blood pressure. A meta-analysis of more than 40 randomized, controlled trials found that decreases are greater in hypertensive subjects (defined as ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) (mean negative values 7.4/5.8 mm Hg) than in normotensives (mean value 2.6/1.8 mm Hg) (Fagard, 1999). These findings may in part reflect the acute effects of exercise, i.e., 'post-exercise

hypotension'. Blood pressure is reduced following a single session of exercise for up to 16 hours. In hypertensive men, mean arterial pressure was lowered by an average of 8 mm Hg for more than 12 hours after cycling for 30 minutes than on control days when only normal daily activities were performed (Pescatello *et al.*, 1991). This is a low-threshold phenomenon and has been noted after exercise at only 40% of maximal oxygen uptake. Like other acute effects, it may be enhanced in people who are regularly active at a high level because they generally expend more energy in a session (Haskell, 1994).

Type II diabetes

A relationship between risk of type II diabetes and physical activity level has been demonstrated in a number of prospective studies. Helmrich *et al.* (1991) assessed the physical activity levels of some 6000 male alumni of the University of Pennsylvania by questionnaire in 1962 and again in 1976. Age-adjusted incidence rates declined as energy expenditure in exercise increased. This relationship remained significant after adjustment for current BMI, history of hypertension and parental history of diabetes. Low physical fitness has also been associated with increased risk. Among American men who had attended a preventive medicine clinic, the least fit 20% had a 3.7-fold higher risk of becoming diabetic during a six-year follow-up than the most fit 40% (Wei *et al.*, 1999). In both these studies, the protective effect was strongest in men at high risk because of overweight, hypertension and a parental history of diabetes. It was evident for non-vigorous as well as vigorous exercise, when the total energy expended was high. Among women participating in the US Nurses' Health Study who did not report engaging in vigorous exercise (Hu *et al.*, 1999b), the risk of developing type II diabetes was inversely related to the volume of walking

(MET \times h per week), even after adjustment for potential confounders (including BMI) (p for trend = 0.01). Faster usual walking pace was also independently associated with lower risk.

Hip fracture

Physical activity decreases the risk of hip fracture. Among 9516 healthy white women of average age 72 years, risk of hip fracture during a four-year follow-up was 30% lower in those who reported regularly walking for exercise than in those who did not walk regularly (Cummings *et al.*, 1995). Risk tended to decrease as the distance walked increased and the effect remained significant even after adjustment for physical frailty and the presence of other chronic diseases. In a case-control study, increased daily activity (including standing, walking, climbing stairs, carrying, housework and gardening) protected against fracture in elderly men and women (Cooper *et al.*, 1988). This effect was not greatly affected by controlling for BMI, smoking, alcohol consumption, history of stroke and use of corticosteroids.

Most hip fractures are precipitated by a fall and regular physical activity may decrease the risk of falling by improving balance and/or lower limb strength. In premenopausal women, a 1.5-year programme of high-impact exercise (three times per week) increased bone mineral density at the femoral neck, compared with the control group (Heinonen *et al.*, 1996); muscle power and dynamic balance were also improved. In another randomized controlled trial over one year (Nelson *et al.*, 1994), postmenopausal women (50–70 years) performed high-intensity strength exercises on two days per week. Not only was bone mineral density at the femoral neck and lumbar spine increased but muscle mass, muscle strength and dynamic balance were increased in exercisers and decreased in controls. A meta-analysis of data from seven randomized, controlled trials con-

cluded that exercise programmes alone appear to reduce the risk of falls by 10%; combining these programmes with balance training reduced the risk by a further 7% (Province *et al.*, 1995).

Other health outcomes

Several studies have found a lower incidence of gallbladder disease in physically active individuals. Among women in the US Nurses' Health Study, for example, physical activity was inversely associated with the risk of cholecystectomy (Leitzmann *et al.*, 1999). Compared with women in the lowest quintile of activity, women in the highest quintile had a multivariate relative risk of 0.69 (95% CI 0.61–0.78). Adjusting for BMI and weight change in the previous two years attenuated the association only slightly (multivariate relative risk 0.79). Not all studies have observed an association between physical activity level and gallbladder disease, however. After adjustment for potential confounders, no association was found among 16 785 men participating in the Harvard Alumni Study (Sahi *et al.*, 1998).

High levels of physical activity maintain functional capacities such as muscular strength, endurance and mobility (Figure 31). Among older persons, this improves measures of quality of life (King *et al.*, 2000), is associated with

a reduced likelihood of hospitalization for cardiovascular disease (LaCroix *et al.*, 1996) and helps maintain a capacity for independent living. Even the frail elderly can achieve important (>100%) gains in muscle strength through regular chair-based exercises (Fiatarone *et al.*, 1994). These gains were associated with significant increases in gait velocity and stair-climbing power.

Physical activity is related to psychological health. It is an effective treatment for mild-to-moderate depression and may reduce symptoms of anxiety (Martinsen & Stephens, 1994). Cross-sectional, population-based studies have shown significant positive associations between physical activity and general well-being and mood and negative associations with depression and anxiety (Stephens, 1988). Limited evidence from prospective studies supports these findings. For example, in a Canadian study with a seven-year follow-up of some 2500 people, baseline physical activity level was predictive of mental health at follow-up (Martinsen & Stephens, 1994). These analyses took into account age, sex, educational level, physical health and baseline psychological status and so constitute strong evidence that physical activity is predictive of future mental health. In one of a number of



Figure 31 Physical activity may decrease the appetite, especially in obese individuals. Physical activity at a moderate rate does not increase the appetite. In some situations, the appetite will actually decrease. Research indicates that the decrease in appetite after physical activity is greater in individuals who are obese than in individuals who are at their desirable body weight.

randomized, controlled intervention trials, moderate-intensity training improved anxiety levels and perceived ability to cope with stress (Moses *et al.*, 1989).

Effects on surrogate markers

Lipids

Regular physical activity leads to changes in blood lipids, particularly increases in HDL cholesterol and decreases in triglyceride levels. Cross-sectional comparisons of endurance athletes with sedentary men and women have typically found HDL cholesterol more than 20% higher in athletes (Durstine & Haskell, 1994). Differences have been related to distance run in both men and women, suggesting a dose-dependence. Among men, every 16-km increment in weekly distance run (up to 64 to 79 km/week) was associated with significant increases in HDL cholesterol (Williams, 1997). These findings may be confounded by genetic and/or other lifestyle characteristics, especially a lower total body and abdominal fat mass. Randomized intervention studies, mainly of moderate-intensity exercise (3–5 days per week, ≥ 30 minutes per session), have yielded less consistent results, from a decrease of 5.8% to an increase of about 25%, with a mean increase of 4.6%. Changes tend to be greater when weight loss accompanies training (Tran & Weltman, 1985). Other reasons for this variability probably include genetic predisposition, inadequate control of dietary habits (energy value and diet composition), blood volume changes, proximity of last exercise session and, in women, phase of the menstrual cycle.

Acute effects of exercise may contribute to the more favourable blood lipid characteristics of physically active people. One session of exercise markedly reduces both fasting and post-prandial triglyceride levels (Gill & Hardman, 2000), possibly by enhancing clearance of triglyceride-rich lipopro-

teins. This effect appears to depend on the energy expended in exercise, rather than on its intensity or pattern. Thirty minutes of brisk walking decreased day-long plasma triglyceride levels in sedentary men and women (compared with an inactive day), whether this was performed in one session before breakfast or in three 10-minute sessions (Murphy *et al.*, 2000b). Faster clearance of triglycerides probably leads to higher HDL cholesterol.

Insulin sensitivity

The mechanisms underlying the enhanced insulin sensitivity in active people were discussed in Chapter 4. Insulin sensitivity appears to increase in relation to the volume of training undertaken (Mayer-Davis *et al.*, 1998), but the benefit of exercise is lost within a few days when training is interrupted. For example, middle-aged men and women who were regularly active in moderate exercise showed a marked deterioration in their response to an oral glucose tolerance test after just three days without exercise (King *et al.*, 1995). This suggests that the acute effects of exercise may account for some of the difference in insulin sensitivity in trained individuals.

Coagulation

Several aspects of haemostasis may be influenced in a beneficial manner by physical activity. Cross-sectional observational studies have consistently found an inverse relationship between plasma fibrinogen and physical activity and/or physical fitness. For example, in men from ten general practices in the United Kingdom, plasma fibrinogen decreased with the frequency of reported participation in vigorous exercise (Connelly *et al.*, 1992). This epidemiological finding could partly explain the lower risk of CHD in active persons, but has not been reproduced consistently in randomized intervention trials. One reason may be that study designs have seldom taken proper

account of the acute effects of the last exercise session.

People who are physically active do not experience the platelet activation and platelet hyperreactivity seen in sedentary individuals (Kestin *et al.*, 1993). A possible reason is the less marked catecholamine response to exercise in habitually active people.

Flow-mediated dilatation

Physical activity may also influence the acute phase of cardiovascular disease by reducing endothelial dysfunction. Among asymptomatic men known to exhibit features of the metabolic syndrome, 12 weeks of training significantly increased flow-mediated dilatation measured at rest in the brachial artery (Lavrencic *et al.*, 2000). In men with coronary artery disease, a brief (four-week) period of exercise training improved endothelium-dependent vasodilatation in both epicardial coronary vessels and in resistance vessels (Hambrecht *et al.*, 2000). Both studies were randomized, controlled trials.

Bone mineral density

Physical activity may influence the risk of osteoporotic fracture through effects on bone mineral density, the microarchitecture of bone and/or the risk of falls. Bone mineral density at age 70 years is determined both by peak bone mass accumulated in youth and the subsequent rate of bone loss. Athletes, particularly those whose sports are associated with high impact, are consistently reported to have higher bone mineral density than sedentary counterparts (for review, see Suominen, 1993). This effect is a local response to local loading and may be most potent during growth. Bone mineral density in arm sites showed significantly greater side-to-side differences (higher in playing arms) in female tennis and squash players than in sedentary controls (Kannus *et al.*, 1995). The difference was four to five

times greater in those who started their playing careers before or at menarche than in those who started more than 15 years after menarche.

Prospective studies show that physical activity is a determinant of peak bone mass. In US college-aged women participating in recreational sports followed up for up to five years, physical activity was monitored at six-month

intervals (Recker *et al.*, 1992). Level of activity was positively related to the rate of increase in spinal bone mineral density. Bone may be particularly sensitive to mechanical loading during the adolescent growth spurt (Haapasalo *et al.*, 1998).

Randomized intervention trials show that physical activity can be effective in maintaining bone mass in pre-

menopausal women and substantially decreasing bone loss in postmenopausal women. The effect is small (typically about 1% per year) and seen in both the lumbar spine and femoral neck.

