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A Simulation Study of the Effects of Assignment of Prior Identity-by-Descent Probabilities to Unselected Sib Pairs, in Covariance-Structure Modeling of a Quantitative-Trait Locus

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Summary

Sib pair–selection strategies, designed to identify the most informative sib pairs in order to detect a quantitative-trait locus (QTL), give rise to a missing-data problem in genetic covariance-structure modeling of QTL effects. After selection, phenotypic data are available for all sibs, but marker data—and, consequently, the identity-by-descent (IBD) probabilities—are available only in selected sib pairs. One possible solution to this missing-data problem is to assign prior IBD probabilities (i.e., expected values) to the unselected sib pairs. The effect of this assignment in genetic covariance-structure modeling is investigated in the present paper. Two maximum-likelihood approaches to estimation are considered, the pi-hat approach and the IBD-mixture approach. In the simulations, sample size, selection criteria, QTL-increaser allele frequency, and gene action are manipulated. The results indicate that the assignment of prior IBD probabilities results in serious estimation bias in the pi-hat approach. Bias is also present in the IBD-mixture approach, although here the bias is generally much smaller. The null distribution of the log-likelihood ratio (i.e., in absence of any QTL effect) does not follow the expected null distribution in the pi-hat approach after selection. In the IBD-mixture approach, the null distribution does agree with expectation.

Introduction

Genetic covariance-structure modeling has recently been extended to include the analysis of quantitative-trait loci (QTL) in sib-pair data (Schork 1993; Amos 1994; Eaves et al. 1996; Fulker and Cherny 1996; Almasy and Blangero 1998). More-traditional methods of linkage analysis using sib-pair data are based either on the regression of squared phenotypic sib-pair differences on the mean proportion of alleles shared identically by descent (IBD) (Haseman and Elston 1972; for a related approach, see either the work of Kruglyak and Lander [1995] or on IBD information alone (Blackwelder and Elston 1985; Risch and Zhang 1995; Gu et al. 1996). Compared with these methods, genetic covariance-structure modeling has several advantages. It is statistically more powerful (Fulker and Cherny 1996), and it is more flexible in that it can handle multivariate data (Eaves et al. 1996) and general pedigrees (Almasy and Blangero 1998). The analysis of multivariate sib-pair data, in turn, has been shown to increase appreciably the power to detect a QTL (Martin et al. 1997; Boomsma and Dolan 1998).

In addition to this advance in genetic covariance-structure modeling, the feasibility of detection of QTLs in humans has been enhanced greatly by selective sampling strategies (Blackwelder and Elston 1985; Carey and Williamson 1991; Cardon and Fulker 1994; Eaves and Meyer 1994; Risch and Zhang 1995, 1996). It is well established that the sib pairs who are extreme and concordant—or extreme and discordant—for the quantitative phenotype provide the most information for detection of the presence of a QTL.

The analysis of selected sib-pair data in genetic covariance-structure modeling poses a missing-data problem. After selection, phenotypic information is available for all sib pairs, but marker data are limited to the selected sib pairs. There are two solutions to this problem. On the one hand, one can analyze the data on the selected sib pairs and discard the phenotypic data on the unselected sib pairs. This option requires a modification of the estimation procedure, to accommodate the effects of selection of the phenotypic bivariate or multivariate distribution. In the case of multivariate normal data, this strategy is feasible. For instance, Neale and Eaves (1993) used this strategy to correct for volunteer bias. On the other hand, one can assign IBD data in the sib pairs who are not selected for genotyping. Eaves et al. (1996) have proposed the use of the expected values of the IBD probabilities in those sib pairs whose marker data are miss-

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ing. This approach has the advantages that it is easy to implement and uses all available phenotypic data.

The aim of the present report is to investigate the effects that this treatment of missing data has on the parameter estimates and goodness-of-fit tests in covariance-structure modeling of a QTL in sib-pair data. Although a number of simulation studies of selective sampling have been reported (e.g., see Cardon and Fulker 1994), we do not know of any results pertaining to estimation bias per se. Here we perform four simulation studies. In each simulation study, we assume that sib pairs are selected, on the basis of a phenotypic criterion, from a large representative sample. In the next section, the model used to simulate and fit the data is presented. Subsequently, we describe the four simulation studies and present the results.

Genetic Covariance-Structure Modeling of a QTL in Sib-Pair Data

Since we are concerned, in our simulations, with a univariate phenotype observed in sibships consisting of two full sibs, we limit our presentation accordingly. Let y_{ij} denote the phenotypic score of sib j ($j = 1$ or 2) in sib pair i ($i = 1, \ldots, N$). The phenotypic scores are modeled as follows:

$$y_{ij} = \mu + aA_{ij} + eE_{ij} + q_a Qa_{ij} + q_d Qd_{ij} \; . \qquad (1)$$

In equation (1), μ is the phenotypic mean, A_{ij} is the additive polygenic deviation score, and E_{ij} is the unshared environmental deviation score. In practice, measurement error is included in E_{ij}. The variables Qa_{ij} and Qd_{ij} represent the QTL; Qa_{ij} is the additive deviation (or centered breeding value), and Qd_{ij} is the dominance deviation (Falconer 1990). All latent random variables (A, E, Qa, and Qd) are standardized (unit variance and zero mean). The contribution of each latent variable to the phenotypic individual differences is determined by the size of the regression coefficients, a, e, q_a, and q_d.

We assume that we have at our disposal marker data at a single marker locus situated 0 cM from the QTL. The marker data are observed both in the sib pairs and in their parents. The degree of genetic relatedness of the members of a sibship at the QTL depends on the number of alleles that they share IBD at the QTL. On the basis of the marker data, the probabilities of the sibs sharing 0, 1, and 2 alleles IBD can be calculated. It is convenient to consider the proportion of alleles shared IBD, instead of the actual number of alleles. These are denoted "$\tau_1 = 0/2$," "$\tau_2 = 1/2$," and "$\tau_3 = 2/2$." The conditional (i.e., on the marker data) probabilities are denoted "$P(0)_i$," "$P(.5)_i$," and "$P(1)_i$," where the parentheses contain the proportions and the subscript i indicates sib pair. Given random mating, the prior values of these probabilities are $P(0) = .25$, $P(.5) = .5$, and $P(1) = .25$. Note that we drop the sib-pair index to denote the expected values.

The phenotypic mean and variance do not depend on the IBD status, but the phenotypic covariance of the sibs does. Let the vector $\mathbf{y}_i$ equal $[y_{i1}\ y_{i2}]^\tau$. Conditional on IBD status, this vector is distributed approximately as $\mathbf{y}_i \mid \tau_k \sim N(\boldsymbol{\mu}, \Sigma_{\tau_k})$. Except for the constraint that the phenotypic mean of sib 1 equals that of sib 2, the mean vector is not modeled. The (2 × 2) phenotypic covariance matrix is modeled as follows: $\Sigma_{\tau_k} = \boldsymbol{\Lambda}\boldsymbol{\Psi}_{\tau_k}\boldsymbol{\Lambda}^\tau$. The matrix $\boldsymbol{\Lambda}$ contains the regression coefficients, or factor loadings:

$$\boldsymbol{\Lambda} = \begin{bmatrix} a & e & q_a & q_d & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a & e & q_a & q_d \end{bmatrix} .$$

The symmetric matrix $\boldsymbol{\Psi}_{\tau_k}$ is the correlation matrix of the latent variables in the model:

$$\boldsymbol{\Psi} = \begin{bmatrix} 1 & & & & & & & \\ 0 & 1 & & & & & & \\ 0 & 0 & 1 & & & & & \\ 0 & 0 & 0 & 1 & & & & \\ .5 & 0 & 0 & 0 & 1 & & & \\ 0 & 0 & 0 & 0 & 0 & 1 & & \\ 0 & 0 & \rho_{a_{\tau_k}} & 0 & 0 & 0 & 1 & \\ 0 & 0 & 0 & \rho_{d_{\tau_k}} & 0 & 0 & 0 & 1 \end{bmatrix} .$$

If $k = 1$ (IBD = 0), $\rho_{a_{\tau_k}}$ and $\rho_{d_{\tau_k}}$ both equal 0; if $k = 2$ (IBD = 1), $\rho_{d_{\tau_k}}$ equals 0 and $\rho_{a_{\tau_k}}$ equals .5; finally, if $k = 3$, $\rho_{a_{\tau_k}}$ and $\rho_{d_{\tau_k}}$ both equal 1 (IBD = 2).

The variance components, q_a^2 and q_d^2, and the mean, μ, depend on the biallelic QTL. Let p denote the frequency of the increaser allele, B. Furthermore let the midparent point and the genotype deviation associated with BB equal 0 and d, respectively. Finally, let h denote the dominance deviation associated with the heterozygote (Bb). Under random mating, we have $\mu = (p - q)d + 2p(1 - p)h$, $q_a^2 = 2pq\{d + [p - (1 - p)]h\}^2$, and $q_d^2 = 4p^2(1 - p)^2h^2$ (e.g., see Falconer 1990).

Following Fulker and Cherny (1996, eqq. [8] and [12]), we estimate maximum-likelihood parameters by maximizing either of two raw-data log-likelihood functions. The first takes into account the fact that, given less than perfectly informative markers, the phenotypic distribution is a normal mixture:

$$L_{\text{mix}}(\theta) = \sum_{i=1}^{N} \ln\left\{\sum_{k=1}^{3} P(\tau_k)_i (2\pi \mid \Sigma_{\tau_k} \mid)^{-\frac{1}{2}} \exp\left[-\frac{1}{2}(\mathbf{y}_i - \mu)^\tau \Sigma_{\tau_k}^{-1}(\mathbf{y}_i - \mu)\right]\right\} . \qquad (2)$$

Table 1

Distribution of π and IBD Probabilities, as a Function of *m,* the Number of Equifrequent Marker Alleles

					Frequency When m =			
π	$P(0)$	$P(\frac{1}{2})$	$P(1)$	Proportion	8	12	48	∞
0	1	0	0	$[\frac{1}{4}(m^3 - 2m^2 + 1)]/m^3$	.1880	.2085	.2396	.25
$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{2}$	0	$(m - 1)/m^2$	.1094	.0764	.0204	0
$\frac{1}{2}$	0	1	0	$[\frac{1}{2}(m^2 - 2m + 1)]/m^2$	.3828	.4201	.4794	.5
$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	$1/m^2$	.0156	.0069	.0004	0
$\frac{1}{2}$	$\frac{1}{2}$	0	$\frac{1}{2}$	$[\frac{1}{2}(m - 1)]/m^3$	.0068	.0032	.0002	0
$\frac{3}{4}$	0	$\frac{1}{2}$	$\frac{1}{2}$	$(m - 1)/m^2$	.1094	.0764	.0204	0
1	0	0	1	$[\frac{1}{4}(m^3 - 2m^2 + 1)]/m^3$	.1880	.2085	.2396	.25

The parameter vector θ equals either $\theta^\tau = [a\ e\ q_a\ q_d\ \mu]$ or $\theta^\tau = [a\ e\ q_a\ \mu]$, depending on the gene action at the QTL.

The second log-likelihood function is based on the expected sib-pair covariance matrix, Σ_i. This matrix equals

$$\Sigma_i = \sum_{k=1}^{3} P(\tau_k)_i \otimes \Sigma_{\tau_k} = \Lambda\left[\sum_{k=1}^{3} P(\tau_k)_i \otimes \Psi_{\tau_k}\right]\Lambda^\tau ,$$

where $\otimes$ denotes the kronecker product. The log-likelihood function is

$$L_\pi(\theta) = \sum_{i=1}^{N} \ln\left\{(2\pi \mid \Sigma_i \mid)^{-\frac{1}{2}} \exp\left[-\frac{1}{2}(\mathbf{y}_i - \mu)^\tau \Sigma_i^{-1}(\mathbf{y}_i - \mu)\right]\right\} .$$

In this approach the correlation between the variables Qa_{i1} and Qa_{i2} is equal to the expected proportion of alleles shared IBD by sib pair *i,* given their marker data. This correlation, which is denoted "π_i," equals $.5 * P(.5)_i + P(1)_i$. The correlation between the variables Qd_{i1} and Qd_{i2} equals $P(1)_i$. We refer to model fitting based on $L_{mix}(\theta)$ as the "IBD-mixture approach" and to model fitting based on $L_\pi(\theta)$ as the "pi-hat approach."

Given equal frequency of the marker alleles, we observe a limited number of IBD probabilities, which define a total of seven possible groups. Using the results of Haseman and Elston (1972, table 2) and Boomsma and Dolan (1998), we can derive the expected frequency of each group. These are shown in table 1.

As mentioned, Eaves et al. (1996) suggest that, when marker data are available for only a selected subsample of sib pairs, the IBD probabilities in unselected sib pairs be fixed to equal their prior values—$P(0) = .25$, $P(.5) = .5$, and $P(1) = .25$. To investigate the effects of assign the prior values of IBD probabilities, we performed three simulation studies. A fourth simulation study was performed to investigate the effect on the probabilities of false positives in likelihood-ratio testing based on the functions L_{mix} and L_π.

Method

A FORTRAN program was written to simulate phenotypic data, determine the IBD probabilities, and maximize the raw-data log-likelihood functions—L_{mix} and L_π—before and after sib-pair selection. The parental and offspring biallelic QTL data and marker data were simulated in the manner described by Eaves and Meyer (1994). The parental marker and QTL data were used to create the offspring marker and QTL data. Given the marker data of the parents and the sib pairs, table 2 of Haseman and Elston (1972) was used to determine the

Table 2

Percentages Associated with FI- and NI-Selection Criteria Used in Simulation Study 1

	Discordant[a]		Concordant[b]	
Selection	Low	High	Low	High
N = 5,000:				
NI	21	79	11	89
FI:				
p = .2	33	90	07	83
p = .5	20	80	13	87
p = .7	13	70	15	90
N = 10,000:				
NI	17	83	08	92
FI:				
p = .2	38	93	03	90
p = .5	15	85	08	92
p = .7	13	80	10	97

[a] One member of each of the selected sib pairs has a phenotypic score below the "low" percentile, and the other has a phenotypic score above the "high" percentile.

[b] Both members of each of the selected sib pairs have a phenotypic score above (below) the "high" percentile ("low" percentile).

IBD probabilities for each sib pair. Additive polygenic and environmental data on the sib pairs were simulated by means of GGNSM, an IMSL (1979) routine to generate zero mean multivariate normal data.

The log likelihoods are maximized by means of the FORTRAN routine VARMET, which performs unconstrained optimization by means of the variable-metric algorithm (Koval 1997). To facilitate optimization, the exact gradients of the raw-data log-likelihood functions were programmed. These derivatives are given in the Appendix.

In selecting the sib pairs, we adopt two different selection criteria. These criteria are based on results that have been presented by Dolan and Boomsma (1998), who derive optimal selection strategies to maximize the power of the EDAC (extremely discordant and concordant) test (Gu et al. 1996). The EDAC test combines pi-hats observed in concordant and discordant sib pairs. The first criterion does not take into account any prior knowledge concerning the QTL. We refer to this selection as "no information selection" (NI selection). The second selection criterion is supposed to be optimal in that it is based on prior knowledge concerning both QTL-allele frequency and gene action. We call this "full information selection" (FI selection). We include the two selection criteria to obtain an indication of how the recommendations presented by Dolan and Boomsma (1998) perform in tests based on genetic covariance-structure modeling and to investigate the effects that different selection criteria have on the parameter estimates.

Simulation Study 1

The objective of the first simulation study is to investigate both (1) the effects of assigning prior IBD probabilities in the case of a codominant QTL and (2) the effects of the two sib pair–selection strategies mentioned above. The design of this simulation study involves three between-case factors and one within-case factor. A case is a single simulated data set. The between-case factors are (1) total sample size, with two levels (N = 5,000 and N = 10,000); (2) number of equifrequent marker alleles, with three levels (8, 12, and 48 alleles); and (3) QTL (increaser) allele frequency, with three levels (.2, .5, and .7). The factor relating to the number of alleles can also be defined in terms of PIC (e.g., see Sham 1998): PIC ≈ .861, PIC ≈ .910, PIC ≈ .978. The within-case factor has seven levels, denoted (1) "all-L_{mix}," (2) "all-L_{π}," (3) "NIsel L_{mix}," (4) "NIsel L_{π}," (5) "FIsel L_{mix}," (6) "FIsel L_{π}," and (7) "no QTL." The designation "all" means that all phenotypic and marker data were used in the analysis; "NIsel" means that all phenotypic data were used but that the marker data were limited to a subsample that was selected with the NI-selection criterion, and "FIsel" is defined analogously for the FI-selection criterion; "L_{π}" and "L_{mix}" denote the log-likelihood function that was optimized; and "no QTL" refers to the analysis in which the QTL effect is dropped from the analysis ($q_a = 0$). This analysis provides a baseline log likelihood for calculation of log-likelihood–ratio statistics.

The additive polygenic variance equals 2, the unshared environmental variance equals 2, and codominant QTL variance equals 1. So we have $a = e = \sqrt{2}$, $q_a = 1$, and $q_d = 0$. Given the QTL allele frequency, we choose the values of d such that $q_a = 1$; that is, the QTL-effect size remains constant, although the QTL frequency varies. In this way we can study the effect of QTL-allele frequency on sib-pair selection, given a constant QTL-effect size. Figure 1 shows the effects that allele frequency has on the values of pi-hat, in two situations.

The phenotypic mean depends only on the QTL, and so it varies with the QTL-allele frequency. For a frequency of p = .2, $\mu \approx -1.061$; for p = .5, $\mu = 0$; and, for p = .7, $\mu \approx .617$. The between-subject design gives rise to 18 (3 × 3 × 2) cells. Within each cell, 500 data sets were simulated, comprising N = 5,000 or N = 10,000 sib pairs. The number of selected sib pairs is fixed at 500. When the selection was performed, the selection percentages were changed slightly, to ensure that the number of selected sib pairs equaled 500 ± 5; the specified selection criteria are given in table 2.

Like Fulker and Cherny (1996), we found very little difference between the results obtained in the all-L_{π} conditions and those obtained in the all-L_{mix} conditions. We therefore discarded the results obtained in the all-L_{π} condition. Parameter estimates of μ, the phenotypic mean, have not been reported; in no condition of any of the simulation studies reported here did these estimates deviate appreciably from their expected values. Finally, PIC was found not to have any important effect on bias of parameter estimates. We therefore limit our presentation of results to the PIC = .910 (12 equifrequent alleles) conditions.

Table 3 contains the noncentral (NC) χ^2 statistics and the observed power, given α's of 10^{-5} and 10^{-4}. Observed power is expressed as the percentage of cases in which the QTL was detected. Compared with that in the all-L_{mix} conditions, the power in the NIsel L_{mix} conditions is appreciably lower. Limiting the discussion to case of α = .00001, we observe a drop in power from ~83%-89% to ~35%-41%, in the N = 5,000 conditions, and from 100% to ~66%-76%, in the N = 10,000 conditions. Comparing the results in the all-L_{mix} conditions versus those in the NIsel L_{π} conditions, we find that the pi-hat approach is more powerful than the IBD-mixture approach: the drop in power after selection is from ~83%–89% to 68%–71% (for N = 5,000) and from 100% to 93%–95% (for N = 10,000). Comparing

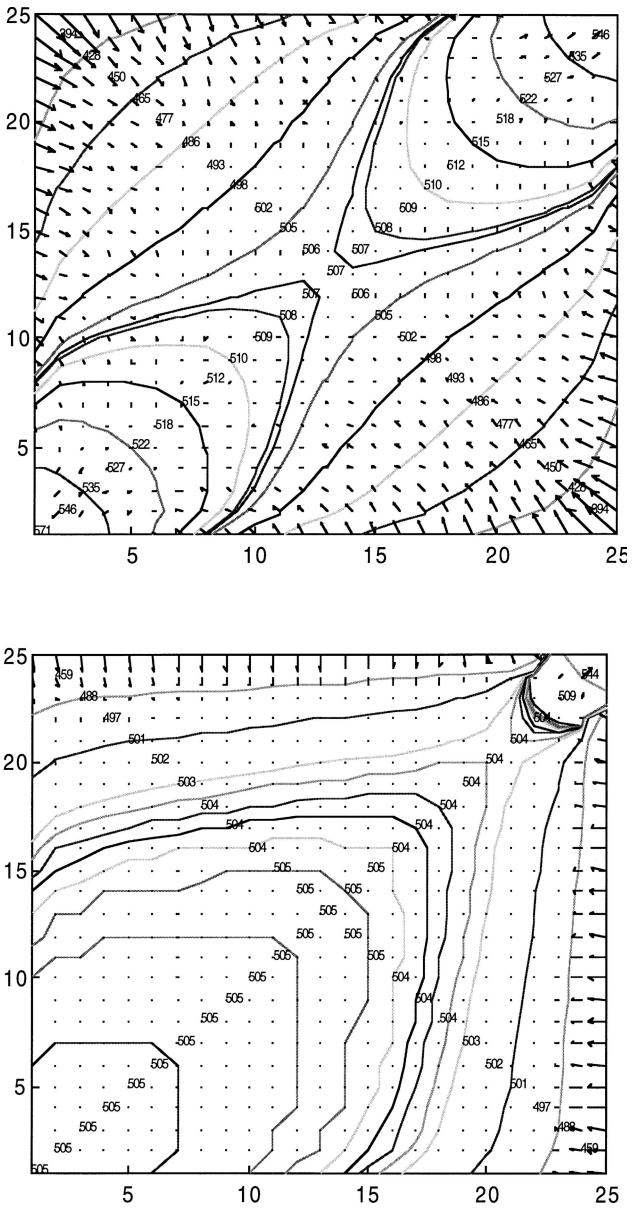

Figure 1 Pi-hat as a function of sib-1 and sib-2 phenotypic scores (score range 1–25). *Top,* Codominant QTL, $p = .5$. *Bottom,* Recessive QTL, $p = .2$. Contour lines are chosen arbitrarily. Arrows indicate the steepness of the gradient of the pi-hat surface. The arrows point in the direction of increasing pi-hat.

the two selection strategies, we find that the FI-selection strategy results in a clear increase in power only if the allele frequency equals .2. In the $p = .5$ conditions, FI selection results in a decrease in power. In the $p = .7$ conditions, we observe little difference in power after NI selection and FI selection when $N = 5{,}000$ and only a slight gain in favor of FI selection when $N = 10{,}000$.

Figure 2 shows bar plots of the errors in the parameter estimates. Prior to selection, there is hardly any bias in the estimates. After selection, we find that there is some bias in the estimates of the polygenic- and QTL-factor loadings in the NIsel L_{mix} conditions. Although this bias is clearly visible when $N = 10{,}000$, it is still relatively small. In the NIsel L_{π} conditions, the bias in the genetic-factor loadings is very large. The QTL effect is overestimated, and the polygenic effect underestimated. Full information selection appears to exacerbate the bias. Especially in the frequency $p = .2$ conditions, the bias is evident, regardless of the choice of log-likelihood func-

Table 3

NC χ^2's (df = 1) and Observed Power, Given Two α Levels, in Simulation Study 1

Conditions and Statistic	IBD			PI	
	All	NI	FI	NI	FI
.2/12/5,000:					
NC χ^2:					
Mean	31.9	18.6	19.5	28.2	30.1
SD	10.7	8.3	8.4	12.6	13.1
α:					
.00001	89	41	46	71	78
.0001	96	59	66	86	89
.2/12/10,000:					
NC χ^2:					
Mean	61.3	26.8	31.0	47.3	49.2
SD	14.9	9.8	11.2	17.2	17.7
α:					
.00001	100	76	85	95	98
.0001	100	89	94	97	99
.5/12/5,000:					
NC χ^2:					
Mean	31.5	18.2	17.4	27.9	27.9
SD	11.3	8.6	8.4	13.2	13.6
α:					
.00001	85	41	35	71	71
.0001	94	59	56	83	82
.5/12/10,000:					
NC χ^2:					
Mean	61.3	24.4	23.1	43.6	43.2
SD	15.5	9.6	9.5	17.3	17.7
α:					
.00001	100	66	63	93	92
.0001	100	85	81	97	97
.7/12/5,000:					
NC χ^2:					
Mean	30.6	17.5	17.2	26.7	26.9
SD	10.7	7.8	7.8	11.9	12.1
α:					
.00001	83	35	32	68	69
.0001	93	56	57	84	83
.7/12/10,000:					
NC χ^2:					
Mean	61.0	25.4	26.5	45.4	46.5
SD	15.4	10.1	10.4	18.2	18.2
α:					
.00001	100	68	73	95	96
.0001	100	87	87	97	98

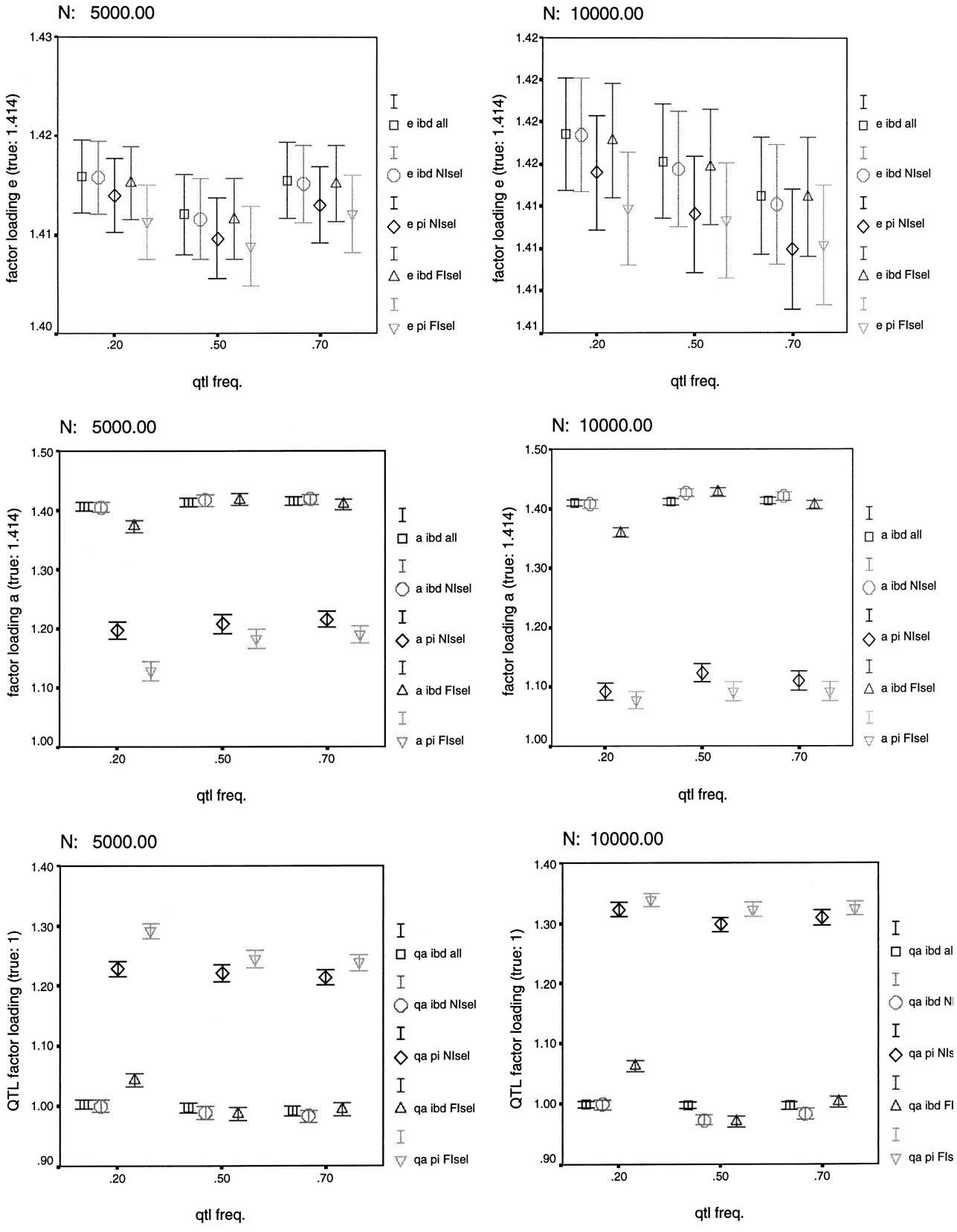

Figure 2 Study 1: unshared environmental-, polygenic-, and QTL-factor loadings. Error bars represent 95% confidence intervals.

Table 4

Percentages Associated with FI-Selection Criterion Used in Simulation Study 2, for N = 20,000

	DISCORDANT		CONCORDANT	
p	Low	High	Low	High
.2	35	97	3	93
.5	13	90	3	93

NOTE.—Definitions/categories are as described in the footnotes to table 2.

tion. It appears that, insofar as FI selection increases power, it does so at the cost of increased bias (i.e., overestimation of the QTL effect).

Simulation Study 2

The aim of the second simulation study is to investigate the effects of assigning prior IBD probabilities in the case of a recessive QTL. This simulation study involves two between-case factors and one within-case factor. The between-case factors are (1) QTL-allele frequency, with two levels (.2 and .5), and (2) number of equifrequent marker alleles, with three levels (8, 12, and 48). A low increaser-allele frequency is known to have a strong effect on the pi-hat surface when the QTL is recessive (see fig. 1). The additive polygenic variance equals 2, the unshared environmental variance equals 2, and QTL variance equals 1. So we have $a = e = \sqrt{2}$. In the $p = .2$ conditions, we have $q_a \approx .577$ and $q_d \approx .816$, and, in the $p = .5$ conditions, we have $q_a \approx .816$ and $q_d \approx .577$. Each data set consists of 20,000 sib pairs, and the number of selected sib pairs equals 500. We choose a large N, because dominance-variance components are hard to detect in humans (Eaves et al. 1978; Neale et al. 1994). Within each of the six conditions defined by the between-case factors, 500 data sets are generated. Each data set is analyzed in five ways: (1) all-L_{mix}, (2) all-L_π, (3) FIsel L_{mix}, (4) FIsel L_π, and (5) no QTL. The selection percentages, which are shown in table 4, are chosen to maximize the effect of the EDAC test, given prior knowledge of both allele frequency and QTL-gene action (i.e., FI). For the reasons mentioned above, we have limit our discussion to the PIC = .910 (12 marker alleles) results. We do, however, report results obtained for the all-L_{mix} and all-L_π conditions, since they differ slightly.

Table 5 contains the NC χ^2's. In the $p = .2$ conditions, we find that the NC χ^2's are much larger after selection than before selection. Comparing the FIsel L_{mix} and the FIsel L_π conditions, we find that the NC χ^2's are greater in the latter conditions than in the former conditions. Given $p = .5$, in contrast, the NC χ^2's are a good deal smaller in the FIsel L_{mix} conditions and the FIsel L_π conditions than they are in either the all-L_{mix} conditions or the all-L_π conditions.

Figure 3 displays the bar plots of the error of the parameter estimates. Prior to selection, very slight bias is observed. The all-L_{mix} and all-L_π conditions do not produce exactly the same estimates, but the differences are small. After selection, the bias is severe in the frequency $p = .2$ conditions. Both QTL parameters (i.e., q_a and q_d) are overestimated. The degree of overestimation is greater in the FIsel L_π conditions than it is in the FIsel L_{mix} conditions. The large overestimation of the QTL effects explains the inflated NC χ^2 values (table 5). When $p = .5$, we find that the pi-hat approach still produces seriously biased estimates. The IBD-mixture approach, in contrast, performs a lot better, although some bias is still visible.

Simulation Study 3

The aim of the third simulation study is to investigate the effect of sib-pair selection when the codominant QTL is fitted to data containing recessive QTL effects. It is likely that, in practice, a codominant model will not be rejected, even though the QTL action is actually recessive or dominant.

The present design has three between-case factors: (1) number of marker alleles (8, 12, and 48), (2) QTL-allele frequency (.2 and .5), and (3) total sample size (N = 5,000 and N = 10,000). The parameter values equal those of the previous simulation study. The selection criteria are chosen without regard for either allele frequency or mode of QTL-gene action (i.e., NI selection). The criteria are shown in table 2. The present design gives rise to six cells. Within each cell, 250 data sets are generated. Each data set is analyzed five times: (1) all-L_{mix}, (2) all-L_π, (3) NIsel L_{mix}, (4) NIsel L_π, and (5) no QTL. The number of selected sib pairs equals 500, regardless of N. We limited our presentation of results to the PIC = .910 (12 marker alleles) conditions. As in simulation study 1, the differences between the all-L_{mix} and all-L_π conditions are very small. We therefore discard the results observed in the all-L_π conditions.

Table 6 contains the NC χ^2 values and the observed

Table 5

NC χ^2's (df = 2) in Simulation Study 2

CONDITIONS AND NC χ^2 PARAMETERS	ALL		FI	
	IBD	PI	IBD	PI
.2/12/20,000:				
Mean	147.5	144.3	224.4	327.3
SD	25.7	25.2	33.5	48.2
.5/12/20,000:				
Mean	128.5	128.4	38.6	81.0
SD	21.2	21.2	11.9	25.3

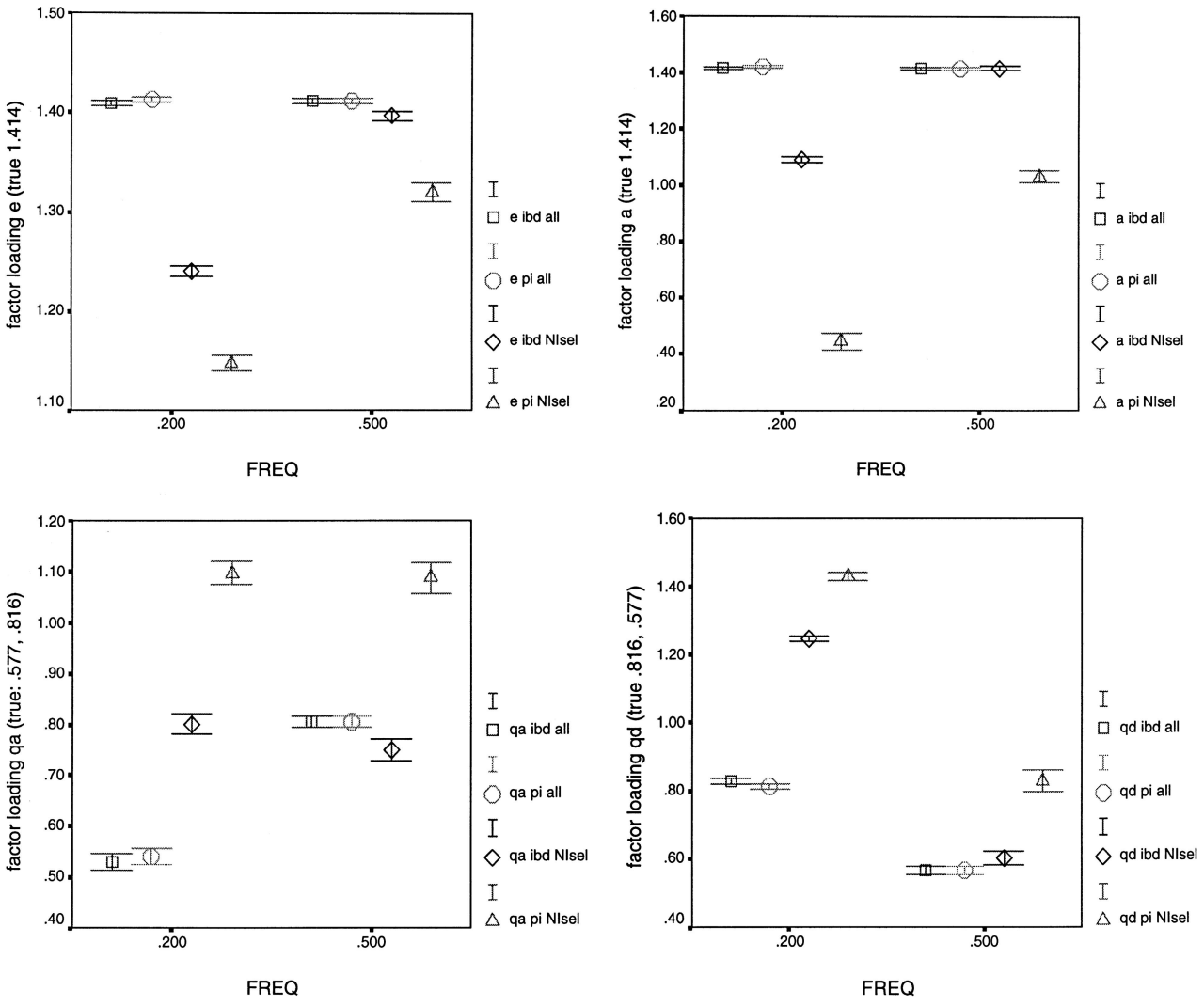

Figure 3 Study 2: unshared environmental-, polygenic-, and QTL-factor loadings. Error bars represent 95% confidence intervals.

power, given $\alpha = .0001$ and $\alpha = .00001$. When $p = .2$, we again find that the pi-hat approach produces larger NC χ^2 values when selected data are analyzed than when all data are analyzed. It is striking that the larger mean NC χ^2 is not accompanied by greater power (i.e., all-L_{mix} is ~85%, and NIsel L_{π} is ~82%, for $\alpha = .00001$). This indicates that the log-likelihood–ratio statistics produced by NIsel L_{π} deviates somewhat from its expected NC χ^2 (df = 1) distribution (presumably its tail is lighter). In the $p = .5$ conditions, the NC χ^2 observed in the NIsel L_{π} conditions are smaller than those observed in the all-L_{mix} conditions. As above, we find that, after selection, the pi-hat approach appears to be a lot more powerful than the IBD-mixture approach.

Figure 4 displays plots of the error of the parameter estimates. After sib-pair selection, the pi-hat approach produces very biased estimates, regardless of the QTL-allele frequency. As expected now, the QTL effect is overestimated, and the bias is greatest in the $p = .2$ conditions. The overestimation of the QTL effect is accompanied by an underestimation of the polygenic effects. The environmental effects are overestimated in the $p = .2$ conditions but are quite accurate in the $p = .5$ conditions. After sib-pair selection, the IBD-mixture approach also produces biased results in the $p = .2$ conditions; the QTL effect and the environmental effects are overestimated, and the polygenic effects are underestimated. Overall the bias is considerable, but it is a lot smaller than the bias observed when the pi-hat approach is used. In the $p = .5$ conditions, there is some evidence of bias in the $N = 10{,}000$ conditions; however, this bias is very slight.

Table 6

NC χ^2's (df = 1) and Power, Given Two α Levels, in Simulation Study 3

Conditions and Statistic	IBD	NI	
	All	IBD	PI
.2/12/5,000:			
NC χ^2:			
Mean	30.6	25.2	32.6
SD	11.7	11.0	14.2
α:			
.00001	85	69	81
.0001	92	80	88
.2/12/10,000:			
NC χ^2:			
Mean	62.1	55.0	77.2
SD	16.5	17.7	24.4
α:			
.00001	100	99	100
.0001	100	100	100
.5/12/5,000:			
NC χ^2:			
Mean	31.0	17.9	27.3
SD	10.9	8.1	12.6
α:			
.00001	85	35	68
.0001	95	60	84
.5/12/10,000:			
NC χ^2:			
Mean	61.4	25.5	44.3
SD	15.7	10.1	18.0
α:			
.00001	100	72	94
.0001	100	87	98

Simulation Study 4

The aim of the final simulation study is to investigate the distribution of the log-likelihood–ratio statistic in the absence of any QTL effect. This statistic is distributed asymptotically as a .5:.5 mixture of a $\chi^2(1)$ and a point mass at 0 (Sham 1998, p. 93).

In the present simulation study, the parameter values are $a = e = \sqrt{2}$, and $q_a = q_d = 0$. The design has two between-case factors: frequency (.2, .5, and .7) and number of marker alleles (8, 12, and 48). Within each of the nine cells of this design, we simulate 1,000 data sets. Each data set comprises 5,000 sib pairs, of which 500 are selected. The same (i.e., NI) selection criterion is used as is used in simulation study 1 (see table 2). Each data set is analyzed five times: (1) all-L_{mix}, (2) all-L_π, (3) NIsel L_{mix}, (4) NIsel L_π, and (5) no QTL. The models with and without the parameter q_a are fitted to each data set, and, as above, the log-likelihood–ratio statistic is calculated as minus twice the difference in the two log likelihoods.

Table 7 contains the mean and the SDs of the log-likelihood–ratio statistics (χ^2's), and the false-positive error rate is $\alpha = .025$. The results in table 7 indicate clearly that, following selection, the pi-hat approach does not produce the expected distribution of the goodness-of-fit statistic. The results produced by all-L_{mix}, all-L_π, and NIsel L_{mix} do agree with expectation.

Comparison with the Power of the EDAC test

The results of the present studies provide some insight into the power of QTL-effect tests based on covariance-structure modeling, before and after sib-pair selection. We are not aware of any comparison of the power afforded by the EDAC test versus the power of covariance-structure modeling. To obtain an indication of the difference in power, we replicated a small number of the conditions of simulation studies 1 and 3. We report the observed power for the 12-marker-allele and $N = 5{,}000$ conditions. Selection is again limited to 500 sib pairs (see table 2). The observed power is expressed as the percentages of cases in which the QTL is detected. In each condition, we perform 500 replications. In addition to the observed power, given the 12-allele-marker condition, we report the expected power for PIC = 1. Power for PIC = 1 is calculated analytically (not by means of simulation) in the manner described by Gu et al. (1996) and Risch and Zhang (1995).

Table 8 contains the results of the simulations and of the power calculations. As in simulation studies 1 and 3, we report the results for $\alpha = .0001$ and $\alpha = .00001$. Comparing the results in tables 3 and 8, we find that the power afforded by the EDAC test is much lower. After selection, the power afforded by the EDAC test is ~21%, given $\alpha = .00001$. The power of the IBD-mixture approach is ~38%, and the power of the pi-hat approach is ~70%. After FI selection, we find the following percentages: 26% (EDAC), 36% (IBD mixture), and 73% (pi-hat). Similar results are observed in the conditions of simulation study 3. The expected power of the EDAC test when PIC = 1 is found to be comparable to the power of the IBD-mixture approach, given a 12-allele marker (PIC = .91), and is much smaller than the power of the pi-hat approach.

Discussion

On the basis of the present results, we can draw a number of conclusions. First, after the assignment of prior IBD probabilities, the pi-hat approach produces seriously biased parameter estimates. The QTL effect is found to be consistently overestimated. The degree of overestimation varies with the selection criterion and the allele frequency of the QTL. The more extreme the allele frequency, the greater the bias. Compared with the NI-selection strategy, the FI-selection strategy produces greater bias. The degree of bias is most evident in simulation study 2, in which the FI-selection strategy was adopted and the allele frequency was low ($p = .2$). The

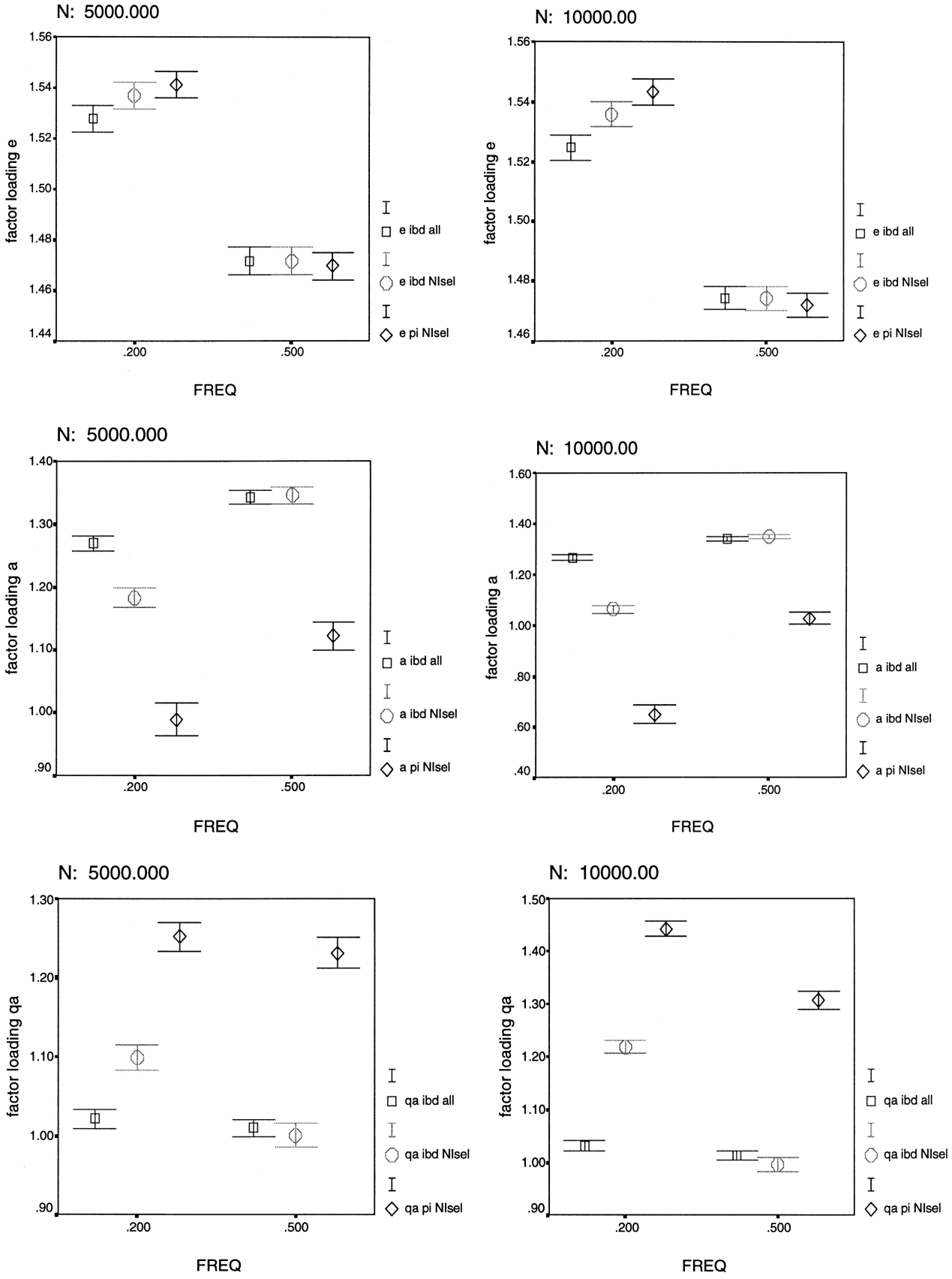

Figure 4 Study 3: unshared environmental-factor loadings and additive polygenic-factor loadings. Error bars represent 95% confidence intervals.

Table 7

Simulation Study 4: Data for −2 × Difference in Log Likelihood, and for $\alpha = .025$, Calculated With And Without the Absent QTL Effect, for $N = 5{,}000$

Condition and Parameter[a]	All		NI	
	IBD	PI	IBD	PI
.2/8:				
Mean	.455	.455	.458	.688[b]
SD	1.14	1.14	1.11	1.66[b]
False positive (%)	2.0	1.9	2.1	5.1[c]
.2/12:				
Mean	.550	.550	.573[b]	.862[b]
SD	1.00	1.00	1.10	1.81[b]
False positive (%)	2.8	2.8	2.7	6.7[c]
.2/48:				
Mean	.539	.539	.544	.816[b]
SD	1.22	1.22	1.14	1.71[b]
False positive (%)	3.0	3.0	2.9	6.1[c]
.5/8:				
Mean	.534	.535	.515	.782[b]
SD	1.14	1.14	1.09	1.67[b]
False positive (%)	3.2	3.3	2.5	6.0[c]
.5/12:				
Mean	.518	.518	.527	.797[b]
SD	1.15	1.15	1.19	1.79[b]
False positive (%)	2.6	2.6	2.8	5.6[c]
.5/48:				
Mean	.483	.483	.452	.682[b]
SD	1.16	1.16	1.09	1.64[b]
False positive (%)	2.7	2.7	1.9	4.8[c]
.7/8:				
Mean	.513	.512	.500	.754[b]
SD	1.15	1.15	1.17	1.71[b]
False positive (%)	2.7	2.7	2.2	5.5[c]
.7/12:				
Mean	.533	.533	.526	.796[b]
SD	1.13	1.13	1.21	1.83[b]
False positive (%)	2.7	2.7	3.0	5.8[c]
.7/48:				
Mean	.478	.478	.477	.720[b]
SD	1.06	1.06	1.13	1.71[b]
False positive (%)	2.5	2.5	3.3	5.5[c]

Note.—Summary statistics are based on 1,000 replications. Expected value of mean = .50 (approximate 99% confidence interval = .417–.561); value of SD = 1.118 ($\sqrt{1.25}$) (approximate 99% confidence interval = .889–1.33); and expected value of false-positive rate = 2.5.

[a] False-positive rates are for $\alpha = .025$.

[b] Outside 99% confidence interval.

[c] $P < .001$.

overestimation of the QTL effect results in an increase in power of the log-likelihood test of the QTL effect. In extreme cases (e.g., simulation study 2), the power after selection exceeds that observed when all marker data are analyzed. This finding is reminiscent of a finding presented by Gershenfeld et al. (1997): in mapping QTLs for open-field activity in mice, they report a significant result in phenotypically selected mice, which disappeared when the entire sample was analyzed. In human samples, a similar discrepancy could arise because of the overestimation of the QTL effect, especially after highly selective sampling.

The conclusions concerning the pi-hat approach apply to the IBD-mixture approach, but to a lesser extent. In the first simulation study, the estimates of the QTL effects are seriously biased only when the allele frequency is extreme and the selection strategy is based on FI. Compared with the bias observed in the pi-hat approach, the bias is a lot smaller. There is other evidence of bias, but this bias is relatively small. In both simulation study 2 and simulation study 3, the bias produced by the IBD-mixture approach is evident when $p = .2$.

The final simulation study of the behavior of the log-likelihood ratio under the null model indicates that the ratios produced by the pi-hat approach after selection are not distributed according to the expected distribution. In the IBD-mixture approach, on the other hand, the means and SDs of the expected distribution are in line with expectation.

A secondary aim of the present paper has been to compare the performance, in genetic covariance-structure modeling, of FI selection versus that of the more realistic, NI selection. Compared with NI selection, FI selection was effective only when the allele frequency was extreme. Elsewhere, FI selection is quite ineffective—or even counterproductive. Specifically, in simulation study 1, FI selection was counterproductive when $p = .5$. We performed additional simulations involving

Table 8

Power of EDAC in $N = 5{,}000$ Conditions of Simulation Studies 1 and 3

Simulation Study and Condition	T	σ	$\alpha =$ .0001	$\alpha =$ .00001
I (codominant QTL):				
NI:				
.2/12	.112	.032	.42	.20
.5/12	.113	.032	.41	.21
.7/12	.112	.032	.42	.22
.2/∞	.123	.032	.56	.35
.5/∞	.125	.032	.55	.37
.7/∞	.124	.032	.57	.36
FI:				
.2/12	.125	.034	.49	.27
.5/12	.117	.033	.42	.21
.7/12	.118	.033	.43	.25
.2/∞	.140	.035	.62	.41
.5/∞	.130	.033	.58	.36
.7/∞	.130	.032	.61	.40
III (recessive QTL), NI:				
.2/12	.088	.032	.17	.06
.5/12	.112	.032	.43	.24
.2/∞	.100	.032	.29	.13
.5/∞	.122	.032	.55	.33

Note.—EDAC test statistic = T/σ, which has a standard normal distribution under the null hypothesis of no QTL effect (Gu et al. 1996, p. 516).

other selection criteria, to get an idea of the sensitivity of NC χ^2 to selection. Simulation study 1 was repeated, with two extreme selection strategies: one in which the majority (>90% of a total of 500 sib pairs) of selected sib pairs were discordant and one in which the majority (>95%) of sib pairs were concordant. Limiting ourselves to the IBD-mixture approach and to $N = 5{,}000$, we observe a drop in NC χ^2, from ~31.5 to 9.0, when mainly concordants were selected, and from ~31.5 to 17.0, when mainly discordants were selected. This difference is expected, since discordant sib pairs are generally more informative than concordant sib pairs (e.g., see Eaves and Meyer 1994; Risch and Zhang 1995). The mean NC χ^2 observed in simulation study 1 went from ~31.1 to ~17.9, given NI selection, and from 31.1 to ~19.8, given FI selection. These findings suggest that, as long as the majority of the selected sib pairs are discordant, the NC χ^2 is relatively insensitive to the exact selection criterion.

An additional result observed after the selection of mainly concordant or mainly discordant sib pairs is that the selection of mainly discordant results in a lot less bias when the pi-hat approach is used. After the selection of mainly concordants, the means of the polygenic- and QTL-factor loadings are ~.973 (true: $\sqrt{2}$) and ~1.366, respectively (true: 1.00). After the selection of mainly discordants, these means were found to be ~1.331 and ~1.09, respectively—a lot closer to their true values. A similar result is observed in simulation study 1, in which FI selection resulted in the selection of more concordants (see table 1)–and, consequently, in more bias (see fig. 2).

To explore the effects that the background correlation has on the parameter estimates after sib-pair selection, we repeated simulation study 1, with a background correlation of 0. This implies the absence of shared environmental or polygenic influences. The unshared environmental effects explained 80% of the variance. After NI selection (see table 2), we observed very little bias in the estimates of the codominant QTL and the unshared environmental effects. Parameter bias was absent in both the pi-hat approach and the IBD-mixture approach. So, in addition to the selection criterion, the background correlation is an important contributing factor to bias, after the assignment of prior IBD probabilities. Apparently, a larger background correlation is associated with greater bias.

The assignment of prior IBD probabilities in genetic covariance-structure modeling of a QTL cannot be trusted to produce unbiased parameter estimates. However, if it assumed that the QTL frequencies are not too extreme (>.2) and NI selection is applied (which will generally be the case), the bias produced by the IBD-mixture approach may be slight. Both the IBD-mixture approach and the pi-hat approach can be used to *detect* the presence of a QTL. The null distribution of the log-likelihood ratio produced by the IBD-mixture approach was not found to deviate from the expected distribution. The pi-hat approach produces excessive false positives, but this can be counteracted, to a degree, by adjustment of the α level.

We have been concerned mainly with the estimates and power of genetic covariance-structure modeling of QTL effects after sib-pair selection; however, we did consider the power of the EDAC test (Gu et al. 1996) in the $N = 5{,}000$ conditions of simulation studies 1 and 3. The EDAC test is found to be consistently a lot less powerful. Clearly, in terms of power, genetic covariance-structure modeling of QTL effects in sib-pair data is superior to tests based on allele-sharing information.

We have limited our attention to the assignment of prior IBD probabilities as suggested by Eaves et al. (1996). There are other ways of obtaining IBD probabilities in sib pairs whose marker data are missing. As discussed by Sham (1998, p. 266), posterior IBD probabilities can be based also on the phenotypic data (instead of the marker data), by application of Bayes's theorem. In normal mixture analysis, this is the standard method of calculating posterior probabilities of component membership (e.g., see Everitt and Hand 1981, p. 10). Another possibility is to exploit the regularity of the pi-hat surface (see fig. 1). It may be possible to construct the whole pi-hat surface from the parts of the surface that are observed by means of interpolation. These possibilities have yet to be investigated properly.

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Appendix

Derivatives of the pi-hat and IBD-Mixture Approach: Raw-Data Likelihood Functions

We first consider the log-likelihood function $L_{mix}(\theta)$ (eq. [2]). Let $f_{\tau_k}(\mathbf{y}_i; \boldsymbol{\mu}, \Sigma_{\tau_k})$ denote the bivariate normal distribution conditional on the marker data. Let $\mathbf{g}_i = \Sigma_{k=1}^{3} P(\tau_k)_i \mathbf{f}_{\tau_k}$, and let $\omega_{\tau_k} = P(\tau_k)_i \mathbf{f}_{\tau_k}(\mathbf{y}_i; \mu, \Sigma_{\tau_k})/\mathbf{g}_i$. We require the derivatives

$$\partial L_{mix}(\theta)\partial \Lambda = \sum_{i=1}^{N} \sum_{k=1}^{3} \partial L_{mix}(\theta)/\partial \Sigma_{\tau_k} \; \partial \Sigma_{\tau_k}/\partial \Lambda \; ,$$

where

$$\partial \mathrm{L}_{\mathrm{mix}}(\theta)/\partial \Sigma_{\tau_k} = \frac{1}{2}\omega_{\tau_k i}[\Sigma_{\tau_k}^{-1}(\mathbf{y} - \mu_i) (\mathbf{y} - \mu_i)^{\tau}\Sigma_{\tau_k}^{-1} - \Sigma_{\tau_k}^{-1}] ,$$

and $\partial \Sigma_{\tau_k}/\partial \Lambda = 2\Lambda\Psi_{\tau_k}$. The matrix $\partial \mathrm{L}_{\mathrm{mix}}(\theta)/\partial \boldsymbol{\Lambda}$ contains the derivatives of $\mathrm{L}_{\mathrm{mix}}$ with respect to the parameters *a, e,* q_a, and q_d. Furthermore we require the derivatives of $\mathrm{L}_{\mathrm{mix}}$ with respect to the phenotypic mean vector, $\boldsymbol{\mu}$. This equals

$$\partial \mathrm{L}_{\mathrm{mix}}(\theta)/\partial \mu = \sum_{i=1}^{N}\sum_{k=1}^{3} \omega_{\tau_k i}\Sigma_{\tau_k}^{-1}(\mathbf{y}_i - \mu) .$$

Likewise, for the log-likelihood function, L_{π} we have

$$\partial \mathrm{L}_{\pi}(\theta)/\partial \Lambda = \sum_{i=1}^{N} \partial L_{\pi}(\theta)/\partial \Sigma_i \, \partial \Sigma/\partial \Lambda ,$$

where

$$\partial \mathrm{L}_{\pi}(\theta)/\partial \Sigma = \frac{1}{2}\left[\Sigma_i^{-1}(\mathbf{y}_i - \mu)(\mathbf{y}_i - \mu)^{\tau}\Sigma_i^{-1} - \Sigma_i^{-1}\right] ,$$

and $\partial \Sigma_i/\partial \Lambda = 2\Lambda\Psi_i$. Finally, we require

$$\partial \mathrm{L}_{\pi}(\theta)/\partial \mu = \sum_{i=1}^{N} \Sigma_i^{-1}(\mathbf{y}_i - \mu) .$$

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