# Comparing Apples and Oranges: Equating the Power of Case-Control and Quantitative Trait Association Studies

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Genome-wide association studies have achieved unprecedented success in the identification of novel genes and pathways implicated in complex traits. Typically, studies for disease use a case-control (CC) design and studies for quantitative traits (QT) are population based. The question that we address is what is the equivalence between CC and QT association studies in terms of detection power and sample size? We compare the binary and continuous traits by assuming a threshold model for disease and assuming that the effect size on disease liability has similar feature as on QT. We derive the approximate ratio of the non-centrality parameter (NCP) between CC and QT association studies, which is determined by sample size, disease prevalence ($K$) and the proportion of cases ($v$) in the CC study. For disease with prevalence $<0.1$, CC association study with equal numbers of cases and controls ($v = 0.5$) needs smaller sample size than QT association study to achieve equivalent power, e.g. a CC association study of schizophrenia ($K = 0.01$) needs only ~55% sample size required for association study of height. So a planned meta-analysis for height on ~120,000 individuals has power equivalent to a CC study on 33,100 schizophrenia cases and 33,100 controls, a size not yet achievable for this disease. With equal sample size, when $v = K$, the power of CC association study is much less than that of QT association study because of the information lost by transforming a quantitative continuous trait to a binary trait. *Genet. Epidemiol.* 2009. 

**Key words: association; case-control study; quantitative trait**

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## INTRODUCTION

The first wave of genome-wide association studies (GWAS) has identified an unprecedented number of genetic variants that influence disease risk or quantitative trait (QT) variation. Most associated variants have small effect sizes and account for only a small fraction of phenotypic variation [Goldstein, 2009; McCarthy et al., 2008; Visscher, 2008; WTCCC, 2007]. More studies are on the way either for case-control (CC) association study of disease or for QT association study of complex phenotypes. One question that arises is: What is the equivalence between CC and QT association studies in terms of detection power and sample size? For example, how many cases and controls are needed for a CC association study of schizophrenia to achieve equivalent power of an association study for height? Results from GWAS studies suggest a large number of variants with small effects underlying most common diseases. Therefore, the liability-threshold model is likely to be a reasonable description of the relationship between the unobserved disease liability (continuous) and the observed disease status (all-or-none) [Dempster and Lerner, 1950; Falconer and Mackay, 1996; Gottesman and Shields, 1967]. On the one hand, CC association studies necessarily use observations on the less informative observed disease scale, but are enriched by gathering a greater proportion of cases than in the general population. What is the trade-off between these two? In this study, we derive a simple analytical equation to calibrate the relationship of CC and QT association studies on power and sample size issues. We show how the disease prevalence and the proportion of cases in the sample balance the loss and gain of power for CC association study as compared with QT association study.

## METHODS

Consider a complex disease with population prevalence of $K$, and assume a causal variant having two alleles (A and a) with frequencies of $p$ and $(1-p)$. Let $(1-p)^2$, $2p(1-p)$ and $p^2$ be the frequencies of genotypes aa, Aa and AA (in Hardy-Weinberg equilibrium), with risks of $f_0$, $f_1$ and $f_2$. If we assume a multiplicative model [Risch, 1990], then $f_1 = f_0 \times \lambda$ and $f_2 = f_0 \times \lambda^2$, where $\lambda$ is the relative risk with respect to the causal variant. For a CC association study, let $p_1$ and $p_2$ be the frequency of allele A in cases and controls, respectively, with

$$p_1 = \frac{p\lambda}{p\lambda + 1 - p}$$

and

$$p_2 = \frac{p}{1-K}\left(1 - \frac{K\lambda}{[1 + p(\lambda - 1)]}\right)$$

(Appendix). The non-centrality parameter (NCP) of a $\chi^2$ test for association in the CC design is

$$\mathrm{NCP}_{01} = \frac{(p_1 - p_2)^2}{\mathrm{var}(\hat{p}_1 - \hat{p}_2)}$$

with $\mathrm{var}(\hat{p}_1 - \hat{p}_2) = \frac{1}{2}p(1-p)N_{01}(\frac{1}{v} + \frac{1}{1-v})$, where $N_{01}$ is the sample size, and $v$ is the proportion of cases. So,

$$\mathrm{NCP}_{01} = \frac{2p(1-p)(\lambda-1)^2 v(1-v)N_{01}}{(1-K)^2[1+p(\lambda-1)]^2}$$

Under a liability-threshold model, denote $q^2$ as the proportion of liability variance explained by the causal variant. If $\lambda$ is small, $[1+p(\lambda-1)]^2 \approx 1$ and $q^2 \approx 2p(1-p)(\lambda-1)^2/i^2$ [Dempster and Lerner, 1950; Lynch and Walsh, 1998], where $i = z/K$ with $z$ the height of standard normal curve at the truncation point pertaining to a disease prevalence of $K$, e.g. if $K = 0.05$, $z = 0.103$, $i = 2.063$. Hence,

$$\mathrm{NCP}_{01} \approx \frac{i^2 v(1-v)N_{01}q^2}{(1-K)^2} \quad (1)$$

For QT association study, assuming that we have $N_{\mathrm{QT}}$ individuals randomly sampled from the general population, we can detect the a causal variant with an effect on the variance of $q^2$ by

$$\mathrm{NCP}_{\mathrm{QT}} = \frac{N_{\mathrm{QT}}q^2}{1-q^2} \quad (2)$$

If the effect size is small, $1 - q^2 \approx 1$, then $\mathrm{NCP}_{\mathrm{QT}} \approx N_{\mathrm{QT}}q^2$. Therefore, the ratio of NCP between CC and QT association is

$$\frac{\mathrm{NCP}_{01}}{\mathrm{NCP}_{\mathrm{QT}}} = \frac{i^2 v(1-v)N_{01}}{(1-K)^2 N_{\mathrm{QT}}} \quad (3)$$

Hence we only need to know the disease prevalence and proportion of cases and controls to be able to compare the power to detect a locus affecting a disease in a CC study and the power to detect a locus affecting a QT which has the same properties as the liability underlying the disease. We used the Genetic Power Calculator [Purcell et al., 2003] to check the results of Equation (3).

# RESULTS

Under the assumption that the effect size is small, the ratio of NCP between CC and QT is independent from $q^2$ and $p$, and we take the arbitrary parameters $q^2 = 0.1\%$ and $p = 0.5$. We set a range of $K$ from 0.0001 to 0.1 and a range of $v$ from 0.1 to 0.5. We calculated the approximate values of NCP ratios by Equation (3) and plotted them against the exact values calculated by Genetic Power Calculator (Fig. 1). The result shows that the approximate values are highly consistent with the exact values with regression coefficient of 1.04 and $R^2$ of 0.998. Then, we used Equation (3) to compare CC and QT association studies in two scenarios: (I) to compare the required sample size to achieve equivalent detection power (Fig. 2); (II) with equal sample size, to compare the detection power via the

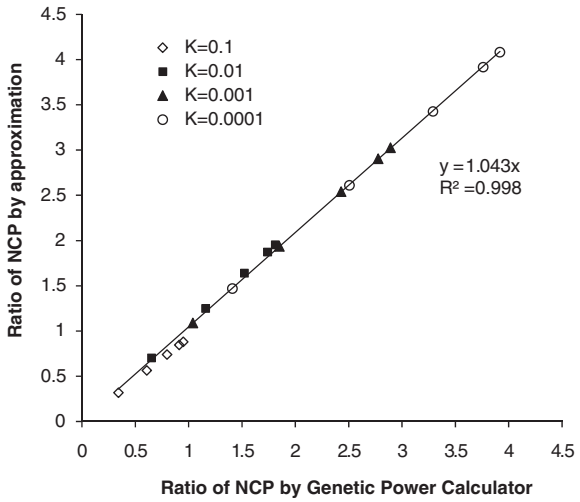


**Fig. 1. Plot of approximate ratio of non-centrality parameter (NCP) between case-control and quantitative trait association studies by Equation (3) against that calculated by Genetic Power Calculator [Purcell et al., 2003] for disease prevalence ($K$) ranging from 0.0001 to 0.1 and proportion of number of cases ranging from 0.1 to 0.5.**

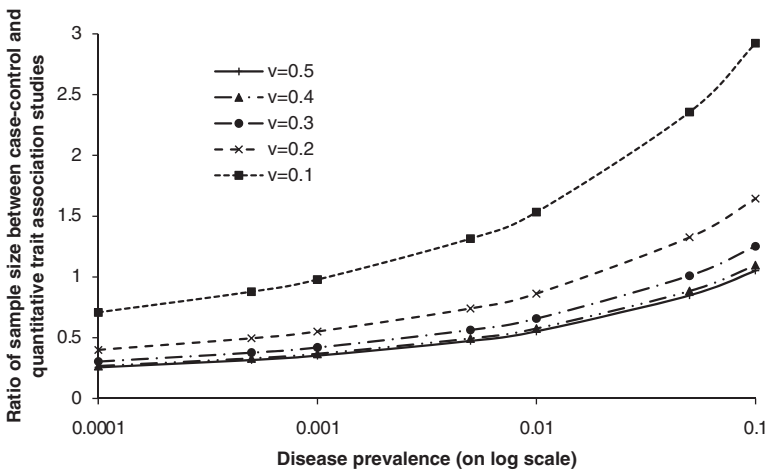


**Fig. 2. Ratio of sample size between case-control and quantitative trait association studies with equivalent detection power. $v$ is the proportion of number of cases.**

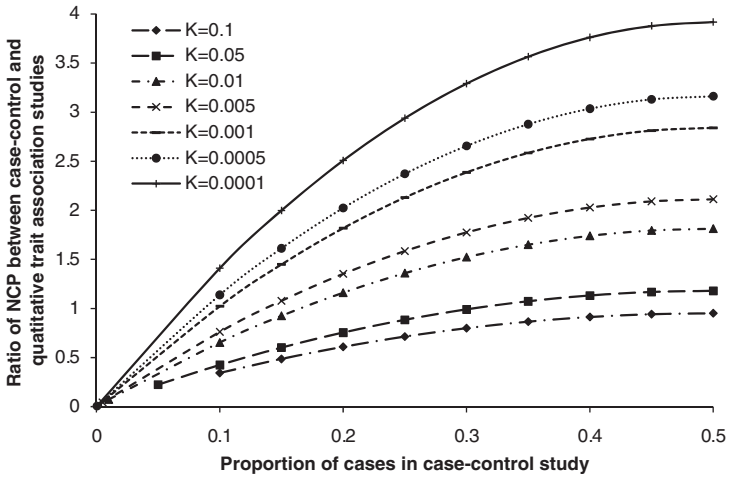


**Fig. 3. Ratio of non-centrality parameter (NCP) between case-control and quantitative trait association studies with equal sample size. For the first point of each plot, the proportion of number of cases is equal to the disease prevalence (*K*).**

ratio of NCP (Fig. 3). When $NCP_{01} = NCP_{QT}$ and $v = 0.5$, Equation (3) reduces to $N_{01}/N_{QT} = 4(1-K)^2/i^2$, which ranges from 0.26 to 1.05 for $K$ from 0.00001 to 0.1. Therefore, for diseases with prevalence $<0.1$, CC association study with equal numbers of cases and controls needs smaller sample size than QT association study to achieve equivalent power. For example, a CC association study of schizophrenia with prevalence of 0.01 [Sullivan et al., 2003], needs only 55% of sample size required for a QT association study of height, assuming equal effect sizes on the liability scale for schizophrenia and the observed scale of height.

If the subjects in a CC study are randomly sampled from the general population, we can derive how much power of association is lost by transforming the continuous disease liability (if we could measure it) to a dichotomous scale. In this case, $N_{01} = N_{QT}$ and $v = K$, thus $NCP_{01}/NCP_{QT} = i^2K/(1-K)$ [Dempster and Lerner, 1950; Lynch and Walsh, 1998], which ranges from 0.0016 to 0.34 for $K$ from 0.0001 to 0.1 (starting point of each plot in Fig. 3). For schizophrenia and height, the ratio of NCPs is ~0.07 when $v = 0.01$, which means a loss of power of 93% for schizophrenia due to the transformation of underlying scale to observed scale, however, NCP increases to ~1.81 when $v = 0.5$, which means a gain in power of 174% by collecting proportionally 50 times more cases in the sample than that in the general population.

The power to detect an associated variant of a CC association study does not dramatically decrease with decreasing of $v$ from 0.5 to 0.2 (Fig. 3). For diseases with prevalence rates ranging from 0.0001 to 0.01, when sample sizes are equal, CC association studies with 20% cases have already equal or more power than QT association studies.

# DISCUSSION AND CONCLUSIONS

We derived an approximate analytical equation to calibrate the relationship of CC and QT association studies in terms of power to detect an associated variant and sample size. When compared with QT association on a continuous phenotype, CC association on binary trait loses a certain amount of power but usually gains more when having at least 20% of cases in the sample. For diseases with prevalence $<0.1$, the commonly used CC association study with equal numbers of cases and controls needs a smaller sample size than a QT association study, i.e., CC association is more powerful. Qualitatively these results may not be surprising, but we provide a simple quantification of this relationship in Equation (3). Let us consider samples sizes for a CC association study of schizophrenia, compared to the sample size for a QT association study of height; we choose to compare these complex phenotypes because each is estimated to have heritability of ~80% for the normally distributed phenotype. The planned GIANT meta-analysis of height [Hirschhorn, Personal Communication] of ~120,000 individuals is equivalent to ~33,100 cases and ~33,100 controls for schizophrenia. As compared with the planned meta-analysis for schizophrenia of ~9,600 cases and ~13,500 controls [Cichon et al., 2009], the planned meta-analysis of height has approximately 5 times more sample size, and will have ~3 times more detection power ($NCP_{QT}/NCP_{01} \approx 3$).

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# APPENDIX [Risch, 1990; Wray et al., 2007]

The frequencies of genotypes AA and Aa in cases are

$$P(\mathrm{AA}|\mathrm{case}) = \frac{P(\mathrm{case}|\mathrm{AA})P(\mathrm{AA})}{P(\mathrm{case})} = \frac{p^2 f_0 \lambda^2}{K}$$

$$P(\mathrm{Aa}|\mathrm{case}) = \frac{P(\mathrm{case}|\mathrm{Aa})P(\mathrm{Aa})}{P(\mathrm{case})} = \frac{2p(1-p)f_0\lambda}{K}$$

So, $p_1 = 0.5P(\mathrm{Aa}|\mathrm{case}) + P(\mathrm{AA}|\mathrm{case}) = f_0(p\lambda + 1 - p)p\lambda/K$. Since $K = p^2 f_0 \lambda^2 + 2p(1-p)f_0\lambda + (1-p)^2 f_0$, we can get $f_0 = K/[1 + (\lambda - 1)p]^2$. Therefore,

$$p_1 = \frac{K}{(p\lambda + 1 - p)^2}\frac{(p\lambda + 1 - p)p\lambda}{K} = \frac{p\lambda}{p\lambda + 1 - p}$$

Similarly,

$$P(\mathrm{AA}|\mathrm{control}) = \frac{P(\mathrm{control}|\mathrm{AA})P(\mathrm{AA})}{P(\mathrm{control})} = \frac{p^2(1 - f_0\lambda^2)}{1 - K}$$

$$P(\mathrm{Aa}|\mathrm{control}) = \frac{P(\mathrm{control}|\mathrm{Aa})P(\mathrm{Aa})}{P(\mathrm{case})} = \frac{2p(1-p)(1 - f_0\lambda)}{1 - K}$$

we get

$$\begin{aligned} p_2 &= 0.5P(\mathrm{Aa}|\mathrm{control}) + P(\mathrm{AA}|\mathrm{control}) \\ &= \frac{p}{1-K}(1 - f_0\lambda[1 + p(\lambda - 1)]) \end{aligned}$$

Substitute $f_0$ by $K/(p\lambda + 1 - p)^2$,

$$p_2 = \frac{p}{1-K}\left(1 - \frac{K\lambda}{[1 + p(\lambda - 1)]}\right)$$