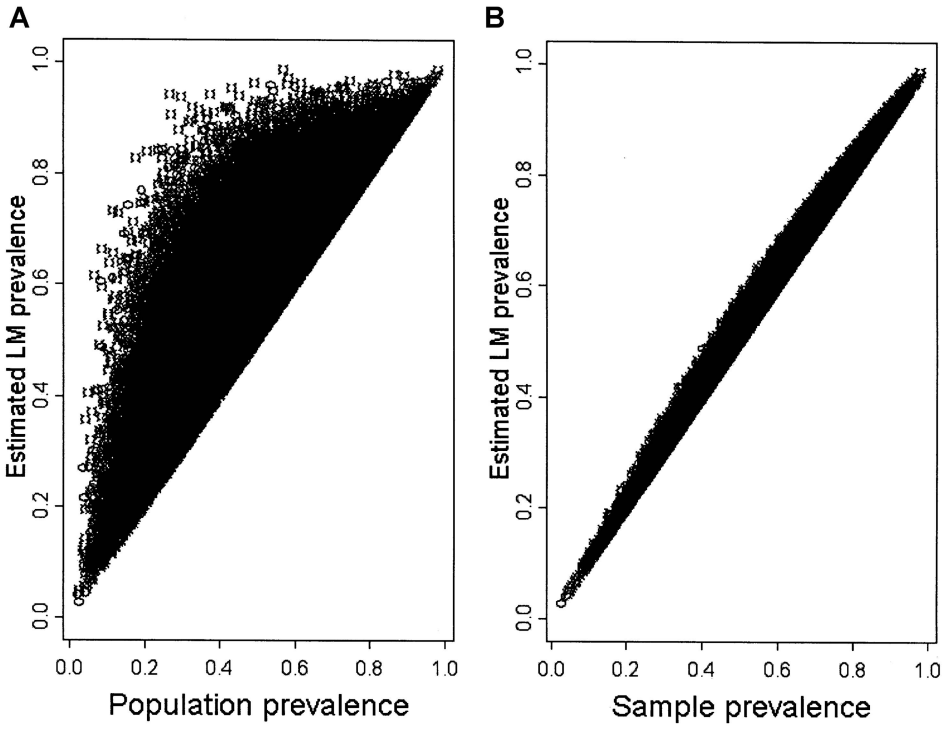

Figure 1 Scatter plots of the estimated prevalence of a disease, based on the Li-Mantel (LM) estimator. *A*, $\hat{p}_{LM}$ vs. p_P. *B*, $\hat{p}_{LM}$ vs. p_A. Data are based on 100,000 simulations of a scenario described in the text.

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Response to Epstein et al.

To the Editor:

We entirely agree with the statement in a recent article by Epstein et al. (2002) that the likelihood used in our example 1 (Burton et al. 2000) fails because it inappropriately assumes marginal independence: marginal dependence is introduced because the unobserved determinants of stratum-specific risk are shared by siblings. However, that is the whole point. It is an analysis of this type that is carried out whenever (as is usual) such heterogeneity is ignored. The reality is that, despite advances in both biology and biostatistics, we are a long way from being able to claim that the modeling of unobserved heterogeneity is "solved," and, until we can, the relevant interpretational problems (Burton et al. 2000) remain real.

There is one important area where our interpretation does differ from that of Epstein et al. This is in our contention that when heterogeneity is ignored, the resultant ascertainment-adjusted estimates reflect parameters in the ascertained sample rather than those in the original population. Epstein et al. state that the estimates "generally do not reflect the true values in either the original population or the ascertained subpopulation" (2002, p. 886). We do not agree. Relationships B1, B2, and B3 in Appendix B of the article by Epstein et al. (2002) all represent weighted means for the prevalence in stratum k (p_k). Because the weights under B2 (which generate the disease prevalence in the ascertained subpopulation [p_A]) are different from those under B3 (which generate the Li-Mantel estimate [$\hat{p}_{LM}$]), we agree that the latter does not provide

a consistent estimate of the former (see also Olson and Cordell 2000). However, the word "reflect" does not imply a "consistent estimator," and we did not use the latter term; in fact, we used phrases such as "good approximations." It is easy to see that the ratio of the weight under B3 for any given stratum to that under B2 for the same stratum must lie between 1:1 and 2:3, the latter ratio being attained only as p_k tends to 0. This means that the estimates under the two weighting systems are unlikely to be seriously discrepant.

To illustrate, we generate 100,000 simulated data sets, each equivalent to the general case considered in Appendix B of the article by Epstein et al. (2002), which itself corresponds to example 1 given by Burton et al. (2000). For each of four strata ($k = 1, \ldots, 4$), p_k is the stratum-specific prevalence of disease and π_k is the proportion of the original population in that stratum. In each simulation, each p_k and each π_k are randomly sampled to take any real value between 0 and 1, with uniform probability. Each π_k is then normalized (divided by $\sum_{k=1}^{4} \pi_k$) so that, after normalization, $\sum_{k=1}^{4} \pi_k = 1$ in every simulated data set. We then used the expressions B1, B2, and B3, given by Epstein et al. (2000), to obtain the prevalence in the original population (p_P), p_A, and $\hat{p}_{LM}$, respectively. Figure 1*A* illustrates the resultant relationship between $\hat{p}_{LM}$ and p_P, and figure 1*B* illustrates that between $\hat{p}_{LM}$ and p_A. The latter is a straight line with a gradient of 1.004 and a correlation of 0.996. The maximum discrepancy between p_A and $\hat{p}_{LM}$ across all 100,000 simulations is 0.085 (corresponding to $p_A = 0.401$ and $\hat{p}_{LM} = 0.486$). In 95% of simulations, the difference is <0.042. In contrast, the relationship between p_P and $\hat{p}_{LM}$ is much weaker. The maximum discrepancy across the 100,000 simulations is 0.67 (corresponding to $p_P = 0.27$ and $\hat{p}_{LM} = 0.94$); and, in 38% of simulations, the absolute discrepancy is >0.10. Consequently, we remain faithful to our contention that, unless something formal is done to address an unobserved heterogeneity in risk that is shared by family members and therefore introduces marginal dependence, $\hat{p}_{LM}$ reflects the marginal distribution of prevalence in the sample, not the general population. The extent to which this important conclusion may be extrapolated to other scenarios and to analyses based on statistics other than the Li-Mantel estimator warrants further study.

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References

Burton PR, Palmer LJ, Jacobs K, Keen KJ, Olson JM, Elston RC (2000) Ascertainment adjustment: where does it take us? (erratum 67:672 [2001]) Am J Hum Genet 67:1505–1514

Epstein MP, Lin X, Boehnke M (2002) Ascertainment-adjusted parameter estimates revisited. Am J Hum Genet 70:886–895

Olson JM, Cordell HJ (2000) Ascertainment bias in the estimate of sibling genetic risk parameters. Genet Epidemiol 18: 217–235

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