IMPROVING THE POWER TO DETECT INDIRECT EFFECTS IN MEDIATION ANALYSIS

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Abstract. Causal mediation analysis seeks to determine whether an independent variable affects a response variable directly or whether it does so indirectly, by way of a mediator. The existing statistical tests to determine the existence of an indirect effect are overly conservative or have inflated type I error. In this article, we propose two methods based on the principle of intersection-union tests that offer improvements in power while controlling the type I error. We demonstrate the advantages of the proposed methods through extensive simulation. Finally, we provide an application to a large proteomic study.

Keywords: Intersection-union test, Sobel test, product-normal distribution, joint significance test, S-test, p-value threshold

1. Introduction

Causal mediation analysis seeks to determine the pathways by which an independent variable affects a response variable: either directly or through some additional variable. If the independent variable affects the response through a secondary variable, called a mediator, there is said to be an indirect effect [Alwin and Hauser (1975)]. Mediation analysis has been used extensively, especially in social sciences [MacKinnon et al. (2007)] and public health sciences [Bellavia et al. (2019); Richiardi et al. (2013)], and has become increasingly popular in genetics [Barfield et al. (2017); Cardenas et al. (2019); Huang et al. (2014); Hutton et al. (2018); Raulerson et al. (2019)].

Detecting an indirect effect is seemingly simple but actually very difficult [Biesanz et al. (2010); Huang and Pan (2016); Vanderweele and Vansteelandt (2009); Zhong et al. (2019)]. Let \( \beta \) and \( \gamma \) denote, respectively, the effect of the independent variable on the mediator and the effect of the mediator on the response variable, and let \( \hat{\beta} \) and \( \hat{\gamma} \) denote the corresponding maximum likelihood estimators, which are independent under a no unmeasured confounding assumption [Imai et al. (2010)]. In the product of coefficients method [Alwin and Hauser (1975); MacKinnon et al. (2007),]
the null hypothesis of no indirect effect means $\beta\gamma = 0$, which is true if one of the two parameters is zero or both are zero. If $\beta = \gamma = 0$, the asymptotic distribution of $\hat{\beta}\hat{\gamma}$ is the product of two zero-mean normal random variables, rather than the normal distribution. If either $\beta$ or $\gamma$ is non-zero, but not both, the asymptotic distribution of $\hat{\beta}\hat{\gamma}$ is a zero-mean normal [Kisbu-Sakarya et al. (2014); Wang (2018)]. In practice, one does not know which distribution is correct because both scenarios constitute the null hypothesis. The well-known test of Sobel [Sobel (1982)] uses the normal distribution for $\hat{\beta}\hat{\gamma}$ and is overly conservative if $\beta = \gamma = 0$, whereas the test based on the product-normal distribution [MacKinnon et al. (2002, 2004)] is too liberal if $\beta$ or $\gamma$ is non-zero.

In this paper, we develop new methods to detect indirect effects based on the principle of intersection-union tests [Berger (1997)]. The proposed tests have correct type I error whether one or both parameters are zero and have good power when both parameters are non-zero. We demonstrate the advantages of the proposed methods through extensive simulation studies and provide an application to the Sub-Populations and Intermediate Outcome Measures in COPD Study (SPIROMICS) [Couper et al. (2014)].

2. Methods

We are testing the null hypothesis $H_0 : \{\beta = 0\} \cup \{\gamma = 0\}$ against the alternative hypothesis $H_A : \{\beta \neq 0\} \cap \{\gamma \neq 0\}$. Thus, this problem can be cast within the framework of intersection-union tests [MacKinnon et al. (2002)]. Berger [Berger (1997)] proposed the so-called S-test for this problem with normally distributed data, although not in the context of mediation analysis. Let $T_\beta$ and $T_\gamma$ be the test statistics for testing the null hypotheses that $\beta = 0$ and $\gamma = 0$, respectively. Assume the statistics $T_\beta$ and $T_\gamma$ are independent with distribution functions $F_{\beta}(\cdot)$ and $F_{\gamma}(\cdot)$, respectively. Write $U_\beta = F_{\beta}(T_\beta)$ and $U_\gamma = F_{\gamma}(T_\gamma)$. We reject $H_0 : \{\beta = 0\} \cup \{\gamma = 0\}$ if $(U_\beta, U_\gamma)$ falls into the rejection region $S$ shown in Figure 1a, which consists of three distinct regions, $S_1$, $S_2$, and $S_3$. In $S_1$, $U_\beta$ and $U_\gamma$ are less than $\alpha/2$ or greater than $1 - \alpha/2$; in $S_2$, the difference between $U_\beta$ (or similarly $1 - U_\beta$) and $U_\gamma$ is less than $\alpha/4$; and in $S_3$, $U_\beta$ and $U_\gamma$ are greater than $\alpha/2$ or less than $1 - \alpha/2$ and the difference between a specified $U$ value and 0.5 is small (or similarly, large) compared to the remaining $U$ value. The S-test has level $\alpha$ because $\Pr\{(U_\beta, U_\gamma) \in S\} = \alpha$ when either $U_\beta$ or $U_\gamma$ has the standard uniform distribution.
As shown in Figure 1a, \( S_1 \) is comprised of the four squares in the corners. In each square, \( U_\beta \) and \( U_\gamma \) are either less than \( \alpha/2 \) or greater than \( (1 - \alpha/2) \). Thus, \((U_\beta, U_\gamma) \in S_1\) if \( T_\beta \) and \( T_\gamma \) are both significant at the \( \alpha \) level, i.e., the maximum of the two \( p \)-values is less than \( \alpha \). We refer to the test based on \( S_1 \) alone [Cohen and Cohen (1983); MacKinnon et al. (2002)] as \( \text{maxP} \). Due to the additional rejection regions \( S_2 \) and \( S_3 \), the S-test is guaranteed to be more powerful than \( \text{maxP} \).

Unfortunately, the S-test has some undesirable properties which make it inappropriate for testing \( H_0 \). First, it can reject \( H_0 \) at a certain value of \( \alpha \) but fail to do so at a larger value of \( \alpha \). An example of this non-compatibility is given in Figure 1b: \( S_2 \) for \( \alpha = 0.05 \) will reject \( H_0 \) for some values of \((U_\beta, U_\gamma)\) that would not cause \( H_0 \) to be rejected for \( \alpha = 0.10 \) near the point where \( S_1 \) and \( S_2 \) meet; the location of \( S_3 \) depends on the value of \( \alpha \), with a smaller value of \( \alpha \) causing \( S_3 \) to be closer to the edge of the graphed region, enclosing values of \((U_\beta, U_\gamma)\) not included by any larger value of \( \alpha \). Second, the S-test may reject \( H_0 \) when the indirect effect is estimated at zero. Indeed, if \( \hat{\beta} = 0 \) and \( \hat{\gamma} = 0 \), then \( U_\beta = U_\gamma = 0.5 \), which is the center of \( S_2 \).

We propose two methods to address the shortcomings of the S-test. In the first method, we alter the rejection region and use \( p \)-values to determine significance; we will refer to this method as the PS-test. Specifically, we remove \( S_3 \) since it is a major contributor to non-compatibility and is not a very meaningful rejection region. In addition, we remove the portion of \( S_2 \) near \((0.5, 0.5)\), where the two diagonal bands cross, so as to avoid rejecting \( H_0 \) when the indirect effect is estimated at zero. Finally, we define the \( p \)-value as the smallest value of \( \alpha \) at which \( H_0 \) is rejected. This step enlarges the rejection region between \( S_1 \) and \( S_2 \), as shown in Figure 1c. The added rejection region, denoted as \( S_m \), takes the form of eight right triangles with base \( \alpha/4 \) and height \( \alpha/6 \).

The addition of \( S_m \) increases the type I error. If \( \beta = \gamma = 0 \), then both \( U_\beta \) and \( U_\gamma \) have the standard uniform distribution. The total area of \( S_m \) is \( \alpha^2/6 \). Removing \( S_3 \), which is comprised of four triangles each with base \( \alpha/2 \) and height \( \alpha/4 \), reduces the type I error by \( \alpha^2/4 \), and the removal of the central section eliminates an additional \( \alpha^2/8 \). Thus, the final rejection probability is \( \alpha(1 - (5\alpha/24)) \), such that the type I error rate is guaranteed not to be inflated. If only one of the two parameters is equal to zero, the change in the type I error is more complex. However, we show in the Appendix that the potential inflation of the type I error is negligible.
The second method we propose here also changes the rejection region of the original S-test and utilizes $p$-value thresholds. However, the rejection region is different from that of the PS-test in order to avoid potential inflation of the type I error. As shown in Figure 1, the rejection region consists of multiple squares of the size of $S_1$, the squares ascend (or descend) from each corner towards the
center, and each square meets at diagonal corners. We refer to this method as the ascending squares (ASQ) test.

To preserve compatibility, the significance level thresholds must be chosen such that each level divides evenly into all larger levels. Without this restriction, the rejection region for a smaller significance level will fail to lie within that of larger levels. To prevent inflation of the type I error, each level must divide evenly into 1.0. This restriction ensures that the centermost squares will not have inappropriate overlapping.

Given the predetermined significance levels, the ASQ-test begins at the largest significance level and continues down to the next largest, determining at each level whether \((U_\beta, U_\gamma)\) lies within the rejection region. If \((U_\beta, U_\gamma)\) is within the rejection region at a specific significance level, we conclude that the true \(p\)-value for the test is less than this significance level. By proceeding through the predetermined significance levels, the smallest significance value for which the null hypothesis \(H_0\) is rejected is determined, and that value is considered the \(p\)-value threshold; the true \(p\)-value is less than this value.

We may limit the degree that the bands for the PS-test or the squares for the ASQ-test are allowed to extend toward the center. This will alleviate the requirement that each \(\alpha\) divides evenly into 1.0 for the ASQ-test and also reduces the potential inflation of the type I error by the PS-test. To avoid rejecting \(H_0\) when \(\hat{\beta} = \hat{\gamma} = 0\), the ASQ-test must omit the center-most squares. The decision on how far the bands or squares are allowed to extend is based on a trade-off between power and type I error.

3. Simulation Studies

We conducted extensive simulation studies to evaluate the performance of the proposed and existing methods. We let independent variable \(G\) be Bernoulli(0.5), mediator \(M = \beta G + \epsilon_M\), and response variable \(Y = 0.2G + \gamma M + \epsilon_Y\), where \(\epsilon_M\) and \(\epsilon_Y\) are independent standard normal random variables. We varied \(\beta\) and \(\gamma\) from 0 to 0.4 and set the sample size \(n\) to 100, 500 or 1,000. For each combination of simulation parameters, we used 20,000 replicates to estimate the type I error or power of each test at \(\alpha = 0.05\). For the proposed methods, the band or squares were limited to 50% of the possible extension.
The results for the type I error are shown in Table 1. The S-test maintains type I error around the nominal level. The type I error of the PS-test, ASQ-test, and maxP is lower than that of the S-test and approaches the nominal level as $\beta$ or $\gamma$ increases. The Sobel test is very conservative when $\beta$ or $\gamma$ is zero or very small and when $n$ is small. By contrast, the product-normal test is anti-conservative when $\beta$ or $\gamma$ is not 0.

The results for power are given in Table 2. (The results for the product-normal test are omitted due to its highly inflated type I error.) The Sobel test is the least powerful, especially for small $n$.

### Table 1. Empirical Type I Error Rates at the Nominal Significance Level of 0.05

| $\beta$ | $\gamma$ | $n$   | Sobel  | maxP  | normal | S-test | PS-test | ASQ-test |
|---------|---------|-------|--------|-------|--------|--------|---------|----------|
| 0       | 0       | 100   | <0.001 | 0.003 | 0.054  | 0.053  | 0.026   | 0.025    |
|         |         | 500   | <0.001 | 0.003 | 0.048  | 0.049  | 0.025   | 0.024    |
|         |         | 1000  | <0.001 | 0.003 | 0.051  | 0.049  | 0.024   | 0.024    |
| 0.1     | 0       | 100   | 0.001  | 0.008 | 0.110  | 0.049  | 0.033   | 0.032    |
|         |         | 500   | 0.005  | 0.028 | 0.303  | 0.050  | 0.047   | 0.047    |
|         |         | 1000  | 0.012  | 0.041 | 0.459  | 0.047  | 0.047   | 0.046    |
| 0.2     | 0       | 100   | 0.004  | 0.023 | 0.261  | 0.047  | 0.042   | 0.042    |
|         |         | 500   | 0.029  | 0.051 | 0.613  | 0.051  | 0.051   | 0.051    |
|         |         | 1000  | 0.038  | 0.048 | 0.723  | 0.048  | 0.048   | 0.048    |
| 0.3     | 0       | 100   | 0.013  | 0.042 | 0.435  | 0.051  | 0.051   | 0.050    |
|         |         | 500   | 0.041  | 0.052 | 0.740  | 0.052  | 0.052   | 0.052    |
|         |         | 1000  | 0.044  | 0.049 | 0.814  | 0.049  | 0.049   | 0.049    |
| 0.4     | 0       | 100   | 0.023  | 0.048 | 0.564  | 0.050  | 0.050   | 0.050    |
|         |         | 500   | 0.045  | 0.051 | 0.801  | 0.051  | 0.051   | 0.051    |
|         |         | 1000  | 0.045  | 0.048 | 0.861  | 0.048  | 0.048   | 0.048    |

The results for the type I error are shown in Table 1. The S-test maintains type I error around the nominal level. The type I error of the PS-test, ASQ-test, and maxP is lower than that of the S-test and approaches the nominal level as $\beta$ or $\gamma$ increases. The Sobel test is very conservative when $\beta$ or $\gamma$ is zero or very small and when $n$ is small. By contrast, the product-normal test is anti-conservative when $\beta$ or $\gamma$ is not 0.

The results for power are given in Table 2. (The results for the product-normal test are omitted due to its highly inflated type I error.) The Sobel test is the least powerful, especially for small $n$. 
| β  | γ   | n  | Sobel | maxP | S-test | PS-test | ASQ-test | Sobel | S-test | PS-test | ASQ-test |
|----|-----|----|-------|------|--------|---------|----------|-------|--------|---------|----------|
| 0.05 | 0.03 | 100 | <0.001 | 0.003 | 0.052  | 0.028   | 0.026    | 0.04  | 20.02  | 10.65   | 9.85     |
|     |      | 500 | 0.001  | 0.010  | 0.054  | 0.037   | 0.035    | 0.07  | 5.70   | 3.87    | 3.73     |
|     |      | 1000| 0.002 | 0.019  | 0.064  | 0.052   | 0.050    | 0.10  | 3.27   | 2.67    | 2.59     |
| 0.1 | 0.1  | 100 | 0.001 | 0.011  | 0.053  | 0.039   | 0.038    | 0.10  | 4.69   | 3.44    | 3.38     |
|     |      | 500 | 0.033 | 0.122  | 0.148  | 0.149   | 0.148    | 0.27  | 1.21   | 1.21    | 1.21     |
|     |      | 1000| 0.152 | 0.307  | 0.317  | 0.320   | 0.317    | 0.49  | 1.03   | 1.04    | 1.03     |
| 0.2 | 0.1  | 100 | 0.007 | 0.037  | 0.065  | 0.061   | 0.061    | 0.18  | 1.73   | 1.64    | 1.64     |
|     |      | 500 | 0.132 | 0.198  | 0.198  | 0.198   | 0.198    | 0.67  | 1.00   | 1.00    | 1.00     |
|     |      | 1000| 0.311 | 0.351  | 0.351  | 0.351   | 0.351    | 0.89  | 1.00   | 1.00    | 1.00     |
| 0.3 | 0.1  | 100 | 0.023 | 0.066  | 0.075  | 0.075   | 0.074    | 0.35  | 1.14   | 1.14    | 1.13     |
|     |      | 500 | 0.175 | 0.202  | 0.202  | 0.202   | 0.202    | 0.87  | 1.00   | 1.00    | 1.00     |
|     |      | 1000| 0.327 | 0.342  | 0.342  | 0.342   | 0.342    | 0.96  | 1.00   | 1.00    | 1.00     |
| 0.4 | 0.1  | 100 | 0.041 | 0.076  | 0.078  | 0.078   | 0.078    | 0.54  | 1.02   | 1.02    | 1.02     |
|     |      | 500 | 0.190 | 0.202  | 0.202  | 0.202   | 0.202    | 0.94  | 1.00   | 1.00    | 1.00     |
|     |      | 1000| 0.337 | 0.345  | 0.345  | 0.345   | 0.345    | 0.98  | 1.00   | 1.00    | 1.00     |
| 0.4 | 0.1  | 100 | 0.020 | 0.083  | 0.112  | 0.111   | 0.109    | 0.24  | 1.36   | 1.35    | 1.32     |
|     |      | 500 | 0.485 | 0.595  | 0.595  | 0.596   | 0.596    | 0.82  | 1.00   | 1.00    | 1.00     |
|     |      | 1000| 0.860 | 0.883  | 0.883  | 0.883   | 0.883    | 0.97  | 1.00   | 1.00    | 1.00     |
| 0.2 | 0.1  | 100 | 0.093 | 0.242  | 0.269  | 0.274   | 0.270    | 0.38  | 1.11   | 1.13    | 1.11     |
|     |      | 500 | 0.971 | 0.987  | 0.987  | 0.987   | 0.987    | 0.98  | 1.00   | 1.00    | 1.00     |
|     |      | 1000| 1.000 | 1.000  | 1.000  | 1.000   | 1.000    | 1.00  | 1.00   | 1.00    | 1.00     |
| 0.3 | 0.1  | 100 | 0.225 | 0.414  | 0.425  | 0.428   | 0.426    | 0.54  | 1.03   | 1.03    | 1.03     |
|     |      | 500 | 0.992 | 0.994  | 0.994  | 0.994   | 0.994    | 1.00  | 1.00   | 1.00    | 1.00     |
|     |      | 1000| 1.000 | 1.000  | 1.000  | 1.000   | 1.000    | 1.00  | 1.00   | 1.00    | 1.00     |
| 0.4 | 0.1  | 100 | 0.348 | 0.485  | 0.487  | 0.488   | 0.488    | 0.72  | 1.00   | 1.01    | 1.00     |
|     |      | 500 | 0.993 | 0.994  | 0.994  | 0.994   | 0.994    | 1.00  | 1.00   | 1.00    | 1.00     |
|     |      | 1000| 1.000 | 1.000  | 1.000  | 1.000   | 1.000    | 1.00  | 1.00   | 1.00    | 1.00     |

Note: Relative efficiency is the power relative to maxP.

and small effect sizes. The PS-test and ASQ-test are nearly as powerful as the S-test. In addition, they are considerably more powerful than maxP when effect sizes are small.

Figure 2 shows the changes in the power and type I error when the length of the bands for the PS-test varies. For small n, a larger rejection region greatly increases the power (Figure 1a) but also increases the type I error (Figures 1c and 1d). At small α, only a small increase in the rejection region is necessary to achieve a large increase in power (Figure 1b) without markedly increasing the type I error. While different analyses may necessitate different limits, the simulation results suggested limiting the bands of the PS-test to 50% of the possible extension. A similar conclusion was reached on the squares of the ASQ-test.
Figure 2. Power and type I error for the PS-test across different lengths of the center band under 4 scenarios.

4. Application to SPIROMICS

SPIROMICS is a multi-center study designed to guide future development of therapies for COPD patients [Couper et al. (2014)]. Between November 2011 and January 2015, the study enrolled over 2,900 patients with varying disease severity. Participants underwent a baseline visit that included a variety of measurements, and many different biospecimens were collected and stored. A major goal of the study was to identify biomarkers as intermediate outcomes in order to reliably predict clinical benefits.

A biomarker panel for 114 blood proteins was assayed through multiple Myriad-RBM multiplex technologies. The biomarkers were selected because of known or potential links to COPD pathophysiology [O’Neal et al. (2014); Sun et al. (2016)]. We removed 24 biomarkers with fewer than 500
measurements and excluded the patients without measurements. We replaced any measurement below the detection limit by half of the detection limit and set any measurement above the detection limit to the upper limit. Finally, we applied the inverse-normal transformation to each of the remaining 90 biomarkers.

Genotype data for 2,714 participants were obtained from Illumina OmniExpress plus Exome GeneChip, with a total of 673,688 single nucleotide polymorphisms (SNPs). After removing any SNP with greater than 10% missing values or minor allele frequency less than 1%, we were left with 615,535 autosomal SNPs.

We focused on the phenotype emphysema, which is quantified by the percentage of lung voxels greater than or equal to 950 Hounsfield Units on full inspiratory CT scans. We considered the 1,589 patients with available phenotype, biomarker, and emphysema data. We performed principal component analysis on common SNPs and included the top five principal components as covariates in the models to account for population stratification. We also included age, gender, body mass index, smoking pack years, and current smoking status as covariates.

We conducted mediation analysis for each combination of SNPs and biomarkers, with the biomarker as the mediator. Using each SNP as the independent variable, we assume there is no unmeasured confounding. We tested for indirect effects with the Sobel test, maxP, S-test, PS-test, and ASQ-test. Figure 3 provides the quantile-quantile (QQ) plots for four biomarkers. The results for the S-test and ASQ-test are highly similar to those of the PS-test and thus are omitted. All four QQ-plots for the PS-test are well behaved. The QQ-plots for the Sobel test are highly deflated for three out of the four biomarkers, and one of the QQ-plots for maxP is also highly deflated.

Using an earlier version of the SPRIROMICS data, Sun et al. (2016) found evidence of indirect effect for biomarker C3; however, Figure 3 shows no such evidence. Unlike Sun et al. (2016), the PS-test, maxP, and Sobel test found an indirect effect through AGER; this finding is consistent with the report of Zhang et al. (2018). In addition, the PS-test and maxP found a potential indirect effect in CRP, which is consistent with Aref and Refaat (2014), whereas the Sobel test did not. The PS-test found a potential indirect effect for SFTPD, whereas the Sobel test and maxP did not. This result, which is consistent with the
findings of Obeidat et al. \cite{obeidat2017}, can further the understanding of a biological process associated with COPD.

![Figure 3](image-url)

**Figure 3.** Quantile-quantile plots of the $-\log_{10} p$-values for testing the indirect effects in the SPIROMICS study: the results for the PS-test, maxP, and Sobel test are shown in blue, green, and red, respectively. For AGER and CRP, the results of the PS-test and maxP are indistinguishable. For SFTPD, the results of the Sobel test and maxP are indistinguishable.

5. **Discussion**

Existing methods for detecting indirect effects in mediation analysis are either overly conservative or anti-conservative. We have presented powerful tests that preserve the type I error. Such tests are much needed in the field of genetics, where the effects tend to be small and controlling the type I error is paramount. By making use of the cumulative probabilities from any distribution, our
methods extend the S-test to allow test statistics that are not normally distributed. [Berger (1997)]. In addition, we address the inherent limitations of the S-test.

In many genetics studies, such as SPIROMICS, mediators may not be measured on all study participants because of cost or other constraints. It is possible to construct an appropriate likelihood to accommodate missing values on a mediator [Lin et al. (2020)]. The resulting maximum likelihood estimators of $\beta$ and $\gamma$ are generally no longer independent. We are currently extending our methods to allow dependence of the estimators.

We have focused on the case of a single mediator. In some applications, investigators are interested in multiple mediators [VanderWeele and Vansteelandt (2013)], which may jointly affect the response variable or may affect one another. We are currently extending our framework to such scenarios.

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**APPENDIX: POTENTIAL INFLATION OF THE TYPE I ERROR FOR THE PS-TEST**

Due to the symmetric nature of the rejection region, the potential inflation of the Type I error for the PS-test is the same when $\gamma = 0$ and $\beta \neq 0$ versus when $\beta = 0$ and $\gamma \neq 0$. Thus, we assume that $\gamma = 0$ and $\beta \neq 0$, in which case $U_\gamma$ is standard uniform. The probability that $(U_\beta, U_\gamma)$ lies within the rejection region depends on the value of $\alpha$ (just like the original S-test) and on the value of $U_\beta$ (unlike the original S-test). Let $g(u_\beta)$ denote the probability that $H_0$ is rejected for the chosen $\alpha$ when $U_\beta = u_\beta$, and let $f_{U_\beta}(u_\beta)$ denote the density function of $U_\beta$. The probability of making a type I error at the significance level $\alpha$ equals $\int_0^1 g(x) f_{U_\beta}(x) dx$. We can determine the noncentrality
parameter of $T_\beta$ that causes the largest type I error for any value of $\alpha$ and then determine the maximum inflation of the type I error over all possible values of $\alpha$.

We use numerical integration to calculate the type I error. We consider both small-sample and asymptotic scenarios, using a noncentral $t$-distribution with five degrees of freedom and a normal distribution with mean equal to the noncentrality parameter and unit variance. In the small-sample scenario, the maximum possible type I error rate occurs when $\alpha \approx 0.002$ and is approximately 1.0001 times $\alpha$. In the asymptotic case, the maximum type I error occurs when $\alpha \approx 0.028$ and is approximately 1.0084 times $\alpha$. In each case, the increase in the type I error for the PS-test is less than 1% of $\alpha$, and more common choices of $\alpha$ have even lower inflation of the type I error.

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