American Journal of Epidemiology
Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health 2010.

Vol. 173, No. 1
DOI: 10.1093/aje/kwq341
Advance Access publication:
November 8, 2010

Commentary

Reverse Causation and Illness-related Weight Loss in Observational Studies of Body Weight and Mortality

Katherine M. Flegal*, Barry I. Graubard, David F. Williamson, and Richard S. Cooper

* Correspondence to Dr. Katherine M. Flegal, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Road, Room 4336, Hyattsville, MD 20782 (e-mail: kmf2@cdc.gov).

Initially submitted June 5, 2010; accepted for publication September 10, 2010.

In studies of weight and mortality, the construct of reverse causation has come to be used to imply that the exposure-outcome relation is biased by weight loss due to preexisting illness. Observed weight-mortality associations are sometimes thought to result from this bias. Evidence for the occurrence of such bias is weak and inconsistent, suggesting that either the analytical methods used have been inadequate or else illness-related weight loss is not an important source of bias. Deleting participants has been the most frequent approach to control possible bias. As implemented, this can lead to deletion of almost 90% of all deaths in a sample and to deletion of more overweight and obese participants than participants with normal or below normal weight. Because it has not been demonstrated that the procedures used to adjust for reverse causation increase validity or have large or systematic effects on relative risks, it is premature to consider reverse causation as an important cause of bias. Further research would be useful to elucidate the potential effects and importance of reverse causation or illness-related weight loss as a source of bias in the observed associations between weight and mortality in cohort studies.

bias (epidemiology); body mass index; body weight; confounding factors (epidemiology); epidemiologic methods; mortality; selection bias

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IRWL, illness-related weight loss.

Many analyses have investigated the association of relative weight or body mass index (BMI) with mortality with broadly consistent results. Studies in young and middle-aged individuals often show a curvilinear relation with increased mortality risk at both low and high BMI values (1–3). Relative risks of mortality in these studies are usually below 2.0 and often below 1.5. Studies in the elderly often show the highest relative risks at low BMI levels, with little excess risk at higher BMI levels (4, 5). It is sometimes suggested that these observations result from reverse causation, namely, bias caused by preexisting illness and attendant weight loss (6–8). In this commentary, we discuss some unresolved methodological issues regarding the concept of reverse causation and the effects of preexisting illness in studies of weight and mortality and make some brief suggestions for directions in future research. This is not intended as a comprehensive literature review of this complex topic.

UNRESOLVED ISSUES

Definition of reverse causation in studies of weight and mortality

Reverse causation ordinarily refers to the situation in which the outcome precedes and causes the exposure instead of the other way around (9–11). In much of the epidemiologic literature, the term ''reverse causation'' is used in this standard sense in contexts as varied as studies of asthma and antibiotics (are people with asthma prone to infections, or do antibiotics increase the risk of asthma?) (12), cancer and cholesterol levels (is low cholesterol a risk factor for cancer, or does cancer cause low cholesterol levels?) (13), and BMI and depression (are those with high BMI more likely to be depressed, or does depression lead to high BMI?) (14).

In 1999, the term ''reverse causation'' began to be used in studies of weight and mortality in a different (and somewhat

Table 1. Examples of Published Descriptions of Reverse Causation or Reverse Causality

First Author (Reference)	Direct Quotation (Page No.)
Adams (44)	Reverse causation owing to preexisting chronic disease and inadequate control for smoking status can distort the true relation between body weight and the risk of death, because chronic illness and smoking are associated with both decreased BMI and an increased risk of death. (p. 764)
Flanders (104)	Reverse causality, in which obesity-related disease leads to both weight loss and higher mortality . . . Reverse causality, a form of bias, must be considered when interpreting studies of obesity and mortality. The basic issue is that obesity-related diseases that result in death can lead to intermediate weight loss and thus obscure the obesity–mortality relationship. (p. S43)
Janssen (105)	There are several hypotheses as to why BMI is a poor indicator of mortality risk in the elderly, among them being a reverse-causation bias due to the unintentional weight loss caused by illness and chronic disease. (p. 2504)
Lewis (106)	Reverse causality is a term used in the literature to refer to the confounding introduced when occult or preexisting diseases that increase mortality rate also cause weight loss (e.g., tobacco related cancers). (p. 3264)
Manson (7)	The key problem in studies of weight and mortality is reverse causation, or the fact that low weight can result from illness rather than leanness causing illness. Because of this phenomenon, leaner persons are a mix of healthy individuals and those who are ill and have lost weight because of their disease (weight loss may have occurred unintentionally as a result of underlying disease or intentionally because of increased motivation to lose weight). (p. 168)
Reeves (107)	For many cancers, weight loss often precedes clinical recognition of the disease and, in affected patients, BMI recorded before diagnosis is an underestimate of their usual BMI. This potential bias, termed reverse causality, can give rise to spuriously increased risks at low levels of BMI. (p. 1138; p. 9 in online version)
Robins (101)	. . . unmeasured confounding by undiagnosed preclinical disease (that is, reverse causation) that can cause both poor weight gain and premature mortality. (pp. S16–S17)
Stampfer (108)	The third and most difficult issue in studies of overweight and mortality is reverse causation, the impact of disease on body weight. This can occur either through the biological impact of a condition (diagnosed or preclinical) or as an inducement to attempt to lose weight as a means to improve health. (p. e181)
Sun (109)	. . . we were concerned about the possibility of reverse causation—that is, BMI or weight change being a consequence rather than the cause of health problems. Specifically, most of the components of our outcome can have long latency periods, and women beginning to develop these health problems might lose or gain weight. (p. 2 of 8 in online version)
Willett (8)	Reverse causation is the most serious problem associated with using total mortality as an outcome; people frequently lose weight as a result of an illness that is ultimately fatal, a situation that creates the appearance of higher mortality among those with lower weights. Conditions that cause weight loss may remain undiagnosed for several months or years, as could be the case for occult neoplasms, chronic lung or cardiac disease, alcoholism, or depression. (p. 428)
Whitlock (93)	Some uncertainties persist, however, about the relation between BMI and mortality, including whether some of the reported positive or inverse associations have been distorted by weight loss because of pre-existing disease (reverse causality) or by inadequate control for the effects of smoking. (p. 1083)

Abbreviation: BMI, body mass index.

incorrect) sense to mean that illness affects both the exposure (body weight) and the outcome (mortality) (8). This would more usually be described as confounding, not as reverse causation. Some descriptions of reverse causation in the context of weight and mortality are displayed in Table 1. Although the descriptions are broadly similar, they do not completely agree in their specific details, for example: Does reverse causation refer to effects of undiagnosed disease only; does it occur only when death is from the same illness that caused weight loss; is it an effect of disease on weight loss or also on weight gain; does it refer to voluntary as well as involuntary weight loss; or does it refer simply to confounding by chronic illness? Because most refer to potential bias arising from illness-related weight loss (IRWL), we use IRWL here as an operational definition for purposes of discussion.

The proportion of study participants with IRWL prior to baseline

In analyses using baseline weight as the exposure, the question of interest from an epidemiologic perspective is what proportion of study participants is likely to have had substantial IRWL prior to baseline. Without a clear way to identify such participants, this proportion is difficult to estimate. Patients with extreme weight loss are often very severely ill and tend to have short survival times, often under a year (15). This minimizes the likelihood that many such patients would be included in a baseline sample of participants in an observational study. According to several descriptions in Table 1, weight loss prior to baseline may be due to undiagnosed cancers. Several studies show that undiagnosed cancers may be associated with weight loss and that a substantial minority of patients referred because of weight loss may have undiagnosed cancers (16–21). As noted by Lankisch et al. (17, p. 45), several investigations of weight loss (16–18) ''reveal that non-malignant, rather than malignant, diseases are the major cause of weight loss, and that gastrointestinal tract disorders predominate in both categories.''

Available data suggest little effect of undiagnosed neoplasms on baseline weight in population studies. In an Austrian study of 65,000 participants, with weight measured annually for 7 years before baseline and cancer incidence determined for 8 years after baseline, there was no clear association between all-cancer incidence and either weight gain or weight loss (22). In a group who had had weight

measured every 2 months, Kritchevsky et al. (23) found that men who eventually developed cancer weighed 0.1 kg less 6–7 years before diagnosis and 1.2 kg less within the 6 months preceding diagnosis. Wilcosky et al. (24, p. 750) found that ''decedents from cancer in the early years of follow-up were no leaner at baseline than were those who died in the later years'' and felt that this argued against reverse causation. Peterson and Trell (25) found that men who died of cancer did not differ in weight from survivors. Rose and Shipley (26) addressed ''unsuspected sickness'' as a possible explanation for low cholesterol and cancer and found that seemingly healthy men who died of cancer within the first few years after baseline tended to have lower cholesterol levels, but not lower weight levels, than men dying of cancer after the first few years. In the Physicians' Health Study, the relative risk for incident prostate cancer was the same for BMI at baseline as for BMI from 8 years before baseline (27). In the Austrian study (22) and the Health Professionals Follow-up Study (28), the diagnosis of colon cancer was preceded by weight gain rather than by weight loss. Several other studies of weight change prior to cancer diagnoses show an association of weight gain, rather than loss, with cancer incidence (29–33).

Weight loss prior to diagnosis of other conditions has been reported. Chen et al. (34) found a reported loss of 5.2 pounds (2.4 kg) in the 10 years prior to the diagnosis of Parkinson's disease. Johnson et al. (35) found that the rate of weight loss approximately doubled, from 0.6 pound (0.3 kg) per year to 1.2 pound (0.5 kg) per year, in the year preceding a diagnosis of Alzheimer's disease and that participants who eventually developed dementia weighed about 8 pounds (3.6 kg) less than controls even at study entry. Stewart et al. (36) similarly found that in late life men who developed incident dementia lost 0.36 kg/year more than men who did not.

Diagnosed preexisting illness may be associated with either weight loss or weight gain, perhaps due to treatment. For example, in the Atherosclerosis Risk in Communities Study (37), participants with preexisting illness (cardiovascular disease, cancer, or self-reported poor health) were about equally likely to have gained 3 or more BMI units (6.4%) as to have lost 3 or more BMI units (4.8%) in the 3 years prior to baseline. Among participants with cancer, 4.4% lost 3 or more BMI units, and 5.9% gained 3 or more units. Breast cancer patients often gain weight after treatment (38, 39). Parkinson's disease is associated with weight loss, but some treatments for Parkinson's lead to marked weight gain (40). Treatment of hyperthyroidism led to an average gain of more than 9 kg over a 4-year period (41). Weight changes after a diabetes diagnosis ranged from gain to loss (42). Several drugs for the treatment of migraine are associated with weight gain (43).

Nature and direction of potential bias due to IRWL

Discussions of potential biases due to IRWL do not always distinguish between weight loss and low BMI. Moderate weight loss may not lead to a low BMI, and low BMI is not necessarily the result of weight loss. IRWL is sometimes thought to bias relative risks upward at low BMI levels and downward at higher BMI levels, but the possible mechanisms of such bias have not been completely described. Most discussions have focused on the effects at very low BMI levels. The proposed mechanism of bias is that some severely ill people lose sufficient weight as a result of their illness to fall into the very low BMI category. The prevalence of very low BMI, particularly among nonsmokers, is often so low that the admixture of even a small number of severely ill people at high risk of mortality could potentially increase the apparent risk in this group.

Even though it is sometimes assumed that IRWL will bias relative risks downward at somewhat higher BMI levels, there has been little discussion of the possible type and direction of bias at higher BMI levels. For example, chronically ill obese people might migrate into the overweight category, thus increasing rather than decreasing the apparent risk in the overweight group. The expected effects of IRWL on relative risks in any weight category depend on a number of variables, including the relative prevalence of each weight category, the probabilities of weight change (in either direction), and the absolute mortality risk in each group. As a consequence, any effects of IRWL on relative risks are not readily predictable and might vary in magnitude and even in direction from cohort to cohort.

Sometimes circular reasoning, based on a priori assumptions about the direction of the expected bias from IRWL, is used to infer the presence of IRWL bias. If an analytical maneuver intended to reduce IRWL bias leads to small changes in relative risk in the expected direction, this may be taken as evidence that the assumed bias was present (44). However, if the changes are not in the expected direction, then this may be interpreted as evidence that the adjustment for bias was insufficient, rather than as an absence of bias. For example, Baik et al. (45, p. 270) state: ''... we found evidence that reverse causation strongly influenced the shape of the relation between body mass index and mortality in these data. Even with careful attempts to reduce this artifact by excluding persons who reported chronic disease at baseline and those with recent weight loss, we were unable to completely avoid the effects of reverse causation.''

In general, the prevalence of existing disease is the same or higher among those who are overweight and obese as among those of lower weights (44, 46). This suggests that the effect of preexisting disease without IRWL might be to introduce positive confounding, biasing the relative risks upward.

Controlling for IRWL in statistical analysis

If one had ideal data including detailed health status at baseline and subsequent mortality data, then the BMI-mortality dose-response could be defined separately in the several strata defined by baseline health status, age, and smoking. One could look at healthy nonsmokers and determine whether their dose-response to relative weight was different from those in other strata. Perhaps arguments about reverse causation would largely disappear if such data were available. However, there is no clear way to identify healthy participants or participants who have lost weight due to

illness. Various maneuvers have been proposed to compensate for the lack of direct information. These approaches can be applied regardless of whether any of the participants have IRWL.

The method most frequently proposed to control for possible IRWL bias is to create a subgroup by excluding participants from the definitive analyses. Willett et al. (8, p. 428) suggested the following approach to exclude study participants who might have lost weight prior to baseline because they were ill:

> Subjects with diagnoses that might affect weight and subjects who report recent weight loss, such as during the previous five years, can be excluded from a prospective study. Deaths that occur during the first several years of follow-up—possibly as a result of conditions that caused lower weights at base line—can also be excluded.

With this indirect approach, those with IRWL are not necessarily excluded and those who are excluded do not necessarily have IRWL. Such exclusions do not specifically target people with low BMI and often result in the deletion of as many or more overweight and obese people as lean people (2, 45, 47). The probability that those excluded actually have IRWL is difficult to estimate and may vary considerably from cohort to cohort. To the extent that those excluded are likely to have preexisting disease but not weight loss, these exclusions become in effect some degree of control for preexisting disease among participants without IRWL.

The scale of these proposed deletions can be quite large. It has been explicitly argued (7) that it is necessary to start with very large data sets because most of the data will have to be excluded in order to get the correct (i.e., unbiased) results. Similar deletions, combined with exclusion of current and former smokers, can result in deletion of almost 90% of the deaths in a sample. For example, in both a report of the Nurses' Health Study (2) and the National Institutes of Health (NIH)-AARP Study (44), final analyses included only 11% of the original deaths.

A number of studies have applied some variant of this approach by complete exclusion of part of the sample or by stratification (refer to Table 2 for some examples). Of these suggestions, deleting early mortality has been most frequently used. Excluding early mortality is intended to at least partially reduce any potential bias arising from IRWL among participants who were at high mortality risk at baseline due to illness. Studies of the effects of deleting early mortality have shown little effect except perhaps in the first year after baseline (37, 48–52). One of the reasons why the deletion of early mortality tends to make little difference may be because studies with measured weight and height include only participants who are able to attend an examination, thus in practice excluding sicker participants.

Some studies allow for comparison of results before and after exclusions. Careful investigations in a number of cohorts (53–65) have not shown any marked or systematic impact of deletion or adjustment for illness, weight loss, or early mortality, although the approaches used are heterogeneous Large-scale deletions in some cohorts (2, 44, 45, 47, 66) show small changes in relative risks that are not always in the hypothesized directions. In the Nurses' Health Study (2), the multivariate relative risk for BMI of 32 or above increased from 1.9 to 2.2 among nonsmokers after excluding women who had gained or lost at least 4 kg in the first 3 years after baseline and excluding the first 4 years of mortality. Among never smokers in the Cancer Prevention Study II, the relative risk for a BMI of 25–26.4 was 1.01 for men without prevalent disease and 1.05 for men with prevalent disease; corresponding values for women were 1.03 and 1.06 (66). In the Health Professionals Follow-up Study (45), the relative risk for a BMI of 30 or above fell from 1.50 to 1.49 after excluding participants with at least 10-pound (4.5-kg) weight losses before baseline and excluding the first 4 years of mortality. In the Physicians' Health Study (47), the relative risk for a BMI of 30 or above rose from 1.67 to 1.71 after excluding the first 2 years of mortality. In middle-aged adults in the US Health and Retirement Study, the relative risk for a BMI of 35 or above dropped from 1.53 to 1.29 after adjusting for disease history and health status and was 1.52 when analyses were limited to those in good or excellent health (61).

Do these methods eliminate bias or introduce bias?

The use of numerous exclusions and subsets of the data in studies of weight and mortality is, in effect, analysis of subgroups, which can lead to many known methodological problems (67–71). The approaches used in weight and mortality studies are often inconsistent with recommended practices for subgroup analyses, such as using predefined subgroups, presenting results for all subgroups, not only for selected subgroups, and using formal tests of heterogeneity. Wang et al. (71, p. 2193) note that subgroup analyses "can lead to overstated and misleading results" and caution: "Avoid overinterpretation of subgroup differences. Be properly cautious in appraising their credibility, acknowledge the limitations, and provide supporting or contradictory data from other studies, if any."

Results obtained after extensive exclusions do not necessarily provide a more valid and less biased estimate. They could also be simply an artifact of random variability from excluding such large proportions of the sample (72) or be biased by the effect of the exclusions themselves. The exclusions reduce statistical power, selectively affect certain causes of death, and may introduce additional, unrecognized sources of bias. In the large data sets needed to accommodate large-scale exclusions, weight and height are often self-reported, a characteristic that itself may lead to bias (73). It is possible, particularly with self-reported weight and height, that the deletions lead to a subgroup with measurement errors different from the full sample or to a subgroup that has different confounding characteristics (74).

In general, the effect of these exclusions is to create a subgroup that is poorly characterized. A subgroup may be described as "healthy" after a small number of health conditions are excluded (7, 44, 66); however, generally other health conditions, such as diabetes, are not excluded, and there is no control for risk factors such as hypertension or dyslipidemia. There may be little or no difference in overall health status between those included and those excluded.

Table 2. Some Examples of Exclusions Used in Studies of Weight and Mortality[a]

First Author (Reference)	Prior Illness	Weight Loss/Change	Early Deaths Excluded	Other
Ajani (47)	Myocardial infarction, angina, stroke, transient ischemic attacks, cancer, liver disease, or renal disease	None	2 years	
Baik (45)	Myocardial infarction, angina, coronary artery bypass grafting or angioplasty, stroke, transient cerebral ischemia, peripheral venous thrombosis, intermittent claudication, pulmonary embolus, heart-rhythm disturbances, cancer, renal failure, chronic pulmonary disease	Reported weight loss of 10 pounds (4.54 kg) or more in 5 years prior to baseline	4 years	Statistical adjustment for smoking. Excluded BMI outside the range of 15–50 kg/m^2
Calle (66)	Cancer, heart disease, stroke, respiratory disease, any current illness at baseline	Reported weight loss of 10 pounds or more in year prior to baseline	Not excluded	
Durazo-Arvizu (56)	Cardiovascular disease or cancer	None	4 years	
Gu (58)	Cardiovascular disease, cancer, stroke, chronic obstructive pulmonary disease, end-stage renal disease	None	5 years	Excluded participants with heavy alcohol use
Hozawa (90)	None	None	5 years	Excluded participants with total cholesterol of <4.1 mmol/L
Jee (91)	Atherosclerotic cardiovascular disease, cancer, liver disease, diabetes, or a respiratory disease at or before the initial study visit	None	2 years	Excluded participants with BMI of <16 kg/m^2 or stature of <1.3 m
Lawlor (110)	None	None	5 years	
Lee (111)	History of coronary heart disease, stroke, or cancer	None	5 years	
Lindsted (112)	Heart disease, stroke, or cancer or severe physical complaints (e.g., chest pain, shortness of breath, loss of appetite)	Loss or gain of >10 pounds in 5 years before baseline	15 years	Excluded deaths due to poisoning, accidents, or congenital malformations
Manson (2)	Cancer or cardiovascular disease	Gain or loss of 4 kg or more after baseline	4 years	
Whitlock (93)	None	None	5 years	Statistical control for smoking

Abbreviation: BMI, body mass index.
[a] Except as noted, all the studies listed also excluded current and former smokers.

Repeated deletions followed by repeated statistical testing increase the likelihood that false positive associations will be detected. In studies of weight and mortality, the data are sometimes analyzed with a sequence of exclusions, each time testing the relative risks in the new subgroup without adjustments for the multiple comparisons, until a monotonic relation is observed. The probability of a false research finding is increased by this procedure, by the small effect sizes (relative risks) characteristic of weight and mortality studies, by the small data sets that may be created by excluding 70%–90% of the deaths, and by nonstandardized approaches that vary between studies (75). Comparisons between the relative risks before and after exclusions are often done by inspection, and point estimates of relative risk may be described as being different between 2 subgroups without any statistical testing (2, 44).

Interpretive biases (76) may arise because of prior assumptions about the direction and importance of the effects of IRWL. Findings of other-than-expected weight–mortality associations have sometimes been attributed to some undetected source of reverse causation bias. For example, after Fontaine et al. (77) found a weaker association between weight and mortality in blacks than in whites, Manson and Bassuk (78) speculated that these differences might be explained by effects of reverse causation affecting blacks more than whites because blacks might be more likely than whites to suffer from undiagnosed disease. Gelber et al. (79) suggested that the curvilinear rather than monotonic relation found by Calle et al. (66) among healthy never-smoking participants with no recent weight loss may have been due to the failure of the investigators to exclude participants with early deaths. Lee and Manson (80) interpreted a modestly

curvilinear relation after excluding the first 15 years of mortality as an indication that bias due to preexisting disease remained. However, findings that are contrary to expectations are not necessarily the result of reverse causation bias.

Bias or causality?

It is sometimes assumed that, if illness leads to low weight, then the association of low weight with increased mortality is not causal. Low weight itself, however, may also contribute to increased mortality, perhaps from a different cause than the illness causing weight loss. For example, low weight can lead to lower bone density (81, 82), which is a risk factor for mortality from complications subsequent to hip fracture (81–86). A large study of colon cancer patients found that underweight patients were at significantly increased risk of mortality from causes other than colon cancer (87). Studies of patients with chronic obstructive pulmonary disease (COPD) suggest that not only is low weight associated with increased mortality after controlling for disease severity but also weight gain improves mortality outcomes, suggesting that the low weight itself is in part the causative factor (88). A study using Mendelian randomization suggested that the inverse association of obesity and lung cancer may be causal rather than artifactual (89). Large studies in the United States, the United Kingdom, India, Japan, Korea, and China have shown increased mortality at low BMI values among never smokers after deletions for prevalent illness and early mortality (44, 58, 64, 66, 90–93). Thus, at least some of the increase in mortality at low BMI levels does not appear to be artifactual and cannot be explained solely by reverse causation.

The impact of a given weight level on mortality is a function of the effects of weight on disease incidence, the effects of disease on weight, and the effects of weight on survival in patients with that disease. It is difficult to distinguish among these effects, and all may be occurring within a given sample, as discussed, for example, by Jee et al. (91) for COPD. Any effect of weight loss leading to poorer survival should not be considered a form of bias. According to Baik et al. (45, p. 269), ''[T]he interpretation of the elevated mortality among the leanest older men depends heavily on whether being lean causes chronic pulmonary disease or is the result of chronic pulmonary disease''; however, these authors overlooked the third possibility that leanness increases mortality in COPD patients. A body of evidence has begun to accumulate suggesting that, in numerous health conditions, low weight is associated with poorer survival even after adjustments for disease severity (94–97). To the extent that this is the case, it is unnecessary to invoke bias to explain the numerous studies showing an inverse BMI-mortality relation in the elderly.

FUTURE DIRECTIONS

It cannot be ruled out that bias due to preexisting illness may affect weight-mortality studies, possibly through mechanisms other than IRWL. Attempts to adjust for biases due to IRWL, however, have provided little evidence to date for the existence of such biases. This might be because the actual prevalence of IRWL prior to baseline is very low in most cohorts or because IRWL is offset by illness-related weight gain. Another possibility is that IRWL produces little or no bias or that the bias is in the opposite direction of that hypothesized. The effects of low weight on mortality may be causal, not artifactual, and thus not be a form of bias. Yet another possibility is that bias occurs, but the crude approach of deleting large numbers of participants is an ineffective way to control bias. Exclusions of large numbers of participants without IRWL may mask the effects of deleting some individuals with IRWL. The deletions themselves may increase rather than reduce bias.

There are no agreed-upon definitions of reverse causation in studies of weight and mortality, no good evidence as to how often this phenomenon occurs, and little theoretical or empirical basis for describing what type of bias it might cause. Furthermore, we have no good way to control for this putative bias, and the proposed methods may actually cause bias rather than correct for bias.

Indirect methods such as deleting large amounts of data do not appear to be likely to lead to further insights. In future research, it would be preferable to avoid the use of vague terms such as ''reverse causation'' or ''healthy'' and to create testable hypotheses for specific effects in specific cohorts. Standard methods for assessing subgroups should be used, including statistical testing of interactions (98, 99). More focused and detailed investigations would be useful, such as those carried out by Stevens et al. (37) on weight change and health, as well as the use of more recent methods for causal modeling (100, 101). Cohorts with repeated measures of weight and health status could be exploited for this purpose, as has been done with data on smoking and smoking cessation (102, 103).

CONCLUSIONS

At present, there is little evidence that observed associations between weight and mortality in cohort studies are biased by effects of preexisting illness. Continued application of indirect approaches to adjust for IRWL may introduce new sources of bias. Because it has not been demonstrated that these procedures give more valid results or have large or systematic effects on relative risks, it is premature to consider reverse causation as an important cause of bias. Further research would be useful to elucidate the potential effects and importance of reverse causation or illness-related weight loss as a source of bias in the observed associations between weight and mortality in cohort studies.

ACKNOWLEDGMENTS

Author affiliations: National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland (Katherine M. Flegal); Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Barry I. Graubard); Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia (David F. Williamson); and Department of Preventive Medicine and Epidemiology,

Loyola University Medical School, Maywood, Illinois (Richard S. Cooper).

There was no external funding for this work.

The findings and conclusions in this report are those of the authors and not necessarily those of the agency.

Conflict of interest: none declared.

REFERENCES

1. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. National Institutes of Health. *Obes Res.* 1998; 6(suppl 2):51S–209S.
2. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *N Engl J Med*. 1995;333(11): 677–685.
3. McGee DL. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. Diverse Populations Collaboration. *Ann Epidemiol*. 2005;15(2):87–97.
4. Heiat A, Vaccarino V, Krumholz HM. An evidence-based assessment of federal guidelines for overweight and obesity as they apply to elderly persons. *Arch Intern Med*. 2001; 161(9):1194–1203.
5. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev.* 2007;8(1):41–59.
6. Manson JE, Stampfer MJ, Hennekens CH, et al. Body weight and longevity. A reassessment. *JAMA*. 1987;257(3):353–358.
7. Manson JE, Bassuk SS, Hu FB, et al. Estimating the number of deaths due to obesity: can the divergent findings be reconciled? *J Womens Health (Larchmt)*. 2007;16(2):168–176.
8. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med*. 1999;341(6):427–434.
9. Bowling A, Ebrahim S, eds. *Handbook of Health Research Methods: Investigation, Measurement, and Analysis*. Maidenhead, Berkshire, England: McGraw-Hill, Open University Press; 2005.
10. Szklo M, Nieto FJ. *Epidemiology: Beyond the Basics*. Sudbury, MA: Jones and Bartlett Publishers; 2006.
11. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology.* 3rd ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2008.
12. Pekkanen J. Commentary: use of antibiotics and risk of asthma. *Int J Epidemiol*. 2004;33(3):564–565.
13. Ding EL, Hu FB. Cancer and cholesterol: understanding the V-shaped association in patients with diabetes. *CMAJ*. 2008;179(5):403–404.
14. Magnusson PK, Rasmussen F, Lawlor DA, et al. Association of body mass index with suicide mortality: a prospective cohort study of more than one million men. *Am J Epidemiol*. 2006;163(1):1–8.
15. Lainscak M, Podbregar M, Anker SD. How does cachexia influence survival in cancer, heart failure and other chronic diseases? *Curr Opin Support Palliat Care*. 2007;1(4):299–305.
16. Hernández JL, Riancho JA, Matorras P, et al. Clinical evaluation for cancer in patients with involuntary weight loss without specific symptoms. *Am J Med.* 2003;114(8): 631–637.
17. Lankisch P, Gerzmann M, Gerzmann JF, et al. Unintentional weight loss: diagnosis and prognosis. The first prospective follow-up study from a secondary referral centre. *J Intern Med*. 2001;249(1):41–46.
18. Marton KI, Sox HC Jr, Krupp JR. Involuntary weight loss: diagnostic and prognostic significance. *Ann Intern Med*. 1981;95(5):568–574.
19. Metalidis C, Knockaert DC, Bobbaers H, et al. Involuntary weight loss. Does a negative baseline evaluation provide adequate reassurance? *Eur J Intern Med*. 2008;19(5):345–349.
20. Rabinovitz M, Pitlik SD, Leifer M, et al. Unintentional weight loss. A retrospective analysis of 154 cases. *Arch Intern Med*. 1986;146(1):186–187.
21. Wigmore SJ, Plester CE, Richardson RA, et al. Changes in nutritional status associated with unresectable pancreatic cancer. *Br J Cancer.* 1997;75(1):106–109.
22. Rapp K, Klenk J, Ulmer H, et al. Weight change and cancer risk in a cohort of more than 65,000 adults in Austria. *Ann Oncol*. 2008;19(4):641–648.
23. Kritchevsky SB, Wilcosky TC, Morris DL, et al. Changes in plasma lipid and lipoprotein cholesterol and weight prior to the diagnosis of cancer. *Cancer Res.* 1991;51(12):3198–3203.
24. Wilcosky T, Hyde J, Anderson JJ, et al. Obesity and mortality in the Lipid Research Clinics Program follow-up study. *J Clin Epidemiol*. 1990;43(8):743–752.
25. Peterson B, Trell E. Premature mortality in middle-aged men: serum cholesterol as risk factor. *Klin Wochenschr.* 1983; 61(16):795–801.
26. Rose G, Shipley MJ. Plasma lipids and mortality: a source of error. *Lancet*. 1980;1(8167):523–526.
27. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol*. 2008;9(11):1039–1047.
28. Thygesen LC, Grønbaek M, Johansen C, et al. Prospective weight change and colon cancer risk in male US health professionals. *Int J Cancer.* 2008;123(5):1160–1165.
29. Chow WH, Gridley G, Fraumeni JF Jr, et al. Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med*. 2000;343(18):1305–1311.
30. Nichols HB, Trentham-Dietz A, Egan KM, et al. Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiol Biomarkers Prev.* 2009;18(5): 1403–1409.
31. Samanic C, Chow WH, Gridley G, et al. Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control.* 2006;17(7):901–909.
32. Trentham-Dietz A, Nichols HB, Hampton JM, et al. Weight change and risk of endometrial cancer. *Int J Epidemiol*. 2006;35(1):151–158.
33. Trentham-Dietz A, Newcomb PA, Nichols HB, et al. Breast cancer risk factors and second primary malignancies among women with breast cancer. *Breast Cancer Res Treat*. 2007; 105(2):195–207.
34. Chen H, Zhang SM, Hernán MA, et al. Weight loss in Parkinson's disease. *Ann Neurol*. 2003;53(5):676–679.
35. Johnson DK, Wilkins CH, Morris JC. Accelerated weight loss may precede diagnosis in Alzheimer disease. *Arch Neurol*. 2006;63(9):1312–1317.
36. Stewart R, Masaki K, Xue QL, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol*. 2005;62(1):55–60.
37. Stevens J, Juhaeri Cai J. Changes in body mass index prior to baseline among participants who are ill or who die during the early years of follow-up. *Am J Epidemiol*. 2001;153(10): 946–953.
38. Irwin ML, McTiernan A, Baumgartner RN, et al. Changes in body fat and weight after a breast cancer diagnosis: influence

of demographic, prognostic, and lifestyle factors. *J Clin Oncol*. 2005;23(4):774–782.
39. Rock CL, Flatt SW, Newman V, et al. Factors associated with weight gain in women after diagnosis of breast cancer. Women's Healthy Eating and Living Study Group. *J Am Diet Assoc.* 1999;99(10):1212–1221.
40. Montaurier C, Morio B, Bannier S, et al. Mechanisms of body weight gain in patients with Parkinson's disease after subthalamic stimulation. *Brain*. 2007;130(pt 7):1808–1818.
41. Dale J, Daykin J, Holder R, et al. Weight gain following treatment of hyperthyroidism. *Clin Endocrinol (Oxf)*. 2001;55(2):233–239.
42. Feldstein AC, Nichols GA, Smith DH, et al. Weight change and glycemic control after diagnosis of type 2 diabetes. *J Gen Intern Med*. 2008;23(9):1339–1345.
43. Taylor FR. Weight change associated with the use of migraine-preventive medications. *Clin Ther.* 2008;30(6): 1069–1080.
44. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006;355(8):763–778.
45. Baik I, Ascherio A, Rimm EB, et al. Adiposity and mortality in men. *Am J Epidemiol*. 2000;152(3):264–271.
46. Ringbäck Weitoft G, Eliasson M, Rosén M. Underweight, overweight and obesity as risk factors for mortality and hospitalization. *Scand J Public Health.* 2008;36(2):169–176.
47. Ajani UA, Lotufo PA, Gaziano JM, et al. Body mass index and mortality among US male physicians. *Ann Epidemiol*. 2004;14(10):731–739.
48. Allison DB, Heo M, Flanders DW, et al. Examination of "early mortality exclusion" as an approach to control for confounding by occult disease in epidemiologic studies of mortality risk factors. *Am J Epidemiol*. 1997;146(8):672–680.
49. Allison DB, Faith MS, Heo M, et al. Meta-analysis of the effect of excluding early deaths on the estimated relationship between body mass index and mortality. *Obes Res.* 1999; 7(4):342–354.
50. Allison DB, Heo M, Flanders DW, et al. Simulation study of the effects of excluding early deaths on risk factor-mortality analyses in the presence of confounding due to occult disease: the example of body mass index. *Ann Epidemiol*. 1999;9(2):132–142.
51. Bamia C, Halkjaer J, Lagiou P, et al. Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-elderly network on ageing and health study. *J Intern Med.* 2010; 286(2):133–144.
52. Wedick NM, Barrett-Connor E, Knoke JD, et al. 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): 1810–1815.
53. Al Snih S, Ottenbacher KJ, Markides KS, et al. The effect of obesity on disability vs mortality in older Americans. *Arch Intern Med*. 2007;167(8):774–780.
54. Berraho M, Nejjari C, Raherison C, et al. Body mass index, disability, and 13-year mortality in older French adults. *J Aging Health.* 2010;22(1):68–83.
55. Dolan CM, Kraemer H, Browner W, et al. Associations between body composition, anthropometry, and mortality in women aged 65 years and older. *Am J Public Health*. 2007; 97(5):913–918.
56. Durazo-Arvizu RA, McGee DL, Cooper RS, et al. Mortality and optimal body mass index in a sample of the US population. *Am J Epidemiol*. 1998;147(8):739–749.
57. Flegal KM, Graubard BI, Williamson DF, et al. Impact of smoking and preexisting illness on estimates of the fractions of deaths associated with underweight, overweight, and obesity in the US population. *Am J Epidemiol*. 2007;166(8): 975–982.
58. Gu D, He J, Duan X, et al. Body weight and mortality among men and women in China. *JAMA*. 2006;295(7):776–783.
59. Gulsvik AK, Thelle DS, Mowé M, et al. Increased mortality in the slim elderly: a 42 years follow-up study in a general population. *Eur J Epidemiol*. 2009;24(11):683–690.
60. Lang IA, Llewellyn DJ, Alexander K, et al. Obesity, physical function, and mortality in older adults. *J Am Geriatr Soc.* 2008;56(8):1474–1478.
61. Mehta NK, Chang VW. Mortality attributable to obesity among middle-aged adults in the United States. *Demography.* 2009;46(4):851–872.
62. Reuser M, Bonneux LG, Willekens FJ. Smoking kills, obesity disables: a multistate approach of the US Health and Retirement Survey. *Obesity (Silver Spring)*. 2009;17(4):783–789.
63. Reuser M, Bonneux L, Willekens F. The burden of mortality of obesity at middle and old age is small. A life table analysis of the US Health and Retirement Survey. *Eur J Epidemiol*. 2008;23(9):601–607.
64. Thorogood M, Appleby PN, Key TJ, et al. Relation between body mass index and mortality in an unusually slim cohort. *J Epidemiol Community Health*. 2003;57(2):130–133.
65. Mikkelsen KL, Heitmann BL, Keiding N, et al. Independent effects of stable and changing body weight on total mortality. *Epidemiology.* 1999;10(6):671–678.
66. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*. 1999;341(15):1097–1105.
67. Brookes ST, Whitley E, Peters TJ, et al. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. *Health Technol Assess*. 2001; 5(33):1–56.
68. Brookes ST, Whitely E, Egger M, et al. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. *J Clin Epidemiol*. 2004;57(3):229–236.
69. Guillemin F. Primer: the fallacy of subgroup analysis. *Nat Clin Pract Rheumatol*. 2007;3(7):407–413.
70. Mills JL. Data torturing. *N Engl J Med*. 1993;329(16): 1196–1199.
71. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189–2194.
72. Effect of smoking on the body mass index-mortality relation: empirical evidence from 15 studies. BMI in Diverse Populations Collaborative Group. *Am J Epidemiol*. 1999;150(12): 1297–1308.
73. Chiolero A, Peytremann-Bridevaux I, Paccaud F. Associations between obesity and health conditions may be overestimated if self-reported body mass index is used. *Obes Rev.* 2007;8(4):373–374.
74. Heid IM, Küchenhoff H, Wellmann J, et al. On the potential of measurement error to induce differential bias on odds ratio estimates: an example from radon epidemiology. *Stat Med*. 2002;21(21):3261–3278.
75. Ioannidis JPA. Why most published research findings are false [electronic article]. *PLoS Med*. 2005;2(8):e124.
76. Kaptchuk TJ. Effect of interpretive bias on research evidence. *BMJ*. 2003;326(7404):1453–1455.
77. Fontaine KR, Redden DT, Wang C, et al. Years of life lost due to obesity. *JAMA*. 2003;289(2):187–193.

78. Manson JE, Bassuk SS. Obesity in the United States: a fresh look at its high toll. *JAMA*. 2003;289(2):229–230.
79. Gelber RP, Kurth T, Manson JE, et al. Body mass index and mortality in men: evaluating the shape of the association. *Int J Obes (Lond)*. 2007;31(8):1240–1247.
80. Lee IM, Manson JE. Body weight and mortality: what is the shape of the curve? *Epidemiology*. 1998;9(3):227–228.
81. De Laet C, Kanis JA, Oden A, et al. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int*. 2005;16(11):1330–1338.
82. Ensrud KE, Fullman RL, Barrett-Connor E, et al. Voluntary weight reduction in older men increases hip bone loss: the Osteoporotic Fractures in Men Study. *J Clin Endocrinol Metab*. 2005;90(4):1998–2004.
83. Cauley JA, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. *Osteoporos Int*. 2000; 11(7):556–561.
84. Ensrud KE, Lipschutz RC, Cauley JA, et al. Body size and hip fracture risk in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Am J Med*. 1997;103(4):274–820.
85. Ensrud KE, Cauley J, Lipschutz R, et al. Weight change and fractures in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med*. 1997;157(8):857–863.
86. Ensrud KE, Ewing SK, Stone KL, et al. Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. *J Am Geriatr Soc*. 2003;51(12):1740–1747.
87. Dignam JJ, Polite BN, Yothers G, et al. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. *J Natl Cancer Inst*. 2006;98(22):1647–1654.
88. Schols AM, Slangen J, Volovics L, et al. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998; 157(6 pt 1):1791–1797.
89. Brennan P, McKay J, Moore L, et al. Obesity and cancer: Mendelian randomization approach utilizing the *FTO* genotype. *Int J Epidemiol*. 2009;38(4):971–975.
90. Hozawa A, Okamura T, Oki I, et al. Relationship between BMI and all-cause mortality in Japan: NIPPON DATA80. *Obesity (Silver Spring)*. 2008;16(7):1714–1717.
91. Jee SH, Sull JW, Park J, et al. Body-mass index and mortality in Korean men and women. *N Engl J Med*. 2006;355(8): 779–787.
92. Pednekar MS, Hakama M, Hebert JR, et al. Association of body mass index with all-cause and cause-specific mortality: findings from a prospective cohort study in Mumbai (Bombay), India. *Int J Epidemiol*. 2008;37(3):524–535.
93. Prospective Studies Collaboration, Whitlock G, Lewington S, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373(9669):1083–1096.
94. Doehner W, Clark A, Anker SD. The obesity paradox: weighing the benefit. *Eur Heart J*. 2010;31(2):146–148.
95. Hogue CW Jr, Stearns JD, Colantuoni E, et al. The impact of obesity on outcomes after critical illness: a meta-analysis. *Intensive Care Med*. 2009;35(7):1152–1170.
96. O'Brien JM Jr, Phillips GS, Ali NA, et al. Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. *Crit Care Med*. 2006;34(3):738–744.
97. Rice TW. Obesity in acute lung injury: the ''weight'' is over. *Chest*. 2007;131(2):333–334.
98. Cooper RS. Which factors confound or modify the relationship between body weight and mortality? *Int J Obes (Lond)*. 2008;32(suppl 3):S47–S51.
99. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses [electronic article]. *BMJ*. 2010; 340:c117.
100. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health*. 2006; 60(7):578–586.
101. Robins JM. Causal models for estimating the effects of weight gain on mortality. *Int J Obes (Lond)*. 2008; 32(suppl 3):S15–S41.
102. Kenfield SA, Stampfer MJ, Rosner BA, et al. Smoking and smoking cessation in relation to mortality in women. *JAMA*. 2008;299(17):2037–2047.
103. Kenfield SA, Wei EK, Rosner BA, et al. Burden of smoking on cause-specific mortality: application to the Nurses' Health Study. *Tob Control*. 2010;19(3):248–254.
104. Flanders WD, Augestad LB. Adjusting for reverse causality in the relationship between obesity and mortality. *Int J Obes (Lond)*. 2008;32(suppl 3):S42–S46.
105. Janssen I, Bacon E. Effect of current and midlife obesity status on mortality risk in the elderly. *Obesity (Silver Spring)*. 2008;16(11):2504–2509.
106. Lewis CE, McTigue KM, Burke LE, et al. Mortality, health outcomes, and body mass index in the overweight range. A science advisory from the American Heart Association. *Circulation*. 2009;119(25):3263–3271.
107. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study [electronic artivle]. *BMJ*. 2007;335(7630):1134.
108. Stampfer M. Weight loss and mortality: what does the evidence show? [electronic article]. *PLoS Med*. 2005;2(6):e181.
109. Sun Q, Townsend MK, Okereke OI, et al. Adiposity and weight change in mid-life in relation to healthy survival after age 70 in women: prospective cohort study [electronic article]. *BMJ*. 2009;339:b3796.
110. Lawlor DA, Hart CL, Hole DJ, et al. Reverse causality and confounding and the associations of overweight and obesity with mortality. *Obesity (Silver Spring)*. 2006;14(12): 2294–2304.
111. Lee IM, Manson JE, Hennekens CH, et al. Body weight and mortality. A 27-year follow-up of middle-aged men. *JAMA*. 1993;270(23):2823–2828.
112. Lindsted KD, Singh PN. Body mass and 26-year risk of mortality among women who never smoked: findings from the Adventist Mortality Study. *Am J Epidemiol*. 1997;146(1): 1–11.