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SYSTEMATIC REVIEW

The association of weight change and all-cause mortality in older adults: a systematic review and meta-analysis

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Abstract

Objective: there may be age-related differences in the impact of weight change on health. This study systematically reviewed the evidence on the relationship between weight change and all-cause mortality in adults aged 65 years and older.
Methods: MEDLINE, EMBASE and CINAHL were searched from inception to 11 June 2020, PROSPERO CRD 42019142268. We included observational studies reporting on the association between weight change and all-cause mortality in older community-dwelling adults. A random-effects meta-analysis was performed to calculate pooled hazard ratios and scored based on the Agency for Healthcare Research and Quality guidelines.
Results: a total of 30 studies, including 1,219,279 participants with 69,255 deaths, demonstrated that weight loss was associated with a 59% increase in mortality risk (hazard ratio (HR): 1.59; 95% confidence interval (CI): 1.45–1.74; $P < 0.001$). Twenty-seven studies that reported outcomes for weight gain (1,210,116 participants with 65,481 deaths) indicated that weight gain was associated with a 10% increase in all-cause mortality (HR: 1.10; 95%CI: 1.02, 1.17; $P = 0.01$). Four studies investigated weight fluctuation (2,283 events among 6,901 participants), which was associated with a 63% increased mortality risk (HR: 1.66; 95%CI: 1.28, 2.15). No evidence of publication bias was observed (all $P > 0.05$).
Conclusion: for community-dwelling older adults, weight changes (weight loss, gain or weight fluctuation) are associated with an increased risk of all-cause mortality risk relative to stable weight. Further research is needed to determine whether these associations vary depending upon initial weight, and whether or not the weight loss/gain was intentional.

Keywords: meta-analysis, weight change, body mass index (BMI), all-cause mortality, older people, systematic review

Key Points

- Weight loss and weight fluctuation are associated with increased risk of all-cause mortality in older adults
- Weak associations were found for weight gain and the risk of all-cause mortality.
- There is a lack of evidence of the association between initial weight, weight change and mortality in older people.

Introduction

Understanding the relationship between weight and mortality in older age is important, given the rising global prevalence of overweight and obesity [1] and population ageing [2]. The association between weight change and health outcomes in older adults may differ compared to younger adults, due to decreases in muscle mass and increases in fat mass in later life [3]. Inconsistencies in the relationship between weight change and mortality risk in later life may also arise from varying definitions of weight-related exposure variables and variability in age or residential status [4, 5]. One study found that weight change was associated with a decreased risk in all-cause mortality in community-dwelling participants aged ≥65 years [6], while another found no association between weight change and all-cause mortality in women aged 50–66 years [7].

A previous meta-analysis of 17 prospective studies examining weight change and all-cause mortality in adults aged ≥60 years included studies published between 1994 and 2014 [8], finding that weight change was associated with elevated mortality risk. A number of studies investigating the associations between weight change and mortality have been published since 2014, against global increasing trends in body mass index (BMI) [9], highlighting the need for an updated analysis.

The aim of this review was to determine the association between weight change (weight loss, weight gain and weight fluctuation, measured by weight or BMI) and all-cause mortality in community-dwelling adults aged ≥65 years, a common definition for older adulthood in high-income countries. We aimed to quantify this association using meta-analysis and determine the extent to which the association is modified in population subgroups.

Methods

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Registration no. CRD 42019142268) and guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search strategy

A literature search was devised with a trained librarian and carried out in MEDLINE, Embase and CINAHL from the date of inception to 11 June 2020 (Supplementary Appendix A, Search strategies). A manual search of references and forward citations of relevant systematic reviews and articles also carried out.

Selection of studies

Identified articles were imported into Covidence software (www.covidence.org) and duplicates removed. Two reviewers (T.A.A. and S.P.) independently undertook the title/abstract screen and then reviewed eligible full-text articles. Disagreement between the two reviewers was resolved by discussion with a third reviewer (A.J.O.).

Eligibility criteria

Inclusion criteria were (i) observational cohort studies, prospective or retrospective, in community-dwelling adults aged 65 years and above; (ii) published in English language; (iii) reported results of weight change (measured by kg, BMI or percentage weight change); (iv) outcome of interest was all-cause mortality and (v) sufficient information reported to obtain relative risk (risk ratio, hazard ratio or odds ratio) for all-cause mortality and associated 95% confidence interval (CI) for weight changes relative to a comparable reference group with minimal/no weight change. If findings were not provided separately for those aged ≥65 years or further clarification needed, study authors were contacted. Studies were excluded if they included (i) a population <65 years old and results for those aged ≥65 years were not available; (ii) study designs other than cohort studies; (iii) drug treatment studies; (iv) studies of patient groups, e.g. HIV, cancer or post-surgery patients and (v) editorial letters, commentaries, systematic reviews and meta-analyses.

Data extraction and quality assessment

The first reviewer (T.A.A.) independently extracted the data, and the second reviewer (S.P.) verified the accuracy and completeness of the extracted data. The extracted data included information on sampled population, weight change measurement, the finding of interest and covariates. Several study authors were contacted to clarify study details and request results for those aged ≥65 years separately. Study quality was assessed independently by two reviewers (T.A.A. and S.P.) using the Newcastle-Ottawa Scale (NOS) scored based on the Agency for Healthcare Research and Quality guidelines [10, 11]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to evaluate the quality of evidence, where we assessed risk of bias, consistency of results (based on heterogeneity), directness (applicability of population differences), precision (summary estimate CIs) and publication bias (funnel plots) [12].

Data analysis

Meta-analysis was performed using a random-effects model of pooled HRs or relative risk (RR) and 95% CIs of all-cause mortality and weight change [13]. Separate analyses were performed for studies that measured weight/BMI loss, weight/BMI gain or weight/BMI fluctuation (loss and regain of weight within a specific period) compared with a reference category. Where studies investigated more than one subgroup of weight/BMI loss/gain, the largest weight/BMI change groups were used, and the most fully adjusted analysis used for meta-analysis, an approach used previously [14]. Heterogeneity across studies was assessed using the

I^2 statistic [15] and P values <0.05 considered statistically significant. Subgroup analyses were identified *a priori* (age, gender, length of follow-up, study quality) or following data extraction (physical activity adjustment, study origin and weight change methodology) and performed to determine whether associations differed by participant characteristics or study design. Publication bias was assessed using funnel plots, Egger's test and Begg's test [16, 17]. Sensitivity analysis was conducted by removing one study at a time to determine the impact this had upon pooled results and by combining similar weight change categories (5% weight change). All statistical analyses were performed using Comprehensive Meta-Analysis software (version 3; Biostat Inc., Englewood, NJ).

Results

Search results

The database search identified 6,593 articles, while 3 additional articles were located via manual searching of references and citations (Supplementary Appendix 1, PRISMA). After full-text screen of 211 articles, 35 studies met inclusion criteria and were included for data extraction.

Study characteristics

In total, the included studies involved 1,273,493 participants with 96,256 all-cause deaths (Supplementary Appendix 3, Included studies). Twenty-nine studies examined change in weight; 17 of 29 studies reported % change and 6 studies examined change in BMI. Nineteen studies were conducted in the USA [4,18–35], nine in Europe [36–42, 43, 44], three in Australia [6, 45, 46] and four in Asia [47–50]. Follow-up duration ranged from 2 [20] to 20 years [40], and participants were aged between 65 and 99 years. Most ($n = 23$) studies included men and women and reported overall results, while seven studies reported separate analyses for men and women [21,25–28,30,36]. Two studies included only men [32,38] and three only women [33,34, 47]. All studies were prospective, except for one retrospective study [29]. In six studies, body weight was self-reported [22,29,31,33,38], and in 29 studies, body weight was objectively measured. Of the 35 studies eligible for inclusion, 30 studies contained sufficient information for meta-analysis inclusion. The five excluded studies comprised one retrospective study where weight change was reported from early adulthood [29]; two studies which did not report CIs/variation [25,42] and two where results could only be approximated from a figure [26,35].

Baseline BMI and amount of weight change varied between studies with some studies reporting multiple comparisons, and for these studies, the largest weight change groups were extracted. One study [33] used average BMI gain as the reference set, while the others used 'weight stable', within 5% or 5 kg change in weight or within 1 kg/m^2 BMI as reference category.

Risk of bias assessment

A total of 25 of 35 studies were rated as good, 2 rated as fair and 8 as poor. Common reasons for poor scores were as follows: use of self-reported weight and height, and lack of control for key covariates (e.g. age, sex, baseline BMI or waist circumference, cancer, smoking, socioeconomic status) (Supplementary Appendix 4). Quality of evidence from observational studies in weight loss, weight gain, weight fluctuation and all-cause mortality was classified as 'moderate' by GRADE criteria (Supplementary Appendix 5). Inconsistency was the only category that varied between the weight exposures, with weight loss studies rated as 'serious', weight gain studies rated as 'moderate' and weight fluctuation studies rated as 'low'.

Weight loss and the risk of all-cause mortality

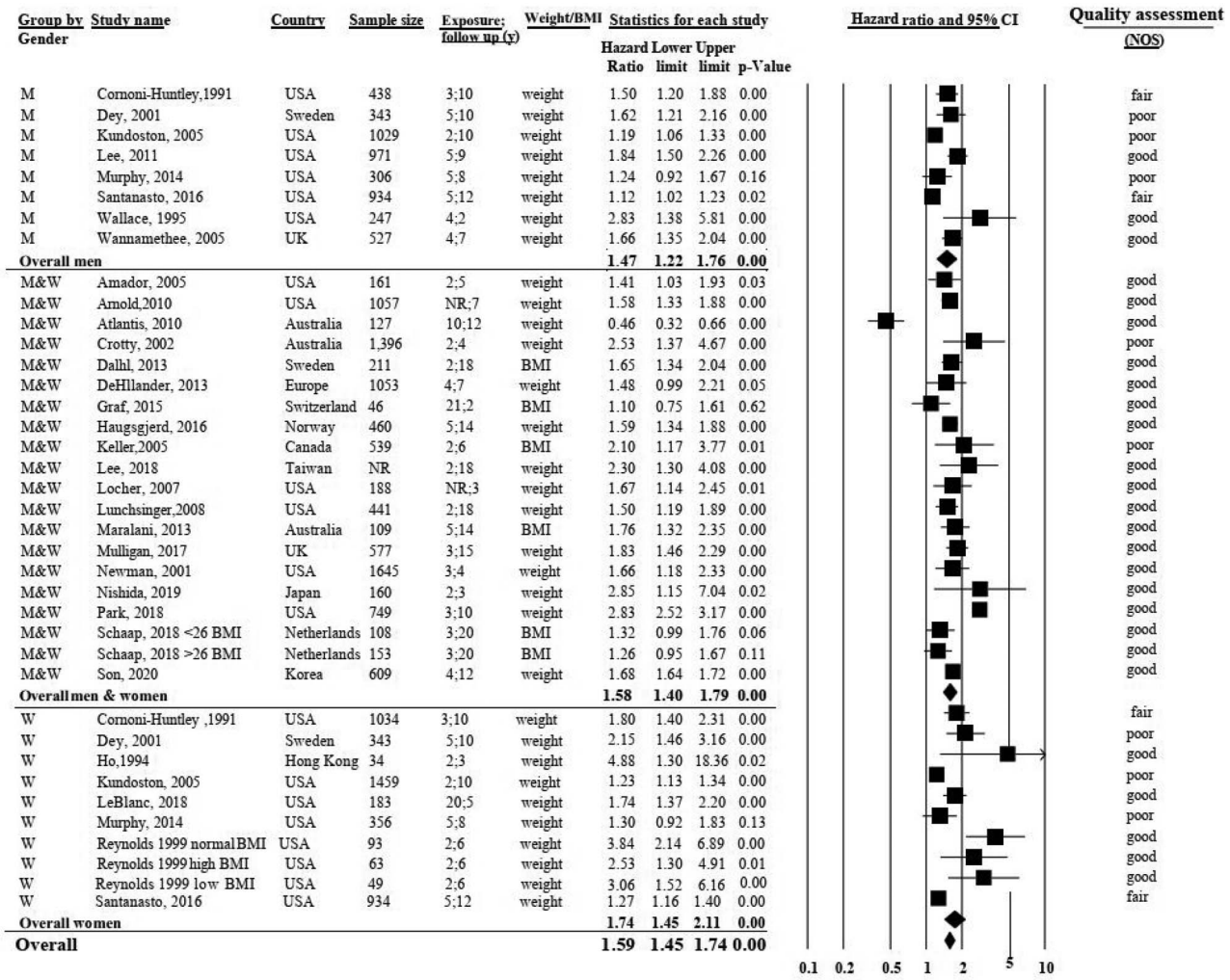
Thirty prospective studies compared weight loss with reference, involving 1,219,279 participants and 69,255 all-cause deaths. Compared to the reference group, adults aged ≥65 years with weight loss were at 59% increased risk of all-cause mortality (HR: 1.59; 95%CI: 1.45–1.74; Figure 1).

Consistent with the inconsistency rating of 'serious' in GRADE, high evidence of heterogeneity was noted among estimates reported by included studies (Q test, $P < 0.001$, $I^2 = 89\%$), (Supplementary Appendix 5) and thus subgroup analyses were performed (Supplementary Appendix 6). Subgroup analyses showed significant effects of physical activity, follow-up duration and method of weight measurement on the pooled HR for weight loss ($P < 0.05$). Studies not including physical activity as a covariate had higher HR than studies that included physical activity (Supplementary Appendix 6). Publication bias was evaluated with funnel plots (Supplementary Appendix 8a). Begg's test ($P = 0.014$), but not Egger's test (P value = 0.69), indicated publication bias. Sensitivity analysis removing one study at a time or assessing 5% weight change did not have a substantial effect on the pooled effect size ('results not shown'). Meta-regression of included studies by year of publication did not indicate alteration over time (Supplementary Appendix 9).

Two studies presented results for 'intentional' weight loss and risk of all-cause mortality [31,38]. The overall pooled random-effects estimate from these studies was 0.92 (95%CI: 0.54–1.54), suggesting that intentional weight loss was not associated with all-cause mortality risk in older adults. Moderate heterogeneity existed among the estimates reported by the included studies (Q test, $P = 0.99$, $I^2 = 56\%$).

Weight gain and the risk of all-cause mortality

Twenty-three studies examined weight gain and all-cause mortality, with a total of 1,210,116 participants and 65,481 all-cause deaths. Weight gain had a small, but significant, association with all-cause mortality compared to reference (HR: 1.10; 95%CI: 1.02–1.17; Figure 2), with low heterogeneity (Q test, $P = 0.01$ $I^2 = 41\%$). In subgroup analysis of



Group by Gender	Study name	Country	Sample size	Exposure; follow up (y)	Weight/BMI	Hazard Ratio	Lower limit	Upper limit	p-Value	Quality assessment (NOS)
M	Cornoni-Huntley,1991	USA	438	3;10	weight	1.50	1.20	1.88	0.00	fair
M	Dey, 2001	Sweden	343	5;10	weight	1.62	1.21	2.16	0.00	poor
M	Kundoston, 2005	USA	1029	2;10	weight	1.19	1.06	1.33	0.00	poor
M	Lee, 2011	USA	971	5;9	weight	1.84	1.50	2.26	0.00	good
M	Murphy, 2014	USA	306	5;8	weight	1.24	0.92	1.67	0.16	poor
M	Santanasto, 2016	USA	934	5;12	weight	1.12	1.02	1.23	0.02	fair
M	Wallace, 1995	USA	247	4;2	weight	2.83	1.38	5.81	0.00	good
M	Wannamethee, 2005	UK	527	4;7	weight	1.66	1.35	2.04	0.00	good
Overall men						**1.47**	**1.22**	**1.76**	**0.00**	
M&W	Amador, 2005	USA	161	2;5	weight	1.41	1.03	1.93	0.03	good
M&W	Arnold,2010	USA	1057	NR;7	weight	1.58	1.33	1.88	0.00	good
M&W	Atlantis, 2010	Australia	127	10;12	weight	0.46	0.32	0.66	0.00	good
M&W	Crotty, 2002	Australia	1,396	2;4	weight	2.53	1.37	4.67	0.00	poor
M&W	Dalhl, 2013	Sweden	211	2;18	BMI	1.65	1.34	2.04	0.00	good
M&W	DeHllander, 2013	Europe	1053	4;7	weight	1.48	0.99	2.21	0.05	good
M&W	Graf, 2015	Switzerland	46	21;2	BMI	1.10	0.75	1.61	0.62	good
M&W	Haugsgjerd, 2016	Norway	460	5;14	weight	1.59	1.34	1.88	0.00	good
M&W	Keller,2005	Canada	539	2;6	BMI	2.10	1.17	3.77	0.01	poor
M&W	Lee, 2018	Taiwan	NR	2;18	weight	2.30	1.30	4.08	0.00	good
M&W	Locher, 2007	USA	188	NR;3	weight	1.67	1.14	2.45	0.01	good
M&W	Lunchsinger,2008	USA	441	2;18	weight	1.50	1.19	1.89	0.00	good
M&W	Maralani, 2013	Australia	109	5;14	BMI	1.76	1.32	2.35	0.00	good
M&W	Mulligan, 2017	UK	577	3;15	weight	1.83	1.46	2.29	0.00	good
M&W	Newman, 2001	USA	1645	3;4	weight	1.66	1.18	2.33	0.00	good
M&W	Nishida, 2019	Japan	160	2;3	weight	2.85	1.15	7.04	0.02	good
M&W	Park, 2018	USA	749	3;10	weight	2.83	2.52	3.17	0.00	good
M&W	Schaap, 2018 <26 BMI	Netherlands	108	3;20	BMI	1.32	0.99	1.76	0.06	good
M&W	Schaap, 2018 >26 BMI	Netherlands	153	3;20	BMI	1.26	0.95	1.67	0.11	good
M&W	Son, 2020	Korea	609	4;12	weight	1.68	1.64	1.72	0.00	good
Overall men & women						**1.58**	**1.40**	**1.79**	**0.00**	
W	Cornoni-Huntley ,1991	USA	1034	3;10	weight	1.80	1.40	2.31	0.00	fair
W	Dey, 2001	Sweden	343	5;10	weight	2.15	1.46	3.16	0.00	poor
W	Ho,1994	Hong Kong	34	2;3	weight	4.88	1.30	18.36	0.02	good
W	Kundoston, 2005	USA	1459	2;10	weight	1.23	1.13	1.34	0.00	poor
W	LeBlanc, 2018	USA	183	20;5	weight	1.74	1.37	2.20	0.00	good
W	Murphy, 2014	USA	356	5;8	weight	1.30	0.92	1.83	0.13	poor
W	Reynolds 1999 normal BMI	USA	93	2;6	weight	3.84	2.14	6.89	0.00	good
W	Reynolds 1999 high BMI	USA	63	2;6	weight	2.53	1.30	4.91	0.01	good
W	Reynolds 1999 low BMI	USA	49	2;6	weight	3.06	1.52	6.16	0.00	good
W	Santanasto, 2016	USA	934	5;12	weight	1.27	1.16	1.40	0.00	fair
Overall women						**1.74**	**1.45**	**2.11**	**0.00**	
Overall						**1.59**	**1.45**	**1.74**	**0.00**	

Figure 1. Weight loss and all-cause mortality in community-dwelling older adults aged ≤65 for men (M), women (W) and both genders combined. All studies used weight as the exposure, except for Keller, Maralani, Dahl, Schaap and Graf, where the exposure was BMI. NOS was used to assess quality of included studies [10, 11].

weight gain studies, analysis by gender showed a higher all-cause mortality risk in women compared to men (HR: 1.62 95%CI: 1.20–2.17 for women versus 1.00 (0.87–1.16) in men). There were no other subgroup effects on the pooled HR for weight gain (Supplementary Appendix 7). The funnel plot for weight gain and all-cause mortality appeared symmetrical (Supplementary Appendix 8b) and did not suggest evidence of bias, confirmed by Egger's ($P = 0.57$) and Begg's ($P = 0.45$) tests. Sensitivity analysis removing one study at a time or assessing 5% weight change did not have a substantial effect on the pooled effect size (results not shown). Meta-regression indicated that the effect of weight gain did not alter over time, based on year of publication (Supplementary Appendix 9).

Weight fluctuation and the risk of all-cause mortality

Four studies [4,6,21,33] explored the relationship between weight fluctuation and all-cause mortality, a total of 2,283 events among 6,901 participants. The overall pooled HR indicated a 63% increased risk of all-cause mortality with weight fluctuation compared to the stable weight reference (HR: 1.66; 95%CI: 1.28, 2.15 Figure 3). No significant heterogeneity was evident among estimates from included studies (Q test, $P = 0.31$, $I^2 = 14.6\%$). Subgroup analyses were not performed due to small-study effects. The funnel plot of the weight fluctuation and all-cause mortality appeared symmetrical (Supplementary Appendix 8c) and did not suggest evidence of bias, confirmed by Egger's ($P = 0.71$) and Begg's ($P = 0.54$) tests. Sensitivity analysis removing one study at a time or assessing 5% weight change did not have a substantial effect on the pooled effect size (results not shown).

Discussion

This study found that weight change (as weight or BMI change) is associated with an increased all-cause mortality

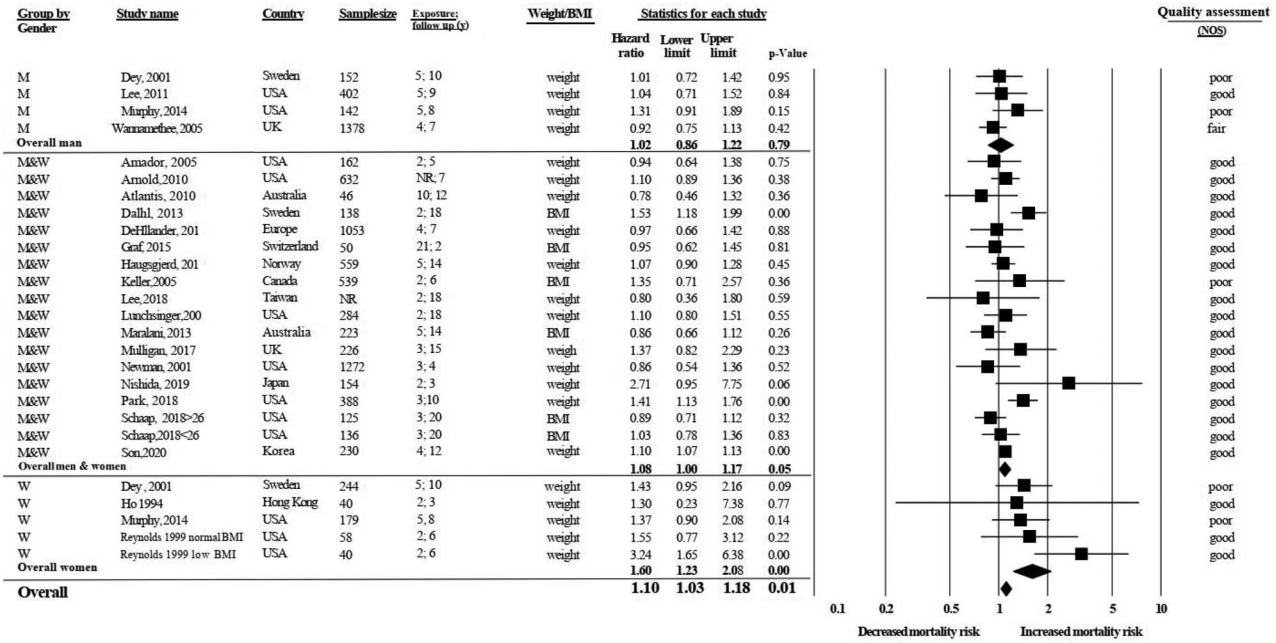


Figure 2. Weight gain and all-cause mortality in community-dwelling older adults aged ≤65 for men (M), women (W) and both genders combined. All studies used weight as the exposure, except for Keller, Maralani, Dahl, Schaap and Graf, where the exposure was BMI. NOS was used to assess quality of included studies [10, 11].

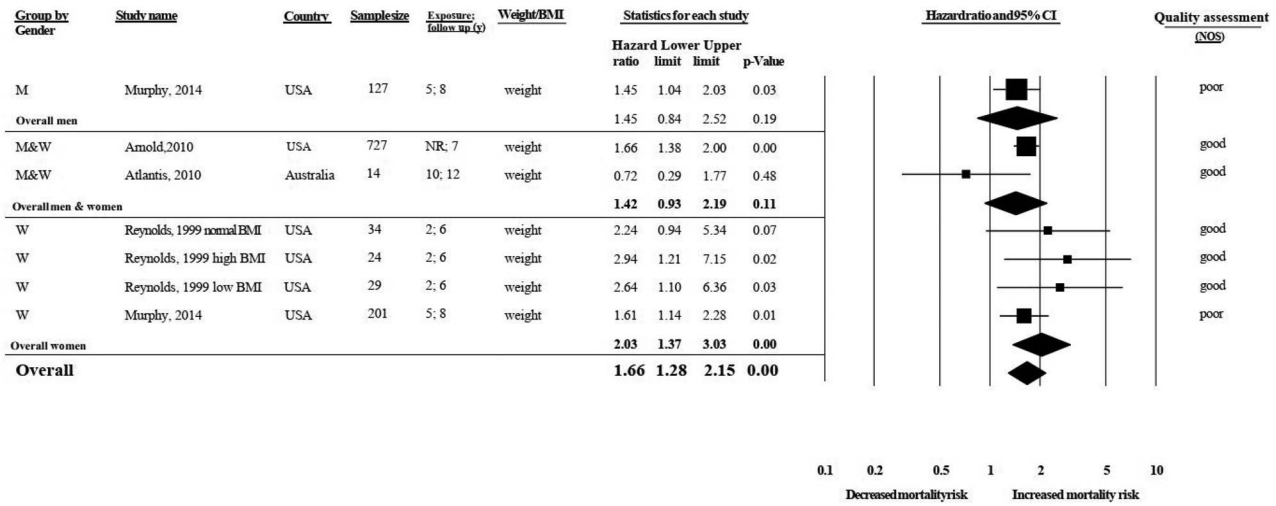


Figure 3. Weight fluctuation and all-cause mortality in community-dwelling older adults aged ≤65 for men (M), women (W) and both genders combined. All studies used weight as the exposure. NOS was used to assess quality of included studies [10, 11].

risk in community-dwelling adults aged ≥65 years, with a 59% increased risk of mortality for weight loss and 66% increased risk of mortality for weight fluctuation, compared to stable weight. By comparison, the effect of weight gain on mortality was more modest (10% increase in all-cause mortality risk).

Our findings are largely consistent with previous meta-analyses, suggesting that recent population BMI trends [1] have not markedly affected the effect. Karahalios *et al.* [14] reported that weight loss was associated with a 45% increase in all-cause mortality risk (95%CI: 1.34, 1.58), whereas weight gain was associated with a slight 7% increase in mortality risk (95%CI: 1.01, 1.13) [14], consistent with the results of our study. However, Karahalios *et al.* [14] included weight change measured between mid-life and older adulthood, while our analysis specifically assessed weight change that occurred in older adulthood when loss of muscle mass may be accelerated [3]. A meta-analysis of 17 studies by Cheng et al. [8] in mostly overweight/obese participants aged ≥60 years reported a 67% increase in all-cause mortality risk for weight loss (95%CI: 1.51, 1.85), 21% for weight gain (95%CI: 1.09, 1.33) and 53% for weight fluctuation

(95%CI: 1.36, 1.72). Generalisability to those without elevated BMI is unclear, and it should be noted that obesity and body weight may vary across different ethnic and racial groups [51].

Of studies meeting inclusion criteria for this analysis, 27 of 30 found that weight loss was associated with increased risk of all-cause mortality. The findings from the two studies [6,39] reporting no association between weight loss and mortality may have been affected by small sample sizes and/or variability of methods for assessing weight loss. It is not uncommon for weight change to occur in older age, associated with changes to appetite, physical activity and metabolism [52]. The point at which weight loss may indicate increased mortality risk is not clearly defined, but our study suggests increased risk associated with weight loss in the order of ≥5% of body mass.

In this review, only four [29,33,37,40] studies reported the effects of weight change stratified by baseline BMI, and the association between weight loss and mortality persisted in people with normal and overweight BMI, providing no evidence that initial BMI was an effect-modifier. Given the small number of studies, further examination of whether baseline BMI modifies the association between weight change and mortality in older adults is needed.

One complexity in considering weight loss in older age is the increased risk of unintentional weight loss in older age compared to mid-life [53], which may be a marker of underlying ill health. In 2009, Harrington *et al.* [54] reported a greater risk of all-cause mortality for unintentional weight loss (HR: 1.27; 95%CI: 1.09, 1.47) compared to intentional weight loss (HR: 1.11; 95%CI: 1.00, 1.22) in middle-aged and older adults [54]. Among the studies contributing to our analysis, most ($n = 29$) did not distinguish between intentional and unintentional weight loss. Wannamethee *et al.* [38] suggest that mortality risk associated with intentional weight loss may be reduced compared to unintentional weight loss, and Locher *et al.* [31] found no difference in mortality risk for intentional weight loss versus no weight loss. Intentionality in weight change and mortality risk remains unresolved and is complicated by inconsistent measurement of frailty.

A common challenge facing meta-analysis is disparity in confounders employed in adjusted models of contributing studies, and this was apparent herein. Some studies over-adjusted analyses by including an intermediate factor in the hypothesised causal pathway. Our results showed that studies not adjusting for physical activity found a higher risk of mortality when compared to those that adjusted for physical activity. Additionally, most studies had a relatively short follow-up (<10 years) and found a stronger association with all-cause mortality risk compared to studies with ≥10-year follow-up. Deaths occurring early in follow-up may reflect pre-existing illness, which is often addressed by excluding early deaths in statistical modelling. The use of this approach differed among studies, with exclusion periods ranging from <1 month [38] to 5 years [36].

Gender-stratified analyses indicated that the association between weight loss and all-cause mortality risk was similar in both men and women. In contrast, weight gain (compared to being weight stable) was associated with a 62% increase in risk of all-cause mortality in women, while no relationship was observed between weight gain and all-cause mortality in men. In contrast, previous meta-analyses by Cheng *et al.* [8] and Karahalios *et al.* [14] reported that the association between weight change and total mortality did not vary significantly by gender. The effect of gender on the association between weight fluctuation and all-cause mortality was not able to be explored due to a relatively small number of studies ($n = 4$) [4,6,21,33]. Our findings suggest that further research is needed to explore gender differences in the association between weight gain and mortality.

Strengths and limitations

A systematic and comprehensive search strategy was used to identify studies for this review to ensure relevant studies were captured and PRISMA guidelines were followed. Study quality was assessed using the validated NOS. Subgroup analyses were undertaken to explore potential sources of heterogeneity, and sensitivity analyses performed [55].

This study has some limitations. The outcome was all-cause rather than cause-specific mortality, thus findings cannot be generalised to specific causes of death. As included studies examined those who were community dwelling at baseline, the findings may not be generalisable to older adults living in aged care, who may be frailer or living with disabling disease. Studies were predominantly conducted in higher income settings in North America, Europe, Australia and East Asia except one [51], limiting generalisability to low-income countries. Reporting of weight change was inconsistent across studies, with heterogeneity in weight change categories and methods of weight assessment. Subgroup analysis indicates that self-reported weight change measurement had higher HRs than studies where weight was objectively measured. Other potentially relevant factors, such as the impact of frailty on the association, were not consistently reported in the included papers, preventing consideration in this review. The inclusion of non-English language publications is unlikely to alter findings [56].

Conclusions

This systematic review and meta-analysis of 35 studies of weight change and mortality risk in community-dwelling adults aged ≥65 years found that weight loss, weight fluctuation and weight gain were all associated with an increased risk of all-cause mortality, with some evidence that women may have a greater risk imposed by weight gain than men. Further research is required to assess these relationships for different BMI categories, and whether risks differ by intentionality of weight loss.

Supplementary Data: Supplementary data including PRISMA checklist (Supplementary Appendix 10) and full reference list (Supplementary Appendix 11) are available to subscribers in *Age and Ageing* online.

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Declaration of Conflicts of Interest: None.

Declaration of Sources Funding: None.

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