When Assessing Twin Concordance, Use the Probandwise Not the Pairwise Rate

by Matt McGue

Abstract

Geneticists and twin researchers have long debated the relative merits of two alternative measures of twin concordance: the pairwise and probandwise concordance rates. The results of this debate are now quite clear, for almost every application the probandwise rate is preferred over the pairwise rate. In a recent review of schizophrenia twin studies, however, Torrey (1992) chose to analyze pairwise rather than probandwise rates. Torrey's use of pairwise rates led him to conclude that the monozygotic twin concordance for schizophrenia is weaker than what is widely accepted, and that, by implication, the magnitude of the genetic contribution to schizophrenia has been overestimated. In this brief commentary, we review the relative strengths and weaknesses of the pairwise and probandwise rates and show that Torrey's conclusion is based upon his incorrect use of pairwise rates. Twin studies of schizophrenia continue to support the existence of a strong genetic influence on the development of schizophrenia.

Dr. Torrey's article (1992, this issue) raises several important questions about twin studies of neurological disorders in general, and schizophrenia in particular. He notes that the study of monozygotic (MZ) and dizygotic (DZ) twins has provided psychiatry with a powerful tool for establishing the existence of genetic influences on complex phenotypes. He catalogs the many neurological disorders for which the MZ twin concordance substantially exceeds the DZ twin concordance, and in doing so implicates genetic factors as playing a significant role in the etiologies of a wide range of central nervous system diseases. He sounds an appropriately cautionary note in considering the effects of ascertainment scheme, diagnostic criteria, and zygosity determination on the validity of a twin study. Unfortunately, however, Torrey also falls prey to an old yet commonplace error in the twin research literature: the use of pairwise rather than probandwise concordance rates. The purpose of this brief comment is to identify this error and repair it.

Measuring Twin Concordance at the Population Level

Table 1 depicts a fictitious population of 100,000 MZ twin pairs classified according to the schizophrenic status of each member of the pair. The population was generated to be more or less typical of what is found in twin studies of psychiatric phenotypes. One member of each generated twin pair was arbitrarily designated Twin A with the other designated Twin B. The results given apply also to all alternative orderings of the two members of a pair.

Although there are innumerable statistical measures of association for a 2 × 2 table (Goodman and Kruskal 1954) twin researchers have typically focused on two; both are conditional probabilities. The first is the probability that both members of a twin pair are affected given that at least one member of the pair is affected. In table 1 there are 1,400 twin pairs with at least 1 affected member, and in 600 of these, both members are affected. The condi-

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Table 1. Fictitious population of 100,000 monozygotic twin pairs classified according to their schizophrenic status.

	Twin A		
	Schizophrenic	Non-schizophrenic	Total
Twin B			
Schizophrenic	600	380	980
Non-schizophrenic	420	98,600	99,020
Total	1,020	98,980	100,000

tional probability that both members of a twin pair are affected given at least one is affected is thus 600/1,400 or 0.429.

The second conditional probability of interest is the probability that a twin is affected given that his/her co-twin is affected. To derive this conditional probability, one needs to appropriately weigh two other probabilities. First, the conditional probability that Twin B is affected given that Twin A is affected, which in this case equals 600/1,020 or 0.588. And second, the probability that Twin A is affected given that Twin B is affected, which in this case equals 600/980 or 0.612. The overall conditional probability is obtained by weighing these two probabilities according to the chance that Twin A is affected, and the chance that Twin B is affected, respectively. That is, the conditional probability that a twin is affected given his/her co-twin is affected equals

$$(600/1{,}020) \times (1{,}020/100{,}000) + (600/980) \times (980/100{,}000)$$

divided by

$$(1{,}020/100{,}000) + (980/100{,}000).$$

which with cancellation becomes

$$(600+600)/(1{,}020+980) = 0.600.$$

Note that, in effect, the calculation of the second conditional probability involves counting each concordant pair twice, both in determining the numerator and in determining the denominator; that is, instead of 600/1,400 we have (600+600)/(1,400+600).

Geneticists have termed the first conditional probability the pairwise concordance rate, and the second conditional probability the casewise concordance rate. Whatever their designation, however, it is important to note that both refer to conditional probabilities, one applying to twin *pairs* and the other applying to twin *individuals*, and therein lies the basis for preferring one over the other; geneticists are primarily interested in forecasting risk at the level of the individual rather than at the level of the pair. For example, in a genetic counseling situation, what is needed is the risk that the individual will become affected given knowledge that his/her relative is affected. In the twin example above, that individual risk rate is given by the casewise concordance of 0.600, and not the pairwise rate of 0.429. Furthermore, only casewise rates can be directly compared to risk rates reported for other familial pairings and to population prevalence figures. For example, when considering parent-offspring studies of schizophrenia, we do not analyze, report, or interpret the conditional probability that both parent and offspring are affected given that at least one of the pair is affected (a rate that would be analogous to the pairwise rate given above). Rather we report and interpret the conditional probability that an offspring is affected given that his/her parent is affected (a rate which is analogous to the casewise rate given above). Inferring the strength of genetic influence involves comparing the relative magnitude of individual not pair conditional probabilities. Finally, as will be shown below, defining an appropriate sample estimate is difficult when estimating the population pairwise rate, but relatively straightforward when estimating the population casewise rate.

Assessing Concordance in an Ascertained Sample

In twin studies of psychiatric phenotypes, only that subset of the population of twin pairs containing at least one affected member is typically sampled. Thus, a common ascertainment scheme involves identifying those members of a psychiatric case registry who are also twins. Each *independently* ascertained twin is called a proband (Morton 1959). Twin pairs are thus ascertained because either one or both members achieved proband status. Twin pairs with two probands are said to be doubly ascertained pairs; those with a single proband are singly ascertained. The chance that a twin pair in the population will be included in the sample will depend upon two factors: (1) the number of affected members in the pair, and (2) the thoroughness of ascertainment. If ascertainment is complete, every affected twin is a proband so that all pairs with at least one affected member are included in the sample, and all concordant twin pairs are doubly ascertained. Incomplete ascertainment occurs when the probability that an affected twin is sampled (termed the ascertainment probability, which we designate here as π) is less than 1.0.

If only pairs with at least one affected member are ascertained, then the twin sample will consist of up to three types of twin pairs: (1) doubly ascertained concordant pairs (the number of which we designate as C1), (2) singly ascertained concordant pairs (C2), and (3) discordant pairs (D), which necessarily have only one proband member. Three sample twin concordance rates can be derived from these three numbers. The first two, the sample casewise and pairwise rates, are direct analogs to concordance rates defined at the population level. The third, the probandwise rate, was first proposed by Weinberg (1928) more than 60 years ago, and appears as if it were a hybrid of the other two. That is, whereas the casewise rate involves counting all concordant twin pairs twice, the probandwise rate involves counting only doubly ascertained pairs twice. Thus, the three sample rates are given as pairwise = (C1 + C2)/(C1 + C2 + D); probandwise = (2C1 + C2)/(2C1 + C2 + D); casewise = (2C1 + 2C2)/(2C1 + 2C2 + D). It is easy to see that the magnitude of the three sample concordance rates obeys the ordering: casewise ≥ probandwise ≥ pairwise.

In an excellent article, Allen and Hrubec (1979) present a general model of ascertainment and apply it to evaluate these three alternative sample estimates of twin concordance. Here, for the sake of exposition, we consider only a special case of the general model. Nonetheless, the conclusions we draw apply also in the general case. The interested reader is referred to Allen and Hrubec for a comprehensive treatment of this problem. In the special case we consider here, it is assumed that the probability that an affected twin is ascertained as a proband is independent of his/her co-twin's status and equal to the overall ascertainment probability π. In this case, the probability that a twin pair is ascertained can be derived through the binomial expansion, so that the probability that a concordant pair is doubly ascertained equals π^2, the probability that a concordant pair is singly ascertained is given by $2\pi(1-\pi)$, and the probability that a discordant pair is ascertained is π. Consequently, expected values for C1, C2, and D can be derived as a function of π and the number of concordant and discordant twin pairs in the population as: expected (C1) = π^2 × (number of concordant pairs in the population); expected (C2) = $2\pi(1-\pi)$ × (number of concordant pairs in the population); and expected (D) = π × (number of discordant pairs in the population).

So that, in our example, expected (C1) = π^2 × (600); expected (C2) = $2\pi(1-\pi)$ × (600); and expected (D) = π × (800).

These expected values can be used to determine the effect of incomplete ascertainment on the three sample estimates of twin concordance. An "expected" sample concordance can be specified by substituting expected values for C1, C2, and D in the concordance rate formulas given above.[1] In table 2, we have made these calculations for four different values of the ascertainment probability, π = 0.1, 0.4, 0.7, 1.0 (the latter corresponding to complete ascertainment). Several features of table 2 warrant comment. First, the expected pairwise and casewise rates vary with the thoroughness of ascertainment, both being largest when the ascertainment probability is smallest. Because they vary with the ascertainment probability, sample pairwise and casewise rates are not directly comparable from one study to the next unless all studies achieve a similar level of ascertainment. Second, unless ascertainment is complete (i.e., π = 1.0), neither the sample pairwise nor the sample casewise rate is a particularly good estimate of their corresponding population values. Indeed, both tend to overestimate their population values, especially when the ascertainment probability is low. In contrast, the expected probandwise rate does not vary with the ascertainment probability, and is found to equal, on average, the population casewise rate.

In summary, the pairwise concordance rate has the following identifiable weaknesses: First, it forecasts risk at the level of the pair rather than the individual. Second, pairwise twin concordance rates are not directly comparable to rates reported for other relative pairings nor are they directly comparable to the overall population prevalence of the disorder. Third, the sample pairwise rate varies with the thoroughness of ascertainment, so that pairwise rates are not directly comparable across studies unless all studies have similar ascertainment probabilities. Finally, the sample pairwise rate is not an accurate estimate of the population pairwise rate. In contrast, the probandwise rate can be compared across studies even when the studies are characterized by different ascertainment probabilities. It accurately estimates the population casewise rate, and the population casewise rate is the quantity we desire to esti-

[1]Strictly speaking, the ratio of two unbiased estimates is itself not necessarily unbiased. Nonetheless, to keep the mathematical detail to a minimum, we have evaluated the accuracy of sample estimates by considering whether the ratio of the estimate's expected numerator to its expected denominator equals the population quantity estimated.

Table 2. Effect of ascertainment on three sample measures of twin concordance

Ascertainment probability	Number of pairs observed				"Expected" concordance		
	C1	C2	D	Total	Pairwise	Probandwise	Casewise
0.10	6	108	80	194	0.588 (114/194)	0.600 (120/200)	0.740 (228/308)
0.40	96	288	320	704	0.545 (384/704)	0.600 (480/800)	0.706 (768/1088)
0.70	294	252	560	1106	0.494 (546/1106)	0.600 (840/1400)	0.661 (1092/1652)
1.0	600	0	800	1400	0.429 (600/1400)	0.600 (1200/2000)	0.600 (1200/2000)

Note.—C1 = expected number of doubly ascertained concordant pairs; C2 = expected number of singly ascertained concordant pairs; D = expected number of discordant pairs. "Expected" sample concordance derived by taking the ratio of expected numerator to expected denominator for each of the three sample estimates.

mate because it forecasts risk at the individual rather than pair level. Finally, the probandwise rate can be directly compared to risk rates reported for other relative pairings, and to the population prevalence rate. It is little wonder, then, that geneticists and twin researchers show a strong preference for the probandwise rate.

Application to Schizophrenia

In his table 1, Torrey (1992, this issue) reports pairwise MZ and DZ twin concordances from eight twin studies of schizophrenia. Those familiar with twin studies of schizophrenia are aware that each study is not easily summarized by a single MZ and a single DZ concordance rate. Most studies report a range of concordances depending upon the specific diagnostic criteria used. Generally, where multiple concordance rates were reported, Torrey has used the pairwise concordance rate that corresponds to the most exclusive diagnosis of schizophrenia. To focus our discussion on the effect of alternative concordance measures, we, with few exceptions, accept the rates Torrey uses. The interested reader is urged to consult Gottesman and Shields (1982) for a more comprehensive treatment of concordance in twin studies of schizophrenia.

In our table 3, we reproduce the pairwise rates reported by Torrey as well as the corresponding probandwise and casewise rates for that sample and diagnosis. In only two cases do we report rates different from those reported by Torrey. For both Kringlen (1967) and Slater and Shields (1953), we report concordance rates for same-sex DZ twins only. The rates Torrey reports for these two studies are based upon mixed opposite-sex and same-sex samples. Also given in table 3, are the weighted (by sample size) and unweighted mean concordance rates, the chi-square statistics for testing the homogeneity of the eight sample proportions, and the unweighted standard deviation of the sample proportions. Several features of the table warrant comment. First, Torrey's conclusion that the MZ twin concordance for schizophrenia is lower than typically reported is due largely to his having used pairwise rather than probandwise rates. The average probandwise concordance for the eight studies analyzed by Torrey (0.40 weighted and 0.45 unweighted) is clearly consistent with averages reported in other reviews of the schizophrenia twin literature (e.g., Gottesman and Shields 1982 report a weighted average MZ probandwise concordance rate of 0.46 for recent schizophrenia twin studies). Second, between-study variability, as reflected by both the chi-square test statistics and the standard deviations of the proportions, is minimized with the probandwise rate. This is to be expected given the theoretical treatment above. The casewise and pairwise rates vary with the ascertainment probability, but the probandwise rate does not. Thus, if studies vary in respect to the completeness of ascertainment (which they most likely do), between-study heterogeneity will be greater with the pairwise and casewise rates than with the probandwise rates. Nonetheless, it is important to note that use of the probandwise rate minimizes but does not eliminate between-study variability. There are many factors which contribute to between-study variability that neither we nor Torrey have

Table 3. Alternative measures of twin concordance in eight twin studies of schizophrenia

	MZ concordance			DZ concordance		
Study	Pairwise	Proband-wise	Casewise	Pairwise	Proband-wise	Casewise
Essen-Möller (1970)	0.500 (4/8)	0.500 (4/8)	0.750 (8/12)	0.074 (2/27)	0.074 (2/27)	0.138 (4/29)
Slater and Shields (1953)	0.649 (24/37)	0.683 (28/41)	0.787 (48/61)	0.138 (8/58)	0.180 (11/61)	0.242 (16/66)
Tienari (1975)	0.150 (3/20)	0.261 (6/23)	0.261 (6/23)	0.071 (3/42)	0.133 (6/45)	0.133 (6/45)
Kringlen (1967)	0.311 (14/45)	0.456 (26/57)	0.475 (28/59)	0.067 (6/90)	0.125 (12/96)	0.125 (12/96)
Fischer (1973)	0.238 (5/21)	0.360 (9/25)	0.385 (10/26)	0.098 (4/41)	0.178 (8/45)	0.178 (8/45)
Gottesman and Shields (1972)	0.500 (11/22)	0.577 (15/26)	0.667 (22/33)	0.091 (3/33)	0.118 (4/34)	0.167 (6/36)
Kendler and Robinette (1983); NAS-NRC	0.183 (30/164)	0.309 (60/194)	0.309 (60/194)	0.034 (9/268)	0.065 (18/277)	0.065 (18/277)
Onstad et al. (1991)	0.333 (8/24)	0.484 (15/31)	0.500 (16/32)	0.036 (1/28)	0.036 (1/28)	0.069 (2/29)
Mean						
Weighted	0.290	0.402	0.452	0.062	0.101	0.116
Unweighted	0.358	0.454	0.517	0.076	0.114	0.140
Heterogeneity						
Chi-square (7 *df*)	41.2	27.7	58.4	11.3	13.8	20.9
p-value	< 0.001	0.001	< 0.001	0.13	0.06	0.004
SD	0.164	0.130	0.186	0.032	0.048	0.054

Note.—MZ = monozygotic; DZ = dizygotic; NAS-NRC = National Academy of Sciences–National Research Council; *df* = degrees of freedom; SD = standard deviation.

considered including, for example, sample sex ratio, diagnostic standards, whether probands were ascertained from resident populations, and the age of the sample. Again, interested readers are encouraged to consult Gottesman and Shields (1982) for a more comprehensive treatment of these issues.

Conclusion

Torrey has made an important observation in noting that genetic factors are implicated in a wide range of neurological disorders. His exclusive reliance on pairwise concordance rates, however, led him to the erroneous conclusion that schizophrenia was less heritable than implied in recent reviews of the schizophrenia research literature. When proband-wise rates are considered for the eight studies surveyed by Torrey, the pooled rates correspond closely to what others have reported and continue to confirm a strong genetic influence on schizophrenia risk. Moreover, the inference that genetic factors play a significant role in the development of schizophrenia does not rest with twin studies alone. For example, we have previously analyzed twin and family data for schizophrenia, and reported that the estimated heritability of schizophrenia liability is strong (in the 0.6 to 0.7 range) regardless of whether the twin concordance rates are included in the analysis (McGue et al. 1983).

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