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A review and meta-analysis of the effect of weight loss on all-cause mortality risk

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Overweight and obesity are associated with increased morbidity and mortality, although the range of body weights that is optimal for health is controversial. It is less clear whether weight loss benefits longevity and hence whether weight reduction is justified as a prime goal for all individuals who are overweight (normally defined as BMI $> 25\,kg/m^2$). The purpose of the present review was to examine the evidence base for recommending weight loss by diet and lifestyle change as a means of prolonging life. An electronic search identified twenty-six eligible prospective studies that monitored subsequent mortality risk following weight loss by lifestyle change, published up to 2008. Data were extracted and further analysed by meta-analysis, giving particular attention to the influence of confounders. Moderator variables such as reason for weight loss (intentional, unintentional), baseline health status (healthy, unhealthy), baseline BMI (normal, overweight, obese), method used to estimate weight loss (measured weight loss, reported weight loss) and whether models adjusted for physical activity (adjusted data, unadjusted data) were used to classify subgroups for separate analysis. Intentional weight loss *per se* had a neutral effect on all-cause mortality (relative risk (RR) 1·01; $P = 0{\cdot}89$), while weight loss which was unintentional or ill-defined was associated with excess risk of 22 to 39 %. Intentional weight loss had a small benefit for individuals classified as unhealthy (with obesity-related risk factors) (RR 0·87 (95 % CI 0·77, 0·99); $P = 0{\cdot}028$), especially unhealthy obese (RR 0·84 (95 % CI 0·73, 0·97); $P = 0{\cdot}018$), but appeared to be associated with slightly increased mortality for healthy individuals (RR 1·11 (95 % CI 1·00, 1·22); $P = 0{\cdot}05$), and for those who were overweight but not obese (RR 1·09 (95 % CI 1·02, 1·17); $P = 0{\cdot}008$). There was no evidence for weight loss conferring either benefit or risk among healthy obese. In conclusion, the available evidence does not support solely advising overweight or obese individuals who are otherwise healthy to lose weight as a means of prolonging life. Other aspects of a healthy lifestyle, especially exercise and dietary quality, should be considered. However, well-designed intervention studies are needed clearly to disentangle the influence of physical activity, diet strategy and body composition, in order to define appropriate advice to those populations that might be expected to benefit.

Weight loss: All-cause mortality: Meta-analyses

Introduction

Weight loss has been reported to result in several health benefits, such as significant improvements in CVD risk factors (blood pressure, lipid profiles, glucose tolerance)[1,2]. It may therefore be reasonable to expect that weight loss would lead to decreased mortality in the long term. Indeed, this seems to be the case in obese individuals with serious medical complications[3,4] or when substantial weight loss has followed surgical procedures[5]. However, the long-term effects of more moderate degrees of weight loss for those who are not severely obese and do not have co-morbidities are unclear. Many prospective studies show conflicting results, while some recent studies indicate either excess[6–9] or unchanged mortality[10] following weight loss. Reviews of the data suggest that inconsistent results might be due to failure to control for known confounding factors (for example, underlying disease, intention to lose weight)[11,12] while also noting that many of the existing studies were not specifically designed to test the hypothesis that weight loss increases or decreases

Abbreviation: RR, relative risk.

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Table 1. Prospective studies of weight loss and mortality*

Study reference	Population	Referent group	Weight loss subgroup	Sample size (*n*)	Mean baseline age and/or range (years)	Baseline weight (kg) or BMI (kg/m^2)	Weight (kg) or BMI loss (kg/m^2)	Data adjustments	Relative risk	95 % CI	Exclusions
Harris *et al.* (1988)[38]	Apparently healthy men and women	0–9 % BMI gain	Men: weight loss intention unspecified	–	55–65	–	≥10 % BMI	Baseline weight	1·9	1·1, 3·2	Smokers, ex-smokers
	Framingham Heart Study						0–9 % BMI		1·4	1·0, 1·9	
	Change in BMI from age 55 to 65 years		Women: weight loss intention unspecified	–	55–65	–	≥10 % BMI		1·8	1·2, 2·6	
							0–9 % BMI		1·1	0·8, 1·4	
Pamuk *et al.* (1992)[39]	Apparently healthy men and women	<5 % maximum weight loss	Men: weight loss intention unspecified	68	45–74	26– <29 kg/m^2	6·5 % weight	Age, race, smoking parity, pre-existing illness, maximum BMI	1·7	1·1, 2·7	Deaths in first 5 years
	NHANES I			279		<26 kg/m^2	9·4 % weight		1·4	1·0, 1·8	
				97		<26 kg/m^2	20·3 % weight		2·4	1·7, 3·5	
				172		≥29 kg/m^2	8·8 % weight		0·7	0·5, 1·0	
				204		26– <29 kg/m^2	9·7 % weight		0·8	0·6, 1·1	
				34		≥29 kg/m^2	18·1 % weight		0·8	0·4, 1·5	
				68		26– <29 kg/m^2	20 % weight		1·1	0·7, 1·6	
				105		<26 kg/m^2	23·2 % weight		1·4	1·0, 2·0	
			Women: weight loss intention unspecified	38	45–74	26– <29 kg/m^2	6·6 % weight		1·4	0·6, 2·9	
				223		<26 kg/m^2	10·2 % weight		1·6	1·0, 2·6	
				128		<26 kg/m^2	20·3 % weight		2·2	1·3, 3·6	
				230		≥29 kg/m^2	9·3 % weight		1·0	0·7, 1·4	
				168		26– <29 kg/m^2	9·8 % weight		1·5	1·0, 2·1	
				97		≥29 kg/m^2	20·9 % weight		1·4	0·9, 2·1	
				80		26– <29 kg/m^2	20·9 % weight		1·4	0·9, 2·1	
				151		<26 kg/m^2	25·5 % weight		1·9	1·3, 2·6	
Lee & Paffenbarger (1992)[1]	Apparently healthy men	Weight stable	Men, weight loss intention unspecified	1293	58	78 kg	>5 kg weight	Age, height, smoking, physical activity	1·57	1·34, 1·84	Baseline CVD, cancer
	Harvard Alumni Health Study			2730	58	78 kg	1–5 kg weight		1·26	1·10, 1·46	
Higgins *et al.* (1993)[40]	Apparently healthy men and women	No change in BMI	Men	–	45·5	27·1 kg/m^2	0·52 kg	Age, BMI, systolic blood pressure, cholesterol, glucose intolerance, left ventricular hypertrophy, smoking	1·33	1·06, 1·68	Deaths in first 4 years
	Framingham Study		Women	–	45·8	25·7 kg/m^2	0·39 kg		1·28	0·98, 1·68	
Chaturvedi & Fuller (1995)[41]	NIDDM men and women	Weight stable	European men and women	252 (52 deaths)	35–55	<26 kg/m^2	>2 kg/m^2	Age, sex, duration of diagnosed diabetes	3·05	1·26, 7·36	–
	WHO study		Weight loss intention unspecified		35–55	26–29 kg/m^2	>2 kg/m^2		2·02	1·00, 4·08	
					35–55	≥29 kg/m^2	>2 kg/m^2		0·84	0·40, 1·74	

Iribarren *et al.* (1995)[42]	Apparently healthy men	Loss of 2·5 kg to gain of 2·4 kg	Men Weight loss intention unspecified	744	54·6	25·2 kg/m^2	>4·5 kg	Age, average weight, smoking, alcohol consumption, physical activity, total energy intake, employment, pre-existing illness	1·21	1·02, 1·43	Deaths in first 5 years
	Honolulu Heart Program			928	54·2	24·3 kg/m^2	2·6–4·5 kg		1·29	1·10, 1·51	
Manson *et al.* (1995)[43]	Apparently healthy women	Weight stable (<4 kg) since age 18 years	Women Weight loss intention unspecified	Sample size not reported				Age, BMI, smoking			Baseline CVD, cancer, deaths in first 4 years
	Nurses' Health Study			16 deaths	30–55	–	≥10 kg		0·7	0·4, 1·4	
				54 deaths	30–55	–	4–9 kg		1·2	0·9, 1·6	
Wallace *et al.* (1995)[44]	Unhealthy men	Non-weight losers	Unintentional	54 (175 non-weight losers)	73·9	80·8 kg	5·6 kg	Age, BMI, tobacco use, hypertension, health status, cholesterol, albumin levels	2·83	1·38, 5·81	Diseases that affect nutritional status or body weight
Williamson *et al.* (1995)[45]	Healthy and unhealthy women	No weight change	Healthy					Age, baseline BMI, education, alcohol intake, physical activity, health conditions			Deaths in first 3 years
	American Cancer Prevention Study		Unintentional	942	52·9	30·9 kg/m^2	4·9 kg/m^2		1·20	0·93, 1·55	
			Intentional 1–19 lbs	2745	51·7	30·4 kg/m^2	3·1 kg/m^2		1·12	0·94, 1·33	
			Intentional ≥20 lbs	3018	50·8	33·1 kg/m^2	6·5 kg/m^2		0·98	0·82, 1·17	
			Unhealthy								
			Unintentional	812	55·3	31·9 kg/m^2	5·6 kg/m^2		1·00	0·83, 1·20	
			Intentional 1–19 lbs	1550	53·8	31·5 kg/m^2	3·0 kg/m^2		0·80	0·68, 0·94	
			Intentional ≥20 lbs	2598	53·7	34·8 kg/m^2	7·0 kg/m^2		0·81	0·71, 0·92	
Yaari & Goldbourt (1998)[46]	Unhealthy men Israeli Ischemic Heart Disease Study	Weight stable	Weight loss intentional (dieters)	2471	Not given	78·2 kg	≥5 kg >5 kg	Age, BMI, systolic blood pressure, cholesterol, smoking, diabetes, cancer, history of myocardial, infarction, angina, chronic lung disease, baseline dieting, peripheral artery disease	1·30 1·3	1·02, 1·65 1·02, 1·65	–

Table 1. *Continued*

Study reference	Population	Referent group	Weight loss subgroup	Sample size (n)	Mean baseline age and/or range (years)	Baseline weight (kg) or BMI (kg/m^2)	Weight (kg) or BMI loss (kg/m^2)	Data adjustments	Relative risk	95 % CI	Exclusions
French *et al.* (1999)[47]	Apparently healthy women	Never ≥20 lbs weight loss	Intentional	4300	66·6	30·3 kg/m^2	≥9·1 kg	Age, BMI, waist:hip ratio, education, marital status, smoking, oestrogen use, cancer, diabetes, angina, stroke, heart attack, hypertension	1·18	0·94, 1·48	–
	Iowa Women's Health Study		Unintentional	5008	68·0	26·1 kg/m^2	≥9·1 kg		1·33	1·13, 1·57	
Williamson *et al.* (1999)[48]	Healthy and unhealthy men	No weight change	Healthy					Age, BMI, smoking, education, alcohol intake, physical, activity, health complaints			BMI < 27 kg/m^2, non-Caucasian
	American Cancer Prevention Study		Unintentional	1474	52·0	29·2 kg/m^2	3·2 kg/m^2		1·04	0·91, 1·19	
			Intentional 1–19 lbs	2834	51·5	29·0 kg/m^2	1·8 kg/m^2		1·09	0·98, 1·21	
			Intentional ≥20 lbs	2610	51·5	31·4 kg/m^2	4·5 kg/m^2		1·07	0·96, 1·20	
			Unhealthy								
			Unintentional	917	54·4	29·7 kg/m^2	4·2 kg/m^2		1·15	1·04, 1·27	
			Intentional 1–19 lbs	1310	53·4	29·1 kg/m^2	1·9 kg/m^2		1·01	0·91, 1·12	
			Intentional ≥20 lbs	2614	53·6	31·6 kg/m^2	4·9 kg/m^2		1·02	0·94, 1·11	
Williamson *et al.* (2000)[4]	Unhealthy men and women	No or unknown weight change	Intentional	1669	54·5	33·5 kg/m^2	5·8 kg/m^2	Age, sex, BMI, race, smoking, education, alcohol intake, physical activity, disease history	0·75	0·67, 0·84	BMI < 27 kg/m^2
	American Cancer Prevention Study		Unintentional	649	55·6	31·8 kg/m^2	5·9 kg/m^2		0·98	0·85, 1·13	
Newman *et al.* (2001)[49]	Older men and women	Weight stable, i.e. weight within ±5 % of baseline	Weight loss intention unspecified	126 deaths	77·4	27 kg/m^2	≥5 % weight	Age, sex, race, cognitive function, medication, smoking, waist circumference, mobility impairment	1·67	1·29, 2·15	Living in an institution, wheelchair use, cancer treatment
				62 deaths	77·4		≥5 % weight		1·66	1·18, 2·33	Plus interim illness
Wannamethee *et al.* (2002)[50]	Apparently healthy men	Weight stable	Weight loss intention unspecified	950	40–59 years	26·6 kg/m^2	2·11 kg/m^2	Age, social class, smoking, physical activity, BMI, CVD, cancer, poor health, diabetes	1·34	1·09, 1·63	–
	British Regional Heart Study										

Gregg *et al.* (2003)[31]	Overweight or obese men and women	Weight stable	Overall (unspecified)	1931	Over 35 years (mean 54·1)	30·8 kg/m^2	7 kg	Age, sex, race, smoking, education, BMI, self-rated health, diabetes, acute and chronic conditions, functional limitations due to CVD or cancer, hospital bed days	1·09	0·90, 1·32	Baseline BMI < 25 kg/m^2
	NHIS US cohort		Unintentional	188	–	–	6·9 kg		1·31	1·01, 1·70	
	Retrospective weight change. 9-year follow-up		Intentional	827	–	–	7·1 kg		0·76	0·60, 0·97	
Gregg *et al.* (2004)[51]	Unhealthy men and women (diabetics) from NHIS US cohort (9-year follow-up)	Weight stable	Overall (unspecified)	629	–	33·0 kg/m^2	6·80 kg	Age, sex, race, BMI, smoking, education, self-rated health, diabetes, medication, length of disease, functional limitation, hypertension, stroke, heart disease, retinal disease, neuropathy, hospital days, doctor visits	1·19	0·9, 1·47	Baseline BMI < 25 kg/m^2
			Unintentional	365	–	–	6·80 kg		1·58	1·08, 2·31	
			Intentional	34	–	–	6·80 kg		0·83	0·63, 1·08	
Maru *et al.* (2004)[52]	Healthy women	Weight stable, i.e. < 5 % weight change	Moderate weight loss	531	50–66 years	Median BMI 25·4 kg/m^2	5–9 % weight	Age, smoking, BMI	1·14	1·1, 1·6	Medication for hypertension, CVD, diabetes, restriction diet
	DOM Dutch cohort		Severe weight loss	108		IQR 23·3– 27·8 kg/m^2	10–14 % weight		0·9	0·5, 1·4	
	Weight change in 1-year follow-up Median follow-up 17 years		Extreme weight loss	43			≥ 15 % weight		0·8	0·4, 1·8	
Diaz *et al.* (2005)[6]	Apparently healthy men and women NHANES I and follow-up	Weight stable	Weight loss intention unspecified	711	51·6	30·8 kg/m^2	5·55 kg/m^2	Age, sex, race, BMI, smoking, health status, poor health, incapacitated	3·36	2·47, 4·55	Diabetes, CVD, cancer
Drøyvold *et al.* (2005)[7]	Apparently healthy men and women	Weight stable, i.e. change in BMI ≤ 0·1 per year	Weight loss intention unspecified					Age, BMI, systolic blood pressure, blood pressure medication, smoking, alcohol intake, physical activity, marital status, education			CVD, diabetes, cancer
	Nord-Trøndelag Health Study		Men	1319	54·3	26·9 kg/m^2	2·2 kg/m^2		1·6	1·4, 1·8	
			Women	1971	54·0	27·7 kg/m^2	2·7 kg/m^2		1·7	1·5, 2·0	

Table 1. *Continued*

Study reference	Population	Referent group	Weight loss subgroup	Sample size (*n*)	Mean baseline age and/or range (years)	Baseline weight (kg) or BMI (kg/m^2)	Weight (kg) or BMI loss (kg/m^2)	Data adjustments	Relative risk	95 % CI	Exclusions
Elliott *et al.* (2005)[53]	Apparently healthy women Oral Contraception Study	Weight change from −1·81 to +1·36 kg	Weight loss intention unspecified	964	42–81 years	–	116·58–1·81 kg	Social class, BMI, parity, smoking, hormone replacement therapy	0·96	0·65, 1·43	–
Sørensen *et al.* (2005)[8]	Apparently healthy men and women	Weight stable	Intentional	398	41·5	27·4 kg/m^2	1·21 kg/m^2	Age, sex, BMI, hypertension, smoking, alcohol, physical activity, life satisfaction, work status, drugs	1·87	1·22, 2·87	Angina, myocardial infarction, diabetes, CVD, lung disease, hypertension, prescription drugs, unemployment
	Finnish Twin Cohort		Unintentional	728	42·6	26·72 kg/m^2	1·09 kg/m^2		1·17	0·82, 1·66	
Wannamethee *et al.* (2005)[10]	Apparently healthy men	No weight change	Unintentional	527	40–59	25·6 kg/m^2	3·91 kg/m^2	Age, smoking, social class, physical activity, alcohol intake, obesity, perceived health status, CVD, cancer, hypertension, stroke	1·71	1·33, 2·19	–
	British Regional Heart Study		Intentional	342	40–59	28·0 kg/m^2	2·37 kg/m^2		1·00	0·91, 1·10	
			Intentional, personal reason	178	40–59	26·9 kg/m^2	2·31 kg/m^2		0·59	0·34, 1·00	
			Intentional, physician's advice	164	40–59	28·5 kg/m^2	2·44 kg/m^2		1·37	0·96, 1·94	
Breeze *et al.* (2006)[54]	Apparently healthy men	Minimal weight change, i.e. loss 0–3 kg or gain 0–3 kg	Weight loss intention unspecified	554	40–69	–	≥10 kg	Age, marital status, employment, smoking, respiratory symptoms, heart disease indicators, diastolic blood pressure, total cholesterol	1·88	1·6, 2·2	–
	Whitehall Cohort			1190	40–69	–	4–9 kg		1·26	1·1, 1·5	
Nilsson *et al.* (2002)[55]	Healthy Swedish men (*n* 5194)	Weight stable (±0·1 kg/m^2)	Weight loss unspecified (no direct question)	464	47 years (38–52 years)	22–25 kg/m^2	–	Age	1·39	0·98, 1·95	Cancer deaths, disease at baseline, deaths in year 1 of follow-up
				482		26+ kg/m^2			1·71	1·18, 2·47	

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Wedick *et al.* (2002) (56)	California, USA	Weight stable (loss < 10 lbs or gain)	Weight loss unspecified		71 years at start of 12-years mortality follow-up		> 10 lbs	Age, current and past smoking, exercise less than 10 years earlier			–
			Healthy men	628		26			1·38	1·06, 1·8	
			Healthy women	933		24			1·76	1·33, 2·34	
			Diabetic men	140		26			3·66	2·15, 6·24	
			Diabetic women	90		25			1·65	0·7, 3·87	
			International weight loss Total	642							
			Healthy men						1·27	0·94, 1·71	
			Healthy Women						1·28	0·95, 1·73	

NHANES, National Health and Nutrition Examination Survey; NIDDM, non-insulin-dependent diabetes mellitus; NHIS, National Health Interview Survey; DOM, Diagnostisch Onderzoek Mammacarcinoom (Diagnostic Investigation into Breast Cancer); IQR, interquartile range.
* 1 lb = 0·4536 kg.

relative risk (RR) of all-cause mortality[13,14]. Methodological problems have also been identified, for example, the method by which the weight loss was achieved has usually not been reported (although dietary energy restriction is likely to have been a major factor), while weight changes before and after the recording periods have usually not been determined[12–16].

In light of the current obesity epidemic and the resulting focus on encouraging those with BMI above 25 kg/m^2 to lose weight by changing their diet and lifestyle[17], it is important to establish whether the long-term effects of weight loss benefit life expectancy. The current advice from the UK Department of Health's Obesity Care Programme is for those who are overweight or obese to reduce energy intake and increase physical activity as a method of lifestyle modification[18]. Further treatment and advice may need to consider a broad spectrum of evidence so as not to rule out potential investigations that identify subgroups of patients, or certain conditions, where weight loss may be detrimental to health and increase mortality[19].

The aim of the present study was to examine the available evidence of the impact of weight loss, as a lifestyle intervention, on the RR of all-cause mortality and to quantify this using meta-analysis. Data were pooled in a number of different ways in order to examine the influence of a number of possible confounders. Meta-analysis was used to provide a more objective appraisal of the evidence, integrating data from multiple prospective cohort studies to increase the power and precision of estimates of effect and reducing the likelihood of false negative results[20,21].

Methods

Search strategy

A literature search was carried out independently by two investigators to identify prospective cohort studies that evaluated the effect of weight loss as a lifestyle intervention on mortality risk. A web search was undertaken on PubMed/Medline and ScienceDirect databases. Articles published between 1987 and 2008 and in the English language were included. Search terms included 'weight, BMI, loss, change, mortality, intentional, unintentional, relative risk, prospective and cohort'. Identified citations and abstracts were obtained from journals, libraries or authors. A hand-search of the bibliographies of retrieved papers and linked articles was also carried out.

Data selection

Inclusion criteria were prospective studies in English of adults (men and/or women) with data on body weight and weight loss over more than 1 year. Studies needed to present RR of mortality and associated 95 % CI for the group that lost weight relative to a comparable reference group who lost minimal or no weight. Drug treatment studies and studies that measured weight loss following bariatric surgery were excluded, as the aim was to assess the effect of lifestyle interventions. Twenty-six publications were identified that met the inclusion criteria. Data on RR of mortality and 95 % confidence limits were extracted for all subgroups presented by the authors (for example, men and women, intentional *v.* unintentional weight loss, obese *v.* overweight).

Data analysis

Meta-analysis was performed using Comprehensive Meta-analysis software (CMA version 2; Biostat Inc., Englewood, NJ, USA). Moderator variables such as baseline BMI (normal, overweight, obese), reason for weight loss (intentional, unintentional), baseline health status (healthy, unhealthy), method used to estimate weight loss (measured weight loss, reported weight loss) and physical activity adjustment (adjusted data, unadjusted data) were used to classify subgroups for separate analysis. For the subgroup analysis based on baseline BMI the ranges used in papers generally corresponded to those recommended by WHO[22]. Analysis was carried out using adjusted data because papers gave insufficient data on CI for unadjusted data. Although multivariable adjustment of the data varied from study to study, all adjusted for smoking. Results are shown in the form of schematic plots (Forest plots), which illustrate the size and direction of effect for each study and the weighted effect of all studies combined, with 95 % (lower and upper) CI. Meta-analysis uses a weighted average of the results, in which the larger and more precise studies have more influence than the smaller ones. Results are shown for the random effects model, which assumes the underlying effect may vary for each population. This is the most appropriate model where heterogeneity is present[20,21]. Statistical significance of the overall pooled effect was based on $P < 0{\cdot}05$.

Health status of group	Study name	Statistics for each study			
		RR	Lower limit	Upper limit	*P*
Healthy	French *et al.* (1999)[47]	1·18	0·94	1·48	0·153
Healthy	Gregg *et al.* (2003)[31]	0·76	0·60	0·97	0·025
Healthy	Sørensen *et al.* (2005)[8]	1·87	1·22	2·87	0·004
Healthy	Wannamethee *et al.* (2005)[10]	1·37	0·96	1·95	0·079
Healthy	Wannamethee *et al.* (2005)[10]	0·59	0·34	1·01	0·055
Healthy	Wedick *et al.* (2002)[56]	1·27	0·94	1·71	0·118
Healthy	Wedick *et al.* (2002)[56]	1·28	0·95	1·73	0·107
Healthy	Williamson *et al.* (1995)[45]	1·12	0·94	1·33	0·201
Healthy	Williamson *et al.* (1995)[45]	0·98	0·82	1·17	0·824
Healthy	Williamson *et al.* (1999)[48]	1·09	0·98	1·21	0·109
Healthy	Williamson *et al.* (1999)[48]	1·07	0·96	1·20	0·235
Healthy	Yaari & Goldbourt (1998)[46]	1·30	0·94	1·80	0·116
Healthy		1·11	1·00	1·22	0·050
Unhealthy	Gregg *et al.* (2004)[51]	0·83	0·63	1·09	0·175
Unhealthy	Williamson *et al.* (1995)[45]	0·80	0·68	0·94	0·007
Unhealthy	Williamson *et al.* (1995)[45]	0·81	0·71	0·92	0·001
Unhealthy	Williamson *et al.* (1999)[48]	1·01	0·91	1·12	0·851
Unhealthy	Williamson *et al.* (1999)[48]	1·02	0·94	1·11	0·641
Unhealthy	Williamson *et al.* (2000)[4]	0·75	0·67	0·84	0·000
Unhealthy		0·87	0·77	0·99	0·028
Overall		1·01	0·93	1·09	0·892

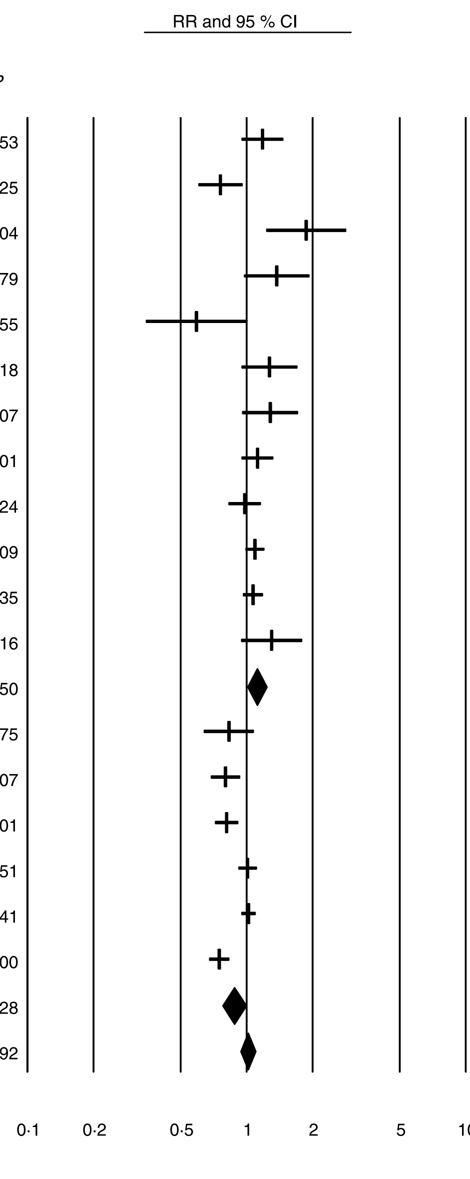

Fig. 1. Mortality risk for intentional weight loss according to health status. RR, relative risk.

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Results

Study characteristics

Table 1 shows a summary of the characteristics of the study populations and subgroups. Sample sizes ranged from 34 to 5008 subjects and the majority of the data was collected from white populations of US and UK origin. All of the studies were designed to investigate RR of mortality and weight change. The stage of life during which weight change occurred varied between adulthood, middle age and old age and the follow-up period ranged from 2 to 20 years.

Quantitative data synthesis

Owing to the acknowledged importance of whether weight loss is intended or not, results are presented for (a) intentional, (b) unintentional and (c) weight loss not specified. For the main category of interest, i.e. intentional weight loss, sub-analyses are given for healthy *v.* unhealthy subjects. These have then been further analysed to examine the influence of moderators and confounders.

Intentional weight loss

Figure 1 shows the RR of all-cause mortality in relation to intentional weight loss. Overall, there was no significant effect (RR 1·01 (95 % CI 0·93, 1·09); $P = 0·89$). However, among healthy subjects, RR was increased 11 % by weight loss (RR 1·11 (95 % CI 1·00, 1·22); $P = 0·05$), whereas it was reduced in unhealthy subjects by a similar amount (RR 0·87 (95 % CI 0·77, 0·99); $P = 0·028$).

Unintentional weight loss

Unintentional weight loss was associated with higher mortality (RR 1·22 (95 % CI 1·09, 1·37); $P = 0·001$) (Fig. 2), as has been shown in other studies. Unintentional weight loss is usually considered an indicator of pre-existing or silent disease and this group was not considered further.

Health status of group	Study name	Statistics for each study: RR	Lower limit	Upper limit	*P*
Healthy	French *et al.* (1999)[47]	1·33	1·13	1·57	0·001
Healthy	Gregg *et al.* (2003)[31]	1·31	1·01	1·70	0·042
Healthy	Sørensen *et al.* (2005)[8]	1·17	0·82	1·66	0·383
Healthy	Wannamethee *et al.* (2005)[10]	1·71	1·33	2·19	0·000
Healthy	Williamson *et al.* (1995)[45]	1·20	0·93	1·55	0·162
Healthy	Williamson *et al.* (1999)[48]	1·04	0·91	1·19	0·567
Healthy		1·27	1·09	1·47	0·002
Unhealthy	Gregg *et al.* (2004)[51]	1·58	1·08	2·31	0·018
Unhealthy	Wallace *et al.* (1995)[44]	2·83	1·38	5·81	0·005
Unhealthy	Williamson *et al.* (1995)[45]	1·00	0·83	1·20	1·000
Unhealthy	Williamson *et al.* (1999)[48]	1·15	1·04	1·27	0·006
Unhealthy	Williamson *et al.* (2000)[4]	0·98	0·85	1·13	0·781
Unhealthy		1·16	0·97	1·38	0·096
Overall		1·22	1·09	1·37	0·001

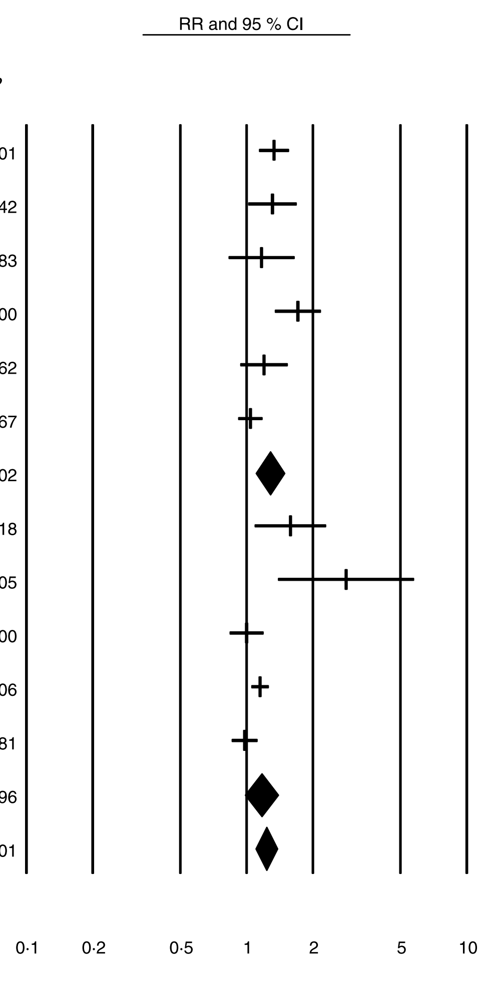

Fig. 2. Mortality risk for unintentional weight loss according to health status. RR, relative risk.

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Health status of group	Study name	RR	Lower limit	Upper limit	*P*
Healthy	Breeze *et al.* (2006)[54]	1·88	1·60	2·20	0·000
Healthy	Breeze *et al.* (2006)[54]	1·26	1·08	1·47	0·003
Healthy	Diaz *et al.* (2005)[6]	3·36	2·48	4·56	0·000
Healthy	Drøyvold *et al.* (2005)[7]	1·70	1·47	1·96	0·000
Healthy	Drøyvold *et al.* (2005)[7]	1·60	1·41	1·81	0·000
Healthy	Elliott *et al.* (2005)[53]	0·96	0·65	1·42	0·839
Healthy	Gregg *et al.* (2003)[21]	1·09	0·90	1·32	0·378
Healthy	Higgins *et al.* (1993)[40]	1·28	0·98	1·68	0·073
Healthy	Higgins *et al.* (1993)[40]	1·33	1·06	1·67	0·015
Healthy	Iribarren *et al.* (1995)[42]	1·21	1·02	1·43	0·027
Healthy	Iribarren *et al.* (1995)[42]	1·29	1·10	1·51	0·002
Healthy	Lee & Paffenbarger (1992)[1]	1·57	1·34	1·84	0·000
Healthy	Lee & Paffenbarger (1992)[1]	1·26	1·09	1·45	0·001
Healthy	Maru *et al.* (2004)[52]	0·80	0·38	1·70	0·561
Healthy	Maru *et al.* (2004)[52]	1·40	1·16	1·69	0·000
Healthy	Maru *et al.* (2004)[52]	0·90	0·54	1·51	0·688
Healthy	Nilsson *et al.* (2002)[55]	1·71	1·18	2·47	0·004
Healthy	Pamuk *et al.* (1992)[39]	1·90	1·34	2·69	0·000
Healthy	Pamuk *et al.* (1992)[39]	1·40	0·99	1·98	0·057
Healthy	Pamuk *et al.* (1992)[39]	1·40	0·92	2·14	0·120
Healthy	Pamuk *et al.* (1992)[39]	0·80	0·41	1·55	0·508
Healthy	Pamuk *et al.* (1992)[39]	1·40	0·92	2·14	0·120
Healthy	Pamuk *et al.* (1992)[39]	1·10	0·73	1·66	0·651
Healthy	Pamuk *et al.* (1992)[39]	1·00	0·71	1·41	1·000
Healthy	Pamuk *et al.* (1992)[39]	0·70	0·49	0·99	0·044
Healthy	Pamuk *et al.* (1992)[39]	1·50	1·04	2·17	0·032
Healthy	Pamuk *et al.* (1992)[39]	0·80	0·59	1·08	0·149
Healthy	Pamuk *et al.* (1992)[39]	2·20	1·32	3·66	0·002
Healthy	Pamuk *et al.* (1992)[39]	2·40	1·67	3·44	0·000
Healthy	Pamuk *et al.* (1992)[39]	1·40	1·04	1·88	0·025
Healthy	Pamuk *et al.* (1992)[39]	1·60	0·99	2·58	0·054
Healthy	Pamuk *et al.* (1992)[39]	1·40	0·64	3·08	0·403
Healthy	Pamuk *et al.* (1992)[39]	1·70	1·09	2·66	0·021
Healthy	Wannamethee *et al.* (2002)[50]	1·34	1·10	1·64	0·004
Healthy	Wedick *et al.* (2002)[56]	1·38	1·06	1·80	0·017
Healthy	Wedick *et al.* (2002)[56]	1·76	1·33	2·33	0·000
Healthy	Yaari & Goldbourt (1998)[46]	1·24	1·08	1·42	0·002
Healthy	Yaari & Goldbourt (1998)[46]	1·06	0·94	1·19	0·333
Healthy	Harris *et al.* (1988)[38]	1·80	1·22	2·65	0·003
Healthy	Harris *et al.* (1988)[38]	1·90	1·11	3·24	0·018
Healthy	Harris *et al.* (1988)[38]	1·10	0·83	1·46	0·504
Healthy	Harris *et al.* (1988)[38]	1·40	1·02	1·93	0·040
Healthy		1·38	1·27	1·49	0·000
Unhealthy	Chaturvedi & Fuller (1995)[41]	3·05	1·26	7·37	0·013
Unhealthy	Chaturvedi & Fuller (1995)[41]	0·84	0·40	1·75	0·642
Unhealthy	Chaturvedi & Fuller (1995)[41]	2·02	1·00	4·08	0·050
Unhealthy	Gregg *et al.* (2004)[51]	1·19	0·93	1·52	0·165
Unhealthy	Newman *et al.* (2001)[49]	1·67	1·29	2·16	0·000
Unhealthy	Wedick *et al.* (2002)[56]	1·65	0·70	3·88	0·251
Unhealthy	Wedick *et al.* (2002)[56]	3·66	2·15	6·24	0·000
Unhealthy		1·75	1·24	2·46	0·001
Overall		1·39	1·29	1·51	0·000

(Statistics for each study)

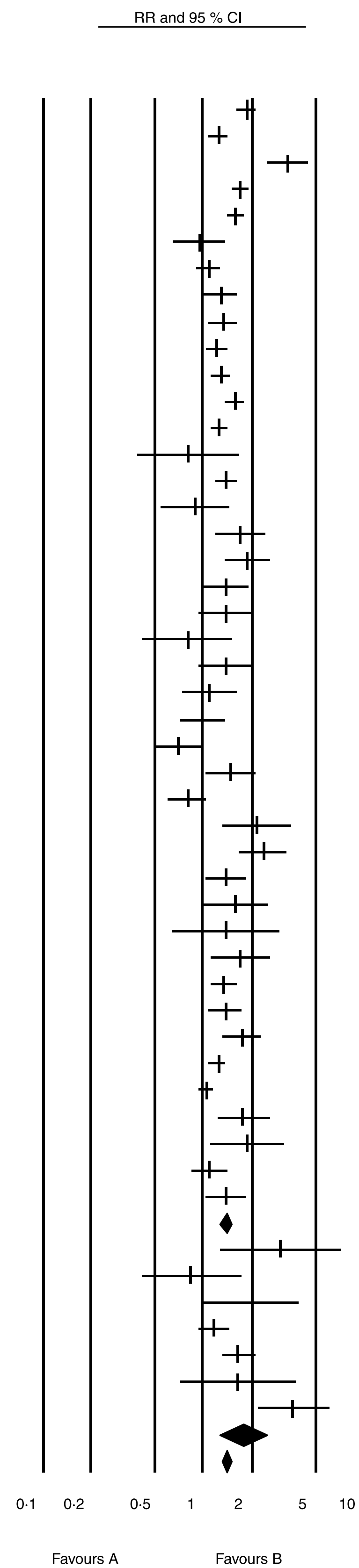

Fig. 3. Mortality risk for weight loss (intention unknown) according to health status. RR, relative risk.

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Unknown or unspecified cause of weight loss

Where the cause of weight loss was unspecified, there was also excess mortality (RR 1·39 (95 % CI 1·29, 1·51); $P < 0.001$) (Fig. 3). Most of these studies were on 'healthy' subjects, but the subgroup who were unhealthy had even higher mortality associated with weight loss (RR 1·75 (95 % CI 1·24, 2·46); $P = 0.001$). Studies where weight loss intention was not explored may suffer from the same problem of confounding by illness as those in which weight loss was unintentional. The remaining analyses were all performed using studies of intentional weight loss only.

Subgroup analyses of intentional weight loss

Relative weight at baseline. Weight loss appeared to benefit obese weight losers who were also classified as unhealthy at baseline (RR 0·84 (95 % CI 0·73, 0·97); $P = 0.018$) but had no benefit for healthy obese (RR 1·02). Overall, there was no change in risk for the obese group (RR 0·94 (95 % CI 0·86, 1·04); $P = 0.002$) (Fig. 4). For intentional weight losers whose baseline BMI was within the normal to overweight range, or for mixed-weight populations, the RR of mortality was increased (RR 1·09 (95 % CI 1·02, 1·17); $P = 0.008$) (Fig. 5).

Method of assessing weight loss. The majority of study groups with data on intentional weight loss (fifteen out of eighteen studies) relied on reported measurements of weight or weight loss. Among these, RR associated with weight loss was near unity. However, the three study groups with actual measurement had a net RR of 1·28 (95 % CI 1·07, 1·53) (Fig. 6).

Physical activity adjustment. Adjustment for physical activity was made in most studies (fourteen out of eighteen studies) but there was essentially no difference in the RR according to whether the models had adjusted for activity or not (RR 0·98 *v.* 1·01 where adjusted for physical activity) (Fig. 7).

Discussion

Main findings

Meta-analysis was used to explore the effect of weight loss on mortality using sensitivity and subgroup analysis to explore some of the likely causes of heterogeneity, especially intentionality, health and baseline BMI. Whereas weight loss for unknown or unspecified reasons was clearly associated with excess mortality, intentional weight loss

Health status of group	Study name	Statistics for each study: RR	Lower limit	Upper limit	P
Healthy	French *et al.* (1999)[47]	1·18	0·94	1·48	0·153
Healthy	Gregg *et al.* (2003)[31]	0·76	0·60	0·97	0·025
Healthy	Williamson *et al.* (1995)[45]	1·12	0·94	1·33	0·201
Healthy	Williamson *et al.* (1995)[45]	0·98	0·82	1·17	0·824
Healthy	Williamson *et al.* (1999)[48]	1·07	0·96	1·20	0·235
Healthy		1·02	0·91	1·15	0·697
Unhealthy	Gregg *et al.* (2004)[51]	0·83	0·63	1·09	0·175
Unhealthy	Williamson *et al.* (1995)[45]	0·80	0·68	0·94	0·007
Unhealthy	Williamson *et al.* (1995)[45]	0·81	0·71	0·92	0·001
Unhealthy	Williamson *et al.* (1999)[48]	1·02	0·94	1·11	0·641
Unhealthy	Williamson *et al.* (2000)[4]	0·75	0·67	0·84	0·000
Unhealthy		0·84	0·73	0·97	0·018
Overall		0·94	0·86	1·04	0·223

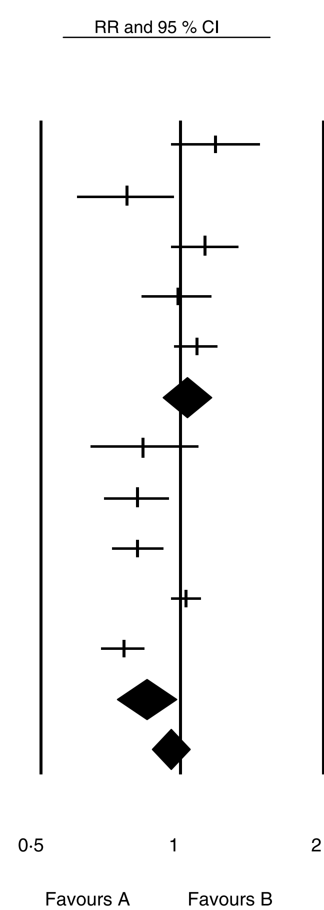

Fig. 4. Mortality risk for intentional weight loss among obese adults. RR, relative risk.

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resulted in virtually no change in mortality overall. Importantly, we found opposing effects among healthy and unhealthy adults and between the obese and those with more moderate degrees of overweight or from the general population. The excess risk of weight loss in healthy adults was estimated to be of the order of 11 %. This was counterbalanced by a benefit of about 13 % among unhealthy adults (i.e. those with diabetes or obesity-related health conditions).

Other studies

The literature is equivocal on the risks and benefits of weight loss(15,16). Many prospective studies and reviews appear to show an increased mortality associated with weight loss(12), which runs counter to conventional wisdom relating to the adverse effects of obesity and the beneficial changes in risk factors associated with weight loss(23). It has been argued that methodological weaknesses explain much of this paradox, including failure to adjust for known confounders(24). In particular, it has been claimed that intentionality of weight loss is key(16) but many studies fail to distinguish between intentional and unintentional weight loss, the latter being a cardinal sign of ill health and a predictor of increased mortality in old age(25,26).

Some clinical trials have demonstrated beneficial effects of weight loss with regard to morbidity in individuals suffering from either diabetes, obesity-related health conditions, cancer or other diseases(3). There are also an increasing number of favourable reports from bariatric surgery, such as the ‘Swedish obese subjects’ (SOS) study which has shown that substantial long-term weight reduction appreciably improves the cardiovascular risk profile of morbidly obese subjects, ultimately resulting in a decrease in overall mortality(12). Although such data may be encouraging, their success cannot necessarily be extrapolated to the public health setting where the weight losses normally achieved by diet are modest and difficult to sustain, and the subjects generally less severely obese and with few co-morbidities. Another study, due to report in 2015, will provide valuable additional data. This is the Look AHEAD (Action For Health in Diabetes) clinical trial, which is assessing the long-term effects (up to 11·5 years) of an intensive weight-loss programme delivered over 4 years in overweight and obese individuals with type 2 diabetes.

Interpretation of present analysis

In the present review and meta-analysis, intentional weight loss modestly reduced the risk of all-cause mortality only among the subgroup of unhealthy adults (by approximately 13 %), especially among those who were also obese (by approximately 16 %). All these studies relied on reported estimates of body weight. Self-reporting of body weight may be cheap and easily carried out; however, it is affected by a number of biases. Actual measurement of body weight using appropriate devices is recommended for complete accuracy and reliability of the data(27).

Our finding of a marginally increased risk of death among overweight but otherwise healthy adults who lost weight intentionally, if true, has important public health implications. This observation is consistent with recent findings using National Health and Nutrition Examination Survey

Health status of group	Study name	RR	Lower limit	Upper limit	*P*
Healthy	Sørensen *et al.* (2005)(8)	1·87	1·22	2·87	0·004
Healthy	Wannamethee *et al.* (2005)(10)	1·37	0·96	1·95	0·079
Healthy	Wannamethee *et al.* (2005)(10)	0·59	0·34	1·01	0·055
Healthy	Wedick *et al.* (2002)(56)	1·27	0·94	1·71	0·118
Healthy	Wedick *et al.* (2002)(56)	1·28	0·95	1·73	0·107
Healthy	Williamson *et al.* (1999)(48)	1·09	0·98	1·21	0·109
Healthy	Yaari & Goldbourt (1998)(46)	1·30	0·94	1·80	0·116
Healthy		1·15	1·06	1·26	0·001
Unhealthy	Williamson *et al.* (1999)(48)	1·01	0·91	1·12	0·851
Unhealthy		1·01	0·91	1·12	0·851
Overall		1·09	1·02	1·17	0·008

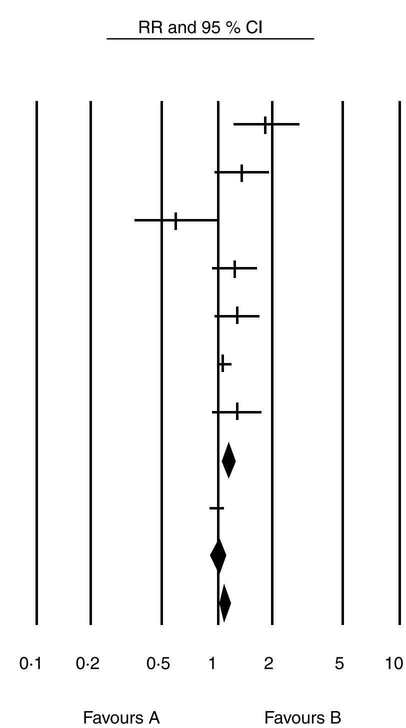

Fig. 5. Mortality risk for intentional weight loss among overweight or mixed populations. RR, relative risk.

(NHANES) data that showed that the ideal weight for longevity was the overweight category, or BMI 23–30 kg/m^{2}[28–30].

Why should intentional weight loss have opposing effects in different groups of individuals? One possibility is that obese individuals with risk factors may show a benefit because they are more motivated to make a series of changes such as reducing fat intake or increasing exercise level, and these may lower RR of mortality by benefiting overall health status[31]. Unhealthy individuals are also more likely to be recipients of health care and medical interventions. It is more difficult to explain why intentional weight loss should have an adverse effect among healthy but overweight individuals. More data on method of weight loss, persistence of weight loss and body composition would be helpful in this regard. Weight loss via energy restriction may do little to alter the relative distribution of body fat and may result in decreased lean body mass. A reanalysis of the Framingham Heart Study and the Tecumseh Community Study suggests that weight loss as a result of a reduction in body fat may reduce all-cause mortality while weight loss as a result of a reduction in lean body mass may increase it[32]. Given the significance of fat distribution and the lean body mass:fat ratio in health prognosis[33], it is imperative that future studies attempt to measure more than just weight or BMI. Furthermore, studies must adequately disentangle the influence of physical activity and/or fitness, which may influence both body weight and the morbidity and mortality outcomes under study. Most studies did not include assessment of physical activity and those that did used questionnaires rather than physical fitness, which is a stronger predictor of mortality[34,35]. The focus of new research may most usefully be directed to examining survival among those population groups that might be expected to benefit most from weight loss. These include those with diabetes, those with obesity-related conditions (such as hypertension) and certain ethnic groups.

Limitations

The present study inevitably has some limitations. The literature search was carried out using only two databases, but was complemented by thorough checking of cross-references and inclusion of new reviews published in 2008. Limitations of the evidence base include the fact that none of the studies provided information on the method of weight loss, which is relevant because it is not clear if weight loss through energy restriction or increased energy expenditure differentially influences long-term outcomes. Second, weight loss was usually assessed retrospectively and subjectively, often at two time points some distance removed from the ultimate outcome, i.e.

Weight loss assessment of group	Study name	RR	Lower limit	Upper limit	*P*
Measured	Wedick *et al.* (2002)[56]	1·27	0·94	1·71	0·118
Measured	Wedick *et al.* (2002)[56]	1·28	0·95	1·73	0·107
Measured	Yaari & Goldbourt (1998)[46]	1·30	0·94	1·80	0·116
Measured		1·28	1·07	1·53	0·006
Reported	French *et al.* (1999)[47]	1·18	0·94	1·48	0·153
Reported	Gregg *et al.* (2003)[31]	0·76	0·60	0·97	0·025
Reported	Gregg *et al.* (2004)[51]	0·83	0·63	1·09	0·175
Reported	Sørensen *et al.* (2005)[8]	1·87	1·22	2·87	0·004
Reported	Wannamethee *et al.* (2005)[10]	1·37	0·96	1·95	0·079
Reported	Wannamethee *et al.* (2005)[10]	0·59	0·34	1·01	0·055
Reported	Williamson *et al.* (1995)[45]	1·12	0·94	1·33	0·201
Reported	Williamson *et al.* (1995)[45]	0·80	0·68	0·94	0·007
Reported	Williamson *et al.* (1995)[45]	0·98	0·82	1·17	0·824
Reported	Williamson *et al.* (1995)[45]	0·81	0·71	0·92	0·001
Reported	Williamson *et al.* (1999)[48]	1·09	0·98	1·21	0·109
Reported	Williamson *et al.* (1999)[48]	1·01	0·91	1·12	0·851
Reported	Williamson *et al.* (1999)[48]	1·07	0·96	1·20	0·235
Reported	Williamson *et al.* (1999)[48]	1·02	0·94	1·11	0·641
Reported	Williamson *et al.* (2000)[4]	0·75	0·67	0·84	0·000
Reported		0·97	0·88	1·06	0·508
Overall		1·03	0·95	1·12	0·504

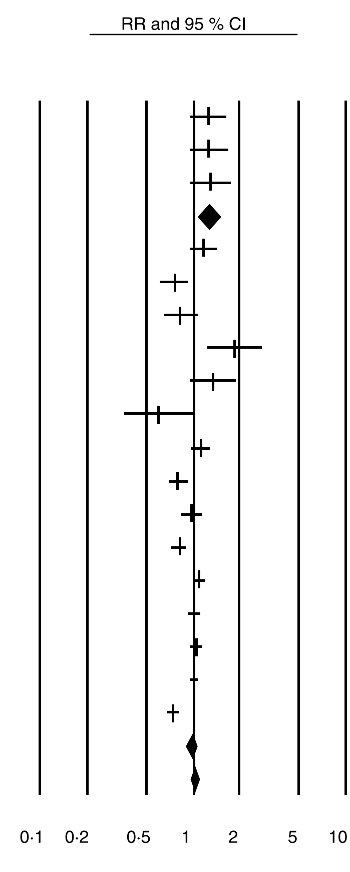

Fig. 6. Mortality risk for intentional weight loss according to weight loss assessment method. RR, relative risk.

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Physical activity adjustment	Study name	Statistics for each study			
		RR	Lower limit	Upper limit	*P*
No	French *et al.* (1999)[47]	1·18	0·94	1·48	0·153
No	Gregg *et al.* (2003)[31]	0·76	0·60	0·97	0·025
No	Gregg *et al.* (2004)[51]	0·83	0·63	1·09	0·175
No	Yaari and Goldbourt (1998)[46]	1·30	0·94	1·80	0·116
No		0·98	0·76	1·27	0·899
Yes	Sørensen *et al.* (2005)[8]	1·87	1·22	2·87	0·004
Yes	Wannamethee *et al.* (2005)[10]	1·37	0·96	1·95	0·079
Yes	Wannamethee *et al.* (2005)[10]	0·59	0·34	1·01	0·055
Yes	Wedick *et al.* (2002)[56]	1·27	0·94	1·71	0·118
Yes	Wedick *et al.* (2002)[56]	1·28	0·95	1·73	0·107
Yes	Williamson *et al.* (1995)[45]	1·12	0·94	1·33	0·201
Yes	Williamson *et al.* (1995)[45]	0·80	0·68	0·94	0·007
Yes	Williamson *et al.* (1995)[45]	0·98	0·82	1·17	0·824
Yes	Williamson *et al.* (1995)[45]	0·81	0·71	0·92	0·001
Yes	Williamson *et al.* (1999)[48]	1·09	0·98	1·21	0·109
Yes	Williamson *et al.* (1999)[48]	1·01	0·91	1·12	0·851
Yes	Williamson *et al.* (1999)[48]	1·07	0·96	1·20	0·235
Yes	Williamson *et al.* (1999)[48]	1·02	0·94	1·11	0·641
Yes	Williamson *et al.* (2000)[4]	0·75	0·67	0·84	0·000
Yes		1·01	0·92	1·11	0·853
Overall		1·01	0·92	1·10	0·898

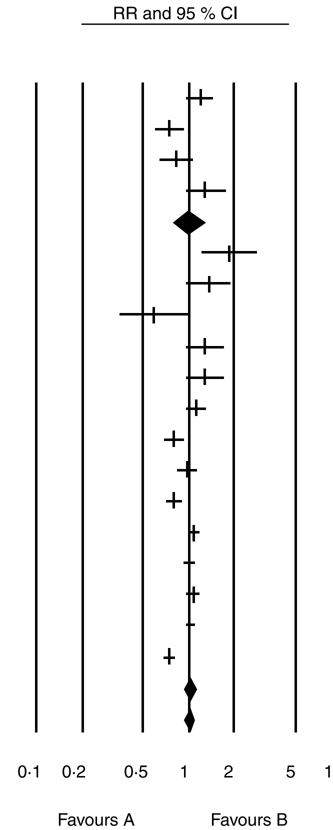

Fig. 7. Mortality risk for intentional weight loss according to adjustment for physical activity. RR, relative risk.

death. It is thus difficult to be sure that the weight loss estimate does not represent a transitory phase and that it is representative of a reasonable period of adult life. Third, the studies differed in the statistical treatment of covariates or confounders in adjusted models (for example, some excluded smokers, others adjusted for smoking). These problems are common to all attempts to review and pool data from different studies, and the present results are consistent with other recent reviews that have not used meta-analysis[16,36]. Furthermore, using a meta-analysis stratified by intentionality, health and baseline BMI, we were able to quantify effect sizes in different groups. The robustness of intentionality measures has been questioned[16] because it depends on the question asked and may change during the course of the follow-up[37]. The study by Sørensen *et al.*[8] was unusual in assessing intentionality prospectively and also reported the largest effect size (RR 1·87)[8]. However, as it was of high quality (as judged by Simonsen *et al.*[16]), we did not consider its exclusion justified in the main analysis. Instead, sensitivity analysis showed that the effect of excluding this paper would be to reduce the RR from 1·11 to 1·09. On balance we think it unlikely that our estimates of higher risk are inflated, since most sources of misclassification and measurement error would tend to result in underestimation of effect (for example, self-reported body weight).

Conclusion

Recently a great emphasis has been placed on weight loss by lifestyle change for everyone who is, even slightly, overweight. However, a review of the available literature, complemented by meta-analysis, suggests that at-risk individuals may benefit, but for healthy overweight individuals intentional weight loss does not decrease mortality and may even increase it. Appropriately designed intervention studies in subgroups differing by age, sex and ethnic group, as well as by risk status, are urgently needed. Until more reliable data are available to demonstrate consistent improvements in survival, the question remains as to whether the correction of obesity *per se* should have such emphasis as a clinical and public health target.

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The authors have no conflicts of interest to declare.

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