It is well accepted that being overweight or obese carries risks to health, but there is less agreement as to whether weight loss produces benefits on mortality and on cardiovascular event rates. The evidence from observational studies is conflicting: some studies have shown weight loss to be associated with increased mortality, but this could be because differentiation was not made between intentional and unintentional weight loss. Mechanistic hypotheses can be raised for both beneficial and harmful effects of weight loss. Randomized controlled clinical trials are needed to establish the effect of intentional weight loss and two large outcome studies are now under way: SCOUT and Look AHEAD. These trials are assessing the effect of weight loss on cardiovascular endpoints. Such trials are complex and expensive to undertake, but are important if we are to establish whether weight loss is truly associated with a reduction in mortality.

KEYWORDS
Cholesterol; Look AHEAD; Mortality; Obesity; Outcome trial; SCOUT; Weight loss

The health risks of being overweight and obese have been clearly demonstrated: obesity is a risk factor for diabetes, cardiovascular disease, and most cancers, and it is associated with shortened life expectancy. The relationship between body mass index (BMI) and risk for mortality is usually shown by a J-shaped curve. Most studies show that mortality risk is lowest for BMI 20–25 kg/m² and large studies demonstrate increases in mortality beginning at BMI 25 kg/m². As the BMI exceeds 30 kg/m², the curve becomes more steep. Evidence for this relationship has been demonstrated in a number of prospective longitudinal studies, including the large American Cancer Society Study. It is also evident from insurance actuarial data that being overweight is a risk to health.

However, the relationship between obesity and increased risk for mortality does not always hold true, and congestive heart failure is one special case. Evidence of a paradoxical relationship between weight and risk for mortality in patients with congestive heart failure has been recently published. An observational study was carried out over 5 years with 1203 individuals with advanced heart failure. Although obesity predisposes to heart failure, this study showed that overweight and obese individuals had a lower risk of mortality than underweight and normal weight people (Figure 1). It has also been demonstrated in numerous studies that weight loss in patients with chronic heart failure is associated with impaired survival. Other cardiovascular risk factors have been demonstrated to have the same reverse effect on prognosis in patients with chronic heart failure.

However, although the risks of overweight and obesity are generally well accepted, there is some controversy as to whether weight loss is beneficial. The popular view is that weight loss is good for you but not all scientists believe that to be the case. Detractors note that a number of observational epidemiological studies have associated weight loss with increased mortality. The Framingham study is one of many studies that have shown a negative relationship between weight loss and mortality. Over an observation period of 20 years, and omitting deaths in the first 4 years, death rates were highest for subjects who lost weight, even when the...
data were adjusted for age, BMI, smoking, and other risk factors. Compared with subjects whose weight did not change, there was a 44% increase in total mortality rate in men who lost weight and a 38% increase in women who lost weight. Many other studies have shown the same relationship. In addition, some of the studies have demonstrated that this relationship exists whether the individual is overweight, normal weight, or underweight.

In view of the observations from these large epidemiological studies, it is valid to question the health benefits of weight loss. One likely explanation for this relationship between weight loss and mortality is that the population studies are observing unintentional weight loss. Most observational studies do not assess intentionality of weight loss. It is unusual in the general population for there to be significant rates of intentional weight loss and, consequently, observed weight loss is for the most part unintentional and associated with disease. To demonstrate the benefits of intentional weight loss, it is necessary to assess intentionality of weight loss and to frame the epidemiological association between intentional weight loss and mortality. The few studies that have addressed this issue show benefit from weight loss on mortality.

Williamson et al. reported a prospective analysis with 12-year mortality follow-up of 4970 overweight individuals with Type 2 diabetes, aged 40–64, who were enrolled in the American Cancer Society’s Cancer Prevention Study I. Subjects were asked about weight change and whether this had been intentional or not. Intentional weight loss was reported by 34% of the cohort. After adjustment for initial BMI, socio-demographic factors, health status, and physical activity, intentional weight loss was associated with a 25% reduction in total mortality (RR = 0.75) and a 28% reduction in cardiovascular disease and diabetes mortality (RR = 0.72). There was a dose-related effect, up to ~30 lb, where the greater the weight loss the greater the reduction in mortality (Figure 2). Weight loss >70 lb was associated with small increases in mortality. However, at the higher levels of weight loss, the numbers of individuals are quite small, limiting interpretation of the data. This study demonstrates that for individuals with Type 2 diabetes, intentional reduction in weight is, indeed, associated with reductions in mortality.

**Mechanistic hypotheses**

The tenets of epidemiology are that evidence from multiple studies is required to confirm an association and, furthermore, the association should always have a reasonable underlying mechanistic hypothesis.

There are many hypotheses to support a relationship between weight loss and improvements in health (Figure 3). Improvements in lipids and in blood pressure will be associated with reduction in cardiovascular risk. Weight loss has a profound effect on insulin secretion, and the role of insulin in promotion of cardiovascular disease and cancer has been receiving considerable attention. In addition to the effect of weight loss on diabetes prevention (which is a very strong association), lowering of the insulin level may play a role in cardiovascular risk reduction as well as cancer risk reduction. Weight loss might also reduce oestrogen levels and improve other endocrine profiles that might contribute to cancer risk. Other potential benefits include reductions in pro-inflammatory cytokines and improvement in the thrombotic profile. There could be reductions in oxidative stress with reduced calorie intake, which could promote reduction in cancer risk and cardiovascular disease risk. In addition, reduction of the fat mass burden could lead to improvements in sleep apnoea and in osteoarthritis.

Conversely, there are several possible ways in which weight loss could be detrimental to health (Figure 4). It is known from weight loss studies that there is a definite risk (up to 5% in some studies) of acute cholecystitis, particularly if the patient has a low fat diet. There is also concern that weight loss could be associated with immune dysfunction and that it might promote the development of eating disorders. One of the benefits of being overweight is that the individual has a decreased risk of osteoporosis and, therefore, there is some concern that weight loss could be associated
with promotion of osteoporosis. Together with reduction in muscle mass, this might be associated with increased risk of falls and fractures and an associated increase in mortality. There are some opinions that mobilizing fat also mobilizes organic toxins that are stored in fat, which might contribute to cancer and other diseases. In addition, if one was achieving weight loss by increasing metabolism through exercise, there could be increased oxidative stress and promotion of cardiovascular disease and cancer.

There are, therefore, reasonable hypothetical mechanisms to support both the argument that weight loss could be beneficial to health and the argument that weight loss could promote disease.

It is known that weight loss has beneficial effects on a number of intermediate endpoints and risk factors, as discussed by Van Gaal, and that maximizing weight loss will maximize these weight loss benefits. There is also an association between weight loss and morbidity. Weight loss has been shown to prevent Type 2 diabetes in the Finnish Diabetes Prevention Study, the Diabetes Prevention Program from the USA, and the Swedish Obese Subjects (SOS) study.

The Diabetes Prevention Program randomized 3234 individuals with impaired glucose tolerance to placebo, treatment with metformin, or a lifestyle modification programme with the goals of weight loss and increased physical activity. After mean follow-up of 2.8 years, the incidence of diabetes was reduced by 58% in the lifestyle intervention group compared with placebo. The metformin arm had an intermediate risk reduction (31% compared with placebo); this group also had an intermediate weight loss. The lifestyle intervention group lost at its maximum, 7% from baseline; the metformin group lost slightly >2% from baseline. Modest weight loss can, therefore, be translated into dramatic benefits in terms of diabetes risk reduction.

The SOS study, with 4047 surgical subjects, is an observational study comparing obese subjects who underwent gastric surgery and matched conventionally treated obese controls. Despite the lack of randomized treatment assignment, it is a valuable long-term observation providing information on the benefits of marked weight loss. Ten-year data from SOS show differences in the amount of weight loss according to the type of surgical procedure used: weight loss was 25% with gastric bypass, 16.5% with vertical banded gastroplasty, and 13.2% with banding;
control group patients gained 1.6% weight. Overall, when the trial arms are collapsed, the weight loss at 10 years is 16.1% from baseline.\textsuperscript{10} This study shows a dramatic reduction in diabetes incidence, both at 2 years and at 10 years (Figure 5). Benefit in terms of the development of hypertension and other risk factors is not as clear-cut as this diabetes association.

The SOS study was powered with overall mortality as the primary endpoint. Despite enrolling over 4000 subjects and having a 75% retention rate, there are, as yet, no data on the evaluation of this endpoint, but mortality data are expected to be released during 2006. It is hoped that SOS will demonstrate that weight loss is beneficial to health. Two large-scale randomized clinical trials will be needed to convince epidemiologists that weight loss is beneficial to health. It is important to note, however, that SOS is not a randomized study; it is an observational study in which the surgical patients are compared with matched controls from a registry. Data from randomized controlled trials will be needed to convince epidemiologists that weight loss is beneficial to health. Two large-scale randomized clinical trials of the effect of weight loss on hard endpoints, i.e. cardiovascular events and mortality, are now under way. The SCOUT trial (Sibutramine Cardiovascular Outcomes Trial) is a double-blind, randomized, placebo-controlled, parallel group, global multicentre study with a single-blind sibutramine lead-in period. It involves 9000 overweight or obese subjects aged $\geq 55$ with Type 2 diabetes and/or established cardiovascular disease. The SCOUT trial is discussed elsewhere in this supplement.\textsuperscript{11}

The other trial is Look AHEAD (Action for Health in Diabetes). This is a large study funded by the US National Institutes of Health to assess the long-term effects of an intensive weight loss programme delivered over 4 years in overweight and obese patients with Type 2 diabetes. The study will enrol 5000 individuals. Patients in the intervention group receive an intensive lifestyle programme that is designed to achieve and maintain weight loss by dietary modification and increased physical activity. The weight loss goal is 10%.\textsuperscript{12}

The primary hypothesis of Look AHEAD is that over the 11.5 year follow-up, the lifestyle intervention will reduce the incidence of the first post-randomization occurrence of a composite outcome (cardiovascular death, non-fatal myocardial infarction, or stroke) compared with a control group of patients who are given diabetes education and support and usual care from their primary care practitioners. Results from this trial are expected in 2012.

Assuming an annual event rate of slightly $\geq 2\%$, the study is powered to detect an 18% relative decrease in the rate of primary outcomes in the lifestyle intervention group with 11.5 year follow-up.

Look AHEAD addresses some of the challenging research issues in outcome studies in the obesity arena. One of the major issues in designing this type of trial is that when the event rate is low, the study requires a large number of subjects and long-term follow-up. It is also important to maximize retention because every patient who is lost from the study affects the ability to assess the outcome. Look AHEAD has an ambitious retention rate: it assumes a 3% loss to follow-up each year. The study participants are aged 45–75, and history of cardiovascular disease is not an exclusion criterion. The lifestyle goal is intended to maximize the effect size and the Data Safety Monitoring Board will question the study if the mean weight loss does not exceed 7% from baseline.

The requirement for large-scale, long-term trials with an emphasis on high retention rates and intensive interventions means that such trials are extremely expensive: Look AHEAD is expected to cost $260 million. In addition, designing a study with a sufficiently high event rate can mean recruitment of sicker subjects. This raises the question of whether the results will be generalizable to the whole population and whether, in these sicker subjects, cardiovascular disease is as reversible by the effects of weight loss as it would be in younger, less sick individuals.

**Randomized clinical trials**

It is important to note, however, that SOS is not a randomized study; it is an observational study in which the surgical patients are compared with matched controls from a registry. Data from randomized controlled trials will be needed to convince epidemiologists that weight loss is beneficial to health. Two large-scale randomized clinical trials of the effect of weight loss on hard endpoints, i.e. cardiovascular events and mortality, are now under way. The SCOUT trial (Sibutramine Cardiovascular Outcomes Trial) is a double-blind, randomized, placebo-controlled, parallel group, global multicentre study with a single-blind sibutramine lead-in period. It involves 9000 overweight or obese subjects aged $\geq 55$ with Type 2 diabetes and/or established cardiovascular disease. The SCOUT trial is discussed elsewhere in this supplement.\textsuperscript{11}

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**Conclusion**

Observational studies have produced conflicting data on whether weight loss is beneficial to health. This appears likely to be because these studies have generally not differentiated between intentional and unintentional weight loss.

Moderate weight loss (5–10% from baseline) improves many intermediate endpoints that are associated with morbidity and mortality and it can prevent diabetes. Randomized controlled trials are required to assess the effects of intentional weight loss on hard clinical endpoints. Two large randomized outcome studies are...
now underway. The Look AHEAD trial is evaluating moderate weight loss produced by intensive lifestyle intervention on cardiovascular events and mortality in Type 2 diabetes, and the SCOUT trial is evaluating the effect of sibutramine on cardiovascular events and mortality in high-risk patients. These trials are important if we are to establish whether weight loss truly is associated with a reduction in mortality, a question of key importance to everyone involved in obesity research.

Key points

- The health risks of obesity are well accepted, but there is some controversy over the benefits of weight loss.
- Despite proven beneficial effects on a number of cardiovascular risk factors, several observational studies have suggested that weight loss is associated with increased mortality; this is probably because the studies did not distinguish between intentional and unintentional weight loss.
- Randomized controlled trials are needed to assess the effects of weight loss on ‘hard’ clinical endpoints. Look AHEAD is a large outcome study that is assessing the effect of weight loss produced by an intensive lifestyle intervention on cardiovascular events and mortality in obese diabetic patients.

Conflict of interest: The author has consulted for Abbott and lectured at Abbott-sponsored symposia.

References