Association of Weight Fluctuation and Increased Mortality in Middle-Aged Populations

Heather Montane

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Abstract
Background: Obesity, a growing epidemic worldwide, has been linked to several comorbid conditions including, but not limited to, heart disease, type 2 diabetes mellitus, and certain types of cancer. To both prevent and treat obesity-associated comorbidities, it is common practice for healthcare providers to prescribe weight loss as a medical intervention. Unfortunately, many individuals who lose weight are unable to maintain it long-term. Therefore, people who are obese commonly experience several weight loss and regain cycles over the course of their lives. The question this review aims to answer is whether these weight fluctuations have an adverse effect on middle-aged individuals’ lifespans and, if so, what can be done to achieve improved weight maintenance.

Methods: An exhaustive search of available medical literature was performed using CINAHL, MEDLINE, and Web of Science. Key terms included: weight fluctuation and mortality. The quality of eligible studies was assessed using GRADE guidelines.

Results: The literature search yielded 33 studies, 4 of which were relative to the clinical question while meeting eligibility criteria. One of the 4 studies was a randomized control trial while the remaining 3 were observational studies. Each of the 4 studies found that weight fluctuations in middle-aged populations are linked to a significant increase in mortality. However, unlike the other studies, the Wannamethee et al study stated these results were markedly attenuated when accounting for other morbidities. While these results are thought-provoking and potentially practice-changing, the quality of the evidence was not shown to be strong. Per the GRADE guidelines, the quality of the randomized control trial was moderate while the quality of the 3 observational studies was very low.

Conclusion: Weight fluctuations in middle-aged populations may be associated with an increased risk of mortality. However, to obtain a more definitive answer, future studies should avoid self-reported data. Additionally, forthcoming research might consider looking at the degree of weight fluctuation to determine if there is a dose-response gradient. Lastly, a distinction between intentional versus unintentional weight fluctuations should be accounted for in subsequent studies. Being that there may be an association between weight fluctuations and increased risk of mortality in middle-aged populations, healthcare providers using weight loss as an intervention to prevent or treat comorbid conditions associated with obesity must be prepared to provide ongoing encouragement and support of weight loss maintenance.

Keywords: Weight fluctuations, mortality, middle-aged populations

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Association of Weight Fluctuation and Increased Mortality in Middle-Aged Populations

Heather Montane

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Faculty Advisor: Brandy Pestka, PA-C, MS
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Biography

Heather Montane, a native Wisconsinite, received a Bachelor of Science degree in Dietetics as well as a certificate in Gender and Women’s Studies from the University of Wisconsin – Madison in 2012. She then relocated to Minnesota to complete her dietetic internship at the University of Minnesota Medical Center, Fairview. After obtaining her RD licensure, she worked as a clinical dietitian in both inpatient and outpatient settings in Minnesota. In the future, she hopes to pursue a career in an area that allows her to marry nutrition therapy with medical therapy to provide comprehensive patient care.
Abstract

Background: Obesity, a growing epidemic worldwide, has been linked to several comorbid conditions including, but not limited to, heart disease, type 2 diabetes mellitus, and certain types of cancer. To both prevent and treat obesity-associated comorbidities, it is common practice for healthcare providers to prescribe weight loss as a medical intervention. Unfortunately, many individuals who lose weight are unable to maintain it long-term. Therefore, people who are obese commonly experience several weight loss and regain cycles over the course of their lives. The question this review aims to answer is whether these weight fluctuations have an adverse effect on middle-aged individuals’ lifespans and, if so, what can be done to achieve improved weight maintenance.

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Results: The literature search yielded 33 studies, 4 of which were relative to the clinical question while meeting eligibility criteria. One of the 4 studies was a randomized control trial while the remaining 3 were observational studies. Each of the 4 studies found that weight fluctuations in middle-aged populations are linked to a significant increase in mortality. However, unlike the other studies, the Wannamethee et al study stated these results were markedly attenuated when accounting for other morbidities. While these results are thought-provoking and potentially practice-changing, the quality of the evidence was not shown to be strong. Per the GRADE guidelines, the quality of the randomized control trial was moderate while the quality of the 3 observational studies was very low.

Conclusion: Weight fluctuations in middle-aged populations may be associated with an increased risk of mortality. However, to obtain a more definitive answer, future studies should avoid self-reported data. Additionally, forthcoming research might consider looking at the degree of weight fluctuation to determine if there is a dose-response gradient. Lastly, a distinction between intentional versus unintentional weight fluctuations should be accounted for in subsequent studies. Being that there may be an association between weight fluctuations and increased risk of mortality in middle-aged populations, healthcare providers using weight loss as an intervention to prevent or treat
comorbid conditions associated with obesity must be prepared to provide ongoing encouragement and support of weight loss maintenance.

**Keywords:** Weight fluctuations, mortality, middle-aged populations
Acknowledgements

To my loving husband: Thank you for your endless encouragement and support throughout this process.
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List of Abbreviations
BMI  Body Mass Index
CAD  Coronary Artery Disease
CI   Confidence Interval
NHANES I  National Health and Nutrition Examination Survey I
NHEFS  NHANES I Epidemiologic Follow-up Study
RCT  Randomized Control Trial
USA  United States of America
Association of Weight Fluctuation and Increased Mortality in Middle-Aged Populations

BACKGROUND

Obesity is a growing epidemic worldwide. According to data from the National Health and Nutrition Examination Survey 2011-2014, 36% of adults and 17% of youth living in the United States are obese.\(^1\) The increasing prevalence of obesity is problematic for several reasons such as the staggering economic consequences. The annual nationwide costs of obesity ranges from $3.38 billion to $6.38 billion.\(^2\) Additionally, obesity has been linked to multiple comorbidities including, but not limited to, heart disease, type 2 diabetes mellitus, and certain types of cancer.

To both prevent and treat obesity-associated comorbidities, it is common practice for healthcare providers to prescribe weight loss via dietary modifications and increased physical activity. When lifestyle modifications are initiated for weight reduction, the peak weight loss typically occurs at 6 months. Unfortunately, in the absence of a weight maintenance program, the weight loss trend begins to reverse after the 6-month timeframe with approximately half of patients returning to their original weight within 5 years.\(^3\) This pattern of weight change is referred to as “weight fluctuation” or “yo-yo dieting.” Because
weight fluctuation is commonplace, this review aims to explore the following question: can weight fluctuations in middle-aged populations increase mortality risk?

METHODS

An exhaustive search of available medical literature was performed using CINAHL, MEDLINE, and Web of Science. Key search terms used were weight fluctuation and mortality. Eligibility criteria included middle-aged individuals with a history of weight fluctuations. Non-human studies, non-English studies, and studies published more than 20 years ago were excluded. Quality assessment of eligible studies was completed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.4

RESULTS

The literature search yielded a total of 33 articles. Each article was screened for relevancy and eligibility criteria. After excluding non-human studies, non-English studies, and studies published over 20 years ago, 4 studies remained. One of the studies was an RCT5 while the remaining 3 studies were observational.6-8 (See Table 1.)

Bangalore et al

This post-hoc analysis5, published in April of 2017, used data from the Treating New Targets trial, an RCT involving 10 001 patients.
The analysis aimed to explore the relationship between body-weight fluctuations and the risk of both cardiovascular events and mortality in patients with known CAD. The primary outcome was the occurrence of a coronary incident including death from coronary heart disease, non-fatal heart attacks, resuscitated cardiac arrest, revascularization, or angina. Secondary outcomes were any cardiovascular event and death.5

The link between risk of outcomes and body-weight variability was then examined. Body-weight variability was defined as a change in weight between visits. Average consecutive change was used as the primary variability measure and was analyzed via 2 methods. The primary method examined weight variability as a time-dependent covariant while the secondary method examined weight variability as a non-time-dependent covariant. Using the secondary method, patients were divided into quintiles of body-weight variability.5

Patients with 2 or more post-baseline measurements were included in the post-hoc analysis. There were 9509 patients enrolled in the RCT that met this criterion. Body-weight was obtained at 3 months, 6 months, 9 months, 12 months and every 6 months following the first year for an average of 4.9 years. The median number of weight measurements obtained was 12 and the average weight variability was 1.76 kg.5
When body-weight variability was examined as a time-dependent covariate, results showed that for every 1.5 to 1.9 kg weight change there was an increased risk of any coronary event, any cardiovascular event, and death. When body-weight variability was examined as a non-time dependent covariant, results showed an increase in the rate of any coronary event, any cardiovascular event, and death with every higher quintile of body-weight variability. When the lowest and highest quintiles were compared, patients in the highest quintile had a 64% increased risk of any coronary event, an 85% increased risk of any cardiovascular event, and a 124% increased risk of death.⁵ (See Table 2.)

Rzehak et al

This 30-year prospective cohort study,⁶ published in October 2007, explored the relationship between weight change and weight fluctuations on all-cause mortality in middle-aged men. Participants were drawn via random sample from residential registry and electoral rolls in the city of Erfurt, Germany. Inclusion criteria were men living in Erfurt, Germany between the ages of 40-59 at the onset of the study, which resulted in 1160 participants. Weight change categories were determined in the first 15 years of the study while survival analysis was completed in the second 15 years of the study. Therefore, survival analysis included 505 of the original 1160 men.⁶
Weight change categories included: stable weight non-obese, stable weight obese, weight gain, weight loss, and weight fluctuations. Weight stability was defined by both a BMI that differed by <3kg/m² and a sum of absolute deviations ≤3.49 kg/m² over the first 15 years of the study. Weight gain and loss were defined by a BMI that increased or decreased by ≥3kg/m², respectively. Weight fluctuation was defined by a BMI that differed by <3kg/m² and a sum of absolute deviations >3.49 kg/m² over the first 15 years of the study. Height and weight were obtained at baseline, a 5-year-follow-up, a 10-year-follow-up, a 15-year-follow-up, and a 30-year-follow-up. BMI was calculated using height and weight values obtained at follow-up periods.⁶

A total of 183 men of the 505 included in the survival analysis died. Results showed that weight fluctuations significantly increased the risk of all-cause mortality after being adjusted for age at the beginning of the survival analysis (HR: 1.86 95% CI: 1.31-2.66). Furthermore, the increased risk of death persisted when adjustments were made for pre-existing disease, smoking, and socioeconomic status. The effect of weight loss was statistically significant only prior to adjustment for pre-existing disease, smoking, and socioeconomic status. Stable non-obese, stable obese, and participants who gained
>3 kg/m² did not appear to be at a significantly increased risk of all-cause mortality.⁶ (See Figure 1.)

**Diaz et al**

This population-based cohort study,⁷ published in June 2005, used data from NHANES I and NHEFS to evaluate the association between weight fluctuations and all-cause mortality. Completed data included 8479 non-institutionalized United States citizens who were between the ages of 25 and 74 years old at the onset of the study. Initial interviews were conducted between 1971 and 1974. Follow-up data was collected 3 more times, 1982-1984, 1987, and 1992, via a questionnaire completed by surviving participants. After calculating each participant’s average BMI, absolute value of difference between each individual BMI measurement and the participant’s average BMI, and the sum of deviations for each person, participants were placed in 1 of 5 categories. The categories included: stable weight non-obese, stable weight obese, weight gain, weight loss, and weight fluctuations.⁷

Results showed that, of the 5 weight categories, both weight loss and weight fluctuation groups had statistically significant increases in all-cause mortality (HR: 3.36, 95% CI: 2.47-4.55 and HR: 1.83, 95% CI: 1.25-2.69, respectively). After adjusting for poor health and incapacity, results remained statistically significant.⁷
This prospective cohort analysis, published in December 2002, used data from The British Regional Heart Study. The analysis aimed to assess weight change and weight fluctuation as they relate to mortality in middle-aged men. Men between the ages of 40 and 59 years old living in 24 different towns in England, Scotland, and Wales were randomly selected from age-sex registers to participate in The British Regional Heart Study. Surviving men received a questionnaire 5 years after the initial examination as well as 12 to 14 years after initial examination. The questionnaire inquired about medical history, body weight, changes in alcohol and smoking habits, and other risk factors. Men with complete information on body-weight for all 3 data collection periods were included leading to a study size of 5608 individuals.

After data collection, men were divided into 5 groups including: stable (<4% change in body weight), sustained gain (≥4% gain in body weight), sustained loss (≥4% loss in body weight), loss with first follow-up questionnaire followed by gain with second follow-up questionnaire, and gain with first-follow-up questionnaire followed by loss with second follow-up questionnaire.

The men who were included were then followed for 8 years after the final data collection period to analyze incidence of all-cause mortality. Of the 5608 participants, 943 died during the 8-year follow-
up period. Those with stable weight had the lowest risk of all-cause mortality. On the other hand, men with sustained weight loss or weight fluctuations (loss-gain and gain-loss) since the initial screen showed a much higher risk of total mortality even after adjustments for age, social class, smoking, physical activity levels, and initial BMI were made (RR: 1.60, 95% CI: 1.32-1.95; RR: 1.50, 95% CI: 1.17-1.91; and RR: 1.63, 95% CI:1.24-2.14, respectively). According to the study, however, sustained weight loss and weight fluctuations were closely linked to pre-existing cardiovascular conditions, malignancy, and self-reported poor health. When men with these conditions were excluded, the association between both sustained weight loss and weight fluctuations with increased mortality risk was attenuated suggesting that weight fluctuations are not associated with increased mortality in healthy, non-smoking men. According to the study, however, those who lost then gained weight continued to show some increase in CVD-related mortality.8

DISCUSSION

According to the United States Census Bureau, there are currently about 325 million people living in the USA. Approximately 77% of those people are adults, defined as ≥18 years old.9 Per data from the National Health and Nutrition Examination Survey 2011-2014, 36% of adults in the US are obese.1 This means roughly 90
million adults living in the USA are currently obese. Due to both the individual and societal consequences associated with obesity, weight loss is a commonly prescribed medical intervention. While patients are often able to lose weight, they are much less likely to maintain weight loss. Unfortunately, healthcare practitioners frequently stop focusing on weight loss once the target weight is obtained. The result of this vicious cycle is multiple episodes of weight loss followed by weight regain throughout the course and an individual’s life. The focus of this systematic review was to determine if weight fluctuations have a detrimental effect on middle-aged populations.

The systematic review included 4 studies\(^5-^8\) that examined whether weight fluctuations are associated with an increased risk of all-cause mortality in middle-aged populations. The 3 most recent studies\(^5-^7\) all showed a statistically significant increase in all-cause mortality risk. The remaining study,\(^8\) published in 2002, also found a statistically significant increase in all-cause mortality in individual’s who had experienced weight fluctuations; however, the study attributed these results to pre-existing cardiovascular conditions, malignancy, and self-reported poor health. The quality of data, evaluated using the GRADE method, revealed 1 moderate-quality RCT study\(^5\) and 3 very low-quality cohort studies.\(^6-^8\)
With increased risk of mortality in patients with weight fluctuations ranging from 1.50- to 1.86-times, additional focus on weight maintenance is imperative. According to data from the National Weight Control Registry strategies for successful long-term weight maintenance include: maintaining a consistent eating pattern that includes breakfast and is low in both calories and fat, participating in high levels of physical activity, and regular self-monitoring of weight.\textsuperscript{10} Additionally, a recent study published by Voils et al\textsuperscript{11} randomized individuals who recently lost a minimum of 4 kg into either a weight maintenance intervention group or a non-weight maintenance intervention group. The weight maintenance intervention group received regular phone calls to discuss satisfaction with outcomes, planning for prevention of relapse, self-monitoring, and social support. The non-weight maintenance intervention group did not receive additional follow-up. Outcomes showed mean weight re-gain was statistically significantly lower in the weight maintenance intervention group than the non-weight maintenance intervention group.\textsuperscript{11} This demonstrates the importance of continued external support, from individuals such as healthcare providers, in achieving long-term weight maintenance.

Several limitations were observed in the studies. The Bangalore et al study,\textsuperscript{5} for example, was a post-hoc examination of an RCT
making it an indirect analysis. Even more concerning, it was funded by Pfizer and looked at low-dose versus high-dose use of atorvastatin, a drug manufactured by Pfizer. Because of this personal interest, publication bias is likely. The 2 primary issues with the Rzehak et al study were small sample sizes in some of the weight change categories, most notably the weight loss category, as well as a large loss to follow-up making attrition bias likely. Both the Diaz et al and Wannamethee et al studies used self-reported data making reduced accuracy of data highly likely. Furthermore, the response options to follow-up questionnaires in the Diaz et al study were limited to loss of >10lbs, maintenance, and gain of >10lbs. Limited response options exclude individuals whose weight may have fluctuated between 1 and 10 lbs. Moreover, limited response options impede the opportunity to determine the existence of a dose-response gradient.

Because the quality of evidence is low secondary to several study limitations, it is difficult draw a definitive conclusion regarding the effect of weight fluctuations and increased mortality risk in middle-aged populations. Therefore, further study would need to be done to obtain a more definitive answer. To improve the accuracy of future studies, self-reported data should be avoided. Additionally, future studies might consider looking at the degree of weight fluctuation to determine if there is a dose-response gradient. Lastly, a distinction
between intentional versus unintentional weight fluctuations should be addressed in further research in the area, especially with the surprising significant findings of increased mortality in the sustained weight loss groups.

**CONCLUSION**

The link between weight-fluctuation and increased mortality risk in middle-aged populations remains slightly controversial from the results of the studies included in this evaluation. Overall, the quality of evidence is low. However, an association is possible given that 3 of the 4 studies reviewed showed a statistically significant correlation including the Bangalore et al study, which had the highest quality evidence. Therefore, when prescribing weight loss as a medical intervention it is important for providers to continue to encourage and support ongoing lifelong weight maintenance at subsequent patient visits.

**References**

1. CDC Website. 


4. GRADE working group. GRADE website. 


9. United States Census Bureau Website. 

10. The National Weight Control Website. 

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<sup>a</sup> The Bangalore et al study is a post-hoc analysis

<sup>b</sup> The Bangalore et al study evaluated data that was funded by the company that manufactured the treatment drug

<sup>c</sup> Greater degrees of body-weight fluctuation were associated with higher event rates

<sup>d</sup> Large loss to follow-up

<sup>e</sup> Reliance on self-reported data

<sup>f</sup> Response options on questionnaire limited to: loss of >10lbs, maintenance, and gain of >10lbs
Table 2: Multivariable Models and Risk of Outcomes in the Highest versus the Lowest Quintile of Variability in Body Weight

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<th>Outcome</th>
<th>Adjusted Hazard Ratio (95% CI)*</th>
<th>P Value</th>
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<tr>
<td>Any Coronary Event</td>
<td>1.64 (1.41-1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Cardiovascular Event</td>
<td>1.85 (1.62-2.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>2.24 (1.74-2.89)</td>
<td>&lt;0.001</td>
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*Results were adjusted for age, sex, race, diabetes, hypertension, and smoking; mean weight and weight change (taking directionality into account); treatment (80 mg of atorvastatin vs 10 mg); baseline levels of LDL cholesterol, HDL cholesterol, and triglycerides; chronic kidney disease and chronic heart failure; and time between initial and final weight measurements.
Figure 1: Survival Curves (Rzehak et al)

Fig. 2 Survival curves of men without (Panel A, C) and with pre-existing disease and smoking history for weight change categories (Panel B, D) for respondents with lower education by age cohort in the ERFORT study (n = 504), Part 1. Legend: 1 Stable non-obese, -2 Stable obese; -3 Weight gain, -4 Weight loss, -5 Weight fluctuations.