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Obesogenic Risks

Change in body size and mortality: a systematic review and meta-analysis

Amalia Karahalios,[1]* Dallas R English[1,2] and Julie A Simpson[1]

[1]Centre for Epidemiology and Biostatistics, University of Melbourne and [2]Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, VIC, Australia

*Corresponding author. Level 3, 207 Bouverie Street, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia. E-mail: emily.karahalios@unimelb.edu.au

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Abstract

Background: Observational studies have reported that weight loss in later life is associated with an increased risk of mortality. However, the association with weight gain is unclear. We conducted a systematic review and meta-analysis of prospective studies assessing the association of weight gain and loss, and mortality.

Methods: We searched PubMed, Scopus and Web of Science for articles published before 5 September 2015. We included prospective studies that reported enough information to extract hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs) for the association between weight gain and/or weight loss, and all-cause and cause-specific mortality. The estimates were pooled using a random-effects model. Meta-regression models were fitted to explore sources of potential between-study heterogeneity.

Results: A total of 25 (providing data from 437 772 participants with 34 038 deaths from all causes) and 24 studies (434 694 participants with 31 978 deaths) presented results for the exposures, weight loss and weight gain. Weight loss compared with a stable weight was associated with an increased risk of all-cause (pooled HR: 1.45; 95% CI: 1.34, 1.58), and cardiovascular disease (CVD) mortality (1.50; 1.32, 1.70) and a slightly increased risk of cancer mortality (1.19; 0.97, 1.46). Weight gain was associated with an increased risk of CVD mortality (1.21; 1.07, 1.36) and a slightly increased risk of all-cause mortality (1.07; 1.01, 1.13) and cancer mortality (1.04; 0.96, 1.13). Considerable heterogeneity was observed; the method used to ascertain body size and the proportion of the baseline sample included in the final analysis explained most of the heterogeneity.

Conclusion: Weight loss and weight gain in midlife are associated with increased risk of all-cause and CVD mortality.

Key words: Meta-analysis, systematic review, weight loss, weight gain, mortality, middle aged

Key Messages

- Weight gain and weight loss are associated with increased risk of all-cause and cardiovascular disease mortality.
- Weak associations were found for weight gain and weight loss and the risk of cancer mortality.
- Future observational studies should account for weight loss intention in the analysis of weight change and mortality.

Introduction

Weight loss, independent of underlying disease, is assumed to be beneficial because of the known increased risks associated with obesity; whereas weight gain is assumed to be detrimental to health.[1] With more cohort studies inviting their participants to return for follow-up waves of data collection, it is becoming increasingly common for studies to assess weight gain and/or weight loss from midlife to older age. Weight gain from midlife to older age might involve different mechanisms (e.g. decreases in muscle mass and increases in fat mass) than from early adulthood to middle age, and the latter time period might correspond to a longer duration of obesity, resulting in increased mortality.[2,3]

A 2009 systematic review and meta-analysis of the association between weight loss (measured by weight or body mass index (BMI)) and the risk of mortality included studies published between 1987 and 2008, and assessed weight loss both retrospectively and prospectively.[4] As well, it included studies assessing weight loss from early adulthood (e.g. age 18 or 21) to midlife and studies of weight loss from midlife to older age.[4] The review did not assess the associations between mortality and weight gain or changes in waist circumference, nor did it look at cause-specific mortality (i.e. mortality from cancer or cardiovascular disease).

In addition to updating the previous systematic review,[4] the aim of this review was to focus on studies that assessed the association between gain and loss of weight and/or waist circumference in healthy adults, measured between midlife and older age, and all-cause and cause-specific mortality, to quantify these associations using meta-analysis and to explore heterogeneity between the studies using meta-regression.

Methods

Search strategy

We searched PubMed, Scopus and Web of Science (Science Citation Index Expanded and Social Sciences Citation Index and Arts & Humanities Citation Index) to identify prospective studies published before 5 September 2015, which assessed the association between gain or loss in weight/BMI and/or waist circumference and all-cause and/or cause-specific mortality (search strategy provided in Table S1, see Supplementary data available at *IJE* online). Next, we hand-searched the bibliographies of retrieved papers to identify additional relevant studies. We then checked the bibliographies of three review papers[4–6] to ensure that all studies in these reviews were included. Finally, we carried out a further search in Google Scholar of known cohort studies (Table S2, see Supplementary data available at *IJE* online); we entered the study name and the terms weight change and (death OR mortality) in the search box, and reviewed the first three pages of Google Scholar results. We did not include any unpublished studies or eligible abstracts that did not have full text available. This systematic review was planned, conducted and reported with adherence to the standards of quality for reporting meta-analyses of observational studies[7] (Table S3, see Supplementary data available at *IJE* online) and was registered with PROSPERO (International Prospective Register Of Systematic Reviews), reference number CRD42014015627.[8]

Eligibility criteria

The inclusion criteria for studies were: (i) prospective studies; (ii) English language; (iii) middle-aged adults (i.e. age at baseline between 40 and 65 years and considered to be healthy); (iv) reported results for change in weight/BMI, and/or waist circumference ascertained at midlife and again in older age (i.e. at least 5 or more years after baseline); (v) outcome of interest was all-cause, cardiovascular disease (CVD) or cancer mortality; and (vi) the study reported enough information to extract hazard ratio (HR) estimates and the corresponding 95% confidence intervals (CIs) (note, where published data were not sufficient, we contacted the corresponding author). Data on the HR of mortality (95% CI) were extracted for all subgroups presented by the authors (e.g. men and women). If results from a single study were reported more than once, we used the most recent report.

Data extraction

The following data were extracted: the first author's last name; year of publication; name of the study; country where the study was performed; participants' sex; mean

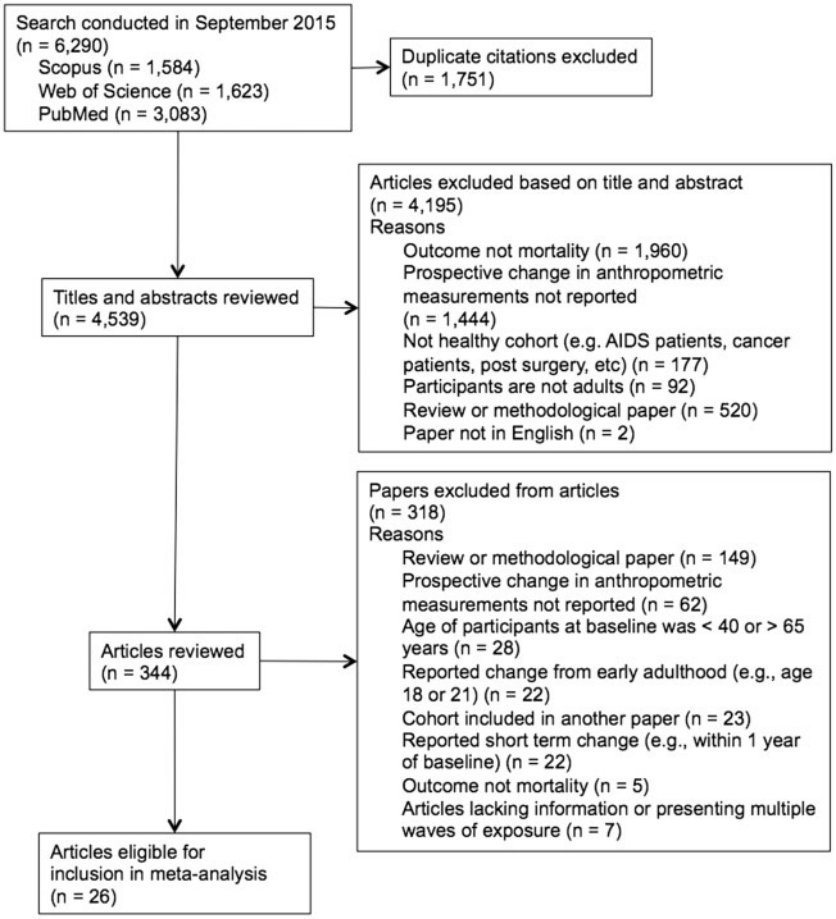

Figure 1. Selection of studies published up to September 2015 for inclusion in a meta-analysis of weight gain and weight loss and all-cause, cardiovascular disease and cancer mortality.

and range of participants' age at baseline; sample size at baseline; weight measure(s) recorded including details of assessment (i.e. directly measured or self-reported); weight/BMI at baseline; weight loss intention; categories of the exposure measure (if presented); number of deaths; person-years; HR and corresponding 95% CI; and potential confounders included in the analysis. We extracted HRs from the most fully adjusted model in each study. If results were reported for two multivariable models, we extracted HRs from the model that did not adjust for possible intermediaries in the causal pathway (i.e. cholesterol, dyslipidaemia, blood pressure, hypertension, insulin resistance, diabetes or cancer). Finally, the freeware software, PlotDigitizer[9] was used to extract HRs and 95% CIs for estimates that were only presented in a figure.

Data analysis

A.K. reviewed the abstracts and full articles. A.K. and J.A.S. independently extracted the data from the included studies, and D.R.E. resolved any discrepancies. We estimated, using meta-analysis with random-effects, the pooled HRs for each study's largest category of weight gain and weight loss compared with the reference category for all-cause, CVD and cancer mortality. Most studies compared weight loss and gain with a stable category that corresponded to a weight change (increase or decrease) of no more than 5 kg.

Assessment of bias

Individual reports were assessed for their risk of bias using the domains of bias from the ROBINS-I tool obtained from [https://sites.google.com/site/riskofbiastool/home]. We visually inspected funnel plots of the study size versus standard error and performed Egger's regression asymmetry test to assess bias due to small study effects.[10]

Statistical heterogeneity between studies was tested with the Q statistic, and quantified with the I^2 statistic.[11] To explore sources of study heterogeneity, we fitted meta-regression models to estimate the association between the log-transformed study-specific HRs and the following pre-specified variables: participants' sex; method used to

Table 1. Characteristics of the 26 papers from 25 studies included in a meta-analysis of Weight/BMI Gain and Loss and All-Cause and Cause-Specific Mortality; 1992-2015

Author year [reference]	Study name (location)	Age (years) at weight/BMI measurement/time to follow-up[a]	Body size measure (baseline mean ± SD[a])	Proportion of baseline sample included in analysis	Analysis	Confounders	Study design
Adams 2014[37]	National Institutes of Health-AARP Diet and Health Study (USA)	Age 50, self-reported Age 62 (baseline), measured Mean time to follow-up: 12.5 years	Weight (NR)	< 70%	Cox proportional hazards model	Age at baseline, baseline BMI, height at age 18, physical activity, alcohol consumption, ethnicity, and education	Cohort
Albanese 2014[29]	MRC National Survey of Health and Development (UK)	Age 43 (baseline), measured Age 53, measured Mean time to follow-up: 12 years	Weight (72.5 ± 13.5 kg)	< 70%	Cox proportional hazards model	Age, sex, weight at baseline, physical activity at baseline and follow-up, education, socio-economic position	Cohort
Allison 1999[38]	Framingham Heart Study (USA)	Age 50 (baseline), measured Age 64, measured Mean time to follow-up: 8 years	Weight (69.9 ± 13.0 kg)	< 70%	Cox proportional hazards model	Age, sex, baseline weight, height, smoking status and baseline subscapular skinfold measurement	Cohort
Breeze 2006[30]	London civil servants (UK)	Age 47 (baseline), measured Age 76, measured Mean time to follow-up: 5 years	Weight (24.5 ± 2.7 kg/m^2)	< 70%	Cox proportional hazards model	Age, baseline BMI	Cohort
Claessen 2012[31]	German construction industry (Germany)	Age 41 (baseline), measured Age 47, measured Mean time to follow-up: 17 years	BMI (26.4kg/m^2)	< 70%	Cox proportional hazards model	Age, smoking status, alcohol intake and nationality	Cohort
Diaz 2005[39]	NHANES I and II (USA)	Age 44 (baseline), measured Age 60, self-reported Mean time to follow-up: 5 years	BMI (25.5 kg/m^2)	Baseline sample size not reported	Cox proportional hazards model	Age, sex, baseline BMI, smoking status, race and health status	Cohort
Droyvold 2005[16]	Nord-Trondelag Health Study (Norway)	Age 44 (baseline), self-reported Age 55, measured Mean time to follow-up: 5 years	BMI (24.8 ± 3.5 kg/m^2)	> 70%	Cox proportional hazards model	Age, baseline BMI, smoking status, physical activity, alcohol intake, education, marital status, systolic blood pressure, and blood pressure medication	Cohort
He 2014[24]	Xi'an Cohort, (China)	Age 44 (baseline), measured Age 61, measured Mean time to follow-up: 17 years	BMI (62.8 ± 6.9 kg)	> 70%	Cox proportional hazards model	Age, sex, change of smoking status from 1976 to 1994, physical activity, alcohol intake, education, occupation,	Cohort

(Continued)

Table 1. Continued

Author year [reference]	Study name (location)	Age (years) at weight/BMI measurement/time to follow-up[a]	Body size measure (baseline mean ± SD[a])	Proportion of baseline sample included in analysis	Analysis	Confounders	Study design
						marital status, history of cardiovascular disease in 1994	
Holme 2015[17]	Oslo Study (Norway)	Age 45 (baseline), measured Age 73, measured Mean time to follow-up: 11 years	BMI (26.3±3.3 kg/m^2)	< 70%	Cox proportional hazards model	Age, smoking status, education, use of antihypertensive medication, use of cholesterol-lowering medication, diabetes, myocardial infarction and cerebrovascular disease	Cohort
Iribarren 1995[25]	Honolulu Heart Program (USA)	Age 54 (baseline), measured Age 57, measured Age 60, measured Mean time to follow-up: 14.5 years	Weight (63.5±9.2kg)	> 70%	Cox proportional hazards model with exposure set as the slope of weight (derived from the 3 measurements) against time	Age, average weight, smoking status, physical activity, energy intake, alcohol intake, occupation, and pre-existing disease	Cohort
Karahalios 2014[42]	Melbourne Collaborative Cohort Study (Australia)	Age 54 (baseline), measured Age 66, measured Mean time to follow-up: 8 years	Weight and waist circumference (72.3± 12.7kg)	< 70%	Cox proportional hazards model	Age, sex, baseline weight/waist circumference, smoking status, physical activity, diet, country of birth, socioeconomic status, and whether the participant lived alone	Cohort
Klenk 2014[32]	Vorarlberg Health Monitoring and Prevention Program (Austria)	Age 43 (baseline), measured Age 48, measured Mean time to follow-up: 10 years	BMI (24.8±3.7 kg/m^2)	> 70%	Cox proportional hazards model	Age, smoking status	Cohort
Lee 1992[40]	Harvard University Alumni (USA)	Age 46 (baseline), self-reported Age 58, self-reported Mean time to follow-up: 11 years	Weight (78.3±9.4 kg)	< 70%	Cox proportional hazards model	Age, height, smoking status and physical activity at follow-up	Cohort
Lee 2011[18]	Aerobics Center Longitudinal Study (USA)	Age 44 (baseline), measured Age 50, measured Mean time to follow-up: 11.4 years	BMI (83.3±12.8 kg)	> 70%	Cox proportional hazards model	Age, BMI, smoking status, physical activity, alcohol intake, year of examination, parental cardiovascular disease, maximal metabolic equivalents at baseline, number of clinic visits between the baseline and last examinations, abnormal	Cohort

(Continued)

Table 1. Continued

Author year [reference]	Study name (location)	Age (years) at weight/BMI measurement/time to follow-up[a]	Body size measure (baseline mean ± SD[a])	Proportion of baseline sample included in analysis	Analysis	Confounders	Study design
						echocardiogram, hypertension, diabetes, hypercholesterolaemia at the baseline and last examinations, and changes in maximal metabolic equivalents	
Myers 2011[22]	Veterans Exercise Testing Study (USA)	Age 59 (baseline), measured Age 66, measured Mean time to follow-up: 7 years	Weight (91±17.3 kg)	< 70%	Cox proportional hazards model	Age, baseline weight, exercise capacity and cardiovascular disease	Cohort
Nanri 2010[19]	Japan Public Health Center-Based Prospective Study (Japan)	Age 57 (baseline), self-reported Age 62, self-reported Mean time to follow-up: 9 years	Weight (58.3±8.0 kg)	> 70%	Cox proportional hazards model	Age, baseline BMI, smoking status, leisure-time physical activity, alcohol consumption, study area, history of hypertension and history of diabetes mellitus	Cohort
Nilsson 2002[23]	Malmo Preventive Project (Sweden)	Age 47 (baseline), measured Age 53, measured Mean time to follow-up: 14 years	BMI (77.1±7.4 kg)	< 70%	Cox proportional hazards model	Age	Cohort
Ostergaard 2010[33]	Copenhagen City Heart Study (Denmark)	Age 56 (baseline), measured Age 61, measured Mean time to follow-up: NR	BMI (median: 27.5 kg/m^2)	< 70%	Cox proportional hazards model	Age, sex, initial BMI, smoking status, pack-years smoked, alcohol intake, education, marital status, time between two examinations and time since second examination	Cohort
Peters 1995[26]	Seven Countries Study (Europe)	Age 59 (baseline), measured Age 69, measured Mean time to follow-up: 12 years	Weight (NR)	Baseline sample size not reported	Cox proportional hazards model	Age, body weight at third examination, smoking status and geographical region	Cohort
Rzehak 2007[34]	Erfurt Male Cohort Study (Germany)	Age 48 (baseline), measured Age 63, measured Mean time to follow-up: 15 years	Weight (26.4±2.6 kg/m^2)	< 70%	Cox proportional hazards model	Age, smoking status, education and pre-existing disease	Cohort

(Continued)

Table 1. Continued

Author year [reference]	Study name (location)	Age (years) at weight/BMI measurement/time to follow-up[a]	Body size measure (baseline mean ± SD[a])	Proportion of baseline sample included in analysis	Analysis	Confounders	Study design
Strandberg 2013[35]	Helsinki Businessmen Study (Finland)	Age 47 (baseline), measured Age 73, self-reported Mean time to follow-up: 12 years	Weight (81.0 kg)	< 70%	Cox proportional hazards model	Age, smoking at baseline and self-rated health at baseline	Cohort
Taing 2012[41]	Women's Health Initiative (USA)	Age 50, self-reported Age 63 (baseline), measured Mean time to follow-up: 7 years	BMI (30.5±5.1 kg/m^2)	< 70%	Cox proportional hazards model	Age, BMI, smoking status, physical activity, alcohol intake, ethnicity, education, income, hormone replacement therapy	Cohort
Wannamethee 2002[36]	British Regional Heart Study (UK)	Age 50 (baseline), measured Age 55, self-reported Age 63, self-reported Mean time to follow-up: 8 years	BMI (25.5 kg/m^2)	> 70%	Cox proportional hazards model	Age, baseline BMI, smoking status, physical activity, social class	Cohort
Wilsgaard 2009[27]	Tromso Study (Norway)	Age 41 (baseline), measured Age 51, measured Mean time to follow-up: 10 years	BMI (24.2±2.6 kg/m^2)	< 70%	Cox proportional hazards model	Age, baseline BMI, smoking status, and physical activity	Cohort
Yaari 1998[20]	Israeli Ischemic Heart Disease Study (Israel)	Age 49 (baseline), measured Age 54, measured Mean time to follow-up: 18 years	Weight (71.3±10.3 kg)	> 70%	Cox proportional hazards model	Age, baseline BMI, smoking status, serum total cholesterol, systolic blood pressure, diabetes, cancer, definite angina, intermittent claudication, myocardial infarction,	Cohort

(Continued)

Table 1. Continued

Author year [reference]	Study name (location)	Age (years) at weight/BMI measurement/time to follow-up[a]	Body size measure (baseline mean ± SD[a])	Proportion of baseline sample included in analysis	Analysis	Confounders	Study design
						history of chronic lung disease, being on a diet in 1963	
Zhang 2014[21]	Aerobics Center Longitudinal Study (USA)	Age 44 (baseline), measured Age 72 (approximately), measured Mean time to follow-up: 12.5 years	BMI (83.5±12.2 kg)	< 70%	Cox proportional hazards model	Age, BMI, smoking status, physical activity, alcohol intake, year of examination, parental cardiovascular disease, maximal metabolic equivalents at baseline, number of clinic visits between the baseline and last examinations, abnormal echocardiogram, hypertension, diabetes, and hypercholesterolemia, and changes in maximal METs	Cohort

All cohort studies were community-based.

EPIC, European Prospective Investigation into Cancer; MRFIT, Multiple Risk Factor Intervention Trial; NHANES, National Health and Nutrition Examination Survey; NIH-AARP, National Institutes of Health - American Association of Retired Persons; NR, not reported.

[a]Mean ± standard deviation reported unless stated otherwise.

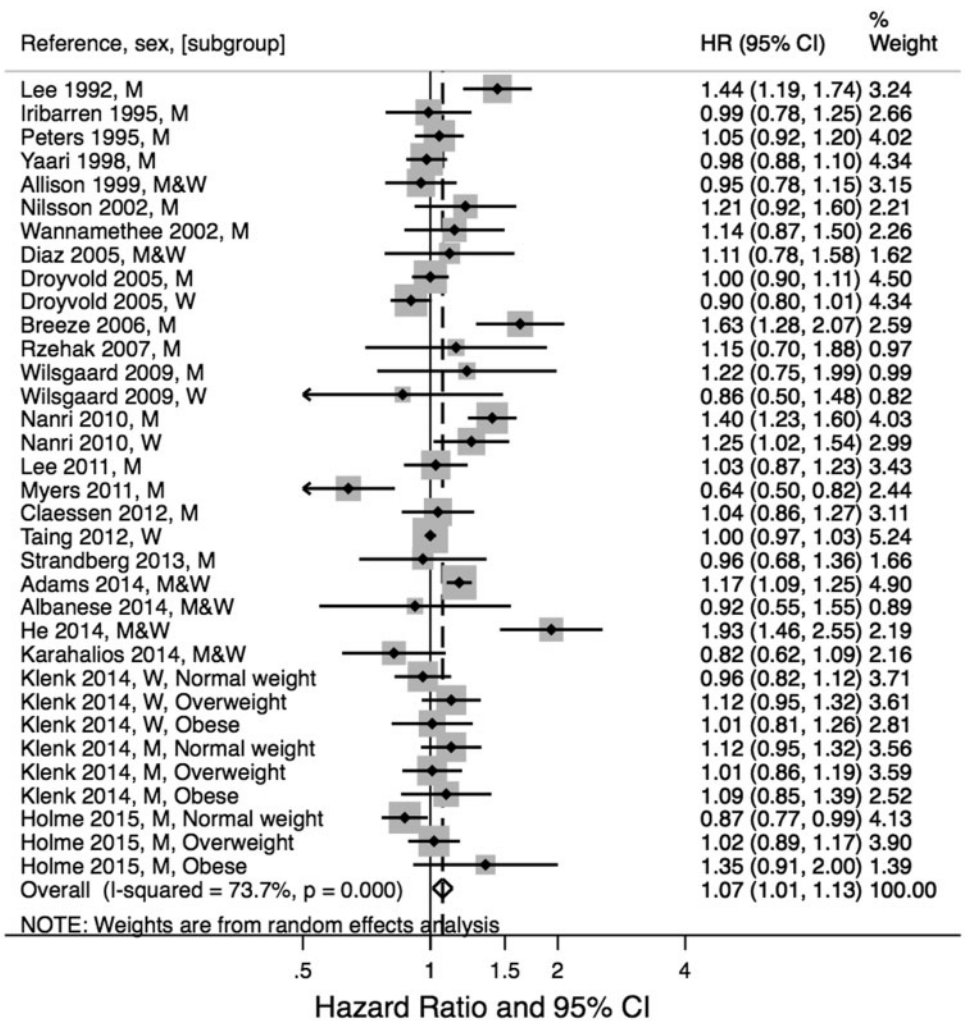

Figure 2. Adjusted hazard ratio for the risk of all-cause mortality comparing the largest weight gain group to the reference group for males (M), females (W) and both sexes combined, 1992 to 2015; dashed line, overall estimate; bars, 95% confidence interval (CI).

measure weight (i.e. measured or self-reported); study design; intentionality of weight loss; whether physical activity was adjusted for in the analysis; and the proportion of the baseline sample included in the analysis. Based on comments from reviewers, we also included time between measures of body size and follow-up time (both categorized as $<= 10$ or > 10 years) as covariates in our meta-regression model.

Nonlinear dose-response analysis

We also assessed a potential nonlinear relationship between weight change and all-cause mortality.[12] Weight change was modelled using restricted cubic splines with three knots at fixed percentiles (25%, 50% and 75%) of the distribution.[13] Restricted cubic spline models were initially computed for each study, taking into account the within-study correlation. Next, a random-effects meta-analysis was performed using the regression coefficients and the variance-covariance matrix from each individual study.[14] Nonlinearity of the dose response curve was assessed by testing the null hypothesis that the coefficient of the second spline was equal to 0.

For this analysis, we excluded papers that reported percentage change because we were unable to convert these to a change in kilograms. For the remaining papers, we used the median/mean values for each category of weight change when presented. When they were not presented, we assigned the midpoint of the cut-points of the category as the dose value. In the example of a weight gain category of 5 kg to 10 kg, the assumed weight gain in this group is 7.5 kg. Using the method described by Il'yasova *et al.*[15] for the largest weight gain category, we assigned the value of its lower bound plus the width of the previous (second-to-highest) interval; and for the largest weight loss category, we assigned the value of its

Table 2. Results from meta-regression analyses of weight gain compared with a no-weight-change group and risk of all-cause mortality

Covariate	**No. of HRs (no. of studies)**[a]	Summary HR	I^2 (%)	**tau**^{2}	Ratio of HRs	*P*-value
Model with no covariates	34 (24)	1.07 (1.00, 1.15)	73.7	0.024	–	–
Sex						
Men and women	6 (6)	1.12 (0.94, 1.34)	70.8	0.025	1.00	–
Men	21 (17)	1.08 (0.99, 1.18)	–	–	0.97 (0.79, 1.18)	0.717
Women	7 (5)	1.02 (0.88, 1.18)	–	–	0.91 (0.72, 1.14)	0.402
Adjusted for physical activity						
No	18 (11)	1.06 (0.97, 1.17)	74.5	0.025	1.00	–
Yes	16 (13)	1.08 (0.98, 1.20)	–	–	1.02 (0.89, 1.17)	0.765
Body size at baseline						
Normal weight, overweight and obese	26 (22)	1.09 (1.01, 1.18)	71.8	0.025	1.00	–
Normal weight only	4 (3)	1.01 (0.84, 1.23)	–	–	0.93 (0.76, 1.14)	0.472
Overweight/obese only	4 (3)	1.02 (0.85, 1.24)	–	–	0.94 (0.77, 1.15)	0.531
Method used to collect weight/BMI at each wave						
Measured at baseline and follow-up wave(s)	27 (18)	1.04 (0.97, 1.12)	64.4	0.016	1.00	–
Measured at baseline, self-reported at follow-up wave(s)	4 (4)	1.04 (0.86, 1.25)	–	–	1.00 (0.82, 1.22)	0.987
Self-reported at baseline and follow-up wave(s)	3 (2)	1.37 (1.13, 1.66)	–	–	1.31 (1.07, 1.61)	0.011
Proportion of baseline sample included in final analysis						
< 70%	24 (16)	1.05 (0.97, 1.14)	74.2	0.025	1.00	–
>= 70%	10 (8)	1.11 (0.99, 1.25)	–	–	1.06 (0.92, 1.23)	0.410
Exposure time						
<= 10 years	22 (14)	1.04 (0.96, 1.13)	74.5	0.024	1.00	–
> 10 years	12 (10)	1.13 (1.01, 1.26)	–	–	1.08 (0.94, 1.25)	0.251
Follow-up time[b]						
<= 10 years	19 (11)	1.05 (0.96, 1.15)	73.6	0.025	1.00	–
> 10 years	14 (12)	1.10 (0.99, 1.23)	–	–	1.05 (0.91, 1.21)	0.457

No., number.

[a]Number of studies sum to more than the total because some studies presented separate results for men and women and/or body weight categories.

[b]One study did not report follow-up time.

upper bound plus half the width of the next (second-to-lowest) interval.

Sensitivity analyses

Six studies[16–21] presented results adjusting for possible intermediates on the causal pathway. Two studies did not adjust for smoking status in their analysis.[22, 23] An additional study included participants who could be deemed to be unhealthy; Myers *et al*. 2011[22] included men who were referred for exercise testing. Two studies were based in Asia and had baseline weight/BMI distributions that were lower than many of the other studies.[19,24] We conducted separate sensitivity analyses excluding the above-mentioned studies. Five papers[16,19,20,25,26] presented additional estimates after excluding deaths that occurred in the first 2 to 6 years of follow-up from the analysis; we conducted an additional sensitivity analysis pooling the results from these studies.

The estimates that we extracted from each study did not distinguish between intentional and unintentional weight loss; however, two studies[20,27] provided additional estimates in their papers for intentional weight loss. We conducted a sensitivity analysis to estimate the association between intentional weight loss and the risk of all-cause mortality by pooling the estimates from these studies using random-effects meta-analysis. All analyses were performed using Stata version 13.1.[28]

Table 3. Results from meta-regression analyses of weight gain compared with a no-weight-change group and risk of cardiovascular disease mortality

Covariate	**No. of HRs (no. of studies)**[a]	Summary HR	I^2 (%)	**tau**^{2}	Ratio of HRs	*P*-value
Model with no covariates	16 (14)	1.22 (1.04, 1.42)	64.4	0.043	–	–
Sex						
Men and women	4 (4)	1.36 (0.94, 1.96)	66.9	0.054	1.00	–
Men	10 (10)	1.18 (0.96, 1.44)	–	–	0.87 (0.57, 1.31)	0.468
Women	2 (2)	1.24 (0.79, 1.96)	–	–	0.91 (0.51, 1.64)	0.743
Adjusted for physical activity						
No	4 (4)	1.17 (0.85, 1.59)	65.8	0.049	1.00	–
Yes	12 (10)	1.24 (1.03, 1.49)	–	–	1.06 (0.74, 1.52)	0.733
Body size at baseline						
All weights	16 (14)	1.22 (1.04, 1.42)	–	–	1.00	–
Method used to collect weight/BMI at each wave						
Measured at baseline and follow-up wave(s)	11 (10)	1.14 (0.97, 1.35)	58.2	0.029	1.00	–
Measured at baseline, self-reported at follow-up wave(s)	2 (2)	1.11 (0.72, 1.71)	–	–	0.97 (0.61, 1.54)	0.887
Self-reported at baseline and follow-up wave(s)	3 (2)	1.61 (1.14, 2.26)	–	–	1.41 (0.97, 2.05)	0.072
Proportion of baseline sample included in final analysis						
< 70%	6 (6)	1.31 (0.99, 1.74)	62.0	0.041	1.00	–
>= 70%	10 (8)	1.17 (0.97, 1.41)	–	–	0.89 (0.64, 1.25)	0.477
Exposure time						
<= 10 years	9 (7)	1.07 (0.92, 1.24)	49.6	0.018	1.00	–
> 10 years	7 (7)	1.46 (1.19, 1.79)	–	–	1.36 (1.06, 1.75)	0.019
Follow-up[b]						
<= 10 years	10 (8)	1.19 (0.97, 1.46)	66.7	0.052	1.00	–
> 10 years	6 (6)	1.27 (0.99, 1.63)	–	–	1.07 (0.78, 1.48)	0.650

[a]Number of studies sum to more than the total because some studies presented separate results for men and women and/or body weight categories.
[b]Two studies did not report follow-up time.

Results

Study selection

The keyword search identified 6290 articles; 1751 duplicate citations were removed and an additional 4,195 articles were excluded based on their title and abstract, leaving 344 articles for further evaluation. Of these, 318 articles were excluded, leaving 26 articles appropriate for the systematic review and meta-analysis. The reasons for excluding articles are shown in Figure 1; 49% were review papers or commentaries and 20% did not report on weight gain or weight loss.

Study characteristics

Table 1 summarizes the 26 papers (from 25 studies) eligible for the meta-analysis. Thirteen studies were conducted in Europe,[16,17,23,26,27,29–36] nine papers (from eight studies) were conducted in the USA,[18,21,22,25,37–41] two in Asia,[19,24] one in Australia[42] and one in the Middle East.[20] Four studies measured weight at baseline and used self-reported measures at the follow-up wave(s),[35,36,39,41] two used self-reported measures of weight at the baseline and follow-up wave(s) of data collection[19,40] and the remaining 19 studies (20 papers)[16–18,20–27,29–34,37,38,42] measured weight at all wave(s). Tables S4, S5 and S6 (see Supplementary data available at *IJE* online) provide details for all-cause, CVD and cancer mortality for each study and the estimates and corresponding 95% CIs extracted for each weight change category. Of the 33 papers eligible for inclusion in the meta-analysis, seven papers did not provide sufficient information to be included in the meta-analysis or reported on weight/BMI measured repeatedly.

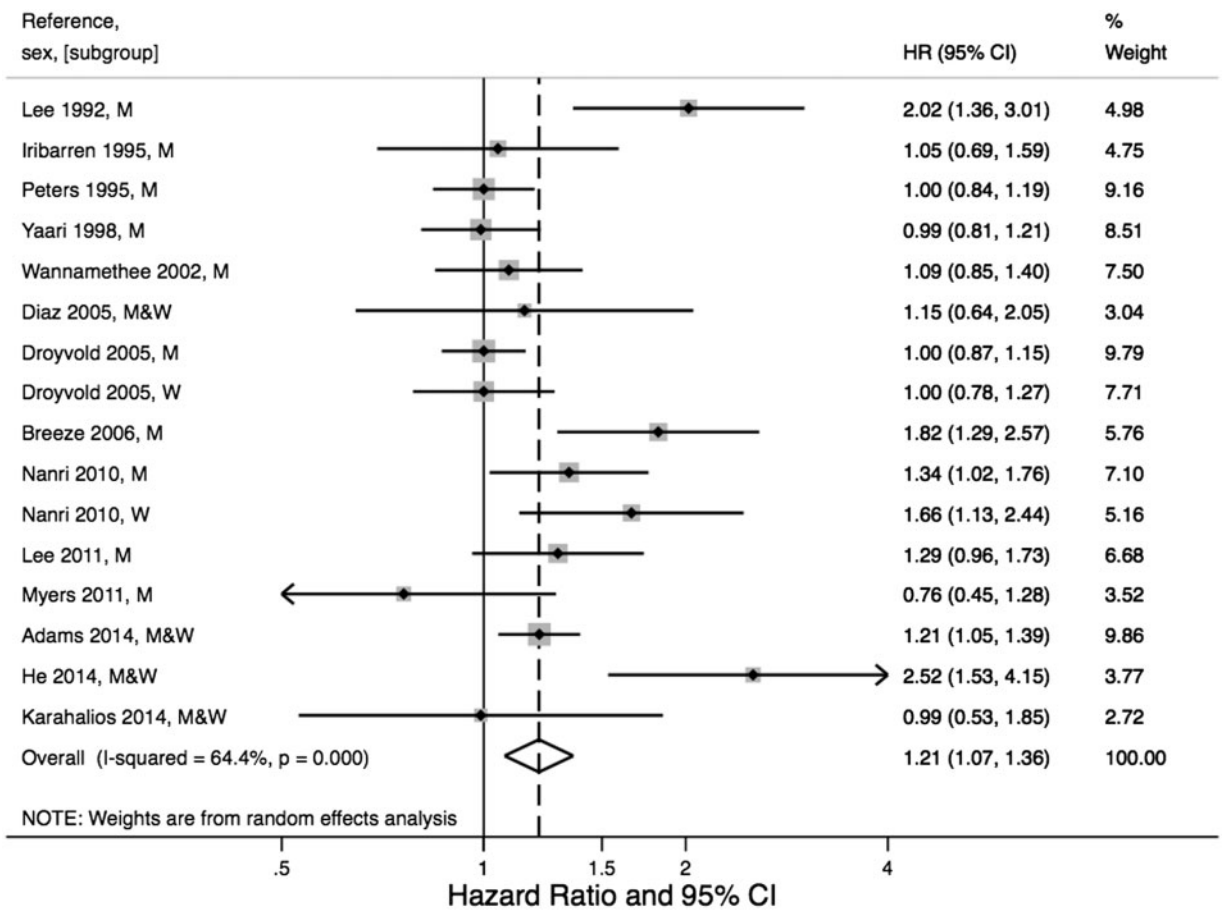

Figure 3. Adjusted hazard ratio for the risk of cardiovascular mortality comparing the largest weight gain group to the reference group for males (M), females (W) and both sexes combined, 1992 to 2015; dashed line, overall estimate; bars, 95% confidence interval (CI).

Risk of bias

We assessed the risk of bias of the included cohort studies against the six domains of bias in the ROBINS-I tool that applied to our study (i.e. bias due to confounding, in selection of participants into the study, in measurement of interventions, due to missing data, in measurement of outcomes and in selection of the reported results). With respect to bias in selection of participants into the study, bias in measurement of outcomes and bias in selection of the reported results, all of the included studies were determined to have a low risk of bias. For the domain of bias due to missing data, all of the studies had a moderate or serious risk of bias. Although the outcome data were reasonably complete for all studies, data were missing for weight change and/or the covariates included in the models. Also, many studies did not differentiate between the amount of data missing for weight change and that missing for the covariates. Bias in measurement of weight change was determined to be low in all except two studies. These two studies relied on recalled weight to assess weight change. Finally, bias due to confounding was determined as serious in all of the studies. We determined a priori that age, sex, physical activity, smoking status, weight at baseline and weight loss intention were 'critically important' confounding domains that should be accounted for the analysis. None of the studies provided information on whether the confounding domains were measured validly or reliably and none of the studies accounted for all of the potential confounding domains.

Weight gain

We pooled the estimates from 24 papers (providing data from 434 694 participants with 31 978 deaths from all-causes) to estimate the risk of all-cause mortality, comparing the largest weight gain category to a reference group (Table S4, see Supplementary data available at *IJE* online). Fourteen studies assessed the association with CVD mortality and seven studies assessed the association with cancer mortality (Tables S5 and S6, see Supplementary data available at *IJE* online). The multivariable-adjusted HRs for each study and all studies combined for all-cause, CVD and cancer mortality are presented in Figures 2, 3 and 4. The pooled estimates for weight gain were slightly elevated

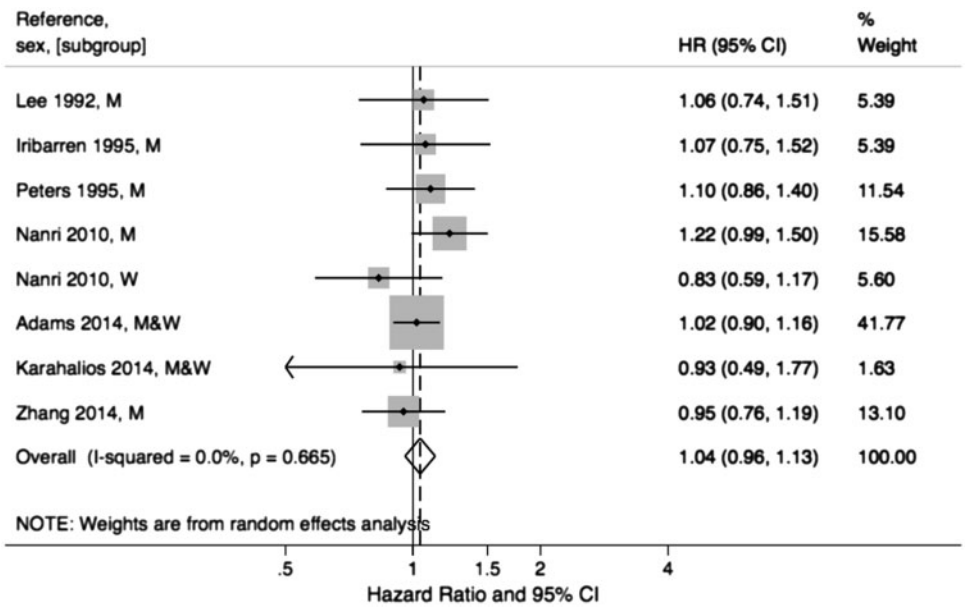

Figure 4. Adjusted hazard ratio for the risk of cancer mortality comparing the largest weight gain group to the reference group for males (M), females (W) and both sexes combined, 1992 to 2015; dashed line, overall estimate; bars, 95% confidence interval (CI).

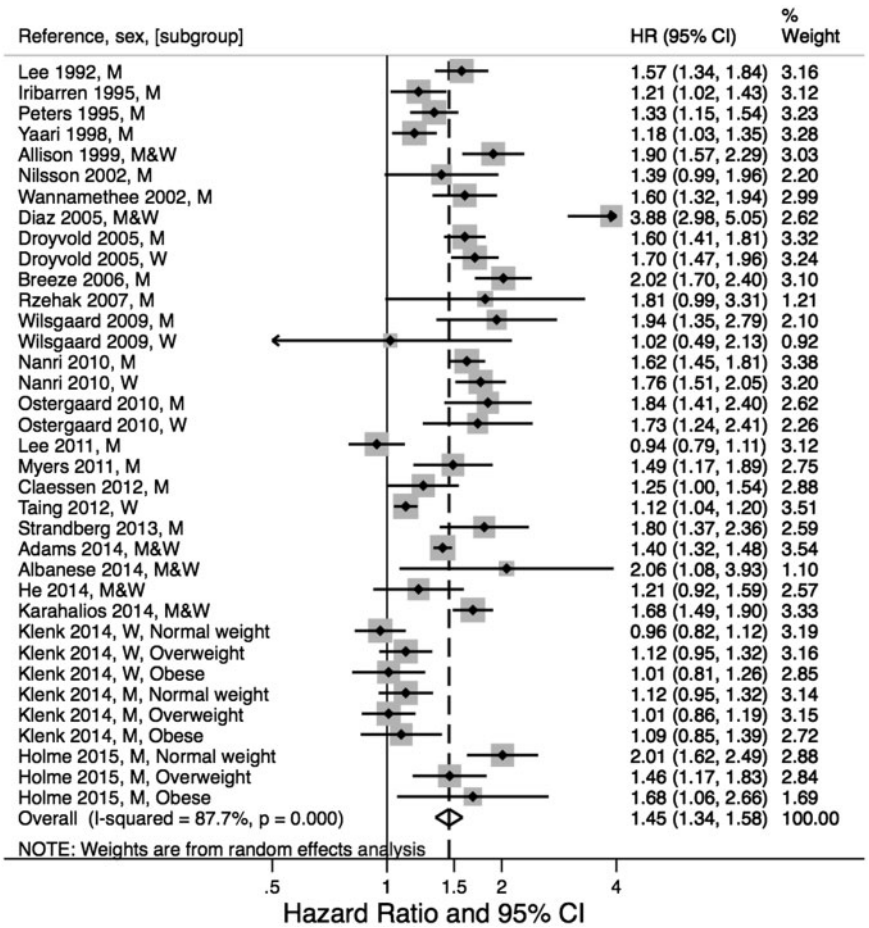

Figure 5. Adjusted hazard ratio for the risk of all-cause mortality comparing the largest weight loss group to the reference group for males (M), females (W) and both sexes combined, 1992 to 2015; dashed line, overall estimate; bars, 95% confidence interval (CI).

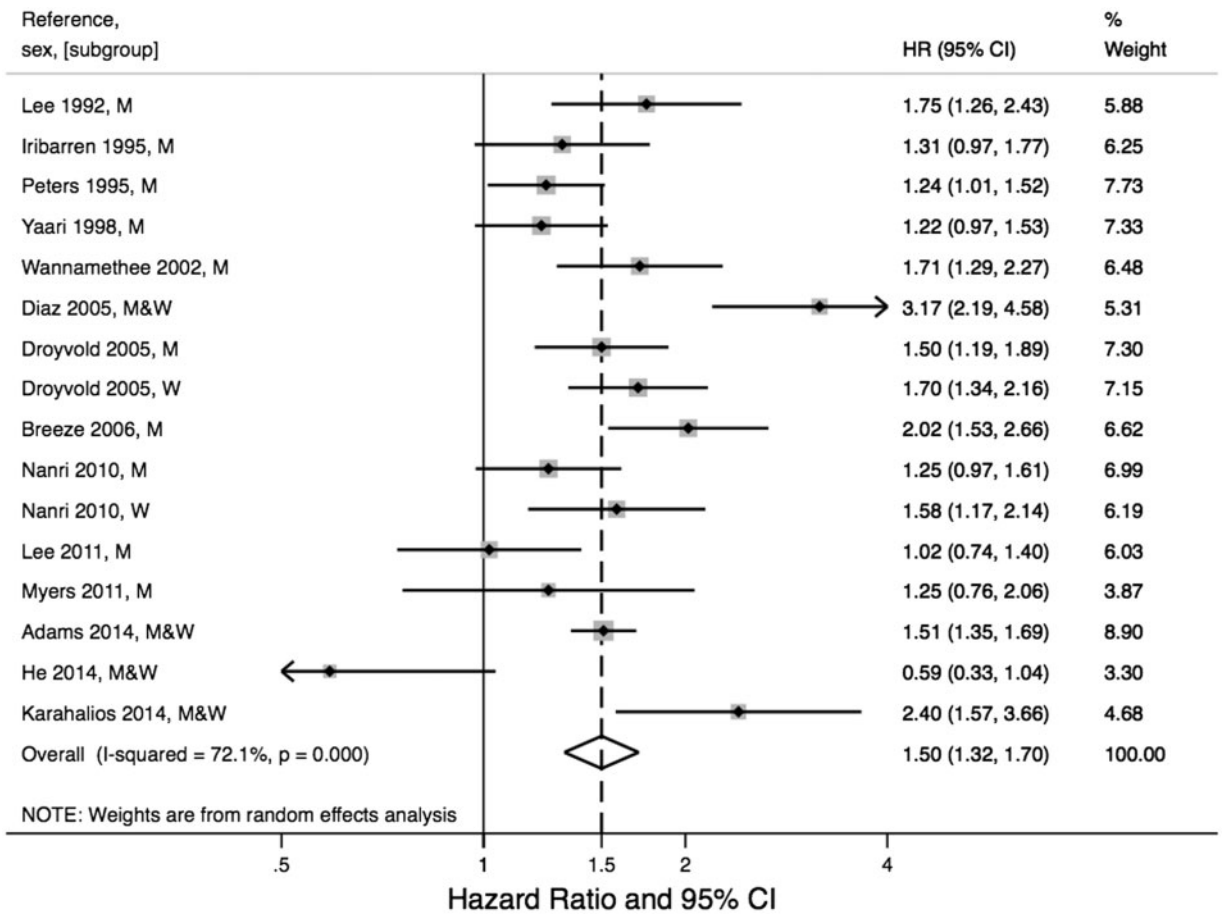

Figure 6. Adjusted hazard ratio for the risk of cardiovascular mortality comparing the largest weight loss group to the reference group for males (M), females (W) and both sexes combined, 1992 to 2015; dashed line, overall estimate; bars, 95% confidence interval (CI).

for all-cause, CVD mortality and cancer mortality (HR: 1.07; 95% CI: 1.01, 1.13, HR: 1.21; 95% CI: 1.07, 1.36, HR: 1.04; 95% CI: 0.96, 1.13, respectively).

The funnel plots did not suggest evidence of bias due to small study effects, which was confirmed by Egger's regression asymmetry test (p-values = 0.20, 0.11, 0.69 for all-cause, CVD and cancer mortality, respectively) (Figures S1a, b and c, see Supplementary data available at *IJE* online).

There was evidence of heterogeneity for weight gain and all-cause and CVD mortality, (all-cause: $I^2 = 73.7\%$, P-value < 0.001; CVD: $I^2 = 64.4\%$, P-value < 0.001), but not for cancer mortality ($I^2 = 0.0\%$, P-value $= 0.665$). In the meta-regression analysis of studies assessing weight gain against a reference group for all-cause mortality, the method used to ascertain weight at each wave explained some of the observed heterogeneity ($\tau^2 = 0.024$ for the model without covariates and $\tau^2 = 0.016$ with method used to assess weight) (Table 2).

For CVD mortality, the time between weight measurements (i.e. greater/less than 10 years) explained much of the variation ($\tau^2 = 0.043$ without and 0.018 with) (Table 3). In the univariable meta-regression analysis, studies with more than 10 years between weight measurements had higher HRs than studies with less than 10 years between weight measurements (ratio of HRs for > 10 years $= 1.36$; 95% CI: 1.06, 1.75).

Weight loss

We included 25 studies (providing data from 437 772 participants with 34 038 deaths from all-causes) in the meta-analysis of weight loss and all-cause mortality (Table S4, see Supplementary data available at *IJE* online). Of these, 14 studies assessed the association for CVD mortality and seven with cancer mortality. The multivariable-adjusted HRs for each study and all studies combined are presented in Figure 5, 6 and 7, for all-cause, CVD and cancer mortality, respectively. Comparing weight loss with the reference group, there was an increased risk of all-cause (HR: 1.45; 95% CI: 1.34, 1.58), and CVD mortality (1.50; 1.32, 1.70) and a weaker association with cancer mortality (1.19; 0.97, 1.46).

Table 4. Results from meta-regression analyses of weight loss compared with a no-weight-change group and risk of all-cause mortality

Covariate	**No. of HRs (no. of studies)**[a]	Summary HR	I^2 (%)	**tau**^{2}	Ratio of HRs	*P*-value
Model with no covariates	36 (25)	1.46 (1.32, 1.61)	87.7	0.067	–	–
Sex						
Men and women	6 (6)	1.83 (1.45, 2.30)	86.6	0.060	1.00	–
Men	22 (18)	1.44 (1.28, 1.62)	–	–	0.79 (0.61, 1.02)	0.071
Women	8 (6)	1.28 (1.05, 1.55)	–	–	0.70 (0.51, 0.95)	0.022
Adjusted for physical activity						
No	20 (12)	1.46 (1.28, 1.67)	88.0	0.070	1.00	–
Yes	16 (13)	1.46 (1.26, 1.69)	–	–	1.00 (0.82, 1.22)	0.989
Body size at baseline						
All	34 (23)	1.47 (1.33, 1.63)	86.6	0.070	1.00	–
Normal weight	1 (1)	1.39 (0.73, 2.65)	–	–	0.94 (0.49, 1.81)	0.855
Overweight/obese	1 (1)	1.12 (0.65, 1.93)	–	–	0.76 (0.44, 1.32)	0.317
Method used to collect weight/BMI at each wave						
Measured at baseline and follow-up wave(s)	29 (19)	1.39 (1.25, 1.55)	87.4	0.064	1.00	–
Measured at baseline, self-reported at follow-up wave(s)	4 (4)	1.82 (1.37, 2.40)	–	–	1.31 (0.97, 1.76)	0.078
Self-reported at baseline and follow-up wave(s)	3 (2)	1.65 (1.21, 2.25)	–	–	1.18 (0.85, 1.64)	0.300
Proportion of baseline sample included in final analysis						
< 70%	26 (17)	1.49 (1.32, 1.68)	88.0	0.070	1.00	–
>= 70%	10 (8)	1.39 (1.17, 1.67)	–	–	0.94 (0.76, 1.16)	0.533
Exposure time						
<= 10 years	24 (15)	1.34 (1.20, 1.50)	87.7	0.056	1.00	–
> 10 years	12 (10)	1.70 (1.46, 1.98)	–	–	1.27 (1.05, 1.53)	0.017
Follow-up time[b]						
<= 10 years	19 (11)	1.47 (1.28, 1.68)	88.8	0.072	1.00	–
> 10 years	14 (12)	1.40 (1.19, 1.65)	–	–	0.95 (0.77, 1.18)	0.644

[a]Number of studies sum to more than the total because some studies presented separate results for men and women and/or body weight categories.
[b]Two studies did not report follow-up time.

The funnel plots showed little (if any) evidence of bias from small study effects for all- cause mortality (Figures S2a, b and c, see Supplementary data available at *IJE* online), which was confirmed by Egger's regression asymmetry test (*P*-values = 0.18, 0.93, 0.84 for all-cause, CVD and cancer mortality, respectively). There was evidence of heterogeneity for all-cause, CVD and cancer mortality (all-cause: $I^2 = 87.7\%$, *P*-value < 0.001; CVD: $I^2 = 72.1\%$, *P*-value < 0.001; cancer: $I^2 = 85.0\%$, *P*-value < 0.001, respectively).

Meta-regression analyses were performed to investigate between-study heterogeneity for all-cause and CVD mortality (Tables 4 and 5, respectively) but not for cancer mortality because it included only seven studies. The covariates identified a priori explained little of the heterogeneity observed for all-cause mortality; the τ^2 estimates were similar to that obtained from the model without any covariates ($\tau^2 \sim = 0.067$ from the meta-regression models) (Table 4). For CVD mortality, the proportion of the baseline sample (i.e. greater/less than 70%) included in the final analysis explained some of the variation ($\tau^2 = 0.069$ without and 0.038 with) (Table 5). In the univariable meta-regression analysis, studies that included less than 70% of their baseline sample in their final analysis had higher HRs than studies that included more than 70% of their baseline sample in their analysis (ratio of HRs for >= 70%: 0.70; 0.51, 0.95).

Nonlinear dose-response analysis

Fourteen studies were included in the assessment of a nonlinear dose-response association between weight loss and

Table 5. Results from meta-regression analyses of weight loss compared with a no weight change group and risk of cardiovascular disease mortality

Covariate	**No. of HRs (no. of studies)**[a]	Summary HR	I^2 (%)	**tau**^{2}	Ratio of HRs	*P*-value
Model with no covariates	16 (14)	1.50 (1.25, 1.79)	72.1	0.069	–	–
Sex						
Men and women	4 (4)	1.72 (1.16, 2.55)	73.1	0.073	1.00	–
Men	10 (10)	1.40 (1.11, 1.77)	–	–	0.82 (0.52, 1.29)	0.355
Women	2 (2)	1.64 (0.98, 2.75)	–	–	0.96 (0.50, 1.83)	0.885
Adjusted for physical activity						
No	4 (4)	1.70 (1.20, 2.42)	73.9	0.075	1.00	–
Yes	12 (10)	1.43 (1.16, 1.77)	–	–	0.84 (0.56, 1.27)	0.382
Body size at baseline						
All	16 (14)	1.50 (1.25, 1.79)	–	–	1.00	–
Method used to collect weight/BMI at each wave						
Measured at baseline and follow-up wave(s)	11 (10)	1.40 (1.14, 1.71)	69.5	0.055	1.00	–
Measured at baseline, self-reported at follow-up wave(s)	2 (2)	2.27 (1.40, 3.67)	–	–	1.62 (0.96, 2.74)	0.066
Self-reported at baseline and follow-up wave(s)	3 (2)	1.50 (1.02, 2.19)	–	–	1.07 (0.70, 1.65)	0.727
Proportion of baseline sample included in final analysis						
< 70%	6 (6)	1.90 (1.48, 2.43)	66.5	0.038	1.00	–
>= 70%	10 (8)	1.32 (1.10, 1.58)	–	–	0.70 (0.51, 0.95)	0.024
Exposure time						
<= 10 years	10 (8)	1.37 (1.11, 1.68)	69.0	0.048	1.00	–
> 10 years	6 (6)	1.78 (1.35, 2.36)	–	–	1.31 (0.92, 1.85)	0.122
Follow-up time						
<= 10 years	9 (7)	1.74 (1.42, 2.14)	67.0	0.043	1.00	–
> 10 years	7 (7)	1.25 (1.00, 1.57)	–	–	0.72 (0.53, 0.97)	0.035

[a]Number of studies sum to more than the total because some studies presented separate results for men and women and/or body weight categories.

weight gain and all-cause mortality. We observed nonlinear associations between weight change and all-cause mortality risk (Figure 8); weight loss of 10 kg and weight gain of 20 kg were both associated with approximately 2-fold increased risks of mortality, whereas weight stability was not found to increase the risk of mortality.

Sensitivity analyses

The results did not change when we excluded studies that did not adjust for smoking or when excluding studies;[23] studies that adjusted for possible intermediates on the causal pathway.[16–21] Excluding the first 2 to 6 years of follow-up emphasized the association between weight gain and all-cause mortality (HR = 1.15; 1.00, 1.32)[19,25,26] but did not materially change the association between weight loss and all-cause mortality (HR = 1.41; 1.27, 1.57).[16,19,20,25,26] Two studies presented additional results for the association between intentional weight loss and the risk of all-cause mortality.[20,27] The pooled random-effects estimate from these studies was similar to the estimate from all studies combined (HR = 1.44; 1.03, 2.00).

Waist circumference change

Only three papers[42–44] reported on the association of increased and/or decreased waist circumference and the risk of all-cause mortality. Berentzen *et al.*[43] did not provide sufficient information to pool their estimate with the other two papers. The pooled HR from the studies by Karahalios 2014[42] and Mousavi 2015[44] was elevated for decreased waist circumference but not for increased waist circumference (decreased waist HR = 1.26; 95% CI: 1.06, 1.49, increased waist HR = 0.92; 95% CI: 0.80, 1.07).

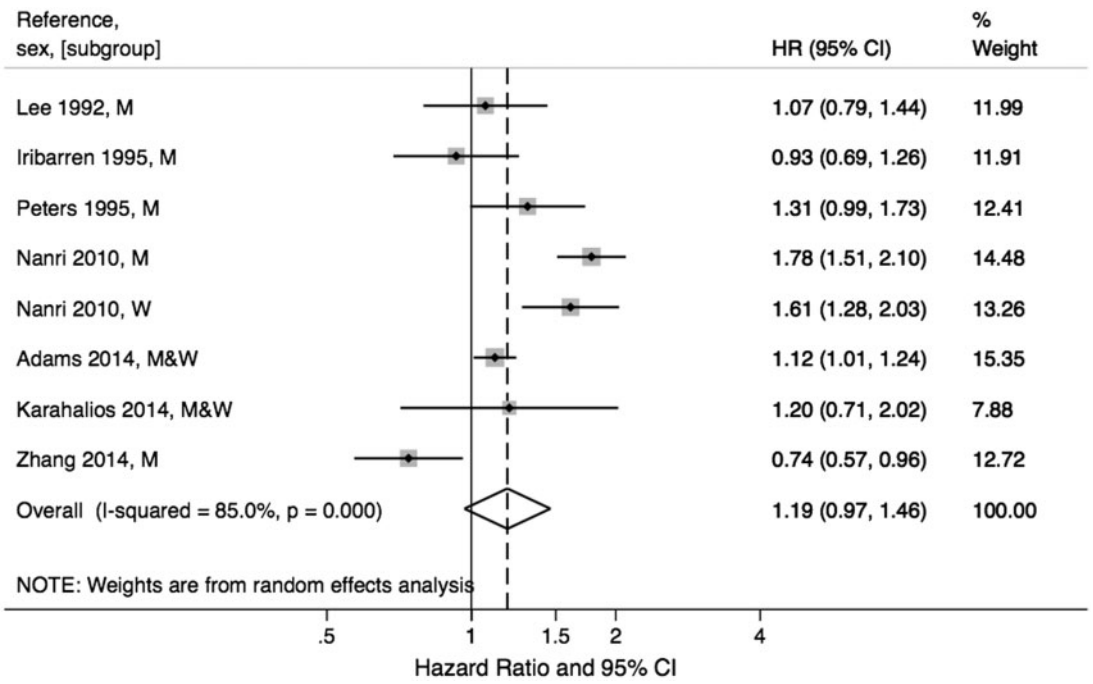

Figure 7. Adjusted hazard ratio for the risk of cancer mortality comparing the largest weight loss group to the reference group for males (M), females (W) and both sexes combined, 1992 to 2015; dashed line, overall estimate; bars, 95% confidence interval (CI).

Because only two studies were available, we did not assess bias due to small-study effects, nor did we perform meta-regression analyses.

Discussion

The findings from this systematic review and meta-analysis of 26 prospective studies of healthy middle-aged adults showed that weight loss and weight gain were associated with an increased risk of all-cause and CVD mortality, with a much stronger association observed for weight loss than for weight gain (HR for loss and all-cause mortality = 1.45, HR for gain and all-cause mortality = 1.07, HR for loss and CVD mortality = 1.50, HR for gain and CVD mortality = 1.21). There were slightly, non-statistically significant, increased risks of cancer mortality associated with weight loss and weight gain (HR for loss = 1.19, HR for gain = 1.04).

These results are broadly consistent with a previous meta-analysis[4] which included studies assessing weight loss from early adulthood (i.e. age 18 or 21) to midlife in addition to weight loss from midlife to older age. Harrington *et al.*[4] found an increased risk of all-cause mortality for intentional and unintentional weight loss for healthy participants (HR = 1.11; 95% CI: 1.00, 1.22 and HR = 1.27; 95% CI: 1.09, 1.47, respectively); the association between weight gain and all-cause mortality was not assessed.

In this review, studies that investigated weight gain or weight loss from early adulthood to middle age were excluded, as the primary focus was weight gain and weight loss from middle age to older age. With age, muscle mass decreases and fat mass increases, with the largest increases in the proportion of visceral and abdominal fat.[3] This change in body composition from midlife to older age suggests that there might be a different mechanism associated with change in body size from early adulthood to midlife, than for change from midlife to older age.[2]

Increases in fat mass with corresponding decreases in muscle mass can lead to sarcopenia in older adults, leading some authors to suggest that weight loss in older age is dangerous.[45] Waist circumference is thought to be a better marker of abdominal or central fat mass than weight.[46] We intended to assess the association between increase and decrease in waist circumference and mortality. However, only two studies presented results for this association. Further research into the associations between gains/losses in fat mass and/or muscle mass, measured by waist circumference, or bioelectrical impedance, and mortality would elucidate these associations.

The method used to ascertain body measurements might lead to bias; self-reported weight data have been shown to vary by sex, age and body size (i.e. lighter participants might overestimate their weight and heavier participants might underestimate their weight), which can lead to upward bias.[47,48] Consistent with other studies of anthropometric measurements, the meta-regression analysis showed that studies using self-reported measures of weight at baseline and at the follow-up wave(s) had higher HRs

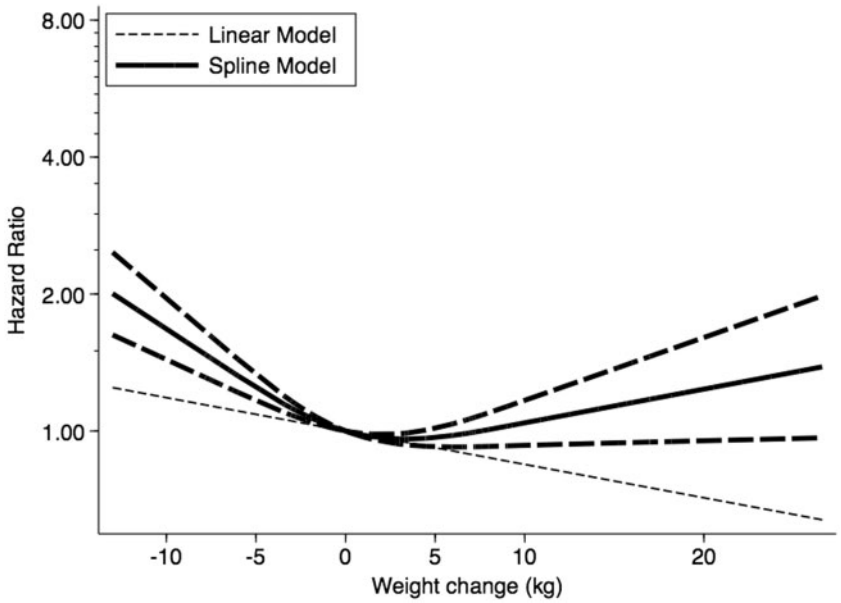

Figure 8. Adjusted hazard ratio of all-cause mortality associated with weight loss and weight gain in a meta-analysis of published studies. The y-axis is on a log scale. Bold line, spline model; long dashed line, upper and lower confidence limits of spline model; short dashed line, linear model.

than studies that measured weight (ratio of HRs = 1.41; 0.97, 2.05 for weight gain and CVD mortality).[49]

In this meta-analysis of weight/BMI change from middle age to older age, we assumed that the height of the participants is changing minimally. Given this, BMI change amounts to a change in weight, and we included both BMI change and weight change in our pooled estimates.

Baseline body weight might modify the association between weight gain/loss and the risk of mortality. None of the studies included participants who were underweight at baseline. As well we, a priori, selected body size at baseline as a covariate in our meta-regression analysis. However, this meta-regression analysis was limited since the majority of studies ($n = 23$) only reported results for normal weight, overweight and obese people combined. Only three studies provided estimates for participants with normal weight and three studies provided estimates for overweight/obese participants. From the meta-regression analysis, studies that presented results for normal weight participants or overweight/obese participants gave similar HRs to studies that presented results for all participants combined (ratio of HRs for normal weight participants compared with all participants: 0.93; 95% CI: 0.76, 1.14 and ratio of HRs for overweight/obese participants compared with all participants: 0.94; 0.77, 1.14 for weight gain and all-cause mortality). Future observational studies should assess whether body size at baseline modifies the association and present the results accordingly.

One of the main criticisms of cohort studies assessing the association between weight loss and mortality is that the participants are not asked about their intention to lose weight. Unintentional weight loss might reflect an underlying disease, resulting in excess mortality, whereas intentional weight loss is assumed to be beneficial, because obesity is associated with increased mortality. In our protocol, we stated that meta-regression analysis by intentionality of weight loss would be conducted. However, the 26 studies that were included in our meta-analysis did not differentiate between intentional and unintentional weight loss in their primary analysis. Two studies[20,27] presented additional estimates by weight loss intention. We pooled the estimates of intentional weight loss from these two studies and found that the pooled estimate was similar to our overall estimate for weight loss and the risk of all-cause mortality. In 2015, Kritchevsky *et al.*[50] published a systematic review and meta-analysis of randomized controlled trials that assessed the effect of intentional weight loss on mortality for obese adults. Pooling the estimates from 12 trials, the authors reported a 15% reduction in all-cause mortality for participants randomized to the weight loss intervention group (RR = 0.85; 95% CI: 0.73, 1.00). Future work that identifies whether weight loss intention modifies the association between weight loss and mortality is necessary to better understand the underlying pathways.

We would expect the associations between weight change and cancer to be different for obesity-related cancers and other cancers. However, it was not possible to explore this further because none of the included studies restricted their analysis to obesity-related cancers nor did

they present separate summary estimates for obesity-related cancers.

To our knowledge, one additional study has been published since 5 September 2015. Klingberg *et al.* 2015[51] examined the association between increased waist circumference over a 6-year period and all-cause and cardiovascular disease mortality using data from the Danish monitoring trends and determinants of cardiovascular disease study and the Swedish Prospective Study of Women in Gothenburg. Up to 5 September 2015, only three studies were published looking at the results of change in waist circumference and the risk of mortality; we pooled the data from two of these studies.[42,44] In line with the pooled estimate for decreased waist circumference (HR = 1.25; 95% CI: 1.06, 1.49), Klingberg *et al.*[51] found an increased, but non-statistically significant, risk of all-cause mortality associated with a decreased waist circumference of more than 0.9 cm (HR = 1.22; 95% CI: 0.93, 1.61). In contrast to the pooled estimate for increased waist circumference (HR = 0.91; 95% CI: 0.80, 1.07), Klingberg *et al.*[51] found a gain in waist circumference of more than 8.1 cm increased the risk of all-cause mortality (HR = 1.72; 95% CI: 1.28, 2.31). Klingberg *et al.*[51] presented results for women only and Mousavi *et al.*[44] focussd on men, whereas Karahalios *et al.*[42] presented results for both sexes combined.

Strengths and limitations

A comprehensive search strategy was used to identify studies for this meta-analysis, resulting in a large number of studies. This made our findings robust to the estimates presented in a single study. Also, a broad search strategy was used to identify studies looking at increased and decreased waist circumference in addition to weight change.

To explore sources of heterogeneity, we used meta-regression with specific pre-specified covariates and sensitivity analyses as recommended.[7] This is preferable to constructing quality scores, which might lack validity, and which might not be associated with study results.[52,53] However, meta-regression is not without its limitations. Meta-regression analysis with few studies is unlikely to be useful and residual heterogeneity is likely. Further, the results of a meta-regression analysis are easier to interpret when there is little within-study variability and large between-study variability.[54]

Our pooled estimates were derived from observational studies and therefore the study-specific estimates might be biased due to residual confounding. All studies controlled for age. The majority of studies ($n = 18$) adjusted for baseline weight or body mass index, whereas only 14 studies adjusted for physical activity. A comparison of studies that adjusted for physical activity with those that did not, found that the results did not materially change; however, other unmeasured factors might still bias the results. To investigate reverse causation, we performed a sensitivity analysis where we pooled the estimates that excluded the first 2 to 6 years of follow-up. Although the association between weight loss and mortality did not materially change, only five studies were available for this analysis.[16,19,20,25,26] We recommend that future studies assess the potential for reverse causation and present a sensitivity analysis where the association excludes the first 5 years of follow-up.

Our review focused on the weight status of participants. However, physical fitness is associated with functional independence, independently of weight status.[55,56] This suggests that physical fitness might be a better indicator of health, and a systematic review with a meta-analysis of the associations between change in fitness levels and mortality in middle-aged adults might be beneficial.

This review has other limitations. To combine the results of the estimated HRs for each category of weight gain or loss, we were limited to the findings presented in each paper. Most studies present change categories corresponding to greater or less than ± 3 to 5 kg. However, some studies present results for changes of greater or less than ± 1 kg, and other studies present results for quintiles or other categories of change. In order to avoid the correlation induced by including multiple subgroups from the same study, we chose the largest category of gain/loss to include in the meta-analyses; this broadly corresponded to changes of more than 3 to 5 kg and allowed us to estimate the associations with large weight gain or loss. Furthermore, the time interval between body size measurements varied greatly from 5 to 29 years across the studies, and therefore for studies with a large time interval (e.g. two studies with interval of 20+ years[30,35]) it is not possible to conjecture if the weight gain/loss occurred in midlife or later life. Exploration, using meta-regression, to assess the influence of exposure time interval on study findings found little evidence of this study covariate modifying the results.

Three outcomes were chosen a priori for this review: all-cause, cancer and CVD mortality. Only seven of the 26 studies presented findings for cancer mortality, making it difficult to interpret the results of the meta-analysis, which could be sensitive to the results of a single study.

Observational studies have the potential to be biased according to at least one of the domains presented in the ROBINS-I tool. The studies included in our analysis were deemed to present a low risk of bias due to measurement of the outcome (i.e. mortality), selection of the reported results and selection of participants into the study. However, bias due to confounding and bias in measurement of the weight change was thought to be at least moderate in all

studies. This is the highest level of evidence possible, given that it is not possible to randomize healthy participants to weight gain or weight loss.

Finally, a pooled analysis of individual participant data from the available cohort studies, such as the one carried out by Cohen *et al*. 2014[57] for body mass index and mortality, would enable a comprehensive analysis of the association between weight change and mortality, and allow for the investigation of potential effect modifiers of this association.

In summary, we found that weight loss and weight gain were associated with an increased risk of all-cause and CVD mortality. These observational data suggest weight stability from middle age; however, further research investigating effect modification by obesity status is warranted. We found only three studies that assessed the association between increase or decrease in waist circumference or fat mass from midlife to older age, and one additional study has since been published. Many large cohort studies were established in the 1990s and have since followed-up their participants to ascertain repeated measures of waist circumference and fat mass; forthcoming accumulated evidence from these studies will further the understanding of how change in lean and fat mass is associated with all-cause and cause-specific mortality.

Supplementary Data

Supplementary data are available at *IJE* online.

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