Systematic Review and Meta-Analysis

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The association between weight fluctuation and all-cause mortality

A systematic review and meta-analysis

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Abstract

Background: Many observational studies have reported an association between weight fluctuation and all-cause mortality. However, the conclusions obtained from these studies have been unclear.

Objective: The current meta-analysis aimed to clarify the association between weight fluctuation and all-cause mortality.

Data source: We electronically searched PubMed, Embase, and Web of Science for articles reporting an association between weight fluctuation and all-cause mortality that were published before April 30, 2018.

Study appraisal and synthesis methods: The methodological quality of each study was appraised using the modified Newcastle Ottawa Quality Assessment Scale. The hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were extracted from the included studies and pooled using random-effect models. Meta-regression approaches were also performed to explore sources of between-study heterogeneity.

Results: A total of 15 studies were eligible for the current meta-analysis. The pooled overall HR for all-cause mortality in the group with the greatest weight fluctuations compared with the most stable weight category was 1.45 (95% CI: 1.29–1.63). Considerable between-study heterogeneity was observed, some of which was partially explained by the different follow-up durations used by the included studies. Moreover, publication bias that inflated the risk of all-cause mortality was detected using Egger's test ($P = .001$).

Conclusion: Weight fluctuation might be associated with an increased risk of all-cause mortality.

Abbreviations: BMI = body mass index, CI = confidence interval, CV = coefficient of variation, HR = hazard ratio, RMSE = root-mean-square-error, SE = standard error.

Keywords: meta-analysis, mortality, obesity

1. Introduction

Overweight and obesity are associated with high risks of many adverse health outcomes.[1–3] Although weight reduction has been suggested as a critical intervention to reduce the detrimental effects of overweight and obesity on health, it is often followed by repeated episodes of subsequent regain of the lost weight. This weight change pattern, which is referred to as weight fluctuation or weight cycling, is often hypothesized to be an indicator of

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declining health. Although many previous studies explored the epidemiological association between weight fluctuation and all-cause mortality, the results from those studies failed to provide a consistent conclusion of whether weight fluctuation was an independent risk factor for all-cause mortality. For example, the Cardiovascular Health Study reported a 2.2-fold higher risk of all-cause mortality in subjects exhibiting fluctuations in body weight.[4] However, several studies only showed very weak or non-significant associations between weight fluctuation and all-cause mortality.[5–7]

Therefore, the present study focused on the studies that examined the association between body weight fluctuations and the risk of all-cause mortality in healthy adults to quantify the association using a meta-analysis and to explore between-study heterogeneity using a meta-regression analysis. If the risk of death increases with greater weight fluctuation, more effort should be devoted to the intervention of weight maintenance after weight loss.

2. Methods

2.1. Study selection

We searched PubMed, EMBASE and the Web of Science to identify prospective studies published before April 30, 2018 that assessed the association between weight instability and all-cause mortality (a detailed list of keywords is provided in Supplemental Digital Content table S1, http://links.lww.com/MD/D288). We did not include any unpublished studies or abstracts for which the full text was not available. This meta-analysis was designed, conducted and reported in adherence to the standards of quality of reporting meta-analyses.[8]

The inclusion criterion for this meta-analysis were:

1. prospective studies;
2. participants were adults who were considered basically healthy;
3. studies that reported hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) based on categorical variables for weight fluctuation, and corresponding standard errors (SEs) could be estimated;
4. outcomes of interest were all-cause mortality; and
5. studies written in English.

2.2. Data extraction

Two authors (Y.Z. and G.S.) independently extracted the following information related to the study characteristics: the first author's name and year of publication; name of the study and the location (country) where the study was conducted; participants' sex and age range at baseline; sample size at baseline, definition of the fluctuated group and reference group; method for collecting weight data (measured or self-reported); duration of weight change measurements; number of years of follow-up to ascertain all-cause death; person-years and number of deaths; HRs and corresponding 95% CIs; proportion of baseline sample included in the analysis; analytical method used to estimate HRs and corresponding 95% CIs; study design and covariates for which the HR was adjusted. Inconsistencies were discussed until an agreement was achieved.

HRs and corresponding 95% CIs of all-cause mortality were extracted for all subgroups provided by the authors (e.g., men and women). If several HRs from many models were presented, the HRs from the most completely adjusted models were extracted. We chose HRs from the model that did not adjust for the covariates that might be potential intermediaries on the causal pathway (i.e., blood pressure, diabetes or cancer) if the author presented them separately.

2.3. Study quality assessment

The methodological quality of each study was appraised using the modified Newcastle Ottawa Quality Assessment Scale (section for cohort-type studies).[9] Briefly, the scale consists of three parts (Selection, Comparability, and Outcome) and includes eight questions. The score for a study ranged from 1 to 9 points, with a higher score indicating a relatively higher methodological quality.

2.4. Statistical analysis

The HRs for the largest category of weight fluctuation compared with the reference group in individual studies were pooled using the inverse variance method to estimate the risk of all-cause death related to weight instability. The result from a random-effects model was chosen if between-study heterogeneity (assessed by I^2) was significant. Otherwise, the result of a fixed-effects model was chosen. To explore potential sources of heterogeneity, stratified analyses were conducted according to the pre-specified study characteristics. In addition, meta-regression models were also fitted to estimate the correlations between the log-transformed HRs and the pre-specified variables.

Two studies[10,11] calculated long-term weight fluctuations using weight data, including recalled weights during early adulthood. One study[7] used the reported number of weight cycles during the participant's lifetime to be the indicator of weight fluctuation. The participants in two studies[6,12] were not recruited from the average population (one study was conducted among nurses, and another study included participants with a high risk of coronary heart disease who were referred for an intervention trial). Separate sensitivity analyses were performed by excluding the studies mentioned above.

Begg's rank correlation test and Egger's regression asymmetry test were performed to assess publication bias due to small study effects, the, and a funnel plot of the study size versus standard error was inspected visually as well. The pooled HR was adjusted for publication bias using the trim-fill method if publication bias was detected. All analyses were performed using Stata version 15.1 software (StataCorp, College Station, TX).

2.5. Ethics

Ethical committee or medical institutional board approval was not necessary for the present study because all of the data used in this manuscript was collected from the available publications. No clinical research was conducted in the present work.

3. Results

3.1. Study selection

Of the 3440 articles identified from the literature search, 3392 were excluded based on the titles and abstracts, leaving 48 articles for further review. Of these publications, 33 articles were excluded based on our inclusion criteria, and thus 15 articles were

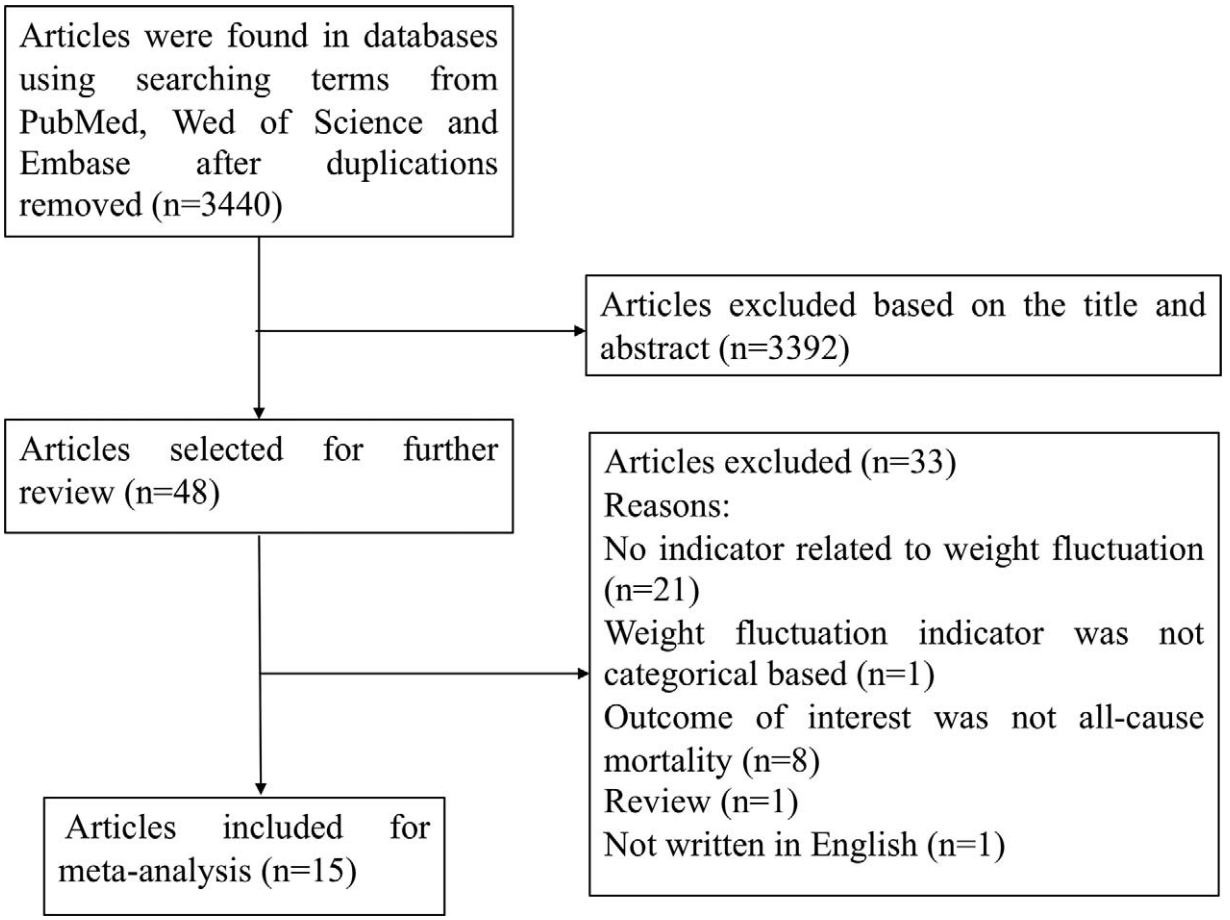

Figure 1. Flow charts of literature searching for eligible studies.

selected for the meta-analysis. The article selection procedure is shown in Figure 1.

3.2. Study characteristics

Table 1 summarizes the characteristics of the 15 articles included in the meta-analysis. All studies employed a cohort design, with 11 studies conducted in the USA[4,6,7,10–17] and one study conducted in Australia,[18] South Korea,[5] Germany,[19] and the UK[20] each. Eight studies included participants of both sexes[4,5,7,11,13,14,16,18] (four did not report sex-specific results), whereas four[12,15,19,20] and three[6,10,17] studies only recruited men or women, respectively. Nine studies[4,5,12,14–19] measured weights at baseline and at each follow-up visit, and the remaining six studies[6,7,10,11,13,20] included self-reported information (weights or the number of weight cycles). The follow-up duration for identifying all-cause mortality ranged from 3.8 years to 32 years (median 10.7 years).

The indicators of weight stability and the definition of the most fluctuated and corresponding reference categories in the included studies are presented in Table 2. Eight studies[4–7,15–17,20] used episodes such as weight cycling or weight regain experiences as the indicator of weight instability, while the other seven studies[10–14,18,19] employed a fluctuation indicator, such as the root-mean-square-error (RMSE) or coefficient of variation (CV), which evaluated the statistical significance of fluctuations in the collected weight data.

3.3. Quality assessment

The results of the quality assessment of the included studies are shown in Supplemental Digital Content table S2, http://links.lww.com/MD/D288. The scores awarded to the studies ranged from 5 to 9 points, with a mean of 7.07 points (standard deviation of 1.22 points), according to the modified Newcastle Ottawa Quality Assessment Scale. Regarding selection bias, the majority of the studies[4,5,7,10,11,13–20] (n = 13) recruited participants from an average population, while the remaining studies[6,12] (n = 2) recruited participants from specified populations. For the domain of comparability, we pre-determined that the initial weight or body mass index (BMI) was the "critically important" confounding factor and physical activity was determined as the "important" confounding factor. However, four studies[14,17–19] did not adjust for any of the pre-determined factors.

3.4. The overall risk of all-cause death in relation to weight stability

The 15 included studies provided data from 623,973 participants with 48,760 deaths from all-cause for this meta-analysis to estimate the risk of all-cause mortality by comparing the group displaying the greatest fluctuations to a reference group. The multivariable-adjusted HRs for each study and all studies combined are presented in Figure 2. The overall HR for all-cause mortality in the group displaying the greatest fluctuations

Table 1

Characteristics of the 15 studies included in a meta-analysis of weight fluctuation and all-cause mortality.

Author, published year	Study, location	Sex	Age range	Method for collecting weight data, duration of weight change measurement	Follow-up duration	Proportion of baseline sample included in the analysis	Analysis	Study design, confounders
Arnold, 2010[4]	Cardiovascular Health Study, USA	Both	65 and older	Measured weights, 7 years	7 years	<60%	Cox proportional Hazard Model	Cohort study Age, sex, height, race, high school education, starting weight
Blair, 1993[12]	Multiple Risk Factor Intervention Trial, USA	Men	35–57 years old	Measured weights, 6–7 years	3.8 years	>60%	Cox proportional Hazard Model	Cohort study Age, race, intervention group, baseline value of diastolic blood pressure, diuretic use, serum cholesterol, body mass index, number of cigarettes smoked per day, reported number of alcoholic drinks consumed per week, and initial level of physical activity compared with the peer group
Cho, 2017[5]	National Health Screening Cohort, South Korea	Both	40–79 years old	Measured weights, 9.3 years (mean)	10.7 years	>60%	Cox proportional Hazard Model	Cohort Study Age, sex, baseline systolic blood pressure, diastolic blood pressure, serum glucose, total cholesterol, smoking status, alcohol consumption, hypertension, diabetes mellitus, mean BMI
Diaz, 2005[13]	The National Health and Nutrition Examination Survey I (NHANES I), NHANES I Epidemiologic Follow-up Study USA	Both	25-74 years old	Measured initial weight and self-reported follow-up weights, 16 years (maximum)	5 years	Unclear	Cox proportional Hazard Model	Cohort Study Age, gender, race, smoking status, initial BMI, Charlson Comorbidity Index score
Field, 2009[6]	Nurses' Health Study USA	Women	30–55 years old	Measured initial weight and self-reported follow-up weights, 20 years	12 years	<60%	Cox proportional Hazard Model	Cohort Study Age, initial BMI, weight change from age 18 years to start of the cycling period, smoking status, menopausal status, postmenopausal hormone therapy, alcohol, activity level, change in activity level, net weight change from the start of the cycling period until 1992, net weight change from the start of the cycling period until 2004 or the end of the follow-up
Folsom, 1996[10]	The Iowa Women's Health Study Cohort USA	Women	55–69 years old	Self-reported weights, weight fluctuation since 18 years old (37–51 years)	6 years	>60%	Cox proportional Hazard Model	Cohort Study Age, waist-to-hip ratio, BMI, BMI^2, smoking status, pack years of cigarettes, education, physical activity, alcohol, marital status and hormone replacement
Hanson, 1996[14]	The Gila River Indian cohort USA	Both	20 and older	Measured weights, 6 years	20 years	Unclear	Cox proportional Hazard Model	Cohort Study Age and sex
Iribarren, 1995[15]	The Honolulu Heart Program USA	Men	45–68 years old	Measured weights, 9 years (maximum)	14.5 years	>60%	Cox proportional Hazard Model	Cohort Study Age, average weight, slope of weight, smoking status, number of cigarettes smoked per day, baseline alcohol consumption, level of physical activity, total caloric intake, job and pre-existing disease

(*continued*)

Table 1

(continued).

Author, published year	Study, location	Sex	Age range	Method for collecting weight data, duration of weight change measurement	Follow-up duration	Proportion of baseline sample included in the analysis	Analysis	Study design, confounders
Lissner, 1991[11]	The Framingham Heart Study USA	Both	30–62 years old	Self-reported initial weight and measured follow up weights Weight fluctuation since 25 years old	32 years	>60%	Cox proportional Hazard Model	Cohort Study Age, level of BMI, slope of BMI
Murphy, 2014[16]	The Health, Aging, and Body Composition Study (the Health ABC study) USA	Both	70–79 years old	Measured weights, 5 years	6.62 years	>60%	Cox proportional Hazard Model	Cohort Study Age, race, education, study site, BMI, smoking status, physical activity, depressive symptoms, cancer, diabetes, hip fracture, hypertension, myocardial infraction, stroke and the Health ABC short physical performance battery score, incidence of hospitalization and days of hospitalization, year 6 lean mass, year 6 fat mass, % change lean mass (year 1 thru year 6), % change fat mass (year 1 thru year 6)
Nguyen, 2007[18]	The Dubbo Osteoporosis Epidemiology Study Australia	Both	60 and older	Measured weights, 8 years (median)	13 years	<60%	Cox proportional Hazard Model	Cohort Study Baseline bone mineral density, rate of bone loss, rate of weight loss, age, smoking status, and concomitant diseases
Rzehak, 2007[19]	The Erfort Male Cohort Study German	Men	55–74 years old	Measured weights, 15 years	15 years	<60%	Cox proportional Hazard Model	Cohort Study Age, pre-existing disease (ischemic heart disease, myocardial infraction, stoke, diabetes, hypertension), smoking and socio-economic status
Stevens, 2012[7]	The Cancer Prevention Study II Nutrition Cohort USA	Both	50–74 years old	Self-reported number of weight cycling, Life-long exposure	16 years	>60%	Cox proportional Hazard Model	Cohort Study Alcohol consumption, race, smoking status, educational level, physical activity level, BMI at baseline, weight change from 18 years of age to baseline, history of diabetes, and total energy
Reynolds, 1999[17]	Baltimore women's cohort USA	Women	65–99 years old	Measured weights, 3 years	6 years	>60%	Cox proportional Hazard Model	Cohort Study Age, education, smoking status, alcohol user, pre-existing illness (cancer, heart troubles, stroke, diabetes)
Wannamethee, 2002[20]	The British Regional Heart Study UK	Men	40–59 years old	Self-reported weights, 12–14 years	8 years	>60%	Cox proportional Hazard Model	Cohort Study Age, social class, smoking status, physical activity, initial BMI.

Table 2

Indicator of weight fluctuation and weight categories applied in the included articles.

Author, year	Indicator	Category	
		Reference	Most fluctuated
Arnold, 2010[4]	Episode*	<5% body weight change from the prior year and from baseline	Undergoing both 5% body weight gain and loss
Blair, 1993[12]	Fluctuation (ISD)	Lowest quartile of ISD	Highest quartile of ISD
Cho, 2017[5]	Episode	<4% change in BMI from baseline to midpoint to last health checkup	BMI loss from baseline to midpoint follow-up, followed by BMI gain from midpoint follow-up to last visit, or BMI gain from baseline to midpoint follow-up, followed by BMI loss from midpoint follow-up to last visit
Diaz, 2005[13]	Fluctuation	No obese individuals with initial and final BMI differing by <3.0 BMI units and the sum of deviations less than the average level	Individuals with initial and final BMI differing by ≥3.0 BMI units and the sum of deviations higher than the average level
Field, 2009[6]	Episode	Women who reported intentionally losing <4.5 kg for <3 times.	Women who reported intentionally losing at least 9.1 kg for 3 or more times
Folsom, 1996[10]	Episode	Gained ≥10% of their body weight during one interval and lost ≥10% during another age interval (regardless of order).	Weight at baseline differed by <5% from reported weight at age 18, and weight change during any interval <5%
Hanson, 1996[14]	Fluctuation (RMSE)	Individuals with RMSE value above the median (3.2 kg)	Individuals with RMSE value below the median (3.2 kg)
Iribarren, 1995[15]	Fluctuation (RMSE)	Lowest quintile of RMSE	Highest quintile of RMSE
Lissner, 1991[11]	Fluctuation (CV)	Lowest tertiles of CV	Highest tertiles of CV
Murphy, 2014[16]	Episode	<5% change of the body weight from year to year of from year 1 to year 6	Gain and loss by at least 5% of the body weight from year to year of from year 1 to year 6
Nguyen, 2007[18]	Fluctuation (CV)	Individuals with CV values of body weight measurements lower than 3%	Individuals with CV of body weight measurements values higher than 3%
Rzehak, 2007[19]	Fluctuation (AD)	Individuals with 1. BMI < 30 kg/m^2 2. the initial and final BMI differed by <3 kg/m^2 3. the sum of the absolute deviations < 3.49 BMI-unit	Individuals with the initial and final BMI < 3 kg/m^2 and the sum of absolute deviations >3.49 BMI-units.
Stevens, 2012[7]	Episode	Self-reported had not experienced weight cycling	Self-reported had experienced 20 times or more weight cyclers
Reynolds, 1999[17]	Episode	<4.5% change in BMI between any observation intervals	More than 4.5% change (gain or loss) in BMI between the first and second interview, and more than 4.5% change in BMI in the opposite direction (loss or gain) between the second and the third interviews
Wannamethee, 2002[20]	Episode	<4% change in body weight between any observation intervals	Weight loss (gain) between the first observation interval followed by weight gain (loss) between the second observation interval

AD = absolute deviation, CV = coefficient of variation, ISD = intrapersonal standard deviation, RMSE = root-mean-square-error.
* Experience of weight regain or weight cycling.

compared with the group with the most stable weight was 1.45 (95% CI: 1.29–1.63). Evidence of between-study heterogeneity was observed ($I^2 = 84.9\%$, $P < .001$).

3.5. Stratified and sensitivity analyses

Table 3 shows the results for all-cause mortality risk in groups stratified by several selected study characteristics. The results of meta-regression analyses are also presented to show the possible cause of between-study heterogeneity. The results from stratified analyses did not modify the relation between weight instability and all-cause mortality. In all the subgroup meta-analyses, significantly greater combined overall HRs for all-cause mortality were observed in the group displaying the greatest fluctuations compared with the most stable group. In the meta-regression models, most of the tau^2 estimates including covariates were very close to the tau^2 value obtained from the model without any covariates ($\tau^2 = 0.05$). However, the follow-up duration of the studies (i.e., less/greater than 10 years) explained 40% of the observed heterogeneity ($\tau^2 = 0.03$ for the model including the follow-up duration). The combined HR of the studies with < 10 years of follow-up was higher than studies with more than 10 years of follow-up (HR: 1.79, 95% CI: 1.63–1.97 VS HR: 1.24, 95% CI: 1.11–1.40, $P < .001$).

The results did not change when we conducted sensitivity analyses. The exclusion of the two studies[10,11] that calculated long-term weight fluctuations beginning in early adulthood produced very similar results (HR: 1.42, 95% CI: 1.26–1.61) to the combined results from all studies. The exclusion of the study[7] that used the reported number of weight cycles as the indicator of weight fluctuation slightly overestimated the association between weight fluctuation and all-cause mortality (HR: 1.54, 95% CI: 1.35–1.75). The result obtained after excluding the two studies that recruited participants from

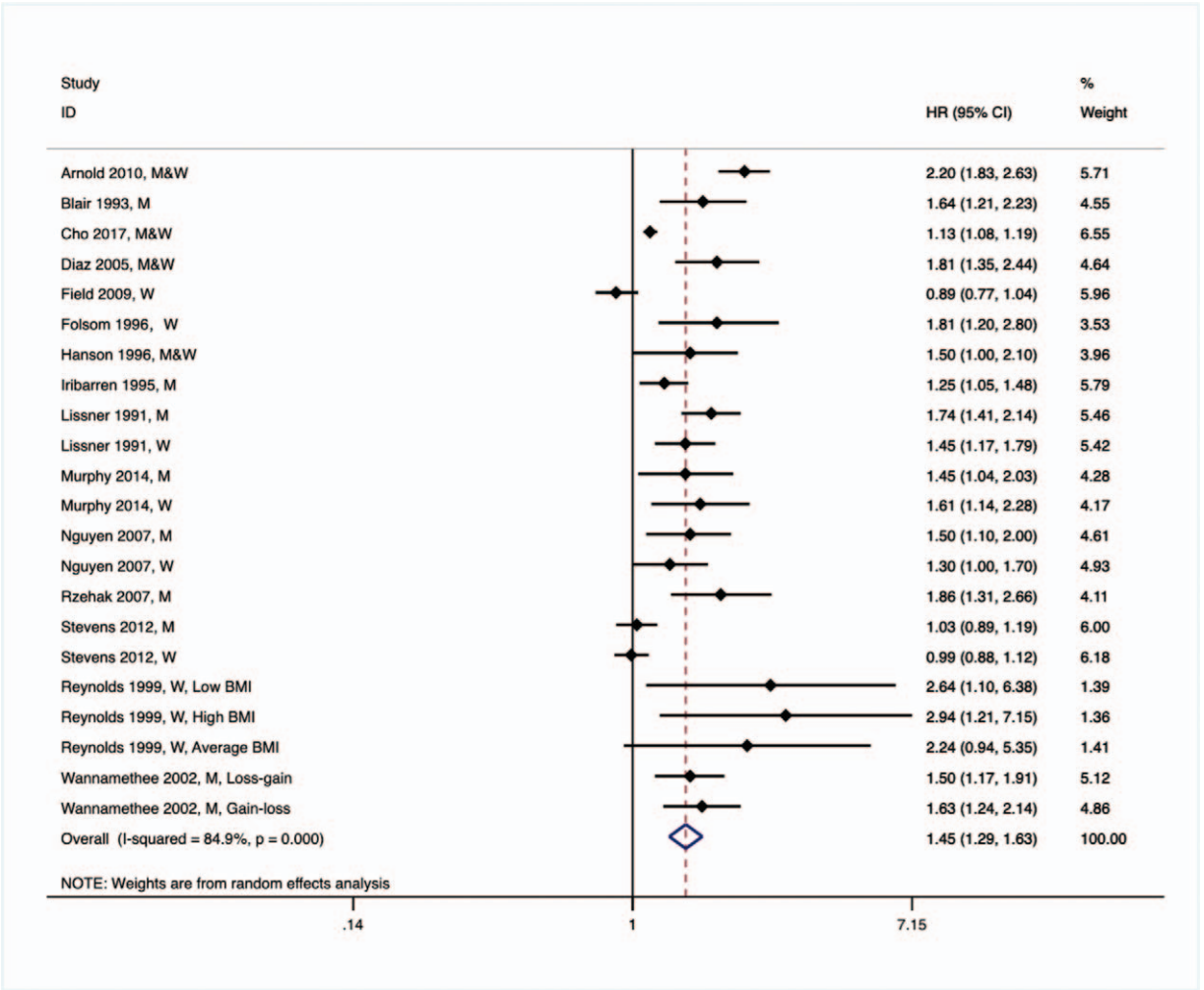

Figure 2. Forest plot of adjusted HR for the risk of all-cause mortality comparing the most fluctuated weight group to the reference group for males (M), females (W) and both sexes combined; Dashed line, overall estimation; bars, 95% confidence interval (CI).

specified populations[6,12] was also similar to the combined result from all studies (HR: 1.49, 95% CI: 1.32–1.68).

3.6. Publication bias

Egger's test ($P = .001$), but not by Begg's test ($P = .071$), indicated publication bias due to small study effects. Figure 3 shows the filled funnel plot of the ln HR for all-cause mortality for the group displaying the greatest weight fluctuations compared with the reference group versus the standard error of the ln HR. The all-cause mortality risk was decreased after an analysis using the trim-fill method (HR: 1.17, 95% CI: 1.04–1.32), indicating that the combined HR for all-cause mortality would be attenuated if some hypothetical studies (indicated by squares in Fig. 3) existed and were published.

4. Discussion

The findings from this meta-analysis of 15 prospective cohort studies showed that weight fluctuation was associated with an increased risk of all-cause mortality. The included studies were conducted using male and female participants in early and older adult stages and included normal weight, overweight and obese individuals. Thus, the findings of this study strongly supported the current clinical recommendation that everyone, despite their sex, age, and weight status, should monitor their body weight frequently to minimize its fluctuation.

One of the possible explanations for this finding is that weight fluctuation has been reported to be linked to several indicators of worse cardio-metabolic function that are associated with an elevated risk of all-cause mortality. For example, weight fluctuation is associated with an increased fasting insulin concentration[21] and C-creative protein level,[22] as well as a lower HDL-C level.[23] Additionally, weight fluctuation might be related to immunocompetence,[24] as shown in a study reporting that weight loss might reduce natural killer cell-mediated cytotoxicity, which might be enhanced by weight fluctuation.[25]

The stratified results from the present study provided limited evidence for the source of between-study heterogeneity. The pooled HR for the studies with < 10 years of follow-up was higher than studies with > 10 years of follow-up. One of the possible explanations was that a longer follow-up duration might underestimate the actual strength of a variable as a predictor of mortality if the variable changes frequently over time (e.g., weight

Table 3

Stratified and meta-regression result from the analyses of the most fluctuated weight category compared with the reference group for the all-cause mortality risk.

Covariates	No. of HRs (studies)	Summarized HR (95% CI)	*Q*-statistics	I^2 (%)	Meta-regression	
					Tau^2	*P*-Value
Models with no covariates	22 (15)	1.45 (1.29–1.63)	139.0	84.9	–	–
Sex[*]						
Men and women	4 (4)	1.61 (1.07–2.41)	57.6	94.8	0.05	–
Men	9 (8)	1.46 (1.26–1.70)	27.7	71.1		.619
Women	9 (7)	1.38 (1.12–1.72)	39.6	79.8		.355
Age group						
Mean age < 60 years	11 (9)	1.42 (1.23–1.64)	63.2	84.2	0.06	–
Mean age ≥ 60 years	11 (6)	1.54 (1.22–1.93)	73.7	86.4		.708
Baseline weights or BMI adjusted						
Yes	15 (11)	1.40 (1.23–1.59)	120.4	88.4	0.05	–
No	7 (4)	1.56 (1.34–1.81)	6.87	12.6		.205
Physical activity level adjusted						
Yes	12 (8)	1.34 (1.16–1.56)	64.3	82.9	0.05	–
No	10 (7)	1.69 (1.33–2.16)	74.3	87.9		.088
Weight data collect method						
Measured only	13 (9)	1.58 (1.32–1.88)	74.6	83.9	0.05	–
Self-reported data included	9 (6)	1.35 (1.12–1.62)	62.9	87.3		.184
Weight stability indicator						
Episode	13 (8)	1.40 (1.19–1.65)	99.5	87.9	0.05	–
Fluctuation	9 (7)	1.51 (1.37–1.67)	10.8	25.7		.417
Duration of assessing weight fluctuation						
<10 years	12 (8)	1.22 (1.17–1.28)	69.2	84.1	0.05	–
≥10 years	10 (7)	1.38 (1.15–1.66)	69.3	87.0		.333
Follow-up duration						
<10 years	11 (7)	1.79 (1.63–1.97)	11.8	15.5	0.03	–
≥10 years	11 (8)	1.24 (1.11–1.40)	53.1	81.2		<.001

[*] Total number of the studies was more than 15 because some studies provided data of both men and women.

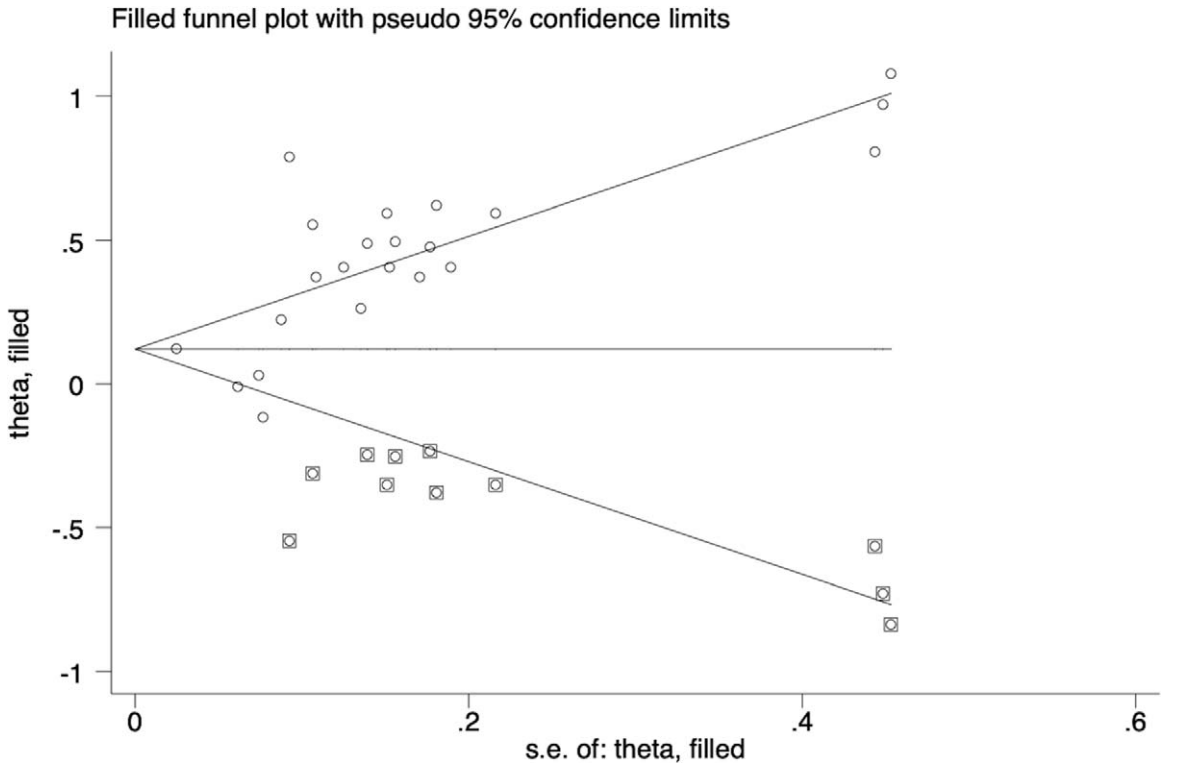

Figure 3. Filled funnel plot of ln HR of all-cause mortality for the most fluctuated weight group compared with the reference group in relation to the standard error against the ln HR.

fluctuation),[26] and thus a lower mortality risk was observed for studies with longer follow-up times. Another explanation for heterogeneity caused by the follow-up period might be reverse causation bias due to latent diseases, which might lead to premature death and weight fluctuation.

Possible biases might exist in the present meta-analysis. First, publication bias that overestimated the all-cause mortality risk in relation to weight fluctuation was suggested. Although the adjusted result obtained from the trim-fill method did not change the significance of the association between weight fluctuation and the all-cause mortality risk, the impact of the unpublished studies that might show non-significant associations was not able to be appropriately estimated. Second, the study-specific results from which our pooled HR was derived might be biased due to residual confounding. All of the included studies did not adjust for pre-determined important covariates, such as baseline weight or BMI and physical activity level. For example, the majority of studies (n=11) adjusted for baseline weight or BMI, but the other four studies did not. Although the results obtained from the meta-regression approach provided little evidence that those covariates modified the pooled results, other factors might exist that still biased the results. Third, the data collection methods were heterogeneous among studies. Therefore, bias due to the measurement of weight fluctuation was thought to be high in several studies. Although neither the results stratified by different data collection methods nor the results obtained from the sensitivity analysis showed evidence of heterogeneity, potential errors might exist in weight fluctuation evaluations.

The present study has several limitations. First, we did not consider the participants' intention to lose weight because this information was not provided by most of the studies. The risk of all-cause mortality might be overestimated if the weight fluctuation was attributed to unintentional weight loss, which might reflect underlying diseases such as cancer. Oppositely, intentional weight loss might be beneficial due to the more frequent implementation of body weight management strategies, thus lowering the risk of all-cause mortality. Second, we were not able to estimate the all-cause mortality risk for the corresponding magnitude of weight fluctuations because the definitions of weight fluctuation were heterogeneous among the included studies. However, we extracted the group displaying the greatest fluctuations from each study, allowing us to evaluate the effect of a large weight fluctuation. Third, as the included studies had a very wide range of exposure durations (ranging from 5 years to life-long), we were unable to differentiate the weight fluctuations from early adulthood to middle-age and middle-age to older age. Since the body composition changes with age (e.g., muscle mass decreases and fat mass increases with aging), the strength and the mechanisms underlying the association of weight fluctuations in early adulthood and later adulthood and all-cause mortality might differ.[27]

In summary, we concluded that weight fluctuation was associated with an elevated risk of all-cause mortality. Interventions aiming to minimize weight fluctuations (e.g., frequent monitoring of body weight) might be beneficial to reduce the risk of all-cause mortality in healthy adults. Future studies should consider utilizing a more standardized definition and indicator of weight fluctuation to enhance the comparability across studies.

Author contributions

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