

Chapter 825

Tests of Mediation Effect in Cox Regression

Introduction

This procedure computes power and sample size for a test of the mediation effect in a Cox regression with a hazard dependent variable λ and an independent (input) variable X . Interest focuses on the interrelationship between Y , X , and a third independent variable called the mediator M . The sample size calculations are based on the work of Vittinghoff, Sen, and McCulloch (2009). Note that their work has been extended in Vittinghoff and Neilands (2015). We are looking into adding those extensions in a later procedure.

Mediation Model

Vittinghoff, Sen, and McCulloch (2009) derived a sample size formula for testing the mediation effect based on testing the significance of β_M in the Cox regression model

$$\log(\lambda) = \beta_0 + \beta_X X + \beta_M M$$

They showed that testing $\beta_M = 0$ is equivalent to testing for a significant mediation effect. In addition to the notation above, they use ρ_{XM} as the correlation between the independent variables X and M and ψ to represent the probability that a subject is uncensored.

Calculating the Power

Power calculations are based on standard normal distribution. They proceed as follows:

1. Determine the critical value $z_{1-\alpha}$ from the standard normal distribution where α is the probability of a type-I error.
2. Calculate: $z_\beta = \sqrt{N\sigma_M^2\beta_M^2(1 - \rho_{XM}^2)\psi} - z_{1-\alpha}$.
3. Calculate: Power = $\Phi(z_\beta)$.

Notes

1. Use $\frac{\alpha}{2}$ instead of α for two-sided test.
2. $\sigma_M^2 = \Pr(M = 1)\Pr(M = 0)$ if M is binary.

Example 1 – Finding Sample Size

Researchers are studying the relationship between an elapsed-time variable (Y) and an independent variable (X). They want to understand the impact of a third variable (M) on the relationship between X and Y, so they decide to carry out a mediation analysis. They decide to determine the sample size based on the significance test of the mediator term in a Cox regression. Using prior analyses, they decide to use $\beta_M = 0.2, 0.3, 0.4$; $\rho_{XM} = 0.3$; $\sigma_M = 1$; and $\psi = 0.7$. They set the power at 0.9 and the two-sided significance level at 0.05.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	N (Sample Size)
Alternative Hypothesis	Two-Sided
Power.....	0.90
Alpha.....	0.05
β_M (Reg Coef of M).....	0.2 0.3 0.4
ρ_{XM} (Correlation of X and M)	0.3
Type of Mediator, M.....	Continuous
σ_M (Standard Deviation of M)	1
ψ (Probability Uncensored).....	0.7

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results

Solve For: N (Sample Size)
 Alternative Hypothesis: Two-Sided
 Hypotheses: H0: $\beta_M = 0$ versus H1: $\beta_M \neq 0$

Power	Sample Size N	Number of Events E	Regression Coefficient of M β_M	Correlation of X and M ρ_{XM}	Standard Deviation of M σ_M	Probability a Subject is Uncensored ψ	Alpha
0.9004	413	289	0.2	0.3	1	0.7	0.05
0.9011	184	129	0.3	0.3	1	0.7	0.05
0.9025	104	73	0.4	0.3	1	0.7	0.05

Model $\log(P/(1 - P)) = \beta_0 + \beta_X(X) + \beta_M(M)$.
 X The primary predictor. It is an independent variable.
 M The mediator. It is a continuous variable.

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
 N The number of observations.
 E The number of events.
 β_M The regression coefficient of the mediator in the model.
 ρ_{XM} The correlation between X and M.
 σ_M The standard deviation of M.
 ψ The probability that a subject is uncensored.
 Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A mediation effect (single group, survival-time response Y versus X with mediator M) design will be used to test whether the mediation effect (β_M) is different from 0 (H0: $\beta_M = 0$ versus H1: $\beta_M \neq 0$). The comparison will be made using a two-sided Cox regression test of the mediation effect coefficient (β_M), with a Type I error rate (α) of 0.05. The continuous mediator, M, is assumed to have a standard deviation of 1. The correlation between X (primary predictor) and M (mediator) is assumed to be 0.3. The probability that a subject is uncensored is assumed to be 0.7. To detect a mediation effect (mediator regression coefficient, β_M) of 0.2 with 90% power, the number of needed subjects will be 413 (or 289 events).

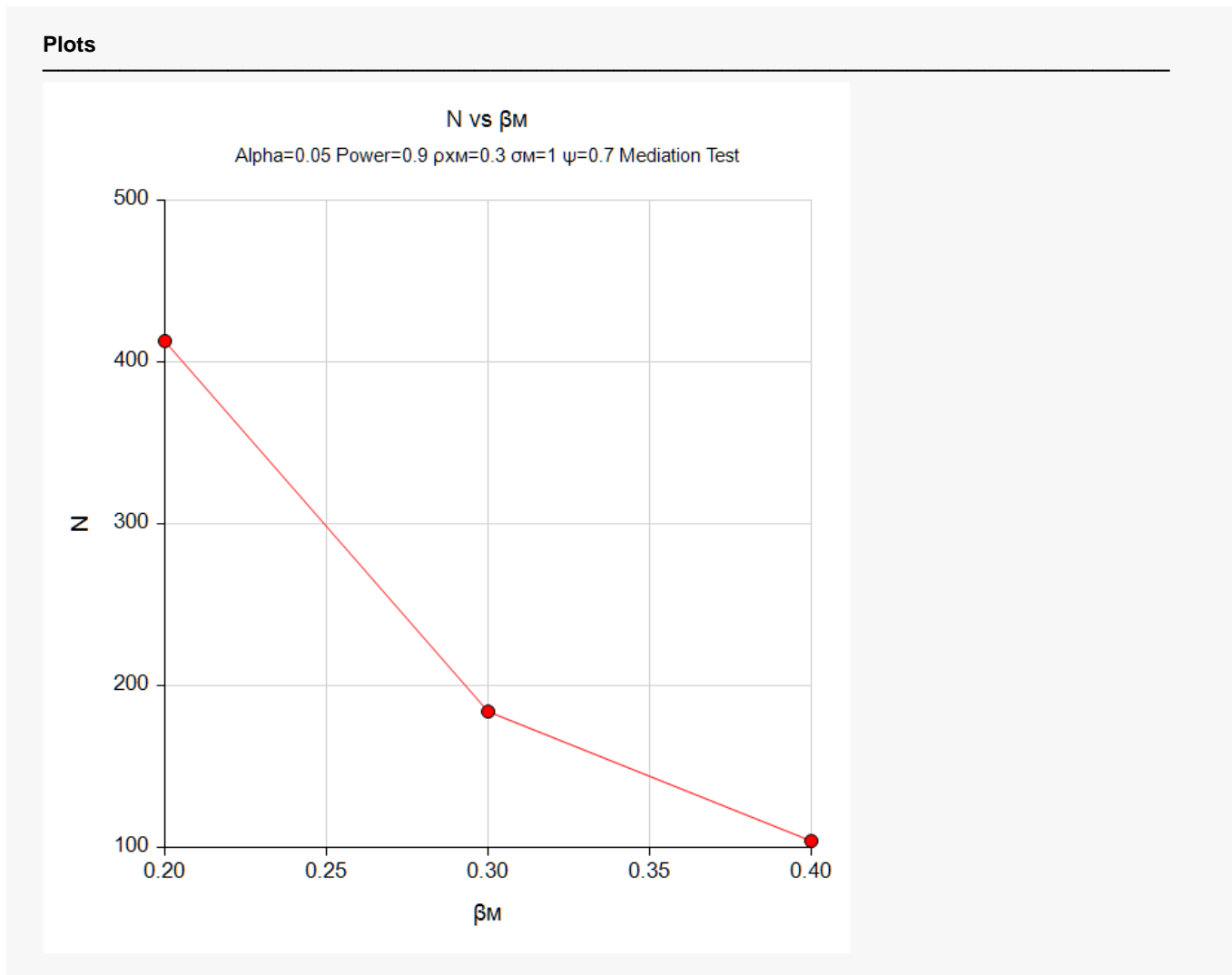
References

Vittinghoff, E., Sen, S., and McCulloch, C.E. 2009. 'Sample size calculations for evaluating mediation.' *Statistics in Medicine*, Vol. 28, Pages 541-557.

This report shows the necessary sample sizes. The definitions of each of the columns is given in the Report Definitions section.

Tests of Mediation Effect in Cox Regression

Plots Section



This plot shows the relationship between sample size and effect size.

Example 2 – Validation using Vittinghoff (2009)

Vittinghoff et al. (2009) present an example on page 545 in which $\beta_M = \log 1.5$ (0.4055), $\rho_{XM} = 0.3$, $P(M=1) = 0.25$, and $\psi = 0.2$. They set the power at 0.8 and the one-sided significance level at 0.025. The computed sample size is 1399.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	N (Sample Size)
Alternative Hypothesis	One-Sided
Power.....	0.80
Alpha.....	0.025
β_M (Reg Coef of M).....	0.4055
ρ_{XM} (Correlation of X and M)	0.3
Type of Mediator, M.....	Binary
Probability M = 1	0.25
ψ (Probability Uncensored).....	0.2

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results							
Solve For:	N (Sample Size)						
Alternative Hypothesis:	One-Sided						
Hypotheses:	H0: $\beta_M \leq 0$ versus H1: $\beta_M > 0$ or H0: $\beta_M \geq 0$ versus H1: $\beta_M < 0$						
Power	Sample Size N	Number of Events E	Regression Coefficient of M β_M	Correlation of X and M ρ_{XM}	Probability M = 1 P(M = 1)	Probability a Subject is Uncensored ψ	Alpha
0.8001	1399	280	0.406	0.3	0.25	0.2	0.025

PASS matches the calculation of N = 1399.