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Nilsson, Peter; Nilsson, Jan-Åke; Hedblad, Bo; Berglund, Göran; Lindgärde, Folke

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Total number of authors:
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LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

The enigma of increased non-cancer mortality after weight loss in healthy men who are overweight or obese

P. M. NILSSON, J.-Å. NILSSON, B. HEDBLAD, G. BERGLUND & F. LINDGÄRDE

From the Department of Internal Medicine, University Hospital, Malmö, Sweden

Abstract. Nilsson PM, Nilsson J-A, Hedblad B, Berglund G, Lindgärde F. (University Hospital, Malmö, Sweden). The enigma of increased non-cancer mortality after weight loss in healthy men who are overweight or obese. *J Intern Med* 2002; **252**: 70–78.

Objective. To study effects on non-cancer mortality of observational weight loss in middle-aged men stratified for body mass index (BMI), taking a wide range of possible confounders into account.

Design. Prospective, population based study.

Setting. Male population of Malmö, Sweden.

Participants. In all 5722 men were screened twice with a mean time interval of 6 years in Malmö, southern Sweden. They were classified according to BMI category at baseline (<21, 22–25, overweight: 26–30, and obesity: 30+ kg m⁻²) and weight change category until second screening (weight stable men defined as having a baseline BMI ± 0.1 kg m⁻² year⁻¹ at follow-up re-screening).

Main outcome measures. Non-cancer mortality calculated from national registers during 16 years of follow-up after the second screening. Data from the first year of follow-up were excluded to avoid bias by mortality caused by subclinical disease at re-screening.

Results. The relative risk (RR; 95% CI) for non-cancer mortality during follow-up was higher in

men with decreasing BMI in all subgroups: RR 2.64 (1.46–4.71, baseline BMI <21 kg m⁻²), 1.39 (0.98–1.95, baseline BMI 22–25 kg m⁻²), and 1.71 (1.18–2.47, baseline BMI 26+ kg m⁻²), using BMI-stable men as reference group. Correspondingly, the non-cancer mortality was also higher in men with increasing BMI, but only in the obese group (baseline BMI 26+ kg m⁻²) with RR 1.86 (1.31–2.65). In a subanalysis, nonsmoking obese (30+ kg m⁻²) men with decreased BMI had an increased non-cancer mortality compared with BMI-stable obese men (Fischer's test: *P* = 0.001). The mortality risk for nonsmoking overweight men who increased their BMI compared with BMI-stable men was also significant (*P* = 0.006), but not in corresponding obese men (*P* = 0.094).

Conclusions. Weight loss in self-reported healthy but overweight middle-aged men, without serious disease, is associated with an increased non-cancer mortality, which seems even more pronounced in obese, nonsmoking men, as compared with corresponding but weight-stable men. The explanation for these observational findings is still enigmatic but could hypothetically be because of premature ageing effects causing so-called weight loss of involution.

Keywords: epidemiology, men, mortality, obesity, skin-fold, social, weight loss.

Introduction

Obesity is a well-known risk factor for type 2 diabetes, cardiovascular disease and increased mortality in both sexes [1, 2]. It is however, less well documented if a weight decrease in obese subjects, either voluntary or not, is truly beneficial to reduce this mortality risk. In contrast, several observational

studies have shown that a weight decrease (weight loss) is frequently associated with an increased mortality risk [3–11]. One explanation for this discrepancy could be the effect of a subclinical wasting disease associated with weight loss, e.g. cancer or depression, or the effects of adverse changes in lifestyle, e.g. initiation of smoking. Only a few studies, e.g. in obese patients with established

hypertension or type 2 diabetes, have provided limited evidence of a better prognosis associated with weight loss even if the benefit seems marginal [12].

Voluntary weight loss might prove more beneficial than unintentional weight loss [13] and loss of fat might be more beneficial than overall weight loss. The latter is a suggestion not easy to assess in most studies as information is lacking on body composition. Surrogate measures such as skin-fold thickness have therefore been used in studies showing that fat loss seems more favourable than overall weight loss [14]. Compared with intentional weight losers in one American study [15], those who lost their weight unintentionally reported engaging in more negative health behaviours (smoking, poor diet) that are related to disease morbidity and mortality. These data suggest that unintentional weight loss may be part of a cluster of behaviours that have a negative health impact.

Weight loss in the obese may have several beneficial effects on symptom reduction, increased well being and better self-esteem, at least in the short run. It has however, been less easy to show benefits in morbidity. After surgical intervention in severely obese subjects to reduce weight the incidence of hypertension and diabetes is lower than expected, but mortality data are still lacking from the surgical Swedish Obesity Study (SOS) [16]. It is, however, less clear if the reduced blood pressure will stay low or not after long-term follow-up [17]. A decrease in the progression rate of carotid atherosclerosis has, however, recently been reported after surgical intervention in these severely obese subjects raising hopes for a reduction of cardiovascular morbidity and mortality [18, 19]. Surgical treatment of severe obesity may also decrease sick leave and disability pension, particularly in middle-aged men and women [20].

If the medical profession should recommend weight loss as an evidence-based treatment modality for overweight or obese individuals in the general population it should be proven safe and with a favourable risk-benefit ratio. Intervention data restricted to severe obese patients are therefore less informative, but today they are the only available.

Weight loss in obese subjects is today heavily promoted in most Western populations, not only for medical but also for commercial and cosmetic reasons. It is therefore of great interest to further

elucidate the question of potential side-effects connected with weight loss. There will probably never be a truly randomized controlled study of nonsurgical, intentional weight loss with an appropriate long-term follow-up in otherwise healthy people, because of the inherent difficulties of such a study. The only available substitute is to conduct well-designed prospective observational studies.

The aim of this study was to investigate the long-term consequences of weight change for non-cancer mortality in a large population of healthy middle-aged men, with special focus on overweight or obese subjects, the latter group also stratified for smoking.

Participants and methods

Subjects

In Malmö, the third largest city of Sweden (250 000 inhabitants), a preventive case-finding programme for cardiovascular risk factors and alcohol abuse, the Malmö Preventive Project (MPP), was started at the Department of Preventive Medicine, University Hospital, in 1974. The aim was to invite and screen large strata of the adult population in order to find high-risk individuals for preventive intervention [21, 22]. All subjects were invited by letter to participate in a broad health screening programme, including a physical examination and a panel of laboratory tests. Additionally, every participant filled in a self-administered questionnaire, including questions on lifestyle, social background characteristics and subjective health. Between 1974 and 1982, a total of 22 444 males answered the call and attended the screening and intervention programme, with an overall attendance rate of 71% (range 64–78%), somewhat differing between years. They were not selected for any degree of obesity at invitation. Various interventions (lifestyle modification, drug therapy) were offered to nearly 25% of the screened subjects with hypertension, hyperlipidaemia or diabetes, for shorter or longer periods [21, 22]. Oral advice was given to obese subjects to improve their lifestyle but no targeted intervention for obesity (weight-control, drugs) was ever implemented [21]. The overall effect of the intervention on morbidity and mortality, as compared with noninvited birth cohorts, was minimal as previously reported [22].

A considerable proportion of the men primarily invited for the baseline examination in the MPP

($n = 5722$), with mean age 47 years (range 38–52 years), was re-screened after 3–8 years (mean 6 years), and forms the basis for this follow-up analysis. These men belonged to a few birth-cohorts (born in 1926–31) and were not selected in any other way. Therefore, they constitute a well defined, but otherwise nonselected subgroup of the total number of men recruited for the MPP. No further clinical examination has so far been carried out in these men.

Screening procedures

Physical examination. All subjects were examined at both baseline and follow-up for height (m) without shoes, and weight (kg) in light in-door clothing. The Body Mass Index (BMI) was calculated (kg m^{-2}). Triceps skin-fold thickness (mm) was measured by use of a Harpenden calliper at the middle of a relaxed forearm, values being log-transformed.

Self-administered questionnaire. A questionnaire was filled in by all participants and included a large number of questions, e.g. on smoking habits, alcohol problematic drinking habits, leisure time physical activity, insomnia, nervous problems, subjective reflections on own weight development, as well as subjective health.

Smoking was defined as self-reported daily smoking. The existence of nervous problems (including psychiatric morbidity and insomnia) was defined as a positive answer to one or more of the following questions:

- 1 Have you ever been treated for nervous disorders or psychiatric disease (yes/no)?
- 2 Have you ever been hospitalized for psychiatric disease (yes/no)?
- 3 Do you find it difficult to fall asleep at night (yes/no)?
- 4 Do you regularly use hypnotics (yes/no)?

Other questions asked on personal background were the following:

- 1 Have you increased >10 kg of weight since 30 years of age (yes/no)?
- 2 Do you want help to loose weight (yes/no)?
- 3 Are you in good personal health (yes/no)?

Register follow-up analyses

Registers on mortality and cancer. All available subjects were followed for a mean of 22 years (range 20–25 years) in national registers for total

and cause-specific mortality, until 31 December 1999. The Swedish Board on Health and Welfare, Stockholm, provided data from national registers on death certificates and cancer diagnoses. The overall autopsy rate was 44% in Malmö during the period when the diagnoses on local death certificates were reasonably trustworthy. All cancer-related deaths were excluded from the analyses, because of expected interference with weight change. In addition all death certificates of deceased obese men ($n = 23$) have been carefully examined.

Of all the men in the re-screened group ($n = 5722$) we excluded men with prevalent disease at baseline ($n = 141$), men with cancer deaths ($n = 365$), men who died within the first year of follow-up ($n = 19$), and men with missing data for BMI at re-screening ($n = 3$). Therefore, the final analyses were based on a total of 5194 men, with 571 deaths during follow-up [ischaemic heart disease (IHD): $n = 270$; Stroke: $n = 49$; Other cardiovascular disease (CVD): $n = 68$; and Other mortality: $n = 184$, including 50 deaths from external causes].

Statistical methods

All subjects were stratified into BMI categories at the baseline screening (<21, 22–25, 26–29 and 30+ kg m^{-2}). At re-screening after 6 years all subjects were also classified according to weight change (decrease, stable weight, or increase) as measured by attained BMI. A stable weight development was defined as a baseline screening $\text{BMI} \pm 0.1 \text{ kg m}^{-2} \text{ year}^{-1}$ at follow-up. This definition was based upon expected weight changes in middle-aged Caucasian men, as presented in the medical literature. In a separate analysis all obese men were additionally stratified for current smoking habits at baseline (smokers, nonsmokers).

A Cox proportional hazard ratio was used for calculating the relative risk (RR) of non-cancer mortality (with 95% confidence intervals) after re-screening but with the first year's mortality excluded, in total 14 years of follow-up for mortality in the three main BMI categories (<21, 22–25 and 26+ kg m^{-2}). The weight stable group was used as a reference population within each BMI category.

Characteristics of nonsmoking obese men at baseline, subdivided into different BMI-change categories, have been expressed as proportions, and

differences were tested by chi-square analyses. Differences in continuous variables (expressed as means and standard deviations; SD) were tested by ANOVA.

Fischer's exact test was used for calculating differences between obese subjects with weight change (increase or decrease) compared with weight-stable subjects, in non-cancer mortality after re-screening but with the first year's mortality excluded, in total 14 years of follow-up for mortality.

A *P*-value less than 0.05 was considered to be significant.

Results

All men – non-cancer mortality

Baseline characteristics of all healthy men are shown in Table 1. Small differences, but significant because of large numbers, were noted in age, height and weight between subgroups.

The RR (95% CI) for non-cancer mortality during follow-up was higher in men with decreasing BMI in all subgroups: RR 2.64 (1.46–4.71, baseline BMI <21 kg m⁻²), 1.39 (0.98–1.95, baseline BMI 22–25 kg m⁻²), and 1.71 (1.18–2.47, baseline BMI 26+ kg m⁻²), using BMI-stable men as reference group. Correspondingly, the non-cancer mortality was also higher in men with increasing BMI, but only in the overweight/obese group (baseline

BMI 26+ kg m⁻²) with RR 1.86 (1.31–2.65) (Table 2).

All men stratified for smoking habits – non-cancer mortality

Nonsmoking obese (30+ kg m⁻²) men with decreased BMI had an increased non-cancer mortality compared with BMI-stable obese men (*P* = 0.001). The corresponding risk for nonsmoking overweight men who increased their BMI compared with BMI-stable men was also significant (*P* = 0.006), but not in corresponding obese men (*P* = 0.094) (Table 3).

In absolute numbers more smoking than non-smoking men had died at follow-up. In smoking obese men the risk for non-cancer mortality in the weight-decrease group was nonsignificant (*P* = 0.465) compared with weight-stable obese men. The same was true for smoking obese men in the weight increase group (*P* = 0.092) (Table 3).

Obese nonsmoking men – non-cancer mortality

Characteristics of the three BMI-change subgroups of 170 healthy, nonsmoking obese (30+ kg m⁻²) men at baseline are shown in Table 4. Men who were later BMI-stable had the lowest proportion of manual workers (32%) compared with men who later either decreased (46%) or increased their weight (58%) (*P* = 0.029). No group differences

Table 1 Baseline characteristics (age, height, weight) of healthy middle-aged men (*n* = 5194) who later had either decreased BMI, a stable BMI, or increased BMI until re-screening after a mean of 6 years. Exclusion criteria were self-reported prevalent diseases at baseline (CVD, diabetes, and history of MI, stroke or cancer). A stable BMI at re-screening was defined as baseline BMI ±0.1 kg m⁻² year⁻¹. Statistical test by ANOVA for differences within BMI-change categories. Means (SD) or proportions

BMI baseline (kg m ⁻²) (<i>n</i>)	BMI-change groups	<i>n</i>	Age (years)	Height (m)	Weight (kg)	Cause of death	
						CVD (<i>n</i>)	Other (<i>n</i>)
<21 (939)	Decrease	79	47.2 (2.9)	1.76 (0.08)*	64.2 (7.0)	9	8
	Stable	354	46.6 (3.4)	1.78 (0.06)	65.1 (5.9)	17	14
	Increase	506	46.2 (3.6)*	1.77 (0.07)	64.3 (6.2)	25	27
22–25 (2671)	Decrease	464	46.9 (3.0)	1.76 (0.07)	75.5 (6.7)	39	15
	Stable	1001	47.1 (2.9)	1.77 (0.06)	75.1 (6.3)	60	24
	Increase	1206	46.8 (3.2)	1.77 (0.06)	74.7 (6.2)	83	40
26+ (1584)	Decrease	482	47.1 (2.8)	1.76 (0.07)	89.1 (10.4)	50	21
	Stable	513	47.4 (2.6)	1.76 (0.07)	87.0 (9.0)**	34	12
	Increase	589	46.9 (3.0)*	1.76 (0.06)	88.1 (9.1)	70	23

CVD: cardiovascular disease; Other: all non-CVD deaths, including trauma and intoxications.

***P* < 0.01; **P* < 0.05.

Table 2 Age-adjusted risk ratio (RR; 95% CI) for non-cancer mortality in three groups of healthy men at screening ($n = 5194$), stratified for body mass index (BMI) at baseline, and into subgroups of weight change from baseline to re-examination. Follow-up time after re-examination was mean 17 years. A stable BMI at re-screening was defined as baseline BMI $\pm 0.1 \text{ kg m}^{-2} \text{ year}^{-1}$ during follow-up (reference group)

BMI baseline (kg m ⁻²)	<i>n</i>	BMI-change	Deaths	Follow-up (years)	Deaths per 10 000 men	RR (95% CI)
<21	79	Decrease	17	1201	142	2.64 (1.46–4.71)
	354	Stable	31	5743	54	1.00
	506	Increase	52	8212	63	1.17 (0.75–1.83)
22–25	464	Decrease	54	7540	72	1.39 (0.98–1.95)
	1001	Stable	84	16 327	51	1.00
	1206	Increase	123	19 657	63	1.21 (0.92–1.60)
26+	482	Decrease	71	7635	93	1.71 (1.18–2.47)
	513	Stable	46	8407	55	1.00
	589	Increase	93	9246	101	1.86 (1.31–2.65)

BMI 26+ category includes both overweight (26–29 kg m⁻²) and obese (30+ kg m⁻²) men.

Table 3 Fischer's exact test for non-cancer mortality in groups of healthy men at screening, stratified for body mass index (BMI) and smoking status at baseline, and into subgroups of BMI change from baseline to re-examination. A stable BMI at re-screening was defined as baseline BMI $\pm 0.1 \text{ kg m}^{-1} \text{ year}^{-1}$ (reference group)

BMI baseline (kg m ⁻²)	<i>n</i>	BMI-change	Deaths	Follow-up (years)	Deaths per 10 000 men	<i>P</i> -value
Nonsmokers						
26–29	199	Decrease	16	3652	44	0.036
	269	Stable	10	4492	22	
	258	Increase	25	4166	60	0.006
30+	61	Decrease	15	933	161	0.001
	44	Stable	1	734	14	
	65	Increase	7	1012	69	0.094
Smokers						
26–29	122	Decrease	28	1839	152	0.360
	114	Stable	23	1790	128	
	131	Increase	31	1993	156	0.308
30+	27	Decrease	4	440	91	0.465
	20	Stable	4	321	125	
	31	Increase	13	422	308	0.092

were detected for proportions of men who were married/cohabiting, or reported nervous problems, insomnia or hospitalization for psychiatric disorders. Self-reported problematic alcohol drinking habits or leisure time physical exercise did not differ between groups (data not shown). Weight-stable obese men more often reported that they were in good general health (86%), than either men decreasing (77%) or increasing (65%) weight ($P = 0.033$). No differences were shown between groups for self-reported need of help to loose weight (a possible marker of intentional weight loss).

No significant differences were noted for the three groups of obese men in biological variables at

baseline, except of height (with men increasing weight being shortest), or in the change of these variables until re-screening (Table 4).

Changes in skin-fold thickness and mortality

Analyses of changes over time (in tertiles) of skin-fold thickness did not alter the results. The mortality rates in all nonsmokers, belonging to the top tertile of skin-fold thickness at baseline, were 54 deaths per 10 000 in men losing most fat mass (tertile 1 of change in skin-fold thickness), 34 deaths per 10 000 in men losing lesser fat mass (tertile 2), and 68 deaths per 10 000 in men with no loss or an

Table 4 Baseline characteristics and medical history of healthy obese (BMI 30+ kg m⁻²) men (*n* = 176) who later had either decreased BMI, a stable BMI, or increased BMI until re-screening after a mean of 6 years. Exclusion criteria were prevalent diseases at baseline (CVD, diabetes, and history of MI, stroke or cancer). Means (SD) and proportions

Variable	BMI change groups			P-value
	Decreased	Stable	Increased	
<i>(a) Personal background and medical history</i>				
N	61	44	65	
Age (years)	47.4 (2.6)	47.4 (2.3)	47.3 (2.6)	0.936
Manual work (%)	46	32	58	0.029
Married – Cohabiting (%)	70	84	85	0.420
No leisure exercise (%)	19	23	25	0.799
Nervous problems (%)*	25	14	20	0.384
'Have you increased >10 kg weight since 30 years age?' (%)	82	75	78	0.689
'Do you want help to loose weight?' (%)	51	52	38	0.255
'Are you in good personal health' (%)	77	86	65	0.033
<i>(b) Biological variables</i>				
Weight (kg)	102.3 (11.0)	98.4 (11.7)	98.0 (10.6)	0.049
Height (m)	1.77 (0.07)	1.76 (0.08)	1.74 (0.08)	0.069
SBP (mmHg)	146.6 (20.8)	144.3 (20.6)	138.7 (14.1)	0.038
SBP change	-11.1 (20.7)	-11.3 (22.2)	-6.0 (16.4)	0.236
Fasting glucose (mmol L ⁻¹)	5.3 (1.0)	5.1 (0.8)	5.1 (0.7)	0.295
Glucose change	1.0 (2.5)	0.4 (0.8)	0.4 (1.0)	0.070
Cholesterol (mmol L ⁻¹)	5.9 (1.0)	5.7 (1.0)	5.7 (0.9)	0.557
Cholesterol change	-0.2 (0.8)	-0.1 (0.6)	0.1 (0.7)	0.096
Fasting insulin (mU L ⁻¹); median (range)	18 (3–70)	17 (3–42)	14 (3–54)	0.471
Insulin change	NA	NA	NA	–

*One or more positive answers to questions regarding nervous problems, hospitalization for psychiatric disorders, insomnia, or regular use of hypnotics (see Methods). SBP: systolic blood pressure; NA: not available. Changes are described in variables between baseline and re-screening.

increase in fat mass (tertile 3). Corresponding figures for obese, smoking men were 112, 135 and 97 deaths per 10 000.

Causes of death in obese men

Death certificates revealed that all non-cancer deaths in the obese men (Table 3), except three were classified as cardiovascular or stroke-related deaths. The only three exceptions were one death attributed to chronic bronchitis (a nonsmoker), one death because of bronchopneumonia (an ex-smoker) and one death because of an accident (a smoker). No suicides were recorded.

Discussion

In spite of the fact that obesity is a well-known risk factor for mortality and morbidity, e.g. type 2 diabetes and cardiovascular disease, it seems that weight loss is not beneficial for longevity in men

according to this study. The non-cancer mortality rate was twofold increased in overweight and obese men combined, and ninefold increased in the clinically important subgroup of nonsmoking obese men. These findings do not negate the possible benefits of weight loss for cardiovascular risk factor reductions, health symptom relief as well as a better quality of life in many obese subjects, but question the arguments for prolonged life and reversal of overall cardiovascular mortality risk. Furthermore, our data are well in line with several other observational studies in Western countries showing that weight loss is most often associated with increased mortality rates [3–11]. This is, therefore, a clinical question, and perhaps a paradox, of utmost importance in view of the current world epidemic of increasing obesity, notably most pronounced in subject's of low socio-economic class from the Western countries and of middle- or high social class in developing countries. In Sweden, currently about 7% of

middle-aged men are obese (BMI >30 kg m⁻²) and an additional 40% are considered overweight (BMI >25 kg m⁻²) reported for 1989 [23], but in the USA about 20% of corresponding males are obese.

Three main objections have been raised against the conclusion that weight loss might be detrimental for longevity, which we have all tried to cope with:

1 The first objection is that weight loss, observed in population-based samples, is confounded either by subclinical disease, incident cancer or smoking habits. In the present study, we therefore excluded all subjects at baseline with a medical history of CVD, MI, diabetes or cancer, as well as all cancer-related deaths during follow-up. After stratification for smoking habits at baseline we further excluded all subjects who started to smoke during the period until re-screening, in order to be able to select a subgroup of obese nonsmoking men.

2 The second objection is that intentional weight loss would be more beneficial than nonintentional weight-loss for the medical outcome. We used self-reported data included in the baseline-screening questionnaire to assess this aspect. It was shown that obese nonsmoking men who later either changed BMI or were BMI-stable did not differ in answering the question 'Do you want help to loose weight?' Additionally, no differences in self-reported nervous problems or psychiatric morbidity were noted between these subgroups, indicating that at least at baseline the obese nonsmoking men were similar in this respect and not prone to losing weight intentionally or unintentionally because of their premorbid personality or depressive traits. No suicides in either group were recorded.

3 The third objection is that weight loss is deleterious but that reduction of fat mass is beneficial for longevity. We could not confirm previous findings in support of this hypothesis [14] as a decrease in triceps skin-fold was also associated with increased mortality in men belonging to the highest tertile of skin-fold thickness at baseline. This may be because of differences in population characteristics or the fact that a single skin-fold measurement is a poor marker for fat mass that ideally should be measured by more sophisticated methods.

A recent Danish study reported an increased mortality rate in a large group of 15 113 men and women with decreasing BMI in different strata of

BMI at baseline [11]. Adjustments were made for pre-existing and subclinical disease, but no information was available for skin-fold or risk factor changes, or for the intentionality of weight loss. Both our studies however, reach the same overall conclusion namely that weight loss is not a neutral phenomenon but seems to somehow increase the mortality rates in healthy men in observational studies. We could not provide information for women, but the Danish study found no differences in the overall outcome pattern in subgroups because of gender or smoking status [11]. Therefore, it seems reasonable to conclude that large-scale observational studies in Scandinavian countries confirm that weight loss, as indicated by BMI decrease, is potentially deleterious and increases mortality rates in the general population. These findings may or may not be different in selected groups of clinically defined patients, as such subgroups were excluded and not specifically studied.

Is a BMI change always a marker of weight change? Recent findings have shown that a decrease in height should also be taken into account when evaluating BMI changes, as height is a factor in constructing BMI. If weight is held constant a decrease in height (squared in BMI) would therefore tend to increase BMI. It has been pointed out that men normally loose 3 cm of height until the age of 70 years, and an additional 2 cm between 70 and 80 years, as part of normal involution processes associated with ageing [24]. This phenomenon is well known but less marked in middle age. It could however, be of some importance in the view of a new hypothesis of premature biological ageing as an explanation for the combined effects of BMI-decrease (weight and height decreases in combination) and the observed increased mortality. This could represent effects secondary to early metabolic and endocrine ageing which are the result of genetic or environmental causation [25]. The relation between changes in weight and height during the adult life course should therefore be more explored in future studies.

If all question marks around the effects of weight loss and BMI-decrease should ever be taken away and the issue clarified, it would take large-scale randomized intervention studies with intentional weight loss in men and women to do so. In such studies both life style interventions, surgical proce-

dures and drug treatment strategies could and should be evaluated. Until we have such data the general evidence-based, public health message based on observational studies is to increase physical activity [26], stop smoking [27], and to aim for weight stabilization in adult life by the use of a prudent diet [28]. The latter conclusion implies avoidance of weight loss, if not supported by good arguments for clinical disease control in some patient groups or for relief of disabling symptoms, as well as weight cycling [9]. Recently, an observational study has however, emphasized the benefits of weight loss amongst overweight individuals with diabetes [29], thus strengthening the arguments in favour of weight loss in some specific groups of patients. This is in sharp contrast to the detrimental effects of both intentional and unintentional weight loss in elderly men who are reported to run an increased mortality risk [30].

However, if the evidence to loose weight is scanty or absent, or even in favour of an increased mortality risk, it should be pointed out that prevention of weight increase, not weight loss, might be the best way of tackling the current global obesity epidemic. This should be achieved through preventive dietary advice and increased physical activity on the population level to avoid rather than to treat obesity. Furthermore, if obesity is already established such a conclusion would merit advice for weight stabilization, not for weight loss in most cases, if mortality risk should be considered as the main target (see the Appendix).

Finally, more biomedical research has to be carried out to elucidate the biological mechanisms involved in weight loss and energy balance, e.g. related to reductions in T3 levels, increased cholinergic activity with resting heart rate decreases, and decreases in total energy requirements [31]. Maintenance of a reduced or elevated body weight is associated with compensatory changes in energy expenditure, which oppose the maintenance of a body weight that is different from the usual weight. These compensatory changes may account for the poor long-term efficacy of treatments for obesity [31].

In conclusion, weight loss in self-reported healthy but overweight middle-aged men, without serious disease, is associated with an increased non-cancer mortality, which seems even more pronounced in obese nonsmoking men, as compared with obese weight-stable men. The explanation for this obser-

vational finding is still enigmatic but could hypothetically be the result of premature ageing effects linked to genetic or environmental traits, which should be the focus of future studies.

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Appendix

What is already known on this topic

- Obesity is an important risk factor for increased morbidity and mortality in many observational studies, e.g. for cardiovascular disease and type 2 diabetes. Trends of increasing obesity in Western countries have, however, also been associated with decreasing trends for cardiovascular disease on the population level (the epidemiological paradox of obesity).
- Weight loss is associated with an improvement in cardiovascular risk factors in both observational and intervention studies of short or medium duration.
- Observational studies of weight loss have indicated an increased mortality rate at follow-up. This finding might often have been confounded by comorbidity.

What this study adds

- Observational weight loss is, as well as weight increase, compared with being weight-stable, associated with an increased long-term, non-cancer mortality risk in self-reported healthy middle-aged men with overweight or obesity.
- The proportion of manual workers in both the weight-decrease and weight-increase groups of obese subjects is higher than in the weight stable group.
- Randomized intervention studies are needed to prove the benefits of intentional weight loss on longevity.

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Correspondence: Peter Nilsson, Department of Medicine, University Hospital, S-205 02 Malmö, Sweden (fax: +46 469 23272; e-mail: peter.nilsson@medforsk.mas.lu.se).