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Title: Long-term weight loss effects on all cause mortality in overweight/obese populations

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ABSTRACT

This systematic review assesses the long-term effectiveness of weight loss on all cause mortality in overweight/obese people. Medline, Embase and Cinahl were searched (1966–2005). Cohort studies and trials on participants with Body Mass Index $\geq$25 kg/m^2, with weight change and mortality with $\geq$ 2 years follow-up were included finally identifying 11 papers based on 8 studies. There may be gender differences in the benefits for all cause mortality. The impact of weight loss in men on mortality was not clear with some studies indicating weight loss to be detrimental, while a recent cohort study showed benefits, if it were a personal decision. Other studies with no gender separation had similarly mixed results. However, one study indicated that overweight/obese women with obesity related illness, who lost weight intentionally within one year, had significantly reduced mortality rates of 19% -25%. In contrast, studies of overweight/obese diabetics irrespective of gender, showed significant benefit of intentional weight loss on mortality in a meta-analysis, HR=0.75(0.67- 0.83). There is some evidence that intentional weight loss has long-term benefits on all cause mortality for women and more so for diabetics. Long-term effects especially for men are not clear and need further investigation.

Introduction

Obesity is now considered a global epidemic. In the last two decades there has been an alarming rise in obesity with one third of the population in the United States being affected.(1) Similar trends have been noticed in Europe. Obesity induces multiple metabolic abnormalities leading to diabetes mellitus and cardiovascular disease and is associated with increased disability, morbidity and mortality.(2-5)

Previous reviews of weight loss studies have reported that moderate weight losses (losses of 5-10%) are associated with improvements in obesity related cardiovascular and metabolic abnormalities.(6-9) It might be expected that this in turn will reduce mortality in the long-term. In recent years, the relationship between weight loss and mortality has raised concerns with studies reporting increased mortality with weight loss.(10;11) It is still unclear, however, whether weight loss in overweight/obese people, either voluntary or involuntary, truly reduces mortality.(12;13)

The aim of this paper was to systematically review the available evidence on the relationship between weight loss in overweight/obese adults and long-term all cause mortality. The intentionality of weight loss and gender differences were also explored in this paper.

Research Methods and procedures

A systematic literature search was undertaken on Medline, Embase, Cinahl electronic bibliographic databases. The review included literature published between 1966 and October 2005 with no language restrictions. Mesh terms and text words for 'cohort studies', 'obesity', ' overweight', 'weight changes' and 'mortality' were used and appropriately combined. The inclusion criteria covered all prospective studies and trials carried out on participants with body mass index (BMI) of greater than, or equal to, 25 kg/m^2. Initially those with BMIs of $\geq$28 were considered since overweight people on the verge of obesity may also experience some of the hazards of obesity. However, due to paucity of studies that met that strict criteria, studies with overweight and/or obese sub-groups (BMI$\geq$25) were also deemed suitable. Cohort studies and randomised controlled trails (RCTs) with weight change measurements, mortality information and a follow-up of more than 2 years were included.

Participant criteria included adults between 18 and 70 years. After 70 years of age weight loss may be confounded with age.(14) Studies on Caucasian, Afro-American, Japanese American and British Asian populations were included in the review. It should be noted that the ethnic minorities in western cultures may adopt the culture and dietary habits of their Caucasian counterparts and may, therefore, have similar risks of obesity. General population studies, animal studies and studies with less than 40% follow-up were excluded.

To identify relevant studies, abstracts were divided up and read by two independent reviewers. Full articles of the studies that met our selection criteria were obtained, and initially assessed by two independent reviewers, and then by one reviewer for methodological quality. Reference lists of all studies and review articles included were also checked to identify other relevant studies. A data extraction form was designed, piloted and amended before being used by two independent reviewers to extract the data from the papers. Researchers consulted regularly with each other to discuss any inclusion queries as they arose. Where relevant and possible, authors were contacted for further information about studies not available from their published papers.

Measures of mortality in all the papers were reported as either relative risk (RR) or hazard ratios (HR). Attempts were made to combine the studies using meta-analysis (methods described by Sutton et al.(15)) when the studies had comparable interventions, settings and test statistics.

Results

In total 8089 abstracts were scanned, and 301 full articles were obtained and critically appraised, of which 11 papers (16-26) published from 8 studies investigated the effects of weight loss on all cause mortality. The characteristics and details of the studies and papers are described in Table 1.

(Table 1 here)

On investigation the results were grouped and presented as the effects of weight loss on mortality for studies presenting only women and only men; other studies combining results for both men and women with no gender separations and finally for studies reporting on those with Type 1 or Type 2 diabetes.

Within the results, the effects of intentionality of weight loss is also presented where intentionality was assessed and reported by the authors of the included studies as part of their results.

Results for women only

Two papers (21;24) reported mortality with weight loss for US white women. Rumpel (21) used the US NHANES cohort, recruited in 1971, using information up to but not including the 1992 wave of data. The other paper was by Williamson (24) using women recruited in 1959 from the US Cancer Prevention Study (CPS-I) monitoring weight in 1960-5 and deaths up to 1972. Both these cohorts involved people with similar average ages spanning mid 40s to mid 50s for 'initial' weight (Table 2). It should be noted that the NHANES cohort used the maximum life time weight assessed retrospectively.

(Table 2 here)

Results from the Rumpel (21) study showed significantly increased mortality for all overweight/obese people with weight loss. After excluding the first 5 years of deaths this was still true for those with losses of ≥8.55% of body weight. In this study, however, the reference group were those of normal weight with small weight loss. The other study by Williamson (24) on the other hand only investigated women who were at the very least over weight. Here they asked about weight loss intention and also about any obesity related illness and in each case used the 'No weight change' sub-group as the reference group . For those with illness and intentional weight loss the mortality risk significantly improved when referenced to similar people with no weight change, except for those with weight loss <20 pounds and who took longer (1 or more years) to lose the weight.

The non-comparable reference groups in the Rumpel study leaves only the Williamson study on which to base any conclusions. This indicates some benefit for women with obesity related illness and intentional weight loss. Meta-analysis was therefore inappropriate in this case with only one study.

Results for men only

Three papers (20;23;25) were reviewed for men only. The Williamson paper was again a sub-group analysis of the CPS-I cohort (25) (recruited in 1959, recordings 1960-5, deaths until 1972). Nilsson (20) reported on the Swedish Malmo Preventative Project (MPP), where men were screened in 1974 and 1982, with deaths being followed up to the end of 1999. Data from the British Regional Heart Study were analysed by Wannamethe (23), recruited in 1978-80, re-measured in 1992-6 with intentionality asked about retrospective weight changes in 1996 and deaths monitored up to October 2003. Two of the studies (20;25) had similar age means (mid 40s to mid 50s) while Wannnamethee (23) included men up to 75 years old (Table 3).

(Table 3 here)

Considering men of the CPS-I cohort, Williamson (25) used the same format as women discussed in the previous section whereby the participants were all at least overweight. Once again the intention of weight loss and those with and without health conditions were subdivided. Despite the comparable reference group of weight stable men, those with intentional weight loss (if carried on for longer than 1 year) was detrimental for all men, except if it was <20 pounds for those with some health conditions. Unintentional weight loss was also marginally detrimental.

Nilsson (20) also reported weight loss as being detrimental, for non cancer mortality, when compared to similar men who were weight stable (Table 3) although intentionality was not reported. These men were not ill despite being overweight/obese giving comparable results for the similar group described by Williamson.

The analysis on overweight men by Wannamethee (23) was adjusted for several variables accounting for demographic variations and probably underlying ill health. The men in this study showed that compared to the weight stable sub-group those with intentional weight loss (if a personal decision) was extremely beneficial, although it made no difference if the men were ill and or told to lose weight by their doctor.

Overall the impact of weight loss on mortality in men is not clear. Two studies (20;25) indicate weight loss to be detrimental while the most recent cohort (23) shows clear benefits if the loss is a personal decision. When all papers are combined using a random effects meta analysis model, then compared to the reference group in each study of overweight weight stable men, the overall effective weight loss is slightly detrimental with a Hazard Ratio of HR=1.15(1.08, 1.01). Combination of pairs of studies as a sensitivity analysis did not alter this finding unless Williamson's study was excluded when it became non significant with wide confidence intervals. When studies with only intentional weight loss are considered, then the hazard ratio as a fixed effect model, becomes non-significant, HR=1.01(0.99,1.09).

<u>Results for men and women combined studies</u>

Mortality and weight loss for obese men and women together, with no gender separation was reported in three papers (17;18;22) detailed in Table 4. Gregg 2003 (18) used the National Health Interview Survey (NHIS) conducted in 1989 with self reported intention of weight loss and vital status followed for 9 years. Christou 2004 (17) reported two Canadian cohorts running together between 1986 and 2002, where one cohort had surgical interventions while the other acted as a standard treatment control group. Sørensen 2005 (22) reported on the Finnish twin cohort for men and women born before 1958, still alive in 1967 with self-reported measures in 1975 along with attempts to lose weight (defined as intention) and weight change noted in 1981 where mortality was recorded up to 1999.

(Table 4 here)

All three papers cover a similar era with mortality being recorded from the mid-eighties to the millennium although the participants of Gregg's paper from the NHIS study (18) were about a decade older so that the average age varied slightly between the studies, 40 up to 57 years old.

The analysis from Gregg's (18) study adjusted for more than 13 variables, including demographic variables but also attempted to account for known underlying illnesses. Of all those who were not trying to lose weight, people who actually gained had a marginally beneficial effect with respect to mortality, when compared to those who were weight stable. When smokers were excluded this benefit disappears indicating that despite being adjusted for, smoking had remained influential in the original model. In this group trying not to lose weight, those with small amounts of weight loss saw no significant mortality rate differences while larger weight losses were seen to be detrimental. In contrast, for those who claimed to be trying to lose weight the effects were marginally beneficial if they remained weight stable or lost small amounts, the latter remaining significant even when the smokers were excluded.

Another recent study reported by Sørensen (22) also considered intentional weight loss adjusting for demographic and lifestyle variables. Unlike the Gregg paper, weight gain for those not intending to lose weight was seen here to be detrimental. It was observed that even for those with intentional weight loss the effect was also detrimental.

Christou (17) considered very different individuals, all morbidly obese. In this surgical cohort 7/1035 died (losing an average of approximately 33kg) compared to those under standard treatment where 354/5746 died (weight loss not recorded). The results provided are relative risks as well as Kaplan Meier survival analysis although without any obvious adjustments. Usually surgery is only considered for those for whom obesity is life threatening. Consequently, the surgery group does have a substantially reduced mortality risk compared with the similar control group who do not undergo surgery. Similarly, the effects of the surgery are difficult to disentangle from any weight loss benefits for this sub-group. Weight loses possible with surgery are enormous and for this study were between 60-80% of the excess weight 2-5 years after surgery.

In this section, Christou had a completely different approach, weight management being a surgical intervention. Although, the paper claims that the participants had no other pre-existing illness it is likely that they would initially have had a high risk of mortality. The other two papers, however, were comparable (18;22) when considering their interventions analyses and the fact that the reference group was 'overweight/obese weight stable and not trying to lose weight'. This it possible to consider meta-analysis. When all sub-categories from these two papers(18;22) were combined using a random effects model, the result was a non-significant hazard ratio of HR= 1.06 (0.83, 1.34). Assuming that hidden pathology is more likely to be a confounding factor for those who lost weight without trying, meta-analysis was also conducted on just the intentional weight stable/loss sub-categories as a sensitivity analysis. However, the hazard ratio of HR=0.93 (0.71, 1.22) was still non-significant.

Results for overweight/obese people with Diabetes Mellitus

The consideration of weight loss for overweight/obese individuals also suffering from diabetes mellitus was presented by Williamson and Gregg as sub-groups of two American studies already described in this review:

the CPS-I cohort (26) (recruited 1959, recordings 1960-5, death 1972) and NHIS conducted in 1989 (19) and followed for 9 years. Another paper by Chaturvedi (16) reporting on the WHO MSVDD cohort (recruited in 1975-7, measurement follow-up 1983-8, and mortality reported until 1988) also considered those with Type 2 diabetes mellitus for overweight and obese individuals separately. While this latter cohort and paper includes international data, only the results on the European cities are extracted for this review. The Chaturvedi study (16) had smaller undetermined sample sizes for these sub-groups of patients and had slightly younger participants.

(Table 5 here)

The studies overall, described in Table 5, give mixed results. When weight loss intention had been defined, then diabetic obese people seem to benefit from losing weight, although, it should be noted that the two papers (19;26) that illustrate this also adjusted for multiple diabetic related variables both reporting their results as hazard ratios. In contrast, the European analyses from Chaturvedi (16), indicate that weight loss was detrimental for those who were diabetic and overweight having adjusted for only age, sex and duration of diabetes. This latter study had no definition of intention of weight loss and had small sample sizes .

A combined meta analysis of all the studies using a random effects model indicates a non-significant hazard ratio of HR= 0.91 (0.70, 1.18). This non-significant finding was not effected when combination of pairs of studies as a sensitivity analysis was conducted. As before, hidden pathology may well be a confounding factor justifying the removal of unintentional weight loss groups. On this occasion, the reduced analysis from the Williamson and Gregg (19;26) papers only using ‘weight stable and not trying to lose weight’ was the referent for all analyses , shows a significant beneficial effect, HR=0.75 (0.67, 0.83), of intentional weight loss for overweight/obese participants with diabetes.

Discussion

This review aims to determine long-term effectiveness of weight loss on all cause mortality. Gender differences and the impact of co-existing illness have been identified as important, along with the notion of intentionality of the weight loss. With respect to gender, for studies with men only (20;23;25) and those that report men and women together (18;22), the effects of weight loss on mortality were inconsistent regardless of intentionality. An investigation into overweight/obese women with pre-existing obesity related illness on the other hand resulted in a benefit from intentional weight loss albeit that this conclusion was based on only one paper (24). This latter finding raises the question of whether gender differences exist. However, irrespective of gender, those suffering from diabetes, another common obesity related illness, had benefits with intentional weight loss (19;26).

If there is a gender divide as suggested by our review, this could be a result of women being more frequent visitors to healthcare. Studies have shown that there are significant differences in the ways men and women seek medical attention for health.(27) Men tend not to seek early medical attention compared to women, and this in turn leads to poorer health outcomes.(28;29) However, from this review a personal decision by men to lose weight may be beneficial. Otherwise, hidden pathology may go undiagnosed in men more easily than in women, particularly for cancers, which are often initially asymptomatic. The decrease in mortality for those with diabetes could also be attributable to early healthcare advice as a direct result of the more obvious diabetes symptoms, particularly in men.

There have been recent reviews investigating effects of weight change on mortality. However, these reviews assessed the outcomes on the general population (30;31) or focused on specific outcomes. (12) Evidence has shown that there are benefits of weight loss in the short-term but that the sustainability of these benefits in the long-term are debatable. (32) In relation to the general population, the risk of morbidity and mortality is higher for those who are overweight/obese. Consequently, our review on ‘all cause mortality’ addressed these issues collectively by focusing on the available long-term (more that 2 years) evidence specifically for the overweight/obese populations.

Many methodological limitations were identified in the included primary studies relating to either study design and/or statistical issues. These in turn had an impact on the findings and conclusions drawn in this review. Potential bias is inevitable with retrospective studies with recall and self-reporting measure of outcomes including those of weight. This potential bias affected the majority of the included studies except that by Chaturvedi (16) conducted among diabetic patients and the surgical study by Christou (17) both conditions which usually have close monitoring. Any conclusions about gender differences have been limited in this review since one of the two studies on women compared overweight/obese women who lost weight to a referent group who were normal/stable weight and therefore not directly comparable. Our review has confirmed a key concept of intentionality of weight loss as suggested by others.(33) Even when intention has been expressed, there may well be other proximal factors that led to the weight loss that needs to be disentangled. (34)

as interpreted by the authors of each study with no specific definition, which raises a query about consistency. Pooling of evidence, based on meta-analyses, in order to make robust conclusions was restricted given the varying methodology and test statistics quoted and those with comparable results often had multiple and/or different model adjustments.

Considering the limitations and the aims of this review, benefits of weight loss on all cause mortality for overweight/obese populations is meagre. Possible explanations for this are many and varied, the most important being intentionality, self reporting of weight loss and the time lapse between last recorded weight loss measurement and the mortality outcome. Recent discussions (35-37) display the variety of controversy on intentional weight loss benefits on all cause mortality. Although for mortality studies, the follow-up is long-term, patterns of weight change such as weight cycling in between the study measures and death are usually not accounted for. (22) Most recently the concept of weight loss type (such as fat-free vs fat) seems to have an impact on all cause mortality. (36;38-40) These indicate that even for intentional weight loss programs, the type of weight loss may be important for this ultimate health outcome.

The highlighted issues of intentionality, type of weight loss and objective measurements of weight changes still need to be investigated in well designed prospective studies to assess the real impact of weight loss on all cause mortality in the long term for overweight/obese populations. Given that mortality studies are generally long-term, consistent follow-up of measurements of weight change would further strengthen results.

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Table 1: Basic characteristics of included studies

Author/year/country	Study + Description of sample		Mortality record Follow-up	Follow-up Time
Rumpel 1993 (21) White Women USA White Women	NHANES I (1971-4) interviews and examinations. Followed up by NHEFS (1982-4) n= 14,407, with two follow-up waves until 1987, when they were measured and asked what and when their maximum weight was. Included those 65-74 years old in 1982-4, however at maximum weight participants were Mean (sd) Age of 54 (14) years old. Excluded small numbers of non-white, missing data for height, missing max lifetime weight leaving n=1450		1554 deaths of which 97.5% had death certificates	Median follow-up 13.6 years for Survivors
Williamson 1995 (24) USA never smoking, over weight white women	Prospective cohort: overweight recruited in 1959 from Cancer Prevention Study CPS-I (n=1,078,894). Vital status determined annually 1960-5. Weight change asked about retrospectively along with intention Aged 40-64 at baseline Death certificates recorded 1971-2.	Included overweight, never smoking, white women Excluded those who died in first 3 years of follow-up No pre-existing disease n=28,388 Obesity related illness n=15,069	91.0% complete mortality follow-up	survivors 12 years decedents 7.5 years
Williamson 1999 (25) USA White men		Included initial BMI>27 white men with data on weight (change, direction, time and intent), current health and without pre-existing cancer or other disease. No health condition n=36,280 With health problems n=13,057	91.0% complete mortality follow-up	12 years survivors 12.9 years decedents 7.3 years
Williamson 2000 (26) USA Diabetic patients		Excluded missing data on weight (change, direction, amount and intent), smoking, alcohol education physical activity and race Overweight, with diabetes n=4,970	91.0% complete mortality follow-up	12 years survivors 12.9 years decedents 7.1 years
Chaturvedi 1995 (16) European Results: Men and women with Type 2 Diabetes Mellitus	Cohort Study- World Health Organization Multinational Study of Vascular Disease in Diabetes (WHO MSVDD) 14 centres in 3 geographical areas. European included London, Switzerland, Berlin, Warsaw and Zagreb Base exams 1975-7, Aged 35-55 years old, morbidity and height and weight follow up 1983-8. Mortality until 1988 European BMI>25 with NIDDM: men n=445; women n= 507. However, only n=581 with initial weight, weight change and mortality.		95% mortality records complete. But proportion with weight change data & mortality 848/1,446=58.64%	unknown for after weight change > 6 years for whole study
Nilsson 2002 (20) Sweden Overweight, obese otherwise healthy men	Malmo Preventative Project (MPP) 5722 men screened twice 1974 and 1982. Interventions: Lifestyle and drug. Physical exam at base and follow-up. Self questionnaire on smoking, nervous, weight changes and health. Aged 38-52 years old at baseline Mortality register recorded up to Dec 1999 Excluded those with prevalent disease at base, cancer, died in 1st year and missing weight change information. n=5194, with 571 deaths			6 years for weight change average 22 years for whole study

Gregg 2003 (18) USA Overweight or obese	The National Health Interview Survey (NHIS) + supplemental survey conducted in 1989 with self reported intention of weight loss n=20,847. Vital status followed for 9 years: n= 20,439	Mean Age 54.2 years old Excluded: BMI < 25 before weight loss, <35 years old, any with missing data: hence n=6391	98% for vital status	9 years after weight change (Mean 8 years)
Gregg 2004 (19) USA Overweight or obese diabetic patients		Selected those ≥ 18 yrs old with diabetes n=2531 linked n=2459 to death register Mean Age 16.2 years old Excluded: BMI < 25 before weight loss and any with missing data: ie n=1,401	97% for vital status	
Christou 2004 (17) Canada Men and women	2-cohort study: 1986-2002 ie surgery vs control groups 7 different surgeons, 3 type of surgery; RY isolated gastric bypass (79.2%); VGB (18.7%) laporoscopic RY (2.2%)	Bariatric surgery (n=1035) vs Matched (age, gender) morbidly obese controls (n=5746) [6 controls for every bariatric surgery]. Those with medical conditions other than obesity were excluded. Mean (sd) Age Surgery group 45.1 (11.6) Control group 46.7 (13.1)	100% of mortality records for both cohorts Measurement follow up ≈82% up to 5 years	Max of 5 years Bariatric surgery 2.5 (sd=1.4) years Controls 2.6 (sd=1.5) years
Wannamethee 2005 (23) Britain Men	Prospective Study: British Regional Heart Study, 24 British towns; Men aged 40-59 at recruitment. 1978-80 questionnaire height and weight, smoking, alcohol, physical activity and med history; A similar questionnaire to survivors in 1992 and 1996. Later also asked for intentional and unintentional weight loss over preceding 4 yrs. 5265 survivors, 5267 completed 1996 questionnaire and 4869 men age 56-75 years provided weight change data in 1996 questionnaires. Mortality recorded up to Oct 2003. Excluded 83 with fluctuating weight leaving 4786 with weight loss. In 1992 the cohort had BMI<28 n=3613 and BMI ≥ 28 n=1061		99% of cohort	7 years
Sørensen 2005 (22) Finland Men and women	The Finnish Twin Cohort: same sex twin born before 1958 and both still alive in 1967. (n=19,993) in 1975 self-reported height, weight, lifestyle and current attempts to lose weight (intention). 1981 current weight, Ages 24-60 years. Only those BMI ≥ 25 at base considered here (n=4,466). Mortality recorded up to 1999 Exclusions: Any with (pre-)existing disease between 1972-82, not working any missing data ie. n=2,957 of which 2,067 did not have a co-twin, any within-pair correlation of phenotypes adjusted for.		89% of those eligible responded in 1975. 91% of those still alive then responded in 1981	18 years after recorded weight change

Table 2: Mortality rate ratios – Women (The reference group is highlighted for each study)

Author year	Status	Group of interest	Age Mean	Age (sd)	Sample size	All cause Mortality Deaths	All cause Mortality rate ratios (95%CI)
Rumpel 1993 Women ‡ (21)	Unknown weight change intention and illness status	**All deaths**					
		BMI<23 weight loss <8.55%	44 II	(18)	364	197	1 (RR adj 2 vars)
		BMI 26-29 weight loss <8.55%	56 II	(13)	363	163	1.20 (0.80, 1.80) †
		BMI 26-29 weight loss ≥8.55%					1.90 (1.30, 2.90) †
		BMI≥29 weight loss <8.55%	58 II	(14)	362	185	1.50 (1.00, 2.30) †
		BMI≥29 weight loss ≥8.55%					2.30 (1.50, 3.40) †
		Exclude first 5 year follow-up deaths □					
		BMI<23 weight loss <8.55%	-	-	-	-	1 (RR adj 2 vars)
		BMI 26-29 weight loss <8.55% (5yr)	-	-	-	-	1.10 (0.70, 1.70)
		BMI 26-29 weight loss≥8.55% (5yr)	-	-	-	-	1.80 (1.20, 2.80) †
		BMI≥29 weight loss <8.55% (5yr)	-	-	-	-	1.40 (0.90, 2.20)
		BMI≥29 weight loss≥8.55% (5yr)	-	-	-	-	2.10 (1.30, 3.40) †
Williamson 1995(24) Overweight, never smoking, white women §	No pre-existing illness	No weight change	52.2	(6.5)	14,093	755	1 (HR adj 6+ vars)
		Unintentional weight loss	52.9	(6.6)	942	67	1.20 (0.93, 1.55)
		Intentional weight loss of <20lbs	51.7	(6.3)	2,745	156	1.12 (0.94, 1.33)
		under 1 year	-	-	-	*116*	*1.05 (0.86, 1.28)*
		1 or more years	-	-	-	*40*	*1.40 (1.02, 1.93)* †
		Intentional weight loss of >20lbs	50.8	(6.4)	3,018	156	0.98 (0.82, 1.17)
		under 1 year	-	-	-	65	0.77 (0.59, 1.00) *
		1 or more years	-	-	-	91	1.22 (0.98, 1.53)
	Obesity related illness	No weight change	54.1	(6.4)	7,494	1,038	1 (HR adj 6+ vars)
		Unintentional weight loss	55.3	(6.1)	812	136	1.00 (0.83, 1.20)
		Intentional weight loss of <20lbs	53.8	(6.3)	1,550	175	0.80 (0.68, 0.94) *
		under 1 year	-	-	-	*128*	*0.75 (0.62, 0.90) **
		1 or more years	-	-	-	*47*	*0.98 (0.73, 1.31)*
		Intentional weight loss of >20lbs	53.7	(6.3)	2,598	341	0.81 (0.71, 0.92) *
		under 1 year	-	-	-	*158*	*0.78 (0.66, 0.93) **
		1 or more years	-	-	-	*183*	*0.84 (0.71, 0.99) **

* Significant decrease (p≤ 0.05); † Significant increase (p≤ 0.05); - Not Available Data
‡ Proportional hazard model to obtain Relative Risk adjusted for 2 variables: age and smoking.
§ Proportional hazard model adjusted for 6(+?) variables: age at base, initial BMI, education, alcohol consumption, physical activity, and all health conditions. Deaths in first three years excluded.
II Mean age at maximum weight; **(HR)** Hazard ratio; **(RR)** Relative Risk; **(adj n vars)** adjusted for n covariables
□ Sample sizes, deaths and summary statistics unknown for this reduced group

Table 3: Mortality rate ratios – Men (The reference group is highlighted for each study)

Author year	Status	Group of interest	Age Mean	Age (sd)	Sample size	All cause Mortality Deaths	All cause Mortality rate ratios (95%CI)
Williamson 1999 (25)	No pre-existing illness	No weight change	51.4	(5.9)	19,064	2558	1 (HR adj 7+ vars)
		Unintentional weight loss	52.0	(6.1)	1,474	234	1.04 (0.91, 1.19)
Overweight, white men ‡		Intentional weight loss of <20lbs	51.5	(5.8)	2,834	381	1.09 (0.98, 1.21)
		under 1 year	-	-	-	*273*	*0.98 (0.87, 1.12)*
		1 or more years	-	-	-	*108*	*1.48 (1.22, 1.80)* †
		Intentional weight loss of >20lbs	51.5	(5.9)	2,610	412	1.07 (0.96, 1.20)
		under 1 year	-	-	-	*226*	*0.98 (0.85, 1.13)*
		1 or more years	-	-	-	*186*	*1.20 (1.03, 1.40)* †
	With health conditions	No weight change	53.3	(6.0)	6,043	1,990	1 (HR adj 7+ vars)
		Unintentional weight loss	54.4	(6.3)	917	391	1.15 (1.04, 1.27) †
		Intentional weight loss of <20lbs	53.4	(5.9)	1,310	440	1.01 (0.91, 1.12)
		under 1 year	-	-	-	*327*	*0.99 (0.88, 1.11)*
		1 or more years	-	-	-	*113*	*1.07 (0.88, 1.29)*
		Intentional weight loss of >20lbs	53.6	(6.0)	2,614	1,098	1.02 (0.94, 1.11)
		under 1 year	-	-	-	*555*	*0.94 (0.85, 1.04)*
		1 or more years	-	-	-	*447*	*1.13 (1.03, 1.26)* †
Nilsson2002 (20)Swedish Men § **	BMI ≥26 but healthy	Stable	47.4	(2.6)	513	46	1 (RR adj 14+ vars)
		Decrease	47.1	(2.8)	482	71	1.71 (1.18-2.47) †
Wannamethee 2005: (23)British Men BM I≥ 28 II	Random from GP registers in 1978. Illness not specified	No weight change:	Whole study 56-75 years old		426	99	1 (RR adj 14+ vars)
		Unintentional weight loss:			108	40	1.48 (0.99, 2.21)
		Intentional weight loss (personal decision)		-	48	4	0.23 (0.06, 0.95) *
		(Drs advice/ill health)			82	19	0.97 (0.57, 1.64)

* Significant decrease (p≤ 0.05); † Significant increase (p≤ 0.05); - Not Available Data
‡ Proportional hazard model adjusted for 7(+) variables: age at base, initial BMI, smoking, education, alcohol consumption, physical activity, and all health conditions.
§ Cox proportional hazard model to estimate Age adjusted relative risk for non-cancer mortality
II Cox proportional hazard model to assess Relative risk adjusted for 14(+) variables: age, smoking, social class physical activity, current BMI, social class, perceived health status, history of hypertension, coronary heart disease, stroke, diabetes, other cardiovascular disease conditions and cancer
****** A split into smoking Y/N with overweight/obese combinations was available, but was univariate analysis with multiple testing
(HR) Hazard ratio; **(RR)** Relative Risk; **(adj n vars)** adjusted for n covariables

Table 4: Mortality rate ratios – Men and Women (The reference group is highlighted for each study)

Author year	Status	Group of interest	Age Mean	Age (sd)	Sample size	All cause Mortality Deaths	All cause Mortality rate ratios (95%CI)
Christou 2004 (17) Morbidly obese Men & women §	No (other) pre-existing illness	Control group (36% men)	46.7	(13.1)	5746	354	1 (RR adj ? vars)
		Bariatric surgery group (34.4% men)	45.1	(11.6)	1035	7	0.11 (0.04, 0.27) *
Gregg 2003 (18) Overweight, obese men & women ‡, **	11.5% had DM, cancer or CVD. 8 year	**Not trying to lose weight** (64.5% men)	56.3	-	2766	-	
		Gain	-	-	-	-	0.62 (0.39, 0.99) ††
		No weight change:	-	-	-	-	1 (HR adj 13+ var)
		1-9 kg lost	-	-	-	-	1.05 (0.74, 1.49)
		>9kg lost	-	-	-	-	1.72 (1.24, 2.38) †
		Trying to lose weight (47.9% men)	52.5	-	3625	-	
		Gain	-	-	-	-	0.95 (0.65, 1.38)
		No weight change: (58.2% men)	-	-	-	-	0.81 (0.65, 1.00) ††
		1-9 kg lost	-	-	-	-	0.70 (0.53, 0.92) *
		>9kg lost	-	-	-	-	0.90 (0.64, 1.25)
Sørensen 2005:(22) Overweight, obese men & women II	Self-reported weight and Intention of weight loss	**No intention to lose weight** (73.0% men)	**42.2**	**(9.0)**	**1,899**	**106**	
		Loss	42.6	(9.3)	728	-	1.17 (0.82, 1.66)
		Stable	43.5	(8.7)	586	-	1 (HR adj 11 vars)
		Gain	40.4	(8.7)	585	-	1.58 (1.08, 2.30) †
		Intended to lose weight (52.8% men)[a]	**42.2**	**(9.0)**	**1,058**	**162**	
		Loss	41.5	(9.4)	398	84	1.87 (1.22, 2.87) †
		Stable	43.4	(8.4)	303	34	0.84 (0.49, 1.48)
		Gain	41.9	(8.9)	357	44	0.93 (0.55, 1.56)

* Significant decrease (p≤ 0.05); † Significant increase (p≤ 0.05); †† Borderline significant decrease (p≈ 0.05); - Not Available Data

‡ 8 year cumulative mortality rates: Cox proportional hazard model adjusted for 13(+) variables age, sex, ethnicity, initial BMI, smoking, education, self-rated health, diabetes, acute and chronic conditions, functional limitations due to cardiovascular disease or cancer, bed days and hospital days.

§ 5 year mortality relative risk. Includes perioperative deaths in surgery group (0.4%). Unknown adjustments. NB follow-up mean 2.5 years. However, results verified by significant Kaplan-Meier survival curves.

II Cox proportional hazard model adjusted for 11 variables age (in 1981), sex, BMI (in1975), hypertension, smoking, alcohol, physical activity, life satisfaction, work status and income.

** NB if smokers are excluded (n=4957) then only intentional weight loss is significant

(HR) Hazard ratio; **(RR)** Relative Risk; **(adj n vars)** adjusted for n covariables.

Table 5: Mortality rate ratios – Diabetes (DM) or Non insulin dependent diabetes (NIDDM) (The reference group is highlighted for each study)

Author year	Status	Group of interest	Age Mean	Age (sd)	Sample size	All cause Mortality Deaths	All cause Mortality rate ratios (95%CI)
Williamson 2000(26)Overweight people with **DM** ‡	No other pre-existing illness	No weight change (and unknown)	54.5	(6.0)	2,493	980	1 (HR adj 10+ vars)
		Unintentional weight loss	55.6	(5.7)	649	280	0.98 (0.85, 1.13)
		Intentional weight loss	54.5	(6.0)	1,669	561	0.75 (0.67, 0.84) *
Chaturvedi 1995(16) People with **Type 2 DM** §, ‡‡	Weight change intention unknown	**Base 26<BMI<29**:	48	(5.8)	-		
		lost > 2 BMI	-	-	<252	<52	2.02 (1.00, 4.08) ††
		no weight change	-	-	<581	<35	1 (RR adj 3 vars)
		gain > 2 BMI	-	-	<159	<14	0.73 (0.23, 2.67)
		Base BMI≥29:	48	(5.6)	-		
		lost > 2 BMI	-	-	<252	<52	0.84 (0.40, 1.74)
		no weight change	-	-	<581	<35	1 (RR adj 3 vars)
		gain > 2 BMI	-	-	<159	<14	1.74 (0.74, 4.06)
Gregg 2004(19) overweight & obese people with **DM** II, **	No other pre-existing illness	**Not trying to lose weight** (55.4% men)	64.2	-	427	-	
		Stable/Gain	-	-	-	-	1 (HR adj 17 vars)
		(Lost median 15 pounds)	-	-	-	-	1.58 (1.08, 2.31) †
		*BMI ≥30 ** *	-	-	-	-	*3.29 (1.55,6.98)* †
		*BMI 25-29 ** *	-	-	-	-	*1.20 (0.80,1.81)*
		Trying to lose weight (36.4% men)	59.9	-	974	-	**0.77 (0.61, 0.99) ***
		Stable/Gain	-	-	-	-	0.72 (0.55, 0.96) *
		(Lost median 15 pounds)	-	-	-	-	0.83 (0.63, 1.08)
		*BMI ≥30 ** *	-	-	-	-	*1.17 (0.72, 1.92)*
		*BMI 25-29 ** *	-	-	-	-	*0.62 (0.46, 0.83)* *
		*No loss **** *	-	-	-	-	*0.64 (0.42,0.97)* *
		*Weight loss **** *	-	-	-	-	*0.58 (0.43, 0.84)* *

* Significant decrease (p≤ 0.05); † Significant increase (p≤ 0.05); †† Borderline significant increase (p approximately 0.05); - Not Available Data
‡ Proportional hazard model adjusted for 10(+) variables: age, sex, race, smoking, initial BMI, education, drinking, physical activity, disease history and current signs and symptoms. Includes all deaths with diabetes listed as primary, secondary, or tertiary cause of death.
§ Proportional hazard model to estimate Relative Risk adjusted for 3 variables: age, sex, and duration of diabetes.
II Cox proportional hazard model adjusted for 17 variables: age, sex, ethnicity, initial BMI, smoking, education, self-rated health, diabetes medication, duration of disease, functional limitations, hypertension, heart disease, stroke, retinal disease, neuropathy symptoms, hospital days, and doctors visits.
** Results extracted from text assumed to have the same adjustments as the main model.
‡‡ sample size and number of deaths for all weight change categories. **(DM)** Diabetes Mellitus: **(HR)** Hazard ratio: **(RR)** Relative Risk: **(adj n vars)** adjusted for n covariables.