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*Letter to the Editor*

# A Response to Holm

# Primary and Secondary Ascertainment in Twin Studies

**Gordon Allen[1] and Zdenek Hrubec[2]**
[1]*National Institute of Mental Health, Rockville, Maryland*
[2]*National Institute of Environmental Medicine, Stockholm*

Dr. Holm was kind enough to send us a prepublication draft of his note [2] on ascertainment under the Allen-Hrubec model, and we appreciate the opportunity to comment on it. There appears to be no basic disagreement between Holm and us about the mathematical basis of the proband concordance rate. However, he seems to have misunderstood the purpose of the Allen-Hrubec model.

The main theme of our paper might be expressed as follows: "In a twin study that meets realistic sampling criteria, accuracy of the estimate of concordance rate by the proband method is independent of the primary ascertainment probability and depends only on completeness of secondary ascertainment."

Holm discards the Allen-Hrubec model on two alleged grounds: first, that the term "ascertainment" is inappropriate for the detection of secondary cases, and second, that any proper twin study excludes twin pairs in which all the cotwins cannot be classified with complete confidence as either affected or unaffected. Neither of these arbitrary stipulations in any way invalidates the model. The first is purely semantic and the second disregards all but ideally perfect twin studies, a course that would admittedly make our model useless but would probably leave no twin studies to be considered.

Twin samples are generally compiled through one operation and evaluated intensively through another, and the completeness of detection in the two operations is bound to differ, often by design. Only under hypothetical, ideal conditions is this operational structure irrelevant to the outcome. The consequences of the operations employed can

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be complex, and might sometimes be better described by models other than ours. But the problem cannot be made to disappear by "discontinu[ing] . . . the concept of secondary ascertainment."

The mere fact of examining every cotwin does not assure that disease in every affected cotwin will be detected (as Holm states), and completeness of detection is not assured by the examiner's opinion of his own thoroughness. Furthermore, in many important twin studies some cotwins cannot be examined at first hand. To exclude such pairs would often introduce greater bias than relying on medical histories or autopsy reports. The completeness of ascertainment (or detection if Holm insists) in secondary cases is thus a central issue in designing and evaluating any twin study. This is true even if, following Holm, every study is to be discarded in which status of all included cotwins was not determined with absolute certainty. In our paper we stated that complete secondary ascertainment was necessary for the accurate estimation of concordance. We did not advocate any attempt to correct for incomplete secondary ascertainment, but methods similar to those used, for example, to circumvent incomplete penetrance [1], might salvage some twin studies that Holm would forbid us to look at.

Holm considers our model to be of no value because it is true only if the (primary) ascertainment probabilities are identical in twins from concordant and discordant pairs. Far from being a limitation of the model, this condition is the principal and essential result of random sampling. Weinberg described the circumstances for an ideal study thus: ". . . von den Trägern nur ein Teil durch Stichprobenauslese rein zufällig erfasst wird . . ." [3: p 180].

Holm makes a deduction from our model that, by his own quotation from our paper, we assumed as a condition: that any excess ascertainment in some concordant pairs must be exactly compensated in others. When this condition is violated, the overall primary ascertainment probability for concordant twins will be different from that for discordant twins and a valid estimate of the concordance rate is not possible. This will be the case, for instance, if the status of one twin influences primary ascertainment of the partner.

Holm seems to interpret our symbols m and $m_r$ as variables pertaining to twin pairs. Rather, they are constants within any one twin study, each expressing an average probability. He dwells on the idea that $m_r$ is correlated with m. If both quantities are constants, it is meaningless to speak of a correlation between them. On the other hand, we showed in our Equation 6 that a correlation within pairs measured by a significant excess of $m_r$ over m does not affect the proband estimate of concordance, provided that secondary ascertainment is complete. This fact seems important to us because, in this respect, Weinberg's requirement of purely random ascertainment can be violated, at least theoretically.

Incidentally, a value of $m_r$ significantly less than m, suggested by Holm, would imply that primary ascertainment was negatively correlated within pairs, which appears to be impossible under any ordinary procedure of ascertainment.

In correspondence concerning this paper, objection has been raised to our use of the term "model" on the grounds that in the medical field a model is either biological or mechanical. This disregards the application of mathematical or statistical models to biology, or as in this instance to the process of collecting data. The process that is central to our model is a two-stage ascertainment, which we postulate to be reasonably well approximated in many twin studies.

To summarize, the overriding requirement for any good twin study of a qualitative medical condition is that overall primary ascertainment be virtually the same in concordant and discordant twin pairs. Secondary ascertainment should be as complete as possible; any incompleteness reduces the estimate of concordance below the true value, and specification of the degree of resulting inaccuracy is not possible. This almost inevitable inaccuracy will be exaggerated by correlation of primary ascertainment within pairs, although such correlation alone does not affect the estimate of concordance.

## REFERENCES

1. Goldin LR, Kidd KK, Matthysse S, Gershon ES (1951): Power of segregation analysis for traits with incomplete penetrance. In Gershon ES et al (eds): "Genetic Research Strategies in Psychobiology and Psychiatry." Pacific Grove, California: Boxwood Press, pp 305–318.
2. Holm NV (1983): A note on ascertainment probability in the Allen/Hrubec twin model. Acta Genet Med Gemellol 32:37–47.
3. Weinberg W (1927): Mathematische Grundlagen der Probandenmethode. Zeitschr Indukt Abstamm 48:179–228.

**Correspondence:** Dr. Gordon Allen, National Institute of Mental Health, 5600 Fishers Lane, Rm 18c-18, Rockville, MD 20857.