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Chorion type as a possible influence on the results and interpretation of twin study data

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The estimation of genetic effects from twin studies usually relies upon the equal environment assumption – that monozygous (MZ) and dizygous (DZ) twin pairs experience equal similarity of their environments from prenatal experiences through adulthood. However, the sharing of a chorion may make a subset of identical twins more similar, or in some cases, more different, than twins that do not share a chorion. Recent studies suggest monochorionic MZ twins resemble one another more than dichorionic MZ twins in cognitive abilities, personality, and risk for psychiatric disorder. To the extent that prenatal environment affects these characteristics, the traditional twin method will yield biased estimates of genetic and environmental influences. We develop models for quantifying this bias and estimating the influence of chorion type on estimates of heritability.

Keywords: genetics, methodology, maternal influences

Introduction

Monozygous (MZ) twins differ in their placentation. Approximately one third of MZ twins are dichorionic (MZ-DC) and two thirds are monochorionic (MZ-MC),[1] and a portion of MC twin pairs also share an amnion. It appears that differences in chorion/amnion type result from differences in the timing of the twinning process, with the developmental separation of DC twins occurring earliest (3–4 days after ovulation), monochorion/diamnion intermediate (5–7 days after ovulation), and (rarely) monochorion/monoamnion latest (8 or more days following ovulation[2]). Evidence suggests that variation in chorion type is an important correlate of fetal and postnatal development.[3]

Very few twin studies of behavioral characteristics have examined chorionicity effects. Several (4–7) but not all (8–10) have reported greater similarities of MC than DC twins on measures of cognitive ability. Three studies found MZ-MC pairs to be more similar for measures of personality (10–12). In a small study, Davis et al[13] found MZ-MC pairs had substantially greater concordance for schizophrenia than did MZ-DC pairs. These findings raise important questions about the interpretation of results of twin studies involving contrasts of pair-similarity of MZ and DZ twins.

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The standard twin model

The typical twin study involves evaluating MZ and DZ twin pairs on one or more measures and then comparing the similarity of MZ vs DZ pairs. Assuming no covariation or correlation among the components, score variation can be partitioned into three theoretical components: additive genetic variation (A) includes variation from all alleles that combine additively. (Non-additive variation due to epistasis and dominance can also be estimated but is rarely detected in behavioral research on humans.) The common environmental component (C) comprises those experiences and environments shared by members of a twin pair and includes the shared intrauterine environment as well as post-natal experiences, such as family and sociocultural influences. Individual-specific environmental variation (E) includes all non-genetic sources of variation not shared by twins (including, in most cases, measurement error). Assuming no covariance or correlation among the components, the 'score' for an individual, i, on a phenotype, P, is estimated as a linear combination of the three components,

$$P_i = a^* (A_i) + c^* (C_i) + e^* (E_i)$$

where a, c, and e are parameters and A, C and E are individual scores on each of the latent components.

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Assuming the latent components are uncorrelated, the variance of the trait is written as

$$E\{P_i,P_i\} = V_p = a^2 + c^2 + e^2.$$

By these standard definitions, the common environment (C) components of MZ and DZ twin pairs are perfectly correlated. At the time of splitting, MZ twins within a pair share 100% of their genes, so we assume their A scores correlate $r(a_1,a_2) = 1.0$, whilst on average, DZ twin pairs share 50% of their segregating genes, so we assume their A components correlate $r(a_1,a_2) = 0.5$. The expected covariances among MZ and DZ twin pairs are shown in the first row ofTable 1. Estimates of the components can be obtained algebraically, but it is now more common to use structural model fitting which can take into account differences in sample sizes. Heritability (usually abbreviated h^2) is typically reported as the proportion of total variance attributable to genetic variance, in this case

$$h^2 = \frac{a^2}{a^2 + c^2 + e^2}$$

Models for chorion type

Several assumptions are required for valid estimation of heritability using the twin model. With regard to chorionicity, the critical one is the assumption of equal environments across twin types. The standard model assumes that twins of any zygosity and chorion type experience equally similar environments. To the extent that the intrachorion environment influences the trait under study, the similarity of MZ-MC pairs will differ from that of MZ-DC pairs and DZ pairs, all of whom are DC. Thus, MZ-MC pairs can be thought to have additional sources of environmental variation which contribute to their pair covariance, but are not shared by twins from MZ-DC and DZ pairs. As discussed below, the effect of sharing a chorion may be in either direction – increasing or decreasing resemblance within MZ-MC twin pairs.

Increased similarity among monochorionic pairs

Since MC pairs share their placental environment, they are both more likely to experience environmental pathogens (eg viral infections, alcohol and other substances) than are DC twins. This leads to an expectation of greater similarity of MZ-MC twin pairs than MZ-DC pairs. We term the chorion effect k. The expectation for a phenotype is

$$P_i = a^* (A_i) + c'^* (C_i') + k^* (K_i) + e^* (E_i)$$

where c' and C' represent the variance contributed by aspects of the common environment other than from sharing a chorion. We assume the score K is correlated 1.0 for MZ-MC pairs and 0 for other pair types. All subjects have chorionic variance, so have a k component contributing to their phenotype, and all pair types are expected to have the same environmental variance. This aspect of the parameterization differs from a model employed previously by Vlietinck et al.[14] to study chorion effects on birthweight. In their model, the chorion effect contributed to the variance only of MZ-MC twins, leading to an expectation of greater variation (as well as greater convariation) in this group than in other twin types if a chorion effect is present.

If the chorion type of the MZ pairs is known, k can be estimated. The pair covariances for the three twin types are listed in Table 1. However, if chorion type is not known, it typically contributes to the estimate of genetic variation, inflating estimates of heritability. If π_{MC} is the proportion of MZ-MC pairs, and $1-\pi_{MC}$ is the proportion of MZ-DC pairs, the typical MZ pair correlation (pooling across chorion types) is written as

$$E\{C_{MZ1,MZ2}\} = \pi_{MC^*} (a^2 + c'^2 + k^2) + (1-\pi_{MC}) * (a^2 + c^2) = a^2 + c'^2 + \pi_{MC^*} (k^2).$$

Substituting this equation into the equation for MZ covariance from the standard twin model (see Table 1) allows the specification of estimates of the variance components, shown in Table 2. These equations show that when a chorion effect exists, the genetic and common environment parameters estimated under the standard model will be biased. The degree of bias is a function of both k^2, the proportion of variation due to sharing a chorion, and π_{MC}, the proportion of MZ pairs which MC.

Heritability estimates will also be biased when a chorion effect is present. Genetic variance will be overestimated and common environmental variance underestimated. The degree of bias depends on k^2, π_{MC}, and the proportion of MZ and DZ twins in the sample. Figure 1 shows the 'true' heritability plotted against the apparent heritability (estimated using a standard twin model) for values of k^2 ranging from 0 to 0.30. The estimates assume that the proportion of MZ-DC pairs is two thirds of MZ twins and there are equal proportions of MZ and DZ pairs. The figure shows that for modest levels of a chorion effect, only small bias is present. For example, for $k^2 = 0.10$ and a true heritability of 0.33, the estimated heritability from the standard twin model is 0.40. But if $k^2 = 0.25$, the estimated heritability is 0.50, 50% larger than the true value.

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Table 1 Expectations under alternative models for intrauterine effects

Model	Score	Variance	Pair covariance	Heritability
Standard	$P_{MZ\text{-}MC}=P_{MZ\text{-}DC}=P_{DZ}=$ $a(A)+c(C)+e(E)$	$V_{MZ\text{-}MC}=V_{MZ\text{-}DC}=V_{DZ}=$ $a^2+c^2+e^2$	$C_{DZ}=0.5*a^2+c^2$ $C_{MZ\text{-}MC}=C_{MZ\text{-}DC}=a^2+c^2$	$h^2=\frac{a^2}{(a^2+c^2+e^2)}$

Chorion effect	$P_{MZ\text{-}MC}=P_{MZ\text{-}DC}=P_{DZ}=$ $a(A)+c'(C')+k(K)+e(E)$	$V_{MZ\text{-}MC}=V_{MZ\text{-}DC}=V_{DZ}=$ $a^2+c'^2+k^2+e^2=$ $a^2+c^2+e^2$	$C_{DZ}=0.5*a^2+c^2$
			if chorion type unknown:
			$C_{MZ}=\pi_{MC}(a^2+c'^2+k^2)+(1-\pi_{MC})(a^2+c'^2)$ $=a^2+c'^2+\pi_{MC}(k^2)$
			if chorion type known:
			$C_{MZ\text{-}MC}=a^2+c'^2+k^2$
			$C_{MZ\text{-}DC}=a^2+c'^2$
				$h^2=\frac{a^2-\pi_{MC}(k^2)*\Pi_{MZ}}{(a^2+c^2+e^2)}$

Twin transfusion	$P_{MZ\text{-}DC}=P_{DZ}=$ $a(A)+c(C)+e(E)$
	$P_{MZ\text{-}MC}=$
	if status unknown:
	$P=a(A)+c(C)-0.5\tau(T)+e(E)$
	if transfusion status known:
	$P_{MZ\text{-}MCr}=a(A)+c(C)-$ $\tau(T)+e(E)$
	$P_{MZ\text{-}MCd}=a(A)+c(C)+e(E)$
		$V_{DZ}=a^2+c^2+e^2$
		if transfusion status and chorion type both unknown:
		$V_{MZ}=\pi_{MC}(a^2+c^2+e^2)+$ $(1-\pi_{MC})(a^2+c^2+0.5\tau^2+e^2)$ $=a^2+c^2+e^2+0.5\tau^2\Pi_{MC}$
		if transfusion status unknown but chorion type known:
		$V_{MZ\text{-}DC}=a^2+c^2+e^2$
		$V_{MZ\text{-}MC}=a^2+c^2+0.5\tau^2+e^2$
		if transfusion status and chorion type known:
		$V_{MZ\text{-}DC}=a^2+c^2+e^2$
		$V_{MZ\text{-}DCd}=a^2+c^2+e^2$
		$V_{MZ\text{-}DCr}=a^2+c^2+\tau^2+e$
			$C_{DZ}=0.5a^2+c^2$
			$C_{MZ}=a^2+c^2$
				$h^2=\frac{a^2-\pi_{MC}(0.5\tau^2)*\Pi_{MZ}}{(a^2+c^2+e^2+\pi_{MC}(0.5\tau^2)*\Pi_{MZ})}$

a^2 = additive genetic variance; c^2 = common environmental variance; e^2 = specific environmental variance; $c^{2'}$ = common environmental variance other than from shared chorion; k^2 = chorion environmental variance; π_{MC} = proportion of MZ pairs that are monochorionic; Π_{MZ} = proportion of sample that is MZ; τ = transfusion effect; r = recipient twin; d = donor twin.

Decreased similarity among monochorionic pairs

Sharing a chorion may also produce competition for resources within a twin pair. For example, twins may have marked differences in birth weight due to differences in vascular connections to the placenta. MC twins often share arterial systems, but typically have separate venous systems. Twins within a pair may thus differ in the size of the area of venous return, which is positively associated with fetal growth. For example, in a study of 242 MZ pair births, Corey et al[15] reported intra-pair birthweight differences were highest among MZ-MCs, followed by fused MZ-DCs, with unfused chorionic MZ-DCs being most similar.

An extreme form of vascular competition is twin–twin transfusion syndrome (TTTS), in which arterial flow from one twin (the donor or anaemic twin) empties into the vascular system of the recipient (or plethoric) co-twin. TTTS is associated with high perinatal mortality. One review of 910 MZ births reported a 24.8% mortality rate among MC twins

Table 2 Expectations for biometric parameters accounting for chorion effect

	Estimate obtained from standard twin model	Unbiased estimate
MZ pair covariance	a^2+c^2	$a^2+c'^2+\pi_{MC}*(k^2)$
DZ pair covariance	$0.5*a^2+c^2$	$0.5*a^2+c'^2$
Additive genetic variance	a^2	$a^2-(\pi_{MC})*k^2$
Common environmental variance	c^2	$c^2+(\pi_{MC})*k^2$
Specific environmental variance	e^2	e^2
Total variance	$a^2+c^2+e^2$	$a^2+c^2+e^2$

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compared with 10.5% among MZ-DC twins.[1] The incidence of TTTS has been difficult to establish because most reports are from clinical samples.[16] Recent data from the population-based East Flanders Prospective Twin Survey[17] suggests relatively little of this mortality is due to TTTS, with the syndrome occurring in fewer than 5% of MC pairs (R. Derom, personal communication, 24 August 1999).

Among surviving twins, milder forms of TTTS have been associated with a variety of characteristics, including differences in vascular functioning in adolescence,[18] although many cases have been reported to recover completely.[1] In the behavioral domain, several investigators have documented associations between within-pair birth weight differences and later differences in cognitive development, with the smaller twin typically scoring lower on various measures of intellectual functioning.[19,20]

Models for twin or sibling-pair competition generally assume that the effect of such competition is to raise the score of one twin while lowering the score of the other.[21] However, the evidence from studies of birth weight differences and TTTS suggest a model in which there is a negative impact on the recipient twin, but no beneficial effect (or possibly a negative effect) for the donor twin. Under such a model, the expected score and score variance for twin i who is a recipient twin are

$$P_{ri} = a^* (A_i) + c^* (C_i) - t^* (T_i) + e^* (E_i) \text{ and } V_r = a^2 + c^2 + e^2 + t^2$$

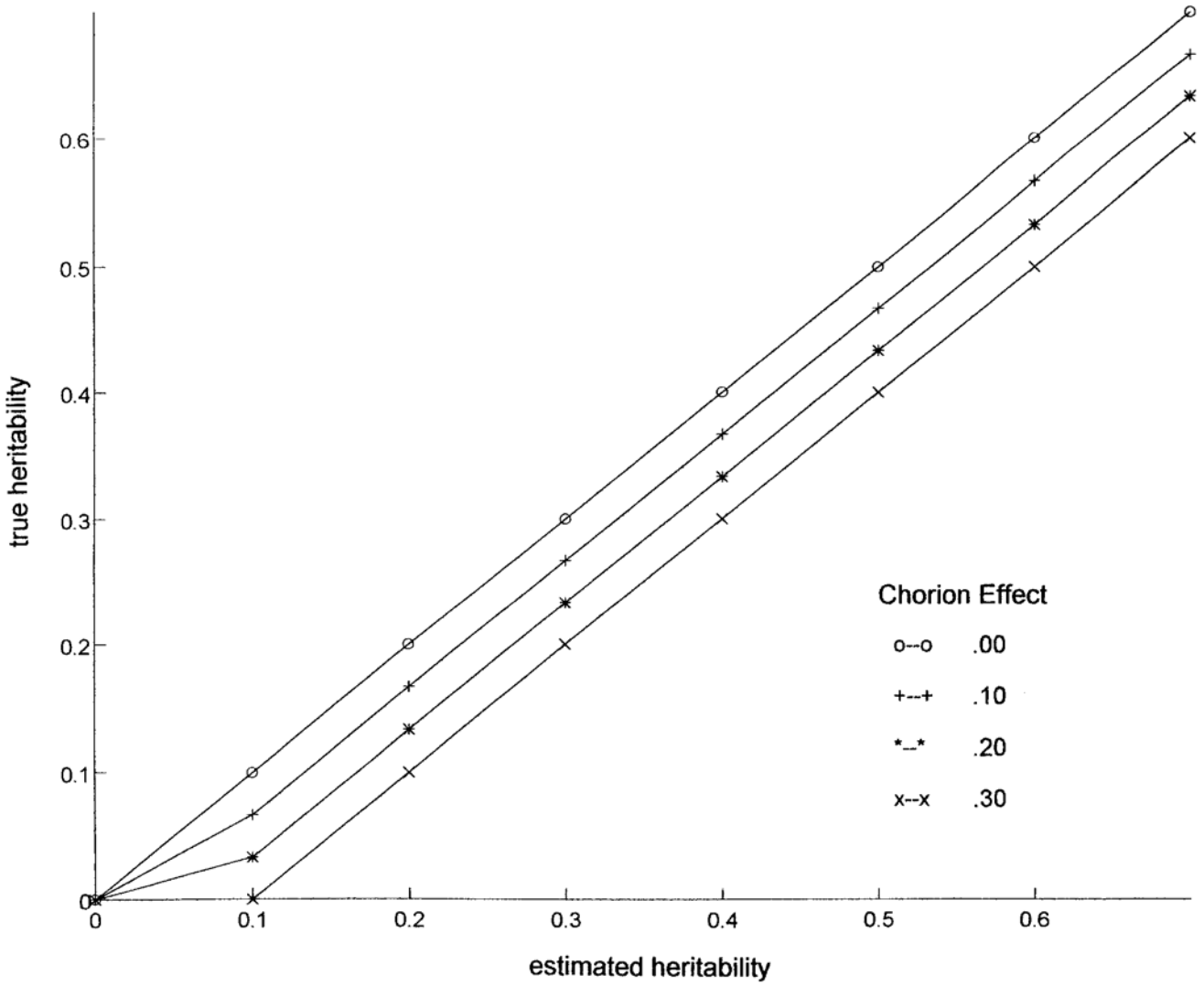

Figure 1 Bias in estimated heritability as a function of chorion effect. Estimates were obtained using the equations in Table 2 and assuming equal numbers of MZ and DZ pairs and that 2/3 of MZ pairs are monochorionic.

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where T is the extent to which the recipient twin is affected by TTTS and t^2 is the variance of this effect among affected twins. Assuming the donor and recipient status of the MC twin pairs is known, and there is no negative impact on the donors, the expected score for the donor twin is unchanged (Table 1). If donor and recipient status is unknown, the combined mean of the MC twin group is expected to be $0.5t^*(T)$ lower than the means for non-MC pairs and the combined variance is increased by $0.5t^2$. The expectations for pair covariance remains the same as under the standard model (see Table 1) since the within-pair covariance for T is zero. However, the variances are expected to differ, so that analyses should be based on twin pair covariances. Heritability estimates based on pair correlations would be biased.

Since the chorion effect and the transmission competition effect described here only operate in MC pairs and act in opposite directions, their effects can offset one another. Indirect evidence that a competition effect exists is provided when the variance of the MZ-MC group exceeds that of the other groups and the MZ-MC mean is lower; but the magnitude of this effect cannot be determined. Other variations on these processes are possible, but would be even more difficult to distinguish. For example, if the transmission effect negatively influenced both donor and recipient, this would alter the expectation for the pair covariance as well as the expectations for the score mean and variance. The extent and direction of the influence on the covariance would depend on the degree to which the negative impact was correlated for twins within a pair.

The extent of the transfusion effect is measurable through pathology studies on the placenta, but these are conducted only in the most dramatic cases. Within-pair differences in birth weight have sometimes been used as an indicator of the transmission effect, but this is unreliable, as there are many other mechanisms which can affect variation in birth weight.

The available data on behavioral measures provide little evidence for a transmission effect. For 19 of 20 clinical and personality measures reported by Sokol et al,[10] the mean and variance of the within-pair difference among MZ-MC pairs were equal to or smaller than those among MZ-DC pairs, consistent with a chorion effect and opposite the prediction of the transmission effect. Similarly, Reed et al[11] found the within-pair variance (an index of twin-pair similarity) on 6 of 8 measures of Type A behavior was equal or lower among MZ-MC pairs. In a study of twin-pair similarity for MMPI personality scores, Bogle et al[12] reported higher intraclass correlations among presumably MZ-MC pairs for 31 of 37 scales examined, although the differences achieved were significant for only 5 scales.

Possible bias in studies of twins reared apart

Chorionic differences among MZ pairs might have an even greater effect on the results of studies of MZ pairs reared apart (MZA[22,23]). MZA pairs often learn about one another's existence through being told about their striking physical resemblance to someone else. If MZ-MC twins resemble one another more than MZ-DC twins in physical appearance, ability, or personality, this might result in a greater proportion of MZ-MC than MZ-DC twins being in similar social milieus and being more likely to learn about one another. If this scenario is correct, separated MZ twins in studies should be MZ-MC more often than the birth ratio of 1/3 DC: 2/3 MC, leading to an even greater bias than obtained in studies of randomly selected twin pairs.

Implications

In addition to the implications for interpreting the results of twin studies, the existence of chorion effects suggests an important role of intrauterine environment on the development of many psychological and behavioral characteristics. The existence of these effects may also help to explain the inconsistencies observed when comparing heritability estimates based on various behavioral genetic designs. It has been widely observed that DZ twins are more similar to each other than siblings for a variety of characteristics.[24–26] This persists even after attempts to correct for dissimilarity due to age differences among siblings, often to the point where investigators include 'special twin environment' parameters in their models.[26,27] A related inconsistency is that heritability estimates obtained from studies of twins are typically larger than those obtained by studies of resemblance between adoptees and their biological and adoptive families,[24,28] even for characteristics where non-additive genetic sources of variation seem unlikely. Comparing the similarity of separated DZ twins with that of separated siblings could help determine whether the excess similarity in DZs is attributable to (non-chorionic) intra-uterine effects rather than post-natal environments. Unfortunately, separated DZ twins are rarely included in twin studies of behavioral characteristics, such as that by Bouchard and McGue.[24]

In conclusion, the reliance on the traditional twin design and the resulting potential overestimation of

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genetic determination may obscure evidence for important environmental influences on a variety of psychological characteristics. The magnitude of the chorion effect for behavioral characteristics is unknown. Whilst population values of 0.25 seem unlikely, the growing evidence suggests that some small but not negligible chorion effects may contribute to individual differences in behavioral traits. Whenever possible, investigators studying twins should obtain and employ indices of chorion type when estimating environmental and genetic influences on human variation. A recent report by Monteiro et al.[29] that X-choromosome inactivation may serve as an indicator of chorion type among female twins offers one possibility for including this information in studies of twins who are not ascertained at birth.

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