A test for treatment effects in randomized controlled trials, harnessing the power of ultrahigh dimensional big data

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Abstract

Background: The randomized controlled trial (RCT) is the gold-standard research design in biomedicine. However, practical concerns often limit the sample size, $n$, the number of patients in a RCT. We aim to show that the power of a RCT can be increased by increasing $p$, the number of baseline covariates (sex, age, socio-demographic, genomic, and clinical profiles et al, of the patients) collected in the RCT (referred to as the ‘dimension’).

Methods: The conventional test for treatment effects is based on testing the ‘crude null’ that the outcomes of the subjects are of no difference between the two arms of a RCT. We propose a ‘high-dimensional test’ which is based on testing the ‘sharp null’ that the experimental intervention has no treatment effect whatsoever, for patients of any covariate profile.

Results: Using computer simulations, we show that the high-dimensional test can become very powerful in detecting treatment effects for very large $p$, but not so for small or moderate $p$. Using a real dataset, we demonstrate that the $P$ value of the high-dimensional test decreases as the number of baseline covariates increases, though it is still not significant.

Conclusion: In this big-data era, pushing $p$ of a RCT to the millions, billions, or even trillions may someday become feasible. And the high-dimensional test proposed in this study can become very powerful in detecting treatment effects.

Abbreviations: OC = operating characteristic, RCT = randomized controlled trial.

Keywords: big data, biostatistics, data mining, potential-outcome model, randomized controlled trial, sample size, sharp null

Strengths and limitations of this study

1. This paper presents a test for treatment effects in randomized controlled trials, which harnesses the power of ultrahigh dimensional big data.
2. The proposed high-dimensional test increases the power of a RCT by increasing $p$, the number of baseline covariates (sex, age, socio-demographic, genomic, and clinical profiles et al, of the patients), rather than the usual $n$, the number of patients.
3. The proposed high-dimensional test can become very powerful in detecting treatment effect for large $p$, but not so for small or moderate $p$.

1. Introduction

The randomized controlled trial (RCT) is the gold-standard research design in biomedicine and provides the most rigorous way of determining whether a cause-effect relation exists between treatment and outcome. Randomization (random allocation of patients to intervention groups) and double blinding (neither the patients or investigators being aware of the treatment assignments
made very large. We will also use a real dataset to demonstrate genomic, and clinical pro-
RCT (two equalities: 

![Image]

In a typical RCT comparing an experimental intervention and a
control (intervention \(n = 1\) for experimental
intervention; \(A = 0\) for control), \(Y\), the outcome, and \(z\), a vector
of baseline covariates (with a dimension of \(p\)). We use the generic
notation, \(f()\), to denote the (joint) probability density or mass
function of a random variable (vector), where appropriate. The
conventional test for treatment effects is based on testing the
following ‘crude null’:

\[
f(Y|A = 1) = f(Y|A = 0),
\]

That is, the outcomes of the subjects are of no difference
between the 2 arms of a RCT.

By contrast, the proposed high-dimensional test is based on
testing the following “sharp null”,

\[
f(Y|A = 1, z) = f(Y|A = 0, z).
\]

That is, the experimental intervention has no treatment effect
whatsoever, for patients of any covariate profile. In practice, we
can dichotomize \(Y\) into \(Y^\prime\), such as ‘favorable’ \((Y = 1)\) and
‘unfavorable’ \((Y = 0)\) outcomes, based on some suitable criteria. 
\((Y^\prime)\) may already be a binary variable, such as ‘survival’ \((Y = 1)\)
and ‘death’ \((Y = 0)\). This case is then simply \(Y^\prime = Y\) Supplementary
Note, http://links.lww.com/MD/D302 shows that alternatively,
we can test the sharp null in a RCT, based on the following
two equalities:

\[
f(z|A = 1, Y^\prime = 1) = f(z|A = 0, Y^\prime = 1)
\] and

\[
f(z|A = 1, Y^\prime = 0) = f(z|A = 0, Y^\prime = 0).
\]

This alternative sharp-null formulation implies no difference in
the baseline covariates between the two arms of a RCT,
separately for those with favorable outcomes (3) and those with
unfavorable outcomes (4).

Assume that a RCT recruits a total of \(n \ (i = 1, \ldots, n)\) subjects.
The data collected consists of the treatment assignment indicator,
\(A_i\), the outcome (and the dichotomized outcome), \(Y_i\) (and \(Y_i^\prime\)),
and a total of \(p \ (i = 1, \ldots, p)\) baseline covariates, \(Z_i\), for \(i = 1, \ldots, n\). To test the crude null (1), one can use the usual
two-sample test,

\[
T_{\text{crude}}^2 = \left(\frac{\sum_{i=1}^n Y_i - \sum_{i=1}^n Y_i^\prime}{\sum_{i=1}^n Y_i + \sum_{i=1}^n Y_i^\prime} \right)^2 / \left(\frac{\sum_{i=1}^n Y_i + \sum_{i=1}^n Y_i^\prime}{n_1 + n_0}\right),
\]

where \(n_1(n_0)\) is the number of subjects receiving the experimental (control)
intervention \((n_1 + n_0 = n)\), and \(\sigma_i^2 = \frac{1}{n_1 + n_0} \times \sum_i (Y_i - \bar{Y})^2\) is an estimate of the variance of the
outcome under the crude null. \(T_{\text{crude}}^2\) in (5) is distributed
asymptotically as a chi-squared distribution with one degree of
freedom under the crude null. The same can be done for the
dichotomized outcome, \(Y_i^\prime\).

To test the sharp null using (3) and (4), we can construct a test
statistic for the \(j\)th baseline covariate,

\[
T_j^2 = \left(\frac{\sum_{i=1}^n A_i Y_i^\prime - \sum_{i=1}^n A_i Y_i^\prime^\prime}{n_1} \right) \left(\frac{\sum_{i=1}^n A_i Y_i^\prime - \sum_{i=1}^n A_i Y_i^\prime^\prime}{n_0}\right)^2 / \left(\frac{\sum_{i=1}^n Y_i^\prime + \sum_{i=1}^n Y_i^\prime^\prime}{n_1 + n_0}\right)
\]

\[
+ \left(\frac{\sum_{i=1}^n A_i Y_i^\prime - \sum_{i=1}^n A_i Y_i^\prime^\prime}{n_1} \right) \left(\sum_{i=1}^n A_i Y_i^\prime - \sum_{i=1}^n A_i Y_i^\prime^\prime\right)^2 / \left(\frac{\sum_{i=1}^n Y_i^\prime + \sum_{i=1}^n Y_i^\prime^\prime}{n_1 + n_0}\right),
\]

where \(n_1(n_0)\) and \(n_{10}(n_{00})\) are the numbers of subjects
receiving the experimental (control) intervention and ultimately
leading to, respectively, favorable and unfavorable outcomes
\((n_1 + n_0 + n_{10} + n_{00} = n)\), and \(\sigma_j^2 = \frac{1}{n_1 + n_0} \times \sum_i (Y_i^\prime - \bar{Y})^2\) and \(\sigma_j^2 = \frac{1}{n_1 + n_0} \times \sum_i (Y_i^\prime - \bar{Y})^2\) are the estimates of the
variances of the \(j\)th baseline covariate under the sharp null among
subjects with, respectively, favorable and unfavorable outcomes.
The first term to the right of the equality sign in (6) is a test
statistic based on (3), and the second term, that based on (4). These
2 terms involve different sets of subjects and are independent of one another. Under the sharp null, \(T_j^2\) in (6) is therefore distributed
asymptotically as a chi-squared distribution with 2 degrees of
freedom.

Next, we sum up the statistics of all \(p\) baseline covariates as our
high-dimensional test,

\[
T_{\text{sharp}}^2 = \sum_{j=1}^p T_j^2.
\]

The ordinary chi-square approximation may not apply for
\(T_{\text{sharp}}^2\) in (7) because the baseline covariates themselves may not be
independent of one another. We, therefore, propose performing
Monte-Carlo permutations for the sampling distribution of
\(T_{\text{sharp}}^2\) under the sharp null. To be precise, we fix \(z\) and shuffle (\(A\), 
\(Y\)) among the study subjects (or vice versa). The permutation-based
high-dimensional test is a distribution-free test, suitable for
use with normal or non-normal data and in large or small RCTs.
2.2. Simulation study

We considered a small RCT with $n = 50$ and a large one with $n = 250$. Each patient is randomized either to the treatment or the control arm, with equal probability. The outcomes of the trials (survival or death) are recorded for each patient. The trials also collected $p$ baseline covariates for each patient.

We assume a potential-outcome model\cite{3,5} for a particular disease: the experimental treatment is beneficial to 15\% of patients (they will live upon being given the treatment and will die otherwise), is harmful to 5\% of patients (they will instead die upon being given the treatment but will live otherwise), and is of absolutely no effect on the rest (30\% and 50\% of patients are destined to live or die, respectively, regardless of the treatment given). We also consider a stochastic version of the model, in which those who will live or die as per the above deterministic model will succumb to the same fate, not absolutely but with a probability of 0.9. To check the validity of the high-dimensional model, we construct a null of a deterministic potential-outcome model where no one is responsive to the treatment (assuming 40\% patients are destined to live, and the other 60\% will die, regardless of the treatment).

We assume that the baseline covariates are normally distributed with a constant variance of one, but with slightly different means for subjects of different potential-outcome types. To be precise, the type-specific means are randomly sampled from a $N(0,\Delta^2)$ normal distribution. In the simulation, we consider 3 scenarios for the association between the measured baseline covariates and the assumed potential-outcome types: (i) weak-to-moderate association ($\Delta^2 = 0.03$), (ii) weak association ($\Delta^2 = 0.01$), and (iii) ultra-weak association ($\Delta^2 = 0.005$). The baseline covariates are assumed to be independent of one another conditional on the potential-outcome types. We also considered the cases of weakly and strongly correlated covariates, where the correlation coefficients between the $i$th and the $j$th baseline covariates are assumed to be $0.5^{i\cdot j}$ and $0.9^{i\cdot j}$, respectively.

We simulate a hypothetical omniscient test to serve as an upper bound for what a real-world high-dimensional test can achieve. To be precise, an omniscient trial analyst knowing the potential-outcome types of all patients and puts this piece of information into the analysis; he/she creates four indicator variables, each indicating whether a subject belongs to a specific potential-outcome type, and then calculates a high-dimensional test treating these indicator variables as four “baseline covariates”.

The “operating characteristic” (OC) of a test is its statistical power averaged over a uniformly distributed $\alpha$-level between 0 and 1. The OC is a value between 0.5 (no power at all) and 1 (highest power possible). It can be converted to a power at a specified $\alpha$-level, if the test statistic is normally distributed: $1 - \Phi(Z_{1-a/2} - \delta) + \Phi(Z_{a/2} - \delta)$, where $\delta = \sqrt{2 \times \text{ZC}}$; and $\Phi(\cdot)$ is the cumulative distribution function, and $Z_c$ the $x$th quantile of the standard normal distribution. In the simulation study, the OC is estimated as the proportion of the simulations that result in a test statistic larger than the same statistic under a random permutation of the data (as described before). If a test statistic happens to be equal to its permuted counterpart, a 0.5 count is assigned.

For each sharp-null scenario, we performed a total of 10,000 simulations to estimate the OC and the type I error rate at $\alpha = 0.05$ (with 99 permutations to derive the null sampling distribution in each round of the simulation).

2.3. Real data analysis

We re-analyzed Gene Expression Omnibus dataset (GSE118657) to illustrate the methodology.\cite{6} The dataset is a Phase II randomized controlled trial assessing the effect of lactoferin on critically ill patients undergoing mechanical ventilation (a total of 61 patients, 32 patients in the lactoferin group, and the remaining, the placebo group). Gene expressions with a total of 49,495 genes were measured at the first day of admission for each patient. The proposed high-dimensional test was used to test the effect of lactoferin treatment using all gene expressions as the baseline covariates ($p = 49,495$). We also examined the effects of using reduced numbers of genes ($p = 1, 2, 5, 10, 20, 50, 100, 200, 500, 1000, 2000, 5000, 10,000, 20,000$, respectively) randomly sampled from the total 49,495 genes (100 random samples were taken and the results were averaged for each scenario). A total of 9999 permutations were performed to derive the null sampling distribution for the high-dimensional test.

2.4. Ethical review

This paper is a methodological study (computer simulation study) and does not involve the enrollment of patients. The real data used in this paper is from public domain. Ethical approval is not necessary.

3. Results

3.1. Simulation study

Figure 1 presents the results when the outcomes follow the assumed deterministic potential-outcome model. For a small RCT ($n = 50$), the traditional test (testing the crude null) has a very low OC of 0.57, whereas the omniscient test can have a very high OC of 0.93. When the sample size increases to $n = 250$, the performance of the traditional test improves, though not by very much (OC = 0.78), whereas the omniscient test now functions impeccably (OC = 1.00).

In a real-world RCT, the potential-outcome types of the patients are, of course, unknown. However, we found that the performance of the hypothetical omniscient test can be replicated using a real-world high-dimensional test (Fig. 1). With a large enough $p$ (more than 10 weak-to-moderate covariates, more than 100 weak covariates, or more than 1000 ultra-weak covariates), the high-dimensional test outperforms the traditional test. For a large RCT (such as when $n = 250$) and with a fairly large $p$ (such as when $p > 10^5$), the high-dimensional test can also become impeccably (OC = 1).

The high-dimensional test is, as it should be, bounded above by the omniscient test in terms of its OC, no matter how strong the association is between the covariates used and the potential-outcome types, and no matter how many there are (Supplementary Fig. 1, http://links.lww.com/MD/D302).

Under the sharp null, the high-dimensional test has an OC close to 0.5 (Table 1) and a type I error rate close to the nominal $\alpha$ level of 0.05 for all scenarios studied (Table 2).

Figure 2 presents the results when the outcomes follow the stochastic potential-outcome model. Again, we see that the
traditional test performs very poorly (OC = 0.55 when n = 50; OC = 0.67 when n = 250). With the stochasticity introduced, a perfect knowledge of the potential-outcome types no longer foretells a subject’s fate exactly (only with an accuracy rate of 0.9 for the assumed model). Yet, the omniscient test still performs remarkably better than the traditional test in a small trial (OC = 0.84 when n = 50), and can even become impeccable in a large RCT (OC = 1.00 when n = 250).

Again, the (real-world) high-dimensional test outperforms the traditional test with a large enough p (Fig. 2). It can also become

Table 1
Operating characteristics of the high-dimensional test under the sharp null.

| Number of subjects (n) and strength of the covariates | Number of baseline covariates (p) |
|------------------------------------------------------|----------------------------------|
| n = 50                                               | 1  2  5  10  20  50  100  200  500  1000  2000  5000  10000 |
| weak to moderate                                     | 0.5038  0.5008  0.4993  0.4947  0.4990  0.4977  0.4974  0.4992  0.4943  0.4981  0.5001  0.5024  0.4977 |
| weak                                                 | 0.4972  0.5001  0.5064  0.5087  0.5048  0.5045  0.5016  0.5048  0.5047  0.5057  0.4984  0.4911  0.4918 |
| ultra weak                                           | 0.5014  0.5069  0.4974  0.4961  0.5004  0.5008  0.4983  0.5058  0.5050  0.5062  0.4985  0.5048  0.5019 |
| n = 250                                              | 0.5005  0.4982  0.4952  0.5017  0.5069  0.5158  0.5072  0.5020  0.5017  0.5055  0.5021  0.4877  0.4949 |
| weak                                                 | 0.5033  0.5000  0.4987  0.5021  0.5043  0.4991  0.4967  0.5009  0.4943  0.4990  0.5095  0.4978  0.5000 |
| ultra weak                                           | 0.4998  0.5067  0.5078  0.5017  0.4980  0.4973  0.4965  0.4962  0.4974  0.4957  0.4906  0.4989  0.4999 |
impeccable in a large RCT (n = 250) with p > 10^6, or with a smaller p if the covariates used are more strongly associated with the potential-outcome types (Supplementary Fig. 2, http://links.lww.com/MD/D302).

Table 3 compares the OCs of the high-dimensional test for independent, weakly correlated, and strongly correlated, baseline covariates. With the same number of baseline covariates, the operating characteristic is lower if the baseline covariates are correlated with one

![Graph](image-url)
another. To make up for the power loss in using correlated covariates, one can include more covariates in the high-dimensional test. For all scenarios studied, OC increases as $p$ increases.

We also performed additional simulations for more complexly distributed baseline covariates (non-normal covariates, a mixed panel of binary and continuous variables, and a mixed panel of signals and noises, see Supplementary Table, http://links.lww.com/MD/D302), and for a patient population with a different potential-outcome-type distribution from that assumed in this study (including ‘monotonicity’ scenarios where the experimental treatment can do only good and no harm\(^{(7)}\)). The basic conclusions are the same though some scenarios may call for a larger $p$ to achieve the same OC as in this paper.

However, the high-dimensional test has no power whatsoever to test the sharp null if none of the baseline covariate collected is a signal, or if the signal-to-noise ratio tends to zero as $p$ tends to infinity. The high-dimensional test is also ineffective if the treatment effect is homogeneous across covariate profiles [e.g., all patients are of the same stochastic potential-outcome type: they all have the same survival probabilities of, say, 0.7(0.4), if given (not given) the treatment].

### 3.2. Real data analysis

Figure 3 presents the $P$ values for the lactoferrin treatment. The traditional test (testing the crude null) has a $P$ value of .36. As the number of baseline covariates (genes) increases, the $P$ values of the high-dimensional test decreases. With 20 genes used, the high-dimensional test has a $P$ value of .32, which is smaller than that of the traditional test. With all 49,495 genes used, the high-dimensional test has a $P$ value of .23, though it is still not significant. To achieve significance (if the sharp null is indeed false for this example), one could include more baseline covariates into the high-dimensional test for the total 61 patients in the trial (as the power of the test is an increasing function of the number of covariates), and ideally covariates of diverse types other than the gene expression data currently used (as the power of the test is compromised for highly correlated covariates such as gene expressions).

### 4. Discussion

The proposed high-dimensional test is based on testing the sharp null. The sharp-null formulation in (2) is self-explanatory: the experimental intervention has no treatment effect whatsoever, for patients of any covariate profile. However, the sharp-null formulation in (3) and (4) seems rather peculiar. A simple two-step conditionality argument (Supplementary Note, http://links.lww.com/MD/D302) may help clarify what this alternative formulation means: (the first step) it is true that there shall be no association unconditionally between treatment assignment and each and every baseline covariate in a dutifully conducted RCT.

| Correlation between covariates | Number of baseline covariates ($p$) |
|-------------------------------|------------------------------------|
|                               | 20       | 50       | 100      | 200      | 500      | 1000     |

#### Table 3
Operating characteristics of the high-dimensional test for independent, weakly correlated, and strongly correlated, baseline covariates ($n = 250$; strength of the covariates: weak to moderate).

| Correlation between covariates | 20       | 50       | 100      | 200      | 500      | 1000     |
|-------------------------------|---------|---------|---------|---------|---------|---------|
| Deterministic potential-outcome model |         |         |         |         |         |         |
| independent                   | 0.595   | 0.685   | 0.756   | 0.826   | 0.929   | 0.976   |
| weakly correlated             | 0.604   | 0.631   | 0.686   | 0.772   | 0.851   | 0.920   |
| strongly correlated           | 0.563   | 0.577   | 0.613   | 0.660   | 0.710   | 0.783   |
| Stochastic potential-outcome model |         |         |         |         |         |         |
| independent                   | 0.556   | 0.625   | 0.654   | 0.728   | 0.826   | 0.883   |
| weakly correlated             | 0.559   | 0.574   | 0.606   | 0.650   | 0.751   | 0.826   |
| strongly correlated           | 0.545   | 0.543   | 0.567   | 0.576   | 0.636   | 0.678   |

Figure 3. $P$ values in GEO118657 dataset analysis (high-dimensional test: solid line; traditional test: dotted horizontal line).
where the sign indicates ‘independence’ or ‘no association’), and (the second step) if the sharp null in (2) is also true (A ⊥ Y|p), then (the result) there shall furthermore be no association between treatment assignment and each and every baseline covariate, conditional on the outcome (the alternative sharp-null formulation, A ⊥ z|Y).

Conventional wisdom holds that testing many variables simultaneously incurs a penalty[8] and many researchers turn to dimension reduction methods to mitigate the problem.[9–12] The “p”-based methods developed by previous researchers approached this multiple-testing problem differently, whereby the dimensionality is no longer a curse but in fact a blessing. For example, Hall et al[13] and Ahn et al[14] studied the geometric properties of high-dimension and low-sample-size data and showed that the group memberships of study subjects can be resolved almost perfectly using their pairwise distances (in high dimension), and Lo and Lee[15] constructed a p-based test to detect weak associations (when p is very large) and Lee[16] further developed a p-based adjustment method to correct for unmeasured confounding biases (again, when p is very large). In this paper, we extend the applicability of the “p”-based approach to RCT settings and show that the high-dimensional test can become very powerful in detecting treatment effects for very large p, the number of baseline covariates.

The current practice of RCTs follows the “n”-based paradigm; the power of a test is gauged by n, the number of study subjects.[5] But this has as limit as the n is bounded above by the world population. By contrast, in this big-data era[17–19] pushing the p of a RCT to the billions, trillions or even more may quickly become possible. The high-dimensional test we proposed in this paper thus provides a means to break the dimensionality is no longer a curse but in fact a blessing. For example, Hall et al[13] and Ahn et al[14] studied the geometric properties of high-dimension and low-sample-size data and showed that the group memberships of study subjects can be resolved almost perfectly using their pairwise distances (in high dimension), and Lo and Lee[15] constructed a p-based test to detect weak associations (when p is very large) and Lee[16] further developed a p-based adjustment method to correct for unmeasured confounding biases (again, when p is very large). In this paper, we extend the applicability of the “p”-based approach to RCT settings and show that the high-dimensional test can become very powerful in detecting treatment effects for very large p, the number of baseline covariates.

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For small or moderate p, say, hundreds, thousands or millions, the high-dimensional test by itself may be underpowered and should best be used in conjunction with the traditional test. A possible solution is to combine the “p”-based sharp-null test in (7) and the “n”-based crude-null test in (5): \( w_{\text{sharp}} \times T_{\text{sharp}} + w_{\text{crude}} \times T_{\text{crude}}, \) where \( w_{\text{sharp}} \) and \( w_{\text{crude}} \) are the weights attached, respectively, to the 2 tests. Further work is needed to study how to set the weights and to examine the statistical properties of this combined test. From our simulation study, the power of the high-dimensional test depends on many factors: the number of baseline covariates, the number of study subjects, the strength of the association between the baseline covariates and the potential-outcome types, the nature of the potential outcomes (deterministic or stochastic), the degree of the correlation between the baseline covariates, the distribution of the baseline covariates, the distribution of the potential-outcome types, etc. Further work is also needed to develop power formula for the proposed high-dimensional test.

5. Conclusions
In this big-data era, pushing p of a RCT to the millions, billions, or even trillions may someday become feasible. And the high-dimensional test proposed in this study can become very powerful in detecting treatment effects.

Author contributions
Conceptualization: Wen-Chung Lee.
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Supervision: Wen-Chung Lee.
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Visualization: Wen-Chung Lee.
Writing – original draft: Wen-Chung Lee.
Writing – review & editing: Wen-Chung Lee.

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