an "index subject" who is not simultaneously a "proband." Moreover, our conclusions hold regardless of whether the marginal probabilities of the two siblings being affected are equal: if they are equal, then conditioning on the proband will give an unbiased estimate (our eq. [5]); if they are not equal, then conditioning on the proband who has been defined as such prior to ascertainment will *also* give an unbiased estimate (our eq. [4]).

Finally, to end on a more positive note, we look at the broader context of Guo's paper. We have investigated only two-child families ($k = 2$), and we have investigated those selected under single ascertainment only. Guo may be correct in asserting that there is ascertainment bias in larger families. Moreover, we are certainly not defending the use of λ_S, since we suspect that this measure probably *is* subject to ascertainment bias when ascertainment is other than single (also see Olson and Cordell 2000). We applaud Guo's work on this subject but believe that it will be more useful if he clarifies the definition of sibling recurrence risk in ascertained families.

Acknowledgments

This work was supported by National Institutes of Health grants MH-57813 (to P.J.W.) and MH-48858 and DK-31813 (both to S.E.H.).

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0002-9297/2001/6803-0028$02.00

Am. J. Hum. Genet. 68:810–812, 2001

Reply to Wickramaratne and Hodge

To the Editor:

Sibling recurrence-risk ratio is perhaps the most widely used measure for familial aggregation of complex diseases and is often used as a measure of genetic effect. It is frequently used in power calculations in gene-mapping studies and in exclusion mapping. It is little known among human geneticists, however, that familial clustering of risk factors of an environmental nature also can elevate sibling recurrence-risk ratio, even in the complete absence of any genetic (hereditary) factors (Guo 2000*a*). In addition, ascertainment bias in estimation of sibling recurrence-risk ratio is frequently overlooked or simply ignored in genetic epidemiological studies (Guo 1998). I am very pleased to see the letter of Wickramaratne and Hodge (henceforth, "W&H"), which attempts to further take up this issue.

As a measure of familial aggregation, the original definition of sibling recurrence-risk ratio (see, e.g., Risch 1990) is very intuitive and appealing. My paper (Guo 1998) demonstrates that, when the actual use of this measure deviates from its original definition (i.e., definitions 2 and 3 in Guo 1998), the estimation of sibling recurrence-risk ratio can be artificially inflated if there is ascertainment bias and/or overreporting under single and multiple ascertainment schemes. It should be noted that I did not define sibling recurrence risk in ascertained families, as claimed by W&H, but, rather, that I pointed out the consequence of "misunderstanding of the original definition of λ_S" (Guo 1998).

W&H assert that Guo (1998) finds bias "only because he permits the sibling *who is being conditioned on*… to be other than the sibling *through whom the family is ascertained,*" and that my definition "does not correspond to the definition that researchers in fact use," at least for two-child families. Furthermore, they claim that, under their definition, when the sibship size (k) is two, there is no ascertainment bias under single ascertainment in the estimation.

In many genetic epidemiological studies, especially those cross-sectional or longitudinal studies, researchers often start with a cohort of or a sample of willing participants in their studies, through whom their families are further ascertained. Quite often, the disease statuses of these participants are either apparently normal initially or are unknown and are to be determined by either follow-up observations or subsequent diagnostic tests. A case in point is a study of the impact of family history on early detection of prostate cancer (Narod et al. 1995), which also was mentioned in W&H. In the study by Narod et al., "a total of 26,781 men, aged 45 and above, was selected from the electoral lists and sent a written invitation to participate in the screening project… Of these, 7,277 (27.2%) indicated their willingness to participate (in the study)" (Narod et al. 1995). The subjects were then asked to undergo annual diagnostic screening for prostate cancer. At the publication of the study, "prostate cancer was detected in 10.2% of subjects who reported a brother with prostate cancer. This frequency was 2.62 times greater than for men with no affected first-degree relative" (Narod et al. 1995), a major finding, which was also cited by Monroe et al. (1995).

In this study, the sib being conditioned on (the subject's brother) was obviously different from the sib through whom the family was ascertained (the subject himself), as it was in the study reported by Monroe et al. (1995). Contrary to what W&H claim, these studies do not "always treat the proband as the 'index subject.'" If no measure is taken to adjust for ascertainment and for sibship size, it is very likely that the sibling recurrence-risk ratio can be inflated. In view of this, I found W&H's assertion, that "it is difficult for us to imagine a genetic or family study that *would* use Guo's definition," troubling.

I also found W&H's own definition of sibling recurrence risk unsettling—on two grounds. First, their definition is not backward compatible with the original one. A close inspection of W&H's definition of sibling recurrence risk (eq. (5) in W&H), which is given by $K_R^* = P(2 \text{ siblings affected} \mid \geq 1 \text{ sibling affected, A})$, where A denotes the event that this sibship has been ascertained, reveals that, when ascertainment bias is completely absent, under the situation considered by both Guo (1998) and W&H (2001),

$$\begin{aligned} K_R^* &= P(2 \text{ siblings affected} \mid \geq 1 \text{ sibling affected}) \\ &= P(X_1 = 1, X_2 = 1 \mid \{X_1 = 1\} \cup \{X_2 = 1\}) \\ &= \frac{p^2}{2p - p^2} \\ &= \frac{p}{1 + (1 - p)} < p \end{aligned}$$

This indicates that, under W&H's definition, the sibling recurrence-risk ratio, λ_S, would be <1, even when there is *no* familial aggregation. This, of course, is directly at odds with the original definition (see Risch 1990).

Second, W&H's definition of sibling recurrence-risk ratio is clearly ascertainment dependent and is highly likely to be sibship-size dependent, since they do not provide the definition for sibship sizes greater than two. This raises a serious question as to what they intend to measure, since single ascertainment is just one of countless ascertainment schemes that are often unknown to the investigator.

In summary, many genetic epidemiological studies do not treat the proband as the "index subject," which W&H find objectionable. This is especially true for cross-sectional or longitudinal studies. And W&H's letter actually raises more questions than they have solved: If their definition is not compatible with the original one, what does it truly measure in general cases? How should we define sibling recurrence risk for non-single-ascertainment schemes and/or for families with more than two children? How can we define it when ascertainment scheme is unknown? Nonrandom sampling is almost always by necessity in genetic epidemiological studies. For a huge body of literature either on genetic models based on sibling recurrence-risk ratios or with estimated sibling recurrence risks of various diseases, which apparently has not used W&H's definition, should we trust their results?

Despite these uncertainties, it seems certain that the estimation of sibling recurrence risk can be artificially inflated if there is ascertainment bias and/or overreporting. Furthermore, even if λ_S can be estimated accurately and reliably, it usually tells us little about whether the familial aggregation of disease is either genetic or environmental (Risch et al. 1993; Guo 2000*a* and 2000*b*).

Acknowledgments

This work was supported, in part, by the National Institutes of Health grant R01-GM56515.

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0002-9297/2001/6803-0029$02.00