Survival Analysis for Understanding the Association Between Systolic Blood Pressure and Mortality: The Framingham Heart Study

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Objective: This study assesses the association between systolic blood pressure and mortality, overall and separately for men and women, using a subsample from the Framingham Heart Study.

Methodology: The work analyzes two sets of Cox proportional hazards models to assess the association between systolic blood pressure and mortality; the first studies men and women together, and the second separately. The presence of confounders is evaluated by comparing hazard ratios for a unit change in systolic blood pressure at exam 4, with and without each possible confounder in the model, and with and without all possible confounders. The most likely confounders are age and body mass index (BMI), due to their likely effect on mortality and correlations with systolic blood pressure, but no covariates are found to be confounders.[1] The findings reported are from models that are stratified by age and include age as a covariate, since age is a known predictor of mortality. Additional covariates are included based on their statistical significance in crude models and likely impact on health. Diastolic blood pressure and hypertension are excluded due to their medical relationship with systolic blood pressure.

Cox proportional hazards models assume proportional hazards, noninformative censoring, independence of observations, and linearity of the effects of covariates on the log scale.[2] This study uses Schoenfeld residuals to test for time-varying effects; time-varying covariates are then included to model such effects. Studies of health and mortality often have some informative censoring; sicker patients are more likely to leave the study. Since the dataset lacks information on censoring points, it is impossible to construct a likelihood function that models censoring.[3] Assessment of other assumptions is left to further study.

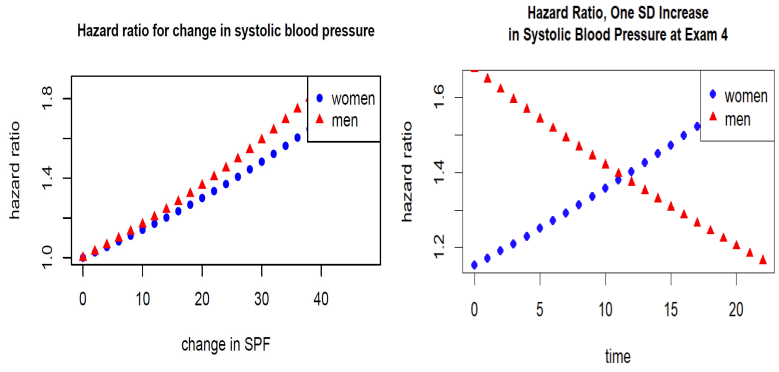
Results: The analyses consistently show an association between systolic blood pressure and mortality that is statistically significant at the 5% level in all reported models but one. Table 2 shows coefficient estimates from models of the full subsample, while Table 3 shows estimates from models that analyze the sexes separately (see Appendix). Model 1 adjusts only for age, while Models 2 and 3 also adjust for sex, an interaction of blood pressure and sex, cholesterol level, cigarettes smoked/day, pulmonary function, and BMI. Because the interaction between sex and blood pressure in Model 2 violates the proportional hazards assumption (p-value for Schoenfeld residuals test 0.045), Model 3 includes time-varying variables for sex, blood pressure, and their interaction, as well as the other covariates. In all models without interaction terms, the coefficient on systolic blood pressure is statistically significant at the $\alpha = 0.001$ level (Wald tests; e.g., Model 1: $p = 2.45e-15$). The terms containing systolic blood pressure are jointly significant in Model 3, with time-varying terms (PLRT $\chi^2 = 59.5$ with 4 d.f., $p = 3.74e-12$), though they are not jointly significant in Model 2, the comparable model without them. Model 3 suggests that the effect of higher blood pressure at exam 4 decreases over time for men, but increases over time for women (Figure (b)).

[1] Inclusion of possible confounders changes coefficient estimates for SPF4 less than 2% in all cases.

[2] BS852 Class Notes Weeks 7-8, Salil Vasudeo Deo et. al., "Survival Analysis Part 2: Cox Proportional Hazards Model," *Indian Journal of Thoracic and Cardiovascular Surgery* (March–April 2021) 37(2):229–233.

[3] Janet M. Box-Steffensmeier and Bradford S. Jones, *Event History Modeling; A Guide for Social Scientists* (Cambridge: Cambridge University Press, 2004), p. 18.

In all models, the estimated association between systolic blood pressure and mortality is substantively large, due to blood pressure's substantial variance (sd $\simeq$ 24.2). In the simple model in column 1 of Table 2, the coefficient estimate of 0.0129 predicts that the hazard of death is 37% higher for a patient with systolic blood pressure one standard deviation above the mean to a patient with mean blood pressure. Figure (a) shows the association between a range of possible disparities in blood pressure and the predicted hazard ratio, using the separate, stratified analyses for men and women (cols. 1 and 2, Table 3), and holding all other covariates constant. (The last model in of Table 3 adjusts for menopause in addition to the other covariates; its association with mortality is statistically insignificant.)



(a) (b)

As Figure (a) shows, the association between systolic blood pressure and mortality (adjusted for cholesterol level, the number of cigarettes smoked/day, pulmonary function, and BMI) differs by sex. At the left-hand side of Figure (a), patients with no difference in systolic blood pressure have the same predicted hazard of death. As the difference in systolic blood pressure between patients rises, so does the increased hazard of death for the patient with the higher blood pressure, whether male or female, but the hazard ratio rises more steeply for men than for women. A female patient with a blood pressure 24 mm Hg higher (approx. full-sample sd) has a hazard of death that is about 37% higher than a female patient with characteristics that are otherwise the same, while a male patient with the same higher blood pressure has a hazard of death that is about 46%.higher than a comparable male patient without the higher blood pressure. (The standard deviation of systolic blood pressure is 4.6 mm Hg higher in the male than in the female subsample.)

Limitations of this study: The covariates in this study do not include coronary heart disease or Type II diabetes, both likely to be associated with mortality. Moreover, researchers and medical professionals may be interested not only in whether the patient dies, but also in how, a question not addressed directly by Cox proportional hazards models. If different characteristics influence death from various medical conditions, such as heart disease and high blood pressure, predictors of mortality might be better studied with a model of competing risks than with the Cox models used in this study (Box-Steffensmeier and Jones 166-8).

Conclusions: This study finds that higher systolic blood pressure is associated with a higher hazard of death in a subsample of the Framingham Heart Study dataset. In a simple model of the full subsample (Model 1), a one-standard deviation (24.2) increase in systolic blood pressure is associated with a 37% higher hazard of death. Higher systolic blood pressure is associated with a greater hazard of death for both sexes, but the association is stronger for men than women. In all models but one, the association between systolic blood pressure, or a group of terms containing it, and mortality is statistically significant at the 5% level.

Appendix: Tables

	Systolic BP, mean [range]	Cholesterol, mean [range]	Age, mean [range]	Menopause, %, values	BMI, mean [range]
Female (n=1027)	135 [88,290]	234 [122,523]	49.8 [34,68]	62.3 (0,1)	25.7 [16.7,44.7]
Male (n=820)	133 [90,252]	225 [122,407]	49.6 [34,69]	NA	26.2 [16.5,40.1]
All (n=1847)	134 [88,290]	230 [122,523]	49.8 [34,69]	NA	26.0 [16.5,44.7]
	Cigs/day,	Pulmonary fcn	Survival,	Death,	
Female (n=1027)	5.05 [0,43]	415 [82,636]	18.5 [0,22]	22.4 (0,1)	
Male (n=820)	12.7 [0,43]	544 [227,833]	17.2 [0,22]	32.8 (0,1)	
All (n=1847)	8.42 [0,43]	472 [82,833]	17.9 [0,22]	27.1 (0,1)	

Table 1: Patients' characteristics, by sex, all variables except survival measured at exam 4

	Model 1	Model2	Model 3
Systolic BP	0.0129***	0.0134***	5.810e-03
Sex (1=male)	–	0.687	-1.080
Sex*systolic blood	–	7.63e-04	0.0154*
Age	0.0807***	0.0755***	0.0747***
Cholesterol	–	5.921e-05	-8.20e-06
Cigarettes/day	–	0.0174***	0.0177***
Pulmonary fcn.	–	-0.00223***	-0.00224***
BMI	–	-0.00502	-0.00454
Sex tt	–	–	0.165*
Sex*Systolic BP tt	–	–	-0.00136*
Systolic BP tt	–	–	6.75e-04
*: significant at 0.05, *** at 0.001, tt: time-varying covariate			

Table 2: *Coefficient estimates*, Cox Proportional Hazards models, stratified by age, N=1847

	Men (n=820)	Women (n=1027)	Women (n=1027)
Systolic BP	0.0155***	0.0131***	0.0133***
Menopause	–	–	0.407
Age	0.0762***	0.0708***	0.0595***
Cholesterol	0.000398	-1.48e-06	-0.000429
Cigarettes/day	0.0129**	0.0298***	0.0291***
BMI	-0.0295	0.0104	0.0106
Pulmonary fcn	-0.00197**	-0.00292**	-0.00286**
: significant at 0.01, * at 0.001			

Table 3: *Coefficient estimates*, Cox proportional hazard models, data stratified by age