Methodological issues in observational studies of obesity and mortality

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ABSTRACT

Obesity has important health hazards, and the epidemic seems to be growing in developed countries. There is scientific evidence for higher risk of earlier death among the obese. However, most evidence of the effects of obesity on mortality comes from observational studies. The aim of this manuscript is to review some of the most important issues in designing, analyzing and interpreting analytic studies of the effects of obesity on mortality. Key issues are clarity in the definition of the effect under study, confounding, measurement error and a phenomenon sometimes termed reverse causality in which obesity causes some diseases, but some of the diseases also affect adiposity and mortality.

INTRODUCTION

Globally, obesity prevalence is increasing and the associated increased risk for morbidity and mortality is a major public health concern.[1-6] Obesity can be operationally defined as a body mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30.0 or more, and overweight defined as a BMI of 25.0 to 29.9.[6] In 2007-2008, the prevalence of obesity was 32.2% among adult men and 35.5% among adult women in the United States (US).[2] The Centers for Disease Control (CDC) claimed that an additional 2.4 million adult Americans were obese in 2009 compared with 2007, representing a rise of 1.1 per cent.[7]

Berghofer et al.[8] concluded from their systematic review that in Europe, obesity has reached epidemic proportions. In Norway, the prevalence of obesity increased in the late 1990's to 15%.[9] Ulset et al.[10] claimed in 2007 that the obesity epidemic had reached Norway. They reported a median obesity prevalence across studies of 19.5% for men and 20.0% for women.

Obesity has important health effects. Obese people have, among other problems, higher risk of diabetes, cardiovascular diseases, selected cancers, and musculoskeletal problems.[11,12] Calle and Thun[13] estimated that overweight and obesity account for one of seven cancer deaths in men and one of five in women in the US. Mental health problems are also related to obesity, as well as personal socioeconomic concerns since obese people may also have a higher unemployment rate than non-obese people.[14] In addition, if obesity in adolescence leads to adult obesity and mortality it is important to develop strategies to prevent the epidemic.[15] The increasing numbers of obese people will affect the health costs, not only individually, but nationally and internationally for prevention, management and treatment.

A healthy diet and regular life-long exercise may be two important ways to lower the risk of obesity.[16-18] Furthermore, physical activity and increased aerobic fitness predict low cardio-metabolic morbidity and mortality.[19,20] Hirayama et al.[21] claimed that promotion of physical activity to prevent the risk of obstructive pulmonary disease should be encouraged. A loss or reduction in skeletal muscle function caused by low physical activity, seem also to be associated with increased morbidity and mortality among the obese.[22]

However, much of the evidence for harmful effects of obesity, especially for premature mortality, comes from observational studies (e.g.,[1,3,23,24,25]). More studies of the effects are needed, particularly among the young. The primary purpose of this commentary is to review some of the important issues in designing, analyzing and interpreting analytic observational studies of obesity and mortality. For simplicity, we focus most of the discussion on questions involving the impact on mortality of being in an obese category relative to a normal category (non-obese), perhaps based on the WHO groupings of BMI,[6] but similar issues arise for overweight and other categories across the spectrum of adiposity.

LACK OF A WIDELY EFFECTIVE INTERVENTION

Investigators seeking to understand the health effects of obesity and overweight, and in particular the effects on mortality, must address numerous questions. Questions about *interventions* to prevent obesity, or to lose weight if obesity is present, are particularly practical and of great public health importance. We consider these questions about interventions first because experimental studies designed to address them are relatively straightforward to design in concept and can provide a possible model for the design of the more challenging observational studies – the main subject of this commentary.

A number of randomized, controlled studies to evaluate effects of weight-loss interventions have been conducted, but the effects studied have not generally been long-term mortality.[26,27] (A prospective study of

bariatric surgery and mortality has been done, but surgery was not randomized.[28]) Interventions that have been evaluated include various combinations of dietary interventions, meal replacement, physical activity and medication. Outcomes evaluated include weight loss itself, lipid levels, and insulin sensitivity. Due to the randomization we expect those receiving the intervention should be similar to those in the comparison group, confounding expected to be absent, and causal effects of the *intervention* to be estimable. Thus, we expect good information about the effects of the *interventions* studied. Such studies would, of course, provide only indirect estimates of the benefits of weight reduction itself. For example, if a group randomized to have increased aerobic physical activity had both reduction in weight and lower mortality, further work would still be needed to attribute the mortality differences to weight loss alone. For example, part of the reduced mortality could be due to increased cardiovascular fitness rather than to the reduced body mass itself. If such studies consistently showed a reduction in mortality, we could then speculate about, and design additional studies to evaluate the extent to which those effects were due to eliminating obesity itself and the extent to which they were due to other aspects of the interventions. Interventions that have few direct effects apart from weight reduction might be expected to provide stronger evidence about the effects specifically due to the weight reduction. We should also consider other types of evidence, such as that from experiments involving animals or biomarkers, in helping to infer causal effects. However, interpretation may be challenging, particularly for modest degrees of overweight, because integrating different types of evidence may not be clear cut, effects of different interventions may be heterogeneous, effects on obesity and weight reduction likely to be modest and inconsistently maintained, and evaluation of the effects on mortality expected to require long term follow-up.

Randomized controlled studies to evaluate effects of interventions intended, at least partly, to *prevent* weight gain have also been conducted.[29,30] If such studies tended to show a benefit of the interventions on mortality, we could speculate about the extent to which the benefit was due to the lower body mass and the extent to which it was due to the some other aspect of the intervention. But studies of interventions designed to prevent weight gain, like studies of weight reduction, also face challenges of maintenance and heterogeneity of effects, modest magnitude of effects on weight, expense and need for relatively long follow-up to address mortality.

Experimental studies of interventions, both of obesity prevention and for weight loss, have several important strengths. First, the effect of interest is clearly defined and corresponds closely with the comparison of study groups. In particular, the effect studied is that due to having been offered the intervention; the intervention group and the comparison group clearly differ in this regard, with the intervention having been offered to one but not the other group; and, the difference in mortality between study groups should estimate this effect. Second, subjects can be randomized to be in the intervention group, a strength which should tend to prevent confounding. Other strengths include the ability to clearly define and determine the intervention and use of a comparison group. Blinding may be possible for some interventions, such as drug treatment, but can be difficult for others depending on the nature of the intervention. These intervention studies also have important limitations. Perhaps the over-riding one that limits the practical importance of their results is the lack of a widely acceptable and effective intervention. Other limitations may include the difficulty in maintaining weight loss, possible lack of generalizability and the feasibility of conducting large clinical trials.

Because of the limitations, researchers often conduct observational studies to assess the effects of obesity on mortality. Researchers who conduct observational studies, however, face several important methodological issues that do not normally arise, or do so differently, in randomized trials. These issues are likely to include: a lack of clarity of the definition of the effect under study that links closely with differences in mortality between study groups; selection bias; measurement error; and reversal of the direction of cause and effect. Each of these potential biases is discussed in the next sections.

DEFINITION OF EFFECT

To illustrate the methodological issues surrounding the definition of the effect of obesity in observational studies of mortality, we consider a cohort study. Study subjects, some of whom are obese, are followed to identify deaths, and the mortality of subjects who are obese at baseline is compared with that of non-obese subjects. This general design is much like that of many published studies (e.g.,[1,24,31]). The study goal is putatively estimation of the effects of obesity on mortality. In counterfactual terms, we might loosely say that the goal is to estimate the causal rate ratio: the mortality of the obese group compared to what the mortality of this group would have been if, contrary to fact, they had not been obese (see Rothman et al. for definitions and discussion of causal parameters[32]).

In a randomized clinical trial, however, we would specify when and how the non-obese state was to have been achieved and/or maintained and also when and how the obese state was to have been achieved and maintained. Any diseases that occur after the trial has begun are not considered to be a source of bias, but rather potential contributors to premature mortality. In an observational study, essentially the same design questions are relevant: when and how were the obese and non-obese (comparison) conditions achieved and/or maintained? Was it through more physical activity and exercise, through caloric restriction, through medication, through the modification of stress, other psycho-

logical factors or other lifestyle changes, through surgery, gene therapy or some other mechanism or through some combination of these preventive measures? Over what time period was the obese state present and when did intermediate effects, such as disease, start to occur as potential contributors to death? Without answers to these questions, the nature of the contrast between the obese and non-obese groups is unclear; how to define a causal effect that corresponds to an observed difference in mortality between groups is uncertain. One answer might be that observed differences in mortality are due to the obesity and to other factors in some unknown combination. This answer, however, is unsatisfying since information added by the study would then be limited: the difference in mortality (assuming one is found) might be documented, but the factors causing the differences would remain uncertain. This lack of clarity differs importantly from a randomized clinical trial in which the cause of differences between groups should be relatively clear – the groups should be similar at baseline apart from having been offered the intervention, the intervention itself is the only difference between groups, and it is the effect of the intervention starting at time of randomization which is under study. Many of these questions are discussed in further detail by Hernán and Taubman.[33,34]

In summary, the causal effect that is estimated by comparing mortality of obese and non-obese groups in many cohort studies (e.g.,[1,24,31]) is complex, perhaps even ill-defined. Formulation of a clear effect definition that corresponds to the difference in mortality between obese and non-obese groups is fraught with challenges due in part to our inability to specify the pathways and mechanisms that led to obesity or non-obesity for study subjects. The mortality difference between obese and non-obese groups does not correspond to an intervention. These difficulties in formulating a clear, relevant effect definition are discussed further and more technically by Hernán and Taubman[33] who note how lack of a clear definition creates a lack of consistency, in which an obese person's observed health outcome may not be equal to what it would have been, if that individual had actually be assigned to be obese in a randomized experiment. VanderWeele[35] refines these concepts, adding that causal inference is often based on the additional assumption that some variations in treatment are irrelevant.

CONFOUNDING

We now consider confounding, a threat to the validity of many observational studies. Confounding is the mixing of the effects of an extraneous factor with those of the factor of interest in a way that distorts the association of interest. Greenland et al. provide this definition: "*Assuming that exposure precedes disease, confounding will be present if and only if exposure would remain associated with disease even if all exposure effects were removed, prevented, or blocked*"[36]; this definition emphasizes causal effects and the counterfactual situation under which the exposure's effects are blocked or prevented.

As noted previously, the factors leading to an obese or non-obese state are numerous, complex, and intertwined. Compared to the obese, the non-obese may engage in more physical activity, either occupationally or during leisure time; may consume fewer calories; may metabolize food differently; may have illness(es), possibly occult; may expend more calories during a given activity; may have different habits, such as smoking; and may have different stress and other psychological factors.

In an attempt to focus on obesity alone, the investigator could restrict both obese and non-obese groups to two groups, thought to be homogeneous apart from differences in body mass index. For example, subjects in the obese group might be required to be female, 30 years old, not physically active, non-diabetic, no chronic disease, non-smoking, and consume between 2000 and 2050 calories daily. Subjects in the non-obese group might be required to have identical characteristics for gender, age, physical activity, diabetes, disease, smoking, and caloric consumption. The question remains: are the groups comparable and similar apart from the one factor which differs by design: obesity? The answer is very likely "no", since one must suspect that some differences (other than gender, age, physical activity, diabetes, disease, smoking, and caloric consumption) explain why one group is obese, the other not. The lack of clarity in the effect estimated noted in the previous section further complicates the identification of confounding. Which factors are extraneous and which factors are a part of the unrecognized differences in explanatory factors which together are the effective, but uncertain "exposure"? Since obesity develops and occurs over time, we should also ask which factors are (intermediate) effects of obesity itself. Again, the answers are unclear, particularly absent a clear definition of the effect to be estimated. The risk ratio is certainly a comparison of the mortality of an obese group with the mortality of a non-obese group, but they almost certainly have some characteristics that differ (those that led to obesity). The extent to which mortality differences are due to the difference in obesity itself, rather than to a confounded mixture of the effects of obesity and extraneous factors, is then speculative.

Because of these many differences in many combinations, the actual comparison in a typical cohort study involves the mortality of an obese group with many diverse characteristics (only one of which is obesity), with a non-obese group with many diverse characteristics (only one of which is non-obesity). Yet additional complexity reflects the myriad feedback loops over the course of life: while obesity may be caused by a sedentary lifestyle, high caloric intake and so on, obesity in turn can be cause one to be more sedentary perhaps because of weight-induced musculoskeletal problems which restrict movement, to consume more calories

and so forth. In fact, the obesity, physical activity, caloric consumption, behaviors, metabolism, stress and other psychological factors may be so inter-twined that they are nearly inseparable, for practical purposes. Differences between groups in some risk factors in addition to obesity itself create the relationships necessary for confounding – effects on mortality of these extraneous factors effects are likely to mix in with and distort the effects of obesity. In other words, the obese and non-obese groups may not be exchangeable[37] (comparable) and confounding must be suspect. (Partial exchangeability is said to hold if the comparison (non-obese) group tells us what the mortality of the obese group would have been, had they been more physically active and non-obese, but otherwise just the same.)

One may attempt to control for differences through restriction, stratification or modeling. Exclusion of first years of follow-up may ameliorate the impact of pre-existing diseases. However, the complex inter-relationships, feedback loops, changes over time and the possibility of induced relationships by selection or stratification make adequate control a challenge. The ability to assess and control for confounding is further hampered by difficulties in forming a clear, sharp definition of the causal effect (lack of consistency, possible relevance of "treatment" variations) as noted in Section "Definition of Effect". In particular, it is difficult to assess whether the obese and non-obese groups are similar (exchangeable), due to lack of knowledge about what caused the obesity and how the counterfactual obese state might be attained. A further problem arises because the exposure and covariates vary with time and affect each other – sometimes called time varying confounding – and requires possibly more complicated analyses such as the g-computation algorithm.[38]

SELECTION BIAS

Selection bias is closely related to confounding. Here we define it as bias due to selection based on a common effect of two or more factors[39]. Excluding subjects deemed ineligible perhaps due to illness, recruiting those who are eligible, willing, obtaining measurements, and even restricting to those who have attained a specific age are all possible selection factors. Such selection can induce an association between any of the factors that led to inclusion, such as obesity, willingness to participate, successful measurement and completion of questionnaires, health status and survival to a particular age. If any of these selection factors is also a risk factor for mortality, bias must be suspected.[39,40] This problem is avoided in a randomized clinical trial, since the intervention is randomized avoiding the associations induced by selection.

MEASUREMENT ERROR

Measurement error is yet another important challenge facing researchers seeking to study the effects of obesity on mortality. It is not the body mass index itself which causes death, but rather the underlying associated physiologic factors, such as fat mass, muscle mass, adiposity, distribution of adipose tissue, metabolic changes, lifestyle effects and resulting disease. Body mass index and the categories of obese and non-obese or normal weight are merely surrogates for these underlying patho-physiologic factors. Thus measurement error, reflecting the difference between body mass index and the underlying processes that might better define obesity, contributes along with selection bias, confounding and lack of clear effect definitions to the potential biases and research challenges.[41] This problem is avoided in a randomized clinical trial, since the exposure is well-defined and measured – the intervention.

REVERSAL OF CAUSE AND EFFECT

A particularly challenging methodological issue facing researchers is the possibility of confounding by pre-existing disease, possibly undiagnosed. Some diseases may both affect adiposity and increase mortality, and thereby create confounding. The issue is even more complex, however, because a possible effect of obesity can be to increase risk of some diseases, such as certain types of cancer. Thus, some diseases may both be intermediates on the causal pathway from obesity to death (caused by obesity), but also may have a reverse effect and lead to changes in adiposity. This is sometimes called reverse causality, referring to the recognized possibility that not only does obesity affect disease occurrence and, in turn, mortality, but also the likelihood that disease affects subsequent adiposity. For example, some with cancer, cardiovascular disease, dementia and many other diseases may lose body mass – either intentionally or unintentionally – as a result of the disease. Thus, in the absence of an effect of obesity on mortality, we would have to expect an association between adiposity and mortality. This reversed direction of cause and (intermediate) effect may partly explain the observation that those with a BMI below 20, have often been found to have a higher mortality (a J-shaped mortality curve).

Many researchers have excluded those with pre-existing disease in an attempt to prevent this bias by exclusion, as the presence of pre-existing disease at the start of follow-up could confound results. The first years of follow-up may also be excluded, in an attempt to reduce the impact of pre-existing diseases. Such exclusions and restrictions, however, are a selection force with the possible exception of restriction to those young initially, and the selection can induce associations as noted above in the Section "Selection Bias." Starting follow-up at a young age may also help, as the prevalence of pre-existing disease should be lower in this group. Thus, some of the possible benefits of exclusion to reduce confounding can be offset by induced confounding and other biases.[42] Furthermore,

disease is an intermediate on the pathway from obesity to death so that excluding those with prevalent disease could mask some effects. These problems are avoided in a randomized clinical trial, since pre-existing disease should be equally distributed between exposure groups and any disease that occurs during the trial is normally considered a possible part of the causal pathway.

SUMMARY AND CONCLUSIONS

The researcher wishing to understand the effects of obesity on mortality faces many challenges. Several of the challenges originate from the difficulties associated with clearly defining a causal effect which corresponds with the type of contrasts used in many types of cohort studies: a comparison of the mortality of an obese group with that of a non-obese group. In particular, the contrast studied typically does not correspond to an intervention. Other challenges include control of confounding particularly from pre-existing disease which can also have been an intermediate effect of obesity as it developed, and accounting for the likelihood of some degree of reverse causality. Design strategies that may help to reduce or address the associated biases include: starting follow-up at younger ages before obesity and most diseases have begun, use of the g-computation algorithm and related approaches,[38,43,44] sensitivity analyses and simulations.[42] Use of additional evidence such as experimental results, use of intermediate outcomes and biomarkers,[45] animal studies,[46-48] as well as other considerations described by Bradford Hill[49] should, of course, help the researcher to evaluate the magnitude of effects, although considerable uncertainty may remain.

Given these methodological challenges, Hernán and Taubman, note that a useful approach may be to focus efforts on the more clearly defined and modifiable lifestyle factors, such as physical activity and nutrition,[33] rather than on obesity per se. This approach has the additional, practical advantage of more directly evaluating possible public health interventions; modifiable lifestyle factors found to increase risk of untoward outcomes can be the focus of interventions designed to modify them in favorable ways. The public health challenge is to find interventions that are widely applicable, acceptable, feasible and effective.

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