Body Mass Index, Obesity, and Mortality– Part I

Associations and Limitations

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The association of obesity with mortality has been the subject of scientific investigation for centuries. Although historical observations, as well as more recent quantitative analyses, demonstrate a relationship of obesity with early death, there remain questions about the degree of the association and how it may vary with age, diet, physical activity, and other life circumstances. The relationship between body mass index (BMI) and mortality is "U-shaped," with the lowest mortality rate observed at a mildly overweight BMI. Many potential explanations have been postulated for higher mortality at both lower and higher levels of BMI, such as occult disease in those at low BMI; difference across categories in weight variability, smoking, and/or distribution of body fat; and the "fit but fat" phenotype. This review discusses some of the continuing questions and hypotheses surrounding the relationship of BMI with mortality and identifies additional research needed. Nutr Today 2023;58(3):92–99

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No funding was provided for the development of this manuscript. T.M. has grant/research support from NIDILRR, NIH, CDC, and PCORI and industry funding from Brigham and Women's Hospital with the overall sponsor as Metro International. He has received consulting fees from Novo Nordisk and editorial fees from the Obesity journal and PLoS One. In the last 24 months, D.B.A. has received personal payments or promises for same from Alkermes, Inc; Amin Talati Wasserman for KSF Acquisition Corp (Glanbia); Clark Hill, PLC; Kaleido Biosciences; Law Offices of Ronald Marron; Medpace/Gelesis; Novo Nordisk Fonden; Sports Research Corp; and Zero Longevity Science. D.B.A.'s institution, Indiana University, and the Indiana University Foundation have received funds or donations to support his research or educational activities from Eli Lilly and Company; Pfizer, Inc; Soleno Therapeutics; WW (formerly Weight Watchers); and numerous other for-profit and nonprofit organizations to support the work of the School of Public Health and the university more broadly. K.C.M. has received research funding and/or consulting fees in the last 24 months from the following: 89bio, Inc, Acasti Pharma Inc, Beren Therapeutics, Bragg Live Products, Cargill, Eli Lilly and Company, General Mills, Greenyn Biotechnology, Hass Avocado Board, Indiana University Foundation, Matinas BioPharma, MediFast, National Cattlemen's Beef Association, National Dairy Council, Naturmega, New Amsterdam Pharma, PepsiCo, and Pharmavite. Funding from these organizations was not used to support this article. The other authors have no conflicts of interest to disclose.

D.B.A. conceptualized and designed the paper. S.T.L. wrote the initial draft. L.M.M. wrote and edited the paper after initial draft by S.T.L. All authors were involved in reviewing or editing the paper and providing the final approval of the submitted and published versions. The opinions expressed are those of the authors and do not necessarily represent those of the funding sources or any other organization.

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DOI: 10.1097/NT.0000000000000609

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INTRODUCTION

The relationship between obesity, as defined by body mass index (BMI) or body fatness, and mortality rate is of great interest to the scientific, clinical, and public health communities and the public. It has now been the subject of formal study for several centuries. However, most of the work of a quantitative statistical and epidemiologic nature has been done in the 20th and 21st centuries.[1–6] Recognition of the relationship between obesity and mortality goes back to at least the time of Shakespeare when in *Henry IV*, Henry reproved Falstaff saying, "Leave gormandizing. Know that the grave doth gape thrice wider for thee than for other men."[7] In doing so, Shakespeare recognized the purported relationship between obesity and earlier death. Many other historical records reference the idea that obesity predisposes to ill health in general and reduced life span, in particular.[2,5] It is important, however, to go beyond these general impressions and buttress them with quantitative data regarding the shape, consistency, and degree of the association and how that association varies with factors, such as diet, life circumstances, secular period, and demographic characteristics of the person in question, and to evaluate the extent to which such associations represent causation. Perhaps because of the complex emotional and social implications of obesity, this has often become a battleground for scholars with opposing views.[3,4,6,8] Some of those have been good-spirited academic debates, and others perhaps a bit more personal and vitriolic than they should have been. Nevertheless, the interested and educated reader who is not a professional epidemiologist or statistician focusing on this topic may be confused by the diverse views presented. We have tried to lay out some of the key elements and questions that are commonly asked and offer plausible responses. This is first of 2 articles on the association between obesity and mortality. This first article reviews the association between obesity and mortality, the shape of the association and how it has changed over time, and the dissimilarity of the association when different measures of body weight and adiposity are used.

DATA FOR RESEARCH—DO WE NEED MORE DATA?

The simple answer is "yes, but…." We do not only need more data. What we need is different data, better data, or data analyzed in a manner that yields new insights. Since the early 1980s, research on obesity-associated mortality has swung like a pendulum between 2 camps: the "broad range of healthy weight" camp[5,6] and the "thinner-is-better" camp,[3] each made distinct by their contrasting analytic strategies and conclusions. However, both camps seem to possess some circularity. First, the choice of the analytic strategy used by the authors seems closely related to which camp they are in (ie, their belief predisposition). Second, the results obtained seem to be heavily dependent on the analytic strategy used. Finally, the results obtained seem to reinforce the belief predisposition and serve as "evidence" for the correctness of the chosen analytic strategy. Along the way, both "broad range of healthy weight" and "thinner-is-better" camps have introspected their belief predisposition based on results from data with 6- and 7-figure sample sizes. Therefore, rather than simply needing more data, we need data that are somehow different or better—perhaps derived from different and robust analytical approaches that would allow us to distinguish between the relative validity of the 2 views.

ASSOCIATION OF HIGHER BODY MASS INDEX AND EXCESS DEATHS—DOES THIS RELATIONSHIP VARY WITH AGE AND HAS THE ASSOCIATION BEEN STABLE OVER TIME?

Figure shows the U-shaped or bathtub-shaped association of BMI category with excess deaths by age group from the combined NHANES (National Health and Nutrition Examination Survey) I, II, and III data sets.[5] Notably, the lowest rate of excess deaths is in the overweight (BMI 25.0–<30 kg/m^2) category. Both underweight (BMI <18.5 kg/m^2) and stage II obesity (BMI ≥35 kg/m^2) are associated with significant elevations in excess deaths compared with the normal weight and overweight categories. The slope of the right side of the curve is less steep with higher age, although this might reflect, in part, a survival bias, because those at highest risk may have already died before reaching the oldest-age categories.

Although the general U-shaped relationship between greater BMI and mortality has been evident in cohort studies for decades, the location of the nadir, that is, the BMI associated with the lowest rate of mortality or excess deaths, appears to have shifted toward higher BMIs over time. This issue came to the fore in 2005 when Flegal and colleagues[5] published an important article. They found that across several waves of the NHANES data sets, it appeared that as time moved from the 1970s into the late 1990s, the strength of the association of elevated BMI (overweight and obesity) with increased mortality rate (roughly speaking decreased longevity[†]) seemed to be declining.[5] This was not a function of individuals' aging, but instead, the fundamental association was changing over the course of recent history. The first question one might ask about this is: Why is this occurring? Before we address that, it is even more important to ask whether it is truly occurring. That is, are we confident that this is not a fluke of one data set or set of data sets? The answer appears to be that it is not a fluke. Several other investigators, including some authors on this article, have published studies that show that the nadir of the roughly U-shaped relationship between BMI and mortality rate seems to have been increasing over the last several decades in the United States and other countries.[5,8–12]

[†]In the context of this article, we will use phrases such as increase in mortality rate interchangeably with phrases such as decrease in longevity, even though we know those two are not mathematically identical.

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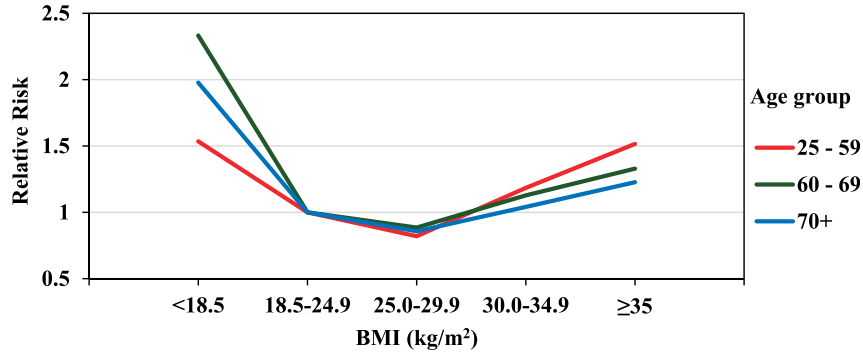

FIGURE. Excess deaths associated with underweight, overweight, and obesity. Adapted from Flegal et al.[5]

Similarly, the slope of the upward part of the curve for a given age category, which is the indication of the extent to which mortality rate increases with higher than presumed healthy BMIs, seems to be decreasing over the last half-century.[13]

Of course, things are never simple, and the extent to which the risk of death associated with elevated BMI is decreasing, or even whether it is decreasing at all, seems to depend at least on age, race, and sex.[10,13] Nevertheless, overall, there does seem to be some decrease in the adverse association. Does this represent a decrease in the true deleterious effect, caused by elevated BMI or adiposity? That is unknown. If there has been a decrease in the deleterious effect over time, to what would it be attributable? One common conjecture is that it results from better treatment of the anatomic and physiologic derangements that tend to follow elevated BMI along the causal pathway toward an early death. For example, perhaps we are better at treating diabetes, hypertension, dyslipidemia, atherosclerosis, chronic inflammation, strokes, and heart attacks than we were in prior times, and thereby, through medical technologies such as stents and statins, we have defanged obesity to some extent. That is a reasonable hypothesis, but whether it is true is unclear. Generally, while better treatments are being developed for obesity-related chronic diseases, a reduction in the deleterious effect of obesity is yet to be established.[14,15] Such reductions, when observed, are sometimes attributed to biases introduced through measurement errors and challenges posed by analytical methods.[16] One example is the use of maximum BMI as the independent variable for the BMI-mortality relationship, which may provide information different from BMI at the time of survey. The use of BMI at the time of survey may underestimate the mortality rate associated with excess weight in the United States because the normal BMI category would include some individuals who may have been obese at one point but who lost weight.[17] By using maximum BMI, the normal BMI category includes only weight-stable individuals who have never exceeded the normal BMI range. Some results also suggest that cumulative length of time of exposure to a higher weight category may be more strongly associated with mortality rate than BMI at the time of survey.[18]

Another factor to consider is that how people become obese may have tended to differ recently as compared with the past, and this pattern of obesity development may be less deleterious. For example, the reason, or part of the reason, obesity was associated with an increased mortality rate in the past was not because the obesity per se completely caused the deleterious associations, but rather because factors leading to obesity, such as inactivity and high energy intake, also contributed directly to mortality risk. Although energy expenditure in physical activity, particularly in occupational activities, has declined in the United States over time,[19] there is evidence that diet quality has been slowly improving.[20–22] If some elements of diet quality have improved, such as a lower ratio of saturated and *trans* fats to unsaturated fats, such dietary changes might lead to a diminution of the association between obesity and mortality. It is hypothesized that a portion of that association was not due to obesity per se, but to confounding by the association of a third factor (diet quality).[23] There may also be value in examining data from countries where obesity developed later than in the United States to determine if similar trends exist. Although limited data from other economically developing countries suggest similar patterns,[24–26] the certainty is low because of lack of availability of comparable analyses. There are yet other factors that could be causing this change in the association, and the topic remains an important area for research.

It is, in the authors' views, ironic that many people saw as the "shocking" element of the article by Flegal et al[5] the suggestion that overweight was not associated with any increase in mortality rate and, in some population subsets, was even associated with a lower mortality rate compared with normal weight, because this was already actually very well known in the literature.

SHAPE OF THE ASSOCIATION—IS THE RELATIONSHIP BETWEEN OBESITY AND MORTALITY RATE REALLY A U-SHAPE?

The most common way to describe the relationship between BMI and mortality rate is to say it is "U shaped". By

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U-shaped, people do not strictly mean exactly shaped like a U, but the resemblance of roughly parabolic or hyperbolic shape that is convex upward. The bottom of the "U" is often referred to as the nadir of the curve. That is, it is the part of the curve associated with the lowest mortality rate. In contrast, a half-century ago, Nobel Laureate Linus Pauling,[27] flipped the curve upside down by making the ordinate (ie, the *y* axis) life span or life expectancy, and we recently did the same.[27,28] That representation is probably a far more intuitive way to present such data to almost anybody other than a statistician or epidemiologist, but in the interest of sticking with the convention in the literature, we will continue to talk about a U-shaped relationship rather than an inverted U as one would get if the ordinate were life expectancy.

Some researchers assert that when one analyzes the data "correctly" by eliminating early deaths, eliminating ever-smokers and controlling for some other key factors, confounding by preexisting occult disease (sometimes incorrectly called reverse causation) or smoking status (due to residual confounding) is eliminated. As a result, the left part of the U curve flattens out, and an "unbiased" monotonic increasing relationship emerges between BMI and mortality rate. If this were true, it would support the famous quotation attributed to the Duchess of Windsor: "You can never be too rich or too thin" (at least the "too thin" part!).

Yet, this is not completely true. When ever-smokers and individuals who die early in follow-up are eliminated, the left end of the curve does not flatten out completely.[3,4,29] It may be reduced, but monotonicity is not observed. In fact, when individuals with recent weight loss, unintentional weight loss, or great weight variability are eliminated, there is a far greater impact on flattening the left part of the curve. However, without rationale for this elimination, doing so may in itself create biases.[16]

Moreover, the original proposal for all of these types of data eliminations was based on ad hoc arguments.[3] The idea of eliminating people with weight loss or weight variability came in later and, in our view, seems to be an example of a logical fallacy of "moving the goalposts."[30,31] Even in those cases when weight variability has been controlled for, it is not clear that there is truly a completely monotonic relationship. In fact, if the relationship were ever completely monotonic, it would be quite shocking because it would imply that starvation, wasting, and anorexia nervosa would, in fact, be healthy states when surely they are not. No one takes seriously the idea that one can never be too thin.

But it does seem that in some populations the people who live the longest are those with "midlevel" BMIs.[32] Studies have established that the U-shaped curve occurs when the lowest mortality rate is observed at intermediate BMIs, which sometimes includes BMI levels typically categorized as "mildly overweight."[31,33] Several researchers have also questioned the U-shaped curve, citing a so-called "obesity paradox," or the observation that in some disease states, individuals with obesity experience lower mortality. Debate continues regarding the existence and application of this paradox, with some contending that it may explain why the nadir of the BMI and mortality rate increases with age,[31] whereas others argue the paradox is likely an artifact of methodological problems and bias.[34]

In conclusions, although it may be that, over most of the BMI range of interest (ie, BMIs greater than approximately 18.5 kg/m^2), the relationship between BMI and mortality may be monotonically increasing, the observed association over the full range of BMI values is not monotonic. Some may choose to believe that the causal effect of increasing BMI increases monotonically after accounting for the effects of occult disease and other factors at the low end of the BMI range, and they may be correct, but alternate hypotheses are plausible and deserve further investigation.

CONSIDERATION OF OVERWEIGHT—IS OVERWEIGHT HEALTHY?

The definition of overweight is somewhat arbitrary; that is, overweight has been defined as a level that researchers define as starting to look unhealthy and have operationally defined as BMI of 25 to <30 kg/m^2. The association of decreased mortality rate at a BMI between 25 and 29.9 kg/m^2 relative to a so-called normal or healthy BMI between 18.5 and 24.9 kg/m^2 has been shown to vary with age, race, and sex.[5,30,31] For instance, the nadir of that BMI mortality curve keeps going up as one moves from early adulthood to late adulthood.[35,36] Still, whether these reported associations reflect causation or not, we do not know. Overweight, or any BMI, does not represent a single condition, and so participants cannot easily be randomly assigned in a clinical trial focused on determining the causal effect on mortality of overweight versus normal weight.

WHAT ABOUT FIT VERSUS FAT?

"Fit but fat" is often embedded in the concept of "metabolically healthy obesity," another controversial topic of research to the medical and fitness communities, as well as the public. Some studies have demonstrated in individuals who are "fit but fat" (ie, persons with obesity and high cardiorespiratory fitness) that their all-cause and CVD mortality risks are not significantly different from their counterparts who were fit, but normal weight.[37] In fact, it has been suggested that moderate to high cardiorespiratory fitness may attenuate the deleterious metabolic consequences of obesity and many other health outcomes in specific populations.[37] Contrary to these findings, other investigators found increased mortality risk among the "fit but fat."[38] Arguments against the "fit but fat" ideas have often cited that throughout the literature, obesity has been consistently associated with morbidity, disability, and all-cause mortality.

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Moreover, most studies by investigators that are proponents in the debate used BMI, which the opponents consider as not being the best measure of obesity. In general, research in human populations and laboratory animals has associated higher physical activity levels with positive health outcomes. However, some highly active individuals with increased muscle mass have BMI in the overweight or obese range. Most of the results that have contributed to the "fit but fat" concepts have come from observational studies,[39,40] and thus more research is necessary to improve our understanding of how physical activity, cardiorespiratory fitness, and BMI (or body composition) may interact to affect mortality rate. Randomized controlled trials (RCTs) are needed before a verdict, or conclusion close to a verdict, can be established regarding whether interventions to enhance cardiorespiratory fitness can attenuate or negate the adverse effects of obesity on adverse outcomes, including mortality. Yet, RCTs of sufficient duration to evaluate effects on morbidity or mortality are unlikely to be feasible because of ethical and compliance concerns. Moreover, the degree to which interventions to increase physical activity and cardiorespiratory fitness may differ in their ability to ameliorate adverse consequences of increased body mass or adiposity on outcomes is uncertain. For example, it is reasonable to hypothesize that the benefits of physical activity and cardiorespiratory fitness might be greater for those with a central/visceral (apple) body fat distribution pattern, which is associated with higher risk for chronic disease and premature mortality, than for others with the same BMI who have a more "gynoid or pear" pattern.[41] However, this remains to be demonstrated in RCTs.

The same can be said for the effects of caloric restriction. Calorie restriction has been shown to extend health span and life span in animal models.[42,43] There is also an indication that in humans such restriction results in metabolic and molecular adaptations that are associated with good health, including slowing the accumulation of molecular damage that would otherwise potentially lead to chronic diseases, disability, and mortality.[44] However, RCTs are needed to demonstrate that such changes will, indeed, improve outcomes.

ARE THE ASSOCIATIONS OF MORE DELETERIOUS EFFECTS OF BMI WITH MORTALITY RATE A FUNCTION OF BODY COMPOSITION AND FATNESS AS OPPOSED TO BODY WEIGHT?

Every few years, it seems the mass media erupts in a self-righteous revelation brought on, frequently, by some analysis or commentary from an academic, indicating the BMI, the index typically used to quantify the distribution of adiposity and/or the frequency of obesity within populations, measures total body mass relative to height and not body composition (eg, body fat, lean mass, muscle mass, etc).[45] Often, this is accompanied by a note that certain professional athletes might have high BMIs putting them in the obese category of BMI greater than 30 kg/m^2, and yet to all appearances, they do not have obesity, nor are they unhealthy.[46] Of course, these revelations are not new. The scientific community has known these points for quite some time. Tools, such as BMI, are valuable only to the extent they have relevance in a specific application. If BMI is being used on an individual clinical basis to determine whether NBA players have obesity, it is clearly an abysmal tool and should not be used. Instead, body composition techniques would be better and have been used for exactly this purpose. However, for characterizing the frequency of obesity in the general population for epidemiologic and public health analyses, BMI may be very appropriate, although this is no to say it is perfect or that there might not be better alternatives now or in the future. This invites the question as to whether BMI perhaps underestimates the deleterious association of adiposity with mortality rate, mischaracterizes the shape of the association, or, in other ways, is less informative or misleading relative to an analysis based on measures of body composition, body fatness, or the distribution of body fatness anatomically. Several researchers have conducted analyses looking at such questions.[47–49]

Although there is no definitive consensus a few items seem certain. First, there is some evidence that when fatness is used as opposed to BMI, the relationships between mortality rate and the adiposity indicators are stronger or more nearly monotonically increasing that is, the nadir of the curves falls at lower points along the distribution than when BMI is used.[47] This may be especially the case when the within-person change in body composition versus body weight is used as the independent variable in an epidemiologic analysis, rather than static body composition versus body weight measurements. However, although this is consistent with much thinking, this has not been found in all studies.[48,50]

Furthermore, looking at total body fatness itself may be less helpful than anatomic distribution of body fat. Distinct types and anatomic depots of body fat may have different associations with health outcomes. Indeed, analyses suggest that when one looks at truncal, intra-abdominal, or visceral adipose tissue mass as the independent variable, the deleterious associations with mortality rate are more pronounced and more nearly monotonically increasing than that with some of the other variables considered. In contrast, when one looks at subcutaneous adipose tissue, especially contingent upon total mass or lean mass, the relationships may even look protective (ie, more nearly monotonically decreasing). This seems to be particularly true for lower-body subcutaneous fat stores.[49] Newer imaging methods

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may also provide more insights on the relationship of body fat distribution and deposition (eg, pericardial fat, hepatic fat, intramuscular fat) and mortality.

Finally, lean mass itself may be protective with respect to mortality rate.[49] Loss of lean mass during aging, also known as sarcopenia, is a risk factor for several adverse health consequences, including increased risk of falls and immobility.

CONCLUSION

In this first of 2 articles, we reviewed the association between obesity and mortality rate and laid out some of the key elements and questions commonly asked and identified important research questions that remain unanswered. More data and higher-quality data analyses are needed to improve our understanding of the association between obesity and mortality and which elements of this association may be causal and thus are amenable to intervention.

The association between obesity and mortality is U-shaped. Factors such as smoking history, occult disease, recent weight loss, unintentional weight loss, weight variability, and body fat distribution pattern may influence the shape of the BMI-mortality association, but simply eliminating individuals from the analysis based on such factors may plausibly create biases.

There is a reasonable degree of consistency of results from different studies that among the BMI categories, using the US cutoffs, the overweight group has the lowest mortality rate compared with the other BMI categories; however, why this occurs is still unknown.

While investigating the "fit but fat" concept, more research is necessary to improve understanding of how physical activity, cardiorespiratory fitness, and BMI or body composition may interact to affect mortality. Data from RCTs might help mitigate the potential confounders or biases that cannot be fully controlled for in observational studies.

Some limitations discussed in this article include unanswered questions, such as why the deleterious effect or association of elevated BMI with increased mortality rate seems to be declining over calendar time, and the lack of consensus on why the association between obesity and mortality varies when using different measures of obesity. The second part of this set of articles will focus on how weight cycling and weight loss influence the association between obesity and mortality.

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