Optimal tests of the composite null hypothesis arising in mediation analysis

Caleb H. Miles, Antoine Chambaz *

Abstract

The indirect effect of an exposure on an outcome through an intermediate variable can be identified by a product of regression coefficients under certain causal and regression modeling assumptions. Thus, the null hypothesis of no indirect effect is a composite null hypothesis, as the null holds if either regression coefficient is zero. A consequence is that existing hypothesis tests are either severely underpowered near the origin (i.e., when both coefficients are small with respect to standard errors) or do not preserve type 1 error uniformly over the null hypothesis space. We propose hypothesis tests that (i) preserve level alpha type 1 error, (ii) meaningfully improve power when both true underlying effects are small relative to sample size, and (iii) preserve power when at least one is not. One approach gives a closed-form test that is minimax optimal with respect to local power over the alternative parameter space. Another uses sparse linear programming to produce an approximately optimal test for a Bayes risk criterion. We provide an R package that implements the minimax optimal test.

Keywords: Bayes risk optimality, Causal inference, Composite null hypothesis, Large-scale hypothesis testing, Mediation analysis, Minimax optimality, Non-uniform asymptotics

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1 Introduction

Mediation analysis is a widely popular discipline that seeks to study the mechanism by which an exposure affects an outcome by learning about intermediate events that transmit part or all of this effect. For instance, if one is interested in the effect of an exposure $A$ on an outcome $Y$, one might posit that at least in part, $A$ affects $Y$ by first affecting some intermediate event $M$, which in turn affects $Y$. The effect along such a causal pathway is known as an indirect effect. Mediation analysis has a long history dating back to the 1920s with the path analysis work of Sewall Wright (Wright, 1921), and has been applied across a vast array of fields, including economics, epidemiology, medicine, nursing, psychology, sociology, and many others. In fact, one foundational article (Baron and Kenny, 1986) currently has well over 100,000 citations. In more recent decades, Robins and Greenland (1992) and Pearl (2001) have grounded definitions of mediated effects in the causally-explicit language of counterfactuals, which has lead to an explosion of mediation research in the field of causal inference (see VanderWeele (2015) for an overview). However, despite this long history and broad application, with a recent exception from contemporary work (van Garderen and van Giersbergen, 2020), existing hypothesis tests of a single mediated effect have been either overly conservative and underpowered in a certain region of the alternative hypothesis space, or do not preserve type 1 error uniformly over the null hypothesis space. In this article, we demonstrate the reason for this suboptimal behavior, and develop new hypothesis tests that deliver optimal power in certain decision theoretic senses while uniformly preserving type 1 error.

We focus on the case in which the indirect effect is identified by a product of coefficients or functions of coefficients that can be estimated with uniform joint convergence to a bivariate normal distribution. In fact, our approach is not limited to the realm of mediation
analysis, but can be applied to test for any product of two coefficients that are estimable in the above sense. We also briefly discuss possible extensions to the setting in which one is testing the product of more than two coefficients being equal to zero.

Briefly, the inferential problem that arises in mediation analysis is that when the mediated effect is identified by a product of coefficients, even while the joint distribution of estimators of these coefficients may converge uniformly to a bivariate normal distribution jointly, their product will not. Thus, asymptotic approximation-based univariate test statistics that are a function of the product of the two coefficient estimates will have poor properties in an important region of the parameter space for any given finite sample. Further, another popular test based on testing each coefficient separately is underpowered near the origin of the parameter space (i.e., where both coefficients are zero) by virtue of taking the intersection of the rejection regions of these two tests. This is a consequence of the nonstandard geometry of this nonconvex composite null hypothesis space.

Previously, MacKinnon et al. (2002) and Barfield et al. (2017) presented results from simulation studies comparing hypothesis tests of a mediated effect. Both articles observed that all existing tests were either underpowered in some scenarios or did not preserve nominal type 1 error in all scenarios. Both articles found the so-called joint significance test to be the best overall performing test, while Barfield et al. (2017) found a bootstrap-based test to have comparable performance across some scenarios, with the exception of the setting with a rare binary outcome. Huang (2019) proved that the joint significance test yields a smaller $p$-value than those of both normality-based tests and normal product-based tests. Others have conducted simulation studies comparing standard error estimators of a mediated effect (Stone and Sobel, 1990; MacKinnon and Dwyer, 1993; MacKinnon et al., 1995). These are closely related to, yet distinct from hypothesis testing, which is the focus
of this article.

Barfield et al. (2017) highlighted the problem of large-scale hypothesis testing for mediated effects, which has become a popular inferential problem in genomics, where genomic measures such as gene expression or DNA methylation are hypothesized to be potential mediators of the effect of genes or other exposures on various outcomes. In fact, the conservative behavior of mediation hypothesis tests are most evident in large-scale hypothesis tests, since one can then compare the distribution of \( p \)-values with the uniform distribution. This was demonstrated by Huang (2019), who showed that the joint significance test and delta method-based tests both generated \( p \)-values forming a distribution that dominated that of the uniform distribution. However, we stress that while this behavior is readily observable in large-scale hypothesis tests, the problem is not different for a single hypothesis test; it is merely less obvious.

Recently, Huang (2019) and Dai et al. (2020) developed large-scale hypothesis testing procedures for mediated effects that account for the conservativeness of standard tests. The method proposed by Huang (2019) is based on a distributional assumption about the two coefficients among all distributions being tested that satisfy the null hypothesis. By contrast, the method proposed by Dai et al. (2020) involves estimating the proportions of three different components of the composite null hypothesis: when both coefficients are zero, when one is zero and the other is not, and vice versa. They then relax the threshold of the joint significance test based on these estimated proportions. Our proposed methods resolve the conservativeness issue across the entire null hypothesis space even for a single test, and hence require neither assumptions about the distributions of the coefficients nor estimation of proportions of components of the null hypothesis space. Instead, we can simply extend our method to the large-scale hypothesis test setting while adjusting for
multiple testing using standard Bonferroni or Benjamini–Hochberg corrections. van Garderen and van Giersbergen (2020) is the most closely related work to this article. They take a similar approach to ours, and develop a test for a mediated effect based on defining a rejection region in $\mathbb{R}^2$. They prove that a similar test does not exist within a certain class of tests. In this article, we show that a similar test does in fact exist in a slightly expanded class of tests, and that it is the unique such test in this class. They focus on developing an almost-similar test, i.e., they attempt to get as close to a similar test as possible while preserving type 1 error by optimizing a particular objective function involving a penalty for deviations from the nominal type 1 error level. By contrast, we consider two approaches for optimizing decision theoretic criteria that characterize power while preserving type 1 error. The solution to one of these has a closed form and is an exactly similar test. The other is an approximate Bayes risk optimal test inspired by Rosenblum et al. (2014).

The remainder of the article is organized as follows: In Section 2, we formalize the problem and explain the shortcomings of traditional tests. In Section 3, we present the minimax optimal test. In Section 4, we present the Bayes risk optimal test. In Section 5, we discuss $p$-values corresponding to the former tests and false discovery rate control. In Section 6, we discuss extensions to tests of products of more than two coefficients. In Section 7, we provide results from a simulation study. In Section 8, we conclude with a discussion.
2 Preliminaries

2.1 General setup

We begin with the general problem statement, which we connect to mediation analysis in Section 2.2. Suppose we have \( n \) independent, identically distributed (i.i.d.) observations from a distribution \( P_\psi \) indexed by the parameter \( \psi \), which contains two scalar parameters \( \delta_x \) and \( \delta_y \), and we wish to test the null hypothesis \( H_0 : \delta_x \delta_y = 0 \) against its alternative \( H_1 : \delta_x \delta_y \neq 0 \). Further, suppose we have an asymptotically normal estimator \((\hat{\delta}_x, \hat{\delta}_y)\) of \((\delta_x, \delta_y)\) where the convergence

\[
\sqrt{n} \Sigma_n^{-1/2} \left( (\hat{\delta}_x, \hat{\delta}_y)^\top - (\delta_x, \delta_y)^\top \right) \Rightarrow \mathcal{N} ((0, 0)^\top, I_2)
\]

is uniform in \((\delta_x, \delta_y)\), \( \Sigma_n \) being a consistent estimator of the asymptotic covariance matrix \((I_2 \) is the \( 2 \times 2 \) identity matrix). We wish to test \( H_0 \) against \( H_1 \) with at most \( \alpha \) type 1 error for each possible \((\delta_x, \delta_y)\) satisfying \( \delta_x \delta_y = 0 \) and maximizing power (in some sense) everywhere else. Clearly, \( H_0 \) is a very particular type of composite null hypothesis, which in the \( \mathbb{R}^2 \) space spanned by \( \delta_x \) and \( \delta_y \) consists of the \( x \) and \( y \) axes since \( \delta_x \delta_y = 0 \) whenever \( \delta_x = 0 \) or \( \delta_y = 0 \).

2.2 The composite null hypothesis in mediation analysis

The composite null hypothesis \( H_0 \) arises naturally in mediation analysis under certain modeling assumptions. In order to define the indirect effect of interest, we first introduce notation as well as counterfactuals and nested counterfactuals. First, suppose we observe \( n \) i.i.d. copies of \( O = (C^\top, A, M, Y)^\top \), where \( A \) is the exposure of interest, \( Y \) is the outcome of interest, \( M \) is a potential mediator that is temporally intermediate to \( A \) and \( Y \), and
$C$ is a vector of baseline covariates that we will assume throughout to be sufficient to control for various sorts of confounding needed for the indirect effect to be identified. Let $Y(a, m)$ be the counterfactual outcome that we would have observed (possibly contrary to fact) had $A$ been set to the level $a$ and $M$ been set to the level $m$. Similarly, let $M(a)$ be the counterfactual mediator value we would have observed (possibly contrary to fact) had $A$ been set to $a$. Lastly, define the nested counterfactual $Y\{a', M(a'')\}$ to be the counterfactual outcome we would have observed had $A$ been set to $a'$ and $M$ been set to the counterfactual value it would have taken had $A$ instead been set to $a''$. The natural direct effect (NDE) and natural indirect effect (NIE) on the difference scale are then defined to be

$$\begin{align*}
\text{NDE}(&a', a'') := E[Y\{a', M(a'')\}] - E[Y\{a'', M(a'')\}] \\
\text{NIE}(&a', a'') := E[Y\{a', M(a')\}] - E[Y\{a', M(a'')\}].
\end{align*}$$

These additively decompose the total effect,

$$
\text{TE}(a', a'') := E[Y\{a', M(a')\}] - E[Y\{a'', M(a'')\}] = E[Y(a')] - E[Y(a'')],
$$

where $Y(a)$ is the counterfactual outcome we would have observed (possibly contrary to fact) had $A$ been set to $a$. Our focus will be on the natural indirect effect.

The natural indirect effect is nonparametrically identified under certain causal assumptions, viz., consistency, positivity, and a number of no unobserved confounding assumptions, which we will not review here for the sake of brevity and because our focus is on statistical inference rather than identification. These assumptions are well documented in the causal inference literature; see VanderWeele (2015) for an overview. The identification formula for the natural indirect effect (also known as the mediation formula) is

$$E \left[ E \{E(Y \mid C, A = a', M) \mid C, A = a'\} \right] - E \left[ E \{E(Y \mid C, A = a', M) \mid C, A = a''\} \right].$$

If the linear models with main effect terms given by

\[ E(M \mid A = a, C = c) = \beta_0 + \beta_1 a + \beta_2^T c \]  
\[ E(Y \mid A = a, M = m, C = c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3^T c, \]

are correctly-specified, then the identification formula for the natural indirect effect reduces to \( \beta_1 \theta_2 \). The *product method* estimator estimates \( \beta_1 \) and \( \theta_2 \) by fitting the above regression models and takes the product of these coefficient estimates. In fact, following the path analysis literature of Wright (1921), Baron and Kenny (1986) originally defined the indirect effect to be \( \beta_1 \theta_2 \), where \( C \) is empty in the above model, rather than in terms of counterfactuals, and proposed the product method estimator. This is an extremely popular estimator of indirect effects. VanderWeele and Vansteelandt (2009) demonstrated the consistency of the product method for the natural indirect effect under the above linear models. Under models (2) and (3) and standard regularity conditions, the two factors of the product method estimator will satisfy the uniform joint convergence statement in (1). In fact, (1) will hold for a more general class of models, though there are important limitations to this class. For instance, consider the outcome model with exposure-mediator interaction replacing model (3):

\[ E(Y \mid A = a, M = m, C = c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4^T c. \]

Under models (2) and (4), the natural indirect effect is identified by \( \text{NIE}(a', a'') = (\theta_2 + \theta_3 a') \hat{\beta}_1 (a' - a'') \), hence the estimator \( \hat{(\theta_2 + \theta_3 a')} \hat{\beta}_1 (a' - a'') \), where \( \hat{\theta}_2 \), \( \hat{\theta}_3 \), and \( \hat{\beta}_1 \) are estimated by fitting the linear regression models (2) and (4), will also satisfy (1) under standard regularity conditions, with \( \delta_x = \theta_2 + \theta_3 a' \) and \( \delta_y = \beta_1 (a' - a'') \) and with the corresponding plug-in estimators for \( \hat{\delta}_x \) and \( \hat{\delta}_y \). This is a key extension, as modern causal mediation analysis’ ability to account for the presence of exposure-mediator interactions is one of
its important advantages over traditional mediation methods such as path analysis and the Baron and Kenny (1986) approach. Unfortunately, the functional form of \( E(Y \mid A = a, M = m, C = c) \) and \( E(M \mid A = a, C = c) \) does not yield NIE estimators that factorize to satisfy (1) in general, as the identification formula can result in sums or integrals of products of coefficients. Handling models that yield such identification formulas will be an important direction in which to extend the work done in the present article. Extending the theory in the present article to more general settings than (1) is also especially important because mediated effects through multiple mediators can also be identified by sums of products of coefficients.

2.3 Problems with traditional tests, and how to circumvent them

The problem with some existing tests of the composite null \( H_0 \) against its alternative \( H_1 \) stems from the fact that while \( (\hat{\delta}_x, \hat{\delta}_y) \) converges uniformly in \( (\delta_x, \delta_y) \), the product method estimator \( \hat{\delta}_x \hat{\delta}_y \) does not. This can be seen by examining the delta method approach proposed by Sobel (1982) (often referred to as the Sobel test). Consider the case in which \( \Sigma_n \) in (1) is diagonal with diagonal elements \( s_x^2 \) and \( s_y^2 \). This will be the case under models (2) and (3) or (2) and (4) due to the required no-unobserved-confounding assumptions. When \( (\delta_x, \delta_y) \neq (0,0) \), the delta method yields \( \sqrt{n}(\hat{\delta}_x \hat{\delta}_y - \delta_x \delta_y) \sim N(0, \delta_y^2 \sigma_x^2 + \delta_x^2 \sigma_y^2) \).

Thus, when precisely one of \( \delta_x \) or \( \delta_y \) is zero,

\[
Z_n = \frac{\sqrt{n}(\hat{\delta}_x \hat{\delta}_y - \delta_x \delta_y)}{\sqrt{\hat{\delta}_y^2 s_x^2 + \hat{\delta}_x^2 s_y^2}} \sim N(0, 1),
\]

where \( s_x^2 \) and \( s_y^2 \) are consistent estimates of \( \sigma_x^2 \) and \( \sigma_y^2 \), respectively. However, as \( (\delta_x, \delta_y) \to (0,0) \), the asymptotic variance shrinks to zero so that, at \( (\delta_x, \delta_y) = (0,0) \), the asymptotic distribution is degenerate. Instead of converging at an \( n^{-1/2} \) rate, \( \hat{\delta}_x \hat{\delta}_y \) converges at an \( n^{-1} \)
rate when \((\delta_x, \delta_y) = (0, 0)\). Specifically, \(n \delta_x \delta_y / s_x^2 s_y^2\) converges in law to the product-normal distribution, i.e., the law of \(W_1 W_2\) when \(W_1\) and \(W_2\) are independently drawn from the law \(\mathcal{N}(0, 1)\). Thus, the convergence in distribution of the delta method test statistic \(Z_n\) is not uniform, because for any given sample size, no matter how large, there will be a region in the parameter space around \((0, 0)\) in which the normal approximation is essentially arbitrarily poor. This is especially problematic, as the region around \((0, 0)\) is precisely where we would expect the truth to often lie, unlike many other cases in which convergence is not uniform but approximations are poor on the boundary of the parameter space. As one moves closer to the origin in the parameter space, the asymptotic behavior of \(Z_n\) begins to more closely resemble the \(n^{-1}\)-rate convergence to the product normal distribution. This is demonstrated by a Monte Carlo sampling approximation of density functions in Figure 1, where we fix \(\delta_y = 0\) and vary \(\delta_x\) from 0 to 0.3. The delta method is using an approximation based on an \(n^{-1/2}\) rate of convergence, when in reality, the test statistic is converging faster, and has a more concentrated distribution than the \(N(0, 1)\) law, as we can see in Figure 1. This explains the conservative behavior of the delta method test near the origin.

Hypothesis tests based on inverting bootstrap confidence intervals are also known to perform poorly near the origin of the parameter space. The reason is that bootstrap theory requires continuity in the asymptotic distribution over the parameter space (Barfield et al., 2017). As we have seen, there is a singularity in the asymptotic distribution at the origin, where the convergence rate differs.

In order to avoid the problems that arise due to non-uniform convergence, we will instead focus on constructing a rejection region in the parameter space spanned by the vector \((\delta_x, \delta_y)\) in \(\mathbb{R}^2\), rather than the parameter space spanned by the product \(\delta_x \delta_y\) in \(\mathbb{R}\). In the former, we know convergence is uniform and there are no discontinuities in the
Figure 1: Density plots estimated by Monte Carlo sampling of $Z_n$ under $\delta_y = 0$ and varying $\delta_x$ with $n = 100$

asymptotic distribution over the parameter space.

Another popular test of the composite null $H_0$ against its alternative $H_1$ is known as the joint significance test or intersection-union test (Cohen et al., 2013), which is based on the simple logic that both $\delta_x$ and $\delta_y$ must be nonzero for $\delta_x \delta_y$ to be nonzero. The joint significance test with nominal level $\alpha$ amounts to testing the two null hypotheses $H_0^x : \delta_x = 0$ and $H_0^y : \delta_y = 0$ against their alternatives $H_1^x : \delta_x \neq 0$ and $H_1^y : \delta_y \neq 0$
separately using the Wald statistics $Z_n^x = \sqrt{n}\hat{\delta}_x/s^2_x$ and $Z_n^y = \sqrt{n}\hat{\delta}_y/s^2_y$, and rejecting $H_0$ for $H_1$ only if $H_0^x$ and $H_0^y$ are both rejected for their alternatives by the corresponding Wald tests with nominal level $\alpha$. As we previously noted, this test has been shown to perform better in simulations than other common tests of $H_0$ against $H_1$. However, it still suffers from the lack of power near the origin of the parameter space we see in other tests. This can be easily understood by examining the rejection region in $\mathbb{R}^2$ corresponding to the joint significance test, which is shown in the plot in Figure 2.

Figure 2: The rejection region of the joint significance test is shown in darker gray. The dashed lines indicate the boundaries of the rejection regions of the Wald tests for $H_0^x$ and $H_0^y$. 

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Consider a sequence of local noncentrality parameters with respect to a given direction \((\delta_x, \delta_y)^\top, (\delta_{x,n}, \delta_{y,n})^\top := (\delta_x/\sqrt{n}, \delta_y/\sqrt{n})^\top\), and define

\[
(\delta_x^*, \delta_y^*)^\top := \text{plim}_{n \to \infty} \sqrt{n} \Sigma_n^{-1/2} (\delta_{x,n}, \delta_{y,n})^\top = \Sigma^{-1/2} (\delta_x, \delta_y)^\top
\]

where \text{plim} stands for the limit in probability. When \(\Sigma\) is diagonal as in the mediation case, \((Z_{x,n}^*, Z_{y,n}^*)^\top\) will simply be the pair of Wald statistics \((\sqrt{n} \hat{\delta}_x/s_x^2, \sqrt{n} \hat{\delta}_y/s_y^2)\) for testing \(H_0^x\) and \(H_0^y\) against \(H_1^x\) and \(H_1^y\) separately as discussed above. Further, define the bivariate test statistic \((Z_{x,n}, Z_{y,n})^\top := \sqrt{n} \Sigma_n^{-1/2} (\hat{\delta}_x, \hat{\delta}_y)^\top\) so that \((Z_{x,n}, Z_{y,n})^\top\) is approximately distributed as \(\mathcal{N}((\delta_x^*, \delta_y^*)^\top, I_2)\). Let \((Z_{x,*}^*, Z_{y,*}^*)^\top\) be a random vector following this limiting distribution exactly. Based on this asymptotic approximation, the probability of the Wald test rejecting \(H_0^x\) for \(H_1^x\) at nominal level \(\alpha\) is \(\alpha\) for all \:\{\((\delta_x^*, \delta_y^*) : \delta_x^* = 0\}\}, and likewise the probability of the Wald test rejecting \(H_0^y\) for \(H_1^y\) at nominal level \(\alpha\) is \(\alpha\) for all \:\{\((\delta_x^*, \delta_y^*) : \delta_y^* = 0\}\}. Thus, when \((\delta_x^*, \delta_y^*) = (0, 0)\), the probability of being in the joint significance test rejection region is \(\alpha^2\), well below the desired level \(\alpha\). By the continuity of the rejection probability in \((\delta_x^*, \delta_y^*)\), the rejection probability is likewise well below \(\alpha\) in a region around the origin, hence the underpoweredness of the joint significance test. That is, the worst-case type 2 error of the joint significance test is

\[
\sup_{(\delta_x^*, \delta_y^*): \delta_x^* \delta_y^* \neq 0} \Pr_{\delta_x^*, \delta_y^*}\{(Z_{x,*}^*, Z_{y,*}^*) \notin R\} = 1 - \inf_{(\delta_x^*, \delta_y^*): \delta_x^* \delta_y^* \neq 0} \Pr_{\delta_x^*, \delta_y^*}\{(Z_{x,*}^*, Z_{y,*}^*) \in R\}
\]

\[
= 1 - \min_{(\delta_x^*, \delta_y^*): \delta_x^* \delta_y^* = 0} \Pr_{\delta_x^*, \delta_y^*}\{(Z_{x,*}^*, Z_{y,*}^*) \in R\}
\]

\[
= 1 - \alpha^2.
\]

Our goal in the following two sections is to define a new test by constructing a rejection region that preserves type 1 error uniformly over the null hypothesis space, but improves
power in the alternative hypothesis space, particular in the region around the origin of the parameter space.

3 Minimax optimal test

In this section, we seek a test defined by a rejection region \( R^* \subset \mathbb{R}^2 \) satisfying

\[
\sup_{(\delta_x^*, \delta_y^*): \delta_x^* \delta_y^* = 0} \Pr_{\delta_x^*, \delta_y^*} \{(Z_x^*, Z_y^*) \in R^*\} = \alpha
\]

(5)

and the minimax optimality criterion

\[
\inf_{(\delta_x^*, \delta_y^*): \delta_x^* \delta_y^* \neq 0} \Pr_{\delta_x^*, \delta_y^*} \{(Z_x^*, Z_y^*) \in R^*\} = \sup_{R \subset \mathbb{R}^2} \inf_{(\delta_x^*, \delta_y^*): \delta_x^* \delta_y^* \neq 0} \Pr_{\delta_x^*, \delta_y^*} \{(Z_x^*, Z_y^*) \in R\}.
\]

(6)

In words, the rejection region \( R^* \) characterizes a test with type 1 error \( \alpha \) that achieves the minimax risk of the 0-1 loss function, i.e., that yields the largest worst-case power. By continuity of the power function in \((\delta_x^*, \delta_y^*)\), the minimax optimal power is upper bounded by \( 1 - \alpha \), since the rejection probability can be at most \( \alpha \) at any given value of \((\delta_x^*, \delta_y^*)\) in the null hypothesis space, and can be arbitrarily close to this rejection probability in a small enough neighborhood around that point, which will contain elements of the alternative hypothesis space. Thus, if (6) is attainable, a minimax optimal test must satisfy

\[
\Pr_{\delta_x^*, \delta_y^*} \{(Z_x^*, Z_y^*) \in R\} = \alpha \quad \text{for all } (\delta_x^*, \delta_y^*) \in \mathbb{R}^2 \text{ such that } \delta_x^* \delta_y^* = 0.
\]

(7)

As pointed out by van Garderen and van Giersbergen (2020), a test satisfying (7) is known as a similar test. (Technically this must only hold on the boundary of the null hypothesis space; however, in our case the null hypothesis space is equivalent to its boundary.)

We now define a rejection region that produces a similar test for any unit fraction \( \alpha \), i.e., any \( \alpha \) such that \( \alpha^{-1} \) is a positive integer, and hence a test that satisfies the minimax
optimality criterion (6). Let \( a_k = \Phi^{-1}(k\alpha/2) \) for \( k = 0, \ldots, 2/\alpha \), where \( \Phi \) is the standard normal distribution function. Define \( R_{mm} \) to be the set

\[
\left\{ \bigcup_{k=1}^{2/\alpha} (a_{k-1}, a_k) \times (a_{k-1}, a_k) \right\} \cup \left\{ \bigcup_{k=1}^{2/\alpha} (a_{k-1}, a_k) \times (-a_k, -a_{k-1}) \right\}.
\]

The region \( R_{mm} \) for \( \alpha = 0.05 \) is depicted in the plot in Figure 3, and consists of squares along the \( y = x \) and \( y = -x \) diagonals. Clearly, \( R_{mm} \) contains the rejection region of the joint significance test, and hence yields a test that is uniformly more powerful.

Figure 3: The rejection region \( R_{mm} \) for \( \alpha = 0.05 \) is shown in dark gray, with the squares in the corners continuing out to infinity.
Theorem 1. The test defined by the rejection region $R_{mm}$ is a similar test.

All proofs are presented in the appendix. The essence of the proof of Theorem 1 is that when $\delta^*_y = 0$, at any given value of $Z^*_y$, the probability of $Z^*_y$ being in $R_{mm}$ will be equal to $\alpha$, since the probability of being in each vertical interval is $\alpha/2$ for a standard normal distribution. The same holds for $Z^*_x$ when $\delta^*_x = 0$ by symmetry.

Corollary 1. The rejection region $R_{mm}$ satisfies the minimax optimality criterion (6) with

$$\inf_{(\delta^*_x, \delta^*_y) : \delta^*_x, \delta^*_y \neq 0} \Pr_{\delta^*_x, \delta^*_y} \{ (Z^*_x, Z^*_y) \in R_{mm} \} = \alpha.$$

van Garderen and van Giersbergen (2020) give a result stating that there is no similar test of $H_0$ within a particular class of tests defined by a rejection region generated by rotating and reflecting about various axes a monotonically increasing function from zero to infinity. While Corollary 1 may appear to contradict this result, $R_{mm}$ does not in fact belong to the class considered by van Garderen and van Giersbergen (2020), but rather belongs to a class that relaxes the restriction that the function must be monotonically increasing to allow for it to be monotonically nondecreasing. In fact, the following theorem states that the test generated by $R_{mm}$ is the only similar test in this relaxed class (up to a set of measure zero).

Theorem 2. Let $\mathcal{F}$ be the class of all monotonically nondecreasing functions mapping all $x$ from the nonnegative real numbers to $[0, x]$, and let $R_f$ be the region generated by taking all possible negations and permutations of the region $\{(x, y) : y \in (f(x), x]\}$, or equivalently reflecting this region about the $x$, $y$, $y = x$, and $y = -x$ axes, and rotating it $\pi/2$, $\pi$, and $3\pi/2$ radians about the origin. The function $f_{mm}(x) := \sum_{k=1/\alpha}^{2/\alpha} a_{k-1} I(a_{k-1} \leq x < a_k)$, which generates $R_{mm}$, is the unique function in $\mathcal{F}$ (up to a set of measure zero) that generates a similar test.
In addition to minimax optimality, this test has other desirable properties. It has a simple, exact closed form, making it very straightforward to implement. Additionally, it is nonrandom, and is symmetric with respect to negation and permutations.

We choose the squares \((a_{k-1}, a_k) \times (a_{k-1}, a_k)\) to be open so that the test never rejects when \(Z_n^x\) or \(Z_n^y\) are precisely zero, though it makes no real difference since the boundaries of these squares make up a set of measure zero. However, it is the case that the test will reject for \((Z_n^x, Z_n^y)\) arbitrarily close to \((0, 0)\). This is a peculiar property of \(R_{mm}\); however, from Theorem 2 we infer that at least within the class of tests generated by \(F\), this is necessary in order to attain the best worst-case power. In fact, more generally, we have the following result.

**Theorem 3.** There is no similar test of \(H_0\) with a rejection region that is bounded away from \(\{(Z^*_x, Z^*_y) : Z^*_x Z^*_y = 0\}\).

This property of \(R_{mm}\) is justified because even when \((\delta^*_x, \delta^*_y) = (0, 0)\), the type 1 error based on the asymptotic approximation remains exactly \(\alpha\) despite rejecting when \((Z_n^x, Z_n^y)\) is arbitrarily close to \((0, 0)\). This is in large part due to the fact that the probability of being in the squares in the rejection region surrounding the origin when \((\delta^*_x, \delta^*_y) = (0, 0)\) is quite small at only \(\alpha^2\). This part of the rejection region is important to improve power for smaller alternatives, under which there is similar probability of being in the origin-adjacent squares to that under \((\delta^*_x, \delta^*_y) = (0, 0)\).

The rejection region \(R_{mm}\) is only defined for unit fractions \(\alpha\). For other values of \(\alpha\), the class of tests generated by \(F\) will not contain a similar test, though nonrandom similar tests may exist outside of this class. Tests at other values of \(\alpha\) are typically of interest for two reasons: using multiple testing adjustment procedures and defining \(p\)-values. We discuss the latter in Section 5. The restriction that \(\alpha\) must be a unit fraction is not a
limitation for the Bonferroni correction procedure, which involves dividing the familywise error rate $\alpha$ by the number of tests, provided the familywise error rate $\alpha$ itself is a unit fraction. However, it is a limitation for the Benjamini–Hochberg procedure, which involves multiplying the false discovery rate $\alpha$ by a sequence of rational numbers, only some of which are unit fractions. We discuss the Benjamini–Hochberg procedure in Section 5.

We now define an extension of the minimax optimal test to non-unit fraction values of $\alpha$. For such values of $\alpha$, this extension may not yield a minimax optimal test, and as previously noted, will not yield a similar test as similar tests do not exist in this class of tests for such values. However, they preserve type 1 error, and have type 1 error that approximates $\alpha$ under the least-favorable distribution in the null hypothesis very closely as $\alpha$ goes to zero. Let $b_0 = 0$ and $b_k = \Phi^{-1}\{1 - ([\alpha^{-1}] - k)\alpha/2\}$ for $k = 1, \ldots, [\alpha^{-1}]$. We define the rejection region $\alpha$ for any $\alpha \in (0, 1)$ to be

$$\left\{ \bigcup_{k=1}^{[\alpha^{-1}]} (b_{k-1}, b_k) \times (b_{k-1}, b_k) \right\} \cup \left\{ \bigcup_{k=1}^{[\alpha^{-1}]} (b_{k-1}, b_k) \times (-b_k, -b_{k-1}) \right\} \cup \left\{ \bigcup_{k=1}^{[\alpha^{-1}]} (-b_k, -b_{k-1}) \times (b_k, b_{k-1}) \right\} \cup \left\{ \bigcup_{k=1}^{[\alpha^{-1}]} (-b_k, -b_{k-1}) \times (-b_k, -b_{k-1}) \right\}.
$$

When $\alpha$ is a unit fraction, this reduces to the minimax optimal test. Otherwise, it corresponds closely to the minimax optimal test in that if $\delta_y^* = 0$, given $Z_x^* = z$ where $z \notin [-b_1, b_1]$, the probability of being in the rejection region is exactly $\alpha$. That is, $\Pr_{\delta_y^*=0} \{(Z_x^*, Z_y^*) \in R^* \mid Z_x^*\} = \alpha$ for all values of $Z_x^*$ except for in the four squares adjacent to the origin. As a consequence, type 1 error is minimized at $(\delta_x^*, \delta_y^*) = (0, 0)$, where it will be $|\alpha^{-1}|\alpha^2 + (1 - [\alpha^{-1}]\alpha)^2$. Between any two consecutive unit fractions, say $K^{-1}$ and $(K+1)^{-1}$, the difference between this actual type 1 error and the nominal type 1 error $\alpha$ will be maximized at the midpoint, i.e., $\{K^{-1} + (K+1)^{-1}\}/2$, and will be $4K(K+1)^{-1} = O(K^{-2})$. 18
Thus, the difference between the nominal and actual worst-case type 1 error will be maximized at $\alpha = 3/4$, where the actual worst-case type 1 error will be $5/8$, $1/8$ less than the nominal type 1 error. However, as noted, this maximal difference shrinks at a quadratic rate in $[\alpha^{-1}]$, and will be at most $1/1680 \approx 0.0006$ for all $\alpha < 0.05$.

The results we have given so far have been in terms of the limiting distribution $(Z_x^*, Z_y^*)$. However, if the joint convergence of $(\hat{\delta}_x, \hat{\delta}_y)$ is uniform in $(\delta_x, \delta_y)$ as in (1), then the test statistic $(Z_{nx}^*, Z_{ny}^*)$ will inherit this uniform convergence such that the power function $\beta_n(\delta_n) := \Pr_{\delta_x, \delta_y} \{(Z_{nx}^*, Z_{ny}^*) \in R_{mm}\}$ for the observed data distribution will converge uniformly to $\beta^*(\delta^*) := \Pr_{\delta_x^*, \delta_y^*} \{(Z_{nx}^*, Z_{ny}^*) \in R_{mm}\}$, i.e., that of the limiting distribution. Thus, for any arbitrarily small tolerance $\epsilon > 0$, there is a sample size $N$ such that $\beta_n(\delta_n)$ will be within $\epsilon$ of $\beta^*(\delta^*)$ for all $(\delta_x, \delta_y)$ and $n \geq N$. In particular, this means violations of type 1 error can be made arbitrarily small uniformly over $H_0$ given a sufficiently large sample size.

4 Bayes risk optimal test

We now consider a Bayes risk optimality criterion. We draw inspiration from and modify the testing procedure of Rosenblum et al. (2014), which gives approximately Bayes risk optimal tests of an entirely different causal hypothesis. They are interested in simultaneously testing for treatment effects both in the overall population and in two subpopulations. Their approach is to discretize the test statistic space into a fine grid of cells, then cast the problem as a constrained optimization problem, where the unknown parameters to optimize over are the rejection probabilities in each cell, resulting in a rejection region that optimizes the Bayes risk they define specific to their problem. This approach turns out to
Figure 4: The power function surface for the minimax optimal test over \((\delta^*_x, \delta^*_y)\). The power function takes the value 0.05 everywhere on the \(\delta^*_x\) and \(\delta^*_y\) axes, and is strictly greater than 0.05 everywhere else, while going to one as \(\delta^*_x\) and \(\delta^*_y\) both go to infinity.

be easily adapted to our problem of testing the composite null hypothesis \(H_0\).

Let \(M = M(Z^*_x, Z^*_y, U)\) be the randomized test mapping into \(\{0, 1\}\), where 1 corresponds to reject, 0 corresponds to not reject, and \(U\) is a uniform random variable with support \([0, 1]\). As in Rosenblum et al. (2014), the choice of a randomized test is purely for computational reasons, as it will yield a linear programming problem rather than an integer programming problem, the latter of which is far more computationally burdensome,
especially for our optimization problem, which will be fairly high dimensional. However, our solution will be almost entirely deterministic, with very few cells having non-degenerate rejection probabilities. Let $L \{ M(Z^x, Z^y, U); \delta^*_x, \delta^*_y \}$ denote a bounded loss function, and $\Lambda$ denote the prior distribution on $(\delta^*_x, \delta^*_y)$. The constrained Bayes optimization problem is the following: For given $\alpha > 0$, $L$, and $\Lambda$, find the function $M$ minimizing the Bayes risk

$$\int E_{\delta^*_x, \delta^*_y} [L \{ M(Z^x, Z^y, U); \delta^*_x, \delta^*_y \}] d\Lambda(\delta^*_x, \delta^*_y)$$

subject to the type 1 error constraint $\Pr_{\delta^*_x, \delta^*_y} \{ M(Z^x, Z^y, U) = 1 \} \leq \alpha$ for all $(\delta^*_x, \delta^*_y) \in H_0$.

To formulate an approximation of this problem, we begin by defining the rejection region outside of $B := [-b, b] \times [-b, b]$ to be the same as the joint significance test, where we select $b = 2\Phi(1 - \alpha/2)$. Specifically, define the rejection region outside of this square to be $R_B := \{(Z^x, Z^y) : |Z^x| \geq \Phi(1 - \alpha/2), |Z^y| \geq \Phi(1 - \alpha/2)\} \setminus B$. The reason for this is that outside of $B$, points $(Z^x, Z^y)$ are very likely to be drawn from distributions far enough away from the origin that the joint significance test will only be negligibly conservative. Next, we denote the full null hypothesis space by $G := \{(\delta^*_x, \delta^*_y) : \delta^*_x \delta^*_y = 0\}$ and a corresponding fine grid within the null hypothesis space by $G' := \{(-2b, 0)^T, -(2b(m-1)/m, 0)^T, \ldots, (2b(m-1)/m, 0)^T, (2b, 0)^T, (0, -2b)^T, (0, -2b(m-1)/m)^T, \ldots, (0, 2b(m-1)/m)^T, (0, 2b)^T\}$ for a suitably large integer $m$. This grid extends beyond $B$, because for distributions centered outside of, but near $B$, there will still be a high probability of being in $B$, and we need to control the type 1 error for such distributions. We then define a $(2m+1) \times (2m+1)$ grid on $B$ by $\{(x, y) : x \in \{-b, -b(m-1)/m, \ldots, b(m-1)/m, b\}, y \in \{-b, -b(m-1)/m, \ldots, b(m-1)/m, b\}\}$, and denote the squares induced by this grid $R_{k,k'} := [2b(k-1)/m - b, 2bk/m - b] \times [2b(k'-1)/m - b, 2bk'/m - b]$ for each $k$ and $k'$ in $1, \ldots, m$. Let $\mathcal{R}$ denote the collection of squares $R_{k,k'}$ for all $k$ and $k'$ in $1, \ldots, m$. Within $B$, we then define a class $\mathcal{M}_\mathcal{R}$ of random rejection regions whose realizations are constant within each square. That is, if $(z^x, z^y) \in R_{k,k'}$,
\begin{align*}
M(z^x, z^y, u) = M(z^x', z^y', u) \text{ for all } (z^x', z^y') \in R_{k,k'} \text{ and all } u \in [0, 1]. \text{ Denote the rejection probability corresponding to each square } r \in \mathcal{R} \text{ by } m_r. \text{ These are the unknown arguments defining the rejection region that are to be optimized over.}

\text{Under a random test defined by the rejection probabilities } m_r \text{ on the squares in } \mathcal{R}, \text{ the Bayes risk in (8) becomes}
\begin{align*}
&\int \sum_{r \in \mathcal{R}} E_{\delta^*_x, \delta^*_y} \left[ L \left\{ M(Z^x_{*}, Z^y_{*}, U); \delta^*_x, \delta^*_y \right\} \mid M(Z^x_{*}, Z^y_{*}, U) = 0, \ (Z^x_{*}, Z^y_{*}) \in r \right] \\
&\quad \times \mathbb{P}_{\delta^*_x, \delta^*_y} \left\{ M(Z^x_{*}, Z^y_{*}, U) = 0 \mid (Z^x_{*}, Z^y_{*}) \in r \right\} \mathbb{P}_{\delta^*_x, \delta^*_y} \left\{ (Z^x_{*}, Z^y_{*}) \in r \right\} \, d\Lambda \left( \delta^*_x, \delta^*_y \right) \\
&= \int \sum_{r \in \mathcal{R}} L \left( 0; \delta^*_x, \delta^*_y \right) (1 - m_r) \mathbb{P}_{\delta^*_x, \delta^*_y} \left\{ (Z^x_{*}, Z^y_{*}) \in r \right\} \, d\Lambda \left( \delta^*_x, \delta^*_y \right) \\
&= \sum_{r \in \mathcal{R}} (1 - m_r) \int L \left( 0; \delta^*_x, \delta^*_y \right) \mathbb{P}_{\delta^*_x, \delta^*_y} \left\{ (Z^x_{*}, Z^y_{*}) \in r \right\} \, d\Lambda \left( \delta^*_x, \delta^*_y \right). \tag{9}
\end{align*}
\end{align*}

The first line follows from the fact that the null hypothesis space is a set of measure zero, so the loss only contributes to the Bayes risk when \( M(Z^x_{*}, Z^y_{*}, U) = 0 \) in the alternative hypothesis space. From the above, we observe that the objective function is linear in the unknown variables \( m_r \).

In addition to the discretized approximation of the objective function, we also define a discretized approximation of the type 1 error constraint. For each \((\delta^*_x, \delta^*_y) \in G'\),
\begin{align*}
\alpha \geq \mathbb{P}_{\delta^*_x, \delta^*_y} \left\{ (Z^x_{*}, Z^y_{*}) \in B \right\} + \mathbb{P}_{\delta^*_x, \delta^*_y} \left\{ M(Z^x_{*}, Z^y_{*}, U) = 1 \mid (Z^x_{*}, Z^y_{*}) \in B \right\} \\
= \mathbb{P}_{\delta^*_x, \delta^*_y} \left\{ (Z^x_{*}, Z^y_{*}) \in B \right\} + \sum_{r \in \mathcal{R}} m_r \mathbb{P}_{\delta^*_x, \delta^*_y} \left\{ (Z^x_{*}, Z^y_{*}) \in r \right\}, \tag{10}
\end{align*}
which is also linear in \( m_r \). Lastly, we need the probability constraints \( 0 \leq m_r \leq 1 \) for all \( r \in \mathcal{R} \). These sets of inequalities along with (9) define a linear optimization problem that approximates the Bayes risk optimization problem in \( m_r \), where all other terms are known. This linear optimization problem is high-dimensional, with the dimension of the
unknowns, $|\mathcal{R}|$, being $4m^2$, and the number of constraints being $8m^2 + 8m + 1$ (including both probability constraints). However, these can be reduced by about a factor of 64 by enforcing symmetry in the rejection region, as the number of unknowns can be cut to about an eighth. In any case, this is also a highly sparse optimization problem, which allows for fairly efficient computing, despite the high-dimensionality. Specifically, the type 1 error constraints in (10) consist of only $8m + 1$ inequalities, and the matrix characterizing the remaining probability constraints contains only one nonzero element per row.

We again use the same 0-1 loss function as we did for the minimax optimal test:

$$L\{M(Z^x_s, Z^y_s, U); \delta^*_x, \delta^*_y\} = M(Z^x_s, Z^y_s, U)I(\delta^*_x\delta^*_y = 0) + \{1 - M(Z^x_s, Z^y_s, U)\}I(\delta^*_x\delta^*_y \neq 0),$$

and we use $\mathcal{N}(0, 4)$ for the prior $\Lambda$. The plot in Figure 5 shows the solution to the linear approximation problem with $\alpha = 0.05$ and $m = 65$. The rejection probabilities are nearly all zero or one. If one prefers a nonrandom test, one can obtain a slightly more conservative test by setting all nondegenerate probabilities to zero. Although we did not enforce symmetry in this particular implementation of the optimization problem, the plot is nonetheless almost completely symmetrical. This test almost contains the entire rejection region of the joint significance test, with the small exception of sixteen symmetrically located cells with nonzero rejection probabilities. The rejection region takes an interesting, somewhat unexpected shape, with four roughly-symmetric disconnected regions inside of the acceptance region. As with the minimax optimal test, it seems that it is important to have part of the rejection region along the diagonals at least somewhat close to the origin, so that smaller alternatives in both $\delta^*_x$ and $\delta^*_y$ have larger rejection probabilities to offset the conservativeness induced by lying in the intersection of two acceptance region bands.

While solving the linear programming problem to produce this test takes a nontrivial amount of time to run, this need only be done once, after which the object is stored and can
Figure 5: The rejection probabilities of the approximate Bayes risk optimal test, with the rejection region defined to be the joint significance test outside of the displayed figure, which are outlined by the continuation of the dashed lines. The dashed lines indicate the boundaries of the rejection region of the Wald tests for $H_0^x$ and $H_0^y$.

be quickly loaded on demand. Unlike the minimax optimal test, the approximate Bayes risk optimal test can be solved for any size $\alpha$. However, the linear optimization problem must be solved separately for each value of $\alpha$, and so cannot be obtained immediately, unless it is a value for which the problem has been previously solved and the solution stored.

As with the minimax optimal test, the approximate optimality of the test defined in this section is in terms of the limiting distribution $(Z^*_x, Z^*_y)$. Assuming uniform convergence of
(\hat{\delta}_x, \hat{\delta}_y) as in (1), the (sample) approximations to the (computational) approximate Bayes risk optimality objective function and type 1 error constraints can be made arbitrarily small uniformly over the parameter space given a sufficiently large sample size.

5 \hspace{1cm} p\text{-values}

A common definition of a \( p \)-value for a simple null hypothesis is the probability of observing the same or more extreme value of the test statistic under the null hypothesis. However, this definition will not apply to our setting for a number of reasons. The first is that we have a composite null hypothesis rather than a simple null hypothesis. For a composite null hypothesis, a \( p \)-value may be defined similarly, but for the least-favorable distribution in the null hypothesis space. However, this definition is ambiguous for a vector-valued test statistic. In fact, it is only useful when rejection regions for each \( \alpha \) can be defined as level sets of some function of \( \alpha \), such that “more extreme” than a certain value can be taken to mean the set of values that the test always rejects whenever it rejects that particular value. However, the tests we have defined in this article admit no such representation, as there are some values of the test statistic that will be rejected for one \( \alpha \) level, but will not be rejected for another smaller \( \alpha \) level. For instance, the minimax optimal test for \( \alpha = 1/3 \) will reject \((Z_{\hat{x}}^n, Z_{\hat{y}}^n) = (\Phi^{-1}(4/5), \Phi^{-1}(5/7))\), but the minimax optimal test for \( \alpha = 1/2 \) will not. Defining \( p \)-values for the minimax optimal test is further complicated by the fact that it is only defined for levels of \( \alpha \) that are unit fractions.

Instead, we adopt the more general definition of a \( p \)-value as a random variable that stochastically dominates the uniform distribution with support \([0, 1]\) for all distributions in the null hypothesis space. We can define the \( p \)-value corresponding to the minimax optimal
test to be $\hat{\rho} := \int_0^1 I\{(Z_{x}^*, Z_{y}^*) \notin R_{\alpha}\}d\alpha$, where $R_{\alpha}$ is the rejection region for a level $\alpha$ test. Of course, this requires the test to be defined for all levels $\alpha$ in the unit interval, and not just unit fractions. To this end, we use the extension of the minimax optimal test to non-unit fraction values of $\alpha$ described in Section 3. We conjecture that this will result in a valid $p$-value in the sense that it will dominate the uniform[0,1] distribution uniformly over the null hypothesis space. The plot in Figure 6 shows the empirical cumulative distribution function of a Monte Carlo sample of this $p$-value under the least-favorable distribution where $(\delta_x^*, \delta_y^*)^T = (0, 0)^T$. We can see that this cumulative distribution function does indeed dominate that of the uniform[0,1] distribution, and yet it is dominated by that of the $p$-value corresponding to the joint-significance test. Having defined a $p$-value corresponding to the extended minimax optimal test, one may use these $p$-values to perform the Benjamini–Hochberg correction to many such independent tests in order to control the false discovery rate.

Since the extended minimax optimal test is conservative for non-unit fraction values of $\alpha$, the $p$-value will also be conservative. Thus, if one is interested in testing at a particular level of $\alpha$, one should reject based on the test defined by the rejection region $R_{\alpha}$ rather than comparing the $p$-value to $\alpha$, as these may not agree and the hypothesis test will be more powerful. Similarly, the actual false discovery rate will be more conservative when applying the Benjamini–Hochberg procedure. Sharpening the test for non-unit fraction $\alpha$ and hence for the corresponding $p$-value is an important topic for future research.

In principle, a $p$-value corresponding to the Bayes risk optimal test can be defined similarly. However, this definition requires the test to be defined on a continuum of $\alpha$, or at least a fine discretization of the unit interval. Given the computationally-intensive nature of solving for the rejection region of the Bayes risk optimal test, this may be overly
Figure 6: Empirical cumulative distribution function plots of the $p$-values corresponding to the extended minimax optimal test and joint significance test based on 10,000 Monte Carlo samples from the bivariate normal distribution with $(\delta^*_x, \delta^*_y)^T = (0, 0)^T$. The cumulative distribution function of the uniform[0,1] distribution is shown in black.

burdensome to implement in practice, especially if close approximations are needed for small $p$-values if correcting for multiple testing.
6 Tests of products of more than two coefficients

We now consider the more general hypothesis testing setting of $H_0^\ell : \prod_{j=1}^{\ell} \delta_j = 0$ when there exists an asymptotically normal estimator $\hat{\delta} := (\hat{\delta}_1, \ldots, \hat{\delta}_\ell)^T$ of $\delta := (\delta_1, \ldots, \delta_\ell)^T$ such that the convergence $\sqrt{n}\Sigma_n^{-1/2}(\hat{\delta} - \delta) \rightsquigarrow \mathcal{N}(0_\ell, I_\ell)$ is uniform in $\delta$, where $\Sigma_n$ is again a consistent estimator of the asymptotic covariance matrix, $0_\ell$ is the $\ell$-vector of zeros, and $I_\ell$ is the $\ell \times \ell$ identity matrix. This setting arises in traditional linear structural equation modeling when one is interested in testing the effect of an exposure along a chain of multiple intermediate variables. Unfortunately, such effects are seldom identifiable in the causal mediation framework. However, this setting can arise in applications beyond mediation analysis. For instance, given multiple candidate instrumental variables, Kang et al. (2020) characterize the null hypothesis of no treatment effect and one valid instrument that is uncorrelated with the other candidates to be the product of multiple coefficients equaling zero.

The over-conservativeness and underpoweredness problems faced by the traditional tests of products of coefficients are in fact exacerbated in higher dimensions. For instance, the generalization of the joint significance test to $\ell$ that rejects when the Wald tests corresponding to $H_{1,0}, H_{2,0}, \ldots, H_{\ell,0}$ all reject, where $H_{i,0} : \delta_i = 0$ for all $i = 1, \ldots, \ell$. Thus, when $\delta^* = 0_\ell$, the rejection probability of the joint significance test will be $\alpha^\ell$. For $\alpha = 0.05$ and $\ell = 3$, for example, this will be 0.000125.

The minimax optimal test does not have an obvious unique natural extension to the setting with more than two coefficients. Nevertheless, for unit fraction values of $\alpha$, we can prove the existence of deterministic similar tests that are symmetric with respect to negations. For $\ell = 3$, these tests can be constructed using Latin squares of order $\alpha^{-1}$. If the Latin square is totally symmetric, then the test will also be symmetric with respect to
permutations. We only provide the result for \( \ell = 3 \); however, we conjecture that these can be readily generalized to higher dimensions using Latin hypercubes, provided they exist for the choice of \( \ell \) and \( \alpha \).

Given a Latin square of order \( \alpha^{-1} \), \( A \), let \( 1, \ldots, \alpha^{-1} \) be the set of symbols populating \( A \), and let \( A_{i,j} \) denote the symbol in the \( i \)-th row and \( j \)-th column of \( A \). Define \( c_k := \Phi^{-1}\{ (1 + k\alpha)/2 \} \) for all \( k = 0, \ldots, \alpha^{-1} \). We define the rejection region \( R^\dagger \in \mathbb{R}^3 \) corresponding to \( A \) to be the following union of open hyperrectangles in the nonnegative orthant of \( \mathbb{R}^3 \):

\[
\bigcup_{i=1}^{\alpha^{-1}} \bigcup_{j=1}^{\alpha^{-1}} (c_{i-1}, c_i) \times (c_{j-1}, c_j) \times (c_{A_{i,j}-1}, c_{A_{i,j}}).
\]

The test corresponding to \( R^\dagger \) rejects if \( (|Z_1^\dagger|, |Z_2^\dagger|, |Z_3^\dagger|)^T \in R^\dagger \).

**Theorem 4.** For a given Latin square of order \( \alpha^{-1} \), \( A \), the corresponding test defined by the rejection region \( R^\dagger \) is a similar test of \( H_{0,3}^\dagger \) that is symmetric with respect to negations. If \( A \) is totally symmetric, then the test is also symmetric with respect to permutations.

For the test to also be consistent, \( A \) must satisfy \( A_{\alpha^{-1}, \alpha^{-1}} = \alpha^{-1} \). This is because under the alternative hypothesis, \( \hat{\delta} \to (\infty, \infty, \infty)^T \) as \( n \to \infty \), and hence the power will only converge to one if the hyperrectangle \( (\Phi^{-1}(1 - \alpha/2), \infty) \times (\Phi^{-1}(1 - \alpha/2), \infty) \times (\Phi^{-1}(1 - \alpha/2), \infty) \) belongs to the rejection region. For any given \( A \), there exists at least one isotopism satisfying this property, i.e., one can permute the rows, columns, and symbols of \( A \) to produce another Latin square with this property. The arrangement of the other items in the Latin square are relatively less important, and likely result in varying amounts of power in different parts of the parameter space. It is not clear whether one Latin square uniformly dominates all others in terms of power.

The Bayes risk optimal test can in theory also be extended to tests of products of \( \ell \) coefficients. The grid in \( \mathbb{R}^2 \) needs to be expanded to \( \mathbb{R}^\ell \), and the grid on the null hypothesis
space must be expanded to each of the $\mathbb{R}^{\ell-1}$ hyperplanes composing the new composite null hypothesis space. Further, the prior on the coefficients must be expanded to an $\ell$-dimensional distribution. However, the computational burden will clearly escalate rapidly with $\ell$, and may not be feasible even for dimensions of four or possibly even three without access to tremendous computing power.

7 Simulation study

To compare the finite sample performances of the minimax optimal, approximate Bayes risk optimal (which we will henceforth refer to as Bayes risk optimal for brevity), and joint significance tests, we performed a simulation study in which we sampled from a bivariate normal distribution with identity covariance matrix and noncentrality parameter $(\delta_x, \delta_y)^T$, where we varied $\delta = \delta_x = \delta_y$ from 0 to 0.4. We drew 100,000 Monte Carlo samples of sample size 50 for each value of $\delta$, and applied the minimax optimal, Bayes risk optimal, and joint significance tests of $H_0 : \delta_x \delta_y = 0$ to each sample. The Monte Carlo power estimates are displayed in the plot in Figure 7. Both the minimax optimal and Bayes risk optimal tests have very close to nominal type 1 error at $\delta = 0$, and greatly outperform the joint significance test in terms of power for smaller values of $\delta$. All three tests begin to converge in power closer to 0.4. The minimax optimal and Bayes risk optimal tests perform nearly identically, with the former having a very slight advantage (at most about 0.008) for values of $\delta$ greater than about 0.25, and the latter having an even slighter advantage (at most 0.002) for most smaller values of $\delta$. Impressively, despite not being a similar test, the Bayes risk optimal test suffers very little in terms of power near the least favorable distribution at $\delta = 0$. 

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Figure 7: Monte Carlo rejection probabilities of the minimax optimal (MMO), Bayes risk optimal (BRO), and joint significance (JS) tests with $\delta$ varying from 0 to 0.4. The nominal $\alpha$ level 0.05 is indicated by the dashed horizontal line.

8 Discussion

We have proposed two new classes of tests for the composite null hypothesis $H_0 : \delta_x \delta_y = 0$ that arises commonly in the context of mediation analysis. This is a challenging inferential task due to the non-uniform asymptotics of estimators and univariate test statistics of the product of coefficients, as well as the nonstandard structure of the parameter space under $H_0$. We have constructed these tests to be both optimal in a decision theoretical sense, and
to preserve type 1 error uniformly over the null hypothesis space – exactly so on both counts in the case of the minimax optimal test, and approximately so in the case of the Bayes risk optimal test. We have described procedures for carrying out large scale hypothesis testing of many product of coefficient hypotheses, controlling for familywise error rate in both cases, and for false discovery rate in the case of the minimax optimal test. We have also defined a generalized $p$-value corresponding to the extended minimax optimal test. Lastly, we have provided an R package to implement the minimax optimal test.

A natural question is which of the proposed tests should be used in practice. There are a few trade-offs between these two tests. As seen in the simulation study, the Bayes risk optimal test offers very slight improvements in power for moderate effect sizes relative to standard error that are greater than the even slighter improvements in power offered by the minimax optimal test for smaller effect sizes. The minimax optimal test has the advantage of having a closed form as well as preserving type 1 error exactly in the limit. The minimax optimal test also can be generated almost instantaneously for all unit fraction values of $\alpha$, and the generalized test can be generated for other values of $\alpha$, whereas for the Bayes risk optimal test, the optimization step to generate the rejection region must be performed each time a test for a new value of $\alpha$ is desired. That said, once the latter test is generated once for a value of $\alpha$, it can be stored and used again without having to ever rerun the optimization. For non-unit fraction values of $\alpha$, the Bayes risk optimal test will likely be better powered than the extended minimax optimal test, especially for values of $\alpha$ furthest away from a unit fraction. On the other hand, $p$-values are readily obtained for the minimax optimal test, whereas it is not yet clear how computationally feasible it will be to compute a $p$-value corresponding to the Bayes risk optimal test as defined in Section 5. Lastly, the minimax optimal test is a strictly deterministic test, whereas the
Bayes risk optimal test contains some (though very few) cells in the rejection region that reject with non-degenerate probability. If a non-random test is desired, the latter can be converted to a slightly more conservative non-random test by changing all non-degenerate rejection probabilities to zero. Overall, we believe the strengths of the minimax optimal test outweigh those of the Bayes risk optimal test, and therefore we recommend the former for practical use. However, the comparison is subjective, and we also believe the Bayes risk optimal test is a perfectly acceptable alternative to apply in practice as well.

There are a number of future research directions that stem from this work. There are many other inferential problems that face similar issues with non-uniform convergence. Examples commonly arise in partial identification bounds, where there are often minima and maxima of estimates involved, which exhibit similar asymptotic behavior. The approaches proposed in this article can likely be adapted to such settings. Not all mediated effect hypotheses take the form of a single product of coefficients, but rather take the form of sums or integrals of products of coefficients. This considerably more complex setting will be important to address to allow for less restrictive models when performing inference on mediated effects. Yet another important direction for future research is to extend to null hypotheses of the products of coefficients being equal to a nonzero scalar, which will allow for the inversion of the hypothesis test to produce confidence intervals with improved finite-sample performance. We plan to further consider the properties of our $p$-value definition in Section 5, and explore its application to other settings where the more traditional $p$-value definition does not apply. Lastly, we also plan to further develop the tests for products of more than two coefficients discussed in Section 6.
**Software**

An R package implementing the minimax optimal test is available at https://github.com/achambaz/mediation.test.

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35
A Proofs

Proof of Theorem 1. When $\delta^*_y = 0$, for any $\delta^*_x$,

\[
\Pr_{\delta^*_x, \delta^*_y} \{(Z^x_*, Z^y_*) \in R^* \} = E_{\delta^*_x} \left[ \Pr_{\delta^*_y} \{ (Z^x_*, Z^y_*) \in R^* \mid Z^x_* \} \right] \\
= E_{\delta^*_x} \left[ \sum_{k=1}^{2/\alpha} I \{ Z^x_* \in (a_{k-1}, a_k) \} \Pr_{\delta^*_y} \{ Z^y_* \in (a_{k-1}, a_k) \cup (-a_{k-1}, -a_k) \mid Z^x_* \} \right] \\
= \alpha E_{\delta^*_x} \left[ \sum_{k=1}^{2/\alpha} I \{ Z^x_* \in (a_{k-1}, a_k) \} \right] \\
= \alpha.
\]

The same holds for any $\delta^*_y$ when $\delta^*_x = 0$ by symmetry. Thus, $\Pr_{\delta^*_x, \delta^*_y} \{(Z^x_*, Z^y_*) \in R_{mm} \} = \alpha$ for all $(\delta^*_x, \delta^*_y) \in \{ (\delta^*_x, \delta^*_y) : \delta^*_x \delta^*_y = 0 \}$, which is equal to the boundary of the null hypothesis space. $\square$
Proof of Theorem 2. For $\delta_y^* = 0$, we wish to find an $R$ such that for all $\delta_x^*$, we will have

$$\alpha = \Pr(\delta_x^*; 0)\{(Z_x^*, Z_y^*) \in R^*\} = E_{\delta_x^*} \left[ \Pr_{\delta_y^* = 0} \{(Z_x^*, Z_y^*) \in R^* \mid Z_x^*\} \right],$$

which implies that $E_{\delta_x^*} \left[ \Pr_{\delta_y^* = 0} \{(Z_x^*, Z_y^*) \in R^* \mid Z_x^*\} \right] - \alpha = 0$ for all $\delta_x^*$. Since $Z_x^* \sim \mathcal{N}(\delta_x^*, 1)$, which is a full-rank exponential family, $Z_x^*$ is a complete statistic, and

$$\Pr_{\delta_y^* = 0} \{(Z_x^*, Z_y^*) \in R^* \mid Z_x^*\} = \alpha \text{ almost everywhere.} \quad (11)$$

**Lemma 1.** Suppose for any $k \in \{0, 1, \ldots, 1/\alpha - 1\}$, $f(x) \geq \Phi^{-1}(\frac{1+k\alpha}{2})$ for all $x > \Phi^{-1}(\frac{1+k\alpha}{2})$. Then (i) $f(x) = \Phi^{-1}(\frac{1+k\alpha}{2})$ for all $x \in (\Phi^{-1}(\frac{1+k\alpha}{2}), \Phi^{-1}(\frac{1+(k+1)\alpha}{2}))$, and (ii) $f(x) \geq \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$ for all $x > \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$.

**Proof of Lemma 1.** (i) Suppose $f(x_0) = y_0 > \Phi^{-1}(\frac{1+k\alpha}{2})$ for some

$$x_0 \in \left( \Phi^{-1}\left(\frac{1+k\alpha}{2}\right), \Phi^{-1}\left(\frac{1+(k+1)\alpha}{2}\right) \right),$$

and let $f^{-1}$ be the generalized function inverse $f^{-1}(y) := \inf\{x : f(x) \geq y\}$. Then $\Phi^{-1}(\frac{1+(k+1)\alpha}{2}) > x_0 \geq \inf\{x : f(x) \geq y_0\} = f^{-1}(y_0)$ by the nondecreasing monotonicity of $f^{-1}$. For all $x' \in [\Phi^{-1}(\frac{1+k\alpha}{2}), y_0]$,

$$\Pr_{\delta_y^* = 0} \{(Z_x^*, Z_y^*) \in R^* \mid Z_x^* = x'\} = 2 \left[ \Phi \left\{ f^{-1}(x') \right\} - \Phi \left\{ f(x') \right\} \right] \leq 2 \left[ \Phi \left\{ f^{-1}(y_0) \right\} - \Phi \left\{ \Phi^{-1}\left(\frac{1+k\alpha}{2}\right) \right\} \right] < 2 \left( \Phi \left\{ \Phi^{-1}\left(\frac{1+(k+1)\alpha}{2}\right) \right\} - \frac{1+k\alpha}{2} \right) = 2 \left( \frac{1+(k+1)\alpha}{2} - \frac{1+k\alpha}{2} \right) = \alpha.$$
Since $[\Phi^{-1}(\frac{1+k\alpha}{2}), y_0]$ is a set of positive measure if $y_0 > \Phi^{-1}(\frac{1+k\alpha}{2})$, this contradicts (11).

Thus, $f(x) = \Phi^{-1}(\frac{1+k\alpha}{2})$ for all $x \in (\Phi^{-1}(\frac{1+k\alpha}{2}), \Phi^{-1}(\frac{1+(k+1)\alpha}{2}))$.

(ii) By (11), for almost every $x \in (\Phi^{-1}(\frac{1+k\alpha}{2}), \Phi^{-1}(\frac{1+(k+1)\alpha}{2}))$,
\[
\alpha = \Pr_{\delta_y = 0} \{(Z^x_*, Z^y_*) \in R^* \mid Z^x_* = x\}
\]
\[
= 2 \left[ \Phi \left\{ f^{-1}(x) \right\} - \Phi \left\{ f(x) \right\} \right]
\]
\[
= 2 \left[ \Phi \left\{ f^{-1}(x) \right\} - \frac{1 + k\alpha}{2} \right],
\]

hence $f^{-1}(x) = \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$ almost everywhere in $(\Phi^{-1}(\frac{1+k\alpha}{2}), \Phi^{-1}(\frac{1+(k+1)\alpha}{2}))$. By nondecreasing monotonicity of $f^{-1}$, $f^{-1}(x) = \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$ for all $x \in (\Phi^{-1}(\frac{1+k\alpha}{2}), \Phi^{-1}(\frac{1+(k+1)\alpha}{2}))$.

Now suppose $x_1 > \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$ and $f(x_1) < \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$. Then for $x'' \in (f(x_1), \Phi^{-1}(\frac{1+(k+1)\alpha}{2}))$, $f^{-1}(x'') > 1 > \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$, which contradicts $f^{-1}(x'') = \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$ since $x'' \in (\Phi^{-1}(\frac{1+k\alpha}{2}), \Phi^{-1}(\frac{1+(k+1)\alpha}{2}))$. Thus, $f(x) > \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$ for all $x > \Phi^{-1}(\frac{1+(k+1)\alpha}{2})$.

By the constraints on $\mathcal{F}$, $f(x) \geq 0 = \Phi^{-1}(1/2)$ for all $x > 0 = \Phi^{-1}(1/2)$. Applying Lemma 1, for each $k \in \{0, 1, \ldots, 2/\alpha - 1\}$, we have $f(x) = \Phi^{-1}(\frac{1+k\alpha}{2})$ for all $x \in (\Phi^{-1}(\frac{1+k\alpha}{2}), \Phi^{-1}(\frac{1+(k+1)\alpha}{2}))$ by induction. That is, $f(x) = a_{k-1}$ for all $x \in (a_{k-1}, a_k)$. Additionally, $f(0) = 0$ must hold. The only set of points on which we have not defined $f$ is
\[
\{a_{1/\alpha + 1}, a_{1/\alpha + 2}, \ldots, a_{2/\alpha}\} = \left\{\Phi^{-1}\left(\frac{1+\alpha}{2}\right), \Phi^{-1}\left(\frac{1+2\alpha}{2}\right), \ldots, \Phi^{-1}(1)\right\},
\]
which is a set of measure zero. Thus, any function $f$ satisfying (11) and hence generating a similar test must be equal to $f_{mm}$ everywhere except for the above set of measure zero.

**Proof of Theorem 3.** Suppose $R^t \in \mathbb{R}^2$ is a rejection region bounded away from $\{(Z^x_*, Z^y_*) : Z^x_* Z^y_* = 0\}$. Then there is some $\varepsilon > 0$ for which $R^t \cap \{(Z^x_*, Z^y_*)^T : -\varepsilon < Z^x_* < \varepsilon\} = \emptyset$. For
all $Z^*_x \in (-\varepsilon, \varepsilon)$, a set of positive measure, $\Pr \{(Z^*_x, Z^*_y)^T \in R^\dagger \mid Z^*_x\} = 0$, hence (11) does not hold for $R^\dagger$. Thus, $\Pr \{(Z^*_x, Z^*_y)^T \in R^\dagger\} = 0.05$ cannot hold for all $(\delta^*_x, \delta^*_y)$ in $H_0$, and $R^\dagger$ does not generate a similar test.

Proof of Theorem 4. Let $|Z_x| := (|Z^*_1|, |Z^*_2|, |Z^*_3|)^T$. When $\delta^*_3 = 0$, for any $\delta^*_1$ and $\delta^*_2$,

$$\Pr_{\delta^*_1, \delta^*_2}\{|Z_x| \in R^\dagger\} = \alpha \sum_{i=1}^{\alpha-1} \sum_{j=1}^{\alpha-1} I \{(|Z^*_1|, |Z^*_2|) \in (c_{i-1}, c_i) \times (c_{j-1}, c_j)\} \Pr_{\delta^*_3}\{|Z^*_3| \in (c_{A_{i,j-1}}, c_{A_{i,j}}) \mid Z^*_1, Z^*_2\}$$

$$= \alpha \sum_{i=1}^{\alpha-1} \sum_{j=1}^{\alpha-1} I \{(|Z^*_1|, |Z^*_2|) \in (c_{i-1}, c_i) \times (c_{j-1}, c_j)\}$$

$$= \alpha.$$

We may alternatively represent $A$ in its orthogonal array representation, which is an array with rows corresponding to each entry of $A$ consisting of the triple (row, column, symbol). Any permutation of the coordinates of these triples yields an orthogonal array corresponding to another Latin square known as a conjugate. Let $A_{132}$ be the conjugate of $A$ generated by exchanging the second and third columns of the orthogonal array representation of $A$. $R^\dagger$ can alternatively be expressed as

$$\bigcup_{i=1}^{\alpha-1} \bigcup_{k=1}^{\alpha-1} (c_{i-1}, c_i) \times (c_{A_{i,k-1}}, c_{A_{i,k}}) \times (c_{k-1}, c_k).$$
When $\delta^*_2 = 0$, for any $\delta^*_1$ and $\delta^*_3$, we have the analogous result:

$$Pr_{\delta^*}\{|Z_*| \in R^\dagger\} = E_{\delta^*_1, \delta^*_3} [Pr_{\delta^*_2}\{|Z_*| \in R^\dagger \mid Z^1_*, Z^3_*\}]$$

$$= E_{\delta^*_1, \delta^*_3} \left[ \frac{2}{\alpha} \sum_{i=1}^{2/\alpha} \sum_{k=1}^{2/\alpha} I \{(|Z^1_*|, |Z^3_*|) \in (c_{i-1}, c_i) \times (c_{k-1}, c_k)\} Pr_{\delta^*_2}\{|Z^2_*| \in (c_{A^1_{i,k}-1}, c_{A^1_{i,k}}) \mid Z^1_*, Z^3_*\}\right]$$

$$= \alpha E_{\delta^*_1, \delta^*_3} \left[ \sum_{i=1}^{2/\alpha} \sum_{k=1}^{2/\alpha} I \{(|Z^1_*|, |Z^3_*|) \in (c_{i-1}, c_i) \times (c_{k-1}, c_k)\}\right]$$

$$= \alpha.$$

The same holds for any $\delta^*_2$ and $\delta^*_3$ when $\delta^*_1 = 0$ by symmetry. Thus, $Pr_{\delta^*}\{|Z_*| \in R^\dagger\} = \alpha$ for all $(\delta^*_1, \delta^*_2, \delta^*_3) \in \{(\delta^*_1, \delta^*_2, \delta^*_3) : \delta^*_1\delta^*_2\delta^*_3 = 0\}$, which is equal to the boundary of the null hypothesis space, so $R^\dagger$ generates a similar test.

Clearly, the test is symmetric with respect to negations by construction. A Latin square is totally symmetric if it is equal to all of its conjugates. Thus, if $A$ is totally symmetric, then $R^\dagger = R^\sigma$ for all permutations $\sigma$ of (1,2,3), and the test corresponding to a totally symmetric Latin square is also symmetric with respect to permutations.