

Title: The Risks of Cardiovascular Disease and Mortality Following Weight Change in Adults with Diabetes: Results from ADVANCE

Running Title: Weight Change, CVD & Mortality

Authors: Alexandra K. Lee, PhD, MSPH,¹ Mark Woodward, PhD,¹⁻³ Dan Wang, MS,¹ Toshiaki Ohkuma, PhD,² Bethany Warren, PhD,¹ A. Richey Sharrett, MD, DrPH,¹ Bryan Williams, MD, PhD,^{4,5} Michel Marre, MD, PhD,^{6,7} Pavel Hamet, MD, PhD,⁸ Stephen Harrap, MD, PhD,⁹ John W. McEvoy, MBBCh, MHS,¹⁰ John Chalmers, MD, PhD,² Elizabeth Selvin, PhD, MPH¹

Affiliations:

¹ Department of Epidemiology and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

² The George Institute for Global Health, Sydney, Australia

³ The George Institute for Global Health, University of Oxford, UK

⁴ Institute of Cardiovascular Sciences, University College London, UK

⁵ National Institute of Health Research UCL Hospitals Biomedical Research Center, London, UK

⁶ Fondation Opthalmologique Adolphe de Rothschild, Université Denis Diderot Paris 7, France

⁷ INSERM U 1138, Paris, France

⁸ Center de Recherche, Center Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec, Canada

⁹ Department of Physiology, Royal Melbourne Hospital, University of Melbourne, Victoria, Australia

¹⁰ School of Medicine, National University of Ireland, Galway Campus, and National Institute for Preventive Cardiology, Galway, Ireland

Corresponding author:

Elizabeth Selvin, PhD, MPH
Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E Monument St, Suite 2-600
Baltimore, MD 21205
(410) 614-6928 (office, Ms. Laura Gottschalk)
eselvin@jhu.edu

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Precis: In observational data on weight loss in type 2 diabetes, large weight loss >10% was associated with increased risk of cardiovascular disease, despite improved cardiovascular risk factors.

Clinical Trial Identifier: NCT00145925, NCT00949286

Keywords: cardiovascular disease, type 2 diabetes, unintentional weight loss, weight change

ABSTRACT

Context: Weight loss is strongly recommended for overweight and obese adults with type 2 diabetes. Unintentional weight loss is associated with increased risk of all-cause mortality, but few studies have examined its association with cardiovascular outcomes in patients with diabetes.

Objective: To evaluate 2-year weight change and subsequent risk of cardiovascular events and mortality in established type 2 diabetes.

Design & Setting: ADVANCE was an international, multisite 2x2 factorial trial of intensive glucose control and blood pressure control. We examined 5 categories of 2-year weight change: >10% loss, 4-10% loss, stable (\pm <4%), 4-10% gain, >10% gain. We used Cox regression with follow-up time starting at 2 years, adjusting for intervention arm, demographics, cardiovascular risk factors, and diabetes medication use from the 2-year visit.

Results: Among 10,081 participants with valid weight measurements, average age was 66 years. By the 2-year exam, 4.3% had >10% weight loss, 18.4% had 4-10% weight loss, and 5.3% had >10% weight gain. Over the following 3 years of the trial >10% weight loss was strongly associated with major macrovascular events (HR 1.75, 95% CI: 1.26, 2.44), cardiovascular mortality (HR 2.76, 1.87, 4.09), all-cause mortality (HR 2.79, 2.10, 3.79), but not major microvascular events (HR 0.91, 0.61, 1.36), compared to stable weight. There was no evidence of effect modification by baseline BMI, age, or type of diabetes medication.

Conclusions: In the absence of substantial lifestyle changes, weight loss may be a warning sign of poor health meriting further work-up in patients with type 2 diabetes.

INTRODUCTION

Type 2 diabetes is characterized by metabolic dysregulation primarily due to excess adiposity, resulting in an increased risk of cardiovascular disease.^{1,2} Intentional weight loss of >5% is strongly recommended for overweight or obese patients with type 2 diabetes (grade A evidence by the American Diabetes Association).³ Numerous studies have shown that intentional weight loss reduces blood pressure and improves lipids and glycemic control in diabetes.⁴⁻⁶ The largest trial of intentional weight loss in diabetes, Look AHEAD, achieved a mean weight loss of 6% in the intervention arm over 4 years,⁴ but did not find a reduction in cardiovascular events, likely due to the substantially lower than expected cardiovascular disease event rate and the uptake of statins and other pharmacological treatments for cardiovascular risk factors, particularly in the control arm.⁷ A post-hoc analysis of Look AHEAD found that participants with >10% weight loss at 1 year had a significantly lower cardiovascular event rate, supporting the original hypothesis that intentional weight loss improves cardiovascular health.⁸ However, only 36% of intervention arm participants achieved >10% weight loss at 1 year. Other studies have also seen considerable challenges in long-term intentional weight loss, even among highly motivated and supported clinical trial participants.⁹ A recent observational study among participants with screen-detected diabetes demonstrated that >5% weight loss in the year following diabetes diagnosis was associated with reduced cardiovascular events after 10 years, suggesting that weight loss may be most beneficial early in the diabetes disease course.¹⁰ Thus, large and sustained intentional weight loss likely improves cardiovascular health in diabetes but is uncommon.

In contrast, unintentional weight loss is generally indicative of deteriorating health and is associated with all-cause and cardiovascular mortality.¹¹⁻¹⁴ Unintentional weight loss of >10 pounds is considered a marker of loss of physiologic reserve¹⁵ and is more likely than intentional weight loss to include loss of fat-free mass, including bone and muscle.¹⁶ It is unclear how unintentional weight loss affects risk of non-fatal cardiovascular events in the setting of diabetes.

Given the strong recommendation for weight loss in diabetes, yet the substantial difficulty in achieving sustained, clinically significant intentional weight loss, it is important to consider the consequences of unintentional weight loss. Unintentional weight loss is a substantial concern among older adults but can also affect younger individuals, particularly those with co-morbid conditions.¹⁷⁻¹⁹ It is possible that large weight loss may affect younger adults with diabetes differently than older adults. Additionally, individuals who are not overweight or obese may have more negative consequences of weight loss compared to overweight or obese. Further, since many diabetes medications influence weight,²⁰ weight changes due to these medications may be less detrimental. The objectives of this study were 1) to determine whether weight change over two years was associated with subsequent cardiovascular outcomes and death in adults with diabetes, and 2) to examine whether this association was modified by baseline BMI, age or type of glucose-lowering medications.

METHODS

Study Population

The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial had a two-by-two factorial design.²¹ One arm tested the effects of intensive glucose lowering (target HbA1c of <6.5% with use of glicazide modified release, plus other drugs as required) vs. standard glucose control targeting HbA1c according to local guidelines. A second arm tested the effects of blood pressure lowering using a combination pill of perindopril (4 mg) and indapamide (1.25 mg) compared to placebo. From 2001 to 2003, the trial enrolled 11,140 participants with type 2 diabetes ≥ 55 years of age, at high risk of cardiovascular disease, without long-term insulin use in 20 countries.²¹ The blood-pressure intervention ended in June 2007 (median follow-up 4.4 years) and the intensive glucose-lowering intervention ended in January 2008 (median follow-up 5.0 years). The trial showed beneficial effects of both intensive glucose-lowering and blood pressure lowering on the primary endpoint of combined microvascular and macrovascular events.^{22,23} Two years after the trial close-out, all study sites were invited to participate in ADVANCE-ON, a five-year observational follow-up of trial participants. Of the original 215 study sites, 172 (80%) agreed to participate, and 10,082 participants were enrolled in ADVANCE-ON beginning in January 2010.²⁴ Closeout visits for ADVANCE-ON were conducted in 2013 and 2014. All participants gave written informed consent.

Of 11,140 ADVANCE participants, we excluded those who died before their year 2 study visit (n=330) or were missing weight either at baseline (n=4) or two years (n=677) (**Figure 1**). We also excluded participants with implausible weights at either baseline or year 2 based on large (>25% or >20 kg) change that was inconsistent with measurements at subsequent clinic visits (n=48). Our study population thus included

10,081 participants with validated measurements of weight at baseline and at two years in ADVANCE. Our analyses using the extended follow-up time from ADVANCE-ON included 8064 participants.

Weight Change

During the ADVANCE trial, weight was measured biannually. We calculated percentage weight change at two years by subtracting the baseline weight from the two-year weight and dividing by the baseline weight. We chose two years after baseline because it represented a long-term change in weight, whereas a one year change may have represented short-term fluctuations that were not sustained. We categorized weight change at two years into 5 groups: >10% weight loss, 4-10% weight less, \pm <4% (stable), 4-10% weight gain, and >10% weight gain. These cutpoints were motivated by the literature on unintentional weight loss: one study showed that 4% was an optimal threshold for defining clinically important unintentional weight loss,¹⁸ while 10% weight loss is indicative of catabolism and significant loss of muscle mass.²⁵

In the context of ADVANCE, participants who were randomized to the intensive glucose-lowering arm were more likely to have received diabetes medications known to increase weight, including sulfonylureas, insulin, and thiazolidinediones (TZD).²³ To account for weight change related to diabetes medication use, we adjusted for medication use at year 2 in our primary analysis. We also conducted sensitivity analyses stratified by medication use after excluding TZDs, given the controversy surrounding TZDs during this time.²⁶

Outcomes

The primary endpoint in ADVANCE was a composite of major macrovascular and microvascular events.²³ Major macrovascular events included death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke. Major microvascular events were new or worsening nephropathy (development of albumin-to-creatinine ratio >300mg/g or doubling of serum creatinine to >2.25mg/dl), the need for renal-replacement therapy, or retinopathy (proliferative retinopathy, macular edema, blindness, or retinal photocoagulation therapy). Cardiovascular death and all-cause death were also recorded. We examined these four endpoints (major macrovascular events, major microvascular events, cardiovascular death, and all-cause death) in ADVANCE. As major microvascular events were not able to be assessed in ADVANCE-ON,²⁴ we examined major macrovascular events, cardiovascular death, and all-cause death in combined data from ADVANCE and ADVANCE-ON.

Statistical Analysis

We examined baseline characteristics of ADVANCE participants by category of 2-year weight change. To examine the association of weight change categories with each endpoint, we used Cox proportional hazards regression. For major macrovascular and major microvascular events, we excluded individuals with that endpoint prior to the 2-year visit and began follow-up time at the 2-year visit. To control for potential confounding, we adjusted for age, sex, country grouping (Asia/Eastern Europe/Established Market Economies), baseline HbA1c, baseline systolic blood pressure, history of macrovascular disease at baseline, history of microvascular disease at baseline, randomized glucose treatment assignment, randomized blood pressure treatment assignment, baseline smoking status (current/former/never), baseline statin

use, and diabetes medication use (metformin/TZDs/sulfonylureas/insulin) at year 2. We also examined whether further adjustment for baseline waist-to-height ratio, a better predictor of cardiovascular disease than BMI,^{27,28} attenuated the results. The proportional hazards assumption was checked using visual examination of the log negative log survival plots.

To determine if the type of glucose-lowering treatment might alter the association between weight change and cardiovascular outcomes, we first excluded the small number of people who took TZDs. We then tested for interaction of weight change categories with metformin, using likelihood ratio tests. We hypothesized that given metformin's known propensity to cause weight loss,²⁰ weight loss with metformin may have neutral or protective effects on macrovascular events and mortality. We additionally conducted sensitivity analyses to determine if the association between weight change and cardiovascular and mortality outcomes varied by baseline BMI (<25 vs. ≥25) or age (<65 vs. ≥65), using likelihood ratio tests. Finally, we tested for potential interaction by blood pressure treatment as well as by diuretic use, since diuretics are known to cause weight loss due to fluid loss.²⁹

Finally, since weight loss benefit for cardiovascular disease is primarily through improvements to cardiovascular risk factors, we examined unadjusted means and standard deviations of 2-year levels and 2-year change in HbA1c, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. We used a linear test for trend to determine whether changes in weight were linearly associated with changes in cardiovascular risk factors.

RESULTS

At two years, of the 10,081 participants, the majority were weight stable (5713, 56.7%), while 432 (4.3%) had weight loss >10%, 1854 (18.4%) had weight loss of 4-10%, 1548 (15.4%) had weight gain of 4-10%, and 534 (5.3%) had weight gain of >10%. Individuals with large weight loss were more likely to be older, female, randomized to perindopril/indapamide, have a larger BMI at baseline, have lower HbA1c and longer diabetes duration (**Table 1**). Individuals with large weight loss were also more likely to have a history of macrovascular disease and were less likely to be on insulin.

Median follow-up time after the year 2 visit for major macrovascular events was 3.0 years during ADVANCE and 8.4 years for ADVANCE-ON; 591 had a major macrovascular outcome during ADVANCE and an additional 978 had this outcome during ADVANCE-ON. For major microvascular events, the median follow-up time after the year 2 visit was 3.0 years and 706 had the endpoint during ADVANCE. For cardiovascular death, median follow-up time was 3.0 years with 290 events during ADVANCE and 8.6 years with 121 additional events during ADVANCE-ON. For all-cause death, median follow-up time was 3.0 years with 600 events during ADVANCE and 8.6 years with 529 additional events during ADVANCE-ON.

After adjustment, large weight loss was strongly associated with the major macrovascular events (hazard ratio, HR 1.75, 95%CI 1.26 - 2.44) during ADVANCE (**Table 2**). Large weight loss was associated with over 2.5 times greater risk of cardiovascular mortality (HR 2.76, 1.87 - 4.09) and all-cause mortality (HR 2.79, 2.10 - 3.79). Moderate (4-10%) weight loss was also associated with increased risk of all-

cause mortality (HR 1.43, 1.16 - 1.76) and was not associated with the other endpoints. Large weight gain (>10%) was marginally associated with major macrovascular events (HR 1.40, 1.00 - 1.95). For all endpoints, adjusting for cardiovascular risk factors after adjusting for demographics only minimally attenuated the results. Additional adjustment for baseline weight-to-height ratio did not change the results (data not shown).

The results for ADVANCE and overall, including ADVANCE-ON, were similar for major macrovascular events, cardiovascular death, and all-cause death (**Figure 2**). For major macrovascular events, both large weight gain and large weight loss appeared more harmful in the short-term rather than the long-term follow-up. For both cardiovascular death and all-cause death, the association of large weight loss was stronger in ADVANCE than after the additional follow-up in ADVANCE-ON.

We found no significant effect modifications of the associations between >10% weight loss, compared to stable weight, and cardiovascular events, cardiovascular death, or death by baseline age BMI or metformin use at year 2 (**Figure 3**). Metformin users with >10% weight loss appeared to not have increased risk of cardiovascular events, but the overall interaction between weight change category and metformin use was not statistically significant (p-for-interaction=0.15). We also did not see any effect modification by blood pressure arm or diuretic use (data not shown).

The associations of 2-year weight change with year 2 levels and 2-year change in cardiovascular risk factors were mixed (**Table 3**). For HbA1c, like baseline levels, year 2 levels were different across weight change categories, but the 2-year changes did not differ by weight change categories in either the intensive or standard glucose treatment arms. For all other cardiovascular disease risk factors, weight change was

significantly associated with both year 2 levels and 2-year changes (except for year 2 levels of LDL cholesterol), with improvement in cardiovascular risk factors among those who lost weight and mixed results among those who gained the most weight.

DISCUSSION

This large prospective study of adults with type 2 diabetes participating in ADVANCE found that >10% weight loss was associated with over two times higher risk of cardiovascular and all-cause mortality and was associated with 75% greater risk of major macrovascular events, compared to adults with stable weight. These associations were not significantly modified by metformin use, age, or baseline BMI. The increased risk of cardiovascular events and death in those with >10% weight loss occurred despite improvements in cardiovascular risk factors. Since cardiovascular risk factors improved more in those with 4-10% weight loss compared to >10% weight loss, it is possible that a fraction of individuals from the >10% loss group had worsening cardiovascular risk factors and were at a higher risk of cardiovascular events and mortality. Our study suggests that >10% weight loss can be a marker of increased cardiovascular risk and mortality.

To our knowledge, this is the first study to demonstrate that substantial weight loss in diabetes may be associated with increased risk of cardiovascular events. Previous studies in the general population found mixed results for weight loss and mortality, but the consensus is that unintentional weight loss is strongly tied to increased mortality.³⁰ These studies also indicated that there is heterogeneity in the effect of weight loss by intentionality.^{11-14, 31-33} In a study of middle-aged men, unintentional

weight loss was associated with 15% increased risk of mortality in individuals with existing health conditions but not in individuals without existing health conditions,¹² whereas intentional weight loss in both groups had no association with death. In an analysis of women from the same cohort, there was no association between unintentional weight loss and risk of mortality, regardless of existing health conditions, while intentional weight loss among those with existing health conditions was protective.³¹ A study of older British men found that unintentional weight loss was associated with a 71% increased risk of mortality, compared to those with stable weight, and that the association of intentional weight loss with mortality differed by whether the weight loss was due to personal choice or due to doctors' advice.¹³ Overall, these studies showed relatively less risk with unintentional weight loss compared to our finding of 179% greater mortality risk with >10% weight loss. This could be due to other studies' reliance on self-reported weight and inclusion of all amounts of weight loss compared to our high threshold of >10% weight loss. Additionally, some but not all studies found older adults had worse outcomes following weight loss,^{11,13} whereas our study found no difference in associations by age. We found that substantial weight loss in adults aged 55-65 with diabetes was similarly indicative of poor prognosis as compared to older adults in our study population.

We also found increased risk of cardiovascular events and mortality following >10% weight loss despite a decrease in cardiovascular risk factors by year 2. While this may seem counterintuitive, this finding is consistent with other literature showing that the association of cardiovascular risk factors with cardiovascular events and mortality becomes weaker and sometimes inverse with increasing age³⁴⁻³⁶ and frailty.^{37,38} Thus,

as overall health declines, cardiovascular risk factors become less indicative of future risk.

The extremes of weight change tended to be more strongly associated with outcomes in the shorter-term follow-up of ADVANCE compared to the longer-term follow-up of ADVANCE-ON. This could be due to subsequently changing weight that reduced the long-term effects, or, for large weight loss, the cardiometabolic benefits of weight loss may act over a longer time frame.

Patterns of intentional weight loss vary substantially, but during intensive weight loss attempts, weight often initially sharply declines during the first few months and then is slowly regained over the subsequent months to years.³⁹ While clinical trials aim for sustained weight loss of 7%,^{7,40,41} in real-world settings, intentional weight loss attempts average between 3-5% during the first 3 months to 1 year.^{42,43} However, the magnitude of unintentional weight loss may be similar to intentional weight loss, with several studies showing self-reported unintentional weight loss around 4-5%.^{13,18} Medicare-certified nursing homes are required to report on individuals losing >5% weight in 30 days or >10% in 180 days, as these rapid losses may indicate failing health. In our study, we defined the highest category of weight loss to be >10% over two years, a high threshold that likely captures mostly individuals with unintentional weight loss and a small fraction of individuals with intentional weight loss. Providers should be aware of the difficulties of achieving sustained intentional weight loss. Even among middle-aged patients with diabetes, modest or large weight loss in the absence of dietary and exercise modifications is potentially a cause for concern.

Other studies have noted that frequent weight changes, or weight cycling, may independently contribute to increased morbidity and mortality.^{44,45} In a sensitivity analysis, we controlled for weight cycling (defined as >5kg gain and loss within the first two years) and our results did not change (data not shown), indicating that weight cycling does not explain the association between large weight loss and cardiovascular disease and mortality.

Unintentional weight loss may be due to a variety of causes. Although unintentional weight loss is often thought to be due to undiagnosed illness, such as cancer, many cases of unintentional weight loss are idiopathic even after clinical investigation.^{25,46} Among older adults, unintentional weight loss may be related to diminished appetite due to decreased physical activity, difficulty with dentition, drug interactions, depression, dementia, or loss in taste and/or smell.²⁵ It is important to identify the causes so the appropriate corrective actions can be taken, such as fitting dentures for people with poor dentition, changing medications or their timing to reduce influence on appetite, and increasing caloric intake through adding preferred foods or increasing the size of the favorite meal of the day.²⁵

Unintentional weight loss likely represents a loss of physical reserve and activation of catabolic pathways with wide-ranging harms. The physiology of unintentional weight loss has primarily been studied in cachexia, in which increases in catabolic cytokines contribute to myocyte apoptosis and inflammation.⁴⁷ Large weight loss with nutritional deficiencies could also lead to electrolyte imbalances, causing cardiac arrhythmias.

There are several limitations to our study. First, we were not able to determine whether weight change was intentional or unintentional. The observed detrimental effects of weight loss on mortality are more consistent with unintentional weight loss, but there was likely a mix of intentional and unintentional weight loss. Second, this trial may miss some of the potential metabolic benefits of weight loss due to the interventions for blood pressure and HbA1c. We observed that while participants' 2-year weight change was not correlated with 2-year HbA1c change, other cardiovascular risk factors did improve with weight loss, suggesting that the cardiometabolic benefits of weight loss were realized except for HbA1c. Third, we were underpowered to look at interactions, and thus results by medication use should be interpreted appropriately. Fourth, we did not have information available on diet, which likely influences both weight and cardiovascular disease.^{48,49} Finally, we were not able to evaluate the long-term association of weight change with microvascular events due to the change in endpoint definition for ADVANCE-ON.

Our study also has several important strengths. ADVANCE was a large trial with ethnically diverse participants and adjudicated endpoints. Second, weight was measured, rather than self-reported, increasing the validity of our primary exposure of interest, weight change. Third, because medications were closely monitored, we were able to determine if glucose-lowering medication use altered the association of weight change with outcomes.

In conclusion, our study demonstrated a detrimental association of weight loss on cardiovascular outcomes and mortality in adults with type 2 diabetes. Since many causes of unintentional weight loss can be mitigated,^{25,46} timely assessment is critical.

Unless patients specifically report lifestyle changes to lose weight, even modest weight loss may be a marker of declining health for which further clinical investigation is merited.

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AKL conceived and designed the study, conducted statistical analyses, and wrote the manuscript. MW provided guidance for the statistical analysis and made critical revisions to the manuscript for important intellectual content. DW also conducted statistical analyses and made critical revisions to the manuscript for important intellectual content. ES helped to conceive and design the study, provided guidance for the statistical analysis, and made critical revisions to the manuscript for important intellectual content. All other authors made critical revisions to the manuscript for important intellectual content.

ES is the guarantor of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but may be available from the corresponding author on reasonable request.

REFERENCES:

1. Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, Deedwania P, Eckel RH, Ershow AG, Fradkin J, Inzucchi SE, Kosiborod M, Nelson RG, Patel MJ, Pignone M, Quinn L, Schauer PR, Selvin E, Vafiadis DK. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. *Diabetes Care*. 2015; 38(9):1777-1803.
2. Halter JB, Musi N, McFarland Horne F, Crandall JP, Goldberg A, Harkless L, Hazzard WR, Huang ES, Kirkman MS, Plutzky J, Schmader KE, Ziemann S, High KP. Diabetes and Cardiovascular Disease in Older Adults: Current Status and Future Directions. *Diabetes*. 2014;63:2578-2589.
3. American Diabetes Association. Standards of Medical Care in Diabetes-- 2019. *Diabetes Care*. 2019;42(Suppl 1).
4. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Hill JO, Brancati FL, Peters A, Wagenknecht L. Benefits of Modest Weight Loss in Improving Cardiovascular Risk Factors in Overweight and Obese Individuals With Type 2 Diabetes. *Diabetes Care*. 2011;34(7):1481-1486.
5. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle Weight-Loss Intervention Outcomes in Overweight and Obese Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *J Acad Nutr Diet*. 2015;115(9):1447-1463.
6. Wing RR, The Look AHEAD Research Group. Long-Term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals with Type 2 Diabetes Mellitus. *Arch Intern Med*. 2010;170(17):1566-1575.
7. The Look AHEAD Research Group. Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. *N Engl J Med*. 2013:155-164.
8. The Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2016;4(11):913-921.
9. Dombrowski SU, Avenell A, Sniehot FF. Behavioural interventions for obese adults with additional risk factors for morbidity: Systematic review of effects on behaviour, weight and disease risk factors. *Obes Facts*. 2010;3(6):377-396.
10. Strelitz J, Ahern AL, Long GH, Hare MJL, Irving G, Boothby CE, Wareham NJ, Griffin SJ. Moderate weight change following diabetes diagnosis and 10 year incidence of cardiovascular disease and mortality. *Diabetologia*. 2019;62:1391-1402.

11. Wedick NM, Barrett-Connor E, Knoke JD, Wingard DL. The relationship between weight loss and all-cause mortality in older men and women with and without diabetes mellitus: the Rancho Bernardo study. *J Am Geriatr Soc*. 2002;50(11):1810-5.
12. Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective Study of Intentional Weight Loss and Mortality in Overweight White Men Aged 40-64 Years. *Am J Epidemiol*. 1999;149(6):491-503.
13. Wannamethee SG, Shaper AG, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. *Arch Intern Med*. 2005;165(9):1035-1040.
14. Chen Y, Yang X, Wang J, Li Y, Ying D, Yuan H. Weight loss increases all-cause mortality in overweight or obese patients with diabetes: A meta-analysis. *Medicine*. 2018;97(35):e12075.
15. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in Older Adults: Evidence for a Phenotype. *J Gerontol*. 2001;56(3):146-156.
16. Ensrud KE, Ewing SK, Stone KL, Cauley JA, Bowman PJ, Cummings SR, Study of Osteoporotic Fractures Research Group. Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. *J Am Geriatr Soc*. 2003;51(12):1740-7.
17. Rabinovitz M, Pitlik SD, Leifer M, Garty M, Rosenfeld JB. Unintentional weight loss: a retrospective analysis of 154 cases. *Arch Intern Med*. 1986;146(1):186-7.
18. Wallace JL, Schwartz RS, LaCroix AZ, Uhlmann RF, Pearlman RA. Involuntary Weight Loss in Older Outpatients: Incidence and Clinical Significance. *J Am Geriatr Soc*. 1995;43:329-337.
19. Thompson MP, Morris LK. Unexplained weight loss in the ambulatory elderly. *J Am Geriatr Soc*. 1991;39(5):497-500.
20. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140-149.
21. ADVANCE Management Committee. Study rationale and design of the ADVANCE study: a randomised trial of blood pressure lowering and intensive glucose control in high-risk individuals with type 2 diabetes mellitus. Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-R. *Diabetologia*. 2001;44:1118-1120.
22. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829-840.
23. ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2008;358(24):2560-2572.
24. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hiraoka Y, Arima H, Monaghan H, Joshi R, Colagiuri S, Cooper ME, Glasziou P, Grobbee D, Hamet P, Harrap S,

- Heller S, Lisheng L, Mancina G, Marre M, Matthews DR, Mogensen CE, Perkovic V, Poulter N, Rodgers A, Williams B, MacMahon S, Patel A, Woodward M. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med*. 2014;371(15):1392-1406.
25. Bouras EP, Lange SM, Scolapio JS. Rational Approach to Patients With Unintentional Weight Loss. *Mayo Clin Proc*. 2001;76(9):923-929.
26. Tanne, JH. FDA places “black box” warning on antidiabetes drugs. *BMJ*. 2007;334(7606):1237.
27. Rådholm K, Chalmers J, Ohkuma T, Peters S, Poulter N, Hamet P, Harrap S, Woodward M. Use of the waist-to-height ratio to predict cardiovascular risk in patients with diabetes: Results from the ADVANCE-ON study. *Diabetes, Obes Metab*. 2018;20(8):1903-1910.
28. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: Systematic review and meta-analysis. *Obes Rev*. 2012;13(3):275-286.
29. Fries ED, Reda DJ, Materson BJ. Volume (weight) loss and blood pressure response following thiazide diuretics. *Hypertension*. 1988;12: 244-250.
30. Harrington M, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev*. 2009;22(1):93-108.
31. Williamson D, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in overweight US white women aged 40 to 64 years. *Am J Epidemiol*. 1995;141:1128-1141.
32. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care*. 2000;23(10):1499-1504.
33. Wannamethee SG, Shaper AG, Walker M. Weight Change, Weight Fluctuation, and Mortality. *Arch Intern Med*. 2002;162:2575-2580.
34. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. *Lancet*. 1997;350:1119-1123.
35. Fried LP, Kronmal RA, Newman AB, Bild DE, Mittlemark MB, Polak JF, Robbins JA, Gardin JM. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *JAMA*. 1998;279(8):585-592.
36. Satish S, Freeman DH, Ray L, Goodwin JS. The relationship between blood pressure and mortality in the oldest old. *J Am Geriatr Soc*. 2001;49(4):367-374.
37. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: The impact of frailty. *Arch Intern Med*. 2012;172(15):1162-1168.
38. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, Guilliford MA. Systolic Blood Pressure Trajectory, Frailty, and All-Cause Mortality >80 Years of Age. *Circulation*. 2017;135(24):2357-2368.
39. Dombrowski SU, Knittle K, Avenell A, Araújo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: Systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2014;348:1-12.

- 560 40. The Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes):
561 Design and methods for a clinical trial of weight loss for the prevention of
562 cardiovascular disease in type 2 diabetes. *Control Clin Trials*. 2003;24(5):610-
563 628.
- 564 41. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA,
565 Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle
566 intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
- 567 42. Ali MK, Echouffo-Tcheugui JB, Williamson DF. How effective were lifestyle
568 interventions in real-world settings that were modeled on the Diabetes Prevention
569 Program? *Health Affairs*. 2012 Jan;31(1):67-75.
- 570 43. Gudzone KA, Doshi RS, Mehta AK, Chaudhry ZW, Jacobs DK, Vakil RM, Lee
571 CJ, Bleich SN, Clark JM. Efficacy of commercial weight-loss programs: an
572 updated systematic review. *Ann Intern Med*. 2015 Apr 7;162(7):501-12.
- 573 44. Mehta T, Smith DL, Muhammad J, Casazza K. Impact of weight cycling on risk of
574 morbidity and mortality. *Obes Rev*. 2014;15(11):870-881.
- 575 45. Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-
576 Weight Fluctuations and Outcomes in Coronary Disease. *N Engl J Med*.
577 2017;376(14):1332-1340.
- 578 46. Marton KI, Sox HC, Krupp JR. Involuntary Weight Loss: Diagnostic and
579 Prognostic Significance. *Ann Intern Med*. 1981;95:568-574.
- 580 47. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cachexia and
581 sarcopenia: Mechanisms and potential targets for intervention. *Curr Opin*
582 *Pharmacol*. 2015;22:100-106.
- 583 48. Mazidi M, Katsiki N, Mikhailidis DP, Sattar N, Banach M. Lower carbohydrate
584 diets and all-cause and cause-specific mortality: a population-based cohort study
585 and pooling of prospective studies. *Eur Heart J*. 2019;0:1-10.
- 586 49. Tobias DK, Chen M, Manson JAE, Ludwig DS, Willett W, Hu FB. Effect of low-fat
587 diet interventions versus other diet interventions on long-term weight change in
588 adults: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol*.
589 2015;3(12):968-979.

Figure 1. Study Design and Identification of the Analytic Cohort.

Participants were excluded from the analysis of major macrovascular events if they had a major macrovascular event before two years (n=249). Participants were excluded from the analysis of microvascular events if they had a microvascular event before two years (n=377).

Figure 2. Adjusted* hazard ratios and 95% confidence intervals of major macrovascular events, cardiovascular death, and all-cause death according to categories of 2-year weight change, ADVANCE and ADVANCE-ON, n=10081.

*Adjusted for age, sex, region, baseline HbA1c, baseline systolic blood pressure, history of macrovascular disease at baseline, history of microvascular disease at baseline, glucose treatment assignment, blood pressure treatment assignment, baseline smoking status (current/former/never), baseline statin use, and diabetes medication (metformin/thiazolidinediones/sulfonylureas/insulin) use at year 2.

Figure 3. Hazard ratios (95%CIs) for major macrovascular events and cardiovascular and all-cause death for >10% weight loss over 2 years (vs. stable weight), by age, BMI, and metformin use.

All p-for-interaction with weight change categories >0.05. Models adjusted for age, sex, region, baseline HbA1c, baseline systolic blood pressure, history of macrovascular disease at baseline, history of microvascular disease at baseline, glucose treatment assignment, blood pressure treatment assignment, baseline smoking status (current/former/never), baseline statin use, and diabetes medication (metformin/thiazolidinediones/sulfonylureas/insulin) use at year 2 (unless variable was being tested for interaction). Models evaluating interaction by metformin use excluded individuals using thiazolidinediones at year 2.