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Heritability Estimation from Concordant Twin Pairs Alone

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Abstract. Heritability estimation is possible from concordant twin pairs alone, based on the proportion of like-sexed pairs among all concordant affected pairs. The method is limited to conditions found in both sexes in the prevalence range 0.1% to 10%, and a relatively large population size is required to give an adequate sample of twin pairs. However, the method has the considerable advantage that zygosity determination is not required and that any bias due to incomplete diagnosis/ascertainment is likely to be small. The method is particularly suited to diseases where registration is obligatory and computerised so that the register can be scanned for pairs of individuals with the same date of birth, place of birth and birth surname.

Key words: Heritability, Twins, Concordance, Disease registers, Zygosity unknown

INTRODUCTION

Estimates of heritability from twin data for multifactorially controlled all-or-none characters, such as disease states, have traditionally been based on the observed numbers of monozygous (MZ) and dizygous (DZ) pairs concordant and discordant for the character being studied. However, it is possible to estimate heritability from concordant twin pairs alone, with no knowledge of the zygosity of individual pairs. With increasing use of large scale computerised disease registers, such an approach might be useful for diseases where registration is obligatory and where the register can be scanned for pairs of individuals with the same date of birth, place of birth and birth surname. The method is based on the

observed proportion of concordant affected pairs that are like-sexed. It relies on the increasing ratio of MZ to DZ concordant affected pairs with increasing heritability and the consequent positive association between heritability and the proportion of like-sexed pairs among all concordant affected pairs (within certain limits of disease prevalence and relative incidence of MZ and DZ pairs in the population). The method cannot therefore be applied to diseases occurring exclusively or almost exclusively in one sex. The only items of information required are the numbers of like-sexed and unlike-sexed concordant affected pairs observed, the ratio of DZ to MZ twin pairs in the general population and the population prevalence of the disease for each sex. Any bias in the heritability estimate due to incomplete diagnosis and/or ascertainment is likely to be small.

THE METHOD

1. General Approach

For any given value of the heritability, h^2, the expected proportion of concordant affected twin pairs like-sexed, P_E, can be calculated as shown below. The estimate of heritability, $\hat{h}^2$, is that value for h^2 which gives P_E closest to P_O, the observed proportion of concordant affected pairs like-sexed, where $P_O = L/(L+U)$ and L and U are the numbers of like-sexed and unlike-sexed concordant affected pairs observed. The estimate is computed by an iterative procedure using a range of possible values for h^2, calculating the corresponding P_E at each iteration and choosing as h^2 that value of h^2 which gives a minimum for $|P_O - P_E|$. The relationships between the constants and variables involved in each estimation are shown in Table 1. These constants and variables are:

Constant for each estimation (from observations)

q_g, the overall prevalence of the disease in the general population;

Table 1. Six Different Categories of Twin Pair (N is the Total Number of Twin Pairs in the General Population)

Twin pair category		Relative pop. freq.	Disease prev. in indivs. of twin's sex (q_1)	Disease prev. in indivs. of cotwin's sex (q_2)	r	Proband concordance rate (q_c)	Number of conc. aff. pairs
Twin	Cotwin						
MZ Female	Female	1/2	$q_f = 2q_g/(1+v)$	q_f	h^2	c_1	$Nq_fc_1/2(1+w)$
MZ Male	Male	1/2	$q_m = vq_f$	q_m	h^2	c_2	$Nq_mc_2/2(1+w)$
DZ Female	Female	w/4	q_f	q_f	$h^2/2$	c_3	$wNq_fc_3/4(1+w)$
DZ Male	Male	w/4	q_m	q_m	$h^2/2$	c_4	$wNq_mc_4/4(1+w)$
DZ Female	Male	w/4	q_f	q_m	$h^2/2$	c_5	$wNq_fc_5/4(1+w)$
DZ Male	Female	w/4	q_m	q_f	$h^2/2$	c_6	$wNq_mc_6/4(1+w)$

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q_f, the prevalence among females;
$q_m = vq_f$, the prevalence among males;
w, the DZ/MZ ratio in the general population;

Varied to find $\hat{h}^2$

h^2, the heritability of the disease;
r, the correlation in liability to disease between relatives;
$c_1 - c_6$, proband concordance rates for the different categories of twin pair.

The expected number of concordant affected pairs falling into each of the six categories (Table 1) is the product of the total number of twin pairs in the general population, the frequency of that category of twin pair, the disease prevalence in individuals of the index twin's sex and the proband concordance rate. Thus, for example, the expected number of concordant affected female MZ pairs is:

$$N[1/2(1+w)]q_f c_1 \quad \text{or} \quad c_1 N q_f/2(1+w)$$

and the expected number of concordant affected DZ pairs where the index twin is female and the cotwin male is:

$$N[w/4(1+w)]q_f c_5 \quad \text{or} \quad wc_5 N q_f/4(1+w)$$

The expected proportion of concordant affected pairs like-sexed is therefore:

$$(1) \qquad P_E = [2(c_1 + vc_2) + w(c_3 + vc_4)]/[2(c_1 + vc_2) + w(c_3 + vc_4 + c_5 + vc_6)]$$

The proband concordance rates are derived through application of the multifactorial liability model [4], modified to take into account the reduced variance in liability of those affected [6,9]. First, the model is applied to estimate x_R for each category of twin pair using the formula:

$$(2) \qquad x_R = (x_2 - ra)/\sqrt{[1 - r^2 a(a - x_1)]}$$

where a is the mean deviate for affected individuals of the twin's sex, x_1 is the threshold value for individuals of the twin's sex, x_2 is the threshold value for individuals of the cotwin's sex and x_R is the difference between the threshold and the mean liability for cotwins of affected twins. The formula is a rearrangement of one that has previously been proposed [10], adjusted to accommodate differences of prevalence between the sexes [11]. Values for x_1 and x_2 are derived from q_1 and q_2, disease prevalences for individuals of the twin's sex and cotwin's sex respectively, using statistical algorithm AS 111 [1]. The value of a is calculated from the formula:

$$a = [1/q_1\sqrt{(2\pi)}]e^{-x_1^2/2} \qquad \text{when } x_1 \geqslant 0$$

$$\text{or} \quad a = [1/q_1\sqrt{(2\pi)}][1 - e^{-x_1^2/2}] \qquad \text{when } x_1 < 0$$

The corresponding proband concordance rate, q_c, for each category of twin pair is then derived from x_R using statistical algorithm AS 66 [5].

For example, suppose the following observations have been made: L = 98, U = 14, q_f = 0.6%, q_m = 1.2% and w = 1.5. Then P_O = 0.875, v = 2 and the values of the constants and variables associated with h^2 = 0.69 are as shown in Table 2.

In applying the method, $\hat{h}^2 > 1$ can produce a negative value for $1 - r^2 a(a - x_1)$,

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Table 2. Values of Constants and Variables Associated with $\hat{h}^2 = 0.69$ for the Example Quoted in the Text

Twin pair			q_1	q_2	x_1	x_2	a	x_R	q_c
MZ	Female	Female	0.006	0.006	2.512	2.512	2.834	0.740	0.230
MZ	Male	Male	0.012	0.012	2.257	2.257	2.603	0.610	0.271
DZ	Female	Female	0.006	0.006	2.512	2.512	2.834	1.625	0.052
DZ	Male	Male	0.012	0.012	2.257	2.257	2.603	1.438	0.075
DZ	Female	Male	0.006	0.012	2.512	2.257	2.834	1.355	0.088
DZ	Male	Female	0.012	0.006	2.257	2.512	2.603	1.708	0.044

Substituting in equation 1: $P_O = P_E = 0.875$

($v = 2$, $w = 1.5$, $c_1 - c_6$ are different values of q_c as shown in Table 1).

making estimation of x_R by equation 2 impossible. This occurs for all values of $h^2 \geqslant 1.1$ in the prevalence range of 0.1% to 10%. For $h^2 < 0$, estimation of $\hat{h}^2$ is also limited since P_E has a minimum (0.5 when $v = 1$) corresponding to all concordant affected pairs DZ. The minimum occurs at different negative values of h^2 depending on disease prevalence. A standard approach is therefore to restrict precise estimation of h^2 to the range $h^2 = 0$ to 1. Values of P_O that are greater than P_E when $h^2 = 1$ are then taken to indicate $\hat{h}^2 > 1$, while values of P_O less than P_E when $h^2 = 0$ are taken to indicate $\hat{h}^2 < 0$.

Approximate 95% confidence limits for $P_O (P' = P_O - 1.96\sigma_{P_O}, P'' = P_O + 1.96\sigma_{P_O})$ can be calculated by applying the formula:

$$\sigma_{P_O} = \sqrt{[P_O(1 - P_O)/(L + U)]}$$

Values of h^2 corresponding to P_E closest to P' and P'' then provide approximate confidence limits for $\hat{h}^2$. In the above example, $\sigma_{P_O} = 0.031$ so that $P' = 0.814$ and $P'' = 0.936$. The value of P' corresponds with $h^2 = 0.26$, while P'' is greater than P_E when $h^2 = 1$ ($P_E = 0.919$). The 95% confidence limits for $\hat{h}^2 = 0.69$ can therefore be given as 0.26 to > 1.0.

2. Common Environment

The extent to which $\hat{h}^2$ can be taken as an indication of genetic determination of the disease depends on the magnitude of any nongenetic familial effects contributing to concordance for the disease within twin pairs. In the absence of contributions to the genetic variance from dominance and epistatic interactions:

$$r_{MZ} = (V_A + V_C)/V \quad \text{and} \quad r_{DZ} = (V_A/2 + V_C)/V$$

where r_{MZ} and r_{DZ} are the correlations in liability to disease for MZ and DZ pairs, V_A is the additive genetic variance, V_C the common environmental variance (assumed to be the same for all categories of twin pair) and V the total phenotypic variance [11].
Thus:

$$r_{MZ} = h^2 + E \quad \text{and} \quad r_{DZ} = (h^2/2) + E$$

where

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$$E = V_C/V \quad \text{and} \quad 0 \leqslant E \leqslant 1 - h^2$$

The effect on $\hat{h}^2$ of different values of E, through substituting the above expressions for r in equation 2, is shown in Table 3 for w = 1.5, the approximate DZ/MZ ratio for

Table 3. Values for $(\hat{h}^2 - h^2)$, where $\hat{h}^2$ is the Heritability Estimate Assuming no Common Environmental Effects, h^2 is the True Heritability and E is the Proportion of the Total Phenotypic Variance Attributable to Common Environmental Effects, for Different Values of v and Different Population Prevalences (q_g) (w = 1.5). *Indicates $h^2 < 0$

			q_g%= 0.1					q_g%= 10.0				
v	E	h^2 = 0.1	0.3	0.5	0.7	0.9	0.1	0.3	0.5	0.7	0.9
1	0.1	-0.02	-0.05	-0.08	-0.08	0.02	-0.01	-0.03	-0.04	-0.02	0.03
	0.3	-0.04	-0.11	-0.16	-0.05		-0.03	-0.07	-0.06	0.04	
	0.5	-0.05	-0.13	-0.11			-0.03	-0.07	0.00		
	0.7	-0.05	-0.09				-0.03	-0.03			
	0.9	-0.03					-0.02				
2	0.1	-0.03	-0.06	-0.09	-0.09	0.02	-0.05	-0.07	-0.07	-0.03	0.02
	0.3	-0.06	-0.13	-0.18	-0.07		*	-0.15	-0.13	0.02	
	0.5	-0.08	-0.16	-0.14			*	-0.17	-0.05		
	0.7	-0.09	-0.12				*	-0.10			
	0.9	-0.06					-0.08				
3	0.1	-0.04	-0.08	-0.11	-0.10	0.02	*	-0.15	-0.13	-0.06	0.02
	0.3	-0.10	-0.17	-0.22	-0.09		*	*	-0.25	-0.01	
	0.5	*	-0.21	-0.18			*	*	-0.13		
	0.7	*	-0.16				*	-0.22			
	0.9	-0.10					*				

many Caucasian populations. Differences between estimated and true heritabilities are generally negative because common environment acts on both MZ and DZ pairs, reducing the difference in concordance between them and, consequently, reducing the proportion of concordant affected pairs that are like-sexed. The underestimation of the true heritability is increasingly marked with higher values of v.

3. Diagnosis and Ascertainment

Not all individuals with the disease may be diagnosed and, among those diagnosed, not all may be ascertained. The combined effects of diagnosis and ascertainment can be taken as the level of 'detection' of the disease. If the probability of detection, d_1, in twins is constant for all levels of liability above the threshold, then the mean liability of twins detected will be the same as the mean liability for all twins with the disease. The prob- and concordance rate for cotwins with the disease will therefore be independent of the level of detection, although only a proportion, d_2, of affected cotwins will be known to have the disease. Under these circumstances (model 1), each of the concordance rate terms in both the numerator and denominator of the expression for P_E in equation 1 would be multiplied by the factor $d_1 d_2$, leaving the values of P_E and $\hat{h}^2$ unchanged.

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On the other hand, if affected twins are divided by a second threshold on the liability scale into those undetected (closer to the threshold for disease) and those detected (further from the threshold for disease), the mean liability for those detected will be higher than for all twins with the disease. This would result in a correspondingly higher proband concordance rate for cotwins with the disease at a given heritability. The effect on $\hat{h}^2$ in such a situation, when $v = 1$, is analogous to that of a difference in prevalence between the sexes and can be demonstrated by using $d_1 q_g$ rather than q_g for the calculation of x_1 in equation 2 but q_g as before for the calculation of x_2. The proband concordance rate derived from x_R would then indicate disease prevalence among cotwins and should therefore be multiplied by d_2 to give the prevalence of detected disease among cotwins. However, the value of P_E is only affected by d_1 since all the concordance rate terms in the expression for P_E (equation 1) would be multiplied by d_2 causing this factor to cancel out. The effect of incomplete detection on $\hat{h}^2$ using this model (model 2) is shown in Table 4.

Table 4. Values for $(\hat{h}^2 - h^2)$, where $\hat{h}^2$ is the Heritability Estimate Assuming Complete Detection and h^2 is the True Heritability, for Different Levels of Detection and Different Population Prevalences (q_g) ($v = 1$, $w = 1.5$, for explanation see text)

		h^2				
Detection	q_g%	0.1	0.3	0.5	0.7	0.9
0.8	0.1	0.00	0.01	0.01	0.02	0.01
	1.0	0.00	0.01	0.02	0.02	0.01
	10.0	0.01	0.02	0.03	0.03	0.02
0.6	0.1	0.00	0.02	0.03	0.04	0.02
	1.0	0.01	0.03	0.04	0.05	0.02
	10.0	0.01	0.05	0.07	0.07	0.03
0.4	0.1	0.01	0.03	0.06	0.07	0.03
	1.0	0.01	0.04	0.08	0.08	0.03
	10.0	0.02	0.08	0.12	0.10	0.02

In practice, the situation is likely to be intermediate between models 1 and 2. The probability of diagnosis may well be related to an affected individual's position on the scale of liability since the severity of disease may increase with distance above the threshold. Ascertainment, however, will probably depend on the completeness and accuracy of a number of clerical steps involved in entering the required information about a patient on the register, and these are unlikely to be related to the level of liability among those cases diagnosed. Any bias in the heritability estimate due to incomplete detection is therefore likely to be relatively small.

4. Age Effects and Mortality

Many diseases vary in prevalence between different age groups. It is therefore important to use the population prevalence appropriate to the age range of the twin pairs studied.

It has been shown that the stillbirth rate is 1.4 times higher and the neonatal morta-

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lity rate 1.2 times higher in like-sexed than in unlike-sexed twins [2]. This was attributed to greater mortality in monochorionic twins, all of whom are MZ. There is no difference in mortality after the first month of life. Thus, different values of w may be appropriate for diseases scored at birth and those scored after the first month of life.

The method described in this paper assumes that MZ pairs are equally likely to be male or female and that DZ pairs are present in the population in the ratio 1:2:1 (male/male:unlike-sexed:female/female). However, at all ages the death rate is higher for males than for females. For example, in Scotland in 1982 the death rate in several age groups between 1 year and 85 years of age was between 1.5 and 3.3 times greater for males than for females [8]. Thus, when using concordant affected twin pairs from older age groups, the method may not be strictly valid unless either (a) the two types of MZ pair and the three types of DZ pair are present in the general population in proportions not significantly different from those given above, or (b) appropriate adjustments are made to the expression for P_E in equation 1.

5. Differences of Disease Prevalence Between MZ and DZ Twins

Monozygous twin individuals have a risk of cardiovascular malformation approximately twice that for DZ twins or singletons. This appears to be the consequence of some form of interaction between the two members of a MZ pair (twin-twin transfusion, unequal division of maternal cytoplasm or disturbance of laterality) with a disturbance of laterality being the favoured explanation [3]. The possible genesis of congenital malformation through such interaction means that the two members of each MZ pair may not be equally prone to abnormality, leading to underestimation of the heritability for such disorders [7]. In this respect, the method described in this paper is no different from any other twin method.

6. Conditions Under Which the Method Might Be Applied

With increasing disparity of disease prevalence between the sexes at high overall disease prevalences, the unique relationship between heritability and the proportion of concordant affected pairs like-sexed is lost. This effect is mediated through the increasingly large contribution to concordant affected pairs made by unlike-sexed DZ twins, especially at lower heritabilities, when the cotwin is of the more frequently affected sex. In graphic terms, the curves corresponding to those in Fig. 1 cross, so that there is no single estimate of heritability for a given proportion of concordant affected pairs like-sexed at a given population prevalence. Within the range $w = 1$ to 5 and $v = 1$ to 3 the maximum overall disease prevalence that can be used while retaining reasonable separation between the curves is 10%.

The confidence limits given in Table 5 provide an indication of the power of the method. Narrower limits are found at lower disease prevalences and lower heritabilities, simply because the heritability curves converge towards a population prevalence of 100% and are more widely spaced in the lower heritability range (Fig. 1). On the other hand, the lower the prevalence and the lower the heritability, the larger will be the population required to yield an adequate sample of concordant affected pairs. Table 6 lists the population sizes required to provide a sample of 100 concordant affected twin pairs, assuming a twinning incidence of 1% of all live births and complete detection, calculated using the expressions in the last column of Table 1. These population sizes, together with the

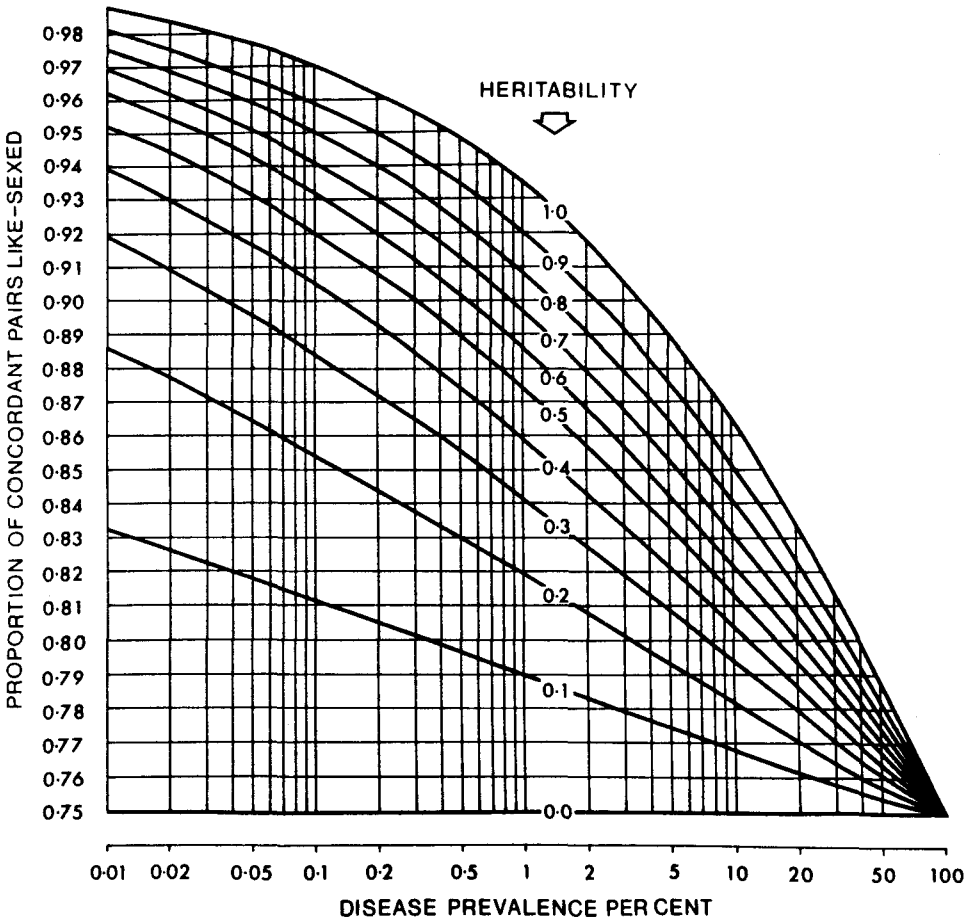

Fig. 1 - The expected proportion of all concordant affected twin pairs that are like-sexed for different disease prevalences and different heritabilities when v = 1 and w = 1.

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Table 5. Approximate 95% Confidence Limits for the Heritability Estimate (n = Number of Concordant Affected Pairs, w = 1.5) * Indicates Limit <0, + Indicates Limit >1

		$\hat{h}^2 = 0.1$			$\hat{h}^2 = 0.5$			$\hat{h}^2 = 0.9$		
v	q_g%	n = 25	100	400	25	100	400	25	100	400
1	0.1	* – 0.80	* – 0.30	0.03 – 0.10	0.11 – +	0.25 – 0.97	0.35 – 0.72	0.32 – +	0.54 – +	0.71 – +
	1.0	* – +	* – 0.46	* – 0.24	* – +	0.16 – 0.99	0.30 – 0.76	0.18 – +	0.47 – +	0.68 – +
	10.0	* – +	* – 0.89	* – 0.47	* – +	* – +	0.14 – 0.90	* – +	0.18 – +	0.53 – +
2	0.1	* – 0.96	* – 0.35	0.02 – 0.20	0.08 – +	0.23 – 1.00	0.34 – 0.75	0.28 – +	0.50 – +	0.69 – +
	1.0	* – +	* – 0.56	* – 0.28	* – +	0.12 – +	0.27 – 0.80	0.12 – +	0.42 – +	0.66 – +
	10.0	* – +	* – +	* – 0.61	* – +	* – +	0.05 – 0.94	* – +	0.05 – +	0.46 – +
3	0.1	* – +	* – 0.43	0.01 – 0.22	0.03 – +	0.19 – +	0.31 – 0.80	0.22 – +	0.46 – +	0.66 – +
	1.0	* – +	* – 0.72	* – 0.34	* – +	0.05 – +	0.23 – 0.85	0.02 – +	0.34 – +	0.62 – +
	10.0	* – +	* – +	* – 0.81	* – +	* – +	* – +	* – +	* – +	0.31 – +

Table 6. Population Size (in Millions) Required to Give a Sample of 100 Concordant Affected Twin Pairs (Twinning Rate = 1% Live Births, v = 1, w = 1.5, Detection Complete)

Population prevalence %	Heritability		
	0.1	0.5	0.9
0.1	4617.1	359.8	48.8
1.0	61.9	12.8	3.5
10.0	0.8	0.4	0.2

confidence limits shown in Table 5, indicate that the range of disease prevalence over which the method might be applied is certainly no less than 0.1% at its lowest and no greater than 10% at its highest.

A SIMPLE NONCOMPUTATIONAL APPROACH

Values of P_E for different disease prevalences and different heritabilities when v = 1 and w = 1 are shown in Fig. 1. An observed proportion of concordant affected pairs like-sexed, P_O, from a population where $w \neq 1$ (but v = 1) can be adjusted to P_A, a value corresponding to w = 1, using the formula:

$$P_A = [w(2P_O - 1) - P_O + 1]/[w(2P_O - 1) - 2P_O + 2]$$

Heritability estimates for populations with different DZ/MZ ratios can therefore be read directly from Fig. 1, provided disease prevalence is equal in the two sexes. The 95% confidence interval for $\hat{h}^2$ can be derived by calculating the confidence limits for P_O, converting each of these to the corresponding P_A value and then reading from Fig. 1.

In order to assess the effect of unequal sex prevalence on $\hat{h}^2$ using this noncomputational approach, heritabilities were estimated on the assumption of equal sex prevalence (v = 1) from P_E values calculated for different true heritabilities and different values of v. Differences between $\hat{h}^2$ and the true heritability are shown in Table 7. Differences are always positive because unequal sex prevalence inflates the proportion of concordant affected pairs like-sexed. Differences increase with overall population prevalence and with v. If v is close to 1 it may be acceptable to use Fig. 1 alone to provide the heritability estimate. For larger values of v (or 1/v), up to a maximum of 3, an approximation for $\hat{h}^2$ can be derived by using Fig. 1 and making an appropriate adjustment using Table 7.

COMPARISON WITH OTHER METHODS

A survey of the literature was made in an attempt to identify published twin data which could be both analysed by the method described and used to obtain heritability estimates by more conventional methods for comparison. Several difficulties were encountered: sample size too small; ascertainment apparently biased towards like-sexed concordant pairs; sexes of the twins not given, only their zygosity; appropriate DZ/MZ ratio and

Table 7. Values for $(\hat{h}^2 - h^2)$, where $\hat{h}^2$ is the Heritability Estimate Assuming Equal Sex Prevalence ($v = 1$) and h^2 is the True Heritability, for Different Values of v (or 1/v) and Different Population Prevalences (q_g) ($w = 1.5$). $+$ indicates $h^2 > 1$

		h^2				
v (or 1/v)	q_g%	0.1	0.3	0.5	0.7	0.9
1.5	0.1	0.02	0.03	0.03	0.02	0.01
	1.0	0.04	0.04	0.04	0.04	0.02
	10.0	0.10	0.11	0.10	0.08	0.05
2.0	0.1	0.07	0.07	0.08	0.07	0.04
	1.0	0.12	0.13	0.13	0.10	0.06
	10.0	0.32	0.31	0.27	0.20	+
2.5	0.1	0.12	0.13	0.14	0.12	0.06
	1.0	0.21	0.23	0.22	0.16	0.09
	10.0	0.57	0.51	0.41	0.29	+
3.0	0.1	0.17	0.19	0.20	0.16	0.08
	1.0	0.32	0.33	0.30	0.22	+
	10.0	0.77	0.65	+	+	+

disease prevalences in the general population not given.

On reflection, some of the deficiencies in the published data were not unexpected. When twins have been used to assess the importance of genetic factors in the aetiology of a disease, the approach has usually been to compare concordance rates for MZ and DZ pairs. Heritability estimates have been derived from these concordance rates and the population prevalence of the disease in question. For these calculations it has not been necessary to know the DZ/MZ ratio in the general population and, when the analysis has been restricted to twins of one sex only, it has been unnecessary to consider differences in disease prevalence between the sexes. However, a large amount of work must be undertaken to establish the zygosity of each twin pair involved. Our method has the considerable advantage that zygosity determination is not required.

For a population in which $w = 1.5$ some 30% of all twin pairs are expected to be of unlike sex. Excluding concordant affected twin pairs of unlike sex from the estimation of heritability, as has been done by many workers, therefore represents a considerable waste of resources. In our method both like-sexed and unlike-sexed pairs are used. Furthermore, the heritability estimate is little affected by ascertainment, provided the level of ascertainment is the same for like-sexed and unlike-sexed concordant pairs.

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REFERENCES

1. Beasley JD, Springer SG (1977): Algorithm AS 111. The percentage points of the normal distribution. Appl Statist 26:118-121.

2. Bulmer MG (1970): "The Biology of Twinning in Man". Oxford, Clarendon Press.
3. Burn J, Corney G (1984): Congenital heart defects and twinning. Acta Genet Med Gemellol 33: 61-69.
4. Falconer DS (1965): The heritability of liability to certain diseases estimated from the incidence among relatives. Ann hum Genet 29:51-76.
5. Hill ID (1973): Algorithm AS 66. The normal integral. Appl Statist 22:424-427.
6. Mendell M, Elston RC (1974): Multifactorial qualitative traits: genetic analysis and prediction of recurrence risks. Biometrics 30:41-57.
7. Price B (1950): Primary biases in twin studies. A review of prenatal and natal difference producing factors in monozygotic pairs. Am J hum Genet 2:293-352.
8. Registrar General for Scotland, Annual Report 1982, Edinburgh, HMSO.
9. Reich T, James JW, Morris CA (1972): The use of multiple thresholds in determining the mode of transmission of semi-continuous traits. Ann hum Genet 36:163-184.
10. Smith C (1972): Correlation in liability among relatives and concordance in twins. Hum Hered 22:97-101.
11. Smith C (1974): Concordance in twins: methods and interpretation. Am J hum Genet 26:454-466.

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