Power of the Classical Twin Design Revisited

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Statistical power of the classical twin design was revisited. The approximate sampling variances of a least-squares estimate of the heritability in a univariate analysis and estimate of the genetic correlation coefficient in a bivariate analysis were derived analytically for the ACE model. Statistical power to detect additive genetic variation under the ACE model was derived analytically for least-squares, goodness-of-fit and maximum likelihood-based test statistics. The noncentrality parameter for the likelihood ratio test statistic is shown to be a simple function of the MZ and DZ intraclass correlation coefficients and the proportion of MZ and DZ twin pairs in the sample. All theoretical results were validated using simulation. The derived expressions can be used to calculate power of the classical twin design in a simple and rapid manner.

Power calculations for twin designs are useful when designing experiments to estimate variance components and to test hypotheses regarding the nature of phenotypic similarity of twins. Power calculations can be performed using asymptotic theory (Lynch & Walsh, 1998; Martin et al., 1978) or computer simulation studies based upon, for example, likelihood theory (Neale et al., 1994; Neale & Maes, 2004; Posthuma & Boomsma, 2000). Martin et al. (1978) provided a comprehensive theoretical analysis of the power of the classical twin design using weighted least-squares to estimate variance components and a goodness-of-fit test to reject 'false' models. Nowadays, maximum likelihood is commonly used to estimate variance component from twins or twin families using versatile computer programs such as Mx (Neale et al., 2002). Surprisingly, most of the literature on the estimation of parameters from twin designs is of the 'black-box' category, in that no explicit equations are given for the sampling variances of the parameter estimates and for statistical power. In this study we derive simple equations to calculate the power of twin designs under the common ACE model, constrasting least-squares with maximum likelihood and goodness-of-fit tests. Equations are presented for the sampling variance of the estimate of the heritability, the proportion of variance due to common environmental effects, and the estimate of the genetic correlation coefficient in a bivariate analysis. The noncentrality parameter for a maximum likelihood-ratio test for genetic variance is given as a simple function of the population parameters. All predictions are verified using computer simulation.

Assumptions and Notation

Throughout, we assume the commonly used ACE model, for which the phenotypic variance is partitioned in an additive genetic (A), common environmental (C) and residual environmental (E) component. The proportions of phenotypic variance due to these random effects are h^2, c^2 and e^2, respectively. Predictions are first made using least squares (LS), from the properties of mean squares, which are the underlying sufficient statistics in the classical twin design. Subsequently, derivations are derived for (residual) maximum likelihood. Parameters are scaled so that total phenotypic variance is 1.0. The total variance (var(y)) is then partitioned as, $\mathrm{var}(y) = h^2+c^2+e^2 = 1$. For a bivariate analysis, a derivation is given for the sampling variance of the estimate of the genetic correlation coefficient, using least squares. Other parameterisations and analysis methods (e.g., Jinks & Fulker, 1970) were not investigated because they are not used in practice.

Theory

Univariate models

Least squares

Consider the between-pair (B) and within-pair (W) observed mean squares (MS) in the standard ANOVA Table for *n* pairs, where the pairs can be either dizygotic (DZ) or monozygotic (MZ)

	df	MS	E(MS)
between pairs	$n-1$	B	$2\sigma_b^2 + \sigma_w^2$
within pair	n	W	σ_w^2

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The expected mean squares and between- and within-pair variances for the ACE model, when scaled by the phenotypic variance, are

	E(B)	E(W)	σ_b^2	σ_w^2
MZ pairs	$2(h^2+c^2) + (1-h^2-c^2)$	$(1-h^2-c^2)$	h^2+c^2	$(1-h^2-c^2)$
DZ pairs	$2(\frac{1}{2}h^2+c^2) + (1-\frac{1}{2}h^2-c^2)$	$(1-\frac{1}{2}h^2-c^2)$	$\frac{1}{2}h^2+c^2$	$(1-\frac{1}{2}h^2-c^2)$

The variance of the observed mean squares (MS) are

$$\text{var(MS)} = 2\ \text{E(MS)}^2/df$$

with *df* the degrees of freedom. Hence the variance of the estimate of the between-pair component is

$$\text{var}(\hat{\sigma}_b^2) = \text{var}((B-W)/2)$$

$$= \tfrac{1}{4}\left(\frac{2E(B)^2}{n-1} + \frac{2E(W)^2}{n}\right)$$

$$\approx \frac{1}{2n}\left(E(B)^2 + E(W)^2\right)$$

From the ANOVA the estimate of the intraclass correlations is calculated as

$$\hat{t} = [(B-W)/2] / [(B-W)/2+W] = (B-W) / (B+W)$$

Doing this for *m* MZ pairs and *n* DZ pairs gives $\hat{t}_{MZ}$ and $\hat{t}_{DZ}$. A first-order approximation of the variance of these correlations is (see, e.g., Visscher, 1998; and Lynch & Walsh, 1998 for balanced one-way designs)

$$\text{var}(\hat{t}_{MZ}) \approx (1-t_{MZ})^2(1+t_{MZ})^2/m = (1-t_{MZ}^2)^2/m$$

$$\text{var}(\hat{t}_{DZ}) \approx (1-t_{DZ})^2(1+t_{DZ})^2/n = (1-t_{DZ}^2)^2/n$$

The estimates of the genetic and common environmental components, and their approximate variances are

$$\hat{h}^2 = 2(\hat{t}_{MZ} - \hat{t}_{DZ})$$

$$\text{var}(\hat{h}^2) = 4\,[\text{var}(\hat{t}_{MZ}) + \text{var}(\hat{t}_{DZ})] = 4[(1-t_{MZ}^2)^2/m + (1-t_{DZ}^2)^2/n] \qquad [1]$$

or, in terms of the causal components,

$$\text{var}(\hat{h}^2) = 4\{\,[1-(h^2+c^2)^2]^2/m + [1-(\tfrac{1}{2}h^2+c^2)^2]^2/n]\,\}$$

Similarly, the estimate and sampling variance of the proportion of variance due to common environmental effects is

$$\hat{c}^2 = 2\hat{t}_{DZ} - \hat{t}_{MZ} \text{ and}$$

$$\text{var}(\hat{c}^2) = 4\text{var}(\hat{t}_{DZ}) + \text{var}(\hat{t}_{MZ}) = 4(1-t_{DZ}^2)^2/n + (1-t_{MZ}^2)^2/m$$

Equation [1] implies that for a given total number ($N = n+m$) of twin pairs, the sampling variance of the estimate of the heritability is minimised when

$$n/m = (1-t_{DZ}^2) / (1-t_{MZ}^2)$$

The optimum proportion of MZ pairs (p_{MZ}) is

$$p_{MZ} = (1-t_{MZ}^2) / [(1-t_{DZ}^2) + (1-t_{MZ}^2)] \qquad [2]$$

Except for the trivial case when $h^2 = 0$, this ratio is smaller than ½. Hence, if the cost of phenotyping is limiting and many twin pairs are available for phenotyping, then an optimum design would have more DZ than MZ twin pairs if the data are analyzed using least squares. For example, for $t_{MZ} = 0.5$ and $t_{DZ} = 0.25$, $n/m = 1.25$, that is, approximately 56% DZ and 44% MZ pairs. If $t_{DZ} = \frac{1}{2}t_{MZ}$ (AE model), and the correlation is small, then $n/m \approx 1 + \frac{1}{2}h^4$. Unless the heritability is very large (>> 0.50), this suggests that the optimum design is close to a 1:1 ratio of DZ and MZ pairs.

Power and sample size. For large samples, the quantity $\lambda = (h^2/SE(\hat{h}^2))$ is the expected mean test statistic of a normal test. Its square is approximately equal to the noncentrality parameter (NCP) of a chi-square test statistic. The NCP per total number of pairs (*N*) is, from Equation [1],

$$NCP_{LS}/N = (t_{MZ}-t_{DZ})^2 / [(1-t_{MZ}^2)^2/p_{MZ} + (1-t_{DZ}^2)^2/(1-p_{MZ})] \qquad [3]$$

For a statistical test we assume that under the null hypothesis of $h^2 = 0$ ($\lambda = 0$)

$$T = \hat{h}^2/SE(\hat{h}^2) \sim N(0,1)$$

Under the alternative hypothesis, $T \sim N(\lambda,1)$. This allows a simple prediction of power. If $z_{1-\alpha}$ is the one-sided (upper tail) threshold from a standard normal distribution corresponding to a type-I error rate of α, and β the type-II error rate, then, for a one-sided test

$$\text{Power} = 1-\beta = \text{Prob}(x > z_{1-\alpha}-\lambda)$$

with x a standard *N*(0,1) random variable. Alternatively we can express the required power for a given value of the heritability in terms of the MZ and DZ sample size

$$z_\beta = z_{1-\alpha}-\lambda, \text{ or, } \lambda = z_{1-\beta} + z_{1-\alpha}$$

Using the variance of the estimate of the heritability

$$\lambda^2 = h^4 / \text{var}(\hat{h}^2) = (z_{1-\alpha} + z_{1-\beta})^2$$

For a given proportion of MZ twins in the sample, the required total number of twins is, from Equation [3]

$$N = 4(z_{1-\alpha}+z_{1-\beta})^2\,[(1-t_{MZ}^2)^2/p_{MZ} + (1-t_{DZ}^2)^2/(1-p_{MZ})]/h^4$$

For example, if $p_{MZ} = ⅓$, $\alpha = 0.05$, $(1-\beta) = 0.80$, $h^2 = 0.5$ and $c^2 = 0.20$, then $z_{1-\alpha} = 1.64$ $z_{1-\beta} = 0.84$ and $N = 172$ twin pairs, $n = 115$ DZ and $m = 57$ MZ pairs. The optimal design for these parameters (from Equation [2]) is $n = 103$ and $m = 66$, for a total sample size of 169 twin pairs.

Table 1

Total Number of Pairs Required for a Power of 0.95 to Reject the CE Hypothesis When it is False at a Type-I Error Rate of 0.05

True model		Martin et al. (1978)		Maximum likelihood	
		pMZ[1]		pMZ	
h^2	c^2	0.5	Optimised[2]	0.5	Optimised
0.8	0.1	68	42 (0.9)	36	33 (0.63)
0.6	0.3	85	59 (0.7)	48	45 (0.61)
0.4	0.5	123	94 (0.7)	74	72 (0.59)
0.2	0.7	277	248 (0.7)	183	180 (0.56)
0.6	0.1	257	235 (0.7)	170	168 (0.55)
0.4	0.3	466	455 (0.7)	316	314 (0.54)
0.2	0.5	1449	1449 (0.5)	1005	1002 (0.52)
0.4	0.1	940	940 (0.5)	650	649 (0.52)
0.2	0.3	3268	3268 (0.5)	2281	2279 (0.51)
0.2	0.1	5110	5110 (0.5)	3574	3573 (0.51)

Note: [1] Proportion of MZ twins among all pairs.

[2] Lowest total number of pairs, with the proportion of MZ pairs in brackets, selected from Table 5 of Martin et al. (1978), where the proportion of MZ twins was varied from 0.1 to 0.9, in steps of 0.2.

Maximum likelihood

Given the sufficient statistics (sums of squares within and between MZ and DZ pairs), there is a close relationship between least squares and ML estimation for balanced designs (e.g., Thompson, 1962). In Appendix A we show the residual maximum likelihood (REML) estimation for ACE and CE models for a mixture of two one-way designs and give the expected value of the likelihood-ratio test statistic per pair from the ACE and CE model

$$\mathrm{NCP}_{\mathrm{ML}} = \ln\{(1-t_{AVE}{}^2) / [(1-t_{MZ}{}^2)^{pMZ} (1-t_{DZ}{}^2)^{(1-pMZ)}]\} \quad [4]$$

with $t_{AVE} = p_{MZ}t_{MZ} + (1-p_{MZ})t_{DZ}$, the weighted average of the two intraclass correlations. Equation [4] contains all of the information required for a power calculation using twin pairs under the ACE model. For $p_{MZ} = ½$, the NCP per pair becomes

$$\mathrm{NCP}_{\mathrm{ML}}|(p_{MZ} = ½) = \ln\{(1-¼(t_{MZ}+t_{DZ})^2 / [(1-t_{MZ}{}^2)^{0.5}(1-t_{DZ}{}^2)^{0.5}]\}$$

If in addition we assume the AE model ($t_{MZ} = 2t_{DZ} = h^2$), then

$$\mathrm{NCP}_{\mathrm{ML}}|(p_{MZ} = ½,\ t_{MZ} = 2t_{DZ}) = \ln\{(1-\tfrac{9}{4}t_{MZ}{}^2) / [(1-t_{MZ}{}^2)^{0.5}(1-4t_{MZ}{}^2)^{0.5}]\}$$

The required sample size, for a given value of p_{MZ} is

$$N = (z_{1-\alpha}+z_{1-\beta})^2 / \mathrm{NCP}_{\mathrm{ML}} = (z_{1-\alpha}+z_{1-\beta})^2 / \ln\{(1-t_{AVE}{}^2) / [(1-t_{MZ}{}^2)^{pMZ} (1-t_{DZ}{}^2)^{(1-pMZ)}]\}$$

For the above numerical example of $p_{MZ} = ⅓$, N = 152 pairs, with 102 DZ and 51 MZ pairs. The optimal design for these parameters is $p_{MZ} = 0.546$, for $N = 127$ (69 MZ and 58 DZ pairs). For $p_{MZ} = ½$, $h^2 = 0.1$ and $c^2 = 0.1$, $N = 9016$ pairs for a type-I error rate of 5% and power of 80%. If the test is two-sided, then the required sample size is 11,446, consistent with the results reported by Posthuma and Boomsma (2000, Figure 2a).

The above equations for required total sample size are remarkably simple, and only require the availability of standard statistical tables and a calculator.

Bivariate Models (Least-Squares)

For bivariate analysis, the main interest is in partitioning the phenotypic covariance in underlying components, and in particular the estimation of the genetic correlation coefficient. For notation, we use X_{ij}^{Z} to denote a mean square or mean cross-product. X is B (between) or W (within), Z is MZ or DZ and i and j are 1 or 2. For example, B_{ij}^{DZ} is the between-pair mean cross-product for DZ twins. The least squares estimate of the genetic correlation can be written as

$$\hat{r}_g = \frac{(B_{12}^{MZ} - W_{12}^{MZ}) - (B_{12}^{DZ} - W_{12}^{DZ})}{\sqrt{[(B_{11}^{MZ} - W_{11}^{MZ}) - (B_{11}^{DZ} - W_{11}^{DZ})][(B_{22}^{MZ} - W_{22}^{MZ}) - (B_{22}^{DZ} - W_{22}^{DZ})}} \quad [5]$$

Table 2

Asymptotic Behaviour of Test Statistics from Least Squares, Goodness-of-Fit and Likelihood Analysis

True model	Expected test statistic		
	Least squares (h2 = 0, one-sided)	Goodness-of-fit (CE model)	Likelihood ratio (ACE vs. CE, one-sided)
E	0.5	2	< 0.5[a]
CE	0.5	2	0.5
ACE (h^2 & c^2 small)	x	x+1	x
ACE (large h^2)	< x	x	> x

Note: [a] Testing for A when the true model is E produces a zero likelihood-ratio test statistic for ACE vs. CE with a probability > 0.5