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The ‘Obesity Paradox:’ a parsimonious explanation for relations among obesity, mortality rate, and aging?

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Abstract

Objective—Current clinical guidelines and public health statements generically prescribe body mass index (BMI; $\frac{kg}{m^2}$) categories regardless of the individual’s situation (age, risk for diseases, etc.). However, regarding BMI and mortality rate (MR), two well-established observations are (1) there is a U-shaped (i.e., concave) association - people with intermediate BMIs tend to outlive people with higher or lower BMIs; and (2) the nadirs of these curves tend to increase monotonically with age. Multiple hypotheses have been advanced to explain either of these two observations. Here we introduce a new hypothesis that may explain both phenomena, by drawing on the so-called obesity paradox: the unexpected finding that obesity is often associated with increased survival time among people who have some serious injury or illness despite being associated with reduced survival time among the general population.

Results—We establish that the obesity paradox offers one potential explanation for two curious but consistently observed phenomena in the obesity field.

Conclusion—Further research is needed to determine the extent to which the obesity paradox is actually an explanation for these phenomena, but if our hypothesis proves true the common practice of prescribing overweight patients to lower their BMI should currently be applied with caution. In addition, the statistical modeling technique employed here could be applied in such other areas involving survival analysis of disjoint subgroups, in order to explain possible interacting causal associations and to determine clinical practice.

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Keywords

Obesity Paradox; Aging; Mortality Rate; Statistics; Mathematical Modeling; Longevity

Introduction

Three seemingly anomalous findings have puzzled obesity researchers and have for some time been the focus of debate. Obesity has long been recognized to impair health and reduce longevity, has been labeled a disease by some for centuries (1) and has now been officially declared a disease by the Obesity Society (2). There is clear evidence that obesity is associated with increased mortality rate (MR) and reduced longevity (3), and the association is believed to be causal--a belief supported by multiple lines of evidence (4, 5). There is also clear evidence that marked caloric restriction leading to substantially lower body weight prolongs life in many model organisms ranging from water fleas to dogs (4, 6). Despite the well-established findings that obesity reduces lifespan and that marked caloric restriction resulting in reduced body weight in model organisms leads to increased lifespan, three curious findings exist in the human literature:

The U-Shaped Curve

Relatively low body mass indices (BMIs; $\frac{kg}{m^2}$), even those well above the range typically thought to represent underweight are also associated with elevated MRs relative to more intermediate BMIs. This finding of lowest MRs occurring at intermediate BMIs, sometimes including BMI levels typically thought of as mildly overweight, is referred to as the “U-shaped curve.” The U-shaped curve is the source of considerable contention with some investigators appearing to believe the association represents causation and others believing that the elevated MRs at the low end of the BMI continuum represent some form of confounding (7) with the debate spilling over into the mass media (8).

The Increasing Nadir

Figure 1 shows that the nadir of the U-shaped curve is higher among older than younger persons and in fact increases in a fairly linear manner with age (9, 10). This has led some to speculate that modest weight gain with aging may be salubrious, yet others believe this idea is inconsistent with evidence about the deleterious effects of overweight and obesity (11).

The Obesity Paradox

The obesity paradox refers to the finding that, despite obesity’s association with decreased survival time in the general population and its status as a risk-increasing factor for many diseases, among persons who have experienced some major injury or illness, obesity often seems to be associated with increased survival time. Once again, the extent to which this association represents causation is controversial (12).

Several explanations for the first phenomenon (the U-shaped curve) described above have been offered. The two most prominent are confounding by smoking, indication, and occult disease or so-called reverse causation (4, 13) and the fact that BMI, its numerator being

composed of both fat and fat-free mass, does not adequately represent the monotonic increasing effects of fat mass and monotonic decreasing effects of fat-free mass on MR (14). Here, we posit a third potential explanation. Specifically, we propose that the obesity paradox in which obesity hypothetically **(a)** causally monotonically increases MR among persons in the absence of major injuries or other diseases; yet **(b)** causally monotonically decreases MR among persons in the presence of certain major injuries or other diseases; can explain both the U-shaped curve and the increasing nadir with age. The existence of major injuries and diseases that satisfy **(b)** at the association level (not necessarily causal) is well-founded. Let the collection of all such injuries or diseases be called *afflictions of type A*. We take no position here regarding the veracity of the causal aspects of point **(b)** above, but merely evaluate the consequences and potential explanatory power of it being true.

Nevertheless, if the obesity paradox does explain the U-shaped curve and the increasing nadir with age, then our model suggests that individuals at risk for certain causes could greatly benefit from increasing their BMIs. Yet many physicians in current practice, when advising a patient, ignore the U-shaped curve and obesity paradox in their prescription and suggest that they lower their BMIs. Although this suggestion fits with the general guidelines, the consequences of a lower BMI could prove iatrogenic. Hence the dilemma physicians face when advising patients.

In conclusion, we are able to bracket the causality debates while pursuing biostatistical models that may explain all the seemingly conflicting viewpoints as results of true causation, but merely among different populations, and then to use those to determine clinical practice. Our example serves as a reminder to those performing statistical analyses that adjusting for covariates or eliminating individuals with certain characteristics may remove the effects of a causal association that should be also considered when determining clinical practice.

Definitions

The probability that an individual survives longer than t units of time can be written as a function of t and is defined by

$$S(t)=\text{Prob}(T>t). \quad (1)$$

Where T is the random variable defined as the time of death of the individual. We will often refer to the independent variable t of this function as *age*. We can manipulate the so-called *survival function* (Eq. 1) into a function of both age t and BMI b by defining

$$S(t|b)=\text{Prob}(T>t|\text{BMI}=b). \quad (2)$$

That is, $S(t|b)$ is the probability that an individual will survive to the specific age t if their BMI is at a particular level b . At this point, we do not incorporate into our model that individual's BMIs often change over time.

Next the *hazard function* of $S(t|b)$ for any given b is defined by

$$\lambda(t|b) = \lim_{\Delta t \downarrow 0} \frac{\text{Prob}(t \leq T \leq t + \Delta t | T > t, \text{BMI} = b)}{\Delta t}. \quad (3)$$

In particular, the *instantaneous MR* (Eq. 3) can be approximated by the probability for an individual at age t with BMI b to die before the age $t + t$. Hence essentially, for any given age t , the existence of a unique BMI b_o such that $\lambda(t|b_o)$ achieves the minimum value (over all possible BMIs, with t constant), implies that b_o is the *optimal BMI* for an individual to have at age t .

Materials and Methods

Our methods do not entail estimating parameters from a statistical analysis of raw data, but instead use a mathematical model that demonstrates the possibility that the obesity paradox may explain observations in the literature. Hence, the parameters are chosen (not estimated) so that the model satisfies the hypotheses and still exhibits a similar trend to observations to the literature. By showing that parameters can be chosen to meet this criterion, we demonstrate the possibility that the obesity paradox may explain observations (i.e., is consistent with) observations in the literature. We describe the mathematical model and explain our choice of parameter values in this section. We stress that the parameters are chosen and not estimated. To begin, we define the *cause-specific hazard functions* by

$$h_C(t|b) = \lim_{\Delta t \downarrow 0} \frac{\text{Prob}(t \leq T \leq t + \Delta t, C | T > t, \text{BMI} = b)}{\Delta t}, \quad (4)$$

so that $h_C(t|b)$ is the hazard function of the probability of survival

$S_C(t|b) = \text{Prob}(t \leq T \leq t + t, C | T > t, \text{BMI} = b)$. for the entire population. The cause-specific hazard function when $C=1$, for example, measures the contribution of the sub-population (i.e., all the individuals who will die with an *affliction of type A*) to the instantaneous MR $\lambda(t|b)$ (Eq. 2) of the total population. It follows that $\lambda(t|b)$ can be determined by

$$\lambda(t|b) = h_0(t|b) + h_1(t|b). \quad (5)$$

Note that the value $h_C(t|b)$ may be quite different from the hazard function that is conditional on the cause C (and BMI b), which is written as

$$\lambda_C(t|b) = \lim_{\Delta t \downarrow 0} \frac{\text{Prob}(t \leq T \leq t + \Delta t | T > t, \text{BMI} = b, C)}{\Delta t}. \quad (6)$$

That is, the relation between BMI and MR in either sub-population may be quite different than the association in the entire population (statisticians can see this as a generalization of the idea underlying Simpson's paradox). Nevertheless, in our case -- due to the independence of the causal events, application of Bayes' Theorem allows one to observe the following relationship.

$$\frac{h_1(t|b)}{h_0(t|b)} = \frac{\text{Prob}(C=1|T \geq t, b)}{\text{Prob}(C=0|T \geq t, b)} \times \frac{\lambda_1(t|b)}{\lambda_0(t|b)} \quad (7)$$

Where $\text{Prob}(C = 1|T \geq t, b)$ is the proportion of individuals with BMI = b and AGE = $T \geq t$ such that $C = 1$. Then this allows us to write

$$h_1(t|b) = \frac{\text{Prob}(C=1|T \geq t, b)}{\text{Prob}(C=0|T \geq t, b)} \times \frac{\lambda_1(t|b)}{\lambda_0(t|b)} h_0(t|b). \quad (8)$$

In what follows, we use the cause-specific hazard function when $C = 0$ and a model of the product of the two ratios (the right side of Eq. 8) under the assumption that the obesity paradox is true. As a consequence of these two models, using the equality in Equation 8 to determine the cause-specific hazard function when $C = 1$, the resulting hazard function $\lambda(t|b)$ of the total population can be determined from Equation 5.

C = 0: Those without any affliction of type A at time of death

Assume that the cause-specific hazard function when $C = 0$, given BMI $b = 18$, can be represented by a Gompertz model of the form

$$h_0(t|b=18) = \exp(\alpha_0 + \alpha_1 t^2), \quad (9)$$

where $\alpha_0, \alpha_1 > 0$. The Gompertz model has been shown to adequately characterize human MRs for the vast majority of the lifespan (for an intuitive discussion, see 32). Figure 3 shows this function, which is the baseline ($b = 18$) estimate for the values of α_0, α_1 that we will use to establish that our model can recapitulate the observations that provide for the basis of the obesity paradox.

Although our model implicitly assumes that 18 is the optimal BMI when $C = 0$, our results do not depend on the value of b chosen for baseline. In particular, if a reader prefers to use a different value of $b \neq 18$, then the corresponding adjustment of Equation 10 will lead to identical results. The value $b = 18$ is chosen simply to make the following idea transparent: There is an effect α_1 of age (independent of BMI) on mortality and there is an effect α_2 of BMI on mortality – this effect, however, depends so on age too.

Next suppose that the hazard ratio (hazard ratios are conceptually similar to relative risks) for mortality when $C = 0$, as a function of BMI and age, is given by

$$HR_0(t, b) = \exp[\alpha_2 t^{1/6} (b - 18)^2]. \quad (10)$$

Where $\alpha_2 > 0$, so that the relative rate of mortality when $C = 0$ increases as BMI deviates from $b = 18$. In addition, notice that the effect of a fixed deviation in BMI from 18 increases as age increases. Finally, note that by Equation 10, it follows that the cause-specific hazard ratio for mortality when $C = 0$ increases symmetrically about $b = 18$ (with t held constant),

at an increasing rate with respect to the distance from b to 18; and also increases at a decreasing rate with respect to t (i.e., as t increases with BMI held constant).

The proportional cause-specific hazard function when $C = 0$, given BMI = b , can be defined by

$$h_0(t|b) = h_0(t|b=18)HR_0(t, b). \quad (11)$$

Since the second derivative of $h_0(t|b)$ with respect to t is always positive, assuming that $a_1 > 0$, observe that the MR among the population always increases at a increasing rate with respect to t (and any b held constant). Figure 4 represents the dependence of the cause-specific hazard function on BMI when $C = 0$, for several different ages. Equivalently, for any given age t , the MR (when $C = 0$) is at its lowest within the population of individuals such that BMI = 18. Thus when using the given parameter values $a_0 = 0$, $a_1 = 0.0001275$, and $a_2 = 0.000425$, the model seems to be a reasonable representation of what one might expect among the population when $C = 0$ (33).

C = 1: Those with an affliction of type A at time of death

To obtain a reasonable model of the cause-specific hazard function when $C = 1$, we use a

model of the product of ratios $\frac{\text{Prob}(C=1|T \geq t, b)}{\text{Prob}(C=0|T \geq t, b)} \times \frac{\lambda_1(t|b)}{\lambda_0(t|b)}$. We model the two ratios separately.

Probability of Disease Ratio—To model the ratio of probabilities, first note that

$\frac{\text{Prob}(C=1|T \geq t, b)}{\text{Prob}(C=0|T \geq t, b)} = \frac{\text{Prob}(C=1|T \geq t, b)}{1 - \text{Prob}(C=1|T \geq t, b)}$. Hence we need only determine a model for the probability of an individual with age t and BMI = b to be in among the sub-population $C = 1$. We obtain the formula for this model by first assuming that the probability mimics the logistic growth equation at baseline (BMI = 18), where $C = 1$ is the maximum probability of an individual with BMI = 18 to be among cause $C = 1$; and then the coefficient

$A_{18} = \frac{MAX_{18} - I_{18}}{I_{18}}$ is determined by initial probability $I_{18} = \text{Prob}(C = 1|T = 20, 18)$. We assume $MAX_{18} = .5$, $I_{18} = .01$ and set the rate of growth to be $a_{18} = 1$. The resulting model is shown in Figure 5. Next we use an observation from heart failure data (34), heart failure being a disease observed to satisfy the conditions of an *affliction of type A* (17,18), to justify our assumption that an elevated BMI when $T = t$ is associated with a relatively greater risk of dying with an *affliction of type A* than when $T = t + 1$. Under this assumption, the logarithmic model of decay

$$rr(t) = \frac{\text{Prob}(C=1|T \geq t, b+1)}{\text{Prob}(C=1|T \geq t, b)} = \frac{MIN_{\Delta b}}{1 + A_{\Delta b} \exp(-a_{\Delta b}[t - 20])} \quad (12)$$

may be an appropriate choice of the relative risk (to be in cause $C=1$) of a single unit increase in BMI. In this case, we would use the following equation to model our desired probabilities;

$$\text{Prob}(C=1|T \geq t, 18) \times [rr(t)]^{(-b+18)} \quad (13)$$

However this equation implicitly assumes that the ratio $\frac{\text{Prob}(C=1|T \geq t, b+1)}{\text{Prob}(C=1|T \geq t, b)}$ is independent of BMI. In particular, $\text{Prob}(C=1|T \geq t, b)$ increases exponentially as b increases until reaching values so large that this growth eventually begins to taper. To check this, we used values from observations of heart failure data (34) to determine appropriate values for the coefficients in the model expressed by equation (12) and (13). We estimated the minimal proportion relative risk at $MIN_b = 1.06$ and initial relative risk (given AGE $t = 20$) to be $I_b = 1.24$. The resulting values determined by introducing these coefficients in the expressions above, quickly exceed reasonable predictions of $\text{Prob}(C=1|T \geq t, b)$ as b increases. For these reasons, we felt obligated make the following adjustments.

In order to maintain reasonable values for $\text{Prob}(C=1|T \geq t, b)$ and yet keep within the observations of data in the literature; we restrain this exponential growth by setting the maximum possible value of $\text{Prob}(C=1|T \geq t, b)$ among any BMI $=b$ from $b=15$ to $b=45$,

as a 60 function of t , to be $M(t) = \frac{60}{1 + \frac{60-P(t)}{P(t)} [rr(t)]^{-27}}$. Finally, we define the probability $\text{Prob}(C=1|T \geq t, b)$ of an individual being in cause $C=1$ (i.e., of having an affliction of type

A), if AGE t and BMI $=b$, by the function $D(t, b) = \frac{M(t)}{1 + \frac{M(t)-P(t)}{P(t)} [rr(t)]^{(-b+18)}}$. See Figure 6.

Hazard Ratio—We use log-hazard rates previously observed for heart failure (17) to determine the polynomial $rm(b)$ shown in Figure 7 (note the minimum takes place near $b = 35$, for every t), in order to mimic the behavior of the mortality rate in heart failure, by $\lambda_1(t|b) = c_1 \exp(rm(b) + t/100 - 3/5)$, with $c_1 = 5$. Finally, the choice of our model for $\lambda_0(t|b)$ is

simply determined to ensure that $\frac{\lambda_1(t|b)}{\lambda_0(t|b)} \geq 1$ and $\frac{h_0(t|b)}{\lambda_0(t|b)} \geq 1$ holds for all values of BMI

and AGE. To do this, we let $\lambda_0(t|b) = \frac{\lambda_1(t|35)}{1 + \frac{\lambda_1(t|35) - h_0(t|b) - p_0}{h_0(t|b) + p_0} \exp[-c_0(b-18)]}$, where $c_0, p_0 > 0$. See Figures 8 and 9.

The resulting product of the two ratios, will be denoted by $PMR(t, b)$. In conclusion, recall that Equation 8 implies that the cause-specific hazard function when $C=1$ may be expressed as the proportional hazard rate (Figure 10)

$$h_1(t|b) = [PMR(t, b)]h_0(t|b). \quad (14)$$

Then the hazard model for the population of all individuals (irrespective of the value of C or disease status) conditional on BMI can be written as:

$$\lambda(t|b)=h_0(t|b)PMR(t,b)+h_0(t|b). \quad (15)$$

Thus we have our hazard model of the survival function of the general population conditional on BMI (see Figure 2).

Results and Discussion

The obesity paradox rests on a comparison between the populations with and without certain types of a serious injury or illness. Hence we suggest a model that is often referred to as the *cause-specific survival model*. Specifically, we attempt to make a distinction of the type of mortality between individuals according to the ‘cause of death’. To do so, we will consider the mortality of the following sub-populations separately.

1. $C = 0$: Those without any *affliction of type A* at the time of death
2. $C = 1$: Those with an *affliction of type A* at the time of death

Recall that an *affliction of type A* is any serious injury or illness for which the MR of the infected individuals decreases monotonically as BMI increases. For example, evidence for such a relationship has been found among individuals with kidney failure (15, 16), heart failure (12, 17, 18), and others (19–22).

Using a Gompertz model for the cause-specific hazard functions, we specify parameter values of the model to produce a mathematical example that demonstrates that the obesity paradox could conceivably explain the data observed in the literature. Using the model we create herein, we obtain a U-shaped relation between MR and BMI very close to that which has been observed in data in the literature and an increasing optimal BMI (the value of BMI corresponding to the lowest MR) with aging (Figure 1). The result observed herein suggests that the obesity paradox may indeed explain data that has previously been observed in literature (Figure 2). Thus we have shown that the obesity paradox, if true, can be represented as a mathematical model that effectively recapitulates associations that are observed in literature among MRs, age, and BMI. Moreover, this recapitulation can be accomplished with remarkable facsimile. See our Methods section for the explicit details of the model and choice of parameters.

In our analyses, we took no position as to the veracity of the premises of the obesity paradox. Moreover, our result clearly does not capture all variation; instead we merely claim to have demonstrated that the obesity paradox *may* partly explain observations in the literature. Certainly, we agree with others that some of the observed association between obesity and reduced MR among persons with major illnesses or injuries that has been observed in the literature may be due to confounding (25). Yet, there are also reasons to speculate that increased fat reserves might offer some benefit in times of illness or injury (26) and omental fat, which is increased among obese persons (27), is also believed to have some beneficial immune-modulating effects in times of biological stress or trauma (28). In

addition, our demonstration indicates that these reasons are mathematically feasible. Hence, we should not prematurely exclude the possibility of causation.

The implication of this demonstration is that the obesity paradox could parsimoniously explain at least two phenomena that have puzzled obesity researchers, namely the U-shaped curve and the increasing nadir of the BMI MR association with age. In turn, from an evolutionary point of view, to the extent that extended survival into late adulthood enhances genetic fitness (29), this could in turn partially explain the increase in body weight that tends to occur with aging (30). Moreover such an explanation, if veridical, could reconcile divergent points of view in the obesity field. People who maintain that, at least until true 'underweight' levels are achieved, thinner is better would be correct for people who are neither diseased nor seriously injured. Of course, since we all have some probability of becoming diseased or injured, had we the ability to control our weights, we might wish to hedge our bets and gradually increase our weight with age to match the nadir of the BMI MR curves. However, these should not be taken as recommendations at this time, but only as speculation. Clearly our model, like virtually all models, is an oversimplification. We have not built in factors such as the differences in body composition that occur with age, the fact that illness often leads to weight loss, and the fact that height typically decreases in late adulthood. Nevertheless, our model is a plausible starting point and future research may incorporate these additional factors. These conceptions may also have implications for the conduct of BMI mortality analyses in terms of the treatment of BMI as a time-varying covariate and the use of multi-state survival models and this deserves further consideration.

Future research should endeavor to test the hypotheses embedded herein. This will be challenging because people cannot be randomly assigned to body weights nor to becoming diseased or injured. Nevertheless, animal models may be used in which, to some extent, one may be able to randomly assign to body composition status (31) and also to injury or illness status.

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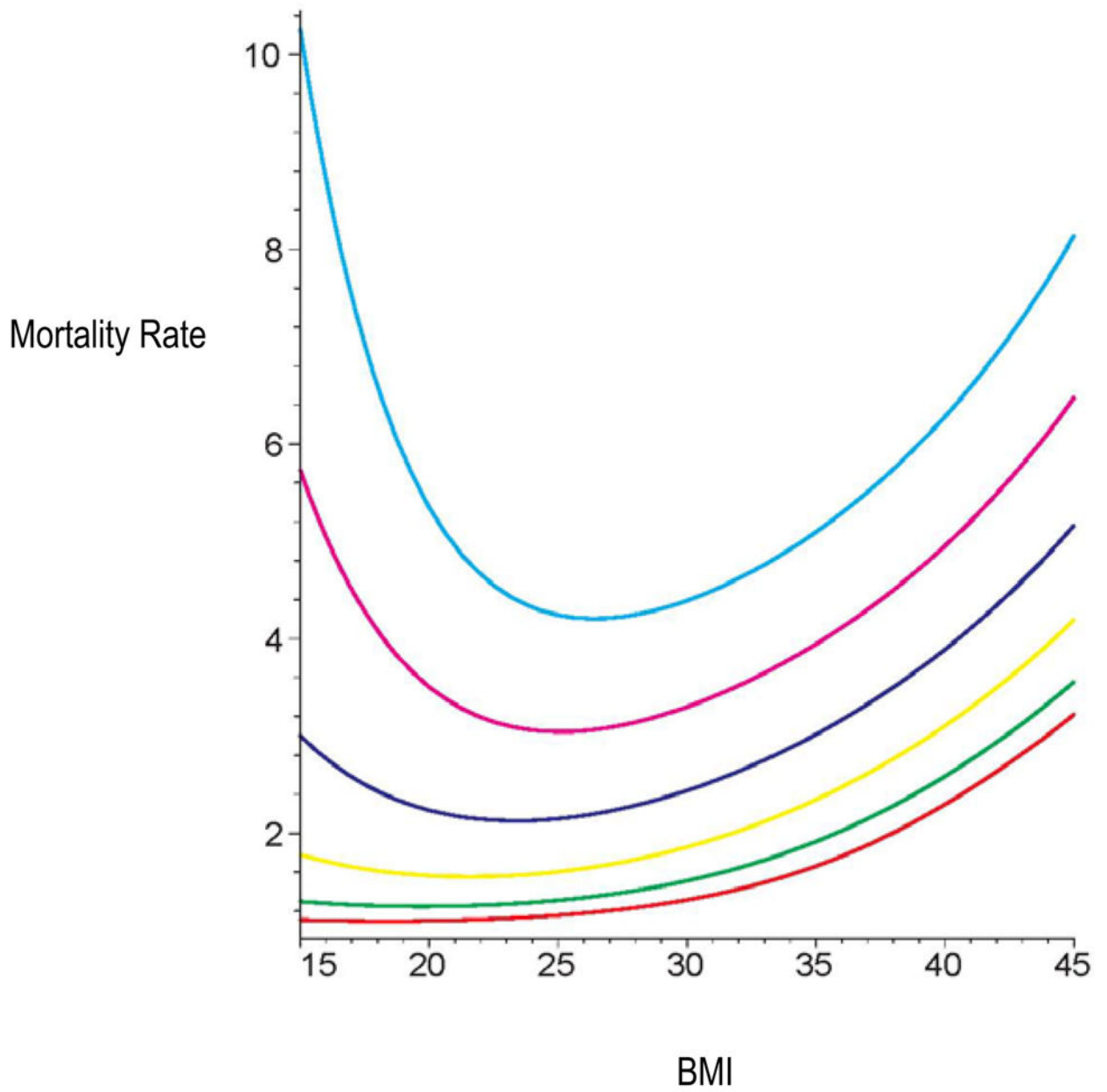


Figure 1. (Mortality Rates) The total mortality rate given BMI = b and age $t = 20$ (red), 30 (green), 40 (yellow), 50 (purple), 60 (magenta), and 70 (blue).

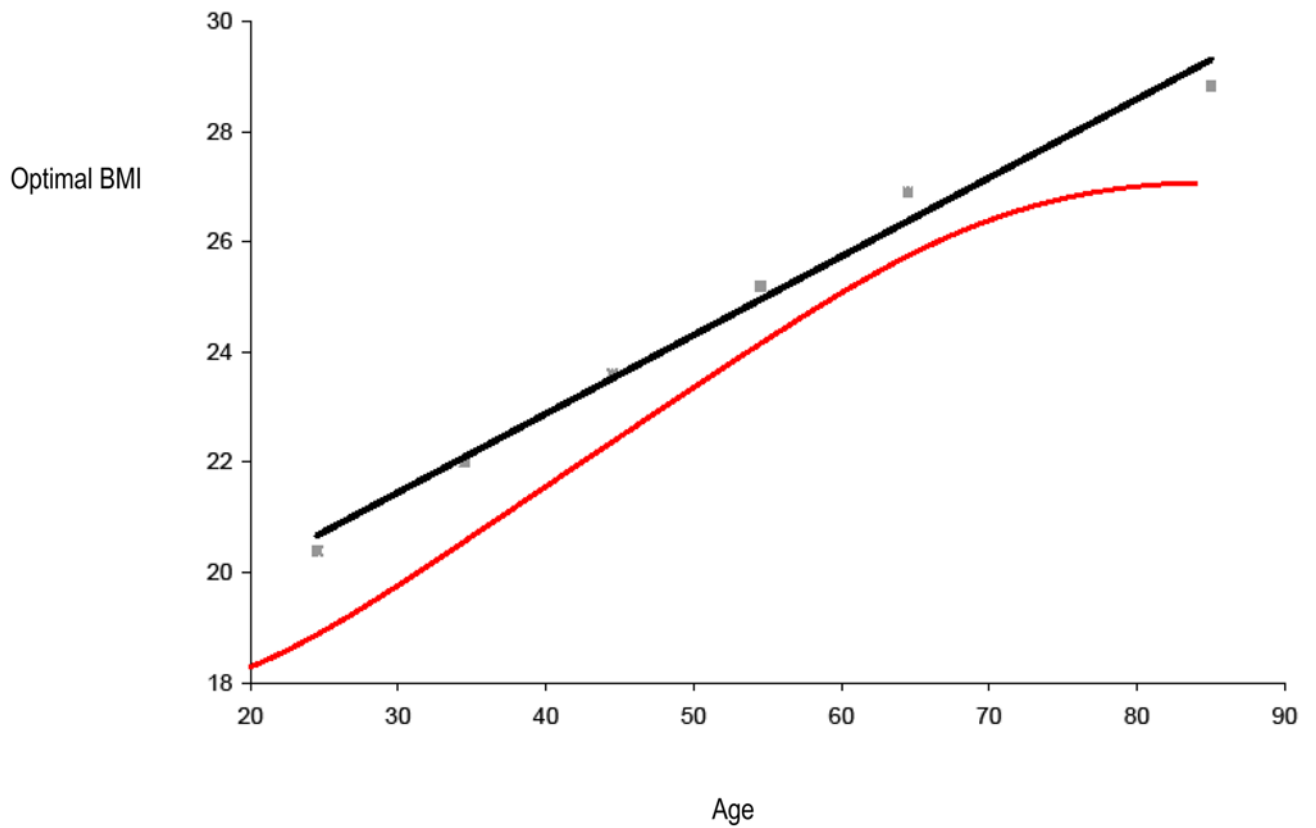


Figure 2. (Optimal BMIs) The optimal BMI as a function of age. The thinner (red) curve represents the function based on our model. The points (gray) are derived from real data as observed in the literature and the bolder (black) line is the linear fit of these points. The points for ages less than 70 represent the average midpoints of the recommended BMIs from Table 29-1 (23) for each category of age. The remaining point was obtained from Table 4 (24).

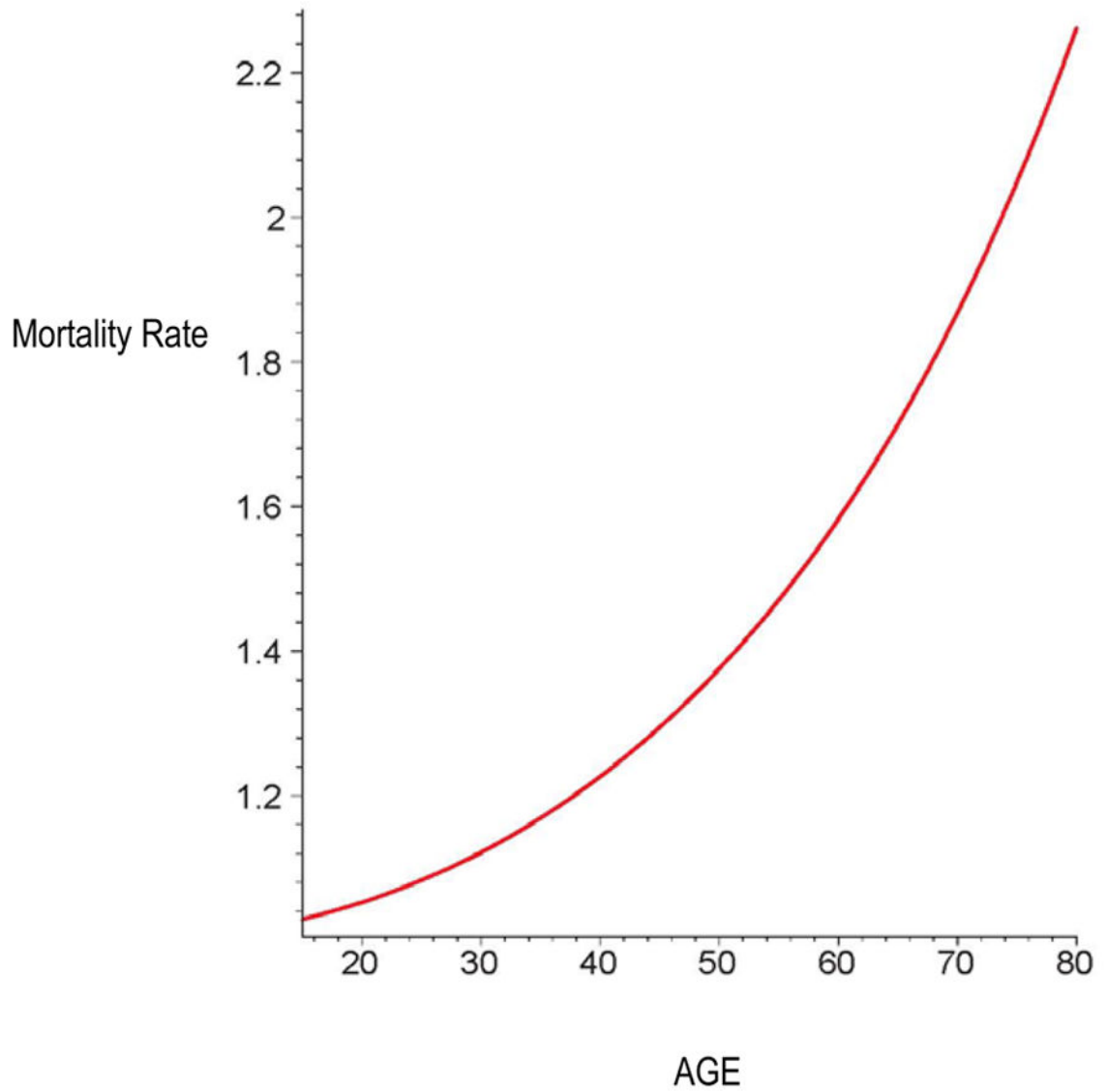


Figure 3.
The situation-specific mortality rate ($C = 0$) given BMI = 18, as a function of age.

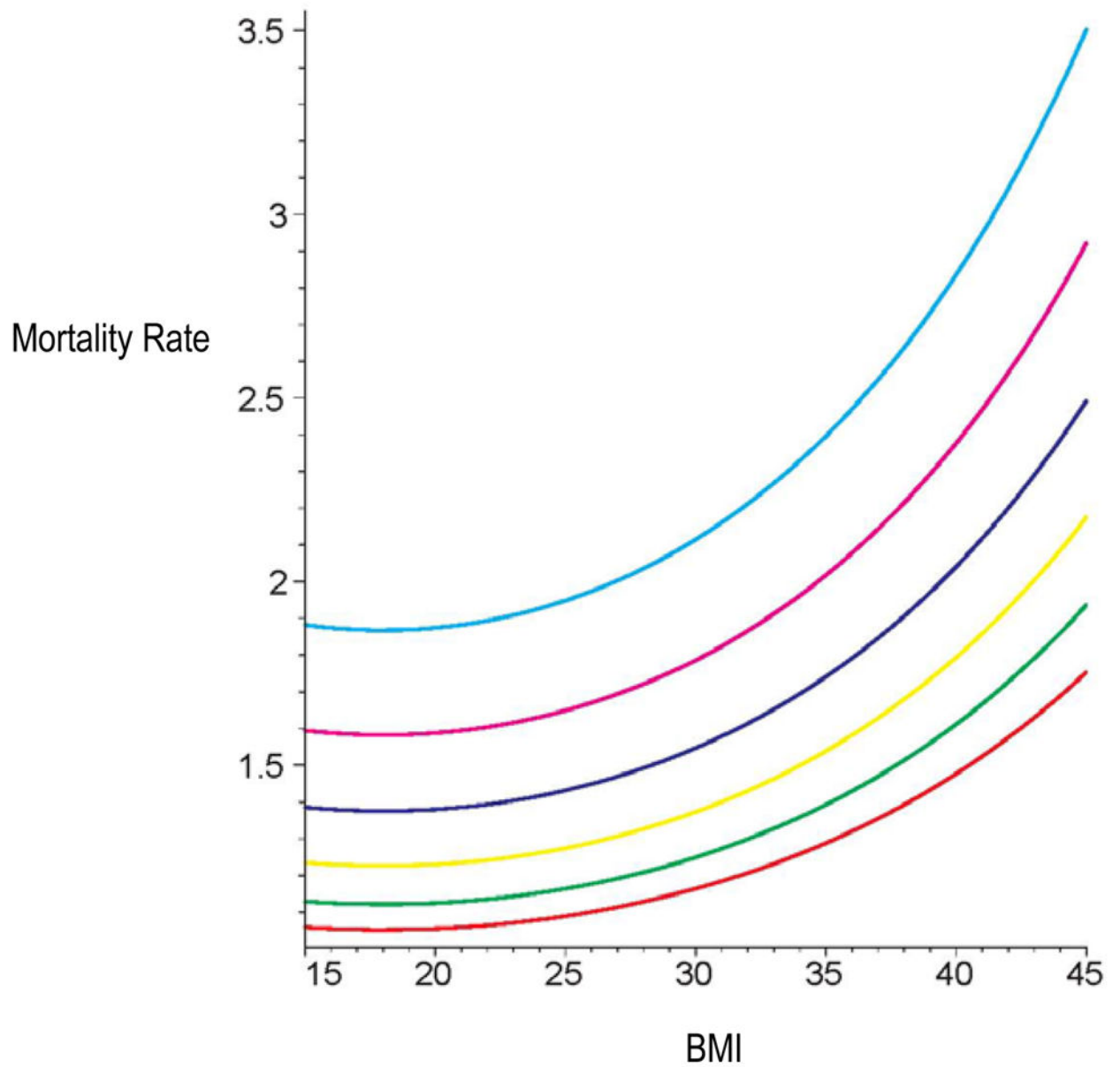


Figure 4. The situation-specific mortality rate ($C = 0$), given a particular BMI and age $t = 20$ (red), 30 (green), 40 (yellow), 50 (purple), 60 (magenta), and 70 (blue).

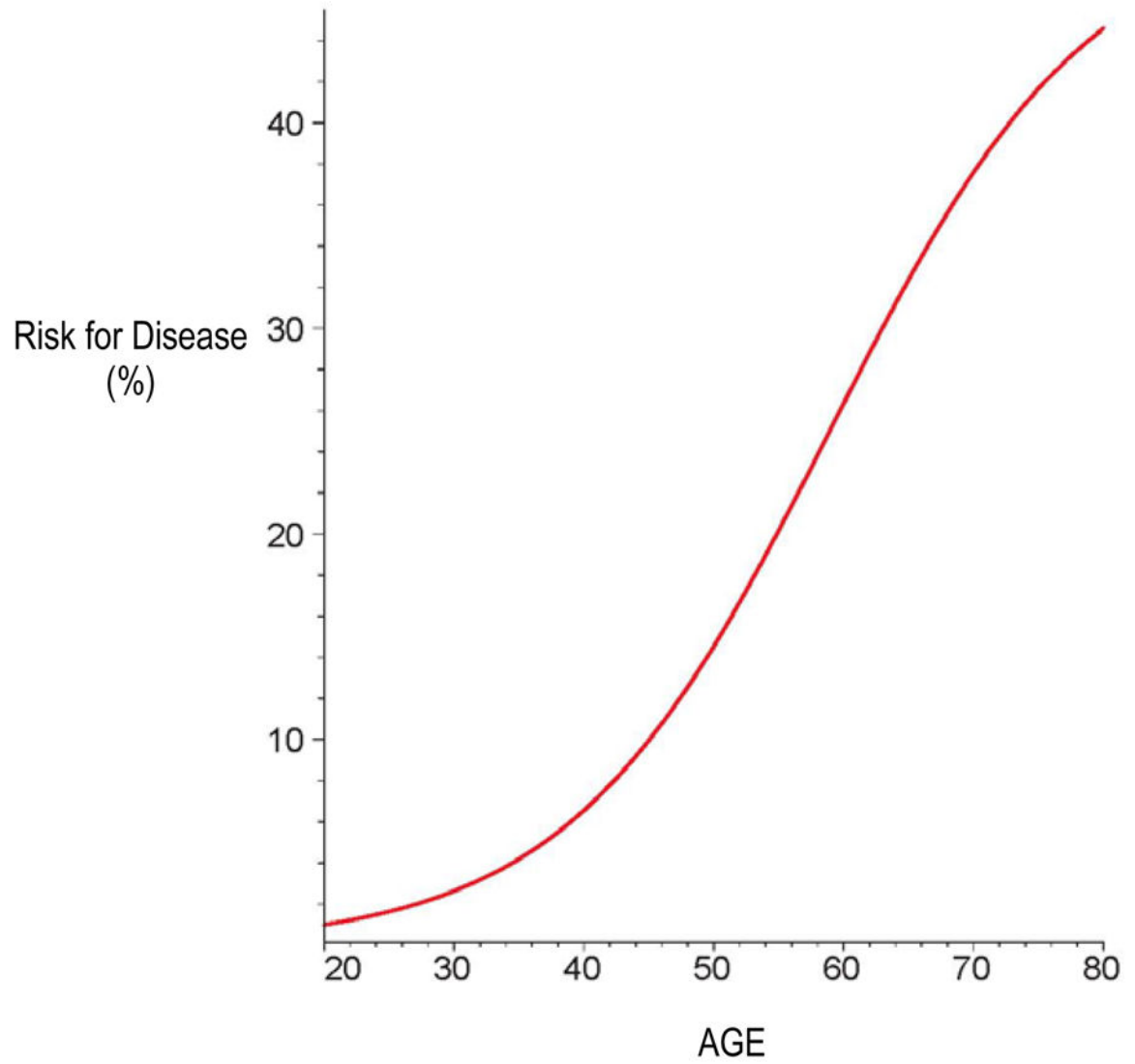


Figure 5.
The probability of disease $C=1$ given $BMI = 18$ as a function of age.

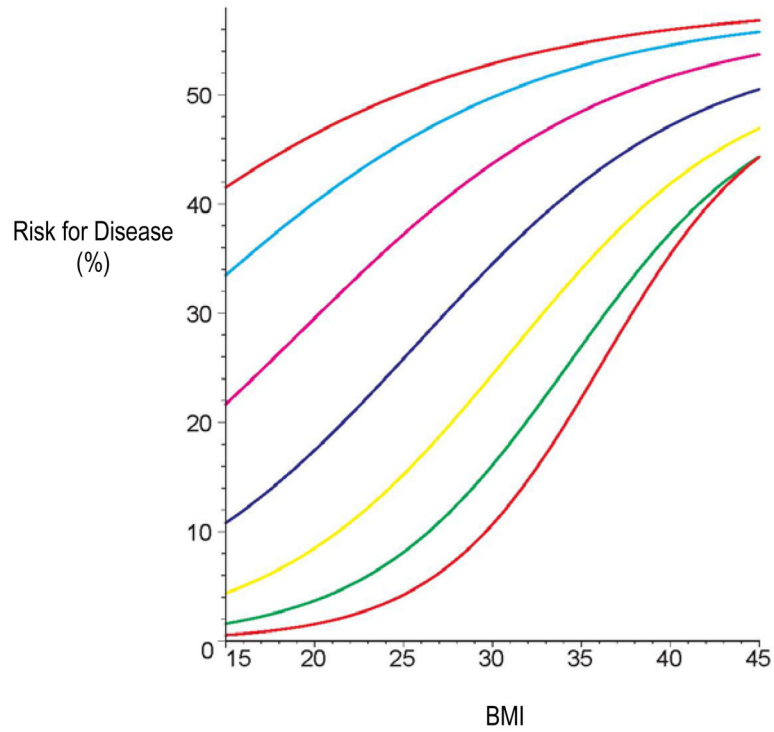


Figure 6. The probability of disease $C=1$ given $BMI=b$ and age $t = 20$ (bottom red), 30 (green), 40 (yellow), 50 (purple), 60 (magenta), 70 (blue), and 80 (top red).

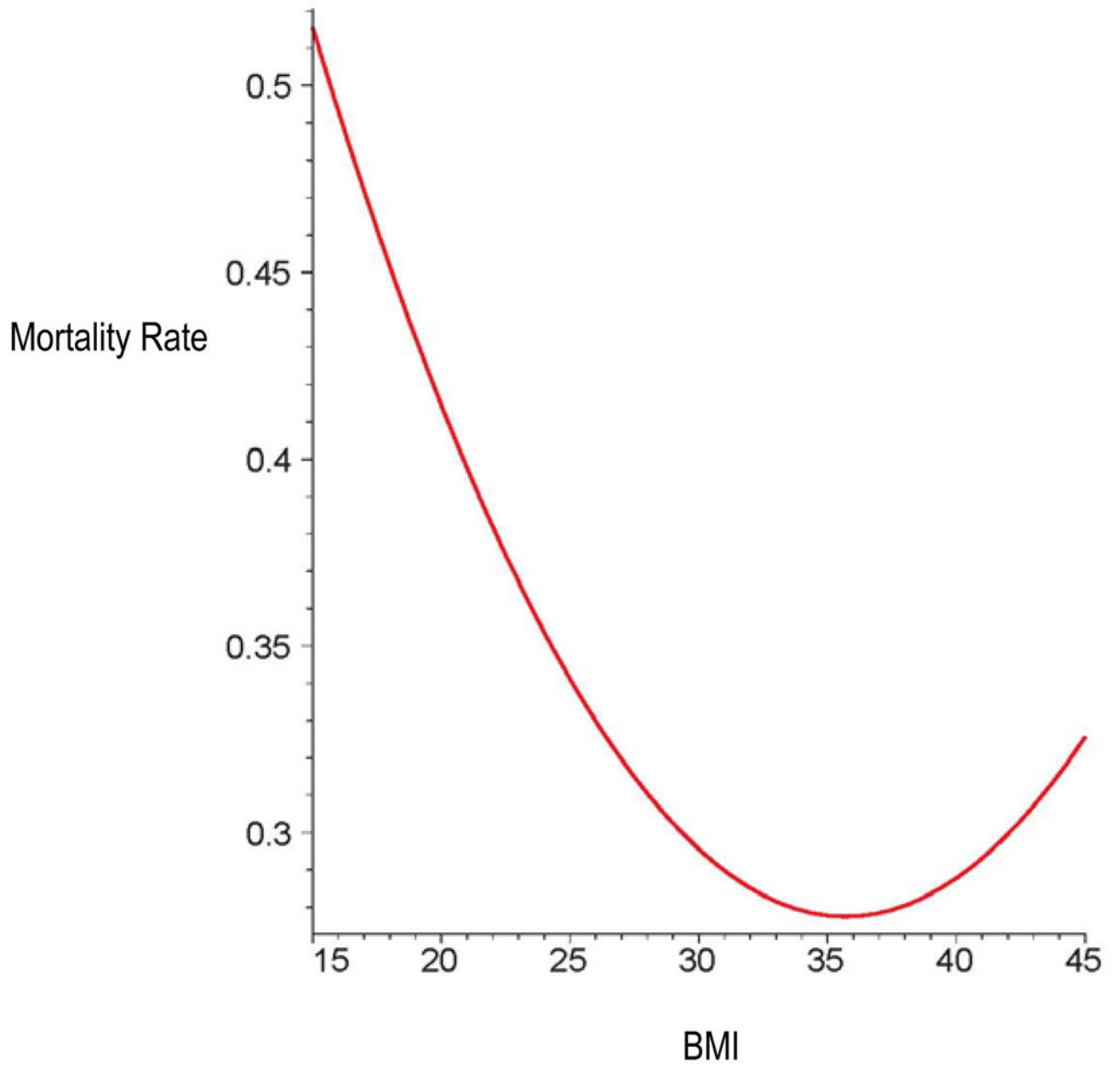


Figure 7.
Our approximation of the quadratic polynomial fit to the log-hazard rate for heart failure (Curtis et al., 2008).

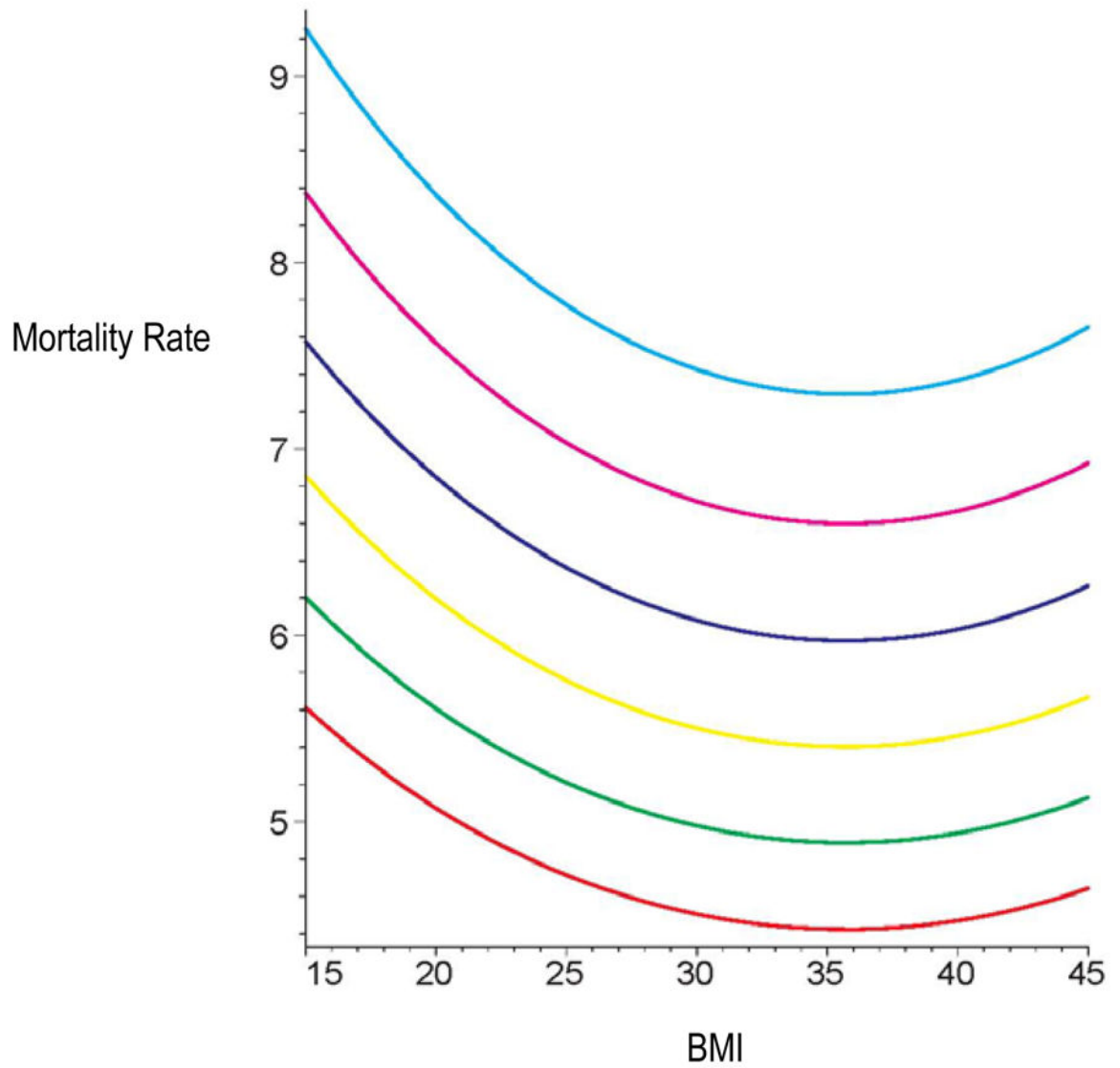


Figure 8. The mortality rate given $C=1$, $BMI = b$ and age $t = 20$ (red), 30 (green), 40 (yellow), 50 (purple), 60 (magenta), and 70 (blue).

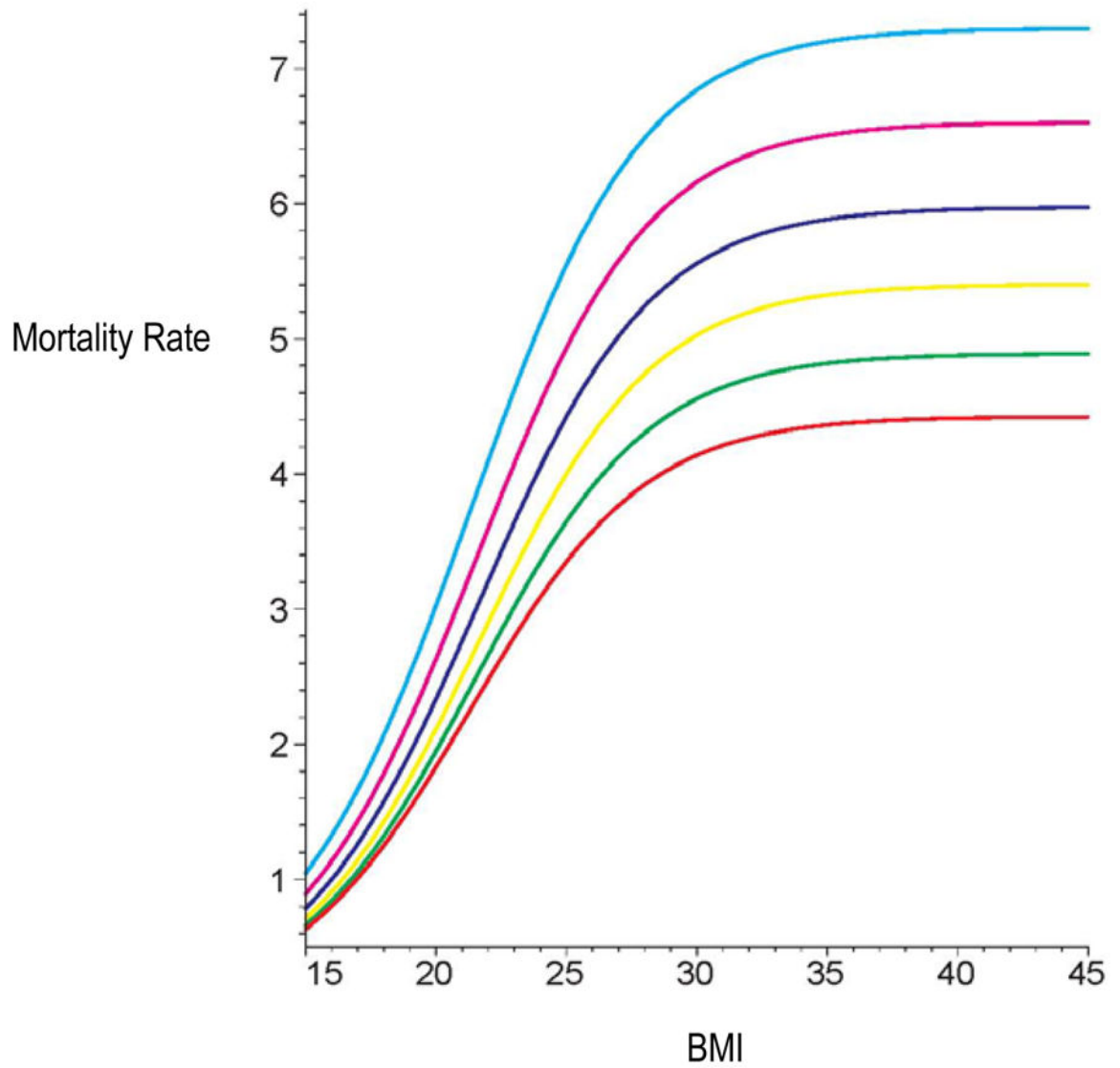


Figure 9. The mortality rate given $C=0$, $BMI = b$ and age $t = 20$ (red), 30 (green), 40 (yellow), 50 (purple), 60 (magenta), and 70 (blue).

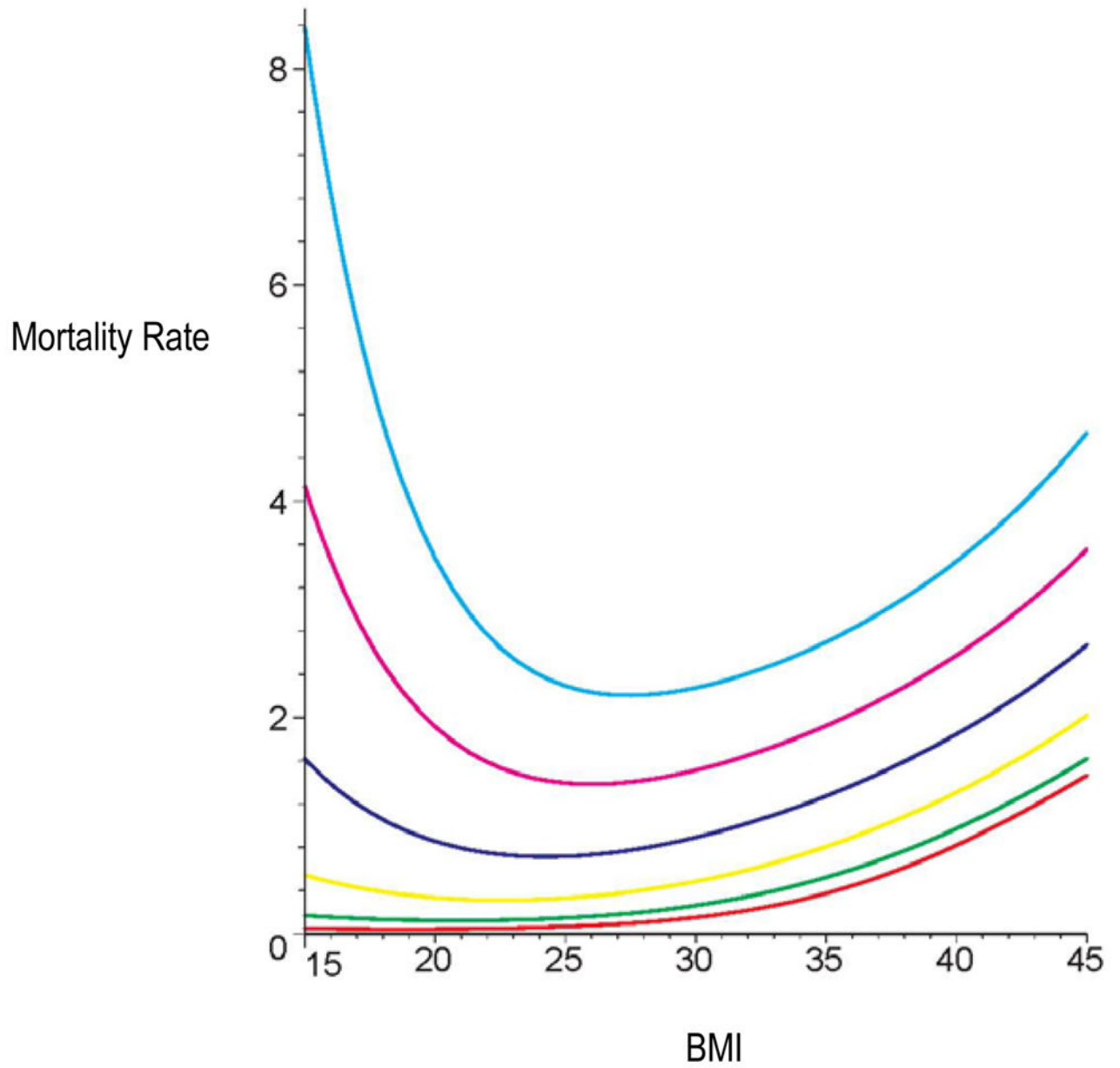


Figure 10.

The situation-specific mortality rate ($C = 1$), given BMI and age $t = 20$ (red), 30 (green), 40 (yellow), 50 (purple), 60 (magenta), and 70 (blue).