ABSTRACT

Motivation: Power and sample size computation plays an important role in the design and analysis of genetic association studies. Unlike when analyzing a continuous trait, the power of association testing between a binary trait and a genetic variant is influenced by covariate effect sizes, in addition to the genetic effect size. Motivated by this phenomenon, we thus propose and implement an unified methodology for power and sample size computation that can account for the presence of covariate effects of different structures.

Results: Extensive simulation studies show that the proposed method is accurate and computationally efficient for both prospective and retrospective sampling designs with various covariate structures. A proof-of-principle application to the UK Biobank data, focusing on the understudied African sample, shows that ignoring covariate age effect leads to overestimated power (or underestimated replication sample size) when analyzing the binary hypertension trait, while the computation for the continuous blood pressure trait is invariant to covariate effect size.

Availability: The real data example uses the UK Biobank dataset which can be found at https://www.ukbiobank.ac.uk. The R package that implements the proposed method can be found at https://github.com/AgueroZZ/SPCompute. The software/web-page that we used for other methods in section 4 can be found at https://pphs.usc.edu/download-quanto/ and https://www.dartmouth.edu/~eugened/power-samplesize.php.

Keywords GWAS · Power Computation · Binary Trait · Covariate Effect · Replication Study

1 Introduction

Power and sample size estimation is crucial to the design of many scientific studies, including the ubiquitous genome-wide association studies (GWAS) of complex and heritable human diseases and traits [10]. It is well known that replication studies with underestimated sample sizes can result in false negatives, missing single nucleotide polymorphisms (SNPs; G’s) that are truly associated with the phenotype of interest (Y) [20]. Additionally, recent work have shown that failure to correctly estimate power can also result in increased false positives in pleiotropy studies, where different traits are jointly analyzed and their GWAS summary statistics are aggregated [33].

The power calculation for a continuous trait is well established, as the phenotype-genotype association analysis is through the ordinary linear regression model, regressing Y on G and important non-genetic covariates E’s. It is then straightforward to show that power of a genetic association test only depends on the effect size and minor allele frequency (MAF) of the SNP, sample size, and the unexplained phenotypic variance [15]. That is, when analyzing a continuous trait, the sample size with sufficient power is determined by the proportion of phenotypic variance explained by genetic variants, which is also called narrow-sense heritability [38, 13].
In contrast, the power calculation for a binary disease outcome requires additional considerations, as the association analysis typically uses a logistic or probit regression model \([25,31]\). Most heritability estimation methods were rigorously developed only for continuous traits \([35,37]\), and their applications to binary traits have been questioned \([9]\). At the same time, when analyzing a binary outcome \(Y\), power of analyzing a SNP \(G\) is additionally affected by the effect size of a non-genetic covariate \(E\), even if \(E\) is independent of \(G\) and/or there is no \(G \times E\) interaction effect \([25,21]\). Therefore, accurate power and sample estimation for analyzing a binary trait must consider the presence of non-genetic covariates.

There have been several attempts in the literature to consider the general problem of power and sample size computation for a logistic regression model. \([36]\) derived an approximation method, assuming that the disease prevalence is small and the covariates have a joint distribution of multivariate exponential. The approach of \([36]\) was similarly considered by \([12,11,18]\). Based on the asymptotic power approximation of the score or likelihood ratio tests under local alternatives, \([27,28]\) proposed an alternative method that accommodates several categorical covariates with finite configurations, which was then extended by \([30]\) to allow for one categorical covariate with infinite configurations.

For genetic association studies, \textit{Quanto} is the most commonly used software in practice, implementing the method of \([7,8]\). The method uses the expected value of a likelihood ratio test (LRT) statistic and accommodates both continuous and categorical \(E\)’s for power analysis of \(G \times E\) interaction. However, the approach of \([8]\) implicitly assumes that \(G\) and \(E\) are independent of each other, which may not hold in practice for complex diseases \([26,22]\). Further, the implemented software \textit{Quanto} does not accommodate the presence of \(E\) unless the power computation is for \(G \times E\) interaction analysis. That is, \(E\) cannot be included when the analysis is for \(G\).

\([2]\) on the other hand, advocated the use of Wald test to do the power and sample size computation of logistic regression, and proposed a method that allows \(E\) and \(G\) to be dependent through a second stage logistic regression model. However, the implemented web-tool \([5]\) only allows the covariate to be binary, as otherwise the computation does not admit a closed-form expression.

\([17]\) proposed a general approach to compute power for generalized linear models, based on the use of an expanded representative dataset. In the paper, \([17]\) illustrated how their proposed method can be used to compute power of logistic regression when the two covariates are jointly normal. The idea of expanded representative dataset though provides very accurate approximation with good computational efficiency when sample size is small to medium, its computation becomes more cumbersome as the sample size gets large.

In this paper, we propose and implement a generalized method of estimating power and sample size for genetic association studies binary traits that, a) take into account different types of non-genetic covariate \(E\), b) with different types of \(G \times E\) relationship, and c) at high computational efficiency regardless of the sample size. As suggested in \([4]\), the choice of the likelihood based test to perform power computation tends to play a crucial role in scenario such as genetic association study and hence should be chosen as the same one for the future significance testing. Therefore, the proposed method will carry out all the sample size and power computations using the Wald test statistics. The utility of the proposed method is illustrated and compared with the existing methods through both simulation and application studies. The R package that implements the proposed approach is available at \https://github.com/AgueroZZ/SPCompute.

## 2 Preliminary

### 2.1 Models

To study the relationship between a trait \(Y\) and a SNP of interest \(G\) conditional on the non-genetic covariate \(E\), we consider the following generalized linear model (glm):

\[
E(Y|X) = \mu = g^{-1}(\beta_0 + \beta_G G + \beta_E E) = g^{-1}(\eta),
\]

where \(g(\cdot)\) is a specific link function connecting the linear predictor \(\eta\) with the mean function of \(Y\). The design matrix \(X\) has rows \(\{(1, G_i, E_i)\}_{i=1}^n\), where \(n\) is the sample size and the first column of 1 is for the intercept \(\beta_0\). A random pair of \(\{1, G, E\}\) sampled from the population will be denoted by \(X\). For the simplicity of notations, we will use \(\beta = (\beta_0, \beta_G, \beta_E)^T\) to denote both the vector of all regression parameters and the vector of their true values. We use the symbol \(\eta\) to denote the linear predictor, computed as

\[
\eta = X \beta := \beta_0 + \beta_G G + \beta_E E.
\]

The SNP \(G\) is assumed to follow the Hardy Weinberg Equilibrium (HWE) with MAF being \(p\), and by default to be coded additively, so that \(P(G = 2) = p^2, P(G = 1) = 2p(1 - p)\) and \(P(G = 0) = (1 - p)^2\). When the genetic effect is dominant or recessive, \(G\) will be coded as an indicator variable with \(P(G = 1) = p^2 + 2p(1 - p)\) or \(P(G = 1) = p^2\).
This glm model accommodates the analysis of both continuous and binary traits. When traits are continuous, the usual model being used is the ordinary linear regression model, where the link function \( g \) corresponds to the identity function. When traits of interest are binary, one can use models such as logistic model or probit model for the analysis, where the link functions \( g \) respectively correspond to \( g(\mu) = \log\left(\frac{e^\mu}{1 + e^\mu}\right) \) and \( g(\mu) = \Phi^{-1}(\mu) \) with \( \Phi \) being the cumulative density function (CDF) of standard normal distribution. Without loss of generality, we will assume that when the trait is binary, the working model will be a logistic regression model for simplicity of the presentation.

### 2.2 Wald Test

To test the genetic association between the SNP \( G \) and the trait \( Y \), i.e., \( H_0 : \beta_G = 0 \) and \( H_1 : \beta_G \neq 0 \), one can consider test such as Likelihood ratio test (LRT), Score test, or Wald test. These tests have similar asymptotic behaviors under the null hypothesis, due to the classical likelihood theory, and they are locally equivalent in the sense that they have similar distributions under alternatives that are close to the null hypothesis [24, 29]. However, as mentioned in [2], these three likelihood based tests are different globally, which means power and sample size computations may produce different results based on different tests. Since Wald test is routinely used as the default method to test the significance of single regression coefficient, we follow the argument of [2], to carry out the power and sample size computation based on Wald test as well.

The test statistics of Wald test in this case, can be written as

\[
Z = \frac{\hat{\beta}_G}{\sqrt{I_X^{-1}(\hat{\beta})_{[2,2]}^{[2,2]}}},
\]

where \( I_X^{-1}(\hat{\beta})_{[2,2]} \) denotes the second diagonal term of the matrix \( I_X^{-1}(\hat{\beta}) \) and \( \hat{\beta} \) is the MLE estimate. The fisher information matrix \( I_X(\beta) \) is defined as:

\[
I_X(\beta) = X^TW(\beta)X,
\]

where \( W(\beta) \) is a \( n \times n \) diagonal matrix. Explicitly, the \( i^{th} \) diagonal term of \( W \) can be computed as

\[
w_i = (\frac{\partial u_i}{\partial \eta_i})^2 / \text{Var}(Y_i|X_i).
\]

Under the null hypothesis, \( Z^2 \) asymptotically follows a Chi-Square distribution with 1 degree of freedom.

Using the above formula for \( W(\beta) \), it can be directly seen that for quantitative trait analyzed using linear regression model, \( w_i = 1 / \text{Var}(Y_i|X_i) \), and for binary trait analyzed using logistic regression model, \( w_i = f(\eta_i) = \frac{\exp(-\eta_i)}{(1+\exp(-\eta_i))^2} \), where \( f \) denotes the density function of the standard logistic distribution.

### 2.3 Power and Sample Size Computation

Assume the significance level of the genetic association test is \( \alpha \), and the sample size is large enough so the asymptotic distribution of Wald test statistics can be used. Let \( V_G := I_X^{-1}(\hat{\beta})_{[2,2]} \) denotes the asymptotic variance of \( \hat{\beta}_G \) evaluated at the alternative value of \( \beta \). Then the power of this test can be computed as

\[
\Phi\left(-Z_{1-\alpha/2} + \frac{\beta_G}{\sqrt{V_G}}\right) + \Phi\left(-Z_{1-\alpha/2} - \frac{\beta_G}{\sqrt{V_G}}\right),
\]

where the symbol \( Z_{1-\alpha/2} \) denotes the \( 1 - \alpha/2 \) quantile of the standard normal distribution.

Note that the above power computation gets the value of conditional power, which is the power of the testing given that the design matrix \( X \) is already observed and fixed. However, in practice such as sample size determination, the power analysis need to be done before any data point being observed. The power in such case is referred as unconditional power.

To compute the unconditional power, we will replaced the conditional fisher information matrix \( I_X(\beta) \) with its unconditional version \( I_1(\beta) \). Let \( I_1(\beta) \) be the corresponding fisher information matrix for a single random pair of \( X = (1, G, E) \). In the logistic regression case, then

\[
E[I_1(\beta)] = \mathbb{E}_{\theta_X}[wX^TX]
= \mathbb{E}_{\theta_X}\left[\frac{\exp(-\beta_0 + \beta_G G + \beta_E E)}{(1 + \exp(-\beta_0 + \beta_G G + \beta_E E))^2}\right]
\begin{bmatrix}
1 & G & E \\
G & G^2 & GE \\
E & GE & E^2
\end{bmatrix},
\]
where the expectation is taken over the distribution of the covariates space \(X\) (i.e. \(G\) and \(E\)), denoted as \(\mathbb{P}_X\).

Once \(E[I_1(\beta)]\) has been computed for a specific choice of \(\mathbb{P}_X\), one can computes the unconditional information matrix for a random sample of size \(n\) being \(I_n(\beta) := nE[I_1(\beta)]\). The unconditional power then can be computed as:

\[
\Phi(-Z_{1-\alpha/2} + \frac{\beta_G}{\sqrt{V_G}}) + \Phi(-Z_{1-\alpha/2} - \frac{\beta_G}{\sqrt{V_G}}),
\]

(2)

where \(V_G := I_n^{-1}(\beta|2,2)\) is evaluated at the alternative value of \(\beta\).

Once the unconditional power can be computed for each \(n \in \mathbb{N}\), the sample size required to reach a specific power can be computed by simply inverting the power function, as power function is monotonic in \(n\).

3 Methods

3.1 Designing The Covariate Space

To compute the unconditional information matrix \(I(\beta)\), one needs to compute the moments and covariance of a random sample pair \((G_i, E_i)\) from the corresponding covariate space \(\mathbb{P}_X\), which is just its joint distribution. An appropriately designed covariate space \(\mathbb{P}_X\) should be flexible enough to accommodate the dependence structure between the SNP \(G\) and the non-genetic covariate \(E\), while remaining conceptually simple enough in the sense that practitioners can make use of the available knowledge based on the previous studies, to control the potential range of the covariate space \(\mathbb{P}_X\).

In the work of [3], the author implicitly assumes the independence between the SNP \(G\) and the non-genetic covariate \(E\). That means, practitioners will only be required to specify potential range for the marginal distributions of \(G\) and \(E\) during the design stage, to fully describe the covariate space \(\mathbb{P}_X\). Although this makes the method easy to implement during the design space, it is likely that the specified \(\mathbb{P}_X\) is not flexible enough, particularly in cases where there exists clear relationship between \(G\) and \(E\) [14][26][22]. Furthermore, the software Quanto associated to the work of [3] only allows the users to consider the presence of non-genetic covariate \(E\) when the target of analysis is the \(G \times E\) interaction effect. When the goal is to analyze genetic effect \(\beta_G\), this software cannot accommodate the presence of non-genetic covariate, which further restricts its flexibility in practical uses. The work of [2] on the other hands, allows the covariate space \(\mathbb{P}_X\) to accommodate the dependence between a binary \(G\) and a binary \(E\) by introducing a second stage logistic regression:

\[
\log \left( \frac{\mathbb{P}(G = 1|E)}{\mathbb{P}(G = 0|E)} \right) = \gamma_0 + \gamma_E E,
\]

(3)

where the parameter \(\gamma_0\) will be determined by the marginal probabilities that the users provide for \(G\) and \(E\). Therefore, the user will only need to input the knowledge on \(\gamma_E\), besides the parameters to quantify the marginal distributions of \(G\) and \(E\), in order to fully specify the space \(\mathbb{P}_X\). However, the method of [2] is designed for binary exposure (in this case, \(G\)) and binary confounder (in this case, \(E\)), and its generalization to different types of \(G\) and \(E\) is not trivial.

In the proposed methodology and the corresponding software, we extend the second stage regression idea as in [2] to a more general setting. Instead of treating the non-genetic confounder \(E\) as the covariate in the second regression, we consider it to be the response variable, such that:

\[
E(G|E) = g_2^{-1}(\gamma_0 + \gamma_G G),
\]

(4)

where \(g_2\) is the link function of the second stage (generalized) linear regression, being identity when \(E\) is continuous and logit when \(E\) is binary. Practitioners do not have to specify the parameter \(\gamma_0\) in general. Instead, \(\gamma_0\) can be computed based on the marginal information the practitioner inputs to \(G\) and \(E\). The dependency between \(G\) and \(E\) is captured by the regression parameter \(\gamma_G\), whose knowledge can be obtained based on the subject expertise or previous studies.

Comparing to the second stage regression model in equation[3] the proposed way can accommodate different kinds of non-genetic confounder \(E\) and allows different inheritance mode of the SNP \(G\) in an unifying framework. The introduced parameter \(\gamma_G\) shares similar interpretation as the the parameter \(\gamma_E\) in equation[3]. When \(E\) is continuous and the link function \(g_2\) is identity, the second stage regression model also requires the value of \(\text{Var}(E|G)\) in order to be fully specified, which is the similar case for the first stage regression when \(Y\) is a continuous trait with \(q\) being identity. The value of \(\text{Var}(E|G)\) (similarly \(\text{Var}(Y|X)\)) will be computed by the software based on the marginal information such as \(\mu_E, \sigma_E\) and \(p\) specified by the users (also requires \(\mu_Y\) and \(\sigma_Y\) for \(\text{Var}(Y|X)\)).

3.2 Method 1: Semi-Simulation

The estimation of unconditional power heavily depends on the computation of the expected fisher information matrix \(I_n(\beta) = nE[I_1(\beta)]\)). However, unless in some special case such as when both \(G\) and \(E\) are binary, the computation of
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\( \mathbb{E}(I_1(\beta)) \) will not have closed-form expression for general \( \mathbb{F}_X \) \footnote{1}. To estimate the expected fisher information matrix \( \mathbb{E}(I_1(\beta)) \), we will plug in its sample mean estimate.

Specifically, for a large integer \( B \), we simulate independent pairs \( \{G_i, E_i\}_{i=1}^B \) from the covariate space \( \mathbb{F}_X \), and for each single pair of \( \{G_i, E_i\} \) we compute the corresponding conditional fisher information matrix \( I_1^{(i)}(\beta) \). By a simple application of law of large number, we know that the sample mean estimate \( \hat{I}_n(\beta) \) defined as:

\[
\hat{I}_n(\beta) := n \sum_{i=1}^B I_1^{(i)}(\beta)/B,
\]

will converge almost surely to the true expected matrix \( I_n(\beta) \) as \( B \) grows. As we will later illustrate in the simulation studies, for an integer \( B \) that is large enough the estimated unconditional power using \( \hat{I}_n(\beta) \) exhibits little variability between different samples, under the covariate space \( \mathbb{F}_X \) we designed at the above section.

Furthermore, compared to the fully simulation-based power estimation methods, the semi-simulation method proposed above by plugging in sample estimate of \( I_n(\beta) \) does not have computational efficiency issue for extremely large sample size \( n \). Since for each \( I_1^{(i)}(\beta) \) we only compute the observed fisher information matrix for a single observation, the computational load is totally independent of the target sample size \( n \).

Once the unconditional (expected) information matrix \( I_n(\beta) \) is replaced by the sample estimate \( \hat{I}_n(\beta) \), the power computation can proceed using the formula described in equation \footnote{1}.

### 3.3 Method 2: Representative Dataset

An alternative method that does not rely on plugging in the sample estimate of the unconditional fisher information matrix, is through the use of an representative dataset, an idea that was originally suggested from \footnote{19}, and later extended in \footnote{17}.

The idea of using representative dataset can be understood as the following: once a sample size \( n \) is fixed, assume there exists an representative sample \( x := \{x_i\}^n_n := \{(G_i, E_i)\}^n_n \) from covariate space \( \mathbb{F}_X \). Then we expand this representative \( x := \{x_i\}^n_n \) to consider both possible outcomes of \( Y \) \( (y = 1 \) and \( y = 0 \)), so that each observation \( x_i \) splits into \( \{x_i, y_i = 1\} \) and \( \{x_i, y_i = 0\} \). For each new observation, we attach a weight component being \( \mathbb{P}(y_i|x_i) \), so the two weights will sum to 1 for each original observation \( x_i \). We will use symbols \( w_i^0 := \mathbb{P}(Y_i = 0|x_i) \) and \( w_i^1 := \mathbb{P}(Y_i = 1|x_i) \) to denote the two weights associated with the observation \( x_i \). Therefore, the original representative dataset \( \{x_i\}^n_n \) will be expanded into the following larger dataset:

\[
\begin{cases}
  x_i, & y_i = 0, \quad w_i^0 \n \begin{array}{c}
  x_i, \\
  w_i^1
\end{array} \
  x_i, & y_i = 1, \quad w_i^1 
\end{cases},
\]

with twice sample size and two additional columns respectively for the trait status and weight. Standard maximum likelihood estimation on the corresponding weighted log-likelihood of the expanded dataset will yield an value of \( \hat{V}_G \) that can be directly plugged into the equation \footnote{1} to complete the power computation \footnote{17}.

It remains to define what is an representative dataset \( \{x_i\}^n_n \) and how it can be obtained. In the case of conditional power analysis where covariates are already observed, the observed covariate values can be directly used as the representative dataset. For unconditional power analysis where there is no observed covariate value, the representative dataset will be defined using the information that practitioners provide for \( \mathbb{F}_X \). \footnote{17} provides examples on how to define the notion of representative dataset for some specific types of \( \mathbb{F}_X \). We followed the procedures of \footnote{17} to extend the notion in similar ways for the types of \( \mathbb{F}_X \) we considered in section 3.1.

When \( E \) is binary and the link function in equation \footnote{1} is logistic, we can compute the expected counts in each category of \( n_{i,j} = n\mathbb{P}(G = i, E = j) \), using the information such as MAF and inheritance mode. Then when the sample size \( n \) is given but no observations have been observed, one can construct an representative dataset by assigning \( n_{i,j} \) observations to be category \( \{(G = i, E = j)\} \), with appropriate rounding to ensure that \( n_{i,j} \) is integer that sums to \( n \).

When \( E \) is continuous and the link function in equation \footnote{1} is identity with \( \text{Var}(E|G) = \sigma_E^2 \), we first categorize the dataset based on the SNP \( G \) alone, such that \( n_i = n\mathbb{P}(G = i) \) and \( n_i \) sums to \( n \). Then within the \( n_i \) observations of \( \{G_j = i\}^n_{j=1} \), each \( E_j \) will be defined as

\[
E_j = \gamma_0 + \gamma G_i + \sigma_G \Phi^{-1}[(j - 0.375)/(n_i + 0.25)], \quad j = 1, \ldots, n_i,
\]

where \( \Phi^{-1} \) is the quantil function of standard normal. This representative dataset has sample properties converging to the property of \( \mathbb{F}_X \), as each \( n_i \) gets large enough.
4 Simulation Studies

4.1 Accuracies of the proposed methods under different scenarios

To demonstrate the accuracy of the proposed power (sample size) computation methods described in sections 3.2 and 3.3, we compare the power (sample size) computed by the proposed methods with the observed empirical power, as well as those computed using methods of [8] and [2], under three different scenarios for $I_X$. Respectively, the three scenarios correspond to a binary covariate $E$ exists, a continuous covariate $E$ exists and no covariate exists. For completeness of the simulation study, we consider the study design being unmatched case-control in the last scenario, and prospective in other scenarios.

The accuracy of each method is assessed by comparing the computed power with the empirical power observed through 1000 independent replications. Because of the large number of replications used to obtain the empirical power, the empirical power can be viewed as the oracle value for comparison purpose. Using this oracle value, we measure the mean(max) absolute error (AE) of each computed power, aggregating results from different sample sizes. The more accurate approach is expected to have smaller value of both mean and max AE.

4.1.1 Scenario 1: Binary covariate exists with prospective design

In the first scenario, we consider the SNP to be dominant with MAF being 0.1, and there exists a binary non-genetic covariate $E$ with population exposure rate being $P(E = 1) = 0.3$. We assume without loss of generality that the disease prevalence is 20 percent, and observations are obtained independently with prospective sampling design. The parameter $\gamma_G$ that quantifies the dependency between $E$ and $G$ as defined in section 3.1 is assumed to be $\log(0.2)$.

However, the software Quanto [8] only allows case-control design, so we used a unmatched case-control with case-to-control ratio of 1 to 4 in its implementation to approximate the result of prospective design with the corresponding disease prevalence of 20 percent. Also when the target of analysis is on genetic effect, Quanto cannot accommodate the presence of non-genetic covariate, so we only input the information on $G$ for its implementation.

We first compared the computed powers of each method with the empirical power obtained from 1000 replications given a particular value of $\beta_G = \log(1.5)$, and summarized the result in figure 1(a) and table 1 (column 1). For completeness, we then compared the computed sample sizes given target power of 80 percent, for a range of $\beta_G$ from $\log(1.1)$ to $\log(2.5)$. This result is summarized in figure 1(b).

From table 1 we noticed significant difference between the computed powers using Quanto with the empirical powers. This is not unexpected as 1. Our implementation of Quanto has to approximate the prospective design with unmatched case-control design, and 2. Quanto cannot make use of the information of $E$ in its power computation, causing the problem of model misspecification. As illustrated in the relevant figures and table, the proposed approach is very accurate for the computed power and hence the computed sample sizes as well.

4.1.2 Scenario 2: Continuous covariate exists with prospective design

For the second scenario, we consider the case where a continuous covariate $E$ exists in the model. The covariate is assumed to follow normal distribution with mean 0 and standard deviation 1. The dependence parameter $\gamma_G$ is assumed to be $\log(0.2)$. The disease prevalence is assumed to be 20 percent, and we again assume observations are obtained independently using prospective design. For the SNP $G$ we still assume a dominant inheritance mode and a MAF of 0.1.

As in the previous scenario, we ignore the information on $E$ for implementation of Quanto. For the computation using the method of [2], we can dichotomize the continuous covariate $E$ into its binary version to make it compatible. To do that, we define a new binary covariate $\tilde{E} := I(E > 0)$. This corresponds to creating two misspecified models:

$$\logit(Y = 1) = \beta_0 + \beta_G G + \tilde{\beta}_E \tilde{E}$$

and

$$\logit(\tilde{E} = 1) = \tilde{\gamma}_0 + \tilde{\gamma}_G G.$$  (8)

The parameter values specified on the true model cannot directly be applied to the two misspecified models. So we estimate the two misspecified parameters $\tilde{\gamma}_G$ and $\tilde{\beta}_E$ by the following. First, we simulate a large a number of observations $\{G_i, E_i, Y_i\}_{i=1}^{3 \times 10^5}$ using the true model with the parameters specified before. Then we dichotomize the continuous covariate $E$ into binary covariate $\tilde{E}$. Using the binary covariate $\tilde{E}$, we estimate two logistic regressions, respectively regressing $Y$ on $G$ and $E$, and regressing $E$ on $G$. The estimates of $\tilde{\beta}_E$ and $\tilde{\gamma}_G$ will be used as the approximate values for the implementation of the method of [2].
An alternative way to implement the method of [2] for such scenario is to ignore the information provided on the covariate $E$, and only input the information on $G$ for the power/sample size analysis. We consider both implementations for completeness of the comparison. The results were summarized into figures [1](c-d) and table [1] in a similar way as the previous simulation scenario. The figure [1](c) and table [1](column 2) compared the computed powers at different sample sizes, given a particular value of $\beta_G = \log(1.3)$, and the figure [1](d) compared the computed sample sizes given target power of 80 percent, for a range of $\beta_G$ from log(1.1) to log(2.5).

As shown in the figures [1](c-d) and table [1] only the proposed method provides accurate power estimates under this scenario. The method of [2] underestimates the power in both of its implementations, and the method of [8] overestimates the power, which also reflects on the required sample sizes. The inaccuracies of the two existing methods are not unexpected, as these methods either ignore the information provided for $E$, or applied the information of $E$ on the approximating misspecified models. The inaccuracies of these methods on the estimated powers are also reflected on their sample sizes computations, where we noticed all of their computed sample sizes are too low to achieve the target power, especially when $\beta_G$ is relatively small, the typical setting of GWAS studies for complex diseases.

4.1.3 Scenario 3: No covariate exists with case-control design

In the last scenario, we consider the setting where only the dominant SNP $G$ with MAF = 0.1 exists in the model. We consider the samples are obtained using a case-control design with the case to control ratio being 1 to 4. Although the intercept parameter will not affect the power of case-control study, we used an intercept parameter $\beta_0 = -2$ for the replications to compute the empirical power. In each replication, we used the true parameter values on the prospective model to generate a large population pool, and then randomly sample cases and controls from the population to achieve the corresponding sample size.

Although all the input parameters for the covariate space $F_X$ are defined in the prospecctive model that generates the population data, we will ignore the inconsistency brought to the covariate space from the case-control sampling design. This is also implicitly assumed in the examples of [2], which is equivalent to saying the covariate space under prospective sampling has similar distribution to its conditional distribution given the case-control sampling ($F_{X|Y}$).

We first consider the parameter $\beta_G$ is fixed at log(1.5), and compared the computed power curves in figure [1](c) and table [1](column 3). We then also computed the required sample size given power being 0.8 for a range of $\beta_G$ from log(1.1) to log(2.5), and summarized the results in figure [1](f).

Based on the figures and table [1] we can see that all the methods give relatively accurate results of computed powers, and hence for the computation of sample sizes. Therefore, the inconsistency brought from plugging in $F_X$ for $F_{X|Y}$ will not affect the power/sample size estimation significantly in this scenario.

Note that in theory, $F_X$ and $F_{X|Y}$ are not guaranteed to agree [27], as the genotypic frequency observed in the population level will not be the same as the frequency observed in the case-control sample if the SNP is casual. This will become a more complex problem once we also introduce the non-genetic covariate $E$, as the dependency parameter $\gamma_G$ may also not agree between population data and the case-control sample.

4.2 Choice of the integer B

In this section, we will illustrate that for the first proposed method based on the idea of semi-simulation in section 3.2, an reasonably large enough $B$ can make the power/sample size estimation stable enough.

Without the loss of generality, we fixed the parameter values to be the same as in the first scenario of section 4.1 with $\beta_G = \log(1.5)$. At each value of $B$, the estimated powers were independently replicated for 1000 times. We then estimated the standard error of the estimated power from these independent replications.

Based on the result of figure [2]b), we can note that the relationship between $B$ and the standard error of estimated power is approximately log-log linear. Our software takes the default value of $B$ being 20000, which in this case will shrink the standard error to be less than 0.005.

4.3 Selection of Method

To select between the two proposed methods described in section 3.2 and section 3.3, the practitioners should pay attention to the influence of the target sample size $n$ to the computation efficiency of each method.

Conceptually, the method proposed in section 3.2 has its computational efficiency depending on the number of independent pairs drawn from $F_X$ in order to estimate the unconditional fisher information matrix. On the other hand,
the method proposed in section 3.3 does not simulate any observations from $F_X$, but create an representative dataset of size $n$ from it, then expand the representative dataset to size $2n$ and fit the weighted logistic model.

To illustrate that, we fixed $B$ to be 10000, and study the computational time of proposed method in section 3.2 and in section 3.3 for different sample sizes, for the same scenario considered in section 4.1. The results are summarized in figure 2(b).

As shown by the figure, the computation time of the second proposed method based on the idea of representative dataset in section 3.3 is growing with the sample size $n$, while the first proposed method based on semi-simulation will not be affected by $n$. The semi-simulation method is slower than the method based on representative dataset for small $n$, but becomes faster when $n$ is larger than 25000. When $n$ is around 100000, it takes six times longer to run the second method than the first method.

Note that the y axis in figure 2(b) measures the run time in seconds for the computation of one set of parameter values. However in practice, it is often necessary to run power/sample size analysis on a fine grid search of a huge number of possible sets of parameter values, so the run time difference will get aggregated significantly.

Therefore, when the target sample size $n$ is relatively large, our software takes the method of section 3.2 as the default. On the other hand, the software will by default utilize method of section 3.3 to do the power computation.

5 Example on UK Biobank Dataset

In this section, we will illustrate the practical utility of the proposed power computation method using the UK Biobank dataset [32, 1]. For this example, we focused on the analysis of blood pressure in the participants with African background.

We started with the 3460 participants with self-reported ancestry being African. To further take into account the potential problem of ancestry bias, we used the first two population principle components (PCs) provided in the UKB dataset to project whole the self-reported Africans into mostly four clusters, as shown in figure 3(b). We then applied K-means algorithm with $K = 4$ to identify the cluster each individual belongs to using data from PC1 and PC2. As illustrated in figure 3(b-d), this clustering algorithm identified individuals with similar genetic structure.

In the subsequent analysis, we restricted the samples to individuals who are classified into the largest cluster (cluster 1), which includes around 86 percent of all self-reported African participants. Then, we computed new PCs using just the genetic data of the self-reported Africans, and confirmed that individuals within this major cluster indeed have more similar genetic structures than individuals from different clusters. Following the common practice, we further filtered observations using each of the twenty newly computed PCs, by removing a few individuals whose PC scores are four standard deviations away from the mean. After applying the 0.25 threshold on the kinship coefficient and 0.2 threshold on the individual missingness, we left with 2512 approximately unrelated African individuals in our analysis, with 1232 females and 1280 males.

We considered two phenotypes of interest in this example, with one binary trait being hypertension and one continuous trait being (diastolic) blood pressure. In this example, we only considered their measurements at the initial assessment, and for the continuous trait we considered the automated reading instead of the manual reading. There are two measurements on the diastolic blood pressure during the initial assessment, and we took their average as the values of the trait. Among the selected individuals, the prevalence rate of hypertension is around 39.5 percent, and the blood pressure has mean 85.4 and standard deviation 10.75.

The SNPs in the dataset were filtered based on the threshold of HWE deviation ($p$-value $1 \times 10^{-10}$), MAF value (0.01), and missing rate per marker (0.2). After these quality control requirements, we left with 379063 SNPs for the analysis. We used additive codings for all the selected SNPs, both in the GW AS step and in the power computation step later.

For illustration purposes, we then carried out two GWAS studies, one for each trait. For both studies, we assumed the covariate being adjusted is age, with mean being 51.2 years old and standard deviation being around 7.9 computed from the samples. The analysis of binary trait is carried on a logistic regression model, and the analysis of continuous trait is on a linear regression model.

The two GWAS results are displayed in figure 4(a-b). As shown in the figure, neither the binary trait hypertension nor its continuous counterpart blood pressure has SNP with effect reaching the genome-wide significance of $5 \times 10^{-8}$. Using the computed powers from the proposed method, we will show that the importance of adjusting for covariate will be much larger in the case of binary trait compared to continuous trait. Because of the complex nature of sex chromosome, only the twenty two autosomes are considered in this application example.
As a proof-of-principle, we focused the SNPs with top five significance in each trait. To utilize the proposed method, information such as covariate effect size and SNP effect size will be needed, and we plugged in their sample estimates as the true values at the alternative hypothesis, and proceed with the power computation. To illustrate the role of covariate age in each trait, we computed powers both with and without considering the influence of age.

For each trait, the computed powers for the top SNPs are shown in figure 5(a-b). As shown in the figure, computed power without considering the presence of age is significantly larger than the computed power with adjustment for age, when the trait is binary. This implies ignoring the covariate effect of age can underestimate the required sample size and hence make results overly optimistic at a given sample size. On the other hand, there is almost no difference between the two computed powers in the analysis of continuous trait. This is not unexpected, as mentioned in section 2.2, the power of testing $\beta_G$ will not depend on the size of $\beta_E$ when the working model is linear regression. Although there are still tiny differences in the computed powers, they are caused by the dependency between age and the SNP (i.e. $\gamma_G$) instead of the covariate effect (i.e. $\beta_E$). Such difference will not be observed if the dependency parameter $\gamma_G$ is zero.

Similarly, the same phenomenon can be observed in terms of the required replication sample size. We computed the required replication sample size for each trait to achieve 80 percent replication power, and summarized the results in figure 5(c-d). It can be noticed that for the binary trait hypertension, ignoring the covariate effect caused obvious under-estimation of the replication sample size, whereas the computed sample sizes are unaffected for the continuous trait blood pressure.

In summary, we have shown in this real data example, that accounting for the covariate is much more important for the analysis of binary trait compared to the analysis of continuous trait, as power of testing $\beta_G$ is both affected by the size of $\beta_E$ and the dependency parameter $\gamma_G$ for binary trait, but only tangentially affected by the dependency parameter $\gamma_G$ for continuous trait. We also illustrated again how the proposed method works well to adjust for the presence of covariate, for both types of traits.

6 Discussion

In summary, we extended the works of [2] and [17], to provide a power/sample size computation methodology (software) for genetic association study with binary traits, that allows different types of covariate effect to be accommodated in a computationally efficient manner. We demonstrated the accuracy and feasibility of the proposed approach in section [4] and used the UKB data to show how the proposed method can be used in practice.

However, there are still some limitations of the proposed method that require future works to address. For example in GWAS studies, winner’s curse where the effect size estimates of significant SNPs are biased upward is known to be a common problem [6, 39, 5]. Therefore, it would be of interest to investigate how to account for the winner’s curse during the power/sample size computation. Another direction of extension would be to take into account the mis-classification of control data during the sampling step, which has been shown to have a influence on the power of association study [16].

Although the proposed method/software by default assumes all the parameters are specified on the prospective model which generates the population data, it can also be applied to data collected through case-control design by modifying the disease prevalence parameter to reflect the assumed case-control ratio, as shown in the example from [2].

We also demonstrated in the simulation section that the proposed methods can still provide reliable estimates when parameters are specified on the prospective model but data are collected through case-control design. However, it should be noticed that unlike the regression parameters $\beta_G$ and $\beta_E$, the covariate space $P_X$ can be very different once being conditioned on the case-control ratio [27, 23].

The above GWAS analysis in section [5] only serves as a proof-of-principle and highlights the practical utility of the proposed power/sample-size computation method. We made several simplifying assumptions to make the example easier to be understood. In practice, there are also issues such as winner’s curse that could significantly biased the computed results, since we only focused on the SNPs with top significance, which introduce a up-ward selection bias on the effect size estimates of $\beta_G$.

The framework of the proposed method/software can be easily generalized to incorporate the gene-gene, gene-environment interaction effect, which we leave to do in our future software updates.

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Data Availability Statement

The UK Biobank data were used under the license for this study (application number 64875). Data are available at https://www.ukbiobank.ac.uk/ with the permission of UK Biobank.
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Figure 1: Simulation results for the three scenarios considered in section 4.1. Scenario 1 (S1) is the prospective sampling design with a binary covariate, Scenario 2 (S2) is the prospective sampling design with a continuous covariate, and Scenario 3 (S3) is the retrospective case-control sampling design without covariates. Red lines represent the power ((a), (c) and (e)) and sample size ((b), (d) and (f)) computed using the ‘semi-simulation’ (Proposed 1) method proposed in Section 3.2, blue lines using the ‘representative dataset’ (Proposed 2) method proposed in Section 3.3, green and pink lines using the method of [2] (in S2 the method of [2] was implemented with dichotomized E and without considering E), and purple lines using Quanto [8]. In figures (a), (c) and (e), the black solid lines represent the (empirical) oracle power.
Table 1: The average and maximum absolute error (AE), across different sample sizes, between the oracle and computed power using different methods for the three scenarios considered; see legend to Figure 1 for details. The Proposed 1 is the ‘semi-simulation’ method in Section 3.2. The proposed 2 is the ‘representative dataset’ method in Section 3.3. In Scenario 2, the method of [2] was implemented with dichotomized $E$ and without considering $E$ (results*).

Figure 2: Figure (a) displays the relationship between the runtime in seconds per computation for each method across different sample sizes, using simulation scenario 1; results for the other two scenarios are characteristically similar. The Proposed 1 is the ‘semi-simulation’ method in Section 3.2. The proposed 2 is the ‘representative dataset’ method in Section 3.3. Figure (b) shows that there is a linear relationship between the log standard error (SE) of estimated power and the log number of replicates (B) used for the proposed ‘semi-simulation’ method 1.
Figure 3: Population principle components (PC) plots for (a) the whole UK Biobank sample, and (b)–(d) the self-reported African sample. In Figures (b)–(d) four clusters were identified by a K-mean algorithm as discussed in Section 5.
Running Title for Header

(a) The (binary) hypertension trait

(b) The (continuous) blood pressure trait

Figure 4: GWAS Manhattan results for the (binary) hypertension trait and the (continuous) diastolic blood pressure trait, using the African sample (n = 2,512) of the UK Biobank data as discussed in Section 5. Leading SNP in each chromosome is annotated by its rs ID. No SNPs reached genome-wide significance level of 5e-8.
Figure 5: Powers ((a) and (b)) and sample sizes ((c) and (d)) estimation for top five-ranked SNPs identified in GWAS of the binary hypertension trait ((a) and (c)) and the continuous diastolic blood pressure trait ((b) and (d)), using the African sample ($n = 2,512$) of the UK Biobank data as discussed in section 5. GWAS results in Figure 4. The red bars are the computed power or sample size (to achieve 80% power at $\alpha = 5e^{-8}$) with adjustment for age, and the blue bars are the values without considering age. The higher blue bars in figure (a) show that ignoring covariate effect leads to overestimated power for analyzing a binary trait. The shorter blue bars in figure (c) show ignoring covariate effect leads to underestimated replication sample size for analyzing a binary trait.
Figure 6: PCs plots of self-reported Africans using the PCs computed from self-reported Africans for section 5. Clusters identified by the K-means algorithm are shown in different colors in (b)-(d). Figure (a) is the elbow plot of newly computed PCs, which shows the first four PCs explained the majority of the total variance.