

# **DIASTOLIC BLOOD PRESSURE, CARDIOVASCULAR DISEASE, and MORTALITY**

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## Summary

**Background** There are two views of the relation between diastolic blood pressure and risks of cardiovascular disease and death. The most widely accepted is that risk is steadily rising with diastolic blood pressure. The other is that the relation follows a “J-curve”, in which risks are also increased at low as well as high pressures. This view is controversial because it is not consistently found. We reanalyzed data from the Framingham study to determine the nature of the relation of cardiovascular risk to diastolic blood pressure, to see why the J-curve is elusive, to seek justification for taking 90 mm Hg as the cut-point for diastolic hypertension, and to determine if the systolic or diastolic pressure is a better predictor of risk.

**Methods** Reanalysis of the Framingham data on diastolic blood pressure using logistic splines.

**Results & Interpretations** (1) The Framingham data rejects the linear logistic model; the risk - diastolic blood pressure relation is not continuous and strictly increasing. (2) The basic relation of risk to diastolic blood pressure is the same as we previously found for systolic blood pressure, namely risk is constant to a threshold at the 70<sup>th</sup> percentile pressure (about 90 mm Hg) and steadily increases thereafter. (3) Rather than being arbitrary, 90 mm Hg is a natural threshold for hypertension. (4) The J-curve phenomenon is a barely detectable effect, hovering on the boundary of statistical significance, that may cause a rise in risk for pressures less than 70 mm Hg. The weakness of this effect may explain why its detection is so elusive (5). Systolic blood pressure and diastolic blood pressure are equivalent predictors of risk. (6) For the soft endpoint of cardiovascular disease incidence there is a sharp jump at 90 mm Hg, with risk being constant to the left of 90 mm Hg, again constant between 90 mm Hg and 104 mm Hg, and a increasing thereafter. The difference between this outcome and the ‘hard’ outcomes suggests that the presence or absence of hypertension may influence the diagnosis of cardiovascular disease.

## INTRODUCTION

Both JNC VI <sup>1</sup> and WHO/ISH <sup>2</sup> support the view that the relation of both diastolic and systolic blood pressure to endpoints such as death due to cardiovascular disease is continuous, strictly increasing, and with no lower bound (Fig. 1). This, they say, is based on the preponderance of evidence from epidemiological studies and randomized trials. Previous analysis from the Framingham study <sup>3,4</sup> was instrumental in propagating this view of the risk - blood pressure relation, primarily by the use of linear logistic smoothing of the data. We previously reported that the relation between cardiovascular risks and systolic blood pressure was not linear but has a threshold level <sup>5</sup>. Risk was not increased at any pressures except for those in the upper 30% of pressure for their age and sex. We also found that the use of 140 mm Hg as the universal division between normal and elevated systolic blood pressure was unjustified; it needed to be replaced by age and sex dependent cut-points.

Unlike the case with systolic pressure, there has long been some opposition to the strictly increasing model of cardiovascular risk with diastolic blood pressure. Starting with Andersen's observation <sup>6</sup> that the same Framingham data considered here apparently showed that the risk of cardiovascular disease decreases (rather than increases) with increasing diastolic pressure to 89 mm hg, this controversy has centered on the "J-curve effect". That effect is an apparent increase in risk at low as well as high diastolic blood pressure <sup>6-21</sup>. This view is controversial, primarily because it is not consistently found.

We reassessed the diastolic pressure data from the Framingham 18 year follow up report <sup>4</sup> for the following outcomes: cardiovascular disease incidence, death due to cardiovascular disease, and overall mortality. Our primary goal was to determine the nature of the relation of these risks to diastolic blood pressure. Secondary goals were to explain why the J-curve effect was so elusive, to see what justification there was for 90 mm Hg being a universal cut-point for diastolic hypertension, and to find whether the diastolic blood pressure or systolic blood pressure was a better predictor of risk.

We chose to reanalyze the Framingham 18-year follow up data because: (1) it was accurately gathered, (2) it was unconfounded by antihypertensive drug intervention, (3) it contained women, (4) it contained older people.

## Methods

The Framingham data <sup>4</sup> are presented separately for each sex divided into three age groups 45-54, 55-64, and 65-74 years. There are 10 blood pressure categories (Table 1)

Unlike the systolic pressures, for persons aged 45-74, the distribution of diastolic pressures does not change much with age and is about the same in both sexes. For practical purposes we can take these distributions to be the same.

We first determined if the relation of overall and cardiovascular disease death to diastolic blood pressure is homogeneous across the six groups, i.e. if the additive model holds. In that model the risk for a person is simply the sum of two effects, one based on the group the person is in and the other from the person's blood pressure. Our analyses were carried out using both the specific rates and the direct group adjusted rate. Models for the specific rates were viewed as sub-models of the additive model.

We modeled the relation of both overall and cardiovascular death to diastolic blood pressure by curves known as logistic splines. A logistic spline is a curve that results from continuously joining two or more logistic curves. The points where two curves join are called knots and the curves are called segments. A logistic spline is parameterized by the location of the knots, an intercept term, and a slope term for each segment. A segment with slope 0 is a horizontal line. In all our models the knots are specified in advance and in some models some of the segments are specified to have 0 slope. Consequently, the number of unknown parameters is  $1 + (\text{number of slope terms} \neq 0)$ .

A 2-spline is a logistic spline curve having two knots, which we will label the left knot and the right knot, and 3 segments. These are a left segment (from the left endpoint to the left knot), a middle segment (from the left knot to the right knot), and a right segment (from the right knot to the right endpoint). A horizontal 2-spline is a 2-spline where the middle segment has 0 slope (i.e. is a horizontal line). A 1-spline has 1 knot and two segments, viz. left and right. A horizontal 1-spline is a 1 spline whose left slope is 0.

Models based on the specific rates required one curve for each age group. Because all models were sub-models of the additive model, these curves had to be parallel. Therefore, they all had the same knots, and for each of the six curves, the corresponding segments had a common slope.

We previously modeled the relation of cardiovascular disease death to systolic blood pressure<sup>5</sup> by a horizontal 1-spline with its knot at the 70<sup>th</sup> percentile pressure. The salient feature of the J-curve effect is the downward trend in the risk as pressures move from the lowest value to more moderate values. We used 2-spline models both to determine if there was a significant J-curve effect and to model it if it was significant. The knots were chosen to produce a model as close as possible to that for the relation of cardiovascular disease death to systolic blood pressure and still allow the possibility for a J-curve effect. Therefore, we chose the right knot at 90 mm Hg and left knot as far to the left as possible. We took the left knot to be the left endpoint of the second lowest class, namely 70 mm Hg. [However, the fit would have been the same for any choice between 67 mm Hg and 72 mm Hg]. In addition to this model we also fitted a horizontal 2-spline with the same knots, and a horizontal 1-spline with its knot at 90 mm Hg. For all models, tests for significance of the slopes of the various segments were done.

The parabolic model consists of logistically fitting a parabola to either the adjusted rates or six parallel parabolas to the specific rates. We also considered parabolic models for both the relation of overall and cardiovascular death to systolic blood pressure. Various tests were performed based upon this model to see if a parabolic relation is real. Parabolic and spline models were compared.

For the relation of incidence of cardiovascular disease to systolic blood pressure we needed to consider a model called the jump model. The jump curve consists of a horizontal line from the initial pressure to 90 mm Hg and a separate horizontal 1-spline with initial point at 90 mm Hg and knot at 104 mm Hg. Such a curve has a jump at 90 mm Hg. The jump model on the specific rates consists of six parallel jump curves. We used the goodness of fit test to see if various models (linear logistic, 1-spline, 2-spline, parabolic, and jump) fit the data.

Two methods were used to compare the predictive ability of systolic blood pressure to that of diastolic blood pressure for cardiovascular death. The first was to compare their error sums of squares. The second was to compare their standardized right slopes.

## Results

Analyses using the specific rates and the adjusted rates yielded the same results.

### **The logistic model does not hold**

The goodness of fit test soundly rejected the linear logistic model ("p-value" < 0.001 for both the specific rates and the adjusted rates).

### **The relation of cardiovascular death to diastolic blood pressure.**

The 2-spline model gave an excellent fit ( "p-value" = 0.821 specific rates, 0.800 for the adjusted rates). Examining the slope terms showed three things: (i) The middle slope could be taken to be 0 ("p-value" = 0.90 specific rates, =0.802, adjusted rates). (ii) The right slope was highly significant ("p-value" = 0.001 specific rates, = 0.002 adjusted rates). (iii) The left slope was almost significant ("p-value" =0.060, specific rates, = 0.104 adjusted rates). Consequently, use of the horizontal 2-spline model was warranted. As judged by the goodness of fit test the horizontal 2-spline model (figure 2) was excellent ("p-value" for fit = 0.900, specific rates, "p-value" for fit = 0.874 adjusted rates). The right slope was again highly significant ( "p-value" < 0.001 for both the specific and adjusted rates). But now, the left slope was also significant ("p-value" = 0.019 for the specific rates and 0.053 for the adjusted rates). The horizontal 1-spline (figure 2) also gave a good fit ("p-value" for fit =0.443 specific rates, = 0.551 adjusted rates). Consequently, there were two choices for the model of the relation of cardiovascular disease death to systolic blood pressure (viz. the horizontal 1- spline and the horizontal 2-spline) one excluding and the other including the J-curve effect. These are virtually identical (figure 2) except for the behavior at pressures below 70 mm Hg.

Previous investigators <sup>9</sup> have represented the J-curve effect by the parabolic model. The goodness of fit test showed that the parabolic model (figure 3) also provides a good fit to the Framingham data (p- value for fit = 0.827, specific rates = 0.872, adjusted rates). That model implies that there is a unique diastolic blood pressure at which risk is a minimum, ( = 81.4mm Hg) with risks smoothly increasing away in both directions from that point (figure 3). However, comparing the horizontal 2-spline and the parabolic models we found that the parabolic model had two serious statistical drawbacks: First, the entire statistical significance of the downward trend to the minimum was due to the leftmost

point. Excluding that point, the test for trend to pressure 82 mm Hg showed there was no significant downward trend ("p-value" for slope = 0.385 using specific rates, "p-value" for slope = 0.485 using adjusted rates). Second, it implied that the risks were continuously increasing for pressures past 81.4 mm Hg. However, the entire significance of the increase came from pressures past 90 mm Hg. A test for trend to pressure 90 mm Hg excluding the leftmost point showed there was none ("p-value" for slope = 0.444 specific rates, = 0.509 adjusted rates). The parabolic model tries to approximate this flat portion, producing a somewhat abnormal residual pattern compared to the horizontal 2-spline (See figures 2 and 3).

### **The relation of cardiovascular Disease Incidence to diastolic blood pressure**

Heretofore, the relation of incidence of cardiovascular disease to diastolic blood pressure has been modeled primarily by the use of adjusted rates using either the linear logistic or the parabolic model. As for cardiovascular disease death, the additive model was valid for the relation between incidence of cardiovascular disease and diastolic blood pressure ("p-value" = 0.864) and the linear logistic model was rejected ("p-value" < 0.001 for both the adjusted and specific rates).

The adjusted incidence of cardiovascular disease rates investigated here are the same data used by Andersen <sup>6</sup> when he found that the risks to pressure 89 mm Hg had a downward slope. However, he did not determine if this slope was significant. The test for trend to this pressure showed that it was not significant ("p-value" = 0.381, adjusted rate, "p-value" = 0.351, specific rate). The parabolic model was rejected ("p-value" for fit = 0.008 for both rates). The 1-spline model was rejected ("p-value" = 0.014 group specific rates, "p-value" = 0.015 adjusted rates) as was the 2-spline ("p-value" ≤ 0.01 for both rates). *Thus all models previously used for relations of cardiovascular risk to diastolic blood pressure were rejected by these data.* On the other hand, the jump model (figure 4) fitted very well ("p-value" for fit = 0.889 specific rates, "p-value" = 0.937, adjusted rates). Tests of the significance of the jump and of the significance of the slope past 104 shows both were highly significant ("p-value" < 0.001 for both specific and adjusted rates for both coefficients). The magnitude of the jump is impressive [odds ratio of risk to left of 90 to risk just past 90 = 1.828 CI (1.312,2.344), specific rates, odds ratio = 1.869 CI (1.346,2.407) adjusted rates].

### **Predictive ability of diastolic versus systolic blood pressure**

Strictly speaking, as judged by the error sums of squares, either of the two diastolic pressure models yielded better predictions of cardiovascular death than did the systolic model ("p-value" for fit: diastolic pressure horizontal 2-spline = 0.945, diastolic pressure horizontal 1-spline = 0.850, systolic pressure horizontal 1-spline = 0.7026). Comparing the standardized right slope in the either of the diastolic models to the right slope in the systolic model showed that there was no significant difference between these slopes. [From our data we could only obtain a rather poor lower bound for the standard error of the difference between the two standardized estimates. This considerably overestimated the exact z-score, but sufficed to show that there was no significant difference between them ("p-value"  $\geq 0.118$ )].



## DISCUSSION

There are currently two theories the relation between diastolic blood pressure and such endpoints as death due to cardiovascular disease, overall mortality, and incidence of cardiovascular disease. The paradigm <sup>1,2</sup> is that the relation is modeled by the linear logistic curve and therefore risk is strictly increasing with pressure.

The Framingham 18-year study data <sup>4</sup> was instrumental in establishing this paradigm. Our reanalysis of these data show that it statistically rejects the linear logistic model for any of these outcomes. This single fact has much broader implications than might first be assumed because it, in and of itself, *proves that the paradigm is false*. Although numerous studies are needed to build confidence that the model may be valid, no number of studies can ever prove that the model is true. In contrast, finding just a single study, that is based on a representative sample from its target population, that statistically rejects the linear logistic model for the risk-diastolic blood pressure relation will definitively prove that the paradigm is false for its target population. Consequently, any study of sufficiently large size that fails to reject the paradigm must either be a sample from a quite different population or it must be seriously biased. Therefore, granting that the Framingham data does constitute a representative sample from its target population (white, urban, middle class Americans) the relation of risk to diastolic pressure in that population is not continuous and strictly increasing for any of the risks investigated here.

The second view is that the relation is given by a “J-curve” in which risks increase with low as well as high pressure. Since its beginnings with Andersen <sup>6</sup> and Stewart <sup>7</sup> this view has been controversial, and the entire J-curve issue is confusing. The causes of this phenomenon and even its existence have been vigorously debated. The phenomenon is found in many, but not all, observational studies and clinical trials <sup>7-21</sup>. It is found more frequently in studies including older persons or those with ischemic heart disease, although it is found in some studies that contain neither <sup>21</sup>. In the main, those studies that fail to exhibit the J-curve phenomenon analyze the data by linear logistic smoothing <sup>11</sup>. This of course would obliterate any trace of the phenomenon. In some studies the J-curve phenomenon was found to hold for incidence as well as cardiovascular death and overall mortality <sup>11</sup>. For others it was found to be present only for death (either all causes, due to

cardiovascular disease, or due to coronary heart disease). Some studies find that it occurs only for those with previous ischemia or with previous myocardial infarction. Most of the studies that did not exclude those with previous ischemia showed the J-curve phenomenon<sup>18</sup>. In contrast, several studies that did exclude those with ischemia did not show this phenomenon<sup>20</sup>. Other studies find it present even for those without previous ischemia<sup>10</sup>. The strongest case to date for the linear logistic relation of diastolic blood pressure to various risks is by MacMahon et al<sup>12,13</sup>. There have been counter arguments to their methods of analysis and conclusions<sup>14-16</sup>.

If there is a J-curve effect, its causes are open to considerable speculation<sup>18,19</sup>. One suggested cause is anti-hypertensive medication. This would seem to be contradicted by the fact that the J-curve phenomenon occurs in studies such as the early Framingham data discussed here, that are relatively free of drug intervention. Coope<sup>21</sup> classifies the two main hypotheses about causation as direct and reverse causation. The former, first suggested by Green<sup>20,21</sup>, is that it is due to coronary ischemia, as diastolic blood pressure drops below some critical value needed to preserve perfusion of the myocardium. If that is the case, then there could well be a critical value of low diastolic blood pressure such that flow is seriously impaired for pressures below that value, but not for pressures above that value. The latter claims that the low diastolic blood pressure is a marker for some preexisting condition.

Until now, whenever modeled, the J-curve effect has been represented as a parabolic type relation between risk and diastolic blood pressure. We believe that such a view is both misleading and not supported by the facts. A parabolic representation portrays the J-curve effect as a steady increase in risk in both directions from a unique point of minimum risk (figure 3). However, our analysis shows that for all adults ages 45-74, there is a large interval of diastolic blood pressure (at least from 70 mm Hg to 90 mm Hg) in which the risks are constant and only begin to rise for pressures above a threshold at 90 mm Hg. There may also be a lower threshold at about 70 mm Hg with risks again rising for pressures below that threshold. Another shortcoming of the parabolic model for the relation of either overall mortality or cardiovascular death to diastolic blood pressure is that it implies that that relation is entirely different than it is for the relation of these risks to systolic blood pressure. This is difficult to understand since, based on data in the national

health examination survey,<sup>22</sup> the two pressures are on average 84% correlated. In particular, it is difficult to understand why there should be an optimal diastolic blood pressure but no such optimal systolic blood pressure. Yet another defect of the parabolic model is that it puts the risks at low and high pressures on an equivalent footing (viewing each as a strong effect). In so doing it provides no explanation for the variability in the ability to detect the J-curve effect.

Our new spline models of the relation of either overall or cardiovascular death to diastolic blood pressure remedy all of these deficiencies of the parabolic model. They show that there is a basic age and sex dependent background risk that is independent of blood pressure. The effect of diastolic blood pressure is to logistically increase risk above background for pressures exceeding a threshold at 90 mm Hg. Since 90 mm Hg is approximately the 70<sup>th</sup> percentile pressure for all persons aged 45-74, the new models show that the relations of risk to diastolic and to systolic pressure are essentially the same. The J-curve effect is now represented as an anomalous effect, which may produce an increase in risk above background for pressures below a second threshold at 70 mm Hg, rather than as a continuous increase in risk away from a unique point of minimum risk (figure 2).

According to the linear logistic model there is no “normal” diastolic blood pressure except by convention. The currently used threshold of 90 mm Hg for diastolic hypertension is considered an arbitrary (and perhaps too high<sup>1,2</sup>) cut-point. On the other hand, our new models indicate that 90 mm Hg is a rather natural cut-point in the sense that it is at that point that risks can first begin to rise above the background risk. However, as discussed with the systolic pressure<sup>5</sup>, that may not be the appropriate cut-point for hypertension. If one adopts the view that the hypertension cut-point should be defined as the point at which intervention is warranted, then taking the 80<sup>th</sup> percentile pressure (about 94 mm Hg) might be more appropriate.

Comparing the results on the left and right slopes in the 2-spline and horizontal 2-spline models we see there is a great difference between the nature of the increase in the risk for pressures above 90 mm Hg with that for the increase for the pressures below 70 mm Hg. There can be no doubt of the increase above 90 mm Hg. We would expect that any data set of comparable size that constituted a representative sample from a target

population similar to Framingham would exhibit such an increase. However, that is not at all the case with the increase to the left of 70 mm Hg. In the Framingham data analyzed here, there is no statistical evidence for its presence in the relation of incidence of cardiovascular disease to diastolic blood pressure, and it is at best equivocal in the relation with either cardiovascular disease death or overall mortality. Since the slope of the middle segment in the 2-spline model is not significantly different than zero, that model and the horizontal 2-spline model are for all practical purposes the same. Yet they lead to different conclusions about the existence of the J-curve phenomenon when statistical significance is taken at the usual 5% level. The fact the J-curve hovers on the threshold of detectability signifies that it is a weak effect. This offers a ready explanation of its inconsistency. We would anticipate that comparable data sets would or would not exhibit the J-curve effect by both the luck of the draw and the type of model used.

The evidence from randomized trials give substantial support for the new view of the relation of risk to diastolic blood pressure proposed here. In particular the recent HOT <sup>17</sup> trial showed there was no benefit to lowering diastolic blood pressure to pressures below 90 mm Hg. To our knowledge, no randomized trial has ever shown that lowering pressures to below 90 mm Hg has had any effect on any of the endpoints considered here.

From the point of view of the treatment of hypertension, our new models and the results of the randomized trials greatly diminish the significance of the J-curve effect. Since there is no reason to try to lower diastolic blood pressure past 90 mm Hg and the increase at risk at the low end does not begin until at least 70 mm Hg the issue of excessive lowering should become moot. This does not say that the potential rise in risk at low diastolic blood pressure is inconsequential. As outlined in the discussion of the J-curve, it may signal the presence of some serious illness or an increase in the risk of myocardial infarction in those with previous ischemia.

The relation of incidence of cardiovascular disease to diastolic blood pressure perplexes us. That outcome is a soft endpoint, which is open to considerably more subjective judgment than hard endpoints such as overall mortality and cardiovascular disease death. As with the relation of cardiovascular disease death to diastolic blood pressure, it is widely believed that that relation is continuous and strictly increasing, which

again is primarily based on the linear logistic model of that relation. The Framingham data shows that that view is false. Not only is the linear logistic model rejected for the relation of incidence of cardiovascular disease to diastolic blood pressure, but that relation is substantially different than that of cardiovascular disease death to diastolic blood pressure. Most remarkably, there is a large jump in the risk precisely at 90 mm Hg. We have no biological explanation for either the jump or why these two relations should be so different. Instead, we believe the explanation lies more in the nature of what constitutes cardiovascular disease and how it is diagnosed clinically. One possibility is that the jump behavior at 90 mm Hg is from observer bias. In the time period covered by the Framingham data used here, the diastolic cut point for hypertension was 90 mm Hg and it was widely believed that diastolic hypertension is a “cause” of cardiovascular disease. The diagnosis of cardiovascular disease can involve a judgment, taking many factors into account. It is conceivable that blood pressure itself might be one of those factors upon which the call is based, with those having diastolic blood pressure greater than 90 mm Hg more likely to be classified as having cardiovascular disease than those with pressures below this value. Should that prove to be the case, it would suggest that drawing conclusions on soft end-point outcomes should be viewed with considerable caution.

Several authors<sup>3,12,13 23,24</sup> have investigated the question whether the systolic blood pressure or the diastolic blood pressure is a better “predictor” of outcomes such as cardiovascular death. They conclude, with minor exceptions, that the systolic is better. To date, two methods have been used to answer this question. The first (a relatively crude method) compares the standardized differences between the mean pressure for the population of those that did and did not have the event in question. The second assumes that the linear logistic model is valid for both pressures and compares the standardized slopes of the two models. We now know that the linear logistic model does not hold for either pressure. Therefore, conclusions drawn on the basis of this model are not valid. Our new models show that the systolic blood pressure is not a better predictor. We find that the two pressures are essentially equivalent predictors with perhaps a slight edge to the diastolic.

Aside from the anomalous rise in risk at the lowest diastolic pressures, the new model of the relation of cardiovascular death to diastolic blood pressure and the model that we previously introduced <sup>5</sup> for the relation of cardiovascular death to systolic blood pressure are identical. For both pressures, risks are constant to the same threshold pressure (the 70<sup>th</sup> percentile pressure) and then rise. The constant risk below the threshold pressure represents underlying basic risk for a person of a given age and sex that is independent of the effect of either blood pressure. This background risk must be the same in both the cardiovascular death-diastolic blood pressure and cardiovascular death-systolic blood pressure models. Their estimates show that they are; each is within a standard error of the other.

## APPENDIX

### Basics

Table 1 gives the ten categories of diastolic blood pressure for each group and the value of the diastolic pressure  $x_k$  for each of the groups following the convention used by the Framingham investigators. We will define groups 1-3 to be these age groups for men and groups 4-6 to be these age groups for women. The probability of an event for a person in group  $j$  and category  $k$  is  $p(j,k)$ . The probability of an event for a person in group  $j$  and at pressure  $x$  is  $p(j,x)$ . The group adjusted rate is  $p(x) = (n_1/n) p(1,x) + \dots + (n_6/n) p(6,x)$ , where  $n_i$  = number of persons in group  $i$  and  $n = n_1 + \dots + n_6$ . Models are developed by fitting logit ( $p(j,x)$ ) [or logit ( $p(x)$ )] by the method of weighted least squares with weights the reciprocal variance of logit ( $p(j,k)$ ) [or logit( $p(x)$ )].

### The Models

#### Group Specific Models

##### Additive model

$$\text{logit}(p(j,k)) = \alpha_j + \beta_k \quad (1)$$

After verifying that this model can be used all models on the specific rates are developed as sub-models of the additive model. Additionally, the verification that the additive model holds justifies the use of the adjusted rates.

##### Quadratic Model

$$\text{Elogit}(p(j,x)) = a_j + bx + cx^2 \quad (2)$$

##### 2-spline model

$$\text{logit}(p(j,x)) = a_j + b((x - k_u)^+ + c x - d(k_l - x)^+ \quad (3)$$

where  $k_u$  and  $k_l$  are the upper and lower knots respectively. The knots are fixed at predetermined values and are not parameters of the model. The lower knot is taken to be 67, the value for the lowest blood pressure category and the upper knot is taken to be a value near the 70<sup>th</sup> percentile pressure ( 90 except for one model where it is taken to be 87).

##### Horizontal 2-spline

$$\text{logit}(p(j,x)) = a_j + b((x - k_u)^+ - d(k_l - x)^+ \quad (4)$$

##### Linear Logistic

$$\text{logit}(p(j,x)) = a_j + cx \quad (5)$$

### **Horizontal 1-spline**

$$\text{logit}(p(j,x)) = a_j + b((x - k_u)^+ + cx$$

### **Jump**

$$\text{logit}(p(j,x)) = a_j + b((x - k_u)^+ + d1_{[x \geq 90]}. \quad (6)$$

Both the quadratic and the 2-spline contain the linear logistic as special cases. For the quadratic it is the case  $c = 0$  and for 2-spline it is the case when  $b = d = 0$ ).

### **Group Adjusted Models**

Replace  $\text{logit}(p(j,x))$  by  $\text{Elogit}(p(x))$  and  $a_j$  by  $a$  in (2)-(6).

### **Goodness of Fit Tests**

All goodness of fit tests using the specific rates are with the context of the additive model. Therefore the error sums of squares is not the ordinary sums of squares SSE but  $\text{SSE} - \text{SSAM}$ , where  $\text{SSAM}$  is the error sums of squares for the additive model.



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## FIGURE LEGENDS

**Fig. 1.** The Framingham logistically smoothed adjusted death rates per 1000 of cardiovascular disease incidence (solid line) and mortality (dashed line) for all persons aged 45-74.

**Fig. 2.** Adjusted cardiovascular death rates per 1000 as a function of diastolic blood pressure. Shown are observed death rates (○), 95% confidence intervals for rates (vertical bars), horizontal 1-spline model (dashed line), horizontal 2-spline model (solid line).

**Fig. 3** Parabolic model and observed rates

**Fig. 4.** Cardiovascular disease incidence and mortality rates per 1000. Shown are observed incidence rates (circles), their 95% confidence intervals (vertical bars), observed death rates (squares). Upper curve: jump model for incidence. Lower curve: horizontal 2-spline model for mortality.

		Table 1 diastolic blood pressure categories (mm Hg)									
Category		1	2	3	4	5	6	7	8	9	10
Range		020-	070-	075-	080-	085-	090-	095-	100-	105-	110-
		069	074	079	084	089	094	099	104	109	160

FIGURE 1

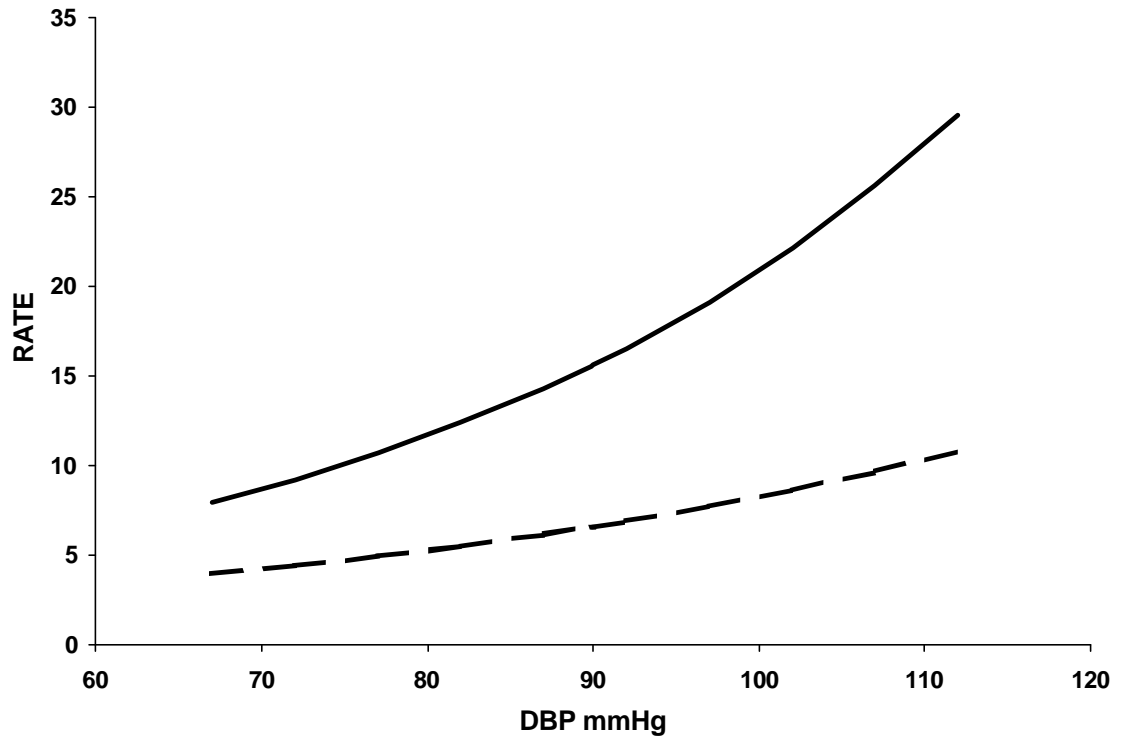


FIGURE 2

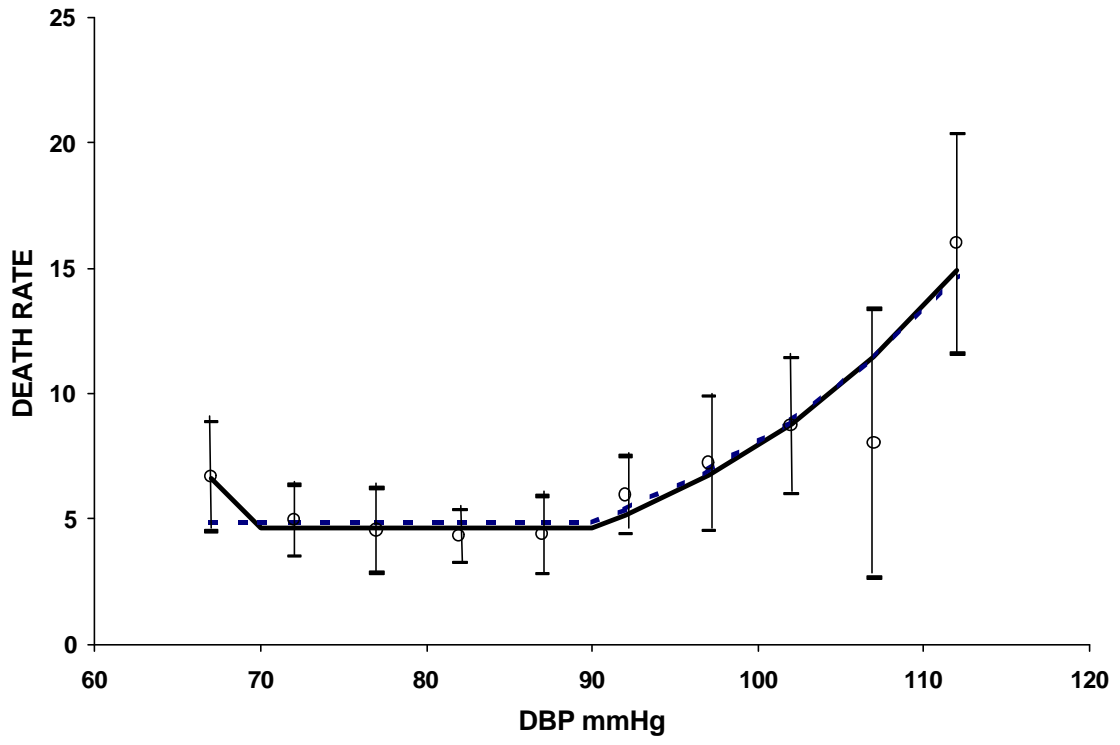


FIGURE 3

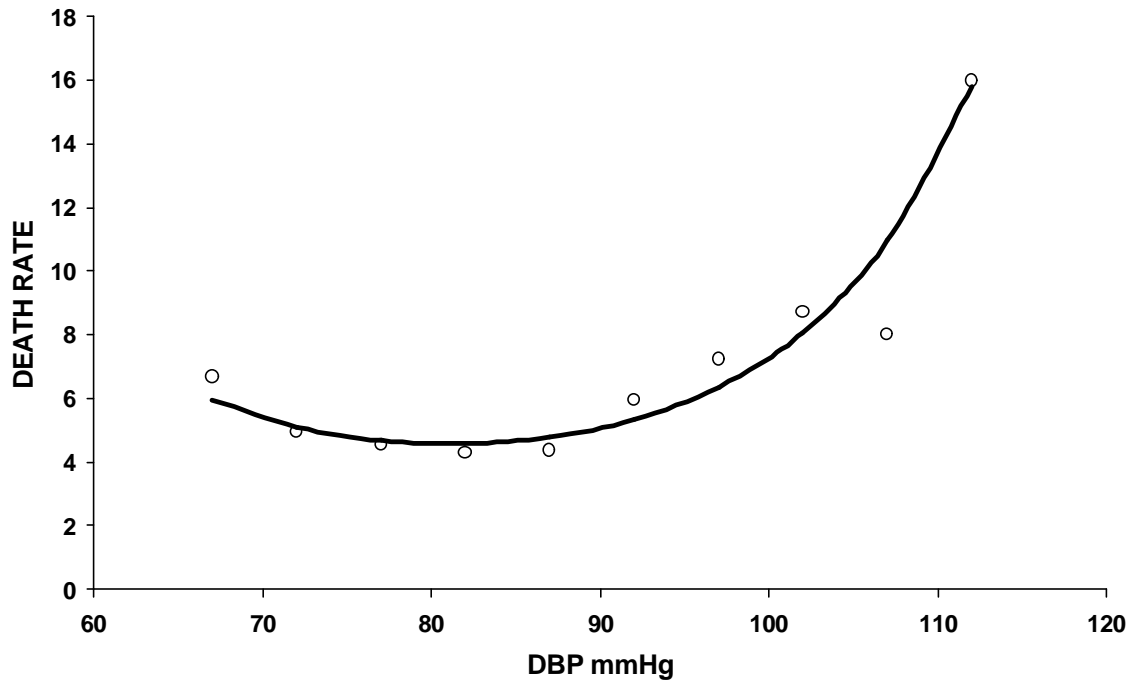


FIGURE 4

