HERITABILITY ESTIMATES FROM TWIN STUDIES

I. Formulae of Heritability Estimates

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Over the past 50 years a large number of methods have been proposed for estimating heritability from twin studies. The present paper describes the most commonly cited of these estimates as a first step in evaluating their usefulness. A critical review will then follow.

Family studies of human quantitative traits have, in general, three goals: first, to determine whether a given phenotypic trait is genetically influenced; second, to determine if discrete segregating genetic factors influence the trait; and third, to determine whether the trait is linked with some other genetic trait. Twin data are often used to attain the first goal by measuring the relative importance of heredity and environment on the development of quantitative traits. The concept of heritability originated in an attempt to describe the degree to which the differences actually observed between individuals arose from differences in genetic makeup between individuals as contrasted to the effects of different environmental forces. For a review of the origin of the concept of heritability, see " Heritability in retrospect " by Bell (1977).

The term heritability is used in both a broad and narrow sense. For the broad sense, the genotype is considered as a unit in relation to the environment. Genes come together in new combinations exhibiting intraallelic interaction (dominance) and interallelic interaction (epistasis). Heritability in the narrow sense considers only the additive portion of the genetic variability in relation to the phenotypic variability. The concepts of heritability and the applications in the field of animal breeding are well defined and readily adaptable to the description of genetic variability. The broad sense heritability is not used in practical applications in breeding; narrow sense heritability is more important because heritability in this sense predicts the speed with which desired changes in a phenotype occur by artificial selection. However, estimates of heritability from twin studies contain additive, dominance and epistatic effects.

The purpose of his paper is to describe the available formulae for estimating heritability as applied to human quantitative twin studies, as a first step in evaluating their usefulness. A review paper will follow, dealing with a critical evaluation of each formula and the use of mean squares vs. expected mean squares in heritability estimation.

The general model of observed traits for the two twins in a given pair can be defined as:

$$X_{1j} = \mu + g_{1j} + e_{1j},$$
$$X_{2j} = \mu + g_{2j} + e_{2j}, \, j = 1, \, 2 \ldots n, \tag{1}$$

where X_{ij} are the phenotypic expressions of a given trait, in each member of a twin pair ($i = 1, \, 2$), μ is the population mean, and g_{ij} and e_{ij} are the genetic and environmental effects, respectively in each member of a pair.

The random variables, g_{ij} and e_{ij}, are taken to have means of zero and variances of σ_g^2 and σ_e^2, respectively. The two variances are measures of the relative effect of heredity and environment. The genetic variance (σ_g^2) can be partitioned into an additive variance component (σ_a^2), a dominance variance component (σ_d^2), and a component due to epistatic variance (σ_i^2) (Falconer 1960).

The earliest heritability measures were based on the sample mean deviation ($\bar{D} = \sum_j |X_{1j} - X_{2j}|/n$). The " difference method " of Lenz and von Verschuer (1928) led to the following statistic as a heritability measure:

$$h^2 = \frac{\bar{D}_{(DZ)} - \bar{D}_{(MZ)}}{\bar{D}_{(DZ)}} . \tag{2}$$

Jensen (1970) proposed that the absolute differences between twins can be used to compute a correlation coefficient and to indicate the degree of similarity between twins relative to the similarity between persons paired at random from the general population. This he called a " difference correlation ", signified as γ_d:

$$\gamma_d = 1 - \left(\frac{|\bar{d}_k|}{|\bar{d}_p|} \right)^2, \tag{3}$$

where $|\bar{d}_k| =$ mean absolute difference between twin members,

$|\bar{d}_p| =$ mean absolute difference between all possible paired comparisons in the general population, and is equal to 1.13 times its standard deviation.

Gottschald (1939) proposed a new measure he called the " quotient method " using the same sample mean deviation:

$$h^2 = \frac{\bar{D}_{(DZ)}}{\bar{D}_{(DZ)} + \bar{D}_{(MZ)}} . \tag{4}$$

Wilde (1941) introduced another formula:

$$h^2 = \frac{\sqrt{\bar{D}_{(DZ)}^2 - \bar{D}_{(MZ)}^2}}{\sqrt{\bar{D}_{(DZ)}^2 - \bar{D}_{(MZ)}^2} + \bar{D}_{(MZ)}} . \tag{5}$$

Heritability can be defined in terms of variances, distinguishing between the broad sense and the narrow sense:

$$h_{(B)}^2 = \frac{\sigma_g^2}{\sigma_g^2 + \sigma_e^2} , \tag{6}$$

$$h_{(N)}^2 = \frac{\sigma_a^2}{\sigma_g^2 + \sigma_e^2} . \tag{7}$$

Holzinger (1929) devised two formulae that compare the influence of nature to the influence of nurture in producing differentiation between twins with respect to a given trait. The first formula [8] measures the relative importance of nature and nurture in determining mean differences:

$$T = \frac{\bar{D}_{(DZ)} - \bar{D}_{(MZ)}}{\bar{D}_{(MZ)}} ,$$ [8]

where $\bar{D}$ is the mean absolute difference between members of a twin pair.
Holzinger's second formula [9] measures the relative importance of nature and nurture in determining variability of twin differences:

$$t^2 = \frac{r_{(MZ)} - r_{(DZ)}}{1 - r_{(MZ)}} ,$$ [9]

where r is the intraclass correlation coefficient.
Beginning with Galton's twin work early measures of heritability were based on the mean deviation or quotient methods. Though these earlier formulae had an intuitive appeal, the intraclass correlation approach [9] was rapidly accepted because at this time variances and standard deviations were becoming almost inevitably used for statistical treatments. Holzinger's expression [9] has been rewritten by various authors in different forms and using different assumptions.
Newman, Freeman and Holzinger (1937) derived an alternate formula [10] from Holzinger's t^2 which used the intraclass correlation of DZ twins in the denominator rather than the intraclass correlation of MZ twins:

$$h^2 = \frac{r_{(MZ)} - r_{(DZ)}}{1 - r_{(DZ)}} .$$ [10]

Clark (1956) presented an estimate of heritability using only within-pair mean squares [11]:

$$h^2 = \frac{\sigma^2_{WDZ} - \sigma^2_{WMZ}}{\sigma^2_{WDZ}} ,$$ [11]

where σ^2_{WDZ} and σ^2_{WMZ} are the within-pair mean squares for dizygotic and monozygotic twins, respectively. Clark suggested that when total variances are computed separately for MZ and DZ twins, an adjusted heritability estimate can be written as:

$$h^2 = \frac{V_M \sigma^2_{WDZ} - V_D \sigma^2_{WMZ}}{V_M \sigma^2_{WDZ}} = \frac{\dfrac{\sigma^2_{WDZ}}{V_D} - \dfrac{\sigma^2_{WMZ}}{V_M}}{\dfrac{\sigma^2_{WDZ}}{V}} ,$$ [12]

where σ^2_{WDZ} and σ^2_{WMZ} are defined previously and V_M and V_D are the total variances of MZ and DZ twins, respectively.
Kempthorne and Osborne (1961) have cast doubt on the meaning of formula 10 in view of common and competitive forces in twin pairs. The possible effects of these forces on heritability estimates can be seen more clearly when Clark's original formula [11] is written in terms of the variances and covariances seen within twin pairs: for example, if σ^2_{DZ} is larger

than σ^2_{MZ} for whatever reason, this estimate of heritability would most likely be biased upward:

$$h^2 = \frac{[\sigma^2_{DZ} - \sigma_{WDZ}] - [\sigma^2_{MZ} - \sigma_{WMZ}]}{[\sigma^2_{DZ} - \sigma_{WDZ}]} ,\qquad [13]$$

where

$$\hat{\sigma}^2_{MZ} = \frac{MSA_{MZ} + MSW_{MZ}}{2} ,$$

and

$$\hat{\sigma}_{WMZ} = \frac{MSA_{MZ} - MSW_{MZ}}{2} ,$$

MSA is the among-pair mean square, MSW the within-pair mean square and the quantities σ^2_{DZ} and σ_{WDZ} are similarly determined for DZ twins.

There are methods of obtaining heritability estimates from twin data in addition to those listed here. Hancock (1952) equated heritability directly with the intraclass correlation coefficient in the case of MZ twins [14]; for DZ twins, heritability was equated with twice the intraclass correlation coefficient (15: Falconer 1960). These estimates are in all probability often biased upward by environmental covariances of twins:

$$h^2 = r_{MZ} ,\qquad [14]$$

$$h^2 = 2r_{DZ} ,\qquad [15]$$

$$h^2 = 2(r_{MZ} - r_{DZ}) .\qquad [16]$$

Nichols (1965) proposed an index [17], in which heritability was defined as the ratio of genetic variance to the variance due to hereditary and environmental effects common to both twins of a set:

$$HR = \frac{2(r_{MZ} - r_{DZ})}{r_{MZ}} ,\qquad [17]$$

where r_{MZ} and r_{DZ} are the intraclass correlation coefficients for MZ and DZ twins, respectively. Jensen (1967) introduced yet another formula for obtaining heritability estimates. He asserted this formula improved upon previous estimates by introducing terms to account for the genetic effects of assortative matings. However, reliable estimates of the effect of assortative mating are needed to take advantage of this improvement:

$$h^2 = \frac{r_{AB} - r_{CD} - E^2(\varrho_{EAB} - \varrho_{ECD})}{\varrho_{GAB} - \varrho_{GCD}} .\qquad [18]$$

In this estimate, ϱ_G and ϱ_E are genetic and environmental correlation coefficients, respectively; E^2 refers to systematic environmental effects (the proportion of total variance due to environmental differences between families, or conversely, the environmental variance common to members of the same family); and AB and CD correspond to two groups of paired individuals such that $\varrho_{GAB} > \varrho_{GCD}$.

Recently Jensen (1976) proposed, based on the solution of a pair of simultaneous quadratic equations, a method estimating the range of heritability under the assumption of assortative mating, environmental correlation and $G \times E$ covariances. Jinks and Fulker (1970) applied

the simultaneous solution to estimates of within- and between - family genetic and environmental components prior to heritability estimates on human behavior.

There are many rationales for, as well as criticisms of, various heritability estimates. A critical review is not undertaken in the present paper, but careful evaluation of different measures of heritability with respect to genetic variance components will be included in a follow-up article.
Several investigators have used Wright's path analysis to describe familial relationships, and this method was applied to twin data to test significant heritability estimates (Wright 1921, Rao et al. 1974, Salzano and Rao 1975). For the twin relationship, expected correlations are:

$$MZT = h^2 \quad + c^2 + 2grc,$$
$$DZT = h^2/2 + c^2 + 2grc. \qquad [19]$$

where h^2 is heritability, c^2 is the effect of common environment, g in the path from midparent genotype to child's phenotype, and r is the covariance between midparent genotype and common environment. For the classical twin studies without parental observation, the parameters g and r are equal to zero. The model then reduces to the traditional approach using intraclass correlations and significance tests for heritability estimates.

In practice, heritability estimates generally require some simplifying assumptions, the most common of which are: (1) the effect of environmental influences on the trait are similar for the two types of twins; (2) hereditary and environmental influences are neither correlated in the same individual nor between members of a twin set; (3) there is no correlation between parents due to assortative mating; and (4) the trait in question is continuously distributed with no dominance and no epistatic variance (narrow sense heritability).
From the analysis of twin data, only six pieces of information are generally used for evaluating a trait: the four mean squares and the number of MZ and of DZ twins. We have proposed even another method of estimating broad heritability based on the analysis of variance model (Christian et al. 1976) and the genetic variance estimates presented:

$$h^2_{CT} = \frac{(M_{AMZ} - M_{ADZ}) + (M_{WDZ} - M_{WMZ})}{1/4\,(M_{AMZ} + M_{WMZ} + M_{ADZ} + M_{WDZ})}. \qquad [20]$$

This single estimate results from an average of all available mean squares and if there is a significant difference between the number of MZ and DZ twins the mean squares can be weighted. The numerator is two times the among-genetic-component estimate of genetic variance (Christian et al. 1974) and the denominator is an estimate of total variance obtained using all four mean squares. We therefore call formula 20 the among-component estimate of heritability (h^2_{CT}).
Recently, Kang et al. (1977) showed the effects of dominance deviations and environmental covariance on various heritability estimates, indicating what we believe to be a general property of h^2_{CT} to be less affected by failure of genetic and environmental assumptions than many other heritability estimates. This estimate, however, was shown to be somewhat less efficient than other estimates when all commonly made assumptions hold, namely: that dominant and epistatic variances are null, the covariance of genetic and environmental influences is zero, the environmental covariances in the two types of twins are the same, and the total variances of MZ and DZ twins are equal.

The documented array of available heritability estimates for twin data must be confusing to investigators because there is little guidance available in the literature about which estimate is appropriate for different situations. Jensen (1967) gave striking examples of how selected heritability estimates could vary on the same set of data. There is great need for comparison of these estimates and guidelines for when they may be used appropriately. If this need is not met, continued random application of these estimates will surely further damage the usefulness of the concept of heritability in human studies.

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