

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.

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. Under most situations, you will select either *Power* or *N (Sample Size)*.

Select *Sample Size* when you want to calculate the sample size needed to achieve a given power and alpha level.

Select *Power* when you want to calculate the power of an experiment.

Test Direction

Alternative Hypothesis

Specify whether the hypothesis test is one-sided or two-sided. When a two-sided test is selected, the value of alpha is automatically divided by two. A two-sided test requires alpha to be less than 0.50.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error (alpha). A type-I error occurs when you reject the null hypothesis when in fact it is true.

Values of alpha must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

N (Sample Size)

This option specifies the value(s) for *N*, the sample size. Note that $3 < N$.

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Effect Size

β_M (Reg Coef of M)

Enter one or more values for β_M , which is the coefficient of M in the Cox regression model

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

where λ is the hazard function, X is the primary predictor variable, and M is the mediator variable.

In this model, β_M can be interpreted as the log of the odds or logit. Hence, if you want to test for an odds of 1.5, enter $\log(1.5) = 0.4055$ here.

Relative Hazard

In this model, β_M can be interpreted as the log of the relative hazard. Hence, if you want to test for a relative hazard of 1.5, enter $\log(1.5) = 0.4055$. Other common values are

| RH | ln(RH) |
|------|---------|
| 0.25 | -1.3863 |
| 0.33 | -1.1087 |
| 0.5 | -0.6931 |
| 0.8 | -0.2231 |
| 0.9 | -0.1054 |
| 1.1 | 0.0953 |
| 1.2 | 0.1823 |
| 1.3 | 0.2624 |
| 1.4 | 0.3365 |
| 1.5 | 0.4055 |
| 2.0 | 0.6931 |
| 3.0 | 1.0986 |
| 4.0 | 1.3863 |

Range

β_M can be any value other than zero.

ρ_{XM} (Correlation of X and M)

Enter one or more values for the correlation of X and M.

Range

$0 < \rho_{XM} < 1$.

Type of Mediator, M

Indicate whether the mediator variable, M, is continuous or binary.

σ_M (Standard Deviation of M)

Enter one or more values for the standard deviation of M, the mediator variable.

Range

$0 < \sigma_M$.

Tests of Mediation Effect in Cox Regression**Probability M = 1**

Enter one or more values of the probability in the population that $M = 1$ when M is a binary variable that takes on the values 0 or 1. This value is used to compute the variance of M using the formula: $\sigma_M^2 = P(M=1) \times (1 - P(M=1))$.

Range

Since this is a probability, it can be any value between 0 and 1.

 ψ (Probability Uncensored)

Enter one or more values of the probability that an observation is uncensored. Hence, the number of events is $N\psi$.

Range

$0 < \psi \leq 1$.

Tests of Mediation Effect in Cox Regression

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests of Mediation Effect in Cox Regression** procedure. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

| <u>Option</u> | <u>Value</u> |
|--|------------------------|
| 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 |

Annotated Output

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

Numeric Results

Numeric Results

Two-sided alternative hypothesis
M is a continuous mediator variable

| | Sample Size | Number of Events | Reg Coef of M β_M | Corr of X and M ρ_{XM} | Std Dev of M σ_M | Prob Subj Uncens ψ | Alpha |
|--------|----------------|------------------------|----------------------------------|--------------------------------------|----------------------------------|----------------------------------|-------|
| Power | N | E | | | | | |
| 0.9004 | 413 | 289 | 0.200 | 0.300 | 1.000 | 0.700 | 0.050 |
| 0.9011 | 184 | 129 | 0.300 | 0.300 | 1.000 | 0.700 | 0.050 |
| 0.9025 | 104 | 73 | 0.400 | 0.300 | 1.000 | 0.700 | 0.050 |

References

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

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Report Definitions

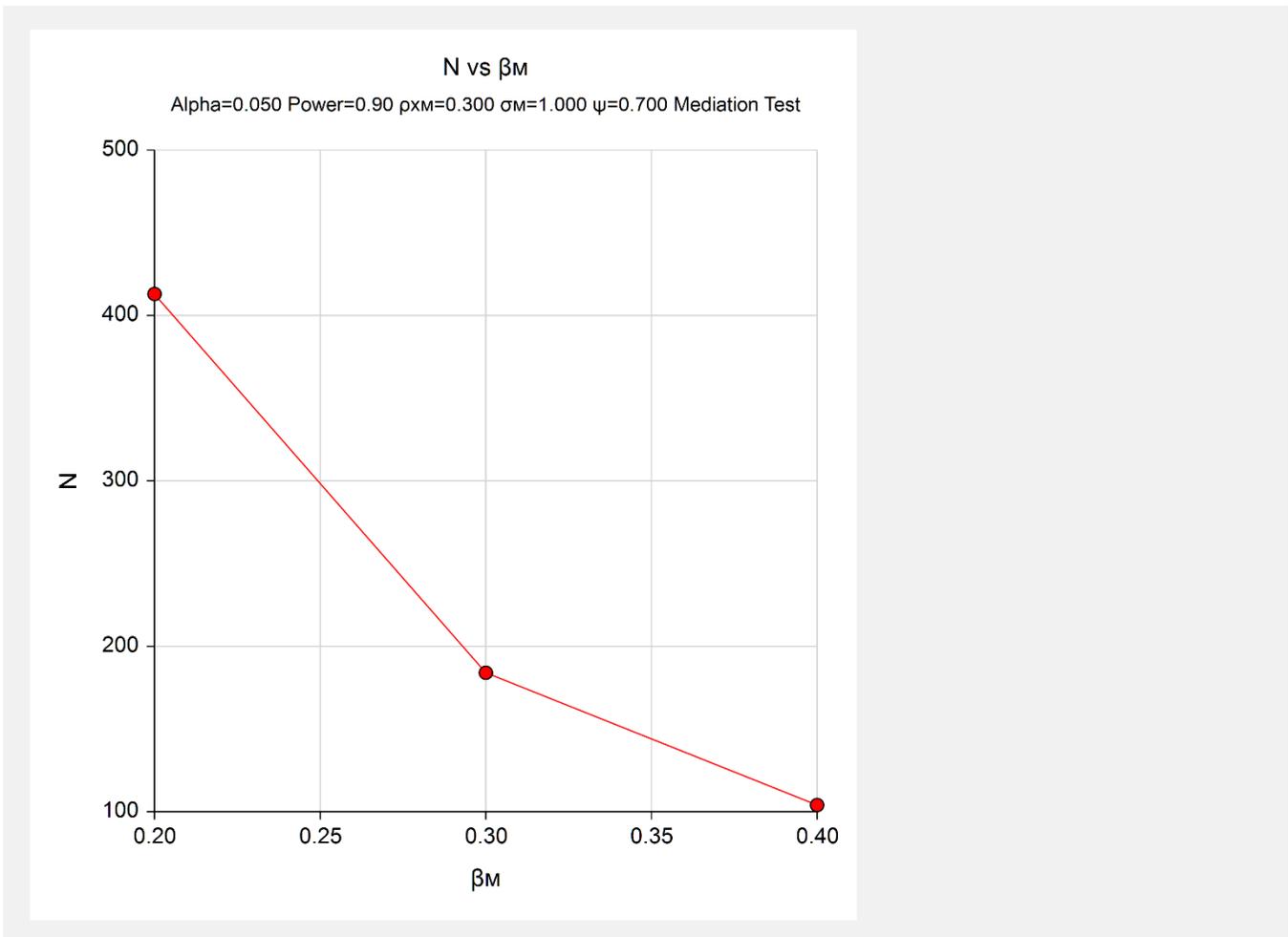
Hypotheses: $H_0: \beta_M = 0$ versus $H_1: \beta_M \neq 0$. (Two-Sided).
 X is the primary predictor. It is an independent variable.
 M is the mediator. It is a continuous variable.
 Model: $\log(P/(1-P)) = \beta_0 + \beta_X(X) + \beta_M(M)$.
 Power is the probability of rejecting a false null hypothesis.
 N is the number of observations.
 E is the number of events.
 β_M is the regression coefficient of the mediator in the model.
 ρ_{XM} is the correlation between X and M.
 σ_M is the standard deviation of M.
 ψ is the probability that a subject is uncensored.
 Alpha is the probability of rejecting a true null hypothesis. It should be small.

Summary Statements

A sample size of 413 (or 289 events) achieves 90% power to detect a mediation effect (as measured by the Cox regression coefficient of M, β_M) of at least 0.200 when the two-sided significance level (alpha) is 0.050. The correlation between X (the primary predictor) and M (mediator) is 0.300. The mediator, M, has a standard deviation of 1.000. The probability that a subject is uncensored is 0.700.

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

Plots Section



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

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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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests of Mediation Effect in Cox Regression** procedure. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

| <u>Option</u> | <u>Value</u> |
|--|------------------------|
| 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

| Numeric Results | | | | | | | |
|----------------------------------|-------------|------------------|-----------------------------|-------------------------------|---------------|--------------------------|-------|
| One-sided alternative hypothesis | | | | | | | |
| M is a binary mediator variable | | | | | | | |
| Power | Sample Size | Number of Events | Reg Coef of M | Corr of X and M | Prob M=1 | Prob Subj Uncens | Alpha |
| | N | E | β_M | ρ_{XM} | P(M=1) | ψ | |
| 0.8001 | 1399 | 280 | 0.406 | 0.300 | 0.250 | 0.200 | 0.025 |

PASS matches the calculation of $N = 1399$.