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Estimated effect of weight loss on risk of coronary heart disease and mortality in middle-aged or older women: sensitivity analysis for unmeasured confounding by undiagnosed disease

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Abstract

Background—The evidence on the effect of weight loss on coronary heart disease (CHD) or mortality has been mixed. The effect estimates can be confounded due to undiagnosed diseases that may affect weight loss.

Methods—We used data from the Nurses' Health Study to estimate the 26-year risk of CHD under several hypothetical weight loss interventions (e.g. maintain baseline weight, lose 5% of weight every 2 years if overweight/obese). We applied the parametric g-formula and implemented a novel sensitivity analysis for unmeasured confounding due to undiagnosed disease by imposing a lag time for the effect of weight loss on chronic disease. Sensitivity analyses were conducted by using only the first 16 years of follow-up, restricting the analysis to women who had reported

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Supplementary Online Material

eText: Technical Appendix

eFigure1: Estimated effects of weight loss on risk of type 2 diabetes using different minimum latent periods, Nurses' Health Study (1982–2008)

eTable 1: Covariates used to model incidence of CHD* in the Nurses' Health Study (1982–2008)

eTable 2: Estimated effects of weight loss, quitting smoking, exercise and drinking alcohol on coronary heart disease using different Minimum Latency Periods, Nurses' Health Study (1982–2008)

eTable 3: Estimated effects of weight loss, quitting smoking, exercise and drinking alcohol on risk of death using different Minimum Latency Periods, Nurses' Health Study (1982–2008)

eTable 4: Estimated effects of weight loss on risk of type 2 diabetes, Nurses' Health Study (1982–2008)

intentional weight loss, those who were younger (<49 years old at baseline), and those who never smoked.

Results—The 26-year risk of CHD under no weight loss intervention was 5.0% (95% Confidence Interval 4.9, 5.3). The estimated risk did not change under hypothetical weight loss interventions using lag times from 0 to 18 years. For a 6-year lag time, the risk ratios of CHD for weight loss compared with no intervention ranged from 1.00 (0.99, 1.02) to 1.02 (0.99, 1.05) for different degrees of weight loss with and without restricting the intervention to participants with no major chronic disease. Similarly, no protective effect of weight loss was estimated for mortality risk. In contrast, we estimated a protective effect of weight loss on risk of type 2 diabetes. The estimated effect of weight loss on CHD and mortality remained null in all sensitivity analyses.

Conclusion—We estimated that maintaining weight or losing weight after becoming overweight or obese does not reduce the risk of CHD or death in this cohort of middle-aged US women. Unmeasured confounding, measurement error, and model misspecification are possible explanations but they did not prevent us from estimating a beneficial effect of weight loss on diabetes.

MeSH headings

weight loss; prevention; lifestyle; coronary heart disease; mortality; parametric g-formula

Introduction

The global prevalence of obesity has almost doubled in the past three decades. In 2008, 12% of adults were obese and 34% were overweight.¹ When compared with normal weight, obesity is associated with an increased incidence of both coronary heart disease (CHD) and all-cause mortality.² The consistent association between obesity and CHD/mortality in observational studies begs the questions of whether weight loss decreases, and weight gain increases, the risk. Unfortunately, there are no randomized trials of weight change with long enough follow-up time to detect changes in event rates and the findings from observational studies range from increased mortality risk after weight gain^{3,4} to increased risk of mortality^{5,6} or CHD^{7,8} after weight loss. Other observational studies have found no association^{9,10} or reduced risk after intentional weight loss.^{11,12} Two observational studies found a lower risk of CHD, diabetes and mortality among obese adults that did versus did not undergo bariatric surgery.^{13,14}

In a previous analysis using the parametric g-formula,¹⁵ we estimated no effect of weight loss on CHD risk in middle-aged or older women who participate in the Nurses' Health Study. However, our estimate may have been biased due to unmeasured confounding by severity of concomitant diseases, frailty, or undiagnosed chronic diseases. Because data on frailty is rarely collected and data on undiagnosed disease is by definition unavailable, this confounding cannot be adjusted for, and one can only evaluate its potential impact on the effect estimates via sensitivity analyses.

Here we implement several sensitivity analyses¹⁶ for the effect of weight loss on CHD and mortality risk. Specifically, we considered the comparative effects of four sustained

interventions on body weight in the Nurses' Health Study: maintain baseline weight, lose 5% of BMI every 2 years if BMI ≥ 25 kg/m², lose 10% every 2 years of BMI if BMI ≥ 25 kg/m², and lose 10% of BMI every 2 years if BMI ≥ 23 kg/m². For comparison purposes, we also considered interventions involving smoking cessation, moderate alcohol drinking, and moderate to vigorous exercise for at least 3.5 hours/week.

Methods

Study population and data ascertainment

The Nurses' Health Study is a prospective cohort study that started in 1976 when 121,740 US female nurses aged 30 to 55 years responded to a mailed questionnaire on sociodemographic, lifestyle, anthropometric, and clinical factors. Biennial questionnaires have been mailed since then to update the information.

CHD was defined as the first occurrence of fatal or non-fatal myocardial infarction as reported by the participants and confirmed by a medical record review.¹⁷ Height in 1976 and weight every two years were self-reported. A validation study on 184 participants in the Boston area found that the correlation between self-reported and measured weight was 0.96 with an average under-reporting of 1.5 kilograms.¹⁸ A composite score¹⁷ of diet during the previous 12 months was derived from a validated food frequency questionnaire mailed in 1980 (short version), 1982, 1984, 1986 and every 4 years afterwards. Exercise was reported in 1980, 1982, 1986, 1988, and every 4 years afterwards using a validated questionnaire on type, frequency and intensity of each activity. We summed up the duration of activities requiring ≥ 3 Metabolic Equivalent Task scores per hour, including brisk walking. To prevent implausible values from affecting the results, we truncated the 0.1% values of BMI outside of the range 15–65 kg/m² and exercise greater than 35 hours per week.

Our analyses were restricted to women who provided adequate dietary and covariate data and had no history of cardiovascular disease, diabetes or cancer at baseline. For each woman, follow-up started in 1982 and finished at CHD, death, incomplete follow-up (i.e., not returning a questionnaire), or administrative end of follow-up in June 2008, whichever happened first.

Weight loss interventions

We considered four different types of hypothetical weight loss interventions: type 1 'forces' all women to maintain their baseline BMI level throughout the follow-up; type 2 forces women who attain a BMI of ≥ 25 kg/m² or higher to lose 5% of their body weight during the next 2-year period; type 3 forces women who attain a BMI of ≥ 25 kg/m² or higher to lose 10% of their body weight during the next 2-year period; finally, type 4 forces women who attain a BMI of ≥ 23 kg/m² or higher to lose 10% of their body weight during the next 2-year period. The Appendix provides a formal definition of these interventions. For comparison purposes, we also considered previously studied interventions on smoking cessation, exercise, and alcohol drinking.

Statistical approach: the parametric g-formula

We used the parametric g-formula to estimate the 26-year risks of the outcome under each of the hypothetical interventions listed above. The primary outcome was CHD and the secondary outcome was all-cause mortality. Because the effect of weight loss on diabetes risk is well established, we also studied diabetes as an outcome for comparison purposes.

Our g-formula estimates were adjusted for the following baseline variables: age (in 5 year categories), family history of CHD, smoking and oral contraceptive use before 1980, marital status, education, husband's education, employment, and stress in daily life and work, BMI, exercise, smoking, dietary score and alcohol use. We also adjusted for the following time-varying covariates: multivitamin, aspirin, statin, post-menopausal hormone and alcohol use; smoking, exercise, dietary score, high blood pressure, high serum cholesterol, type 2 diabetes, stroke, angina or coronary artery bypass graft, cancer, menopause, osteoporosis, incidence of other major cardiovascular diseases (congestive heart failure, peripheral vascular diseases, pulmonary embolism, atrial fibrillation), incidence of major inflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis, gout, ulcerative colitis) and incidence of neurologic and other major chronic diseases (depression, Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, chronic renal failure and emphysema). We adjusted for incident myocardial infarction in analyses with outcomes other than CHD (see eTable 1 for the list of covariates and their functional forms).

The g-formula is the generalization of standardization for time-varying exposures and confounders and has been previously used to estimate the effect of lifestyle interventions on the risk of CHD and diabetes.^{15,19,20} Briefly, the standardized risk is a weighted average of the conditional outcome risks with the conditional probability density functions of the time-varying confounders as weights. The weighted average is approximated using a Monte Carlo simulation (of 10,000 individuals in our analyses) and the conditional distributions of the confounders are estimated via parametric regression models.

We compared the estimated risk under each hypothetical intervention with the risk under no intervention via ratios and differences. To estimate 95% confidence intervals, we used non-parametric bootstrapping with 200 samples. As in previous analyses,^{15,19,20} we also computed the proportion of individuals whose data were not consistent with the hypothetical intervention (i.e., would have to be 'intervened' on) during the follow-up and during each 2-year period on average.

Sensitivity analysis for unmeasured confounding due to undiagnosed chronic diseases

Unlike previous g-formula analyses, ours accommodates a sensitivity analysis for unmeasured confounding due to undiagnosed chronic diseases (often referred to as "reverse causation"). This type of unmeasured confounding occurs because undiagnosed chronic disease can be severe enough to cause weight change and is often a strong determinant of future incidence of the disease or mortality (Figure 1). To implement this sensitivity analysis, we needed to define 1) the set of major chronic diseases that are severe enough to affect both weight change and outcome risk, and 2) the minimum latent period (MLP) required for weight change to affect any of the major chronic diseases or the outcome.

Our set of major chronic diseases included cancer, diabetes, angina pectoris, stroke, myocardial infarction, chronic heart failure, peripheral vascular disease, pulmonary embolism, atrial fibrillation, chronic kidney disease, gout, systemic lupus erythematosus, ulcerative colitis, rheumatoid arthritis, emphysema, depression, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis.

Because the duration of the MLP is unknown and estimates vary substantially across studies,^{21,22} we used an MLP of 6 years for all diseases in the main analysis, and conducted further sensitivity analyses in which the MLP ranged from 0 to 18 years. It follows from results in Reference #16 that if (i) the duration of the MLP is correct, (ii) the duration of MLP is greater than the minimum time required for the undiagnosed chronic diseases to be clinically detectable, and (iii) diagnosis of a major chronic disease (other than the outcome of interest) implies that the disease existed in an undiagnosed or pre-clinical stage for MLP years, then a modified g-formula analysis that lags treatment and covariate data by the MLP can validly estimate the outcome risk under various weight change interventions.

Sensitivity analysis for unmeasured confounding due to disease severity and frailty

Even after making assumptions (i)–(iii) defined as above, the validity of our results requires that we can successfully control for confounding by chronic disease severity and frailty. However, such confounding may be intractable because the data required for adjustment are not available.¹⁶ One way to bypass this potentially intractable confounding is to change the causal question: rather than consider hypothetical interventions that are applied at each time t to everybody, we will consider restricted interventions that are applied at each time t to those individuals who do not have a (clinical or subclinical) chronic disease or frailty (defined as reaching age 70) at t . See a formal description of the restricted interventions in the Appendix.

To see why changing the question circumvents confounding, note that at each time t there are 2 groups of individuals without a diagnosed chronic disease: (a) those with undiagnosed chronic diseases severe enough to influence weight change at t , and (b) those who are free of such diseases. If the confounding by severity cannot be fully adjusted, we cannot unbiasedly estimate the effects of interventions applied to group (a), but we can still unbiasedly estimate the population risk under interventions that are restricted to those without chronic disease at t under the assumption of no unmeasured confounding given the observed covariates in group (b).

Unfortunately, the data observed through t are insufficient to distinguish between individuals in groups (a) and (b); they all appear to be free of disease at t . However, under our assumptions (i)–(iii), anyone with undiagnosed disease at t will have been diagnosed by $t + \text{MLP}$. Therefore, we can determine who is in group (b) by observing whether they develop chronic disease in the next MLP years. As BMI can have no effect on the development of disease within this period, bias is not introduced by this procedure.

The choice between the original and the restricted interventions involves a tradeoff between validity and feasibility. On one hand, by choosing the restricted intervention we increase the plausibility of the assumption of no unmeasured confounding. On the other hand, these

restricted interventions cannot be implemented in practice because the presence of undiagnosed disease at t is not known until later. For example, with an MLP of 6 years, one needs to decide whether to intervene now based on knowledge that will only be obtained when the disease is diagnosed after 6 or more years. Such an intervention is clearly infeasible, but estimating the risk under this intervention is still useful as a sensitivity analysis. Note that in populations with high disease incidence, the restricted intervention may be applied to only a small proportion of the population and might be uninteresting even as a sensitivity analysis.

Other sensitivity analyses

We assessed the sensitivity of our results to several analytic decisions. Specifically, we examined if results were robust to the length of follow-up (using first 16 years instead of 26); ordering of time-varying variables in the modeling process (using BMI as the last variable versus the 11th); the definition of frailty (age 65 versus 70 years); and restriction to never-smoking women at baseline or those who had reported intentional weight loss in 1992. Furthermore, we conducted an analysis where the follow-up started in 1978 (to be able to start the interventions in younger women) and continued the follow-up until 2010. This analysis, however, adjusted for fewer covariates as information on many risk factors were not available in 1978. We also estimated the effect of weight gain (gain 5% of BMI every 2 years if BMI < 30 kg/m² and not intractably confounded). Finally, we conducted a sensitivity analysis for death as an outcome in which the lag time between weight loss and diagnosis is 2 years for diabetes and 6 years for other major chronic diseases or death.

The above procedures are formally described in the Appendix. All analyses were conducted using SAS 9.3 (SAS Institute Inc. Cary, NC). The g-formula SAS macro and its documentation are available at <http://www.hsph.harvard.edu/causal/software>.

Results

Of 73,318 women who were eligible for the main analysis (Figure 2), 2843 had CHD, 7730 died from other causes, and 17,916 had incomplete follow-up (i.e., not responded to a questionnaire). Table 1 shows their baseline characteristics. During the follow-up women gained 1.6 kg/m² on average; 5% of women gained 7.8 kg/m² or more and 5% of women lost 3.5 kg/m² or more.

The estimated 26-year risk of CHD under no weight loss intervention was 5.0% (95% Confidence Interval 4.9, 5.3). The risk estimate did not change under any of the weight loss interventions with an MLP of 6 years (Table 2). Not intervening on intractably confounded subgroups did not affect the results materially though, as expected, the proportion of the study population that had to be intervened on decreased (e.g. from 73% to 43% in the 'lose 5% of BMI each period if above 25 kg/m²' intervention). Increasing the MLP from 0 to 18 years (Figure 3, eTable 2) had no impact on the estimated risk under any weight loss intervention, but attenuated the estimated risk under interventions on smoking cessation, exercise, and alcohol drinking. For all four interventions, increasing the MLP reduced the proportions of person-times that were intervened on. For example, the proportion of person-

times intervened on to increase exercise to 3.5 hours per week was 87% with an MLP of 0 years, 71% with 6 years, and 27% with 18 years (eTable 2).

The estimated 26-year risk of death did not change under any weight loss interventions (Table 3), but decreased under interventions on smoking, alcohol use, and exercise (Figure 4, eTable 3). In contrast with CHD and mortality, the estimated 26-year risk of type 2 diabetes decreased under all the weight loss interventions (eTable 4, eFigure1).

The estimated effects of weight loss interventions did not change materially in any of the sensitivity analyses (Table 4). Using the full sample of 73,318 women instead of a random sample of 10,000 for the simulations did not affect the width of the confidence intervals materially.

Discussion

In this cohort of middle-aged or older women, we estimated that maintaining weight or losing weight after becoming overweight or obese does not reduce the risk of CHD or death. In contrast, we estimated that the same weight loss interventions reduce the risk of type 2 diabetes by one-fifth to one-third. Our inability to detect an effect of weight loss on CHD and death risk may be explained by a truly null causal effect of weight loss in middle-aged women, the inadequacy of self-reported BMI, model misspecification, or bias due to residual confounding.

Weight loss might not affect the risk of CHD in middle-aged women if, for example, established atherosclerosis in coronary arteries could not be reversed with weight loss. Several randomized trials of healthy diet and exercise for weight loss in women did not find slower progression of atherosclerosis measured using carotid artery intima-media thickness over a follow-up period of 2 to 4 years.^{23,24} Similarly, a few trials of drug-induced weight loss failed to show a slower progression of atherosclerosis^{25,26} or reductions in CHD risk.²⁷ Most randomized trials of lifestyle interventions for weight loss have found reductions in CHD risk factors²⁸ and diabetes incidence²⁹ which should theoretically lead to reductions of CHD and mortality risk. However, a recent large randomized trial of intensive lifestyle interventions which led to 8.6% weight loss among type 2 diabetic patients did not reduce cardiovascular mortality.³⁰ Many observational studies found an increased risk of all-cause or cardiovascular mortality after weight loss,^{4,5,9,10} but their estimates may be confounded or confounders may be inappropriately adjusted for.³¹ When using the parametric g-formula, we found no effect of weight loss on CHD risk in the Nurses' Health Study¹⁵ and the Offspring Cohort of the Framingham Heart Study.³² Observational studies evaluating bariatric surgery found a lower risk of diabetes, CHD and mortality among obese adults.^{13,14,33} Bariatric surgery may affect diabetes via its impact on the endocrine functions of the proximal intestine rather than on weight loss.³⁴

BMI may not be a good indicator of abdominal obesity² especially in older individuals and postmenopausal women, in whom weight loss may reflect loss of muscle mass rather than fatty tissue. Thus our null estimates might have missed an effect of reducing abdominal adiposity on CHD risk. Further, weight, height, exercise and diet were all self-reported and

therefore subject to recall or reporting errors, and the resulting bias might obscure an effect (though the magnitude and direction of the bias is hard to predict in time-varying analyses where factors act as both exposure and confounders). Despite these limitations, we were able to find a protective effect of weight loss on diabetes risk.

The validity of our results requires no misspecification of the models used for the parametric g-formula. Though correct specification of the models under intervention cannot be demonstrated, the similarity of the observed and estimated risks indicates that the models for the observed data are not substantially miss-specified under no intervention.

Unmeasured confounding is always a potential limitation of observational studies. We assumed that, after adjusting for covariates, the only residual confounding was due to undiagnosed disease and frailty. We then used novel sensitivity analyses for unmeasured confounding by undiagnosed disease. Our method assumes (1) the existence of a lag (6 years in the main analysis) between weight loss and its potential effects on chronic diseases, (2) that any undiagnosed disease would have either been diagnosed or led to death within this period, and (3) that any diagnosed disease would have been present in an undiagnosed or subclinical level during the specified lag time.

Imposing this latency period and restricting the intervention to those without intractable confounding did not affect the null effect estimate for weight loss interventions on CHD and mortality risk. However, incorporating these changes diluted the effect of weight loss on type 2 diabetes, as well as the effect of lifestyle interventions other than weight loss on CHD. This dilution may occur because the selected latency periods may be longer than the ‘true’ latency period, which would lead to missing the true exposure window,²² and because the intervention affects a lower proportion of the study population.

Our hypothetical weight loss interventions remain vague as to how exactly the participants lost weight.^{35,36} Therefore, our estimates should be interpreted as the effects of weight loss interventions that can be a combination of different interventions---exercise, caloric intake, drugs---that the women who lost weight in the Nurses’ Health Study did indeed use.³⁷ We did not have enough information to distinguish intentional from unintentional weight loss during the entire follow-up. However, restricting the study population to those who had reported intentional weight loss in one questionnaire did not change the results.

Finally, our results may not be directly generalizable to the current context of the obesity epidemic in the US and other developed countries where young adults have gained weight much earlier in their life compared with our sample women who were middle-aged in the 1980s. Future research should focus on prospective studies of younger men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Stevens GA, Singh GM, Lu Y, Danaei G, Lin JK, Finucane MM, Bahalim AN, McIntire RK, Gutierrez HR, Cowan M, Paciorek CJ, Riley L, Ezzati M. National, regional, and global trends in adult overweight and obesity prevalences. *Popul Health Metr*. 2012; 10(1):22. [PubMed: 23167948]
2. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. 2011; 377(9771):1085–1095. [PubMed: 21397319]
3. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women. *N Engl J Med*. 1995; 333(11):677–685. [PubMed: 7637744]
4. Galanis DJ, Harris T, Sharp DS, Petrovitch H. Relative weight, weight change, and risk of coronary heart disease in the Honolulu Heart Program. *Am J Epidemiol*. 1998; 147(4):379–386. [PubMed: 9508105]
5. Mikkelsen KL, Heitmann BL, Keiding N, Sorensen TI. Independent effects of stable and changing body weight on total mortality. *Epidemiology*. 1999; 10(6):671–678. [PubMed: 10535779]
6. Nilsson PM, Nilsson JA, Hedblad B, Berglund G, Lindgarde F. The enigma of increased non-cancer mortality after weight loss in healthy men who are overweight or obese. *J Intern Med*. 2002; 252(1):70–78. [PubMed: 12074741]
7. Lee IM, Paffenbarger RS Jr. Change in body weight and longevity. *JAMA*. 1992; 268(15):2045–2049. [PubMed: 1404740]
8. Nanri A, Mizoue T, Takahashi Y, Noda M, Inoue M, Tsugane S. Weight change and all-cause, cancer and cardiovascular disease mortality in Japanese men and women: the Japan Public Health Center-Based Prospective Study. *Int J Obes (Lond)*. 2010; 34(2):348–356. [PubMed: 19918251]
9. French SA, Folsom AR, Jeffery RW, Williamson DF. Prospective study of intentionality of weight loss and mortality in older women: the Iowa Women's Health Study. *Am J Epidemiol*. 1999; 149(6):504–514. [PubMed: 10084239]
10. 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. [PubMed: 10084238]
11. Gregg EW, Gerzoff RB, Thompson TJ, Williamson DF. Intentional weight loss and death in overweight and obese U.S. adults 35 years of age and older. *Ann Intern Med*. 2003; 138(5):383–389. [PubMed: 12614090]
12. Wannamethee SG, Shaper AG, Walker M. Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes. *J Epidemiol Community Health*. 2005; 59(2):134–139. [PubMed: 15650145]
13. Sjostrom L, Peltonen M, Jacobson P, Sjostrom CD, Karason K, Wedel H, Ahlin S, Anveden A, Bengtsson C, Bergmark G, Bouchard C, Carlsson B, Dahlgren S, Karlsson J, Lindroos AK, Lonroth H, Narbro K, Naslund I, Olbers T, Svensson PA, Carlsson LM. Bariatric surgery and long-term cardiovascular events. *JAMA*. 2012; 307(1):56–65. [PubMed: 22215166]
14. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007; 357(8):753–761. [PubMed: 17715409]

15. Taubman SL, Robins JM, Mittleman MA, Hernán MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. *Int J Epidemiol.* 2009; 38(6):1599–1611. [PubMed: 19389875]
16. Robins JM. Causal models for estimating the effects of weight gain on mortality. *Int J Obes (Lond).* 2008; 32(Suppl 3):S15–S41. [PubMed: 18695650]
17. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *The New England Journal of Medicine.* 2000; 343(1): 16–22. [PubMed: 10882764]
18. Willett W, Stampfer MJ, Bain C, Lipnick R, Speizer FE, Rosner B, Cramer D, Hennekens CH. Cigarette smoking, relative weight, and menopause. *Am J Epidemiol.* 1983; 117(6):651–658. [PubMed: 6859020]
19. Danaei G, Pan A, Hu FB, Hernán MA. Hypothetical midlife interventions in women and risk of type 2 diabetes. *Epidemiology.* 2013; 24(1):122–128. [PubMed: 23222556]
20. Lajous M, Willett WC, Robins J, Young JG, Rimm E, Mozaffarian D, Hernan MA. Changes in fish consumption in midlife and the risk of coronary heart disease in men and women. *Am J Epidemiol.* 2013; 178(3):382–391. [PubMed: 23813701]
21. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation.* 1983; 67(5):968–977. [PubMed: 6219830]
22. Tirosh A, Shai I, Afek A, Dubnov-Raz G, Ayalon N, Gordon B, Derazne E, Tzur D, Shamis A, Vinker S, Rudich A. Adolescent BMI trajectory and risk of diabetes versus coronary disease. *N Engl J Med.* 2011; 364(14):1315–1325. [PubMed: 21470009]
23. Wildman RP, Schott LL, Brockwell S, Kuller LH, Sutton-Tyrrell K. A dietary and exercise intervention slows menopause-associated progression of subclinical atherosclerosis as measured by intima-media thickness of the carotid arteries. *J Am Coll Cardiol.* 2004; 44(3):579–585. [PubMed: 15358024]
24. Kuller LH, Pettee Gabriel KK, Kinzel LS, Underwood DA, Conroy MB, Chang Y, Mackey RH, Edmundowicz D, Tyrrell KS, Buhari AM, Kriska AM. The Women on the Move Through Activity and Nutrition (WOMAN) study: final 48-month results. *Obesity (Silver Spring).* 2012; 20(3):636–643. [PubMed: 21494228]
25. Nissen SE, Nicholls SJ, Wolski K, Rodes-Cabau J, Cannon CP, Deanfield JE, Despres JP, Kastelein JJ, Steinhilb SR, Kapadia S, Yasin M, Ruzyllo W, Gaudin C, Job B, Hu B, Bhatt DL, Lincoff AM, Tuzcu EM. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *JAMA.* 2008; 299(13):1547–1560. [PubMed: 18387931]
26. O'Leary DH, Reuwer AQ, Nissen SE, Despres JP, Deanfield JE, Brown MW, Zhou R, Zabbatino SM, Job B, Kastelein JJ, Visseren FL. Effect of rimonabant on carotid intima-media thickness (CIMT) progression in patients with abdominal obesity and metabolic syndrome: the AUDITOR Trial. *Heart.* 2011; 97(14):1143–1150. [PubMed: 21610270]
27. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, Sharma AM, Shepherd GM, Rode RA, Renz CL. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med.* 2010; 363(10):905–917. [PubMed: 20818901]
28. Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR, Kraemer HC, King AC. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA.* 2007; 297(9):969–977. [PubMed: 17341711]
29. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine.* 2002; 346(6):393–403. [PubMed: 11832527]
30. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M,

- Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013; 369(2):145–154. [PubMed: 23796131]
31. Robins, JM.; Hernán, MA. Estimation of the causal effects of time-varying exposures. In: Fitzmaurice, G.; Davidian, M.; Verbeke, G.; Monenberghs, G., editors. *Longitudinal data analysis. Handbooks of modern statistical methods*. Boca Raton: Chapman & Hall/CRC; 2009. p. 553-599.
32. Robins, JM.; Hernán, MA.; Seibert, U. Effects of multiple interventions. In: Ezzati, M.; Lopez, AD.; Rodgers, A.; Murray, CJ., editors. *Comparative quantification of health risks: Global and regional burden of disease attributable to selected major risk factors*. Vol. 2. Geneva: WHO; 2004. p. 2191-2230.
33. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjöström CD, Sullivan M, Wedel H. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004; 351(26):2683–2693. [PubMed: 15616203]
34. Saeidi N, Meoli L, Nestoridi E, Gupta NK, Kvas S, Kucharczyk J, Bonab AA, Fischman AJ, Yarmush ML, Stylopoulos N. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. *Science*. 2013; 341(6144):406–410. [PubMed: 23888041]
35. Hernán MA. Invited commentary: hypothetical interventions to define causal effects--afterthought or prerequisite? *Am J Epidemiol*. 2005; 162(7):618–620. discussion 621-2. [PubMed: 16120710]
36. Hernán MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes (Lond)*. 2008; 32(Suppl 3):S8–S14.
37. Hernán MA, VanderWeele TJ. Compound treatments and transportability of causal inference. *Epidemiology*. 2011; 22(3):368–377. [PubMed: 21399502]

Figure 1.

Causal diagram showing unmeasured confounding for the effect of weight change on mortality. When U represents an undiagnosed chronic disease, the bias is often referred to as reverse causation because the association between weight and mortality is due to the effect of disease on weight rather than the effect of weight on disease.

U_{t-1} : Unmeasured risk factors for mortality (e.g., frailty, undiagnosed chronic disease)

W_t : Weight at beginning of year t

C_{t+1} : Diagnosis of chronic disease at beginning of year $t+1$

D_{t+1} : Death during year $t+1$

Figure 2.
Flowchart of selection of study participants for coronary heart disease as the outcome,
Nurses' Health Study 1982–2008

Figure 3.
Estimated effects of weight loss on risk of coronary heart disease using different minimum latent periods, Nurses' Health Study (1982–2008)

Figure 4.
Estimated effects of weight loss on risk of death using different minimum latent periods,
Nurses' Health Study (1982–2008)

Table 1

Baseline characteristics of the 73,318 eligible women, Nurses' Health Study 1982

Characteristic	Mean (SD) or %	Characteristic (cont.)	Mean (SD) or %
Age at baseline	48 (7)	Oral contraceptive use in 1980	51
College education	25	Family history of MI at age 60 or less	19
Married	91	Smoking	
Husband education		Past history	56
Not married or less than high-school	30	Current smoker	27
High-school	32	Cigarettes per day (among smokers)	20 (11)
College	21	Alcohol (gram/day)	6 (11)
Graduate school	18	Dietary score	7 (3)
Employment		Multivitamin use	40
Nursing education	14	Activity (hours/week of moderate or vigorous)	2 (2)
Operating room nurse	4	Body Mass Index (BMI)	
Room nurse	3	At age 18 (kg/m ²)	21 (3)
In-patient nurse	20	At baseline	25 (5)
Out-patient nurse	7	High blood pressure	18
Other nursing	26	High cholesterol	6
Non-nursing	6	Osteoporosis	2
Homemaker	20	Aspirin use	
High stress in work or life	67	less than daily	28
Menopause	39	daily or more	12
Postmenopausal hormones	9		

Table 2

Estimated effects of weight loss on risk of coronary heart disease, Nurses' Health Study (1982–2008) using a minimum latent period of 6 years

Intervention	26-year risk under intervention (%) ^a	Population risk ratio	Population risk difference	Cumulative percent intervened on ^b	Average percent intervened on ^c
Natural course, no intervention	5.0 (4.9, 5.3)	1.00	0	0	0
Maintain BMI at baseline level	5.0 (4.9, 5.4)	1.01 (0.98, 1.03)	0 (−0.1, 0.1)	99	54
Maintain BMI at baseline level if not intractably confounded ^d	5.0 (4.9, 5.3)	1.00 (0.99, 1.01)	0 (−0.1, 0.1)	60	33
Lose 5% of BMI each period if above 25 kg/m ²	5.1 (4.9, 5.5)	1.02 (0.99, 1.05)	−0.1 (−0.3, 0)	73	53
Lose 5% of BMI each period if above 25 kg/m ² and not intractably confounded ^d	5.0 (4.9, 5.3)	1.00 (1.00, 1.01)	0 (−0.1, 0)	43	33
Lose 10% of BMI each period if above 25 kg/m ² and not intractably confounded ^d	5.0 (4.9, 5.3)	1.00 (1.00, 1.01)	0 (−0.1, 0)	43	32
Lose 10% of BMI each period if above 23 kg/m ² and not intractably confounded ^d	5.0 (4.9, 5.3)	1.00 (0.99, 1.02)	0 (−0.1, 0.1)	58	44

^aThere were 2843 CHD events among 73,318 eligible women after 1.5 million person-years of follow-up. The observed 26-year risk of CHD was 4.78% (95% CI 4.77, 4.79).

^bThe proportion of individuals that were intervened on in any period

^cThe average proportion of individuals intervened on in each 2-year period, averaged over follow-up

^dIntractably confounded subgroup included women 70 years old or older and those who had chronic heart failure, peripheral vascular disease, pulmonary embolism, atrial fibrillation, chronic kidney disease, gout, systemic lupus erythematosus, ulcerative colitis, rheumatoid arthritis, emphysema, depression, Alzheimer's disease, Parkinson's disease, multiple sclerosis or amyotrophic lateral sclerosis.

Table 3

Estimated effects of weight loss on risk of death, Nurses' Health Study (1982–2008) using a minimum latent period of 6 years

Intervention	26-year risk under intervention (%) ^a	Population risk ratio	Population risk difference	Cumulative percent intervened on ^b	Average percent intervened on ^c
Natural course, no intervention	16.3 (16.1, 17.0)	1.00	0	0	0
Maintain BMI at baseline level	17.5 (17.3, 18.2)	1.08 (1.05, 1.09)	-1.2 (-1.6, -0.9)	99	54
Maintain BMI at baseline level if not intractably confounded ^d	16.5 (16.4, 17.2)	1.01 (1.00, 1.03)	-0.2 (-0.5, -0.1)	59	32
Lose 5% of BMI each period if above 25 kg/m ²	16.6 (16.4, 17.3)	1.02 (1.01, 1.03)	-0.3 (-0.1, -0.6)	73	53
Lose 5% of BMI each period if above 25 kg/m ² and not intractably confounded ^d	16.3 (16.2, 17.0)	1.00 (1.00, 1.00)	-0.04 (-0.1, 0)	42	33
Lose 10% of BMI each period if above 25 kg/m ² and not intractably confounded ^d	16.3 (16.2, 17.0)	1.00 (1.00, 1.01)	-0.05 (-0.1, 0)	42	32
Lose 10% of BMI each period if above 23 kg/m ² and not intractably confounded ^d	16.5 (16.4, 17.2)	1.02 (1.01, 1.02)	-0.3 (-0.2, -0.4)	58	44

^aThere were 9202 deaths among 73,318 eligible women after 1.5 million person-years of follow-up. The observed 26-year risk of death was 15.58% (95% CI 15.56, 15.60).

^bThe proportion of individuals that were intervened on in any period

^cThe average proportion of individuals intervened on in each 2-year period, averaged over follow-up

^dIntractably confounded subgroup included women 70 years old or older and those who had chronic heart failure, peripheral vascular disease, pulmonary embolism, atrial fibrillation, chronic kidney disease, gout, systemic lupus erythematosus, ulcerative colitis, rheumatoid arthritis, emphysema, depression, Alzheimer's disease, Parkinson's disease, multiple sclerosis or amyotrophic lateral sclerosis.

Sensitivity analyses for the estimated effect of weight loss ^a on risk of coronary heart disease, Nurses' Health Study (1982–2008) using a minimum latent period of 6 years

Table 4

Sensitivity analysis	Cumulative risk under no intervention (%)	Cumulative risk under intervention (%)	Population risk ratio	Cumulative percent intervened on ^b	Average percent intervened on ^c
Including only women <49 years old at baseline	2.7 (2.4, 2.9)	2.7 (2.4, 2.9)	1.02 (0.99, 1.04)	54	39
Including only never smokers	3.7 (3.4, 3.9)	3.7 (3.4, 3.9)	1.00 (0.99, 1.01)	46	37
Including only those with intentional weight loss in 1992	4.2 (3.9, 4.5)	4.2 (3.9, 4.5)	1.00 (1.00, 1.01)	38	30
Changing the definition of frailty to >65 year old instead of >70	5.1 (4.9, 5.4)	5.1 (4.9, 5.4)	1.00 (1.00, 1.00)	33	25
Starting the follow-up in 1978 and ending in 2010 ^d	6.0 (5.7, 6.1)	6.0 (5.7, 6.2)	1.00 (0.98, 1.02)	81 ^e	54
Using only the first 16 years of follow-up	2.2 (2.1, 2.4)	2.3 (2.1, 2.4)	1.01 (1.00, 1.02)	39	31
Modeling BMI as the last variable in the set of models	5.1 (4.9, 5.3)	5.1 (4.9, 5.3)	1.00 (1.00, 1.01)	44	34
Effect of weight gain (gain 5% of BMI each period if below 30kg/m ²)	4.6 (4.4, 4.8)	4.6 (4.4, 4.8)	1.00 (0.98, 1.01)	69	63
Assigning a shorter lag time (of 2 years) for diabetes, versus 6 years for other chronic diseases	3.7 (3.6, 3.9)	3.8 (3.6, 3.9)	1.00 (1.00, 1.01)	41	31

^a Lose 5% of BMI every 2 years if above 25 kg/m² and not intractably confounded, as defined in footnote d of Table 2.

^b The proportion of individuals that were intervened on in any period

^c The average proportion of individuals intervened on in each 2-year period, averaged over follow-up

^d This analysis only included models for CHD and death and one model for time-varying BMI which included baseline covariates (see eTable 1) as information for other time-varying covariates are not available in 1978.

^e This model has a much higher proportion of participants intervened in as the intervention cannot be restricted to those without intractable confounding.