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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.

Method: MEDLINE, EMBASE and CINAHL were searched from inception to 11th 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 (AHRQ) 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 (HR: 1.59; 95%CI, 1.45–1.74, $p < 0.001$). The 27 studies which 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: 1.63; 95%CI: 1.37, 1.94, $p < 0.001$). 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; BMI; All-cause mortality; elderly

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 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 ≥ 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 sub-groups.

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 the 11th June 2020 (Supplement A2 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 (TAA and SP) 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 (AO).

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 intervals (CI) for weight changes relative to a comparable reference group with minimal/no weight change. If findings were not provided

separately for ≥ 65 years or further clarification needed, study authors were contacted. Studies were excluded if they (i) included 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 (TAA) independently extracted the data, the second reviewer (SP) 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 (TAA and SP) using the Newcastle-Ottawa Scale (NOS) scored based on the Agency for Healthcare Research and Quality (AHRQ) 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 RRs 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. Sub-group 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 and Begg's tests [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, USA).

RESULTS

Search results

The database search identified 6593 articles, while three additional articles were located via manual searching of references and citations (Supplement A1 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 (Supplement A3 Included studies). Twenty-nine studies examined change in weight; 17 of 29 studies reported % change and six studies examined change in BMI. Nineteen studies were conducted in the USA [4, 18–35], nine in Europe [36–44], three in Australia [6, 45, 46] and four in Asia [47–50]. Follow-up duration ranged from two [20] to 20 years [39], 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 [33,47,34]. All studies were prospective, except for one retrospective study [29]. In six studies, body weight was self-reported [22, 29, 31, 33, 38], 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/m² BMI as reference category.

Risk of bias assessment

A total of 25 of 35 studies were rated as good, two rated as fair, and eight as poor. Common reasons for poor scores were: 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).

Quality of evidence from observational studies in weight loss, weight gain, weight fluctuation and all-cause mortality was classified as ‘moderate’ by GRADE criteria (Supplement A5). Inconsistency was the only category that varied between the weight exposures, with weight loss studies rated as ‘serious’, weight gain studies rated as ‘moderate’ 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. Page: 8

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, $P < 0.001$, $I^2 = 89\%$), 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 (Supplement A8 a). Begg's test ($P = 0.014$), but not Egger's test ($p\text{-value} = 0.69$) 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 (Supplement A9).

Two studies presented results for *intentional* weight loss and risk of all-cause mortality [26, 31]. 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 1210,116 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 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 vs 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 (Supplement A8 b) and did not suggest evidence of bias, confirmed by Egger's (p-value = 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 effect of weight gain did not alter over time, based on year of publication (Supplement A9).

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:1.63, 95%CI: 1.37–1.94) (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 (Supplement A8 c) and did not suggest evidence of bias, confirmed by Egger's (p-value = 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 risk in community-dwelling adults aged ≥ 65 years, with a 59% increased risk of mortality for weight loss and 63% 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 impacted 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. included weight change measured between mid-life and older adulthood [14], 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 [50].

Of studies meeting inclusion criteria for this analysis, 27 of 30 found 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 impacted 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 $\geq 5\%$ of body mass.

In this review, only four [4, 6, 21, 33] studies reported 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. Wannameth 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 years follow-up. Deaths occurring early in follow-up may reflect pre-existing illness, which is often addressed by excluding early deaths in statistical modelling. 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 Newcastle-Ottawa scale. 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. 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 [50], 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 indicate 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.

Acknowledgement

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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.

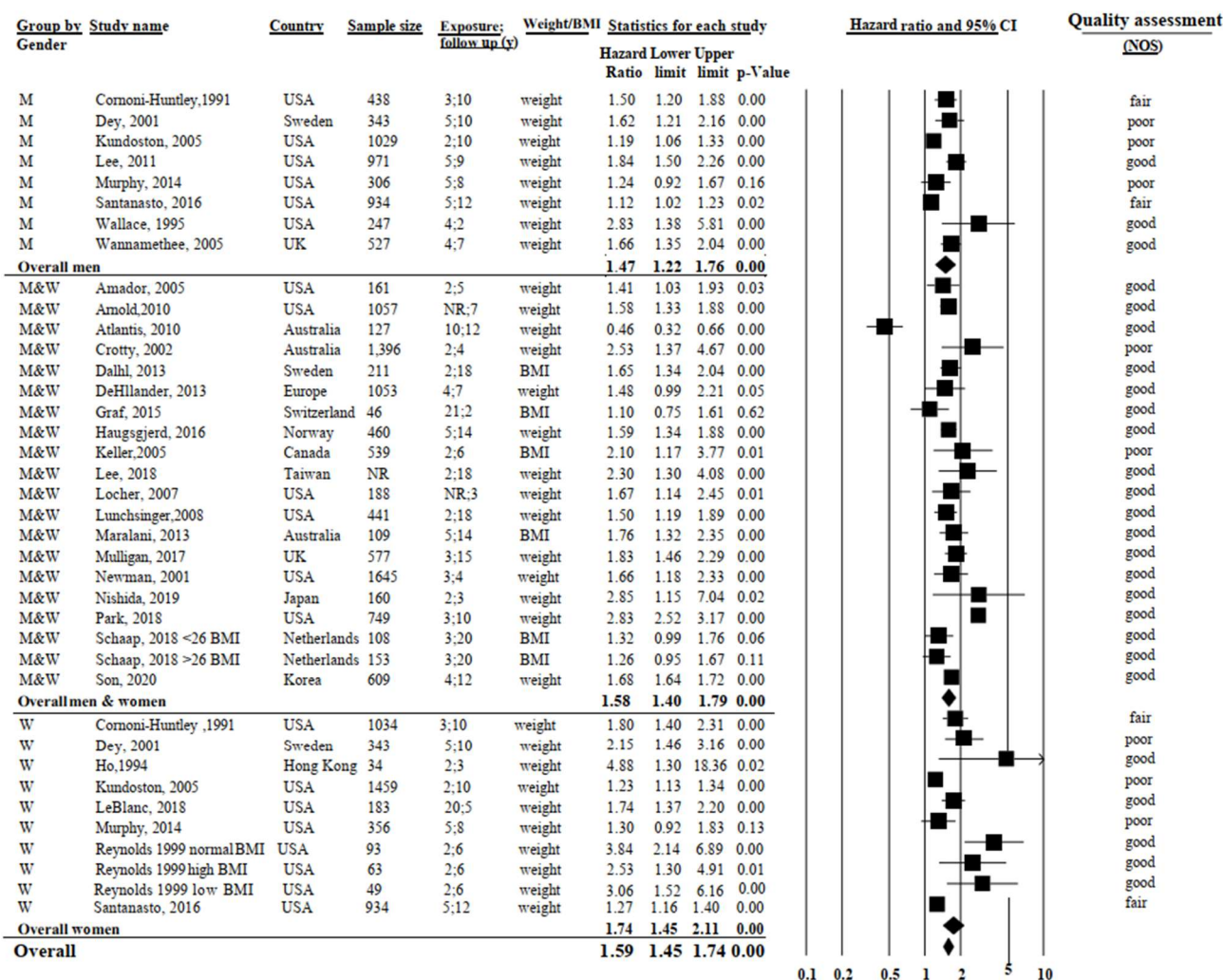


Figure 1. Weight loss and all-cause mortality in community older adults age ≤ 65 for men (M), women (W) and both genders combined.

All studies used weight as the exposure, except for Keller, Maralani, Dahl, Schaap, and Graf, where the exposure was BMI. Newcastle-Ottawa Scale (NOS) was used to assess quality of included studies [10,11].

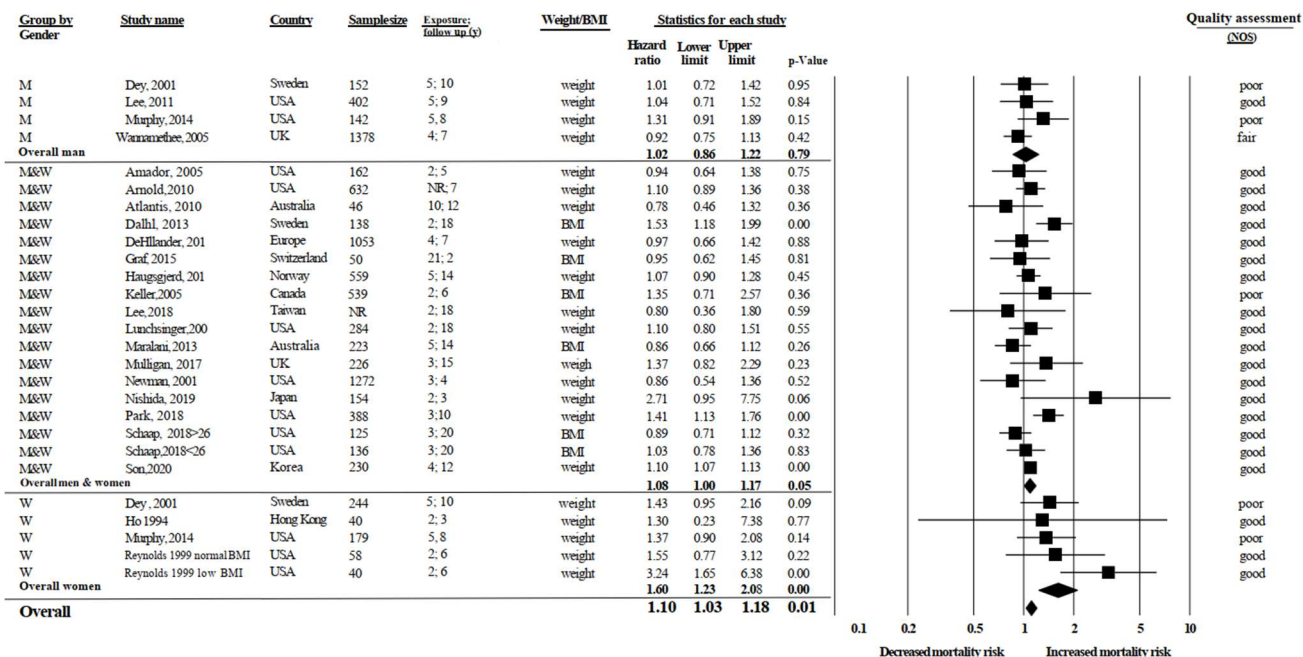


Figure 2. Weight gain and all-cause mortality in community older adults age ≤ 65 for men (M), women (W) and both genders combined All studies used weight as the exposure, except for Keller, Maralani, Dahl, Schaap, and Graf, where the exposure was BMI. Newcastle-Ottawa Scale (NOS) was used to assess quality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

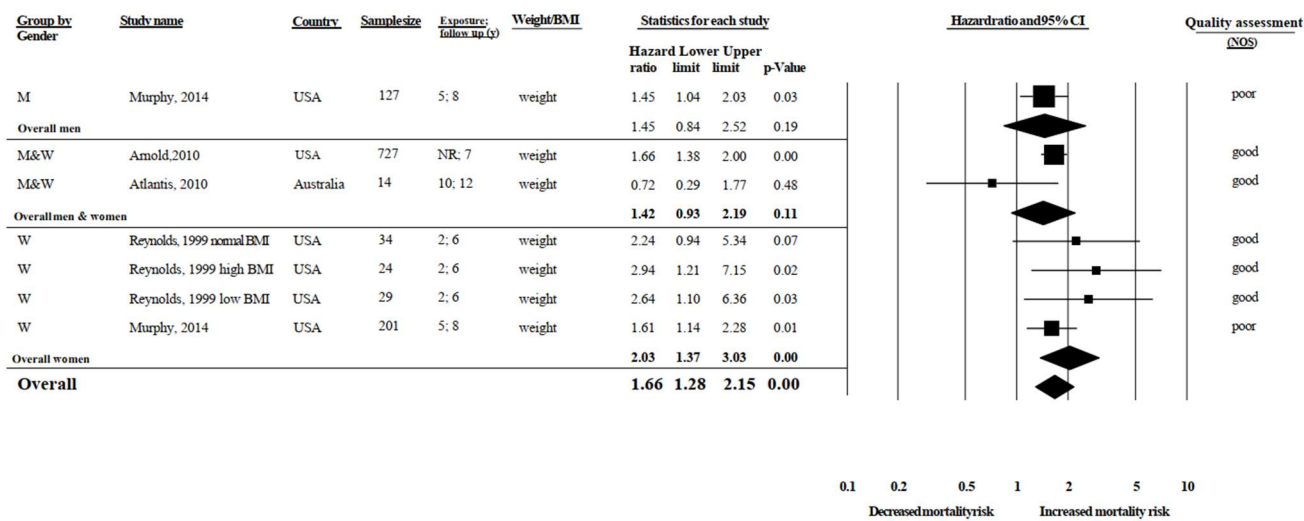


Figure 3. Weight fluctuation and all-cause mortality in community older adults age ≤ 65 for men (M), women (W) and both genders combined. All studies used weight as the exposure. Newcastle-Ottawa Scale (NOS) was used to assess quality of included studies [10,11].

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