Detecting weak signals by combining small P-values in observational studies with multiple testing

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ABSTRACT

Human health is affected by multiple risk factors. Studies may focus on a hypothesis that a particular exposure is a risk factor for disease, but complex outcomes are typically influenced by many genetic and environmental factors. These factors tend to be weak and difficult to detect individually, and methods capitalizing on the combined effect of many weak signals have proven to be more effective for studying genetics of complex health conditions. Based on ideas from meta-analysis, statistical methods have been developed for combining top-ranking associations. For example, Truncated Product Method (TPM)[1] and Rank Truncated Product (RTP)[2] have gained popularity in applications for linking combined contribution of multiple risk factors to disease. Both methods aggregate only top ranking signals, while adjusting for the total number of predictors to assure Type-I error protection. Unlike TPM, the RTP distribution is comparatively unwieldy, which obscures its probabilistic interpretation and makes it difficult to implement. In this article, we develop new ways of evaluating the distribution of RTP and related statistics that not only are mathematically simple, but further lead to powerful extensions for combining top-ranking and correlated weak associations.

Keywords: combining evidence, RTP, mRTP, adaptive RTP
For certain diseases, individuals at risk can be readily identified with the measurement of a few major risk factors that can be used to guide interventions. For example, parental diabetes, obesity, and metabolic syndrome traits are known predictors for type 2 diabetes mellitus (T2DM) and suggest elevated risk. However, unlike Mendelian disorders, complex diseases, such as T2DM, are influenced by multiple risk factors and the accuracy of detecting individuals at risk can be improved by combining multiple weak predictors. The main challenge in discovering these predictors by statistical analysis is their low detection power, so the overall effect of many individually weak signals is typically assessed instead, by combining statistical summaries of associations like P-values. In epidemiological research, methods for combining P-values are commonly associated with meta-analyses that combine results of multiple experiments studying the same hypothesis. The combined P-value then aggregates signals across all $L$ studies, providing a higher level of assurance that the studied risk factor is associated with a disease. Furthermore, if samples in those studies are taken from populations that are similar with respect to the effect size magnitude, the combined meta-analytic P-value will well approximate the one that would have been obtained by pooling together all raw data and performing a single test. Another application of combined P-values is when the $L$ hypotheses are distinct, and the interest is in assessing an overall hypothesis that there is at least one real signal among the $L$ individual hypotheses. For such situations, methods for combining P-values ($P_i, i = 1, \ldots, L$) are often based on the sum of $P_i$'s transformed by some function $H$. For example, Fisher test is based on the log-transformed P-values, $H(P_i) = -2 \ln(P_i)$, which are then added up to form a test statistics $T = \sum_{i=1}^{L} H(P_i) \sim \chi^2_{(L)}$, where $\chi^2_{(L)}$ is a chi-square distribution with $L$ degrees of freedom.

When a portion of $L$ distinct associations is expected to be spurious, it is advantageous to combine only some of the predictors using a truncated variation of combined P-value methods. For instance, Zaykin et al. proposed the Truncated Product Method (TMP) as a variation of the Fisher test, trimmed by the indicator function, $I(P_i \leq \alpha)$, that is equal to zero if $P_i > \alpha$, and one if $P_i \leq \alpha$; $0 < \alpha \leq 1$ is a truncation threshold. The combined
P-value, $P_{TPM}$, for the TPM is then given by the cumulative distribution function (CDF) of $W = \sum_{i=1}^{L} \ln(P_i)I(P_i \leq \alpha)$:

$$P_{TPM} = \Pr \left\{ \prod_{i=1}^{L} P_i^{I(P_i \leq \alpha)} \leq w \right\}$$

$$= 1 - \Pr \left\{ \sum_{i=1}^{L} \ln(P_i)I(P_i \leq \alpha) > \ln(w) \right\}$$

$$= \sum_{i=1}^{L} \left( \begin{array}{c} L \\ i \end{array} \right) (1 - \alpha)^{L-i}$$

$$\times \left( w \sum_{s=0}^{i-1} \frac{(i \ln \alpha - \ln w)^s}{s!} I(w \leq \alpha^i) + \alpha^i I(w > \alpha^i) \right).$$

(1)

With the TPM approach, the threshold $\alpha$ is fixed while the number of P-values that form the sum $W$ is random.

Another popular truncated version of a combined P-value method is the Rank Truncated Product (RTP) by Dudbridge and Koleman. Unlike TPM, with RTP the number of P-values to be combined, $k$, is fixed. The resulting combined P-value can be found from the cumulative distribution of the product:

$$P_{RTP} = \Pr \left\{ \prod_{i=1}^{k} P_{(i)} \leq w \right\}$$

$$= 1 - \Pr \left\{ \sum_{i=1}^{k} \ln [P_{(i)}] > \ln [w] \right\},$$

(2)

where $P_{(i)}$ is the $i$th smallest P-value, $i = 1, \ldots, k$. RTP leads to an appealing extension, where $k$ can be chosen adaptively to maximize statistical power. Generally, adaptive rank truncated product (aRTP) variations optimize selection of the truncation point $k$ among all (or a subset) of possible values $1 \leq k \leq L$. Adaptive extensions for TPM are not as straightforward, because the threshold $\alpha$ is a continuous variable, but one can resort to evaluating the distribution over a set of grid points. In adaptive extensions, the final test statistic is the minimum P-value observed at various candidate truncation points. The
number of points creates a set of correlated combined P-values. The distribution of their
minimum is complicated,[9] but some resampling methods have been proposed. Furthermore,
resampling methods can also be used in cases where P-values are non-independent, as often
the case in genetic association studies.

In practice, researchers typically resort to resampling methods for evaluating the null
distribution for methods with truncation because of distributional complexity. The RTP null
distribution is considerably more complicated than that of TPM. Proposed theoretical forms
of the RTP distribution are cumbersome and result in expressions that involve repeated
integration.[2, 11–13] For example, Nagaraja[13] gives the cumulative distribution for the
statistic \( T_k = -\sum_{i=1}^{k} \ln P(i) \) and \( k < L \), as:

\[
\Pr(T_k > t) = \sum_{j=1}^{k} w_j \exp \left\{ -\frac{c_j t}{c_{k+1}} \right\} \frac{1}{(L - k - 1)!} \int_{0}^{t} \exp \left\{ y d_j \right\} y^{L-k-1} dy \\
+ \sum_{s=0}^{L-k-1} \exp \left\{ -t \right\} \frac{t^s}{s!}, \text{ where }
\]

\[
c_j = L - j + 1, \\
d_j = \frac{k + 1 - j}{L - k}, \\
w_j = \frac{1}{L - j + 1} \frac{L!}{(L - k)! (j - 1)! (k - j)!} \frac{(-1)^k - j}{(k - j)!}. \tag{3}
\]

Complexity of the RTP distribution is due to dependency between ordered P-values.
When \( k = L \), this dependency is inconsequential because a statistic is formed as a sum of \( L \)
terms and its value does not change if the terms are re-ordered. In fact, when \( k = L \), the
RTP P-value is the same as the Fisher combined P-value, derived via a CDF of a sum of
independent chi-square variables. However, if \( 1 < k < L \), the \( k \) smallest \( P \)-values remain
correlated and dependent even if these \( k \) values are randomly shuffled. The dependency is
induced through \( P_{(k+1)} \) being a random variable: when \( P_{(k+1)} \) happens to be relatively small,
the \( k \) P-values have to squeeze into a relatively small interval from zero to that value. This
induces a positive correlation between random sets of \( k \) smallest P-values, similar to the
clustering effect in random effects models. Although this correlation can be eliminated by scaling the largest P-value, $P_{(k)}$, the $k$ values remain dependent, as illustrated in Figure 1 (see “Supplemental Materials (S-1)” for discussion of the decorrelation method).

One of the main goals of this research is to derive a simple and easily implemented theoretical form of the RTP distribution for independent P-values. Applications of combining independent P-values remain important in statistical research, and there is a clear preference among practitioners for methods that are based on simple and transparent approaches, such as the Fisher or the inverse normal (Stouffer’s) tests.[5, 6, 14–17] Further, we extend RTP and related methods by allowing dependence in the observed P-values. Previously published theoretical forms of the RTP distribution (e.g., Equ 3) retain order-specific terms, but we proceed to a simpler representation by noting that every random realization of $k$ smallest P-values can be shuffled. This step does not change the value of the product ($W_k$), which is our random statistic of interest, but implies that we can treat the joint $k$-variate distribution as governed by the same pair-wise dependence for every pair of variables. Moreover, variables of that shuffled distribution are identical marginally. The dependency is induced completely through the randomness of $P_{(k+1)}$, and conditionally on its value, the $\{W_k|P_{(k+1)}\}$ distribution is given by standard independence results (this fact was also noted earlier by Dudbridge and Koeleman[2]). Then, $P_{\text{RTP}}$ is given by the marginal CDF of $W_k$. Based on this conceptual model, we develop new ways of evaluating the distributions of RTP and related statistics. Our approach substantially simplifies analytic forms of the combined P-value.

The rest of this paper is organized as follows. First, we develop several representations of RTP where a single integral is evaluated in a bounded interval $(0, 1)$, which allows one to evaluate the RTP distribution as a simple average of standard functions. Next, we derive a very simple modification of RTP, mRTP. Despite simplicity, mRTP is at least as powerful as RTP, according to our simulation study. We also propose an adaptive statistic in the spirit of RTP and a de-correlation method to allow for dependencies between P-values. Finally, we present an application of our methods using published P-values for association between
dietary patterns and risk of T2DM.

METHODS

Theoretical RTP distribution

We derived a simple expression for the RTP distribution as the expectation of a function of a uniform (0 to 1) random variable:

\[ P_{\text{RTP}}(k) = \Pr(W_k \leq w) = 1 - \int_0^1 G_k \left\{ \ln \left( \frac{B_{k+1}^{-1}(u)^k}{w} \right) \right\} du, \quad (4) \]

where \( B_{k+1}^{-1}(\cdot) \) is inverse CDF of Beta(\( k + 1, L - k \)) distribution, and \( G_k(\cdot) \) is CDF of Gamma(\( k, 1 \)). \( P_{\text{RTP}}(k) \) is the combined RTP P-value. Notably, given the value of the product of \( k \) P-values, \( W = w \), we can simultaneously evaluate \( P_{\text{RTP}}(k + 1) \):

\[ P_{\text{RTP}}(k + 1) = \Pr(W_{k+1} \leq w) = 1 - \int_0^1 G_k \left\{ \ln \left( \frac{B_{k+1}^{-1}(u)^{k+1}}{w} \right) \right\} du. \quad (5) \]

Details and the derivation are given in “Supplemental Materials (S-2)”.

Modified RTP method, mRTP

Next, we develop an alternative to the product statistic for calculating combined P-values. This alternative statistic and its distribution are not an approximations to \( W_k \) and the RTP distribution. However, similarly to RTP the new statistic is designed to capture information contained in the first \( k \) smallest P-values. To construct the new statistic, we propose the following transformation that involves the product \( W_{k-1} \) and the variable \( P_{(k)} \):

\[ A_k = (k - 1) \ln \{ P_{(k)} \} - \ln \{ W_{k-1} \} + G_\lambda^{-1} \left\{ 1 - B_k(p_{(k)}) \right\}, \quad (6) \]
where $G_k^{-1}(\cdot)$ is inverse CDF of Gamma($k,1$),

$$
\lambda = (k - 1) \times \mathbb{E}\{-\ln(p_{(k)})\} = (k - 1)(\Gamma'(L + 1)/\Gamma(L + 1) - \Gamma'(k)/\Gamma(k)),
$$

$\Gamma'$ is the first derivative of a gamma function; and $B_k(x)$ is the CDF of Beta($k, L - k + 1$) distribution evaluated at $x$. Given the observed value $A_k = a_k$, the combined P-value is then:

$$
P_{A_k} = \Pr(A_k \leq a_k) = 1 - G_{k+\lambda-1}(a_k).
$$

Under the null hypothesis, as illustrated by Fig. (2), combined P-values based on the proposed $A_k$ are very similar to $P_{\text{RTP}}$, and approach $P_{\text{RTP}}$ as $k$ increases. However, under the alternative, we found that mRTP has either the same or higher power than RTP. Furthermore, the combined P-value, $P_{A_k}$, can be easily computed in R using its standard functions. A short example and an R code is given in “Supplemental Materials (S-3)”.

**Adaptive RTP method, aRTP**

As we discussed earlier in Introduction, the number of $k$ P-values to be combined by the RTP method is fixed and needs to be pre-specified. The choice of $k$ is somewhat arbitrary, so a researcher may wish to evaluate $P_{\text{RTP}}$ at several values of $k$, consequently choosing $k$ that corresponds to the smallest combined P-value. However, this additional step creates another layer of multiple comparisons, which needs to be accounted for. Yu et al. [8] proposed an empirical procedure to evaluate adaptive rank truncated product (aRTP) method based on the minimum P-value computed over various candidate truncation points. To avoid a cumbersome two-level permutation procedure, they built on the method suggested by Ge et al.[18] to reduce computational time. While computationally efficient, the method requires to store a large $B \times L$ matrix, with every row containing $L$ P-values generated under the null distribution over $B$ simulated experiments. Zhang et al.[9] derived analytic
but mathematically complex aRTP distribution, which needs to be evaluated using high-dimensional integration. Here, we propose a new and easily implemented version of the aRTP theoretical distribution. The method exploits the fact that ordered P-values can be represented as functions of the same number of independent uniform random variable (Supplemental Materials (S-4)).

Correlated P-values

We further extend the proposed methods to combine correlated P-values. Let \( L \) correlated P-values, \((p_1, p_2, \ldots, p_L)\), originate from statistics that jointly follow a multivariate normal distribution, \( y \sim \text{MVN}(\mu = 0, \Sigma) \), under \( H_0 \). Dependent variables can be transformed into independent variables by using eigendecomposition of \( \Sigma \), such that \( \Sigma = Q\Lambda Q^{-1} \), where \( Q \) is a square matrix, with \( i \)th column containing eigenvector \( q_i \) of \( \Sigma \), and \( \Lambda \) is the diagonal matrix of eigenvalues \( \lambda_1, \lambda_2, \ldots, \lambda_L \). Next, define an orthogonal matrix \( H = Q\Lambda^{-1/2}Q^T \) and \( y_e = H^Ty \). P-values are decorrelated as \( 1 - \Phi^{-1}(y_e) \). Then, the first \( k \) smallest decorrelated P-values can be used to calculate various combined statistics.

There are many ways to choose orthogonal transformations, but a valid one needs to have the following “invariance to order” property. Suppose we sample an equicorrelated normal vector \( y \) with a common correlation \( \rho \) for all pairs of variables. Before decorrelating the vector, we permute its values to a different order. A permutation in this example is a legitimate operation, because an equicorrelation structure does not suggest a particular order of \( y \) values. After an orthogonal transformation of \( y \) to \( y_e \), the order of \( y_e \) entries may change due to permutation but their values should remain the same. This would not be the case if one were to use orthogonal matrices, such as the inverse Cholesky factor or \( Q\Lambda^{-1/2} \), to decorrelate \( y \), unless \( k = L \) and the combined P-value distribution was derived from the distribution of quadratic form in all \( L \) variables, \( y^Ty \). Moreover, some transformations of equicorrelated data to independence, such as the Helmert transformation, may change values of \( y_e \) depending on the order of values in \( y \) even in a special equicorrelation case of \( \rho = 0 \),
that is, when normal variables in \( y \) are independent. The proposed \( H \), as defined above, has both the invariance to order property (due to its symmetry) and may be used with P-value transformations other than \( \sum_{i=1}^{L} \chi^2_i \), implied by the quadratic form, \( y^T y \).

RESULTS

Simulation study results

We used simulation experiments to evaluate the Type I error rate and power of the proposed methods relative to the previously studied RTP (defined for a fixed \( k \)) and to the adaptive RTP (where \( k \) is varied and the distribution is evaluated by single-layer simulations as in Yu et al, 2009).[8, 18] Performance of various methods was evaluated using \( k \) first-ordered P-values, with \( k = \{10, 100\} \) and \( L = \{100, 200, 500\} \). Details of the simulation design are given in “Supplemental Materials (S-5)”.

Table 1 and Table 2 present Type I error rates for combinations of independent and decorrelated P-values respectively. In the tables, rows labeled “aRTP(new)” refer to our newly proposed adaptive RTP method, while “aRTP” labels the results of the conventional approach.[8] For the aRTP(new) results, the number in parentheses is the average optimal \( k \) (average across simulations). For the adaptive methods, the sequence of truncation points varied from 1 to \( k \) or from 1 to \( L \), if \( k = L \). Both tables confirm that all methods maintain the correct Type I error rate.

Tables 3-6 summarize a set of power simulations for independent P-values. Results presented in Table 3 were obtained under the assumption that all \( L \) statistics had the same underlying effect size (\( \mu = 0.5 \)). From this table, it is evident that our mRTP has the highest power, closely followed by RTP. The Simes method has the lowest power, which is expected due to homogeneity in effect sizes across \( L \) tests and absence of true nulls. For the results in Tables 4-5, the effect size was allowed to either randomly vary throughout the range from 0.05 to 0.45 (Table 4) or was equally spaced within the same range (Table 5). In
both of these tables, the mRTP method has the highest power, while the Simes method has the lowest power. The power of both adaptive methods is very similar to one another but lower than that of methods based on a fixed $k$ (RTP and mRTP). Nonetheless, in practice, a good choice for $k$ may not be immediately clear, so a small sacrifice in power may be preferable to an arbitrary and possibly poor choice of $k$. However, when $L$ is large, it can be impractical or unreasonable to vary candidate truncation points all the way up to $L$. Finally, Table 6 summarizes results for simulations when some of the $L$ hypotheses were true nulls ($\mu = 0$), while the remaining hypotheses were true signals ($\mu = 0.5$). The results follow the same pattern as in the previous tables, with mRTP having the highest power. Further, “aRTP(new),” appears to outperform the regular aRTP.

Tables 7-9 summarize a set of power simulations for decorrelated P-values. Under the assumption of common effect size across $L$ tests, decorrelation-based methods perform relatively poorly, compared to the empirical combined P-values, where the null distribution of correlated P-values was kept as is, without transformation to independence (Table 7). However, it should be noted that the common effect size assumption is admittedly unrealistic. Also, under this assumption, if $k = L$, an increase in $L$ does not lead to a dramatic increase in power of empirical methods (labeled “RTP” and “aRTP”), for which the null distribution was obtained without the decorrelation step. This is expected, because for MVN distributed $\mathbf{y}$, the noncentrality parameter for sums of squares is approximately $L\bar{\mu}/[(L-1)\bar{\rho} + 1]$, where $\bar{\mu}$ and $\bar{\rho}$ are averaged effect size and correlation values. This sum quickly approaches $\bar{\mu}/\bar{\rho}$ as $L$ increases, subsequently leading to a small power gain for combining more than a few statistical values.

Under heterogeneous effect sizes (Tables 8-9), relative ordering of powers is reversed. Empirical versions of the tests (“RTP”, “aRTP”) still show nearly identical (and low) power for various combinations of $k$ and $L$ values. However, decorrelation-based methods become quite powerful, and their power is increasing with $k$ and $L$. This is expected, because decorrelation induces noncentrality that involves $\sum_{i\neq j}^{L}(\mu_i - \mu_j)^2$ sum, which increases with
the increased heterogeneity of $\mu$.

**Real-data analysis**

We analyzed data on reported associations between various dietary patterns and risk for type 2 diabetes mellitus (T2DM). T2DM is one of the most prevalent diseases in the United States and the effect of increasing the dietary intake of various nutrients on reducing the T2DM risk is not well understood. We collected 7 publications reporting generally weak but significant associations between T2DM and dietary intake of whole grain, protein, fiber, magnesium, calcium, fruit and berries, and alcohol. From these publications, we extracted odds ratios (OR), confidence interval bounds (LCI, UCI), and association P-values (Table 10). To test whether at least one of these nutrients is associated with T2DM, we employed our proposed adaptive RTP with $k$ varying from 1 to 7, and Fisher’s test (or the traditional RTP with $k = L = 7$). The resulting combined adaptive RTP P-value was equal to $2 \times 10^{-6}$ at the value $k=6$, while P-value based on the RTP and mRTP (for $k=6$) were $P_{\text{RTP}}=1.3\times 10^{-9}$ and $P_{\text{mRTP}}=1.8\times 10^{-11}$. Next, we applied both mRTP and RTP to find the minimum value $L^*$, such that the combined P-value would be larger than 0.05. At $L^* = 100$, both P-values are still below 0.05, $P_{\text{RTP}} = 0.001$ and $P_{\text{mRTP}} = 0.001$. At $L^* = 272$, $P_{\text{RTP}} = 0.052$ and $P_{\text{mRTP}} = 0.13$. Therefore, around 270 manuscripts reporting non-significant associations with diabetes, possibly unpublished and tucked away in researchers’ file drawers, would collectively suggest that there is a good possibility of observing such set of P-values as in Table 10 due to chance. Here, we do not intend to cast doubt on the reported diabetes associations but merely want to illustrate one of the possible ways to use the RTP and its variations.
DISCUSSION

Complex diseases are influenced by collective effects of environmental exposures and genetic determinants. There can be numerous weak, but biologically meaningful risk factors. The challenge is to distinguish between real and spurious statistical signals in the presence of multiple comparisons and low detection power. In this article, we derived a mathematically simple form of the rank truncated product P-value distribution that not only makes its evaluation very simple, but also leads to new extensions, such as mRTP (the modified RTP) and our version of adaptive RTP. The mRTP is designed with the same objectives in mind as RTP and TPM: to facilitate detection of possibly weak signals among top-ranking predictors that could have been missed, unless combined into a single score. The mRTP is trivial to implement in terms of standard functions provided by packages such as R, and its P-value under the null hypothesis is closely tracking RTP values (Figure 2). In terms of power, however, mRTP has an edge over RTP: its power is either the same or higher. Further, we developed a fast adaptive algorithm which searches through a number of candidate values of truncation points and finds an optimal number of top ranking predictors to combine, to maximize power of the overall association. We also proposed a powerful analytic solution to accommodate correlated risk factors.

To evaluate performance of our methods, we gauged their power against the Simes test. The Simes test is a useful benchmark, because it is related to the combined P-value methods with truncation, as well as to multiple adjustment procedures. At the extremes, namely, for RTP with \( k = 1 \) and TPM with the threshold set at \( P_{(1)} \), both truncation methods become equivalent to Šidák correction.[19] Šidák correction is approximately the Bonferroni correction,[20] for small P-values and large \( L \). The Simes P-value, \( \min\{kp_{(i)}/i\} \), is at least as small as Bonferroni-corrected P-value. In addition, there is a connection of the Simes test to the Benjamini & Hochberg false discovery rate (FDR).[21] Formally, the Simes test is algebraically the same procedure as the Benjamini & Hochberg FDR but the interpretation is different: FDR method determines the largest \( i \), such that \( P_{(i)} \leq i\alpha/L \), and rejects \( H_0 \) for all
(j), j \leq i, to control the expectation of FDR. TPM was omitted from comparisons, because its performance relative to RTP was extensively studied in previous publications.[2, 22]

Our evaluation of correlated P-values has two main limitations: (1) We make an assumption that the generating mechanism for dependent association statistics is via a multivariate normal distribution, MVN. The association statistics themselves can be distributed differently, for example, marginally follow a chi-square distribution, as in our simulations. The implicit assumption here is that chi-square statistics are transformations of the underlying MVN; (2) The MVN correlation structure is known or well estimated. Future research should explore the extent of measurement error in \( \hat{\Sigma} \) on power of truncation methods.

Finally, in light of replicability crisis, utility of P-values is being re-evaluated. [23] Despite numerous drawbacks, P-values remain a useful filtering tool. They can also be viewed as transformations of standardized effect sizes and contain information that can be converted to approximate posterior probability of a false discovery and to Bayesian effect size estimates. [24–27]

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Figure 1: **Illustration for decorrelated yet dependent P-values;** $k = 2$, $n = 4$.
A plot of simulated and decorrelated values, $U_{(1)}$ vs $U_{(2)}$, reveals a hole in the middle, instead of the complete Malevich black square, indicating dependency.

Figure 2: **Combined P-values based on $A_k$ versus RTP statistic.**
Multiple combined P-values were computed using the two proposed statistics based on either top 10 or top 15 P-values out of $L = 20$ tests.
### Tables

#### Table 1: Type I error at $\alpha = 0.05$ for $L$ true hypotheses

| $L = 4$ | $L = 6$ | $L = 10$ | $L = 100, k = 10$ | $L = k = 100$ |
|--------|--------|----------|-------------------|--------------|
| Mean $\rho$ | 0.2924 | 0.3715 | 0.4178 | 0.4634 | 0.4634 |
| RTP | 0.0463 | 0.0495 | 0.0501 | 0.0538 | 0.0541 |
| RTP(decorr) | 0.0492 | 0.0480 | 0.0515 | 0.0528 | 0.0515 |
| mRTP(decorr) | 0.0504 | 0.0474 | 0.0501 | 0.0514 | 0.0514 |
| aRTP | 0.0466 | 0.0508 | 0.0489 | 0.0538 | 0.0552 |
| aRTP(new, decor) | 0.0492 | 0.05 | 0.0519 | 0.051 | 0.0543 |
| Simes | 0.0516 | 0.0500 | 0.0494 | 0.0510 | 0.0506 |

#### Table 2: Type I error, correlated P-values ($\delta = 1$)

| $L = 10$ | $L = 50$ | $L = 100$ | $L = 200$ | $L = 500$ |
|----------|----------|-----------|-----------|-----------|
| RTP | 0.3517 | 0.4318 | 0.5382 | 0.5001 | 0.7346 | 0.9381 |
| mRTP | 0.3812 | 0.4868 | 0.6286 | 0.4965 | 0.7391 | 0.9542 |
| aRTP | 0.2683 | 0.3268 | 0.4149 | 0.4142 | 0.6106 | 0.8590 |
| aRTP(new) | 0.3409 | 0.4226 | 0.5221 | 0.3489 | 0.5734(40.38) | 0.7868 |
| Simes | 0.1426 | 0.1563 | 0.1720 | 0.1452 | 0.1559 | 0.1711 |

#### Table 3: Power at $\mu = 0.5$ for all $L$ tests
| $k = 10$ | $k = 100$ |
|---------|---------|
| $L = 100$ | $L = 200$ | $L = 500$ | $L = 100$ | $L = 200$ | $L = 500$ |
| RTP | 0.1136 | 0.1298 | 0.1550 | 0.1361 | 0.1874 | 0.2884 |
| mRTP | 0.1201 | 0.1409 | 0.1747 | 0.1353 | 0.1887 | 0.2988 |
| aRTP | 0.0955 | 0.1055 | 0.1220 | 0.1175 | 0.1476 | 0.2038 |
| aRTP(new) | 0.1129 | 0.1307 | 0.1583 | 0.1129 | 0.1533 | 0.2318 |
| Simes | 0.0760 | 0.0796 | 0.0846 | 0.0769 | 0.0776 | 0.0839 |

Table 4: Power for random $\mu$ between 0.05 and 0.45

| $k = 10$ | $k = 100$ |
|---------|---------|
| $L = 100$ | $L = 200$ | $L = 500$ | $L = 100$ | $L = 200$ | $L = 500$ |
| RTP | 0.1106 | 0.1328 | 0.1503 | 0.1335 | 0.1877 | 0.2856 |
| mRTP | 0.1165 | 0.1413 | 0.1711 | 0.1341 | 0.1877 | 0.3014 |
| aRTP | 0.0946 | 0.1086 | 0.1178 | 0.1139 | 0.1461 | 0.2054 |
| aRTP(new) | 0.1111 | 0.1326 | 0.1552 | 0.1132 | 0.1539 | 0.2320 |
| Simes | 0.0744 | 0.0808 | 0.0841 | 0.0780 | 0.0793 | 0.0831 |

Table 5: Power for equally spaced $\mu$ between 0.05 and 0.45

| $k = 10$ | $k =$ No. of false hypotheses |
|---------|-----------------------------|
| fractions | 50 | 80 | 90 | 50 | 80 | 90 |
| RTP | 0.1721 | 0.2680 | 0.3027 | 0.2166 | 0.3571 | 0.4094 |
| mRTP | 0.1848 | 0.2942 | 0.3342 | 0.2191 | 0.3543 | 0.4084 |
| aRTP | 0.1380 | 0.2092 | 0.2340 | 0.1725 | 0.2976 | 0.3418 |
| aRTP(new) | 0.1713 | 0.2661 | 0.2999 | 0.1842 | 0.2494 | 0.2629 |
| Simes | 0.0970 | 0.1266 | 0.1356 | 0.0965 | 0.1270 | 0.1356 |

Table 6: Power assuming $\mu = 0.5$ for a fraction of 100 hypotheses and $\mu = 0$ for the rest

| $L = k = 4$ | $L = k = 6$ | $L = k = 10$ | $L = 100$, $k = 10$ | $L = k = 100$ |
|-------------|-------------|-------------|----------------|-------------|
| Mean $\rho$ | 0.2917 | 0.3713 | 0.4177 | 0.4635 | 0.4635 |
| RTP | 0.3628 | 0.3754 | 0.3955 | 0.3832 | 0.4150 |
| RTP(decorr) | 0.3332 | 0.2735 | 0.2413 | 0.1472 | 0.1797 |
| mRTP(decorr) | 0.3250 | 0.2757 | 0.2391 | 0.1541 | 0.1794 |
| aRTP | 0.3559 | 0.3629 | 0.3789 | 0.3635 | 0.3908 |
| aRTP(new, decor) | 0.2893 | 0.2376 | 0.2012 | 0.1442 | 0.1397 |
| Simes | 0.2644 | 0.2114 | 0.1722 | 0.0927 | 0.0925 |

Table 7: Power, correlated P-values (common $\mu = 1.25$)
\[
\begin{array}{cccccc}
L = k = 4 & L = k = 6 & L = k = 10 & L = 100, k = 10 & L = k = 100 \\
\hline
\text{Mean } \rho & 0.2918 & 0.3711 & 0.4172 & 0.4634 & 0.4634 \\
\text{RTP} & 0.1027 & 0.1058 & 0.1126 & 0.1229 & 0.1085 \\
\text{RTP(decorr)} & 0.1632 & 0.1703 & 0.1840 & 0.3706 & 0.5052 \\
\text{mRTP(decorr)} & 0.1636 & 0.1724 & 0.1863 & 0.4055 & 0.5034 \\
\text{aRTP} & 0.1134 & 0.1142 & 0.1200 & 0.1258 & 0.1188 \\
aRTP(new, decor) & 0.1417 & 0.1504 & 0.1628 & 0.3684 & 0.353 \\
\text{Simes} & 0.1468 & 0.1482 & 0.1464 & 0.1639 & 0.1652 \\
\end{array}
\]

Table 8: Power, correlated P-values (random \( \mu \))

\[
\begin{array}{cccccc}
L = k = 4 & L = k = 6 & L = k = 10 & L = 100, k = 10 & L = k = 100 \\
\hline
\text{Mean } \rho & 0.2922 & 0.3715 & 0.4172 & 0.4635 & 0.4637 \\
\text{RTP} & 0.1050 & 0.1094 & 0.1108 & 0.1248 & 0.1066 \\
\text{RTP(decorr)} & 0.1679 & 0.1658 & 0.1910 & 0.3794 & 0.5146 \\
\text{mRTP(decorr)} & 0.1696 & 0.1688 & 0.1867 & 0.4083 & 0.5028 \\
aRTP & 0.1142 & 0.1188 & 0.1220 & 0.1288 & 0.1204 \\
aRTP(new, decor) & 0.1521 & 0.1484 & 0.1604 & 0.3681 & 0.3536 \\
\text{Simes} & 0.1507 & 0.1463 & 0.1436 & 0.1656 & 0.1636 \\
\end{array}
\]

Table 9: Power, correlated P-values (equally spaced \( \mu \))

| Factor                                      | Odds Ratio | LCI  | UCI  | P-value  |
|----------------------------------------------|------------|------|------|----------|
| Whole grain intake [28]                      | 0.7        | 0.6  | 0.8  | 2.3e-04  |
| Protein intake [29]                          | 1.2        | 1.0  | 1.3  | 1.7e-03  |
| Dietary fiber intake* [30]                   | 0.8        | 0.6  | 0.9  | 5.0e-03  |
| Alcohol consumption[31]                      | 1.7        | 1.1  | 2.5  | 6.6e-03  |
| Fruit and berries [32]                       | 0.7        | 0.5  | 0.9  | 6.8e-03  |
| Dietary magnesium intake [33]                | 0.5        | 0.3  | 0.9  | 9.0e-03  |
| Dietary calcium [34]                         | 0.9        | 0.7  | 1.0  | 2.5e-02  |

Table 10: Publications reporting epidemiological associations T2DM. *indicates risk factors for which Relative Risk (RR) instead of OR was reported.
Supplemental material

S-1 Correlation and dependencies among $k$ smallest P-values

The complexity of analytic forms of the RTP distribution is due to dependency introduced by ordering of $P$-values. Although order statistics are correlated, products and sums are oblivious to the order of the terms, therefore for the case when $k = L$, the statistic $T_k$ follows the gamma distribution with the shape parameter equal to $L$, and the unit scale, i.e., $T_L \sim \text{Gamma}(L, 1)$. This is essentially the same as the Fisher combined $P$-value, where the statistic is $2T_L$, distributed as the chi-square with $2L$ degrees of freedom. However, for $1 \leq k < L$, the $k$ smallest $P$-values remain dependent even if these $k$ values are not sorted (e.g., randomly shuffled). The dependency is induced through $P_{(k+1)}$ being a random variable: when $P_{(k+1)}$ happens to be relatively small, the $k$ $P$-values have to squeeze into a relatively small interval from zero to that value. This induces a positive correlation between random sets of $k$ smallest $P$-values, similar to the clustering effect in the random effects models.

The $k$ smallest unordered $P$-values are equicorrelated and also have the same marginal distribution, which can be obtained as a permutation distribution of the first $k$ uniform order statistics. Assuming independence of $L$ $P$-values and their uniform distribution under the null hypothesis, we can derive the correlation between any pair of unordered $k$ smallest $P$-values as $\rho(k, L) = 3(L-k)/(2+k(L-2)+5L)$. As $L$ increases, the correlation approaches the limit that no longer depends on $L$: $\lim_{L \to \infty} \rho(k, L) = 3/(k + 5)$. The correlation can be substantial for small $k$ and cannot be ignored. There is a very simple transformation that makes a set of $k$ $P$-values uncorrelated. All that is needed to decorrelate these $P$-values is
to scale the largest of them:

\[
\begin{align*}
X_1 &= P_{(1)} \\
X_2 &= P_{(2)} \\
&\vdots \\
X_{k-1} &= P_{(k-1)} \\
X_k &= \sigma P_{(k)},
\end{align*}
\]

where

\[
\sigma = \frac{2L - k + 3 + \sqrt{(k+1)(L+1)(L-k+1)}}{4 + 2L},
\]

and then randomly shuffle the set \(X_1, \ldots X_k\). This scale factor \(\sigma\) can be derived by solving the mixture covariance linear equations induced by the permutation distribution of the first \(k\) order statistics. The decorrelated values can be further transformed so that each has the uniform \((0,1)\) distribution marginally:

\[
\begin{align*}
U_j &= \frac{1}{k} \sum_{i=1}^{k} \text{Beta}(X_j; i, L - i + 1), \quad j = 1, \ldots, k - 1 \quad (S-1) \\
U_k &= \frac{1}{k} \sum_{i=1}^{k} \text{Beta}(X_k/\sigma; i, L - i + 1), \quad (S-2)
\end{align*}
\]

where \(\text{Beta}(x; a, b)\) is the CDF of a beta\((a, b)\) distribution evaluated at \(x\).

Unfortunately, although the scaling and subsequent shuffle removes the correlation, the values remain dependent, as illustrated in Figure 1.

\section*{S-2 Derivation of the RTP distribution}

An intuitive way to understand our derivation of the RTP distribution is through references to simulations. The simplest, brute-force algorithm to obtain the RTP combined P-value
is by simulating its distribution directly. If \( w_k \) is the product of \( k \) actual P-values, one can repeatedly (\( B \) times) simulate \( L \) Uniform(0,1) random variables \( U_i \), sort them, take the product of \( k \) smallest values, and compare the resulting product to \( w_k \). As the number of simulations, \( B \), increases, the proportion of times that simulated values will be smaller than \( w_k \) converges to the true combined RTP P-value.

There are several ways to optimize the above simulation scenario with respect to computational complexity. For instance, sets of ordered uniform P-values can be simulated directly using well-known results from the theory of order statistics. Despite the fact that the marginal distribution of \( i \)th ordered value is Beta\( (i, L - i + 1) \), to create the necessary dependency between the ordered P-values, sets of \( k \) values have to be simulated in a step-wise, conditional fashion. The minimum value, \( P_{(1)} \), can be sampled from Beta\( (1, L) \) distribution. Alternatively, using the relationship between beta and Uniform(0,1) random variables, it can be sampled as \( P_{(1)} = 1 - U_1^{1/L} \). Next, since the value \( P_{(2)} \) cannot be smaller than \( P_{(1)} = p_{(1)} \), conditionally on the obtained value, it has to be generated from a truncated beta distribution. The third smallest value should be sampled conditionally on the second one, and so on.[35] Therefore, the sequence and the product \( w_k \) can be obtained by simulating \( k \) ordered P-values, rather then all \( L \) unsorted values.

\[
P_{(1)} = 1 - U_1^{1/L} \\
P_{(2)} = 1 - u_1^{1} U_2^{\frac{1}{L-1}} \\
P_{(3)} = 1 - u_1^{1} u_2^{1} U_3^{\frac{1}{L-2}} \\
\vdots \\
P_{(k)} = 1 - u_1^{1} u_2^{1} \cdots U_k^{\frac{1}{L-k+1}}. \tag{S-3}
\]

Further optimization of the simulation algorithm is illustrative because it provides intuition for theoretical derivation of the RTP distribution. This optimization is achieved by using the Markov property of order statistics. Specifically, the unordered set \( \{ P_1, P_2, \ldots, P_k \mid p_{(k+1)} \} \)
behaves as a sample of \( k \) independent variables, identically distributed as Uniform \((0, p_{(k+1)})\).

After re-scaling,
\[
\left\{ \frac{P_1}{p_{(k+1)}}, \frac{P_2}{p_{(k+1)}}, \ldots, \frac{P_k}{p_{(k+1)}} \right\} \sim \text{Unif}(0, 1). \tag{S-4}
\]

The capital \( P_i \) notation is used here to emphasize the fact that the variable is random, while the lowercase \( p_{(k+1)} \) refers to a realized value of a random variable, \( P_{(k+1)} = p_{(k+1)} \). Next, given that \( P_{(k+1)} \sim \text{Beta}(k + 1, L - k) \), minus log of the product of independent conditional uniform random variables will follow a gamma distribution. Specifically,
\[
- \ln \prod_{i=1}^{k} \frac{P_i}{p_{(k+1)}} = k \ln p_{(k+1)} - \sum_{i=1}^{k} \ln P_i,
\]

and treating \( p_{(k+1)} \) as a constant,
\[
- \ln \prod_{i=1}^{k} \frac{P_i}{p_{(k+1)}} \sim \frac{1}{2} \chi^2_{2k} = \text{Gamma}(k, 1). \tag{S-6}
\]

The above manipulations reduce the set of \( k \) random variables to a set of just two variables: a gamma and a beta. Therefore, the combined RTP P-value can be evaluated numerically by simulating only pairs of beta- and gamma-distributed random variables as follows. Let
\[
- \ln \left( \prod_{i=1}^{k} P_{(i)} \right) = - \ln \left( \prod_{i=1}^{k} \frac{P_i}{p_{(k+1)}} \right) - k \ln p_{(k+1)},
\]

and define
\[
X = P_{(k+1)} \sim \text{Beta}(k + 1, L - k) \tag{S-5}
\]
\[
Y \mid X = - \ln \left( \prod_{i=1}^{k} \frac{P_i}{p_{(k+1)}} \right) \sim \text{Gamma}(k, 1). \tag{S-6}
\]

The empirical distribution of the product of \( k \) values under \( H_0 \) can then be obtained by
repeatedly simulating $X$ and $Y$, and comparing the observed value of $-\ln(w_k)$ to $Z = Y - k\ln(X)$ in every simulation. $P_{\text{RTP}}$ would then be defined as the proportion of times simulated values of $Z$ were larger than $-\ln(w_k)$.

Further, it is important to note that with the above modifications one can simultaneously evaluate probabilities for two consecutive products,

$$
\Pr(W_k \leq w), \quad \text{and} \quad \Pr(W_{k+1} \leq w),
$$

by reusing the same pair of random numbers, which follows from the fact that

$$
-\ln \left( \prod_{i=1}^{k+1} P_i \right) = -\ln \left( \prod_{i=1}^{k} \frac{P_i}{P_{(k+1)}} \right) - (k + 1) \ln P_{(k+1)}. \quad \text{(S-7)}
$$

In the latter case, $-\ln(w)$ is compared to $Z = Y - (k + 1)\ln(X)$. This simulation method is very fast and approaches the exact solution as the number of simulated pairs increases. Moreover, through these simulation experiments it becomes clear that once one conditions on the observed value of $p_{(k+1)}$, the test statistic is formed as a product/sum of independent random variables. Specifically, Gamma distribution for the $Y$ variable in Equ. (S-6) appears to be conditional on the observed $X = p_{(k+1)}$ when the pairs $(X, Y)$ are simulated. Alternatively, one can first simulate $X = p_{(k+1)}$ and then generate a test statistic using $k$ uniform random variables, $U_1, U_2, \ldots, U_k$, on $(0, p_{(k+1)})$ interval.

We just described a way to evaluate the RTP distribution by repeated sampling of two random variables to elucidate the idea that the combined RTP P-value can be obtained by integrating out the random upper bound $P_{(k+1)}$ over its probability density function. Random $P_{(k+1)}$ has to be at least as large as $p_{(k)}$ but smaller than one, $p_{(k)} \leq P_{(k+1)} \leq 1$. Re-expressing $p_{(k)}$ in terms of the observed product $w = \prod_{i=1}^{k} p_{(i)}$, it becomes evident that $w^{1/k} \leq P_{(k+1)} \leq 1$ because the product is maximized if $p_{(i)} = p_{(k)}$ for all $i = 1, \ldots, k$, so the observed $p_{(k)}$ can be at most $w^{1/k}$. Now, integrating over the beta density, $f(\cdot)$ with
parameters $k + 1, L - k$, of a single variable $P_{(k+1)}$, we treat $w$ as a constant:

$$\Pr(W_k \leq w) = 1 - \int_{w/k}^{1} G_k \left\{ \ln \left( \frac{t^k}{w} \right) \right\} f(t) dt. \quad (S-8)$$

Next, by performing a quantile transformation, we can express the integral as an expectation and make the integration limits to be 0 to 1:

$$P_{\text{RTP}}(k) = \Pr(W_k \leq w) = 1 - \int_{0}^{1} G_k \left\{ \ln \left( \frac{B_{k+1}^{-1}(u)}{w} \right)^k \right\} du, \quad (S-9)$$

where $B_{k+1}^{-1}(\cdot)$ is inverse CDF of Beta($k + 1, L - k$) distribution, and $G_k(\cdot)$ is CDF of Gamma($k, 1$). $P_{\text{RTP}}(k)$ is the combined RTP P-value. Similarly,

$$\Pr(W_{k+1} \leq w) = 1 - \int_{0}^{1} G_k \left\{ \ln \left( \frac{B_{k+1}^{-1}(u)}{w} \right)^{k+1} \right\} du, \quad (S-10)$$

We have now derived a relatively simple expression that involves only a single integral. Moreover, in contrast to the initial form of this distribution in Equ (S-8), integration limits in Equ (S-9) no longer involve a product value $w$ and are conveniently bounded on zero to one interval. Equ (S-9) shows that the RTP distribution is in fact the expectation of a function of a uniform random variable, $U \sim \text{Uniform}(0,1)$. If we let $H(u|k, w) = G_k \left( \ln \left( \frac{B_{k+1}^{-1}(u)}{w} \right)^k \right)$, the unconditional distribution of $W_k$ is

$$\Pr(W_k \leq w) = 1 - \int_{0}^{1} H(u|k, w) du = 1 - E \left\{ H(U|k, w) \right\}.$$ 

Therefore, to evaluate $P_{\text{RTP}}(k)$ numerically, one can simply sample a large number of uniform random numbers, $U$, apply the function $1 - H(U)$ and then take the mean. The corresponding R code using one million random numbers is:

```r
mean(1-pgamma(log(qbeta(runif(1e6),k+1,L-k))*k+z,k))
```

where $z = -\ln(w)$. Using the integration explicitly, the R code is:
\begin{align*}
\text{Ak} &\leftarrow \text{function}(lW, P_{k}, k, L) \{ \\
&\hspace{1cm} d = (k-1) \ast (\text{digamma}(L+1) - \text{digamma}(k)) \\
&\hspace{1cm} ak = (k-1) \ast \log(P_{k}) - lW + \text{qgamma}(1-\text{pbeta}(P_{k}, k, L-k+1), \text{shape}=d) \\
&\hspace{1cm} 1 - \text{pgamma}(ak, \text{shape}=k+d-1)
\} \\
P &\leftarrow \text{sort}(c(0.7, 0.07, 0.15, 0.12, 0.08, 0.09)) \\
L &\leftarrow \text{length}(P) \\
k &\leftarrow 4 \\
Z &\leftarrow \text{sum}(-\log(P[1:k])) \\
lW &\leftarrow \text{sum}(\log(P[1:(k-1)])) \\
P_{\text{rtp}} &\leftarrow \text{integrate(function}(x,y,m,n) 1-\text{pgamma}(\log(\text{qbeta}(x,m+1,n-m)) \ast m+y,m),0,1,Z,k,L)$\text{va} \\
P_{\text{ak}} &\leftarrow \text{Ak}(lW, P[k], k, L)
\end{align*}

The resulting combined P-values are $P_{Ak}=0.045$ and $P_{RTP}=0.047$. Note that all six original P-values are larger than the combined mRTP and RTP. This example demonstrates that week signals can form a much stronger one after they are combined.

**S-4 Transformation to independence in the derivation of the aRTP distribution**

As we discussed, ordered P-values can be represented as functions of the same number of independent uniform random variables (Eq. S-3). This reveals that the jth value, $p_{(j)}$, is a function of all $p_{(i<j)}$ and that in a given set of k variables (i.e., conditionally) all information is contained in k independent random variables, $U_{1}, U_{2}, \ldots, U_{k}$. These independent components can be extracted and utilized. Specifically, by using the conditional distribution of $W_{i}$, which only depends on the two preceding partial products, $W_{i-1}$ and $W_{i-2}$, we define independent variables $Z_{i}$’s as $Z_{i} = \text{Pr}(W_{i} > w_{i}|W_{i-1}, W_{i-2})$. Successive partial products relate to one
another as:

\[ W_k = W_{k-1} - W_{k-1} \left( 1 - \frac{W_{k-1}}{W_{k-2}} \right) U_k^{\frac{1}{L-k+1}}. \]

Since \( U_k^{\frac{1}{L-k+1}} \sim \text{Beta}(L - k + 1, 1) \), the conditional density and the CDF for the product is

\[
f(W_k = x \mid W_{k-1} = t_{k-1}, W_{k-2} = t_{k-2}) = \frac{(t_{k-1} - x)^{L-k}}{B(L - k + 1, 1) (t_{k-1} (1 - \frac{t_{k-1}}{t_{k-2}}))^{L-k+1}}.
\]

Let

\[
1 - Z_i = \Pr(W_i < w_i | W_{k-1} = t_{k-1}, W_{k-2} = t_{k-2})
= \Pr\left( t_{i-1} - t_{i-1} \left( 1 - \frac{t_{i-1}}{t_{i-2}} \right) U_i^{\frac{1}{L-k+1}} < w_i | W_{i-1} = t_{i-1}, W_{i-2} = t_{i-2} \right)
= \Pr\left( -\ln U_i < -(L - i + 1) \ln \left( \frac{1 - p(i)}{1 - p(i-1)} \right) \right).
\]

\[
\Pr(W_k \leq x \mid W_{k-1} = t_{k-1}, W_{k-2} = t_{k-2}) = \int_{t_{k-1}/t_{k-2}}^x f(W_k = x | W_{k-1} = t_{k-1}, W_{k-2} = t_{k-2}) dx
= \frac{1}{B(L - k + 1, 1) (t_{k-1} (1 - \frac{t_{k-1}}{t_{k-2}}))^{L-k+1}} \int_{t_{k-1}/t_{k-2}}^x (t_{k-1} - x)^{L-k} dx
= 1 - \left( \frac{t_{k-1} - x}{t_{k-1} \left( 1 - \frac{t_{k-1}}{t_{k-2}} \right)} \right)^{L-k+1}
= 1 - \left( \frac{1 - p(k)}{1 - p(k-1)} \right)^{L-k+1}.
\]

Thus, we obtain a transformation to new set of independent uniform \((0-1)\) random variables.

\[
Z_i = \left( \frac{1 - p(i)}{1 - p(i-1)} \right)^{L-i+1},
\]

with

\[
Z_1 = (1 - p(1))^L.
\]

Next, define \( Y = \sum_{i=1}^k G_{\lambda_i}^{-1}(1 - Z_i) \), where \( G_{\lambda_i}^{-1} \) is the inverse gamma CDF with the shape \( \lambda_i \) and the scale 1. Under \( H_0 \), \( Y \) has a gamma distribution with the shape \( = \sum_{i=1}^k \lambda_i \). The
combined $P$-value can be obtained as:

$$1 - G_{\sum_{i=1}^{k} \lambda_i} \left( \sum_{i=1}^{k} G_{\lambda_i}^{-1}(1 - Z_i) \right)$$  \hspace{1cm} (S-11)

When $\lambda_i$ is large, the gamma CDF approaches the standard normal CDF, which motivates an alternative, the inverse normal transformation. The quantiles can be calculated by using $\lambda_i \Phi^{-1}(1 - Z_i)$ instead of $G_{\lambda_i}^{-1}(1 - Z_i)$. The inverse normal method is useful for the reason that the joint distribution of the partial sums can be derived to evaluate the adaptive RTP (aRTP) $P$-value. For the aRTP, we define partial sums as:

$$S_k = \sum_{i=1}^{k} \lambda_i \Phi^{-1}(1 - Z_i),$$

where $\Phi^{-1}(\cdot)$ is inverse CDF of the standard normal distribution. Then, under the null hypothesis, $S = (S_1, S_2, \ldots, S_m)^T$ follows a multivariate normal distribution MVN($\mathbf{0}, \Sigma$), with $\Sigma = \mathbf{FWF}^T$ and

$$\mathbf{F} = \begin{bmatrix} 1 & 0 & \cdots & 0 & 0 \\ 1 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 1 & 1 & \cdots & 1 & 0 \\ 1 & 1 & \cdots & 1 & 1 \end{bmatrix}, \quad \text{diag}(\mathbf{W}) = \begin{bmatrix} \lambda_1^2 \\ \lambda_2^2 \\ \vdots \\ \lambda_{k-1}^2 \\ \lambda_k^2 \end{bmatrix}, \quad \text{where } \lambda_i^2 = \frac{k}{k-i+1}.$$

The vector $\mathbf{S}$ can be standardized as $T_i = S_i/\sigma_i$, where $\sigma_i$ are the diagonal elements of $\Sigma$, then $\mathbf{T} \sim \text{MVN}(\mathbf{0}, \mathbf{R})$, $R_{ij} = \frac{\Sigma_{ij}}{\sqrt{\Sigma_{ii} \Sigma_{jj}}}$. The null distribution of $\mathbf{T}$ can be used to evaluate aRTP by using $\Pr(S_i/\sigma_i > s_i)$ probabilities or quantiles to obtain significance thresholds with MVN functions available in R `mvtnorm` package.[36]
**S-5 Simulation setup**

We performed $B = 100,000$ simulations to evaluate the Type I error rate and power of the proposed methods. To study performance of combination methods for independent P-values, in each simulation, we generated $L$ normally distributed statistics, $X \sim N(\mu, 1)$. The squared values of $X$ follow the chi-square distribution with one degree of freedom and noncentrality parameter $\mu^2$, $X^2 \sim \chi^2(1, \mu^2)$. P-values were obtained as one minus the CDF of the noncentral chi-square evaluated at $X^2$, or as $P = 2 - \Phi (|X| + |\mu|) - \Phi (|X| - |\mu|)$ in terms of the normal CDF. P-values generated from normal statistics (without squaring them) were also considered, but these results are omitted for brevity, because the resulting ranking of the methods by power was found to be similar. Under $H_0$, $L$ P-values were sampled from the uniform $(0, 1)$ distribution, which is equivalent to setting $\mu$ to zero.

To study non-independent P-values, we simulated $L$ statistics from a multivariate normal distribution $\text{MVN}(\mu, \Sigma)$ and decorrelated them by eigendecomposition described in Section 2.5. In each simulation, a correlation matrix $\Sigma$ was generated randomly by perturbing an equicorrelated matrix $D$. Specifically, we added perturbation to equicorrelated matrix $D$ with off-diagonal elements $\rho = 0.5$ as:

$$R = D + uu^T,$$

where $u$ is random vector.\[37\] Then, $R$ was converted to a correlation matrix $\Sigma$ with off-diagonal elements $\rho_{ij} = \frac{R_{ij}}{\sqrt{R_{ii}R_{jj}}} = \frac{\rho + u_i u_j}{\sqrt{1 + u_i^2} \sqrt{1 + u_j^2}}$. The amount of “jiggle” in $R$ depends on the variability of elements in $u$. If elements of $u$ are generated in the range between $-\delta$ and $\delta$, the value of $\delta$ would represent the upper bound for the amount of jiggle allowed between pairwise correlations in $\Sigma$. In our simulations, we set $\delta = 1$, allowing for a mix of positive and negative values of $\rho_{ij}$ in $\Sigma$.

The Type I error rate and power performance were computed based on two $B \times k$ matrices of P-values, $P_0$ and $P_A$, every row of which contained $k$ smallest sorted P-values out of $L$. 

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tests across $B$ simulations ($L - k$ P-values were discarded). $P_0$ stored simulated P-values under $H_0$ and $P_A$ under the alternative hypothesis, $H_A$. Taking the product of P-values in each row, we obtain two $B \times 1$ vectors, $w_0$, $w_A$. RTP P-values were computed based on the empirical CDF (eCDF) of $w_0$ evaluated at $B$ values of $w_A$. Power was calculated as the proportion of P-values that were smaller than the significance threshold, $\alpha$.

Finally, when various combined P-value methods are being compared, it is meaningful to gauge their performance against methods designed for multiple testing adjustments. This is especially relevant with methods that employ truncation due to their emphasis on small P-values. Therefore, we included the Simes method[38] in our power comparisons because it can be viewed as a combined P-value method. The Simes method tests the overall $H_0$ without a reference to individual P-values: the $H_0$ is rejected at $\alpha$ level if $P_{(i)} \leq i\alpha/L$ for at least one $i$. Equivalently, the overall (or the “combined”) Simes P-value can be obtained as $\min\{kp_{(i)}/i\}$. 