Blood Pressure and Cardiovascular Disease: A Reevaluation of Their Relationship Using Multiple Logistic Spline Regression *

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Abstract

For roughly 100 years, there has been a widely recognized relationship between high blood pressure (hypertension) and cardiovascular disease. Currently, the prevailing wisdom concerning blood pressure is "the lower the better." The Joint National Committee on Hypertension sets blood pressure cutpoints independent of age and gender. An analysis of the Framingham Study data suggests both of these approaches are wrong.

A multiple logistic spline regression model, which incorporates age and gender and does not assume a simple linear relationship between blood pressure and risk, yields results that may help physicians treat hypertensive patients more effectively.

Blood Pressure

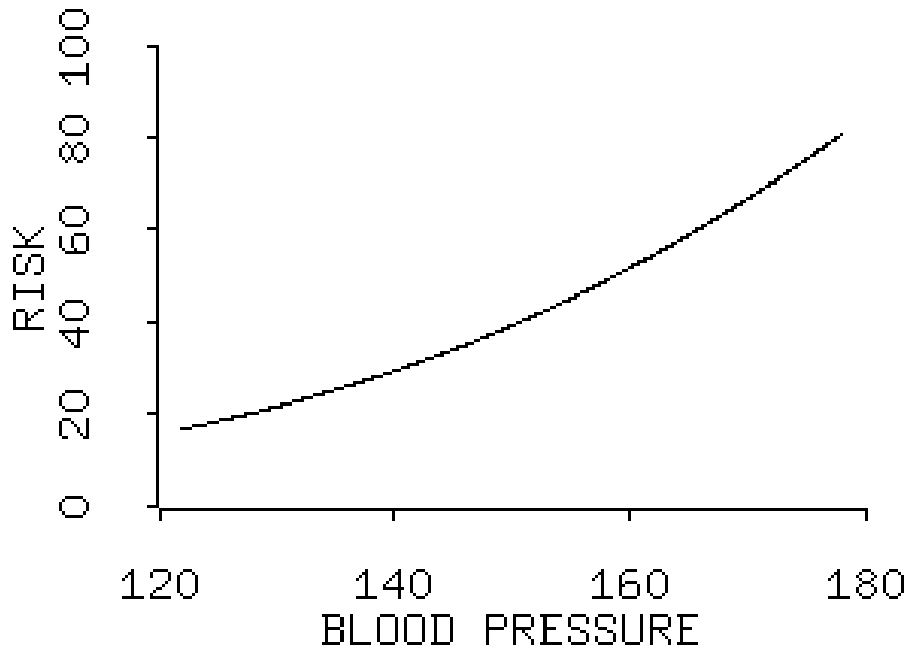
- Sphygmomanometer invented in 1895
- Systolic blood pressure (SBP) is the larger number
- Diastolic blood pressure (DBP) is the smaller number
- Blood pressures usually referred to as systolic over diastolic, e.g. “120 over 80”
- Pulse pressure (PP) is the difference between systolic and diastolic, that is, PP = SBP − DBP

The Prevailing "Wisdom"

- Adults age 18 and older, *regardless of age or gender*, are considered hypertensive if SBP ≥ 140 or DBP ≥ 90

- "...the relative risk of death from coronary heart disease was observed to rise continuously with increasing levels of systolic and diastolic blood pressure ...there was no clearly defined lower level of blood pressure below which the risk did not continue to decline." January 6, 2000, editorial in *The New England Journal of Medicine*

That is, "the lower, the better":



The Framingham Study

- Framingham, Massachusetts, a suburb of Boston
- The study was begun in 1948 with a random sample of $\approx 5,000$ residents
- Each subject undergoes a detailed physical exam every two years
- Our dataset includes up to 16 exams per patient, through 1982

Disposition of Framingham Study Patient Visits

	Age			
	45-54	55-64	65-74	Total
Male	7,231	8,321	4,517	20,069
Female	9,048	10,781	6,471	26,300
Total	16,279	19,102	10,988	46,369

- Each gender-age group has a large sample size

- Each patient visit can be treated as an independent observation because maximum-likelihood solution is equivalent

SBP Deciles

	Age	Min	10%	20%	30%	40%	Median
Male	45-54	80.1	110.2	117.8	120.2	126.0	130.1
	55-64	80.1	113.8	120.0	125.9	130.1	135.8
	65-74	79.9	116.0	123.9	129.9	134.2	139.9
Female	45-54	82.1	109.8	114.8	120.0	124.2	130.0
	55-64	73.9	112.2	120.1	127.8	132.0	138.1
	65-74	85.8	119.8	128.1	133.9	139.9	145.2

	Age	60%	70%	80%	90%	Max
Male	45-54	135.2	140.2	148.1	159.9	240.0
	55-64	140.1	147.8	155.9	169.8	275.9
	65-74	144.2	150.1	159.9	170.1	259.8
Female	45-54	135.0	141.8	150.0	163.9	300.2
	55-64	144.1	150.2	160.1	174.1	300.2
	65-74	150.2	159.8	166.2	180.0	280.0

DBP Deciles

	Age	Min	10%	20%	30%	40%	Median
Male	45-54	20.1	70.0	75.0	79.8	80.1	83.9
	55-64	32.2	69.8	73.8	77.9	80.0	82.0
	65-74	30.2	67.8	70.0	74.0	77.9	80.0
Female	45-54	48.0	69.8	72.0	76.0	79.8	80.2
	55-64	44.8	69.8	71.9	76.1	79.9	81.8
	65-74	29.9	67.8	70.1	74.0	78.0	80.0

	Age	60%	70%	80%	90%	Max
Male	45-54	86.1	89.9	94.0	100.0	160.2
	55-64	85.8	89.8	92.2	99.9	144.8
	65-74	82.1	86.0	90.0	94.2	144.8
Female	45-54	84.1	88.9	91.9	98.2	159.9
	55-64	84.9	88.2	92.1	99.8	160.1
	65-74	82.2	86.0	90.0	96.0	144.1

Why use *deciles* of blood pressure as a predictor?

- Each subject's blood pressure is compared only with gender and age peers

- Makes it possible to pool different gender and age groups in the same model

- Disadvantage:
  May make it difficult to interpret results

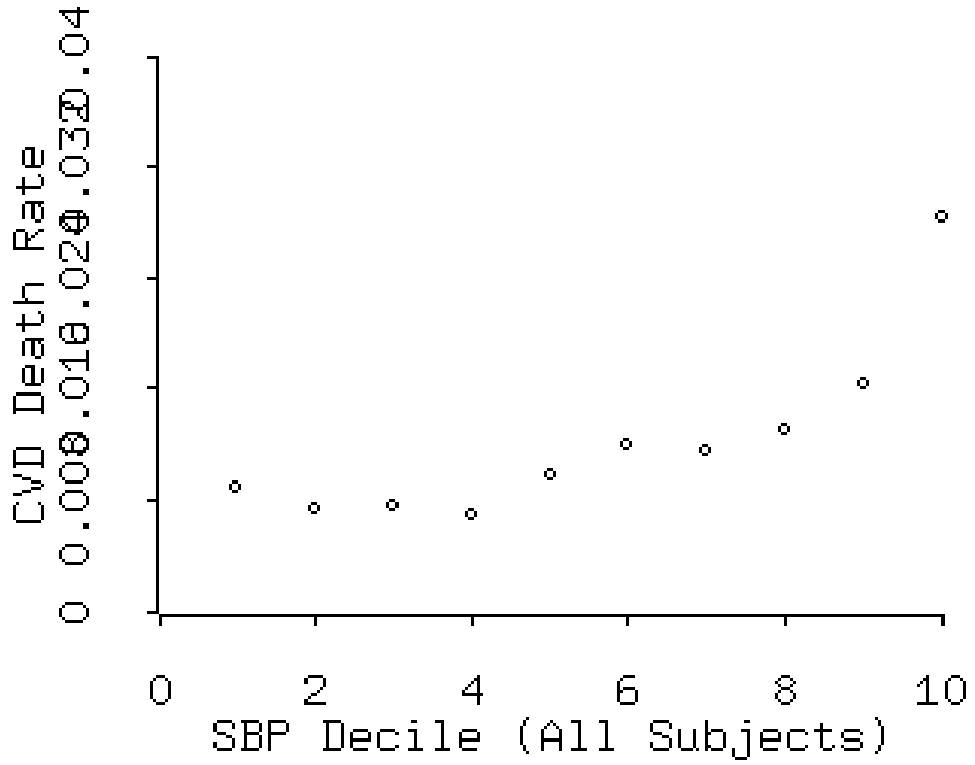
Which endpoint should we use in our analysis?

- Non-death cardiovascular events may be susceptible to misdiagnosis

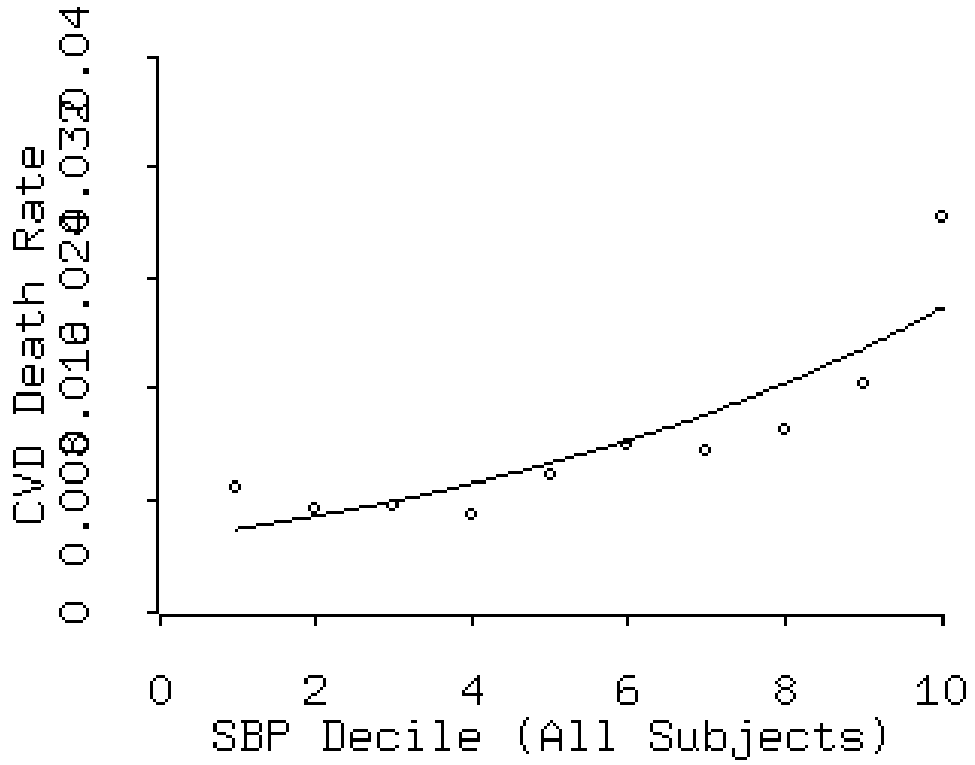
- Our analysis of the Framingham data looked at
  - deaths due to cardiovascular disease ("CVD deaths")
  - all deaths

- For the purpose of this talk, our response variable is the probability of CVD death in the two years following an exam

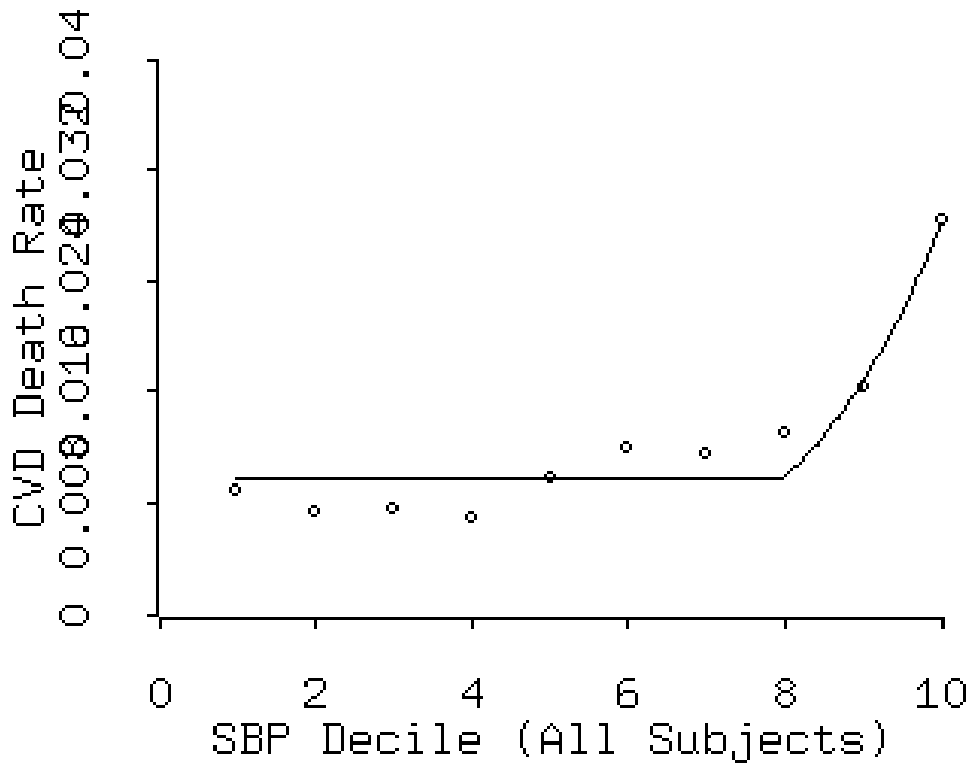
Risk of Cardiovascular Death vs. SBP Decile
All Patient Visits



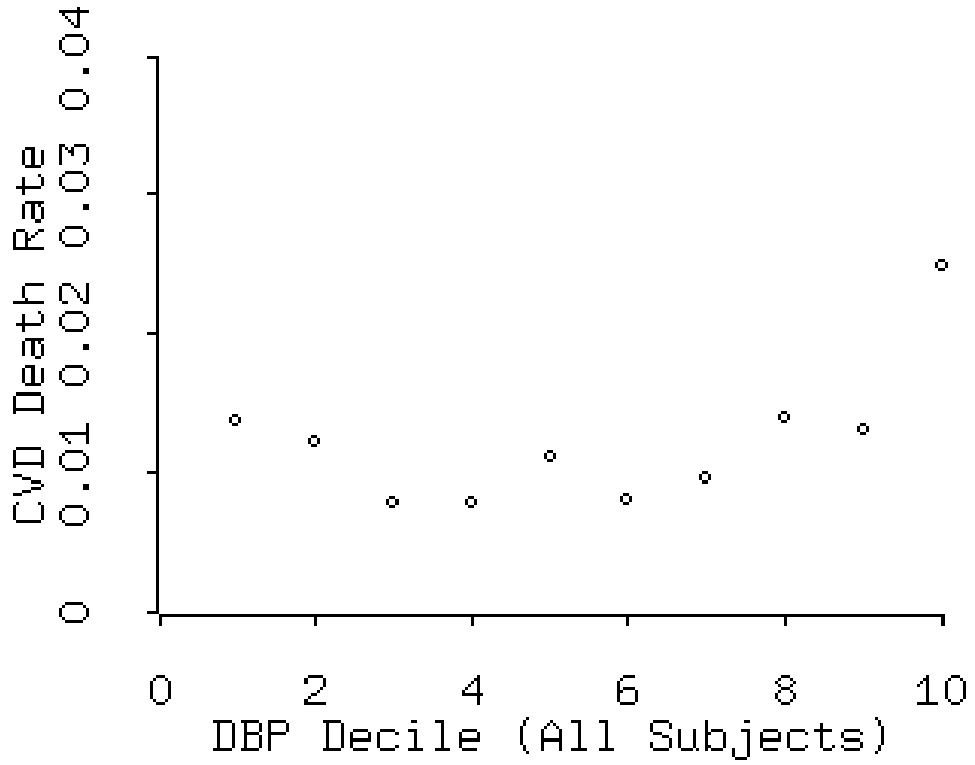
Risk of Cardiovascular Death vs. SBP Decile
Linear Fit



Risk of Cardiovascular Death vs. SBP Decile
Spline Fit



Risk of Cardiovascular Death vs. DBP Decile
All Patient Visits



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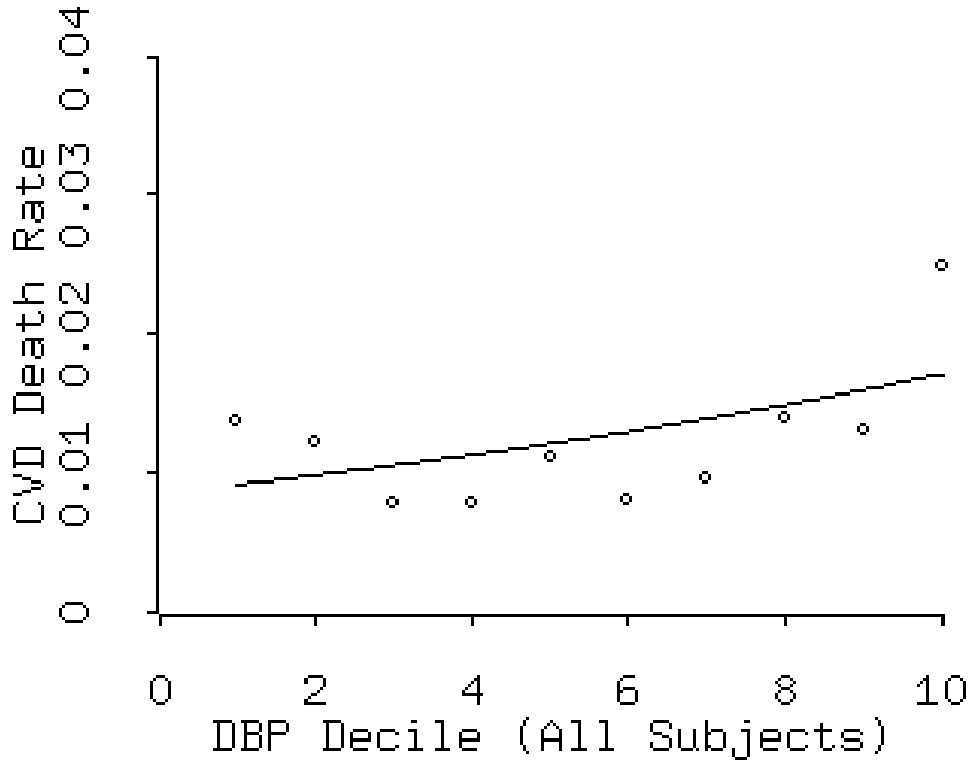
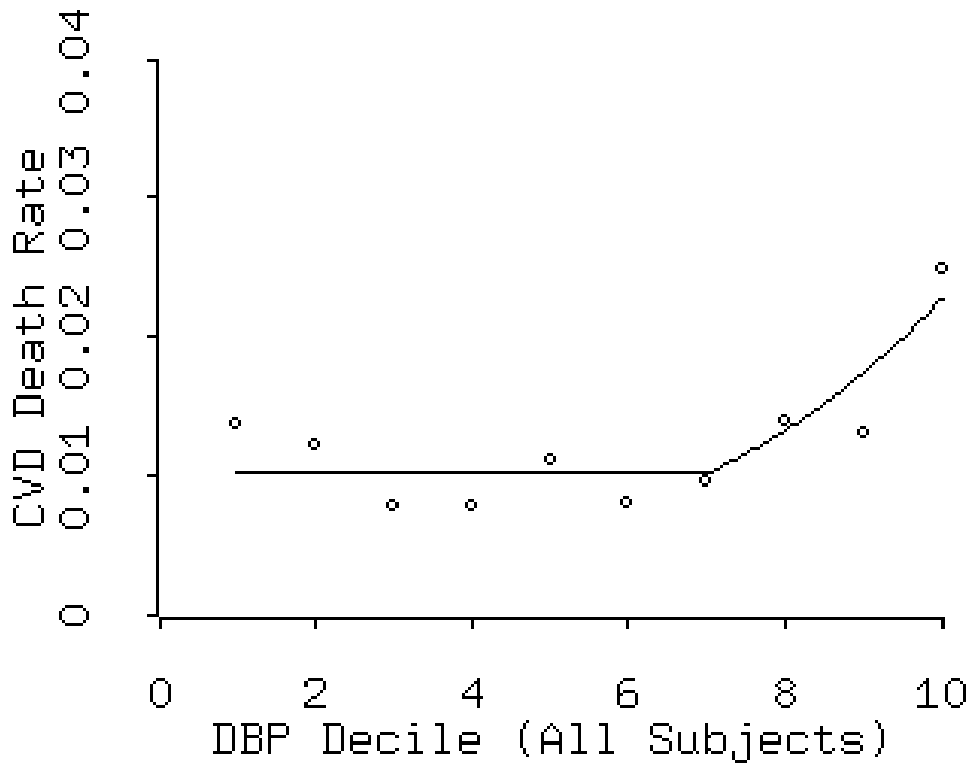
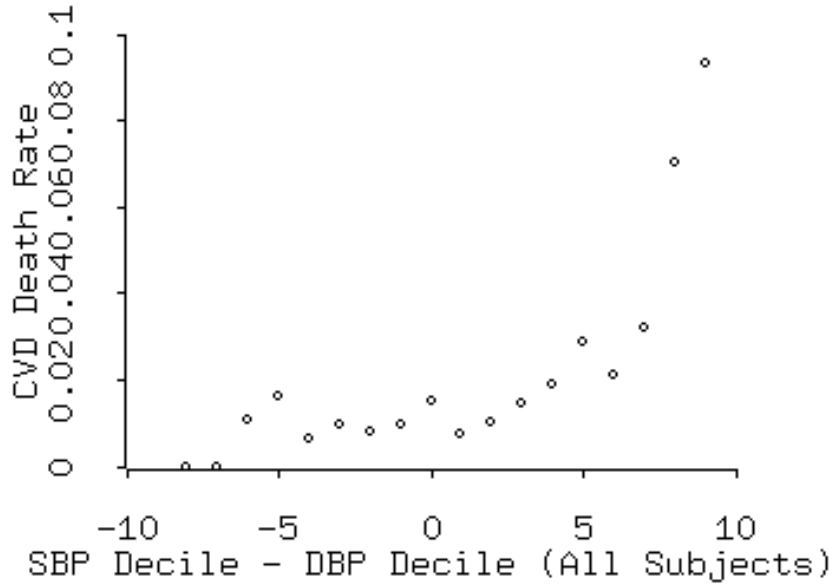


Risk of Cardiovascular Death vs. DBP Decile
Spline Fit



Risk of Cardiovascular Death vs. Difference Between SBP and DBP Deciles



The four extreme points account for only 0.4% of patient visits

The multiple logistic spline regression model

$$\begin{aligned}\text{logit}(Risk) \;=\; & \alpha_i \;+\; \beta_1(SBPdecile - 8)_+ \;+\; \beta_2(DBPdecile - 7)_+ \\ & +\; \beta_3(SBPdecile - DBPdecile - 1)_+\end{aligned}$$

- Recall $\text{logit}(x) = \log(x/(1-x))$ and maps $(0, 1)$ to $(-\infty, +\infty)$
- α_i is the gender- and age-specific intercept term, where $i \in \{1, \ldots, 6\}$
- The spline operator $(\cdot)_+$ returns the positive component of its argument, that is, $(x)_+ = \max(0, x)$

- The model assumes equal risk for patients with

  1. $SBPdecile \leq 8$,

  2. $DBPdecile \leq 7$, and

  3. $SBPdecile - DBPdecile \leq 1$

- Maximum likelihood logistic regression is used to fit this model

Results of model

- 46,369 observations, 572 CVD deaths

- Maximum likelihood estimates

Variable	Parameter Estimate	Standard Error	p-value
α_1 [Men 45-54]	-5.2537	0.1409	0.0001
α_2 [Men 55-64]	-4.2950	0.0907	0.0001
α_3 [Men 65-74]	-3.9305	0.1009	0.0001
α_4 [Women 45-54]	-6.2932	0.2054	0.0001
α_5 [Women 55-64]	-5.4698	0.1296	0.0001
α_6 [Women 65-74]	-4.4785	0.1073	0.0001
$(SBPdecile - 8)_+$	0.2998	0.0685	0.0001
$(DBPdecile - 7)_+$	0.2365	0.0497	0.0001
$(SBPdecile - DBPdecile - 1)_+$	0.2012	0.0311	0.0001

What do our results mean?

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Ten hypothetical case studies

Subject	Age	SBP	DBP
Sam	47	130	70
Marvin	51	130	85
Jack	45	140	70
Peter	49	150	90
David	50	150	70
Mary	69	140	70
Alice	67	164	84
Sally	72	160	80
Sarah	68	160	90
Kathy	70	172	70

Modeled odds ratio for ten hypothetical case studies

Subject	Age	SBP	DBP	Odds Ratio
Sam	47	130	70	1.8
Marvin	51	130	85	1.0
Jack	45	140	70	2.7
Peter	49	150	90	1.6
David	50	150	70	5.5
Mary	69	140	70	1.2
Alice	67	164	84	1.0
Sally	72	160	80	1.2
Sarah	68	160	90	1.3
Kathy	70	172	70	4.2

Comparison of hypertension diagnosis rates

Conventional Diagnosis	New Model	Male 45-54	55-64	65-74
Normal	Normal	58%	54%	48%
Hypertensive	Normal	7	10	13
Normal	Hypertensive	6	5	5
Hypertensive	Hypertensive	29	32	34

Conventional Diagnosis	New Model	Female 45-54	55-64	65-74
Normal	Normal	61%	51%	41%
Hypertensive	Normal	5	14	19
Normal	Hypertensive	5	3	2
Hypertensive	Hypertensive	28	32	38

Conclusions

- Hypertension guidelines need to be gender- and age-specific
- Pulse pressure needs to be considered in assessing risk
- There appears not to be a strictly "the lower, the better" relationship between blood pressure and cardiovascular disease
- The current hypertension guidelines may cause over- and undertreatment of a large number of patients

Future steps

- Take closer look at increase in risk for lower DBP
- Analyze the effect of blood pressure changes over time
- Study different age groups, e.g., Framingham offspring study
- Study different populations, different studies from other geographic areas
- Try similar approach with cholesterol