US Public Health Service

Models of Proband Concordance Rates for Twins in a Clinical Series

G. Allen

With the exception of disorders related to gestation and birth, twins are usually found to be medically representative of the general population; diseases occur among twins with the same frequency as among singletons. As a corollary, in a large series of twins, if members of each pair are assigned randomly to two groups, A and B, *both* groups will be representative of the population. For example, if a disease occurs in 1% of the population, then we can expect it in 1% of twin-group A and in 1% of twin-group B.

Tab. I diagrams a hypothetical population of 15000 twin pairs in which 1% of all persons have the disease in question. Twins A include, in the left column, 150 sick persons. Each of these has a partner, twin B, who may be either sick or well, and so the total number of *pairs* in the left column is 150. The figures are the same when the table is read down or across; that is, the table is symmetrical with respect to twins A and twins B because assignment to A and B was random.

The marginal totals of this table are all determined by the frequency of disease in the population, but the figures in the four inner cells can vary.

Tab. II shows what numbers would occur in the boxes if 2/3 of all affected persons had an affected partner. In other words, the proband concordance rate is 2/3, or 66%. In this series of twins there are 200 pairs affected by the disease, of which 100 are concordant, while in the others either twin A or twin B is alone affected. Hence the *pairwise* concordance rate is 50%.

Tab. III shows the values in the four inner cells for the 15000 pairs of same-sex DZ twins in the same population. The marginal numbers are unchanged; 150 cases of disease occur among twins A and also among twins B. But here the proband concordance rate is only 1/5, or 20%. Conforming to this concordance rate, the 300

* The methods recommended here correct only for sampling; i.e., from sample data they yield consistent estimates of statistics that would be obtained if the whole population were studied by the same methods. Z. Hrubec has shown (paper in preparation) that when incomplete ascertainment is uniform and hence equivalent to incomplete penetrance, the proband concordance rate is reduced in proportion to ascertainment. However, in this case the ratio of observed and expected proband concordance is the same as the true ratio. When ascertainment is complete in partners of index cases, index cases would of course be used alone in the calculations, and the correct estimates would result.

Acta Genet. Med. Gemellol. (1970), 19: 146-149

Tab. I. 15000 pairs of twins, each with members randomly designated A and B. Morbidity rate 1%

		15000 twins A		
		Sick (150 persons)	Well (14850 persons)	Total (15000 persons)
15000 twins B	Sick (150 persons)			150 pairs
	Well (14850 persons)			14850 pairs
	Total (15000 persons)	150 pairs	14850 pairs	15000 pairs

Tab. II. 15000 pairs of MZ twins. Proband concordance rate 66%

		15000 twins A		
		Sick (150 persons)	Well (14850 persons)	Total (15000 persons)
15000 twins B	Sick (150 persons)	100 pairs	50 pairs	150 pairs
	Well (14850 persons)	50 pairs	14800 pairs	14850 pairs
	Total (15000 persons)	150 pairs	14850 pairs	15000 pairs

cases are distributed among 270 pairs, of which 240 are discordant. The pairwise concordance rate is 30/270, or 11%.

These figures describe the twin population. Samples drawn from this population will not necessarily have the same concordance rates. The main point of this paper is that, among twins admitted to a hospital, the proportion of concordant pairs will always tend to be higher than in the population, and this would be true even if admission to the hospital were a random process. A second point of this paper is that this sampling bias affects only the distribution in pairs; it does not alter the proportion of *individuals* who belong to concordant pairs. The proband concordance rate in the hospital cases will consistently estimate the proband concordance rate in the twin population.

Suppose that Dr. X works in Hospital X and sees 50% of the sick population. Dr. Y works in Hospital Y where he sees only 20% of the cases. If visits to the hospital are random within concordant twin pairs, the probability that both members of a concordant pair will be seen in the same hospital is the square of the probability for one person. In Hospital X it is 50% squared, or 25%. In Hospital Y it is 20% squared, or 4%.

Tab. III. 15000 pairs of DZ twins. Proband concordance rate 20%

		15000 twins A		
		Sick (150 persons)	Well (14850 persons)	Total (15000 persons)
15000 twins B	Sick (150 persons)	30 pairs	120 pairs	150 pairs
	Well (14850 persons)	120 pairs	14730 pairs	14850 pairs
	Total (15000 persons)	150 pairs	14850 pairs	15000 pairs

Tab. IV shows the observations in Hospital X if we exclude random sampling errors. This does not exclude the sampling bias inherent in a clinical series of twins. Dr. X will see 125 pairs with the disease, of which 75 will be concordant. This is 60%, whereas in the twin population the pairwise rate was 50%. But when Dr. X counts his patients individually, he finds that 66% come from concordant pairs, which is the true proband concordance rate.

Tab. IV. MZ twin patients seen in Hospital X. 50% of the population

	Out of 100 concordant pairs in the population	Out of 100 discordant pairs in the population	Totals
	25 pairs, both seen 50 pairs, one seen	50 pairs, one seen	
Totals	75 pairs or 100 persons	50 pairs or 50 persons	125 pairs or 150 persons

Pairwise calculations: 75/125 = 0.60 (true rate, 0.50)
Proband calculations: 100/150 = 0.66 (true rate, 0.66)

Now Dr. Y, in his smaller hospital, will see 20% of all cases, and the square of this, 4% of the concordant pairs, will be recorded as complete pairs. Dr. Y finds the pairwise concordance rate to be 64% among the MZ twins, even farther from the true 50% figure than that obtained by Dr. X. But again, when he counts cases, 2/3 belong to concordant pairs. The two doctors will find that, when they discuss their proband concordance rates, their data agree.

Both doctors can indirectly estimate the pairwise concordance rate in the population by means of a simple formula. They need only to use the proband data and divide the number of cases from concordant pairs in half (Tab. VI).

https://doi.org/10.1017/S1120962300025294 Published online by Cambridge University Press

Tab. V. MZ twin patients seen in Hospital Y. 20% of the population

	Out of 100 concordant pairs in the population	Out of 100 discordant pairs in the population	Totals
	4 pairs, both seen 32 pairs, one seen	20 pairs, one seen	
Totals	36 pairs or 40 persons	20 pairs or 20 persons	56 pairs or 60 persons

Pairwise calculations: 36/56 = 0.64 (true rate, 0.50)
Proband calculations: 40/60 = 0.66 (true rate, 0.66)

Tab. VI. Method of estimating pairwise concordance rates

For MZ twins in Hospital X $\frac{100/2}{50 + (100/2)} = \frac{50}{100} = 0.50$ or $\frac{100}{2 \times 50 + 100} = \frac{100}{200} = 0.50$

For MZ twins in Hospital Y $\frac{40}{2 \times 20 + 40} = \frac{40}{80} = 0.50$

Dr. X had 100 persons from concordant MZ pairs and 50 from discordant pairs. Since each concordant pair had two chances to be represented in the hospital, and discordant pairs only one chance, this bias is corrected either by halving the concordant cases or by doubling the discordant ones. Both calculations give the same result.

In Hospital Y there are 40 cases from concordant pairs, 20 from discordant pairs. Dr. Y doubles the number of discordant cases and arrives at the correct estimate of the pairwise concordance rate in the population of twins. But Drs. X and Y will not agree about the pairwise concordance rate unless they apply this correction to their data.

The findings would be essentially the same if MZ concordant pairs went by preference to the same hospital, while DZ pairs chose their hospital randomly. If, however, cases in concordant pairs have a higher *rate of hospitalization* than cases in discordant pairs, no reliable estimate of concordance rates can be obtained from a clinical series. Even in that case, the proband concordance rate entails less error and is usually preferable to the observed pairwise rate.

Gordon Allen, M.D., Dept. of Health, Education and Welfare, NIMH, 9000 Rockville Pike, Bethesda, Md. 20014, USA.

https://doi.org/10.1017/S1120962300025294 Published online by Cambridge University Press