K-RATIO TESTS WITH COVARIATES

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LYNN R. SHEMANSKI. K-Ratio Tests With Covariates (Under the direction of Clarence E. Davis.)

ABSTRACT

This dissertation generalizes Duncan's k-ratio methodology to include a covariate. The analysis assumes proportionality between the covariance matrix of the prior distribution for the true treatment means and the covariance matrix of the conditional distribution of the observations given the values of the true treatment means. When the covariance matrices are known, analysis demonstrates that the power for the covariate k-ratio procedure is increasingly greater than the power of Duncan's k-ratio test as the correlation between the variable under investigation and the covariate increases.

The dissertation also investigates the effect of three nuisance parameters on the power function: the size of the variance of the covariate relative to the variance for the variable under investigation, the value of the constant of proportionality between the covariance matrices of the prior and conditional distributions, and the value of the true treatment mean difference for the covariate.

Assuming a known constant of proportionality, a diffuse prior and normality of the data, results from simulations indicate that very little power is lost when the covariance matrix of the conditional distribution for the observations is estimated from the data.

The dissertation derives two estimators for the covariance matrix of the prior distribution using a multicenter set-up. One of these estimators retains the proportionality assumption between the covariance

matrices, while the other estimator does not rely on that assumption. Simulations comparing the powers of the two multicenter covariate k-ratio procedures to the power of the covariate k-ratio procedure when covariance matrices are known indicate good approximations when the prior is diffuse relative to the observations. In this case, minimal power is lost when estimators for the covariance matrices are used in the covariate k-ratio procedure.

A statistical analysis of total cholesterol and high density lipoprotein levels using data from the LRC-CPPT indicates good agreement between all investigated covariate k-ratio procedures and the Analysis of Covariance. This agreement exists both in the tests of significance for treatment mean differences and in the power of the procedures under repeated sampling assumptions.

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I. LITERATURE REVIEW AND RESEARCH PLAN

This thesis proposes an extension of the k-ratio t-test procedure for bivariate responses in two treatment groups. The following two sections review the k-ratio t-test literature, as well as the pertinent literature on Bayesian multivariate linear models.

1.1 K-ratio t-tests

David B. Duncan and his associates (1961, 1965, 1969, 1974) developed k-ratio t-tests as a response to the problem of multiple comparisons in the simultaneous testing of q treatment means taken a pair at a time. Prior to the formulation of this type of test, analysis of the $q(q-1)/2$ treatment mean differences proceeded by either a comparison-wise or experiment-wise approach.

In a comparison-wise approach, α-level tests are performed for each comparison made. Objections to this approach arise because of the increased probability it gives for finding a significant difference when in fact no such difference exists. As an example, if 100 tests of treatment mean differences are performed with α-level equal to 0.05, and assuming independent comparisons, one would expect 5 significant test statistics due to chance alone. In the case where treatment means are fairly homogeneous, the comparison-wise critical value is intuitively too small, and therefore often results in erroneous conclusions of significant pairwise treatment mean differences. The k-ratio t-test procedure results in a larger critical value in the case of homogeneous outcomes, overcoming this objection.

The experiment-wise approach increases the critical value so that the probability of falsely rejecting all null hypotheses of no pairwise treatment differences equals α. The critical value increases with q in order to ensure a total Type I error probability equal to α. The Tukey, Scheffé and Bonferroni procedures are examples of this approach. Experiment-wise critical values increase dramatically with increasing q, resulting in extremely low power for each pairwise test. In the case where treatment outcomes are heterogeneous, the critical values derived from the experiment-wise approach are intuitively too large. In this situation, one desires a statistical procedure that adjusts the critical value to a less conservative one, as this would allow for sufficiently high power to detect true treatment differences.

The k-ratio test statistic proposed by Waller and Duncan (1969) depends on the between-treatments F-ratio in a manner which overcomes the objections to the comparison-wise approach in the case of homogeneous outcomes and to the experiment-wise approach in the case of heterogeneous outcomes. At F values of 3.0 or greater, the k-ratio critical value is relatively low. In this situation of heterogeneous outcomes, the rule is more powerful (less conservative) and similar to the comparison-wise approach. For data with lower F-values (homogeneous outcomes), the critical value increases. As the F statistic approaches one, the k-ratio rule behaves like an experiment-wise rule, becoming more conservative. Therefore, Duncan's k-ratio methodology possesses the advantages of both experiment-wise and comparison-wise rules without the disadvantages noted above.

In the basic formulation of k-ratio t-tests [Duncan and Dixon (1983)], X is a (q x 1) vector of treatment means for q independent populations with each of its elements X_i based on r replications and independently distributed Normal$(\mu_i, \sigma_e^2/r)$. The density function for the observed treatment mean difference d_{ij} is then normal, with mean δ_{ij} equal to $\mu_i - \mu_j$ and variance $2\sigma_e^2/r$. Denote this probability density function as $f(d|\delta,\sigma_e^2)$. The problem is that of making multiple tests of the hypotheses H_0: $\delta_{ij} \le \delta_0$ vs. H_1: $\delta_{ij} > \delta_0$ where δ_{ij} is any one of the q(q-1) differences $\mu_i - \mu_j$ and δ_0 is an arbitrary constant equal to zero in most applications.

In the k-ratio approach, each of the μ_i's are taken to have the same prior probability density function, namely μ_i is normally distributed with mean Θ and variance σ_μ^2. Therefore each δ_{ij} is distributed normal with mean 0 and variance $2\sigma_\mu^2$. Denote this distribution by $f(\delta|\sigma_\mu^2)$.

The k-ratio methodology uses a linear loss model of the form

$$\begin{aligned} \ell(\ddot{d}_0|\delta_{ij},\delta_0) &= \begin{cases} 0 & \delta_{ij} \le \delta_0 \\ k_0(\delta_{ij}-\delta_0) & \delta_{ij} > \delta_0 \end{cases} \\ \ell(\ddot{d}_1|\delta_{ij},\delta_0) &= \begin{cases} k_1(\delta_0-\delta_{ij}) & \delta_{ij} \le \delta_0 \\ 0 & \delta_{ij} > \delta_0 \end{cases} \end{aligned} \tag{1.1}$$

where $\ddot{d}_0$ and $\ddot{d}_1$ are the decisions for H_0 and H_1, respectively. In addition, if $\ddot{d}_{ij}$ denotes the decision made for the test of the null hypothesis H_0: $\delta_{ij} \le \delta_0$ then the losses are assumed to be additive. That is, $\ell(\cap\, \ddot{d}_{ij}) = \Sigma\ell(\ddot{d}_{ij})$ where the intersection and summation are over all $\ddot{d}_{ij}$'s of interest. This is called the "additive losses" assumption and yields the result that the Bayes rule for the simultaneous test of all treatment mean differences is the application of the component Bayes rule described below.

To derive the Bayes test for δ_{ij} one takes as given the linear loss model above, the variances σ_{μ}^2 and σ_e^2, $f(\delta|\sigma_{\mu}^2)$ and $f(d|\delta,\sigma_e^2)$. Using Bayes rules, one can derive the posterior density $h(\delta|d,\sigma_{\mu}^2,\sigma_e^2)$ where d, again, is the observed treatment mean difference. This posterior density is normal with mean $\mathcal{S}\cdot d$ and variance $\mathcal{S}\cdot\sigma_d^2$ where $\sigma_d^2=2\sigma_e^2/r$ and $\mathcal{S}$ equals $1-[\sigma_e^2/(\sigma_e^2+r\cdot\sigma_{\mu}^2)]$. $\mathcal{S}$ is called a "shrinkage factor" because of its effect on the posterior mean and variance. The k-ratio test rejects H_0 when $(\mathcal{S}\cdot d-\delta_0)/(\mathcal{S}\cdot\sigma_d^2)^{1/2} > z(k)$ or $d/\sigma_d > t(k)$ where z(k) is the solution for z of

$$k = \frac{\phi(z) + z\cdot\Phi(z)}{\phi(-z) - z\cdot\Phi(-z)}, \quad \text{and}$$

$$t(k) = \frac{\delta_0}{\mathcal{S}\cdot\sigma_d} + \frac{z(k)}{\mathcal{S}^{1/2}} \tag{1.2}$$

where $k=k_1/k_0$ and Φ and ϕ are the standard normal distribution and density.

This k-ratio test statistic is comparable to the usual t-test statistic except for the fact that it is based on the posterior mean and variance for δ given d and it does not depend on an alpha level, but on k, the type-I to type-II error seriousness ratio. Values of 50, 100 and 500 are typically used for k, as these are analagous to α-levels of 0.10, 0.05 and 0.01 in the case of a two-sided two-sample t-test and are good approximations overall. Duncan and Waller (1969 and 1972) give tables of the critical values t(k) for the values of k given above and various values of F, the observed between-treatments F ratio.

The joint Bayes rule for the simultaneous test of any two or more of the δ_{ij}'s is the application of the above Bayes rule for each of the δ_{ij}'s of interest. The k-ratio rule is basically independent of q, the number of treatments being compared, and results in a comparison-wise test that does not possess the homogeneous outcomes objection described earlier.

In large sample (large q and r) applications, the observed F-ratio estimates $\mathcal{F}$, the true F-ratio. The observed F can therefore be substituted for $\mathcal{F}$ in the equation $\mathcal{S}=1-(\mathcal{F})^{-1}$, with the resulting estimate of $\mathcal{S}$ used in (1.2). The variance σ_d^2 can be approximated by $S_d^2=2 \cdot S_e^2/r$ where S_e^2 is the observed mean square error [Dixon and Duncan (1975)]. This empirical Bayes rule performs satisfactorily in the large-sample case, but can also yield negative $\mathcal{S}$ values when F is less than one, so caution is advised [Dixon and Duncan (1983)].

The above methodology is expanded upon by the introduction of prior density functions for the nuisance parameters of σ_μ^2 and σ_e^2 [Dixon and Duncan(1983)]. These prior densities are now utilized in the derivation of the posterior density $h(\delta|d)$. The resulting Bayes rule no longer depends on σ_μ^2 and σ_e^2 and behaves well.

In principle any test rule for a parameter can lead to an interval estimate which consists of all those parameter values that are not rejected by the test rule. Minimum Bayes risk simultaneous interval estimates (k-ratio t-intervals) for δ_{ij} equal $\mathcal{S} \cdot d \pm S_d \cdot \mathcal{S}^{1/2} \cdot t(k)$ where these terms are as defined previously. To derive confidence intervals for the $q(q-1)/2$ treatment mean differences, the above formula is computed for each δ_{ij} of interest. These intervals are shown to be minimum Bayes intervals under the assumption of squared-error losses. The width of these k-ratio t-intervals decrease with decreasing F, and are uniformly of less width than the corresponding α-level confidence intervals.

Duncan and Godbold (1979) developed approximate k-ratio tests in the case where treatment replications (r) are unequal, treatment variances unequal or treatment estimates correlated. In each of these cases a problem with the previous k-ratio methodology arises.

In the equal replications situation, the observed F-ratio can be implicitly used as an estimator of σ_μ^2, since the observed mean square error estimates σ_e^2. When the number of replications per treatment group are not equal, however, σ_μ^2 cannot be consistently estimated in this way. The solution to this problem is to introduce an "effective" F ratio, F_{ij}, that is used in place of the overall F in the test of H_0: $\delta_{ij} \le \delta_0$. The estimate of σ_μ^2 is now $(S_T{}^2 - S_e^2)/r_T$ (denote this as S_μ^2) where $S_T{}^2$ is the between-treatments mean square, S_e^2 is the MSE estimate of σ_e^2 and $r_T = \{N - \Sigma(r_i^2)/N\}$ where r_i equals the number of replications in treatment group i, $N = \Sigma(r_i)$ and the summations are over the q treatment groups. For each difference tested, F_{ij} is given by

$$F_{ij} = \frac{r_{ij} \cdot S_\mu^2 + S_e^2}{S_e^2} \qquad \text{with} \qquad r_{ij} = \frac{2 r_i r_j}{(r_i + r_j)} \quad . \tag{1.3}$$

The numerator of F_{ij} is now an unbiased estimate of $r_{ij} \cdot \sigma_\mu^2 + \sigma_e^2$. Therefore, F_{ij} can be used for the implicit estimation of σ_μ^2. The "effective" degrees of freedom associated with the numerator of F_{ij} are adjusted as well (see formula 3 of the referenced article), and the k-ratio test proceeds as before. The critical value t(k) is determined by entering the tables given in Duncan & Waller (1972) with the effective F ratio and the adjusted degrees of freedom. The test is made by comparing d_{ij}/S_d with t(k) where S_d^2 equals $2S_e^2/r_{ij}$ and the null hypothesis is rejected when the test statistic is greater than t(k).

In the case of heteroscedastic and correlated treatment mean estimates, let X_i be the estimate for the i^{th} population mean μ_i. The density for **X**, the q-by-1 vector of the estimated treatment group means is $\text{Normal}_q(\boldsymbol{\mu},\sigma_e^2\cdot\mathbf{V})$. The prior densities for the true means μ_i are independent $\text{Normal}(\theta,\sigma_\mu^2)$ for $i=1,2,\ldots,q$. Tests of contrasts between the means are of the form $\gamma=\Sigma(c_i\mu_i)$, with $\Sigma(c_i)=0$. For this case, the k-ratio procedure involves computation of "effective replication numbers" that correspond to r_{ij} and r_T in the homoscedastic situation. These computations now involve **V** and its inverse.

The above methodology for the heteroscedastic and correlated treatment means case applies to the test of any contrast γ of the form given above. The means of determining the critical value t(k) is independent of the total number of contrasts tested. All differences implicitly present in the data are used taken into account in the determination of the magnitude of the prior variance σ_μ^2.

Stevenson and Bland (1982) analyze the k-ratio test procedure in the case where treatment variances are unknown and not assumed equal. In this case, $X_{ik}\sim\text{Normal}(\mu_i,\sigma_i^2)$, where X_{ik} is the k^{th} observation in the i^{th} treatment group; $i=1,2,\ldots,q$ and $k=1,2,\ldots,n_i$. As before, one wishes to test H_0: $\mu_i\le\mu_j$ vs. H_1: $\mu_i>\mu_j$, where μ_i is again the true mean for treatment group i. It is assumed that prior densities for each μ_i

and σ_i^2 are in the class of conjugate priors for the normal distribution with unknown mean and variance. These priors are completely determined when estimates for μ_i and σ_i^2 (ψ_i and $(s_{ip})^2$) and measures of the amount of the prior information found in ψ_i and $(s_{ip})^2$ (c_i and υ_{ip}, respectively) are specified. For example, if information for μ_i and σ_i^2 comes from a pilot study of size n_i^*, the following specifications are made: $\psi_i=\bar{X}_i$, $c_i=n_i^*$, $(s_{ip})^2=s_i^2$, and $\upsilon_{ip}=n_i^*-1$, where s_i^2 is the usual unbiased estimate of σ_i^2.

The resulting decision rule using the same loss function as used previously is to accept H_0 if $h(t_i,t_j)\geq 0$, otherwise reject H_0 in favor of H_1. Here $h(t_i,t_j)$ is a complicated function of the squared error loss estimators of μ_i and μ_j and of the posterior densities for μ_i, μ_j, σ_i^2 and σ_j^2. In the case of where no prior information is available, the values of c_i and υ_{ip} approach zero. The decision rule now simplifies into accept H_0 if $t_{ij}<-t_k(a,n_i,n_j)$, otherwise do not accept H_0. Here, $t_{ij}=(\bar{X}_i-\bar{X}_j)/(s_i^2+s_j^2)^{1/2}$ and $t_k(a,n_i,n_j)$ is as defined in the referenced article.

Brant and Duncan (1982) further developed k-ratio test methodology for the comparison of q treatment groups to a control group. The k-ratio rule now simultaneously tests the q differences between each treatment group mean and the control mean. The critical value for this rule now depends on the standardized difference t_α between the mean of the treatment means and the control mean. A large t_α, indicating average superiority of treatments over control, results in a smaller critical value in the test of the difference between any one treatment group mean and the control group mean.

Duncan and Dixon (1979) extended the k-ratio rule to the case where treatment rates are compared within subgroups of the data. This application is of particular use in clinical trial analysis, where an insignificant overall chi-square statistic typically results in the comparison of subgroup-specific rates for several different partitions of the data.

In the formulation of this problem, the observed mean responses X_{ij} are independently normal with mean μ_{ij} and variance σ_e^2/r, where i indexes treatment group and j indexes subgroup. Here, a two-way analysis of variance linear model of the form $\mu_{ij}=\mu+\alpha_i+\beta_j+\gamma_{ij}$ is used, with priors for each term of the equation given by $\mu \sim N(\mu_0,\sigma_\mu^2)$, $\alpha_i \sim N(0,\sigma_\alpha{}^2)$, $\beta_j \sim N(0,\sigma_\beta{}^2)$ and $\gamma_{ij} \sim N(0,\sigma_\gamma{}^2)$. Therefore, the prior for μ_{ij} is normal with mean μ_0 and variance-covariance structure as indicated in the reference.

In the case of two treatment groups, comparing responses within subgroup j involves testing the hypothesis H_0: $\delta_j \leq 0$ where $\delta_j=\mu_{1j}-\mu_{2j}$. The critical value t(k) now depends on the subgroup-specific mean difference $X_{1j}-X_{2j}$, the overall mean difference $(X_{1.}-X_{2.})$, and the prior variances given above. If variability from subgroup to subgroup $(\sigma_\gamma{}^2)$ is large, the k-ratio rule depends to a greater degree on the treatment difference seen in subgroup j. However, in the case of small $\sigma_\gamma{}^2$, the rule depends more on the overall treatment difference. So, in the absence of interactions, the critical value will be the same for each subgroup. For the case of unknown variances, it is necessary to develop prior distributions for these variances and, through integration, develop posterior densities which do not depend on these terms.

The above-referenced article proceeds in approximating the k-ratio rule in the case of non-normal endpoints (such as response rates) and unbalanced layout, since the previous derivations have assumed r replications in each treatment-subgroup "cell". The application of these approximations to clinical trial data indicates that the procedure depends on the overall treatment difference in the desired way, namely a conservative rule in the case of homogeneous treatment outcomes, and a smaller t(k) critical value when treatment mean outcomes are heterogeneous.

Dixon, in a paper presented to the Biometric Society in 1983, applies the k-ratio method to the between-treatment comparison of exponential survival rates in subgroups of the data. The survival function for the i^{th} treatment and j^{th} subgroup is $S_{ij}(t)=\exp(-\lambda_{ij}t)$ with the likelihood ratio estimate of λ_{ij}, $\hat{\lambda}_{ij}$, equal to the ratio of the number of deaths seen (n_{ij}) to the total of the observed times in the ij^{th} group. In large samples, $\ln(\hat{\lambda}_{ij})$ is approximately normal with mean $\ln(\lambda_{ij})$ and variance $1/n_{ij}$. Therefore, in the two treatment group situation, the treatment difference $d_j=\ln(\hat{\lambda}_{1j}/\hat{\lambda}_{2j})$ is approximately normal with mean $\ln(\lambda_{1j}/\lambda_{2j})$ and variance equal to $n_{1j}^{-1} + n_{2j}^{-1}$.

In order to derive the posterior mean and variance of $\delta_j=\ln(\lambda_{1j}/\lambda_{2j})$, a Bayesian linear model is used, with **d**, the 1 x p vector of d_j's normally distributed with mean $\mathbf{X}_1 \cdot \boldsymbol{\mathcal{B}}$ and covariance matrix C_1. The matrix $\mathbf{X}_1$ is a 1x2 matrix of ones and $\boldsymbol{\mathcal{B}}$ is the 2 x p matrix with elements $\mathcal{B}_{ij}=(-1)^{i-1}\ln(\lambda_{ij})$, where p is the number of subgroups. Since subgroups are non-overlapping, survival rates between subgroups are independent and C_1 is a diagonal matrix with elements $c_{jj}=n_{1j}^{-1}+n_{2j}^{-1}$. The elements of $\boldsymbol{\mathcal{B}}$ have a prior multivariate normal density with mean matrix $\boldsymbol{\Theta}$ where $\Theta_{ij}=(-1)^{i-1}\ln\theta_j$ and covariance matrix C_2. The posterior density of $\boldsymbol{\mathcal{B}}$, given d, as derived in Lindley and Smith (1972) is normal(B•b,B) where these terms are defined in Dixon(1983). This result can be used to find the posterior mean and variance for $1^T\boldsymbol{\beta}$, the matrix with elements $\ln\lambda_{1j}-\ln\lambda_{2j}$, the subgroup-specific treatment comparisons. Substitution of these posterior mean and variance terms in the formula for the k-ratio critical region leads to rejection of H_0: $\lambda_{1j}=\lambda_{2j}$ when the ratio of the posterior mean to the square root of the posterior variance is greater than z(k), where z(k) is as defined previously.

In the usual case of unknown prior variances, a large sample approximation to the above involves the estimation of the elements of C_2 by a suitable variance components analysis of variance.

Dixon and Divine (1987) derive a k-ratio test procedure for use in the comparison of regression coefficients from a Cox proportional hazards model analysis. Their procedure possesses the desired k-raio adaptability through its adjustment of the critical value for individual comparisons to the degree of heterogeneity found in the data. It also takes account of the correlations that exist between the compared relative risk estimates.

In this application, let **b** be a q-by-1 vector of the log relative risk estimates for q disjoint groups. the vector **b** is distributed q-variate normal with mean $\boldsymbol{\beta}$. Here, the $\boldsymbol{\beta}_i$'s are dependent as each represents a comparison with the same "control" group. The authors consider $\boldsymbol{\beta}_i^*$, where $\boldsymbol{\beta}_i=\boldsymbol{\beta}_i^*-\boldsymbol{\beta}_{q+1}^*$. The $\boldsymbol{\beta}_i^*$'s are roughly log absolute risks, with arbitrary location. The $\boldsymbol{\beta}_i^*$'s are independent and distributed normal. The authors proceed by formulating a "synthetic" between-groups mean square whose expectation is equal to the variance of the difference under consideration. This mean square can then be used as the effective F-ratio in the Waller-Duncan tables of k-ratio critical values. The procedure, although approximate, performs well when used to analyze several datasets.

1.2 Bayesian Multivariate Linear Models

The literature for Bayesian linear models is extensive. Therefore, only articles applicable to the topic of this thesis are summarized here. The reader is referred to Press (1983) for a more-comprehensive list of references.

S. James Press (1980) analyzed Bayesian multivariate linear models of the form $Y|X = X \cdot \beta + U$, where Y is the (N x p) matrix of responses, X the known (N x q) design matrix, β the (q x p) matrix of regression parameters and U the error matrix. The author assumes that $\text{var}(\upsilon_i) = \Sigma$ for all i, where υ_i is the i^{th} row of U. That is, the error vectors have the same covariance structure for all observations. The υ_i vectors are also assumed to be independent and normally distributed with mean 0 (and covariance matrix Σ). The off-diagonal elements of Σ equal the covariances between the p different response variables, and the diagonal elements are of course the variances for each response variable.

In "case 1" of the article, the prior distributions for β and Σ are improper and independent of each other. That is, $p(\beta) \propto 1$ and $f(\Sigma) \propto |\Sigma|^{-(p+1)/2}$. These prior densities imply that each element of β is uniformly distributed over the real line and, for p=1, log Σ is also distributed in this way. For p greater than one, a p-dimensional generalization of this characteristic for the prior of Σ holds. The resulting marginal posterior distribution for β is a matrix T distribution, as defined in Kshirsagar (1960). The rows and columns of β follow a multivariate Student's t-distribution and each element of β

follows a univariate t distribution. Confidence intervals for $\boldsymbol{\beta}$ can be computed using the U distribution, as defined in Anderson (1958). This result was also shown in Geisser(1965).

In "case 2" of his article, Press uses an informative prior of the form $\boldsymbol{\beta}^{*}\sim\text{Normal}_{pq}(\boldsymbol{\phi},\mathbf{F})$ where $\boldsymbol{\beta}^{*}$ is the (1 x pq) vector of the elements of $\boldsymbol{\beta}$. The prior on $\boldsymbol{\Sigma}$, the covariance matrix of the $\boldsymbol{\upsilon}_i$'s, is inverted Wishart, with $p(\boldsymbol{\Sigma}) \propto |\boldsymbol{\Sigma}|^{-m/2} \exp\{-\text{trace}(\mathbf{G}\cdot\boldsymbol{\Sigma}^{-1})/2\}$. The hyperparameters (the parameters of the prior distributions) $\boldsymbol{\phi}$, $\mathbf{F}$, $\mathbf{G}$, and m are assumed to be known. The posterior distribution for $\boldsymbol{\beta}^{*}$ is very complicated, but can be approximated for large samples by a normal distribution with mean and variance as given in equation 13 of this reference.

For the one-way MANOVA situation, assume the fixed effects model of $\mathbf{z}_{ij}=\boldsymbol{\theta}_j + \boldsymbol{\upsilon}_{ij}$, where $\mathbf{z}_{ij}$ is a (p x 1) response vector for replication i in population j, $\boldsymbol{\theta}_j$ the vector of true population means, and $\boldsymbol{\upsilon}_{ij}$ the vector of errors $i=1,\ldots,n_j$, $j=1,\ldots,q$. Let $\mathbf{z}_{ij}$ be distributed $\text{Normal}_p(\boldsymbol{\theta}_j,\boldsymbol{\Sigma})$. If $\mathbf{Y}$ is the (N x p) matrix with rows equal to $\mathbf{z}_{ij}^T$, $\mathbf{U}$ the (N x p) matrix with rows $\boldsymbol{\upsilon}_{ij}^T$, $\boldsymbol{\beta}$ the (q x p) matrix of true population means with rows equal to $\boldsymbol{\theta}_j^T$, and $\mathbf{X}$ the (N x q) block diagonal matrix of the form $\text{diag}(\boldsymbol{\tau}_{n1},\ldots,\boldsymbol{\tau}_{nq})$ where $\boldsymbol{\tau}_{ni}$ is a (n_i x 1) vector of ones, and superscript "T" denotes the transpose operation. The MANOVA model is now of the form $\mathbf{Y}= \mathbf{X}\cdot\boldsymbol{\beta} + \mathbf{U}$, and an analysis can proceed using all the results shown previously.

Specifically, if one wants to analyze a set of r comparisons of the true means, the contrast is of the form $\boldsymbol{\gamma}=C_1\boldsymbol{\beta}^T C_2$ where C_1 and C_2 are constant, known matrices of dimensions (r x p) and (q x 1), respectively. In "case 1" using non-informative priors, $\boldsymbol{\gamma}$ is distributed as multivariate Student's t, and quantiles of that distribution can be used to test H_0: γ=0. In "case 2" above, β^* is assymptotically normal. Since all elements of β^* are jointly normally distributed, all linear combinations of the elements of β^* are also normally distributed. Therefore, the posterior distribution of γ is multivariate normal and can be easily evaluated.

Press and Shigemasu (1985) develop a Bayesian MANOVA model under the assumption that the θ_j's, as defined in Press (1980) are independent and identically distributed for all j. The prior distributions for the θ_j vectors of true population means are $\text{Normal}_p(\mu,\Sigma_p)$, and therefore possess the characteristic of exchangeability. Under this assumption, the rows of β (the θ_j's) are mutually independent. This independence takes advantage of the population structure (independence of responses between populations) and implies that the means of the q populations are uncorrelated. It should be stressed that the elements of the rows of β are not assumed to be independent--the p response variables are correlated with covariance matrix Σ_p.

This assumption of exchangeability differs from the one used in "case 2" of Press (1980). In that formulation, ϕ, the prior vector of means, involved pq hyperparameters, as compared to p hyperparameters for the mean vector for this model. The prior covariance matrix in the former article (F) involved qp(qp+1)/2 hyperparameters, while the current reference uses Σ_p, a covariance matrix with only p(p+1)/2 distinct elements.

Press and Shigemasu use the same linear model structure as found in Press (1980), and as indicated previously. The prior distribution function for Σ, the covariance matrix of the errors, is now assumed to be inverted Wishart, with the two hyperparameters found in this distribution assumed known.

Contrasts of population mean vectors are still of the following form: $\gamma = C_1\beta^T C_2$. The posterior distribution of γ depends on the information one possesses about the prior mean μ and covariance matrix Σ_p. If both of these terms are known, or if Σ_p is known but μ is not (so that the prior on μ is taken to be proportional to a constant), the posterior distribution of β is asymptotically normal, and tests of hypotheses of γ are easily derived. In the case where μ is known, but Σ_p is not, or the case where both of these quantities are unknown, the posterior distribution of β is not easily evaluated, and tests of hypotheses for γ do not exist.

Press and Shigemasu also examine the Bayesian multivariate model under the assumption that the prior on β is $\text{Normal}_p(\mu, \Sigma/\kappa)$. This prior might be thought of as arising from an imaginary experiment where there were κ observations per treatment group, and, prior to this experiment, information for β was vague. In this case, for a balanced design, the marginal posterior distribution of β is a matrix T distribution. Inferences concerning γ can be made using the results of Theorem 6.2.5 of Press (1982).

Lindley and Smith (1972) derive a posterior distribution of true mean vectors for a three-stage hierarchy of multivariate normal distributions. They let Y (conditional on θ_1) be distributed normal with mean $A_1\theta_1$ and covariance matrix C_1. They further assume that, given θ_2, θ_1 is distributed normal $(A_2\theta_2, C_2)$. A_1, A_2, C_1, and C_2 are assumed to be known positive definite matrices. The posterior distribution of θ_1 given Y is normal with mean Bb and variance B, where $B^{-1} = (A_1^T C^{11} A_1) + C^{21}$ and $b = (A_1^T C_1^{-1} Y) + (C_2^{-1} A_2\theta_2)$. Now if one further assumes that, given θ_3, θ_2~Normal($A_3\theta_3$, C_3), the posterior distribution of θ_1 given A_i, C_i, θ_3 and Y is Normal (Dd, D) with these terms as defined in the reference. The posterior mean of θ_1 is shown to be a weighted average of the least squares estimate $\{(A_1{}^T C_1^{-1} A_1)^{-1} A_1{}^T C_1^{-1} Y\}$ and the prior mean $A_2 \cdot A_3 \cdot \theta_3$.

In most applications, the hyperparameters of the second stage (θ_2 and C_2) are relatively easy to formulate. At the third stage, however, the hyperparameters θ_3 and C_3 are difficult to envision. One can express this in the given three-stage model by assuming the matrix C_3 to be large (or let its inverse equal 0). Interestingly, the usual least squares estimates are derived from the above analysis when second stage knowledge is assumed to be weak, by setting $C_2^{-1}=0$.

The James-Stein estimator of a (1 x p) vector Y [James and Stein (1961)], for p>2, is an empirical Bayes estimator, as can be shown as follows. Let $Y|\theta$ be distributed $\text{Normal}_p(\theta, I_p)$, with θ distributed $\text{Normal}_p(0, \sigma^2 I_p)$ and σ^2 is assumed to be known. The posterior mean for θ given Y is equal to $\{1-(1+\sigma^2)^{-1}\}$ Y. The marginal distribution of Y is easily shown to be $\text{Normal}_p(0, (1+\sigma^2)I_p)$. Therefore, $\Sigma\, Y_i/(1+\sigma^2)$, where Y_i is the i^{th} element of Y, is distributed as a Chi-square distribution with p degrees of freedom, and the expectation of $(p-2)/\Sigma Y_i^2$ equals $(1+\sigma^2)^{-1}$. Substituting $(p-2)/\Sigma Y_i^2$ for $(1+\sigma^2)^{-1}$ in the formula for the posterior mean of θ yields the James-Stein estimator of θ equal to $\{1-(p-2)/\Sigma Y_i^2\} \cdot Y$. Under the assumption of a quadratic loss function, this estimator has uniformly smaller risk than than the maximum likelihood estimator for θ.

In the above formulation, the elements of the p-dimensional vector Y are mutually independent. Efron and Morris (1972) derive the posterior distribution for the case where the p response variables are correlated, and now q independent populations are being analyzed. In their notation, let $\mathbf{Y}_i$ be the (1 x p) vector of responses for the i^{th} population, and $\mathbf{Y}$ the (q x p) matrix of responses with rows $\mathbf{Y}_i$, where $i=1,\ldots,q$. If $f(\mathbf{Y}_i|\boldsymbol{\theta}_i)$ is $\text{Normal}_p(\boldsymbol{\theta}_i,\mathbf{D})$ and $f(\boldsymbol{\theta}_i)$ is $\text{Normal}_p(0,\mathbf{A})$, the posterior distribution for $\boldsymbol{\theta}_i$ given $\mathbf{Y}_i$ is $\text{Normal}_p\ \{(\mathbf{I}_p-\mathbf{B})\cdot\mathbf{Y}_i,\ (\mathbf{I}_p-\mathbf{B})\cdot\mathbf{D}\}$ where $\mathbf{B}$ equals $\mathbf{D}\cdot(\mathbf{A}+\mathbf{D})^{-1}$. Using a quadratic loss function, the posterior mean of $\boldsymbol{\theta}$ has Bayes risk given by $p^{-1}\cdot\text{trace}(\mathbf{I}_p-\mathbf{B})$. Efron and Morris also suggest a different estimator for $\boldsymbol{\theta}_i$ given by the formula $\{\mathbf{I}_p-\ (q-p-1)\mathbf{D}\mathbf{S}^{-1}\}\cdot\mathbf{Y}_i$, where $\mathbf{S}=\mathbf{Y}^T\cdot\mathbf{Y}$. The properties of this estimator are analyzed using the loss function given by formula 4.2 in the reference.

1.3 Research Plan

This research will develop a generalization of Duncan's k-ratio procedure to the case of bivariate responses for two treatment groups. In the following analyses, the data consist of two-dimensional vectors where one of the responses represents a covariate and the other response is the variable of interest. It is this latter variable which will be analyzed in regards to treatment group differences, taking into account the observed value of the treatment differences for the covariate.

The chapter which follows will develop the covariate k-ratio test procedure and present the results of power analyses when all variances and covariances are assumed known. The analyses for this chapter involve a proportionality assumption between the covariance matrices of the prior and conditional distributions.

Subsequently, the research will investigate the power of the covariate k-ratio procedure when covariance matrices are estimated from the observed data. This section will still assume the proportionality assumption of the previous chapter, and will also assume that the constant of proportionality is known. The results from simulations will be used to compare power curves for this case to the power curves derived for the "known variance" case of the previous chapter.

The dissertation will then proceed by relaxing the proportionality assumption on the covariance matrices. This section will generalize the covariate k-ratio test procedure to the situation involving a multi-center investigation of two treatment groups, and estimators of all covariance matrices will be derived. The last part of this chapter will compare the power curves from the results of simulations using these estimated covariance matrices in the analysis to the power curves for the "known variances" case investigated previously.

The final chapter of the dissertation will present the results of analysis of data from the Coordinating Center at U.N.C. It will compare the covariate k-ratio test procedure to several standard statistical methods of analyses. Finally, areas for further research in regards to the covariate k-ratio test procedure will be explored.

II. DERIVATION AND POWER COMPARISONS WHEN VARIANCES KNOWN

2.1 Derivation of Covariate K-Ratio Test

This chapter will generalize the k-ratio procedure described previously to the case of bivariate normal observations with a known covariance matrix. This generalization involves a two-dimensional vector of observed treatment mean differences, denoted by $\mathbf{d}$, and a vector of true treatment mean differences, denoted by $\boldsymbol{\delta}$. Although observations are now looked upon as bivariate, the emphasis here is on testing the significance of one of the treatment mean differences (say the first one, δ_1), given the value of the other treatment mean difference.

Let $\mathbf{X}_{ij}$ be the observed vector for the j^{th} subject in the i^{th} treatment group, where i equals 1 or 2 and j goes from 1 to n_i. The conditional distribution of $\mathbf{X}_{ij}$ given $\boldsymbol{\mu}_i$ is assumed to be bivariate normal, with mean $\boldsymbol{\mu}_i$ and known covariance matrix Σ_x, this matrix being equal for the two treatment groups. The conditional distribution, then, of $\mathbf{d}=\overline{\mathbf{X}}_1-\overline{\mathbf{X}}_2$, given $\boldsymbol{\delta}$, is bivariate normal with mean $\boldsymbol{\delta}=\boldsymbol{\mu}_1-\boldsymbol{\mu}_2$ and covariance matrix Σ_d equal to $\Sigma_x \cdot n^{12}$ where n^{12} equals $(n_1)^{-1} + (n_2)^{-1}$. The prior distributions for the $\boldsymbol{\mu}_i$'s are assumed to be independent bivariate normal with mean $\boldsymbol{\Theta}$ and covariance matrix Σ_μ. Therefore, the prior distribution of $\boldsymbol{\delta}$ is normal with mean 0 and covariance matrix Σ_δ equal to $2 \cdot \Sigma_\mu$.

It is straightforward to show that the joint distribution of $\boldsymbol{\delta}$ and d is multivariate normal with mean vector 0 and a 4-by-4 covariance matrix of the form

$$\Sigma^{\delta d} = \begin{bmatrix} \Sigma_\delta & \Sigma_\delta \\ \Sigma_\delta & \Sigma_+ \end{bmatrix} ,$$

where Σ_+ equals $\Sigma_\delta + \Sigma_d$.

Using Bayes' Rule one can derive the posterior density for δ_1 given δ_2 and d. This posterior density, denote it by h, is normal with mean equal to $\Sigma_{12}^{\delta d} \cdot (\Sigma_{22}^{\delta d})^{-1} \cdot (\delta_2 \quad d_1 \quad d_2)'$, where $\Sigma_{12}^{\delta d}$ is a 1x3 vector of the second through fourth elements of the first row of $\Sigma^{\delta d}$, and $\Sigma_{22}^{\delta d}$ is a 3x3 matrix formed from the lower right section of $\Sigma^{\delta d}$. The variance of the posterior distribution h equals $\Sigma_{11}^{\delta d} - \Sigma_{12}^{\delta d} \cdot (\Sigma_{22}^{\delta d})^{-1} \cdot \Sigma_{21}^{\delta d}$, where $\Sigma_{21}^{\delta d}$ equals $(\Sigma_{12}^{\delta d})'$ and $\Sigma_{11}^{\delta d}$ is the first element of the first row of $\Sigma^{\delta d}$. Denote the mean and variance of the distribution h by $\dot{\delta}_1$ and $\dot{\sigma}_1^2$, respectively.

Using the linear loss function as shown in (1.1), with δ_1 replacing δ_{ij} and δ_0 equal to zero, one can derive the critical region for the covariate k-ratio test of H_0: $\delta_1 \leq 0$ versus H_a: $\delta_1 > 0$ by minimizing the posterior Bayes' risk. That is, if the risk (expected loss) for decision $\ddot{d}_0$ (accepting the null hypothesis) is greater than the risk for decision $\ddot{d}_1$ (rejecting the null hypothesis) one then decides in favor of $\ddot{d}_1$. The critical region, then, is of the form

$$\frac{\int_0^\infty k_0 \cdot \delta_1 \cdot h(\delta_1 | \delta_2, d)\, d\delta_1}{\int_{-\infty}^0 k_1 \cdot (-\delta_1) \cdot h(\delta_1 | \delta_2, d)\, d\delta_1} > 1 ,$$

or, equivalently,

$$\frac{\int_0^{\infty} \delta_1 \cdot h(\delta_1 | \delta_2, d)\; d\delta_1}{\int_{-\infty}^{0} (-\delta_1) \cdot h(\delta_1 | \delta_2, d)\; d\delta_1} > k \qquad (2.1)$$

where h is the posterior density for δ_1 indicated previously and $k=k_1/k_0$ is the loss, or type 1-to-type 2 error seriousness ratio.

The numerator of (2.1) equals

$$\int_0^{\infty} (\delta_1) \cdot \frac{\exp\left\{ -\frac{1}{2} \left[\frac{\delta_1 - \dot{\delta}_1}{\dot{\sigma}_1}\right]^2 \right\}}{\sqrt{2\pi} \cdot \dot{\sigma}_1} \; d\delta_1 \quad .$$

Let x equal $(\delta_1 - \dot{\delta}_1)/\dot{\sigma}_1$. The integral above becomes

$$\int_{-\frac{\dot{\delta}_1}{\dot{\sigma}_1}}^{\infty} \frac{(\dot{\sigma}_1 \cdot x + \dot{\delta}_1)}{\sqrt{2\pi}} \exp\left\{ -\frac{1}{2} x^2 \right\} dx =$$

$$\dot{\sigma}_1 \cdot \left[\int_{-\frac{\dot{\delta}_1}{\dot{\sigma}_1}}^{\infty} \frac{x}{\sqrt{2\pi}} \exp\left\{ -\frac{1}{2} x^2 \right\} dx + \int_{-\frac{\dot{\delta}_1}{\dot{\sigma}_1}}^{\infty} \frac{\dot{\delta}_1}{\dot{\sigma}_1 \cdot \sqrt{2\pi}} \exp\left\{ -\frac{1}{2} x^2 \right\} dx \right]$$

Using the facts that, for the standard normal distribution,

$f(x)=f(-x)$,

$$\frac{d\ f(x)}{dx} = -x\ f(x) \qquad \text{and} \qquad \int_{-x}^{\infty} f(x)\ dx = \int_{-\infty}^{x} f(x)\ dx\ ,$$

the numerator of (2.1) becomes $\dot{\sigma}_1 \cdot \{f(z) + z \cdot F(z)\}$, where f and F are the standard normal density and cumulative distribution functions and z equals $(\dot{\delta}_1/\dot{\sigma}_1)$.

The denominator of (2.1) in a like manner simplifies to $\dot{\sigma}_1 \cdot \{f(-z) - z \cdot f(z)\}$. Taking the ratio of the numerator to the denominator, the critical region for the covariate k-ratio test rule equals the set of all z that satisfy

$$\frac{f(z) + z \cdot F(z)}{f(z) - z \cdot F(-z)} > k\ . \tag{2.2}$$

By looking at its first derivative with respect to z, one can show that the left hand side of (2.2) is a monotonically increasing function. Let one define z(k) so that

$$\frac{f(z(k)) + z(k) \cdot F(z(k))}{f(z(k)) - z(k) \cdot F(-z(k))} = k\ . \tag{2.3}$$

Then it is true that for all z greater than z(k), (2.2) will be satisfied. Therefore, the covariate k-ratio test rule becomes: reject the null hypothesis H_0: $\delta_1 \leq 0$ when $\dot{\delta}_1/\dot{\sigma}_1 > z(k)$, where z(k) is defined in (2.3). This Bayes' rule is of the same form as the corresponding right-tail α-level rule except that it is based on the conditional density for δ_1 given δ_2 and d, and the critical value is a function of the k-ratio value, not of an alpha level.

2.2 Covariate k-Ratio Test With Proportionality Assumption

If one assumes that Σ_X, the covariance matrix of the observations X_{ij} is of the form

$$\sigma^2 \begin{bmatrix} 1 & \rho\sqrt{c_2} \\ \rho\sqrt{c_2} & c_2 \end{bmatrix} \qquad c_2>0,$$

and Σ_μ, the covariance matrix of the true treatment means, equals $c_1 \cdot \Sigma_X$, then h, the posterior density of δ_1 given δ_2, d_1 and d_2 is univariate normal with posterior mean $\dot{\delta}_1$ equal to

$$\left[\, 2\ c_1\ \sigma^2\ \rho\sqrt{c_2} \;\middle|\; 2\ c_1\ \sigma^2 \;\middle|\; 2\ c_1\ \sigma^2\ \rho\sqrt{c_2} \,\right] \cdot$$

$$\left[\begin{array}{c|c|c} 2\ c_1\ c_2\ \sigma^2 & 2\ c_1\ \sigma^2\ \rho\sqrt{c_2} & 2\ c_1\ c_2\ \sigma^2 \\ 2\ c_1\ \sigma^2\ \rho\sqrt{c_2} & n_c\ \sigma^2 & n_c\ \sigma^2\ \rho\sqrt{c_2} \\ 2\ c_1\ c_2\ \sigma^2 & n_c\ \sigma^2\ \rho\sqrt{c_2} & n_c\ c_2\ \sigma^2 \end{array}\right]^{-1} \cdot$$

$$(\ \delta_2 \mid d_1 \mid d_2\ )' ,$$

where n_c equals $n^{12} + 2 \cdot c_1$ and n^{12} equals $(n_1)^{-1} + (n_2)^{-1}$.

With the above inverse matrix, denoted by $(\Sigma_{22}^{\delta d})^{-1}$ in the general case, equal to

$$\left[\begin{array}{c|c|c} n_c^2\ (1-\rho^2) & 0 & -2\ c_1\ n_c\ (1-\rho^2) \\ 0 & 2\ c_1\ c_2\ n^{12} & -2\ c_1\ n^{12}\ \rho\sqrt{c_2} \\ -2\ c_1\ n_c\ (1-\rho^2) & -2\ c_1\ n^{12}\ \rho\sqrt{c_2} & 2\ c_1\ (n_c - 2\ c_1\ \rho^2) \end{array}\right] \cdot$$

$$\{\ 2\ c_1\ c_2\ n_c\ n^{12}\ (1-\rho^2)\ \sigma^2\ \}^{-1} ,$$

the expression for $\dot{\delta}_1$ simplifies to

$$\frac{n_c\ \rho\ \sqrt{c_2}\ \ \dot{\delta}_2\ +\ 2\ c_1\ c_2\ d_1\ -\ 2\ c_1\ \rho\ \sqrt{c_2}\ \ d_2}{c_2\ n_c}\ .$$

The variance of the posterior distribution h under the above assumptions equals

$$2\ c_1\ \sigma^2\ -\ \left[\ 2\ c_1\ \sigma^2\ \rho\ \sqrt{c_2}\ \mid\ 2\ c_1\ \sigma^2\ \mid\ 2\ c_1\ \sigma^2\ \rho\ \sqrt{c_2}\ \right]\cdot (\Sigma^{\delta d}_{22})^{-1}\ \cdot \left[\ 2\ c_1\ \sigma^2\ \rho\ \sqrt{c_2}\ \mid\ 2\ c_1\ \sigma^2\ \mid\ 2\ c_1\ \sigma^2\ \rho\ \sqrt{c_2}\ \right]'$$

This simplifies to $2\ c_1\ n^{12}\ (1-\rho^2)\ \sigma^2\ /\ n_c$, and is, again, denoted by $\dot{\sigma}_1^2$.

2.3 Power of Procedure with Proportionality Assumption

It is straightforward to derive the power of the above test procedure under repeated sampling assumptions. The expectation of the posterior mean $\dot{\delta}_1$, given $\boldsymbol{\delta}=\boldsymbol{\delta}_a$, $\boldsymbol{\delta}_a>0$, is equal to

$$\frac{n^{12}\ \rho\ \sqrt{c_2}\ \delta_{2a}\ +\ 2\ c_1\ c_2\ \delta_{1a}}{n_c\ c_2}\ . \qquad (2.4)$$

The repeated sampling variance of $\dot{\delta}_1$ equals $\{4\ n^{12}\ c_1{}^2\ (1-\rho^2)\ \sigma^2\}\ /\ n_c{}^2$, where, again, $n^{12}=(n_1)^{-1}+(n_2)^{-1}$ and $n_c= 2\cdot c_1\ +\ n^{12}$.

Using the above results and letting $\dot{\delta}_p$ denote the expectation of the posterior mean $\dot{\delta}_1$ given by (2.4), and letting $\dot{\sigma}_p^2$ denote the variance of $\dot{\delta}_1$, the power of the covariate k-ratio test procedure is given by

$$\Pr\left\{\mathbb{Z} > \frac{z(k)\ \dot{\sigma}_1 - \dot{\delta}_p}{\dot{\sigma}_p}\right\}$$

where $\mathbb{Z}$ is a random variable with distribution equal to the standard normal density. In the following section, this power function will be compared to the power function of Duncan's k-ratio test, for several values of c_1, c_2, ρ and $\boldsymbol{\delta}_a$.

2.4 Power Comparisons when Variances Assumed Known

In order to compare the power functions of Duncan's and the covariate k-ratio tests under the assumption of known variances, one must specify values for k, σ^2, c_1, c_2, ρ and $\boldsymbol{\delta}_a$, where $\boldsymbol{\delta}_a>0$ is the $\boldsymbol{\delta}$ vector for the alternative hypothesis of interest. Without any loss of generality, one can assume that σ^2 equals one. The constant c_1, the constant of proportionality between the covariance matrices Σ_x and Σ_μ, must be greater than zero. Likewise the constant c_2, the multiplicative factor for the variance of the second variable compared to the first variable, must also be greater than zero. Determination of k is based on the observation that choices of k equal to 50, 100 and 500 are roughly the equivalent of α equal to 0.1, 0.5 and 0.01 in a two-sample two-tailed α-level rule. For this research, k will equal one hundred with the resulting z(k) of (2.3) equal to 1.721.

Power curves for c_1 and c_2 equal to 0.1, 1 or 10 and δ_{2a} equal to 0 or 2 are found in Appendices 2.1 through 2.18. The "ID" variable equals "K" for Duncan's k-ratio test, equals "5C" for the covariate k-ratio test with ρ equal to 0.5 and equals "9C" for the covariate k-ratio test with ρ equal to 0.9. The power curves reflect calculations when the sample sizes are 50 in both of the treatment groups. Table 2.1

summarizes the results of power comparisons looking at these graphs as functions of δ_{2a}, c_1 or c_2.

As one can see by examination of the graphs of power functions, the covariate k-ratio test exhibits consistently higher power than Duncan's k-ratio test when ρ is greater than zero. When ρ is equal to zero, the power of the covariate k-ratio procedure is equal to the power for Duncan's k-ratio procedure, as one would expect. As indicated in Figure 2.1, the power of the covariate test procedure increases as ρ, the correlation between the two variables increases from zero to one. Therefore the greater the degree of association between the two variables of interest, the greater the gain in power one achieves by using the covariate, instead of Duncan's, k-ratio test.

As shown in Table 2.1, looking at the graphs as functions of δ_{2a}, the alternative value for the second variable, with c_1 and c_2 fixed, one can see that for c_1=10 and c_2 equal to 1 or 10, there is no gain in power as δ_{2a} goes from 0 to 2. There is a slight increase in power as δ_{2a} increases when c_1 equals 10 and c_2 equals 0.1. For c_1=1, an increase in power is seen as δ_{2a} goes from 0 to 2. This increase is greater for smaller c_2 values, the power difference being negligible for c_2 equal to 10, slight for c_2 equal to 1 and appreciable when c_2 equals 0.1. For c_1 equal to 0.1 there is a great increase in power as δ_{2a} increases. Again this change in power is of a greater magnitude the smaller the value of c_2.

One can conclude from the above that if one's information on the true treatment mean is very precise ($c_1<1$), or if the variance of the second variable is relatively small compared to the variance of the variable under investigation ($c_2<1$), then the value of the nuisance

TABLE 2.1

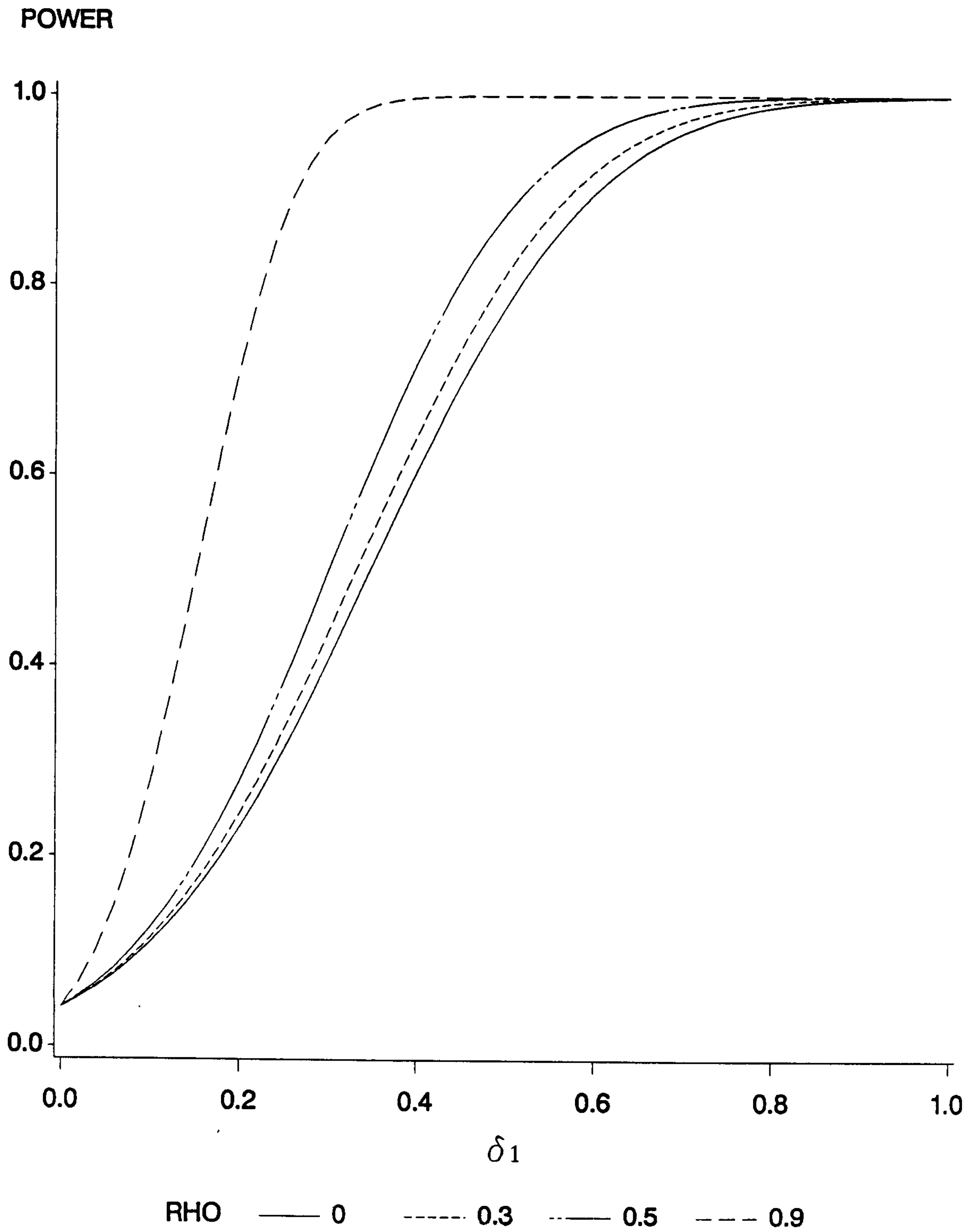
SUMMARY OF POWER COMPARISONS

Values of Other Parameters	Variable Changing (values)	Resulting Change in Power
$c_1=0.1$ $c_2=0.1$	δ_{2a}	Large increase
$c_1=0.1$ $c_2=1$		" "
$c_1=0.1$ $c_2=10$	(0 to 2)	" "
$c_1=1$ $c_2=0.1$		Large increase, but smaller increase than when $c_1=c_2=0.1$
$c_1=1$ $c_2=1$		Slight increase
$c_1=1$ $c_2=10$		Slight increase
$c_1=10$ $c_2=0.1$		Very slight increase
$c_1=10$ $c_2=1$		No change
$c_1=10$ $c_2=10$		No change
$\delta_{2a}=0$ $c_2=0.1$	c_1	Slight increase as $c_1 \to 1$, then no change
$\delta_{2a}=0$ $c_2=1$	(0.1 to 1 to 10)	" "
$\delta_{2a}=0$ $c_2=10$		" "
$\delta_{2a}=2$ $c_2=0.1$		Large decrease
$\delta_{2a}=2$ $c_2=1$		Large decrease, less than when $\delta_{2a}=2$ & $c_2=0.1$
$\delta_{2a}=2$ $c_2=10$		Large decrease, less than when $\delta_{2a}=2$ & $c_2=1$
$\delta_{2a}=0$ $c_1=0.1$	c_2	No change
$\delta_{2a}=0$ $c_1=1$		" "
$\delta_{2a}=0$ $c_1=10$	(0.1 to 1 to 10)	" "
$\delta_{2a}=2$ $c_1=0.1$		Large decrease
$\delta_{2a}=2$ $c_1=1$		Large decrease, less than when $\delta_{2a}=2$ & $c_1=0.1$
$\delta_{2a}=2$ $c_1=10$		Large decrease, less than when $\delta_{2a}=2$ & $c_1=1$

FIGURE 2.1

POWER CURVES FOR DIFFERING RHO VALUES

$C_1=1 \quad C_2=1 \quad \delta_2=0 \quad n=50$



parameter δ_{2a} affects the power of the covariate k-ratio test. If, however, one's information for the prior mean vector is diffuse, meaning its variance is equal to or much greater than the variance for the vectors of observations, and the variance of the second variable is at least as large as the variance of the first variable, then the value of δ_{2a} does not greatly influence the power of the covariate k-ratio test.

Now examining the results of power comparisons as functions of c_2, in all cases where $\delta_{2a}=0$ there is no apparent difference in the power functions as c_2 goes from 0.1 to 1 to 10, as indicated in Table 2.1. When $\delta_{2a}=2$, the greatest change in power for different c_2 values is seen when c_1 is small. Comparing the three graphs (for $c_2=0.1$, $c_2=1$ and $c_2=10$) in the case where $c_1=0.1$ and $\delta_{2a}=2$ indicates a very large decrease in power as c_2 increases. When $c_1=1$ this decrease is large, but of a smaller magnitude, and when $c_1=10$ it is slight.

What the above paragraph implies is that if one believes that the true treatment mean difference on the second variable (the one not under investigation) is small, the value of c_2 does not greatly influence the power of the covariate k-ratio test. If, however, one believes that the true treatment difference on the second variable is large <u>and</u> that the variance of the prior distribution is comparatively small ($c_1<1$), the value of c_2 can have a large impact on the power of the covariate k-ratio test procedure.

The graphs indicate a more-complicated situation as c_1 varies. When $\delta_{2a}=0$, as c_1 goes from 0.1 to 1 there is a slight increase in power. As c_1 goes from 1 to 10, however, there is no change in power. When $\delta_{2a}=2$, as c_1 goes from 0.1 to 1 the power decreases significantly. When c_1 changes from 1 to 10 (with $\delta_{2a}=2$, still), there is a further, albeit slight, decrease in power. This means that if one believes that δ_{2a} is small then the value of c_1 does not greatly influence the power of the covariate k-ratio test.

2.5 Summary of Power Curve Comparisons

Generalizing from all of the above, the power function for the proposed covariate k-ratio test procedure is consistently superior to the power function for Duncan's k-ratio test procedure. The power function changes only slightly for differing values of the nuisance parameters c_1, c_2, and δ_2. The exception to this statement is when either c_1 or c_2 is small and δ_2 is large. In this case, the extreme precision of the true $\boldsymbol{\delta}$ values, along with a large δ_2 value and the positive correlation between δ_1 and δ_2, will lead to large probablities of rejecting the null hypothesis H_0: $\delta_1 \leq 0$. However, when δ_2 is believed to be near zero and the variances of the $\boldsymbol{\mu}_i$'s are at least as large as the variances for the observations, the power function for the covariate k-ratio test is robust against choices for the nuisance parameters. This situation would typically occur in a controlled clinical trial when δ_2 is a baseline covariate and the prior distribution of the $\boldsymbol{\mu}_i$'s is assumed diffuse.

III. EMPIRICAL BAYES RESULTS WHEN VARIANCES ESTIMATED, c_1 KNOWN.

3.1 Assumptions

This chapter compares the power functions for the covariate k-ratio test procedure when variances are assumed known to the power functions when variance terms are unknown, and estimated from the data. This will enable one to determine the necessary sample size in order to achieve a comparable degree of power for the known versus unknown variance situations. The constant of proportionality c_1, defined in the previous chapter via the assumption $\Sigma_\mu = c_1 \cdot \Sigma_X$ is assumed known. The difference between the true treatment means for the variable not under investigation, δ_2, is assumed to have a value of zero. This assumption is a reasonable one in the context of a randomized clinical trial where δ_2 is the expected difference between the two treatment groups on a covariate measured at baseline, or pre-treatment. Additionally, using the conclusions of Chapter 2, when c_1 is large, the value of δ_2 does not greatly affect the power of the covariate k-ratio test procedure. Therefore, in a situation where one's information on the true treatment means is diffuse relative to the observations, this assumption regarding δ_2 will not affect the power of the covariate k-ratio procedure. This chapter assumes equal sample sizes for the two treatment groups, and, again without any loss of generality, σ^2 is set equal to one.

3.2 Statistical Considerations

This chapter of the dissertation uses an "empirical Bayes" approach in order to solve the problem of unknown variance terms. By this is meant that the observed data are used to estimate unknown terms in the prior distribution (called hyperparameters), as well as terms in the posterior distribution. In this application, the elements of Σ_μ form the set of hyperparameters.

The use of empirical Bayes methods often provides estimators that are admissible when the loss function is unbounded [Press (1989)]. In addition, these estimators often have risk less than that of maximum likelihood estimates. However, empirical Bayes procedures violate pure Bayesian philosophy in that the prior distribution now depends on the observed data. The assumptions of conditional probability upon which Bayes' theorem is based, then, are violated. Empirical Bayes estimators can best be viewed as approximate Bayes estimators.

For the analyses of this chapter, the observed pooled-sample covariance matrix is used as an estimator of Σ_X, and, through the proportionality assumption, an estimator of Σ_μ/c_1. The estimated covariance matrices, substituted into the formulae for the posterior mean and variance of $h(\delta_1|d, \delta_2)$, result in an empirical Bayes test procedure. The following paragraphs delineate the statistical foundations for this procedure.

The estimated covariance matrix, $\hat{\Sigma}_X$ converges in probability to Σ_X. Using a multivariate extension of A.14.6 of Bickel and Doksum (1977), for any function g, where g is continuous at Σ_X, $g(\hat{\Sigma}_X)$ converges in probability to $g(\Sigma_X)$. Therefore, substituting $\hat{\Sigma}_d=2\cdot\hat{\Sigma}_X/n$ and $\hat{\Sigma}_\delta=2\cdot c_1\cdot\hat{\Sigma}_X$ into the formula for the posterior variance $\dot{\sigma}_1^2$ results in an estimator that converges in probability to the true value of $\dot{\sigma}_1^2$. Likewise, substituting the estimated covariance matrices into the formula for the posterior mean $\dot{\delta}_1$ results in an estimator that converges in probability to $\dot{\delta}_1$. Using the above observations, along with Slutsky's theorem, it is straightforward to show that the estimated critical value for the empirical covariate k-ratio procedure (using the estimated covariance matrices $\hat{\Sigma}_d$ and $\hat{\Sigma}_\delta$) converges in probability to its true value $\dot{\delta}_1/\dot{\sigma}_1$. Therefore, asymptotically (as the sample size in each treatment group gets large), the empirical Bayes procedure will possess the same distributional characteristics as the procedure using known variances, and is a reasonable one to investigate.

3.3 Description of Computer Program

Appendix 3.1 lists the computer program that performs the simulations used in this chapter. Since the program is well-documented with comments, only a brief description is given here.

For each c_1, c_2, and ρ combination and δ_1 values of 0, 0.2, 0.4, 0.6, 0.8, and 1, the program performs covariate k-ratio test procedures 250 times via simulation of normal data. Each time, the test procedure is assigned a score of one if H_0: $\delta_1 \leq 0$ is rejected and a score of zero if H_0 is accepted. The average of the 250 scores, then, is an estimate of the power for the covariate k-ratio procedure.

Each simulation involves generation of a bivariate normal vector $\boldsymbol{\mu}_2$ representing a realization of the value for the true treatment mean for treatment group 2. The value for the true treatment mean for the first treatment group is set equal to $\boldsymbol{\mu}_2 + \boldsymbol{\delta}$, where $\boldsymbol{\delta}$ equals $(\delta_1 \ 0)$ and δ_1 is fixed at one of the values given above. This formulation of the $\boldsymbol{\mu}_i$

values insures that $\mu_1 - \mu_2$ is identically equal to the desired δ. The mean and covariance matrix from the prior distribution for the μ_i's (θ and Σ_μ) are used for the generation of μ_2, where Σ_μ is of the form

$$c_1 \begin{bmatrix} 1 & \rho\sqrt{c_2} \\ \rho\sqrt{c_2} & c_2 \end{bmatrix}.$$

Section 3.4 addresses issues concerning the choice of values for θ.

Each μ_i value leads to generation of samples of bivariate normal data with mean μ_i and covariance matrix Σ_x equal to Σ_μ divided by c_1. These data are used to derive a pooled sample covariance matrix $\hat{\Sigma}_x$ equal to the sum of the sums-of-squares and cross products matrices for the two treatment groups divided by 2n-2, where n equals the sample size in each treatment group. Substitution of $\hat{\Sigma}_x$ and of $\hat{\Sigma}_\mu$ equal to $c_1 \cdot \hat{\Sigma}_x$ into the formula for the covariate k-ratio test statistic results in an empirical Bayes covariate k-ratio test procedure. This test procedure is assigned a 0 - 1 score as described above and the simulation is repeated a total of 250 times for each c_1, c_2, ρ and δ_1 combination.

3.4 Issues Regarding Choice of θ

The mean for the prior distribution of the μ_i's, denoted by θ, is a nuisance parameter in the simulation described above. Each simulation involves generation of a bivariate normal μ_2 vector with mean θ. The observed μ_2, along with μ_1 equal to $\mu_2 + \delta$, is then used to generate two sets of bivariate normal observations with means μ_i and covariance matrices Σ_x. The distribution for the observed vector of treatment mean differences, d, is, then, bivariate normal with mean $\boldsymbol{\delta}$ and covariance matrix Σ_d equal to $2 \cdot \Sigma_x / n$. The vector $\boldsymbol{\delta}$ is fixed in the simulations by the choice of δ_1, and is therefore independent of $\boldsymbol{\Theta}$. That is, although the location of the observations obviously depends on $\boldsymbol{\Theta}$, the expected value of the treatment mean differences does not. Likewise, the matrix Σ_x is independent of $\boldsymbol{\Theta}$, since it only involves the constants c_2 and ρ. Since the "empirical Bayes" covariate k-ratio test statistic is a function of the observed vector d and the estimated Σ_x matrix, the only remaining issue concerning $\boldsymbol{\Theta}$ is as follows: Does the location of the mean vector $\boldsymbol{\Theta}$ affect the estimation of the covariance matrix Σ_x? Since the answer to this is a negative one, the choice of $\boldsymbol{\Theta}$ should not affect the power function for the covariate k-ratio test procedure.

Additional simulations were performed using several $\boldsymbol{\Theta}$ values in order to substantiate this conclusion. These simulations involved comparisons for $\boldsymbol{\Theta}$ values of 0, 0.5, 1, 10, 100, and 1000. For these simulations, the sample size in each group was equal to 25. Additionally, c_1 and c_2 each assumed the value of one. Figures 3.1 through 3.6 present the resulting power curve comparisons while Table 3.1 summarizes the results.

Examination of the figures and table does not indicate any appreciable differences in the power curves for differing values of $\boldsymbol{\Theta}$. The simulations for ρ equal to zero result in the greatest observed power curve differences, although they still are of a magnitude that could be expected due to the variability found in different simulated data sets. As indicated in Table 3.1, there are no systematic power function departures as functions of increasing $\boldsymbol{\Theta}$. If $\boldsymbol{\Theta}$ influences the power function for the covariate k-ratio test, one would expect a

FIGURE 3.1

POWER CURVE COMPARISONS FOR DIFFERENT Θ VALUES
$C_1=1 \quad C_2=1 \quad n=25 \quad \rho=0$

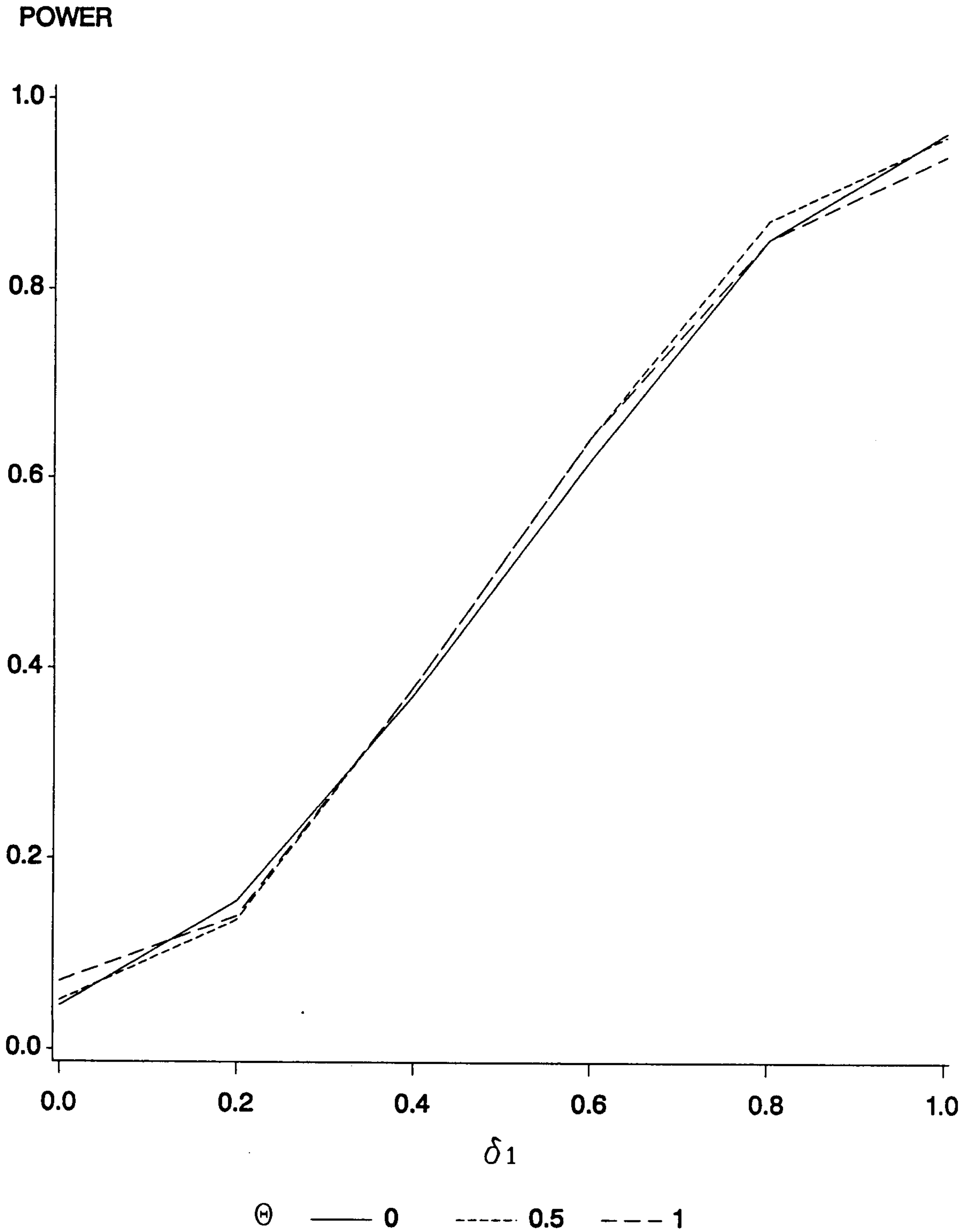


FIGURE 3.2

POWER CURVE COMPARISONS FOR DIFFERENT Θ VALUES
$C_1=1$ $C_2=1$ $n=25$ $\rho=0$

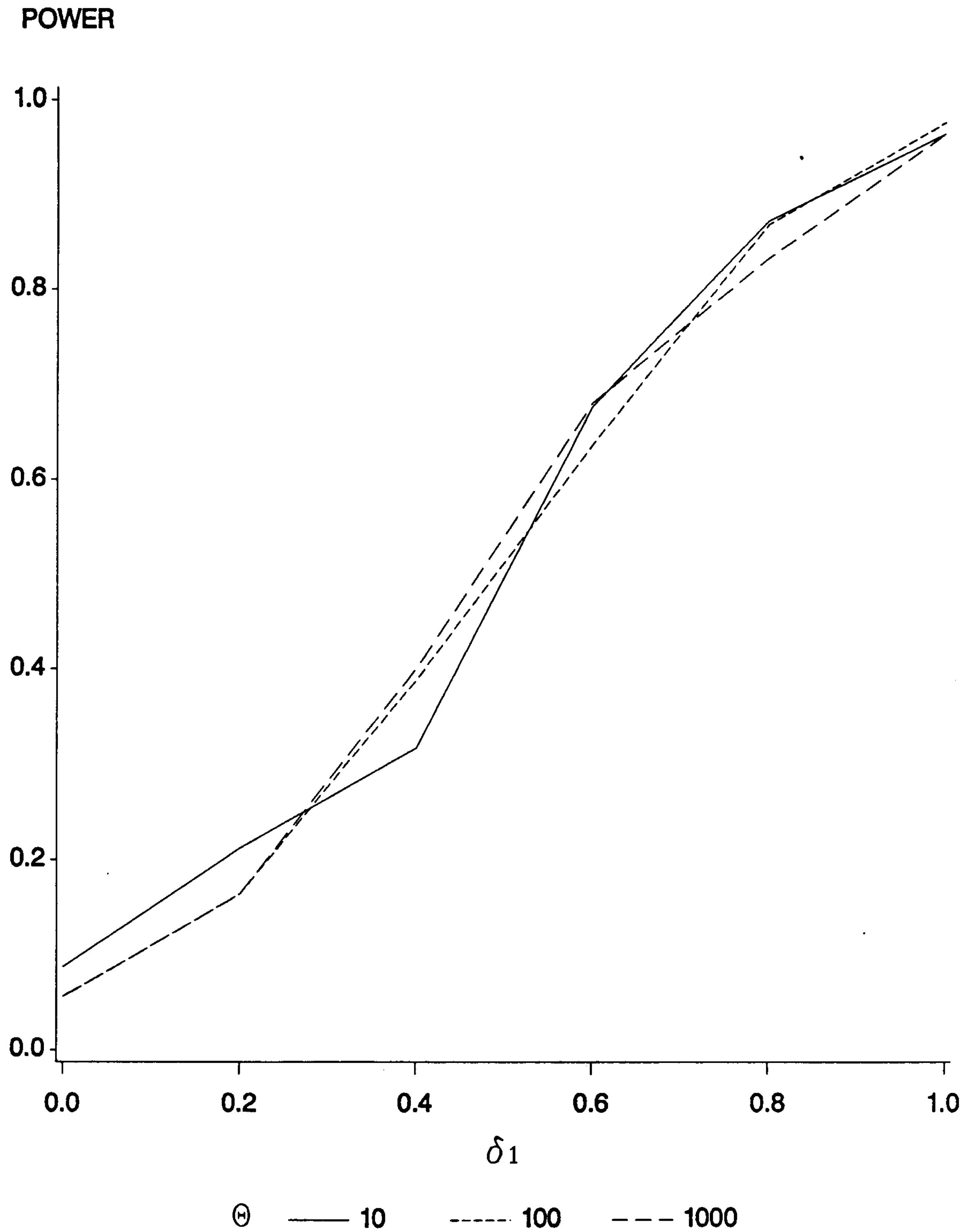


FIGURE 3.3

POWER CURVE COMPARISONS FOR DIFFERENT Θ VALUES

$C_1=1$ $C_2=1$ $n=25$ $\rho=0.5$

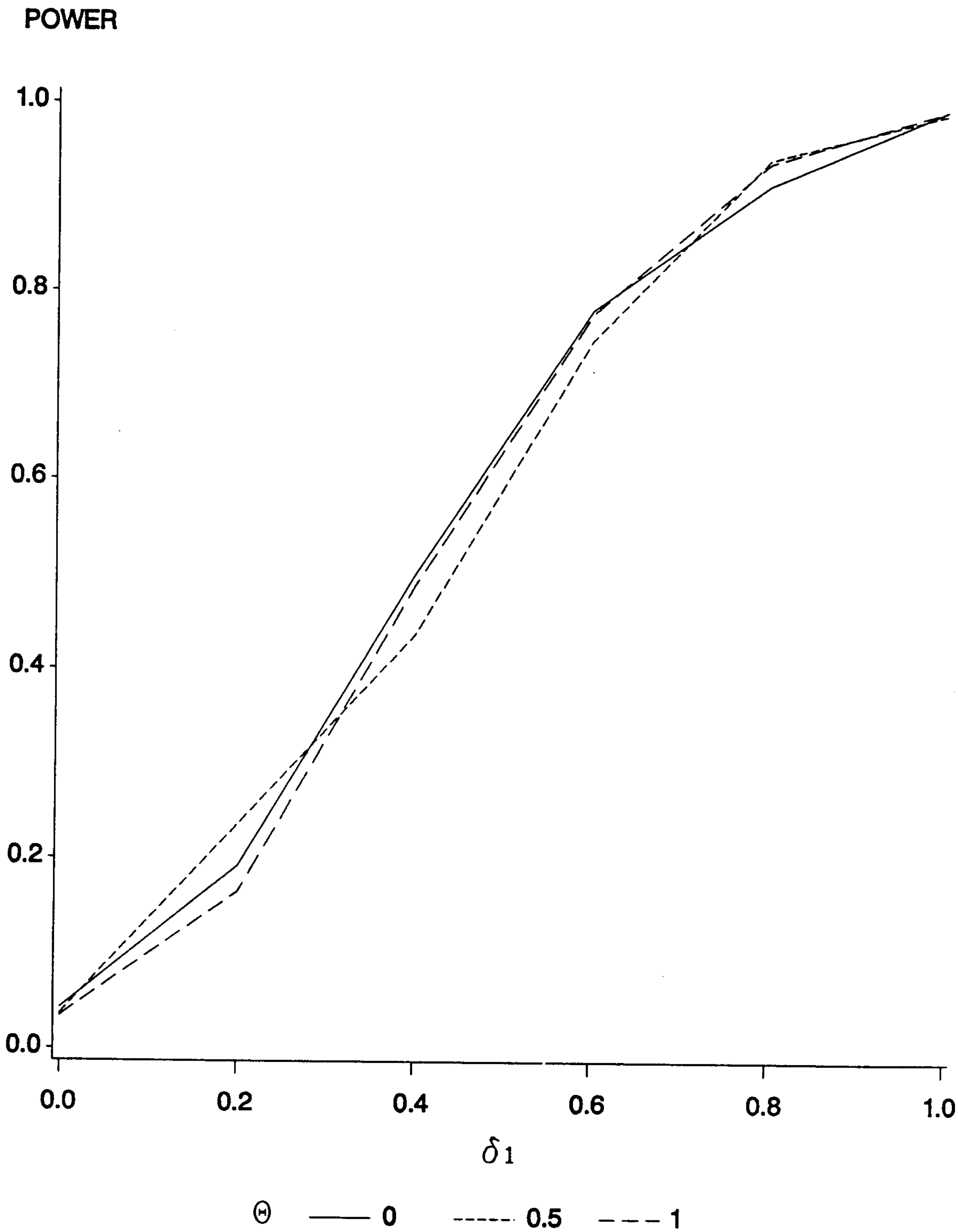


FIGURE 3.4

POWER CURVE COMPARISONS FOR DIFFERENT Θ VALUES

$C_1=1 \quad C_2=1 \quad n=25 \quad \rho=0.5$

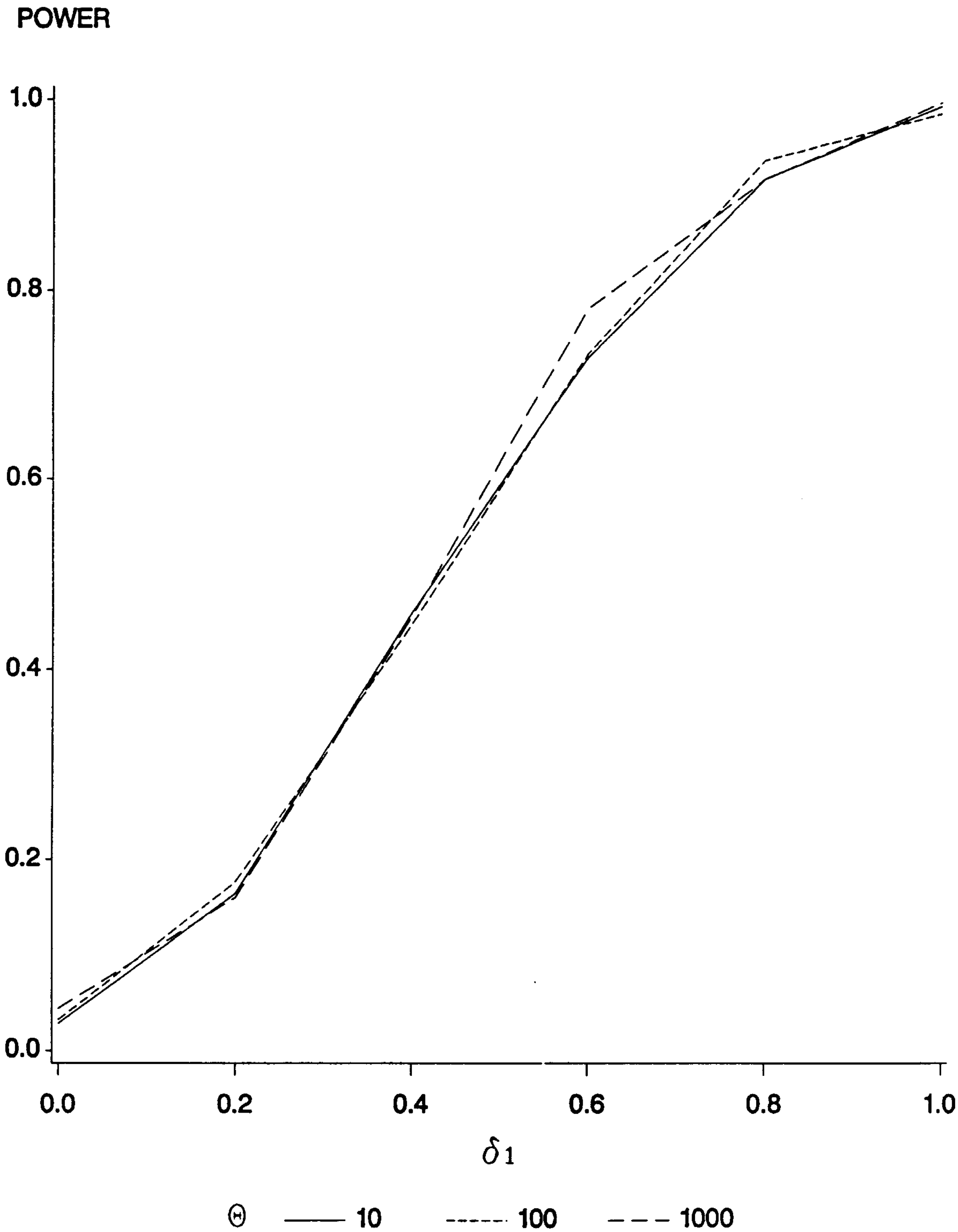


FIGURE 3.5

POWER CURVE COMPARISONS FOR DIFFERENT Θ VALUES
$C_1=1 \quad C_2=1 \quad n=25 \quad \rho=0.9$

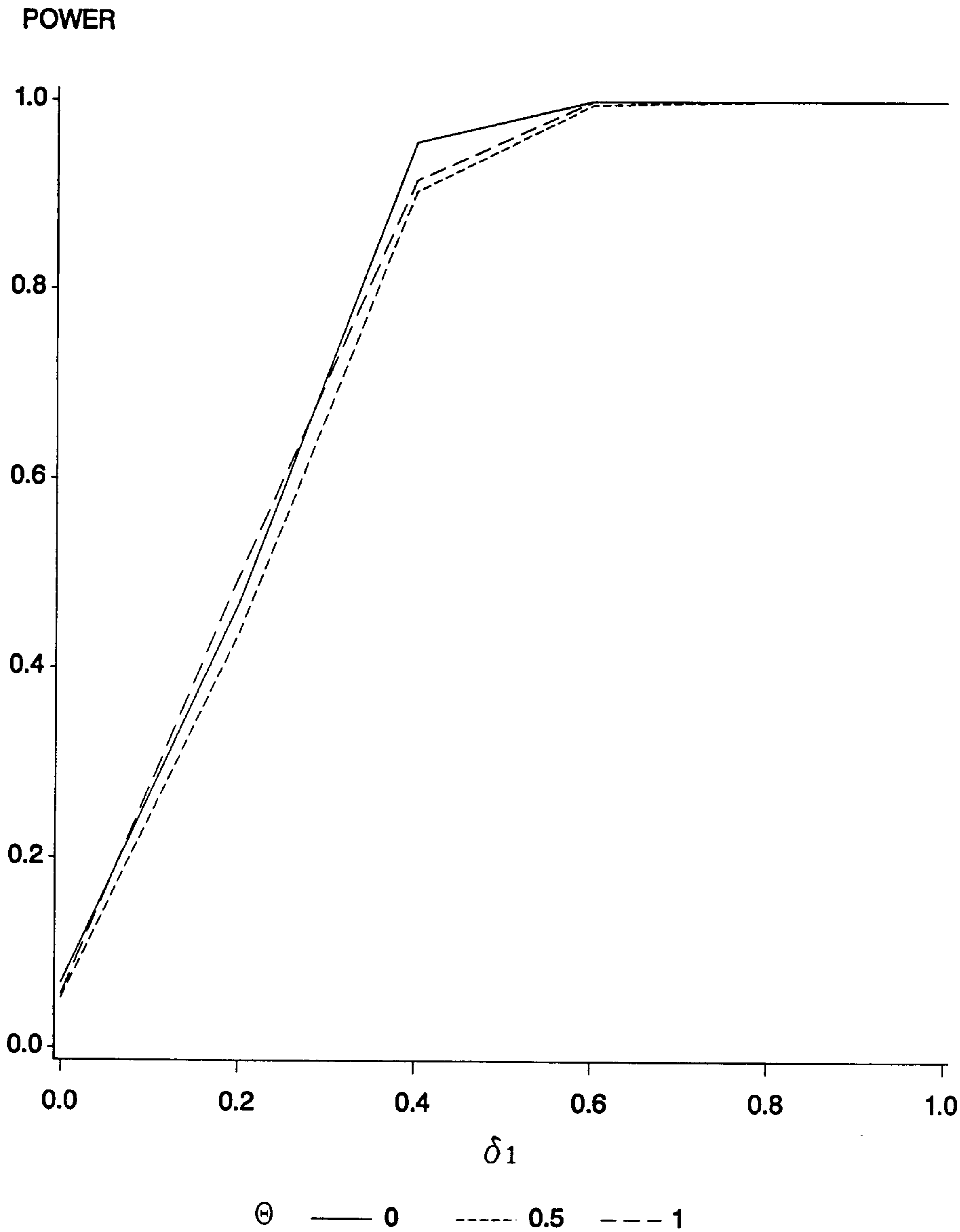


FIGURE 3.6

POWER CURVE COMPARISONS FOR DIFFERENT Θ VALUES

$C_1=1 \quad C_2=1 \quad n=25 \quad \rho=0.9$

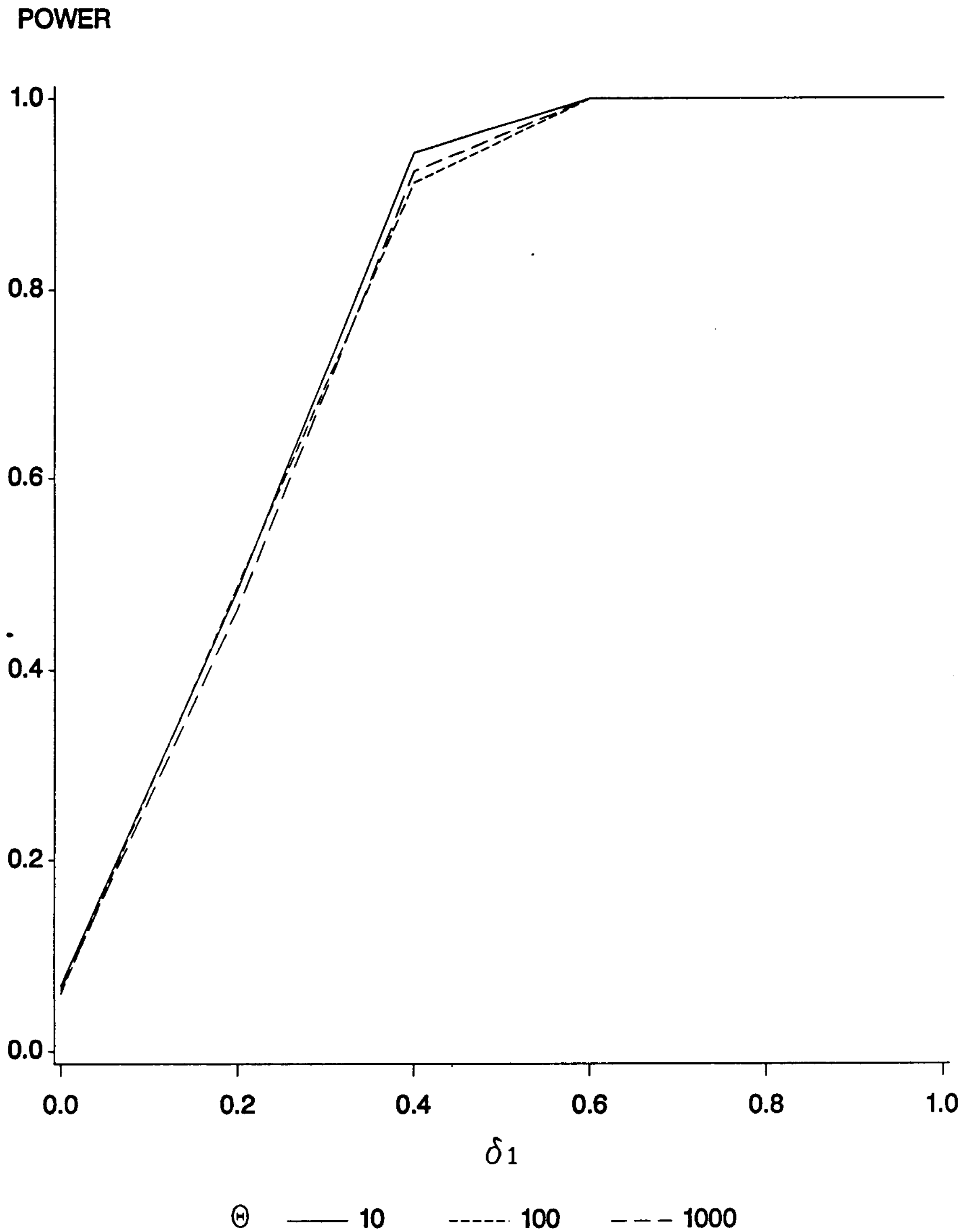


TABLE 3.1

POWER COMPARISONS FOR DIFFERING Θ VALUES

	Θ					
	0	0.5	1	10	100	1000
Rho=0						
δ_1=0	0.046	0.052	0.072	0.088	0.056	0.056
δ_1=0.4	0.372	0.380	0.380	0.316	0.388	0.400
δ_1=0.8	0.852	0.872	0.852	0.872	0.868	0.832
Rho=0.5						
δ_1=0	0.042	0.036	0.034	0.028	0.032	0.044
δ_1=0.4	0.500	0.436	0.488	0.460	0.448	0.456
δ_1=0.8	0.912	0.940	0.936	0.916	0.936	0.916
Rho=0.9						
δ_1=0	0.068	0.052	0.056	0.068	0.060	0.064
δ_1=0.4	0.956	0.904	0.916	0.944	0.912	0.962
δ_1=0.8	1.000	1.000	1.000	1.000	1.000	1.000

consistent change in power across different values of ρ and δ_1 as $\mathbf{\Theta}$ increases. The simulated data do not support this conclusion. Therefore, it is a reasonable to assume that the choice of $\mathbf{\Theta}$ does not influence the power of the covariate k-ratio procedure. The vector $\mathbf{\Theta}$ will therefore be assumed equal to 0 for all simulation analyses.

3.5 Results of Simulations

There are several sources of variability in the empirical Bayes covariate k-ratio test procedure. One of these sources is due to the variability found in the estimation of the k-ratio test statistic, while another source is the variability due to the simulation of numerous different sets of observations. Whereas increasing the sample size for each treatment group will decrease the first source of variability, it will not affect the latter. Therefore, there always will exist differences between the procedure when variances are assumed known and the empirical Bayes covariate k-ratio test procedure when all variance terms but c_1 are estimated from the data.

Figures 3.7 through 3.9 present power functions for $c_1=c_2=1$ for sample sizes of 15, 25 and 50, respectively. In each figure, "emp*i*" reflects the power curve for the empirical Bayes procedure and "known*i*" reflects the power curve for the known variance case for rho equal to 0.*i*. Power curves for other values of c_1 and c_2 are found in Appendices 3.2 through 3.10.

Figure 3.7 indicates that, in regards to power, and for as small a sample size as 15 per treatment group, the empirical Bayes covariate k-ratio test procedure results in a very close approximation to the true covariate k-ratio procedure. This is especially true for $\rho=0.9$.

FIGURE 3.7

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

$C_1=1 \quad C_2=1 \quad \delta_2=0 \quad n=15$

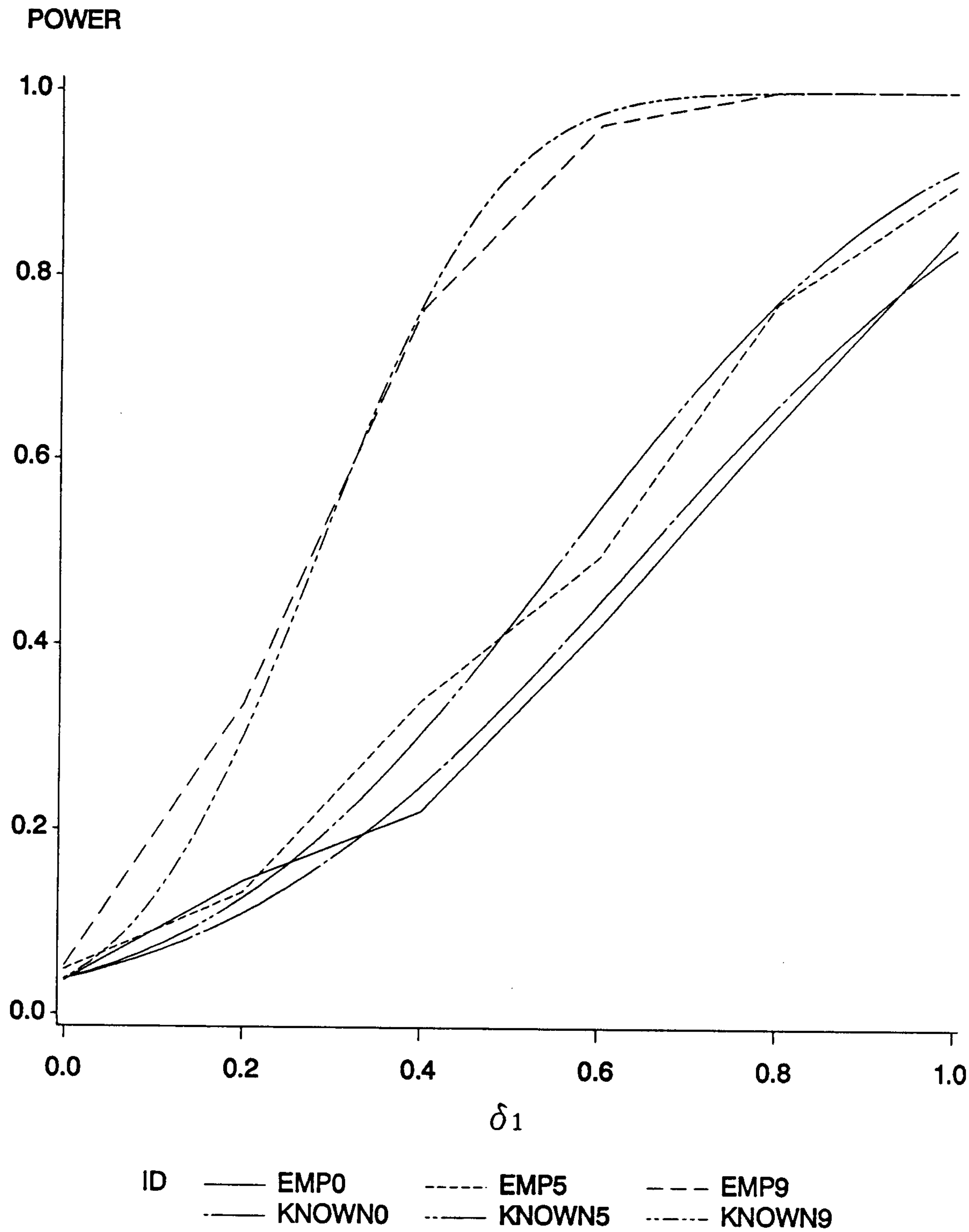


FIGURE 3.8

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

$C_1=1 \quad C_2=1 \quad \delta_2=0 \quad n=25$

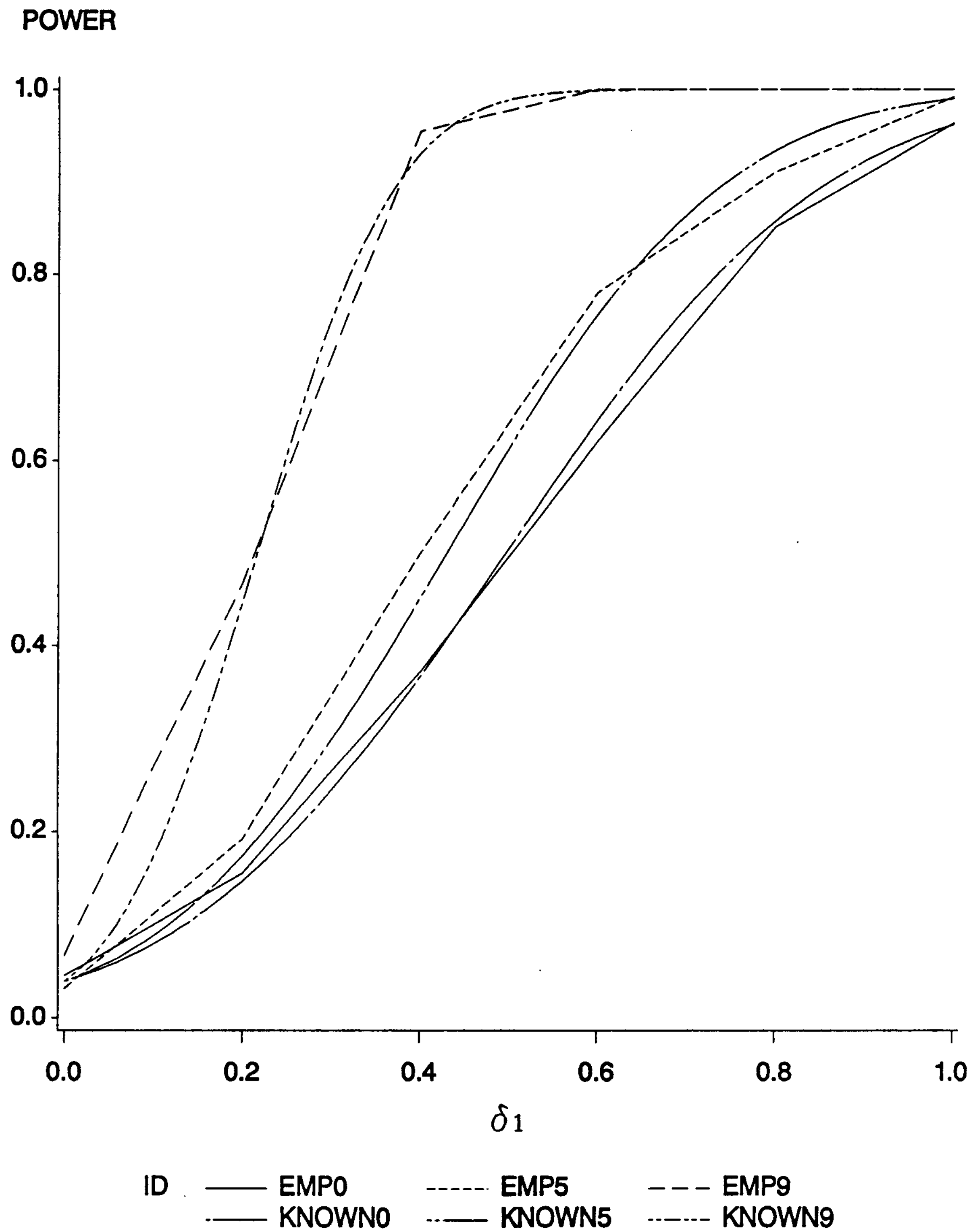
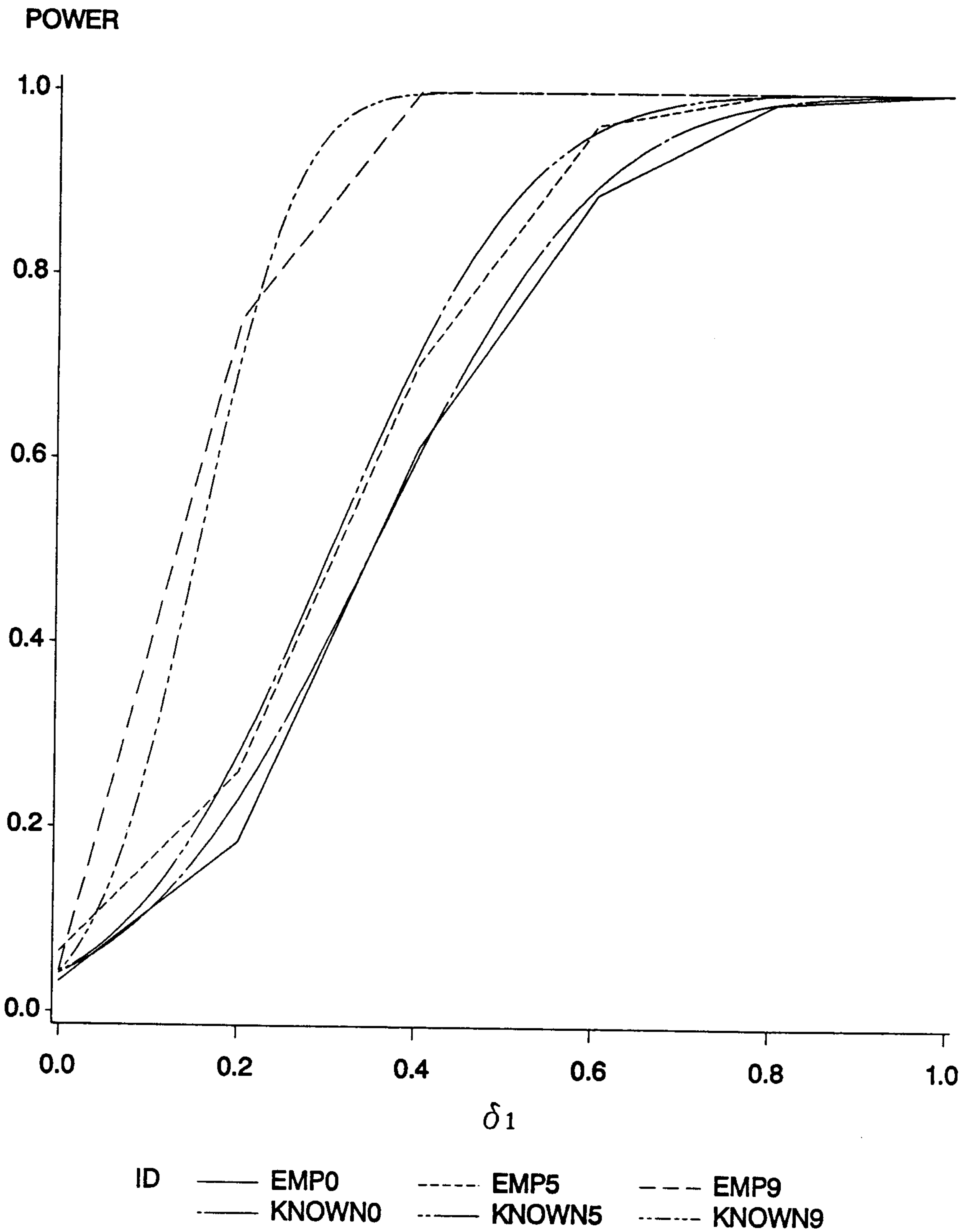


FIGURE 3.9

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

$C_1=1 \quad C_2=1 \quad \delta_2=0 \quad n=50$



Therefore, if one knows that the correlation between the two variables is large, a covariate k-ratio test procedure using estimated variance terms with a sample size as small as 15 per group can achieve roughly the same power as if these variance terms are known.

Figure 3.8, using a sample size of 25 per group, shows an even closer agreement between the true and simulated power curves. For this sample size, the power approximation from the simulated data is very good for all investigated rho values.

Figure 3.9 shows power curve comparisons for sample sizes of 50 per group. The simulated power curves again closely approximate the true power curves for all rho values. As expected, the curves are closer for this sample size than for n=25. However, the gain seen in the power approximation as the sample size increases from 25 to 50 is slight.

The power curves found in Appendices 3.2 through 3.25 substantiate the above observations for all analyzed values of c_1 and c_2. In all cases, at sample sizes of 15 per treatment group, the empirical Bayes covariate k-ratio procedure very closely approximates the covariate k-ratio procedure when variances are known for ρ=0.9, with an inferior approximation for smaller rho values. Using sample sizes of 25 per group results in close approximations for all rho values. Sample sizes of 50 per group do not lead to any greater degree of agreement than for n equal to 25. At sample sizes of 25 per treatment group, then, the variability in the simulated procedure that is due to the estimation of the covariance matrix for the observations is already greatly reduced, with the result that the simulated power curve closely approximates the power curve when variances are assumed known.

IV. EMPIRICAL BAYES RESULTS, c_1 UNKNOWN

4.1 Assumptions

This chapter will present the results of power calculations for the covariate k-ratio test procedure when all covariance matrices are estimated from the observations. The previous chapter used the pooled sample covariance matrix as an estimate of Σ_X, then proceeded to estimate Σ_μ by $c_1 \cdot \Sigma_X$, with c_1 assumed known. This chapter will first derive an estimate for Σ_μ that does not rely on the proportionality assumption and will compare the resulting covariate k-ratio test procedure to the k-ratio test procedure when all covariance matrices are assumed known. The latter sections of this chapter will show how one can estimate Σ_μ retaining the proportionality assumption, and will compare the power of this covariate k-ratio procedure to the power of the procedure when proportionality is not assumed.

In order to derive an estimate of Σ_μ, the data must arise from a multicenter study of two treatment groups. In the multicenter k-ratio analysis, center is regarded as a random effect. One must now assume no treatment-by-center interaction in regards to the bivariate vector of responses. Additionally, one must also assume that the covariance matrices Σ_μ and Σ_X are equal for all centers. That is, the variability of the observations is the same for all centers, and the variability of the prior means also does not vary with center. The assumptions listed in Sections 3.1 and 3.4 are assumed for this chapter as well.

4.2 Statistical Results, Without Proportionality Assumption

Denote the number of centers by m. The estimated pooled-sample covariance matrix $\hat{\Sigma}_X$, equals

$$\sum_{i=1}^{m} \sum_{j=1}^{2} \sum_{k=1}^{n} (X_{ijk}-\bar{X}_{ij.})\cdot(X_{ijk}-\bar{X}_{ij.})' \Big/ (2\cdot m\cdot(n-1)) \qquad (4.1)$$

where i indexes center, j indexes treatment group and k indexes the individual within that treatment-center combination. The quantity $\bar{X}_{ij.}$ denotes the mean for the n individuals for treatment group j within center i. For m=1, (4.1) equals the estimate of Σ_X used in Chapter 3.

In the multicenter covariate k-ratio test procedure, $X_{ijk} \mid \boldsymbol{\mu}_j$ is conditionally distributed bivariate normal with mean $\boldsymbol{\mu}_j$ and covariance matrix Σ_X. Therefore, $\bar{X}_{ij.} \mid \boldsymbol{\mu}_j$ is distributed bivariate normal with mean $\boldsymbol{\mu}_j$ and covariance matrix Σ_X/n. If the prior mean $\boldsymbol{\mu}_j$ is distributed as a bivariate normal variate with mean $\boldsymbol{\Theta}$ and covariance matrix Σ_μ, then the unconditional distribution for each $\bar{X}_{ij.}$ is bivariate normal with mean $\boldsymbol{\Theta}$ and covariance matrix $\Sigma_\mu + (\Sigma_X/n)$. Denote this unconditional covariance matrix by Σ_X^*.

Letting $\bar{X}_j$ denote the mean for treatment group j across all centers and individuals, and remembering that center is a random effect,

$$\sum_{i=1}^{m} \sum_{j=1}^{2} (\bar{X}_{ij.}-\bar{X}_j)\cdot(\bar{X}_{ij.}-\bar{X}_j)' \Big/ 2\cdot(m-1) \qquad (4.2)$$

estimates Σ_X^*. The degrees-of-freedom found in the denominator of (4.2) result from 2•m degrees-of-freedom for two treatment means in each of the m centers minus two degrees-of-freedom for the estimation of the across-center treatment means $\bar{X}_j$.

Letting $\hat{\Sigma}_x^*$ denote the matrix derived in (4.2), Σ_μ is estimated by $\hat{\Sigma}_x^* - \hat{\Sigma}_x/n$, where $\hat{\Sigma}_x$ is computed from (4.1). Substitution of $\hat{\Sigma}_x$ and $\hat{\Sigma}_\mu$ into the formula for the covariate k-ratio procedure results in an "empirical Bayes" procedure which does not rely on the proportionality assumption used in the previous chapters.

4.3 Description of Simulation Program

Appendix 4.1 lists the computer program that performs the simulations used in this chapter. Since the program is a generalization of the program used in Chapter 3, only the differences between the two are indicated here.

For each center i and each treatment group j, the program generates a $\boldsymbol{\mu}_{ij}$ which is distributed bivariate normal with covariance matrix Σ_μ. For all i, the vector $\boldsymbol{\mu}_{i1}$ has mean (δ_1 0) while $\boldsymbol{\mu}_{i2}$ has mean 0. These mean vectors reflect the $\boldsymbol{\theta}$=0 assumption of Section 3.4, with the true treatment mean difference for each center equal to δ_1 for the variable under investigation and equal to 0 for the covariate.

The simulation program proceeds as before, generating, for each center i and treatment group j, n bivariate observations with mean vector $\boldsymbol{\mu}_{ij}$ and covariance matrix Σ_x. For the generation of the simulated data, Σ_x is determined by choosing values for c_2 and ρ, and Σ_μ is determined by selecting c_1 and then using the proportionality assumption $\Sigma_\mu = c_1 \cdot \Sigma_x$.

The program then computes $\hat{\Sigma}_x$ from (4.1) and $\hat{\Sigma}_x^*$ from (4.2). The estimate $\hat{\Sigma}_\mu$ equals $(\hat{\Sigma}_x^* - \hat{\Sigma}_x/n)$. The estimate of the prior covariance matrix for the true treatment difference, $\hat{\Sigma}_\delta$, equals $2 \cdot \hat{\Sigma}_\mu$.

For the multicenter covariate k-ratio test procedure, $\hat{\Sigma}_d$ equals

$2 \cdot \hat{\Sigma}_x$ / (m•n), since the observed **d** vector now equals the average (across centers) of the vector of observed treatment mean differences, or

$$\mathbf{d} = \sum_{i=1}^{m} \mathbf{d}_i \Big/ m,$$

where $\mathbf{d}_i$ is the vector of treatment mean differences for center i. The program then performs the covariate k-ratio procedure by substitution of **d**, $\hat{\Sigma}_\delta$, and $\hat{\Sigma}_d$ into the formulae given in Section 2.1, where no proportionality assumption is made.

For each combination of c_1, c_2, ρ and δ_1, the program performs 250 simulations in order to derive power estimates. The following section will address the problem of negative variance estimates that can arise from the use of the multicenter covariate k-ratio test procedure.

4.4 Issues Regarding Negative Posterior Variance Estimates

Estimation of Σ_μ using (4.2) can lead to a posterior variance estimate which is less than zero. In order to derive power estimates (averages of the 0-or-1 score assigned to each simulation), these negative variances must be dealt with in some manner. For the multi-center covariate k-ratio procedure analyzed in this chapter, any simulation which resulted in a negative estimate of $\hat{\sigma}_1^2$ was "thrown out" of the power analyses. This ensured that the power estimates were not biased. However, the result is that, although 250 simulations were performed for each combination of c_1, c_2, ρ and δ_1, in many cases the actual number of simulations used in the estimation of the power of the procedure was less than 250.

Analysis proceeded by performing simulations for several values of m, and comparing the frequency of negative posterior variance estimates.

The results are presented in Table 4.1 for n equal to five and ten.

As one would expect, the percentage of simulations resulting in a negative posterior variance estimate decreases as the number of centers increase. For $c_1=c_2=1$ and $n=5$, across all δ_1 and ρ values (for a total of 4500 simulations), 6.2% of the posterior variance estimates are negative when m equals three. The percentage of negative posterior variance estimates decrease to 2.5% for $m=5$, 0.9% for $m=7$, and 0.2% for $m=9$.

For smaller c_1 values, the number of centers needed to ensure that the use of (4.2) will likely result in a usable procedure increase. In the case where $c_1=0.1$, $c_2=1$ and $n=5$, simulations result in negative $\dot{\sigma}_1^2$ estimates in 13.5% of the calculations when m equals five, with this figure dropping to 5.6% when m equals nine and 4.6% when m equals twelve.

When c_1 is relatively large, the number of centers that is needed to achieve valid results an acceptable percentage of the time decrease. When n equals five with c_1 equal to ten and c_2 equal to one, a study involving just three centers results in negative $\dot{\sigma}_1^2$ estimates in only 2.5% of the 4500 simulations. When the number of centers increases to five, only 0.1% of the simulations result in negative variance estimates.

Looking at Table 4.1 as a function of n, the sample size in each treatment group in each center, increasing n does decrease the probability of a negative posterior variance estimate, but not to the degree achieved by increasing the number of centers. For $c_1=1$ and $c_2=1$, with m equal to three, 6.2% of the simulations results in an unusable result when n equals 5, compared to 5.3% when n equals 10.

TABLE 4.1

PERCENTAGE OF NEGATIVE VARIANCE RESULTS
USING MULTICENTER COVARIATE K-RATIO TEST

	m				
	3	5	7	9	12
n=5					
$c_1=0.1$ $c_2=1$	-	13.5	-	5.6	4.6
$c_1=1$ $c_2=1$	6.2	2.5	0.9	0.2	-
$c_1=10$ $c_2=1$	2.5	0.1	-	-	-
n=10					
$c_1=0.1$ $c_2=1$	-	8.2	-	4.3	3.0
$c_1=1$ $c_2=1$	5.3	1.6	0.2	0.0	-
$c_1=10$ $c_2=1$	1.9	0.1	-	-	-

Concluding from the above, although use of the covariate k-ratio test procedure of Section 4.2 can result in a variance estimate which is negative, one can likely achieve valid statistical results from a study involving five or more centers with as few as five individuals in each treatment group in each center. The following section will compare the power estimates derived from the multicenter "empirical Bayes" covariate k-ratio test procedure of Section 4.2 to the power of the covariate k-ratio procedure when all covariance matrices are assumed known.

4.5 Power Comparison Results Without Proportionality Assumption

Figures 4.1 through 4.9 present the power curves that result from the application of the multicenter covariate k-ratio procedure with n and m both equal to five, along with the power curves from the "known variance" case of Chapter 2. Similar graphs for the case where n equals ten can be found in Appendices 4.2 through 4.10. On each graph. "ID" equals "emp*i*" for rho equal to 0.*i* using the multicenter covariate k-ratio procedure described in Section 4.2 and "ID" equals "known*i*" for rho=0.*i* under the assumption of known covariance matrices.

The figures indicate a high degree of agreement in power between the multicenter procedure and the procedure when variance terms are assumed known. The only appreciable divergence between the power curves is found when c_1 equals 0.1. In this situation, for all analyzed values of c_2, when δ_1 is near to zero, the power of the empirical Bayes k-ratio procedure of Section 4.2 is greater than the power of the procedure assuming known variances. This indicates that the multicenter covariate k-ratio procedure of Section 4.2 does not preserve the size of the test. The α-levels in this situation are inflated: the test rejects the null

FIGURE 4.1

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE
$C_1=0.1$ $C_2=0.1$ $m=5$ $n=5$

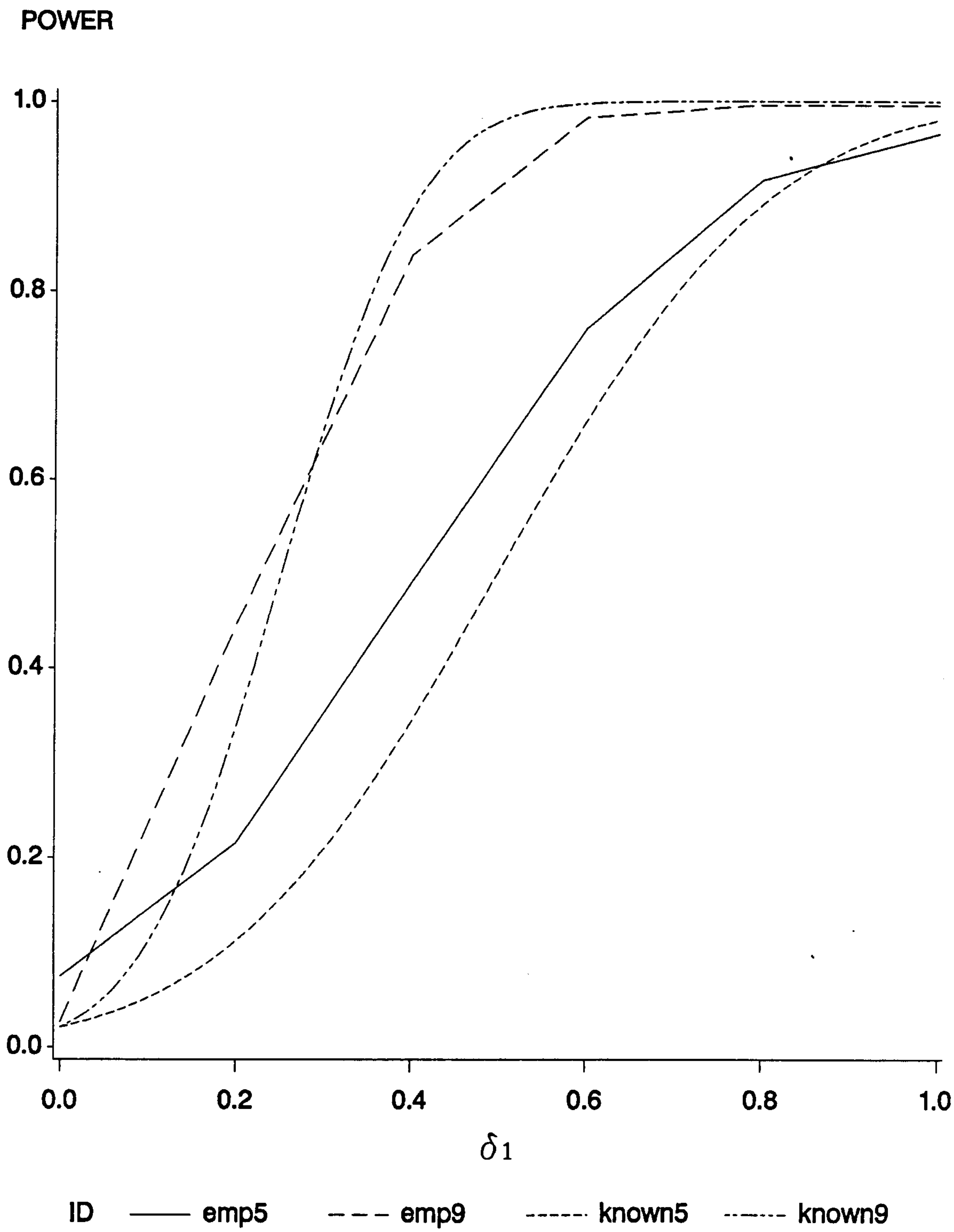


FIGURE 4.2

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

$C_1 = 0.1 \quad C_2 = 1 \quad m = 5 \quad n = 5$

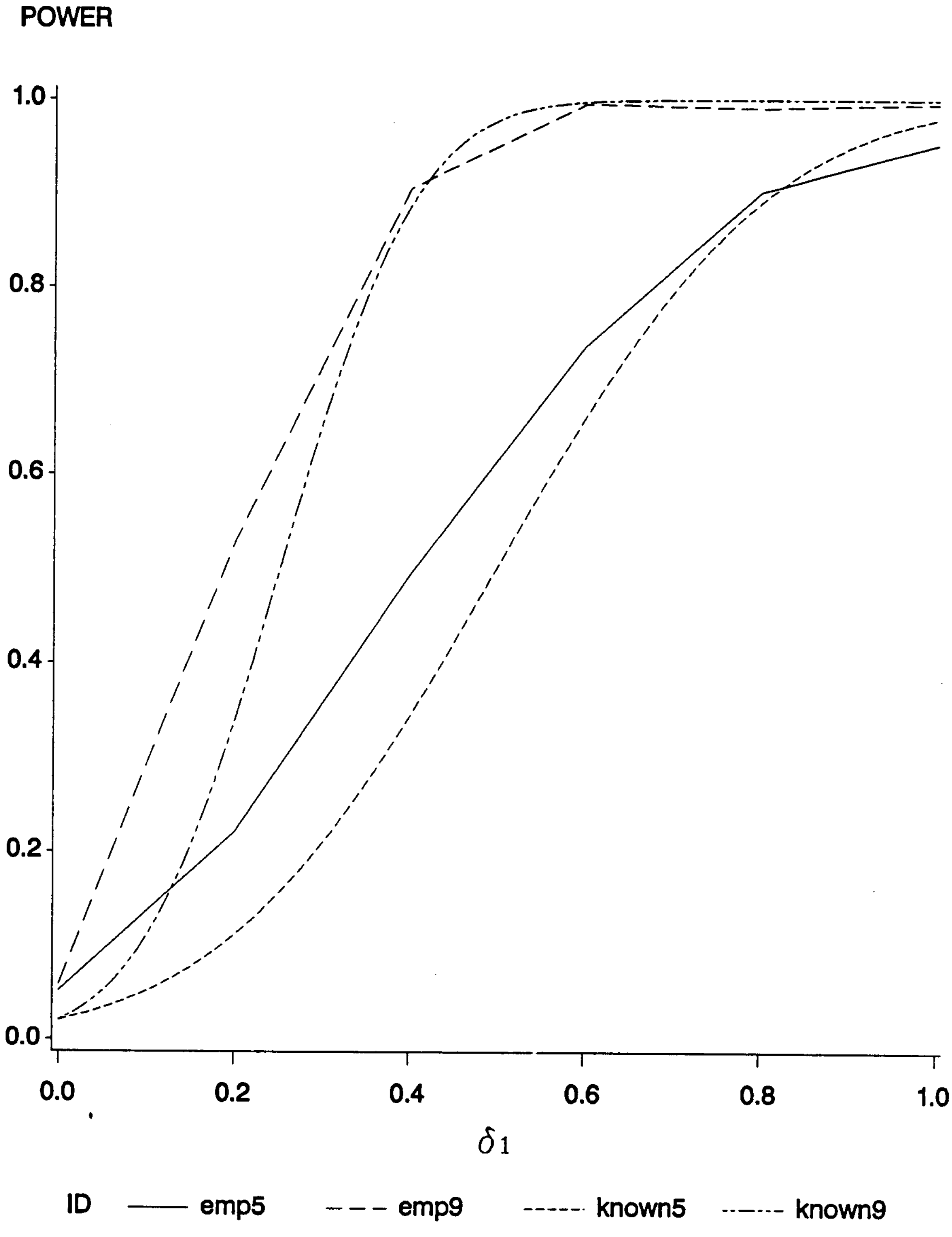


FIGURE 4.3

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE
$C_1=0.1 \quad C_2=10 \quad m=5 \quad n=5$

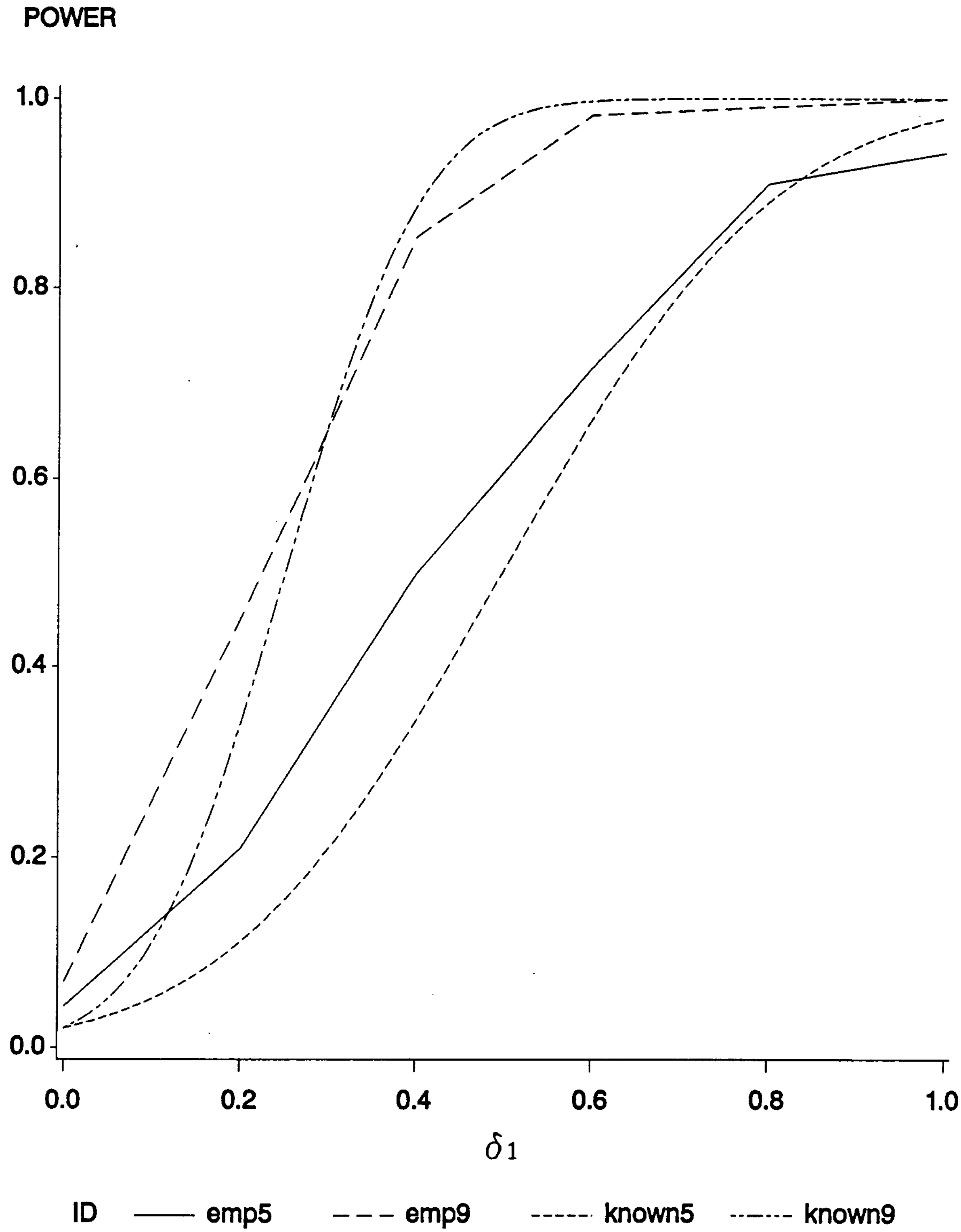


FIGURE 4.4

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE
$C_1=1 \quad C_2=0.1 \quad m=5 \quad n=5$

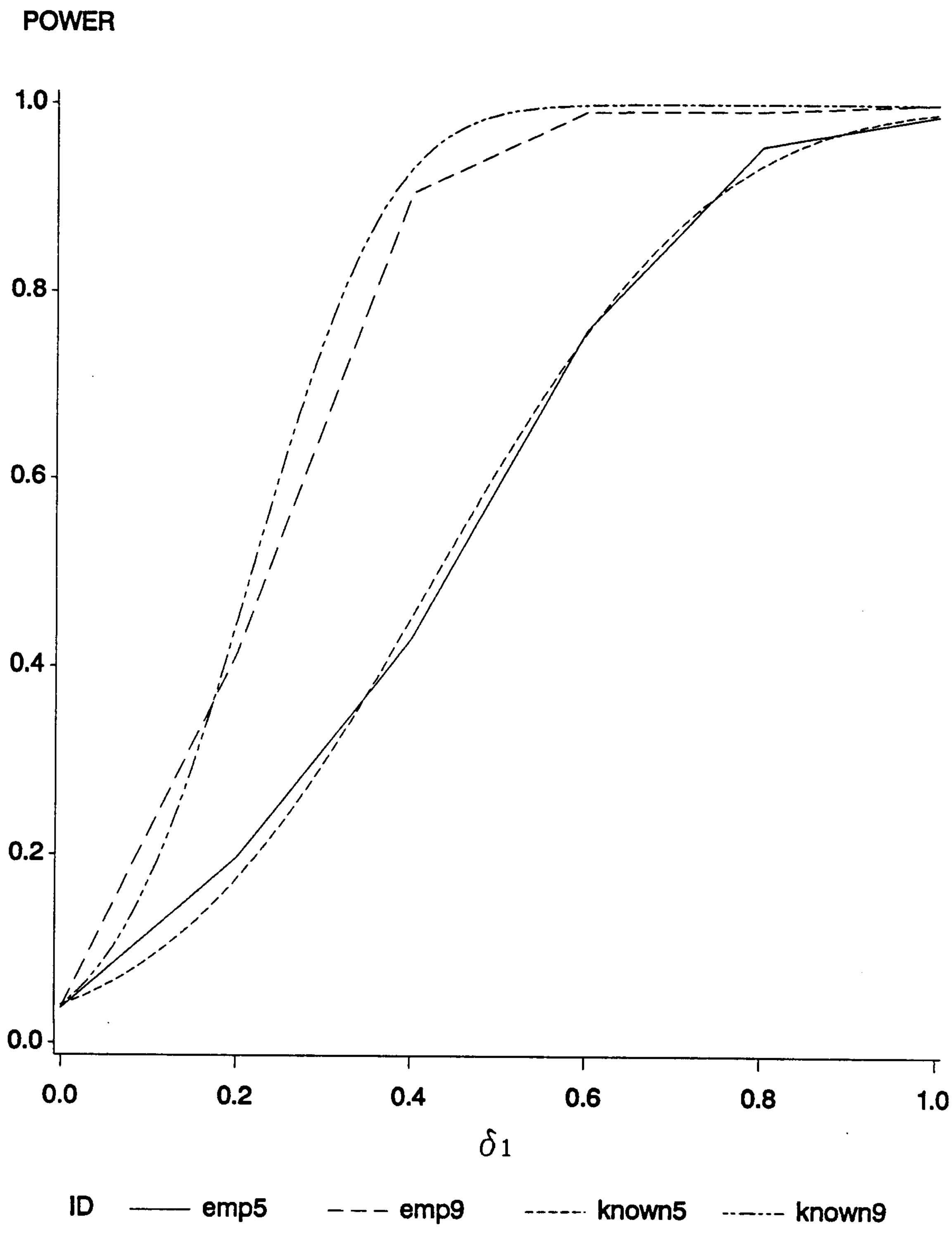


FIGURE 4.5

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE
$C_1=1$ $C_2=1$ $m=5$ $n=5$

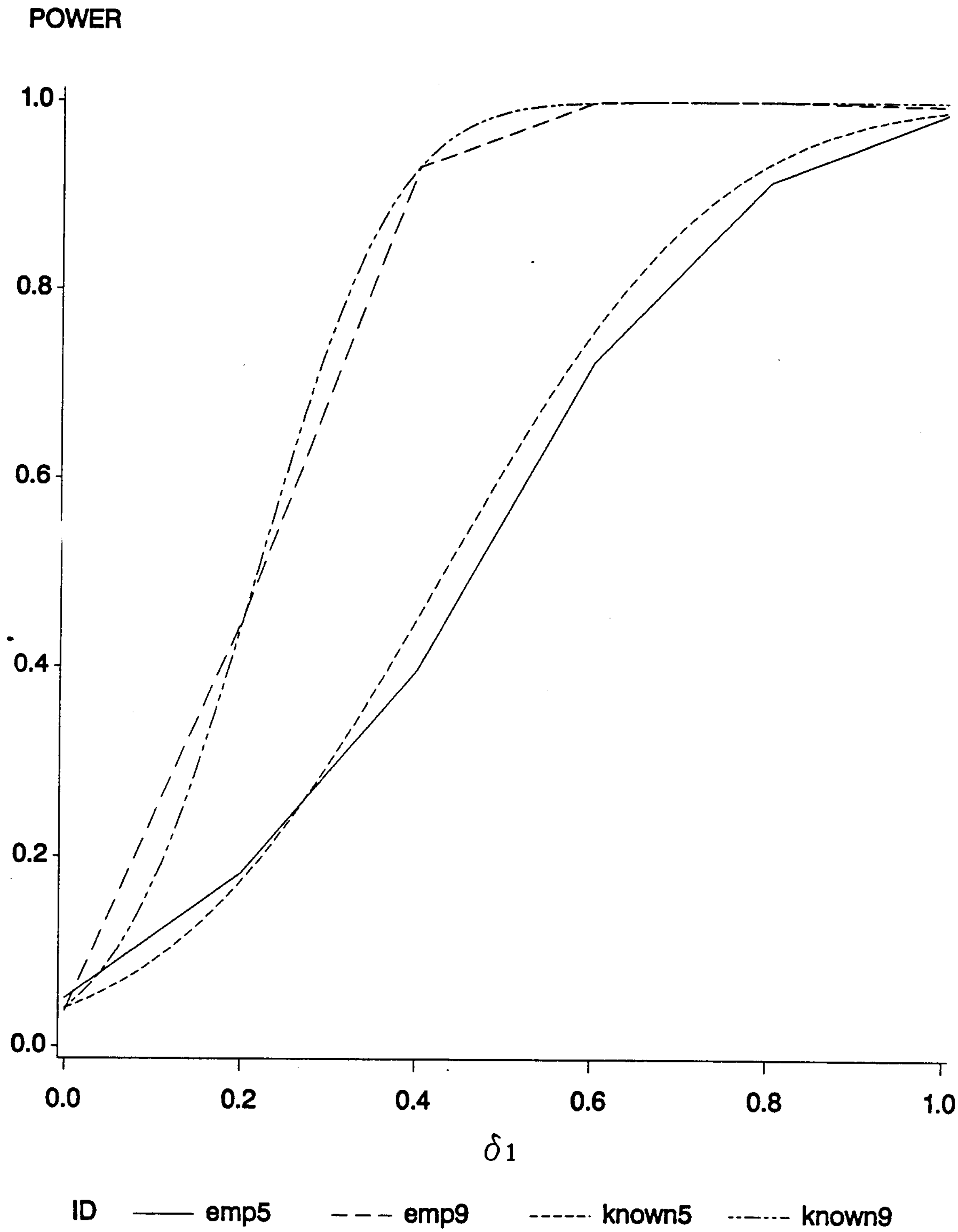


FIGURE 4.6

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

$C_1=1 \quad C_2=10 \quad m=5 \quad n=5$

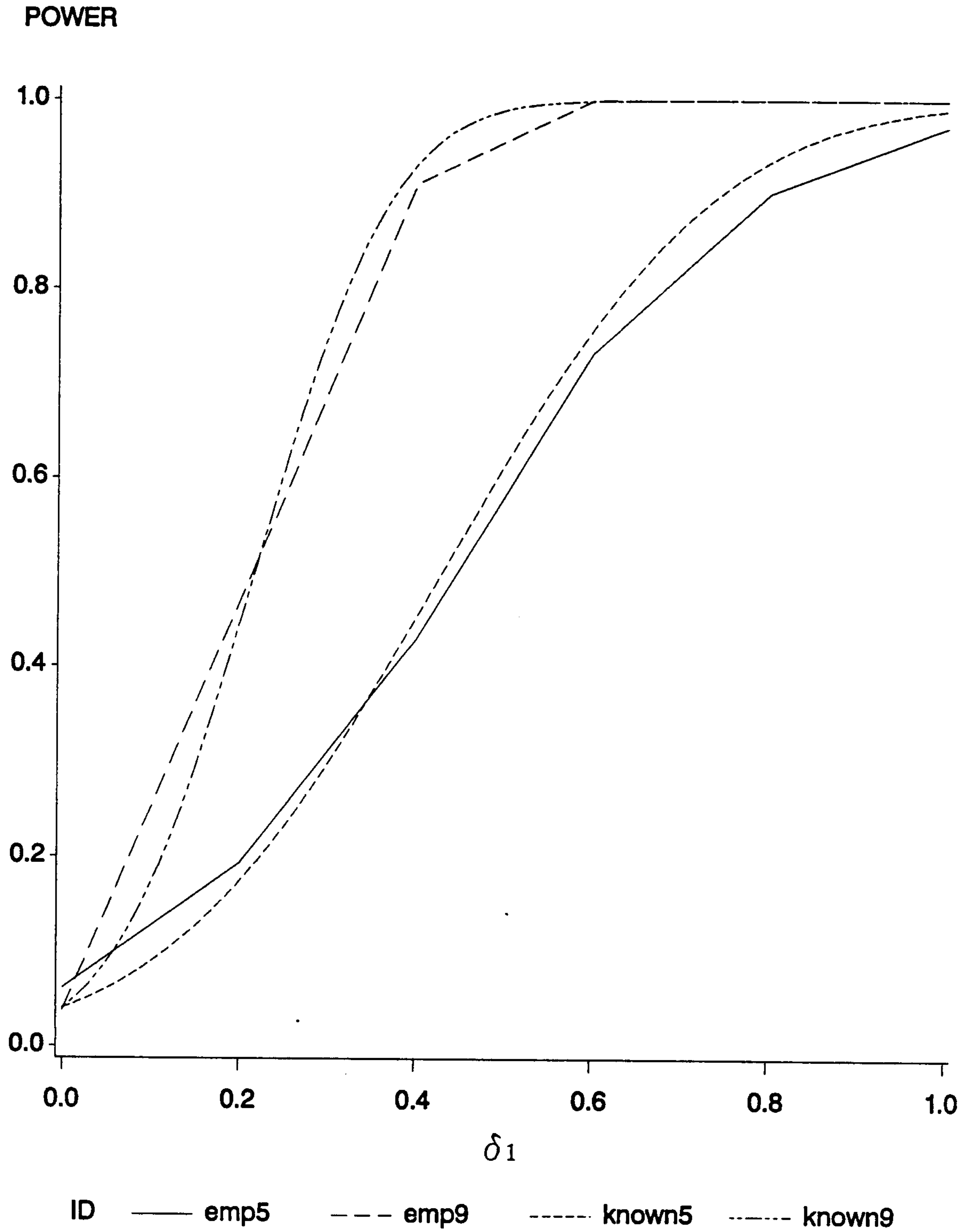


FIGURE 4.7

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE
$C_1=10$ $C_2=0.1$ $m=5$ $n=5$

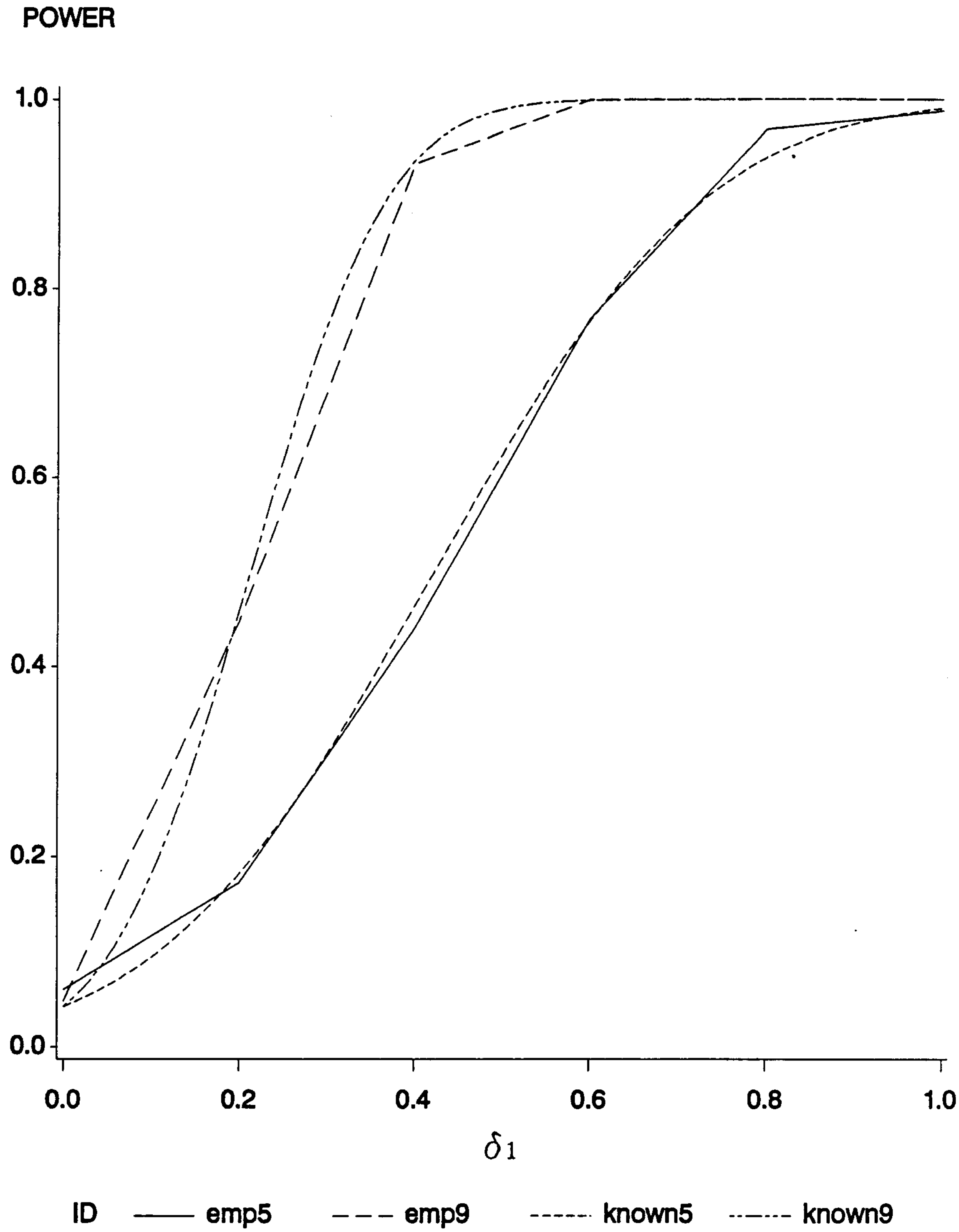


FIGURE 4.8

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE
$C_1=10 \quad C_2=1 \quad m=5 \quad n=5$

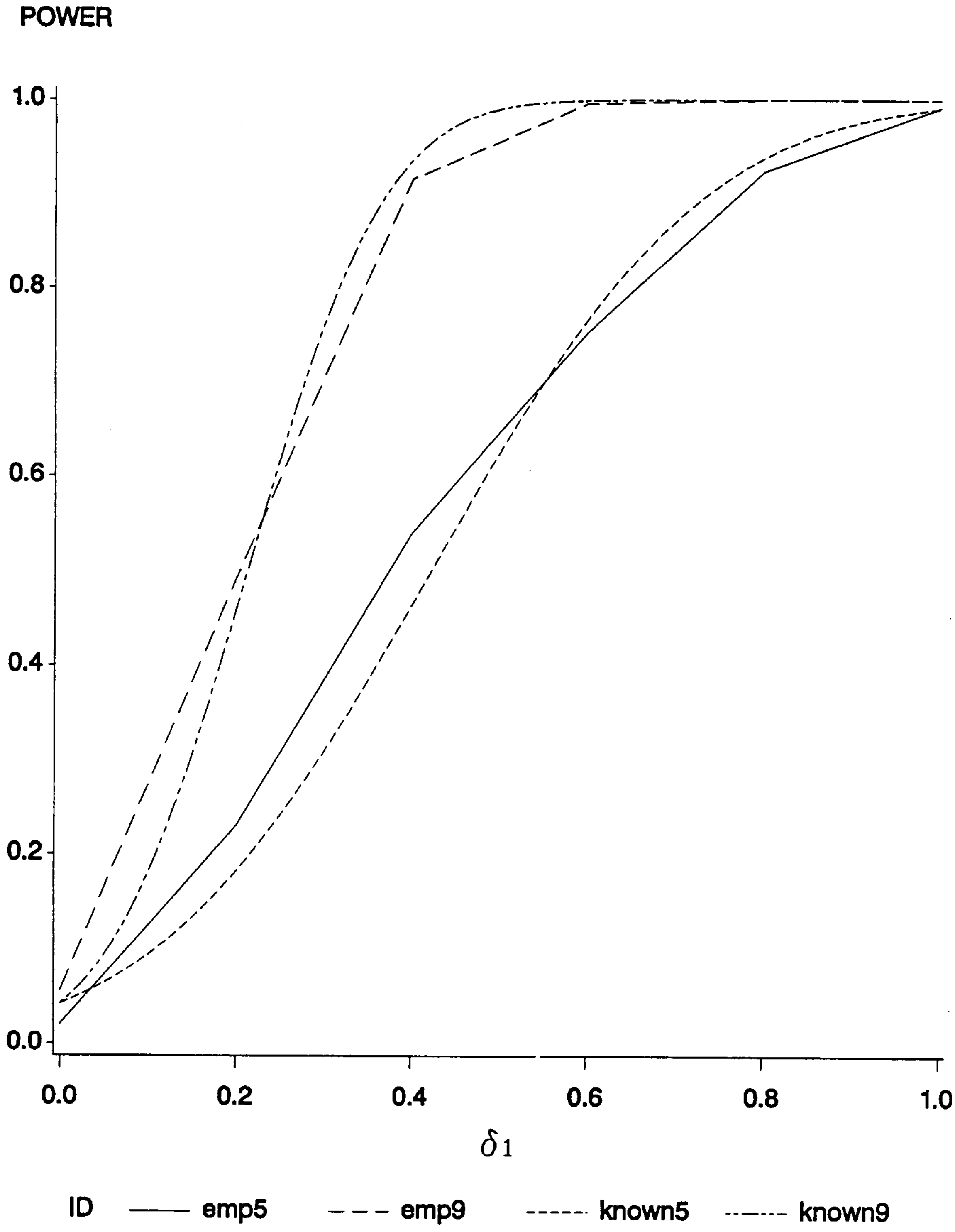
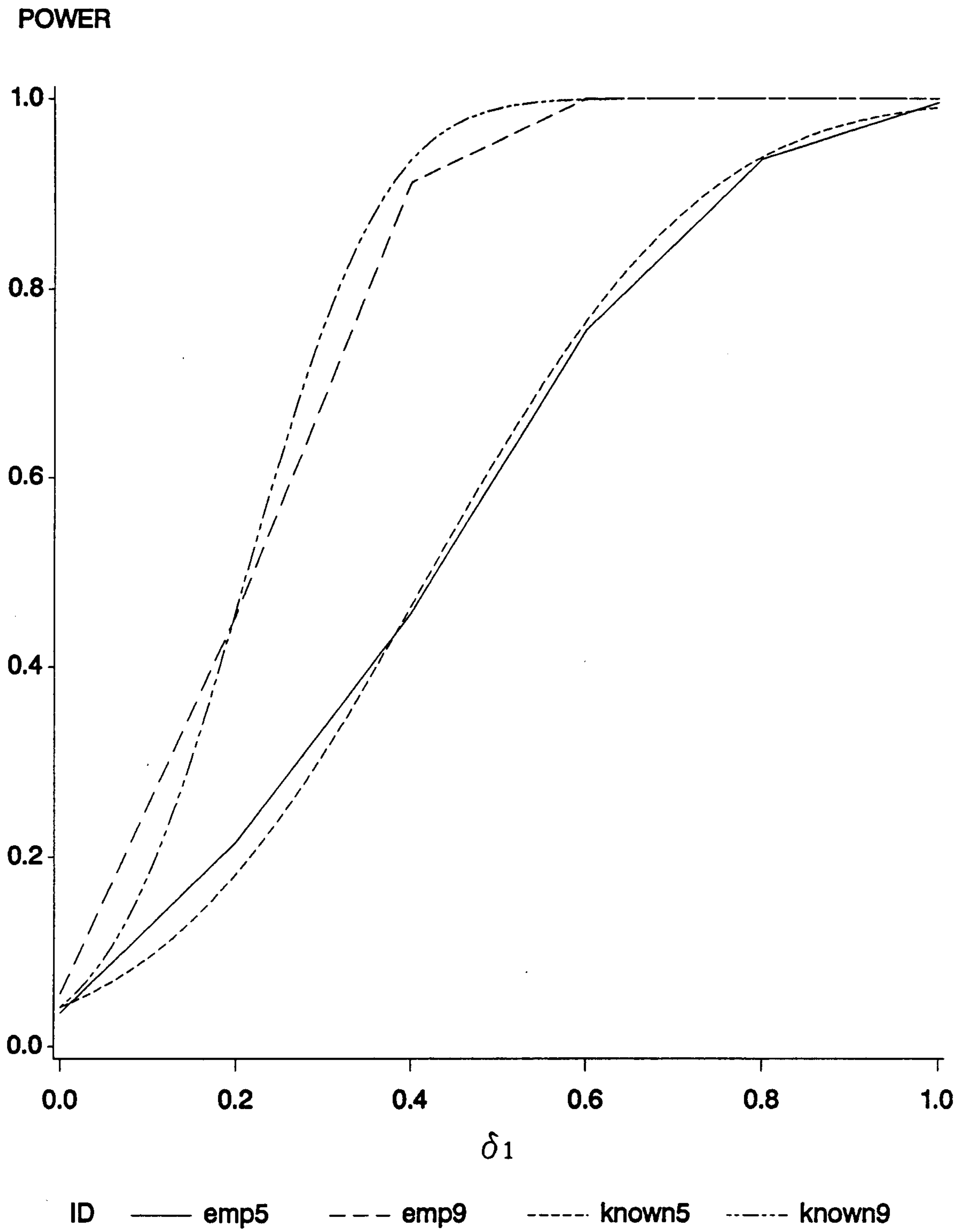


FIGURE 4.9

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

$C_1=10 \quad C_2=10 \quad m=5 \quad n=5$



hypothesis when it is in fact true with a probability greater than 0.05.

Appendices 4.11 and 4.12 list power estimates for n equal to five and n equal to ten, respectively, with m equal to five for both listings. On these appendices, "KNOWN POWER" denotes the power when all covariances are assumed known and "SIGMA POWER" signifies the estimated power for the empirical Bayes k-ratio procedure of Section 4.2. "C1 POWER" can be ignored for the present time. As shown in Appendix 4.11, for $c_1=0.1$ and $c_2=0.1$ the estimated α-level (or power when $\delta_1=0$) of the multicenter covariate k-ratio test is 0.07 for rho=0.5, compared to an α-level of 0.02 for the known variance situation. When n equals ten, the divergence between the power curves is not as great. With this larger sample size, for $c_1=c_2=0.1$ and rho=0.5, the α-levels are 0.05 and 0.03 for the multicenter empirical Bayes and known variance k-ratio procedures, respectively.

The empirical Bayes covariate k-ratio test procedure described in Section 4.2, then, closely approximates the power of the covariate k-ratio procedure when covariance matrices are known. The approximation is a very close one whenever the covariance matrix of the prior distribution for the true treatment means is diffuse relative to the covariance matrix for the observations. In this situation, the procedure produces reasonable power estimates in a study involving only five centers with as few as five individuals in each treatment group in each center.

4.6 Statistical Results with Proportionality Assumption

The analysis of a multicenter study of two treatment groups keeping the proportionality assumption $\Sigma_\mu=c_1\cdot\Sigma_X$ proceeds as follows. The matrix

$\hat{\Sigma}_x^*$ of (4.2) estimates $\Sigma_\mu + \Sigma_x/n$. Under the proportionality assumption, this sum equals $(c_1 + n^{-1})\cdot\Sigma_x$. The matrix $\Sigma_p^* = \{(\hat{\Sigma}_x^*\cdot\hat{\Sigma}_x^{-1}) - (I_2\cdot n^{-1})\}$, then, is an estimate of $c_1\cdot I_2$, where I_2 denotes the 2-by-2 identity matrix. Therefore the average of the diagonal elements of Σ_p^* estimates c_1. Substituting $\hat{\Sigma}_x$ and $\hat{c}_1$ into the equation $\Sigma_\mu = c_1\cdot\Sigma_x$ results in an estimate for Σ_μ. Denote this estimate (as opposed to the estimate $\hat{\Sigma}_\mu$ described in Section 4.2) as $\hat{\Sigma}_{\mu p}$. Substitution of $2\cdot\hat{\Sigma}_{\mu p}$ for Σ_δ in the formulae for the covariate k-ratio procedure results in an empirical Bayes test procedure that retains the proportionality assumption used in Chapters 2 through 3.

4.7 Power Comparisons for Multicenter Empirical Bayes Procedures

The listings found in Appendices 4.11 and 4.12 indicate (for n=5 and n=10, respectively), the power of the covariate k-ratio test procedure when m=5 for the known variance situation of Chapter 2 ("KNOWN POWER"), for the empirical Bayes procedure that uses $\hat{\Sigma}_\mu$ ("SIGMA POWER"), and for the procedure described above that uses $\hat{\Sigma}_{\mu p}$ ("C1 POWER").

For $c_1=0.1$ and for small values of δ_1, the power of the covariate k-ratio procedure which uses $\hat{\Sigma}_{\mu p}$ more-closely approximates the power of the known variance situation than the procedure which uses $\hat{\Sigma}_\mu$. This holds true for both n=5 and n=10. However, for larger values of c_1, the power estimates for the two multicenter procedures do not differ from one another. When c_1 equals one or greater, the multicenter covariate k-ratio test procedure of Section 4.6 results in approximately the same power as the multicenter procedure of Section 4.2.

Another difference between the two multicenter covariate k-ratio procedures involves the frequency of positive estimated posterior variances. Appendices 4.13 and 4.14 list these frequencies for n=5 and n=10, respectively, with m=5. For each line in the listings, the frequency denotes the number of positive posterior variance estimates out of a possible 250.

Again, the greatest difference between the two procedures is found when c_1 is relatively small. In this situation, with n=10, the procedure which uses $\hat{\Sigma}_{\mu p}$ results in a greater percentage of positive variance estimates than the procedure which uses $\hat{\Sigma}_{\mu}$.

It is of interest to note that when n equals five, there are no differences seen between the two multicenter procedures in regards to the frequency of positive posterior variance estimates, for any value of c_1. However, as n increases to ten, the frequency of positive variance estimates greatly increase using the $\hat{\Sigma}_{\mu p}$ procedure, while these frequencies increase to a smaller degree using the $\hat{\Sigma}_{\mu}$ procedure.

Concluding from the above, for c_1 equal to one or greater, the power functions and frequency of positive posterior variance estimates for the two multicenter covariate k-ratio test procedures do not differ. The procedure which uses $\hat{\Sigma}_{\mu}$ results in a higher percentage of unusable variance estimates as well as inflated α-levels when c_1 is less than one.

V. RESULTS FROM THE APPLICATION OF COVARIATE K-RATIO TESTS

5.1 Description of Data and Analyses Performed

The data analyzed in this chapter are a subset of the observations from the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a multicenter randomized double-blind study of drug versus placebo in middle-aged men. For this clinical trial, the administered drug was an agent with blood-cholesterol-lowering properties. Both treatment groups followed a moderate cholesterol-lowering diet.

The data used in the following analyses consist of randomly selected groups of 25 patients from both treatment groups in each of 12 centers, making a total of 600 observations. This chapter will present the results of separate analyses of total cholesterol at visit 7 and high density lipoprotein (HDL) at visit 7. The covariate used in each analysis equals the visit 5 (baseline) value for the variable under investigation.

5.2 Results of Statistical Analyses -- Total Cholesterol

This section will present the results of comparative statistical analyses of the two treatment groups in regards to total cholesterol using several procedures. These procedures include the Student's t-test, the Analysis of Covariance, the covariate k-ratio test procedure of Chapter 3 with c_1 assumed known, and the two multicenter covariate k-ratio test procedures of Chapter 4, for c_1 unknown. For the covariate k-ratio procedure where c_1 is assumed known, the analysis used c_1 values equal to 1, 100, 1000, 5000, and 10,000.

Each of the statistical tests reject the null hypothesis H_0: $\delta_1 \leq 0$ with $p<0.01$. Across all centers, the observed mean difference between the two treatment groups is 46.7 for visit 7 cholesterol and -3.9 for visit 5 cholesterol. Using the estimate of Σ_X given in (4.1) from the multicenter covariate k-ratio procedure, the sample correlation between visit 7 and visit 5 cholesterol levels equals 0.59. The estimated variance of the treatment mean difference in visit 7 total cholesterol equals 8.57 using the pooled two-sample covariance matrix of the t-test, 5.61 using the Analysis of Covariance and 8.24 using the pooled sample covariance matrix of (4.1). Analysis using the multicenter empirical Bayes k-ratio procedure of Section 4.6, which retains the proportionality assumption, results in $\hat{c}_1=0.07$.

Differences seen in the covariance matrices for the two treatment groups violate the assumption of equal covariance structure made in the formulation of the covariate k-ratio test procedure. Similarly, differences in the covariance matrices between centers <u>and</u> between treatment groups within center violate the assumption of covariance matrix equality made in the multicenter covariate k-ratio procedures of Chapter 4. Table 5.1 lists, both by treatment group and by treatment group and center, the estimated standard deviations of visit 7 and visit 5 total cholesterol, as well as the estimated correlation between the two cholesterol levels.

As shown in the "by center" sections of Table 5.1, the estimated standard deviations of visit 7 cholesterol range from 18.7 to 51.9. The estimates of the standard deviation of visit 5 cholesterol are anywhere

TABLE 5.1

TOTAL CHOLESTEROL
SAMPLE STANDARD DEVIATIONS AND CORRELATIONS
BY TREATMENT AND CENTER

	Total Cholesterol Standard Deviation		
	Visit 7	Visit 5	Correlation
Treatment-Drug	39.27	34.82	0.55
Center			
"BA"	51.86	46.42	0.84
"CN"	23.73	20.46	0.00
"GW"	38.24	30.20	0.39
"IA"	26.66	25.82	0.57
"JH"	49.32	51.02	0.78
"LJ"	36.16	28.26	0.38
"MN"	39.94	28.15	0.50
"OK"	42.87	32.29	0.55
"SE"	36.58	28.08	0.43
"ST"	41.13	34.76	0.66
"TR"	34.00	29.20	0.39
"WU"	40.11	25.58	0.14
Treatment-Placebo	32.10	31.34	0.68
Center			
"BA"	40.31	37.71	0.80
"CN"	20.26	26.21	0.45
"GW"	22.84	20.86	0.19
"IA"	19.15	23.67	0.76
"JH"	26.81	29.14	0.56
"LJ"	39.63	42.11	0.76
"MN"	32.41	25.50	0.61
"OK"	36.23	35.22	0.62
"SE"	18.73	26.29	0.47
"ST"	36.85	37.55	0.83
"TR"	35.73	22.98	0.60
"WU"	26.48	18.91	0.51

between 18.9 and 51.0. The estimated correlations between the two variables range from 0.0 to 0.84. These values indicate inequalities between the covariance matrices for the different centers and treatment groups for an analysis of total cholesterol. Therefore, for these data, one should use the multicenter covariate k-ratio test procedures of Chapter 4 with caution.

Looking at the results by treatment group only, one sees smaller differences between the standard deviations and correlations for visit 7 and visit 5 total cholesterol. The values for the "Drug" group do not differ greatly from the values for the "Placebo" group. Therefore, when analyzing total cholesterol, the assumption of Chapters 2 and 3 concerning the equality of covariance matrices for the two treatment groups seems reasonable for this dataset.

5.3 Power Comparisons -- Total Cholesterol

This section will compare the power of the statistical procedures listed above, under repeated sampling assumptions. For the power calculations, the variance of the treatment mean difference for the Analysis of Covariance was approximated by multiplying the estimated variance of the treatment mean difference of the t-test by $(1-\hat{\rho}^2)$.

Table 5.2 presents the powers of the statistical procedures for integer values of δ_1 between 0 and 10. The column under "$\hat{\Sigma}_\mu$" lists powers for the multicenter covariate k-ratio procedure of Section 4.2. The heading "$\hat{c}_1$" indicates the powers for the multicenter covariate k-ratio procedure of Section 4.6. For the covariate k-ratio procedure where c_1 is assumed known, powers are given for c_1 equal to 1, 1000 and 10,000.

TABLE 5.2

POWER COMPARISONS
TOTAL CHOLESTEROL

Statistical Procedures

					c_1		
δ_1	t-test	ANOCOVA	$\hat{\Sigma}_\mu$	$\hat{c}_1$	1	1000	10000
0	0.05	0.05	0.03	0.04	0.04	0.04	0.04
1	0.10	0.11	0.07	0.09	0.10	0.10	0.10
2	0.17	0.21	0.14	0.18	0.19	0.19	0.19
3	0.27	0.35	0.26	0.32	0.33	0.33	0.33
4	0.39	0.52	0.42	0.48	0.50	0.50	0.50
5	0.52	0.68	0.59	0.65	0.67	0.67	0.67
6	0.67	0.81	0.74	0.79	0.80	0.81	0.81
7	0.77	0.90	0.86	0.90	0.90	0.90	0.90
8	0.86	0.96	0.93	0.95	0.96	0.96	0.96
9	0.92	0.98	0.97	0.98	0.98	0.98	0.98
10	0.96	0.99	0.99	0.99	1.00	1.00	1.00

Table 5.2 indicates that the power of the multicenter procedure of Section 4.2 is consistently less than the powers for both the multicenter procedure of Section 4.6 and the Analysis of Covariance. The power of the multicenter covariate k-ratio procedure of Section 4.6 is slightly less than the power of the Analysis of Covariance. For all analyzed values of c_1, the power of the covariate k-ratio procedure of Chapter 3 where c_1 is assumed known is equal to the power for the Analysis of Covariance.

It is of interest to note that for this dataset, and when analysis involves total cholesterol, the power of the covariate k-ratio procedure does not vary greatly as c_1 varies. The power when c_1 equals 0.07 (as estimated by the procedure of Section 4.6) does not differ from the power of the covariate k-ratio procedure when c_1 is assumed equal to either 1, 1000, or 10000.

5.4 Results of Statistical Analyses -- HDL

This section will present the results of comparative statistical analyses of the two treatment groups in regards to high density lipoprotein using the same statistical procedures as for the analysis of total cholesterol given above.

Across all centers, the observed treatment mean difference is 0.792 for visit 7 HDL and -0.073 for visit 5 HDL. None of the statistical tests reject the null hypothesis H_0: $\delta_1 \leq 0$ with $p \leq 0.05$. Analysis of HDL using the multicenter covariate k-ratio procedure of Section 4.2 results in a negative estimated posterior variance. Therefore, one cannot perform a comparative statistical analysis of HDL treatment mean differences using this method. Analysis of visit 7 HDL using Analysis of Covariance results in a treatment mean difference approaching significance, with a one-sided p-value of 0.06. Using the estimate of Σ_x given in (4.1) from the multicenter covariate k-ratio procedure, the sample correlation between visit 7 and visit 5 HDL levels equals 0.73. The estimated variance of the treatment mean difference in visit 7 HDL equals 0.685 using the pooled two-sample covariance matrix of the t-test, 0.319 using the Analysis of Covariance and 0.647 using the pooled sample covariance matrix of (4.1). Analysis using the multicenter empirical Bayes k-ratio procedure of Section 4.6, which retains the proportionality assumption, results in $\hat{c}_1=0.04$.

Table 5.3 lists, both by treatment group and by treatment group and center, the estimated standard deviations of visit 7 and visit 5 HDLs, as well as the estimated correlation between the two HDL levels. As shown in the "by center" sections of Table 5.3, the estimated standard deviations of visit 7 HDL range from 5.44 to 13.73. The estimates of the standard deviation of visit 5 HDL are anywhere between 6.18 and 12.73. The estimated correlations between the two variables range from 0.27 to 0.90. Looking at the results by treatment group only, the values of the descriptive statistics for the "Drug" group do not differ greatly from the values for the "Placebo" group. Therefore, when HDL is the variable of interest in the analysis, the assumptions of Chapters 2 through 4 concerning the equality of covariance matrices for the two treatment groups and between centers seem reasonable for these data.

5.5 Power Comparisons -- HDL

This section will compare the power of the statistical procedures listed above, under repeated sampling assumptions. For the power

TABLE 5.3

HDL
SAMPLE STANDARD DEVIATIONS AND CORRELATIONS
BY TREATMENT AND CENTER

	HDL Standard Deviation Visit 7	HDL Standard Deviation Visit 5	Correlation
Treatment=Drug	10.22	10.11	0.77
Center			
"BA"	9.15	9.59	0.62
"CN"	10.41	11.77	0.85
"GW"	10.63	9.90	0.82
"IA"	8.09	9.51	0.77
"JH"	8.28	8.99	0.57
"LJ"	10.54	10.69	0.86
"MN"	10.92	12.36	0.79
"OK"	7.69	6.18	0.27
"SE"	5.44	6.90	0.52
"ST"	13.73	9.59	0.90
"TR"	10.05	8.01	0.77
"WU"	10.88	11.00	0.77
Treatment=Placebo	10.06	10.14	0.73
Center			
"BA"	10.78	9.58	0.37
"CN"	8.19	7.94	0.83
"GW"	9.62	9.94	0.85
"IA"	11.24	10.90	0.82
"JH"	9.22	10.07	0.76
"LJ"	10.34	12.73	0.87
"MN"	8.81	8.38	0.81
"OK"	7.43	9.30	0.59
"SE"	8.67	8.72	0.86
"ST"	12.51	11.40	0.60
"TR"	11.46	9.32	0.81
"WU"	8.56	10.21	0.54

calculations, the variance of the treatment mean difference for the Analysis of Covariance was again approximated by multiplying the estimated variance of the treatment mean difference from the t-test by $(1-\hat{\rho}^2)$.

Table 5.4 presents the powers of the statistical procedures for values of δ_1 between 0 and 3. The powers for the multicenter covariate k-ratio procedure of Section 4.2 are not available due to the negative estimated posterior variance. Again, the heading "$\hat{c}_1$" indicates the powers for the multicenter covariate k-ratio procedure of Section 4.6.

The power of the multicenter covariate k-ratio procedure of Section 4.6 is slightly less than the power of the Analysis of Covariance. For all analyzed values of c_1, the power of the covariate k-ratio procedure of Chapter 3 where c_1 is assumed known is slightly greater than the power using the multicenter procedure of Section 4.6, and approximately equal to the power for the Analysis of Covariance.

It is again of interest to note that when analysis is of HDL, the power of the covariate k-ratio procedure does not vary greatly as c_1 varies. The power when c_1 equals 0.04 (as estimated by the procedure of Section 4.6) does not differ from the power of the covariate k-ratio procedure when c_1 is assumed equal to either 1, 1000, or 10000.

5.6 Topics For Further Research

Several ideas for future research present themselves at this time. The previous chapters derived and investigated the power function for the covariate k-ratio test procedure. Analysis of relative risk should also be performed, both for the covariate k-ratio procedure of Chapters 2 and 3, and the multicenter procedures of Chapter 4.

TABLE 5.4

POWER COMPARISONS
HDL

Statistical Procedures

					c_1		
δ_1	t-test	ANOCOVA	$\hat{\Sigma}_\mu$	$\hat{c}_1$	1	1000	10000
0	0.05	0.05	N/A	0.04	0.04	0.04	0.04
0.25	0.09	0.11	N/A	0.09	0.10	0.10	0.10
0.5	0.15	0.22	N/A	0.19	0.21	0.21	0.21
0.75	0.23	0.38	N/A	0.33	0.36	0.36	0.36
1	0.33	0.55	N/A	0.51	0.54	0.54	0.54
1.25	0.47	0.71	N/A	0.68	0.71	0.71	0.71
1.5	0.57	0.84	N/A	0.83	0.84	0.84	0.84
1.75	0.68	0.93	N/A	0.92	0.93	0.93	0.93
2	0.78	0.97	N/A	0.97	0.97	0.97	0.97
2.25	0.86	0.99	N/A	0.99	0.99	0.99	0.99
2.5	0.92	1.00	N/A	1.00	1.00	1.00	1.00
2.75	0.95	1.00	N/A	1.00	1.00	1.00	1.00
3	0.98	1.00	N/A	1.00	1.00	1.00	1.00

Additional analyses need to investigate the properties of the covariate k-ratio procedure when there exists negative correlation between the variable under investigation and the covariate. Another topic for further investigation concerns how the covariate procedure performs when data arise from a distribution that is not normal. Future research could also look at the properties of the k-ratio covariate procedure when the covariance matrices are not assumed equal for each treatment group.

The covariate k-ratio procedures of Chapters 3 and 4, where covariance matrices are estimated from the data, could also be investigated when estimated covariance matrices are derived using bootstrapping techniques.

Further research must also develop the empirical Bayes covariate k-ratio procedures of Chapters 3 and 4 when sample sizes in the two treatment groups are not equal. Unbiased estimators of Σ_X and Σ_μ need to be derived for this situation.

Finally, all the research presented here must be generalized to the situation where there are more than two treatment groups. The adaptability of the covariate k-ratio test procedure can thereby be investigated.

5.5 Summary and Conclusions

This dissertation generalizes Duncan's k-ratio methodology to include a covariate. The analysis assumes proportionality between the covariance matrix of the prior distribution for the true treatment means (Σ_μ) and the covariance matrix of the conditional distribution of the observations given the values of the true treatment mean vectors (Σ_X).

When both covariance matrices are assumed known, analysis indicates an increase in power when using the covariate k-ratio test procedure. The power level of the covariate k-ratio procedure is a function of the correlation between the variable under investigation and the covariate: the greater the correlation, the greater the power.

An "empirical Bayes" covariate k-ratio procedure assuming c_1 known (where c_1 is defined through the proportionality assumption $\Sigma_\mu = c_1 \cdot \Sigma_X$) uses the pooled two-sample covariance matrix as an estimator for Σ_X, with Σ_μ then estimated by $c_1 \cdot \hat{\Sigma}_X$. Simulations using this procedure indicate, for normally distributed data and a sample size of at least 25 in each treatment group, minimal loss in power compared to the case where the covariance matrices are assumed known.

Assuming c_1 unknown, two empirical Bayes k-ratio procedures use a multicenter set-up to estimate the covariance matrix Σ_μ. One of these procedures retains the proportionality assumption between the covariance matrices while the other one does not rely on this assumption. Simulations for these procedures, again assuming normally distributed data, indicate good approximations to the "known variances" case when c_1 is greater than one.

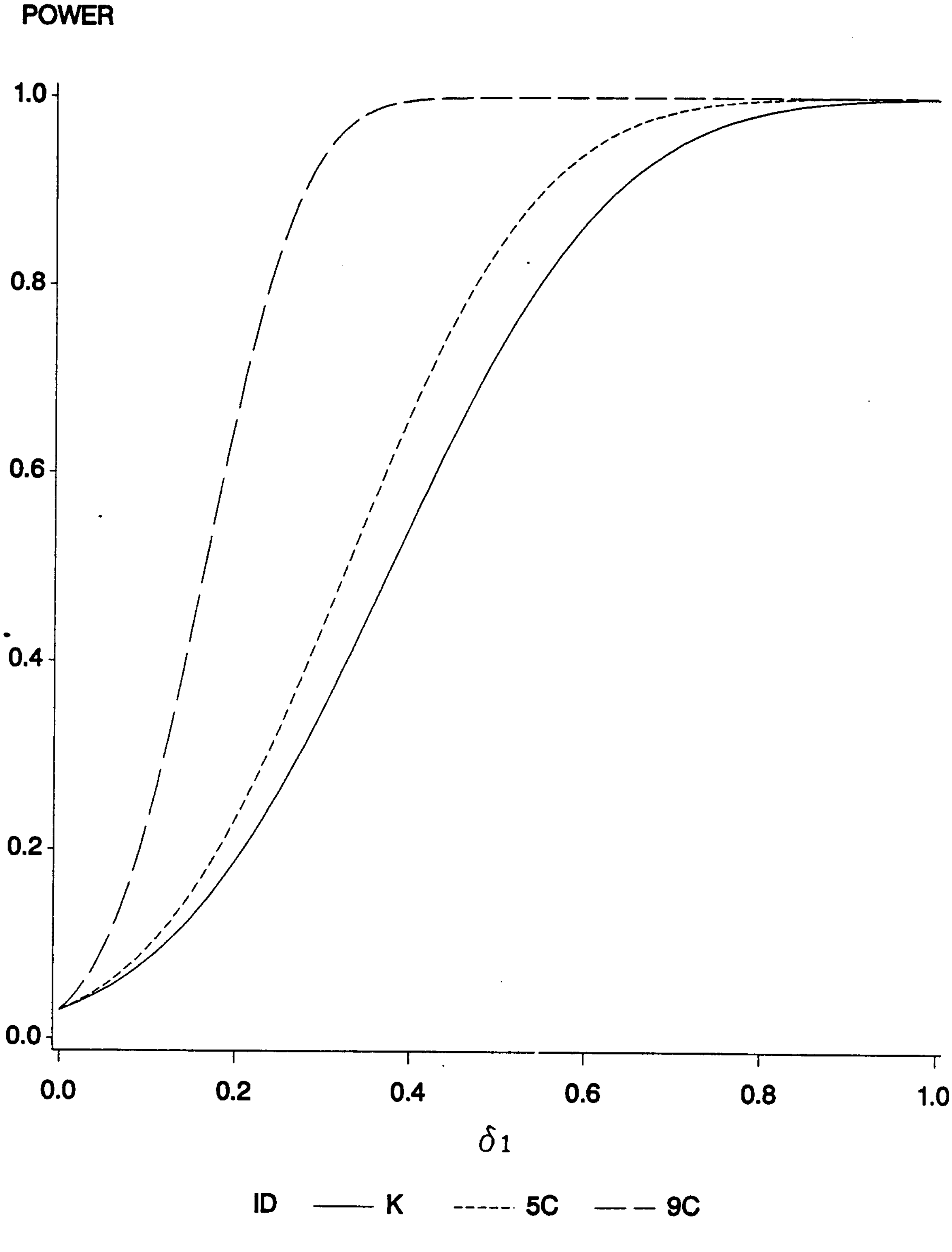
Data analysis using a subset of the observations from the LRC-CPPT study indicates that the covariate k-ratio test procedure compares favorably to the Analysis of Covariance. This result holds true whether c_1 is assumed known, or is estimated from the data.

In conclusion, the covariate k-ratio procedure yields tests with consistently greater power than Duncan's k-ratio test procedure. When data include a covariate, the covariate k-ratio test is a reasonable alternative to the Analysis of Covariance in regards to power. The covariate k-ratio procedure is a valuable addition to the existing statistical methodology for multiple comparison analyses and existing statistical procedures for analyses involving covariates.

APPENDIX 2.1

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

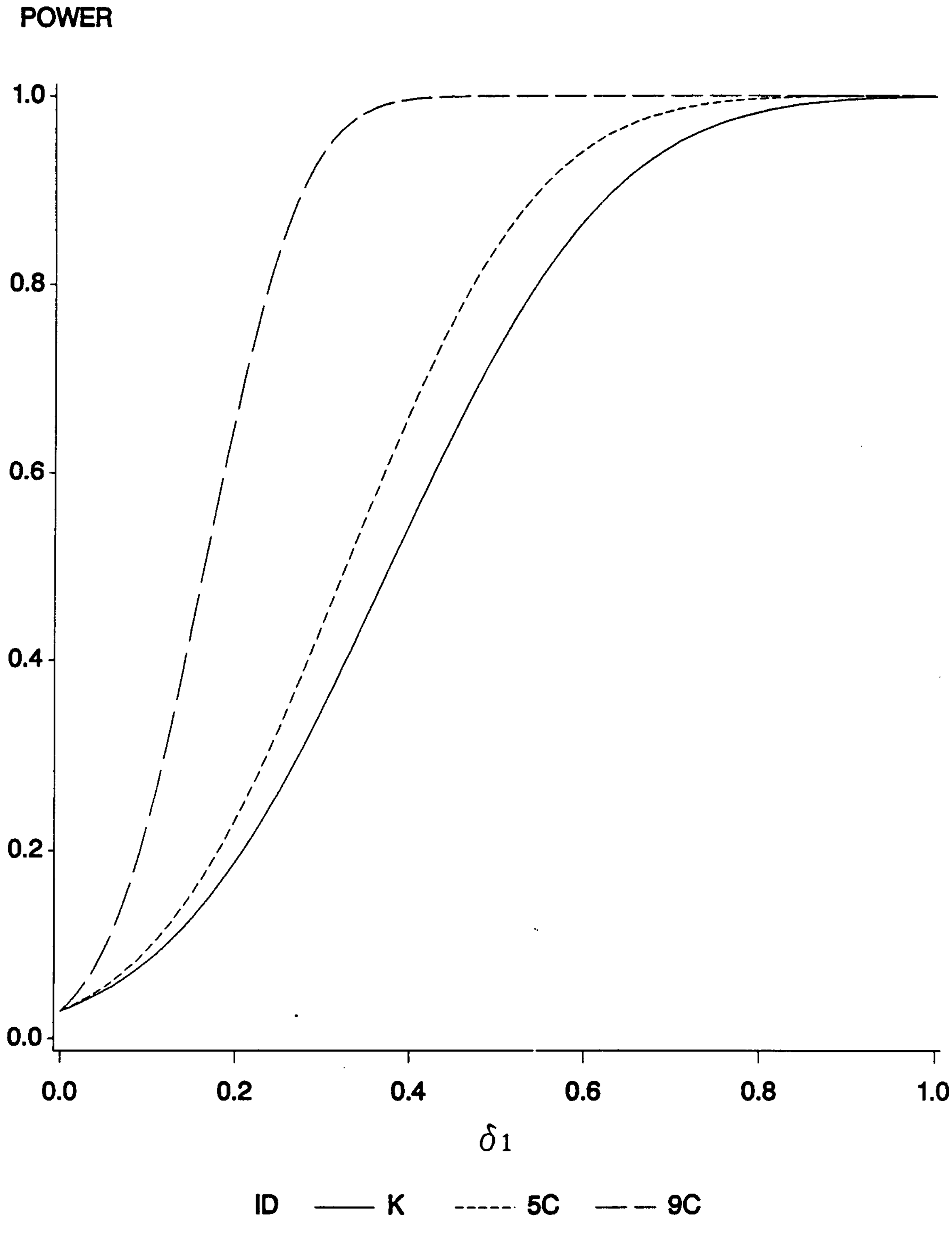
$C_1 = 0.1 \quad C_2 = 0.1 \quad \delta_{2a} = 0$



APPENDIX 2.2

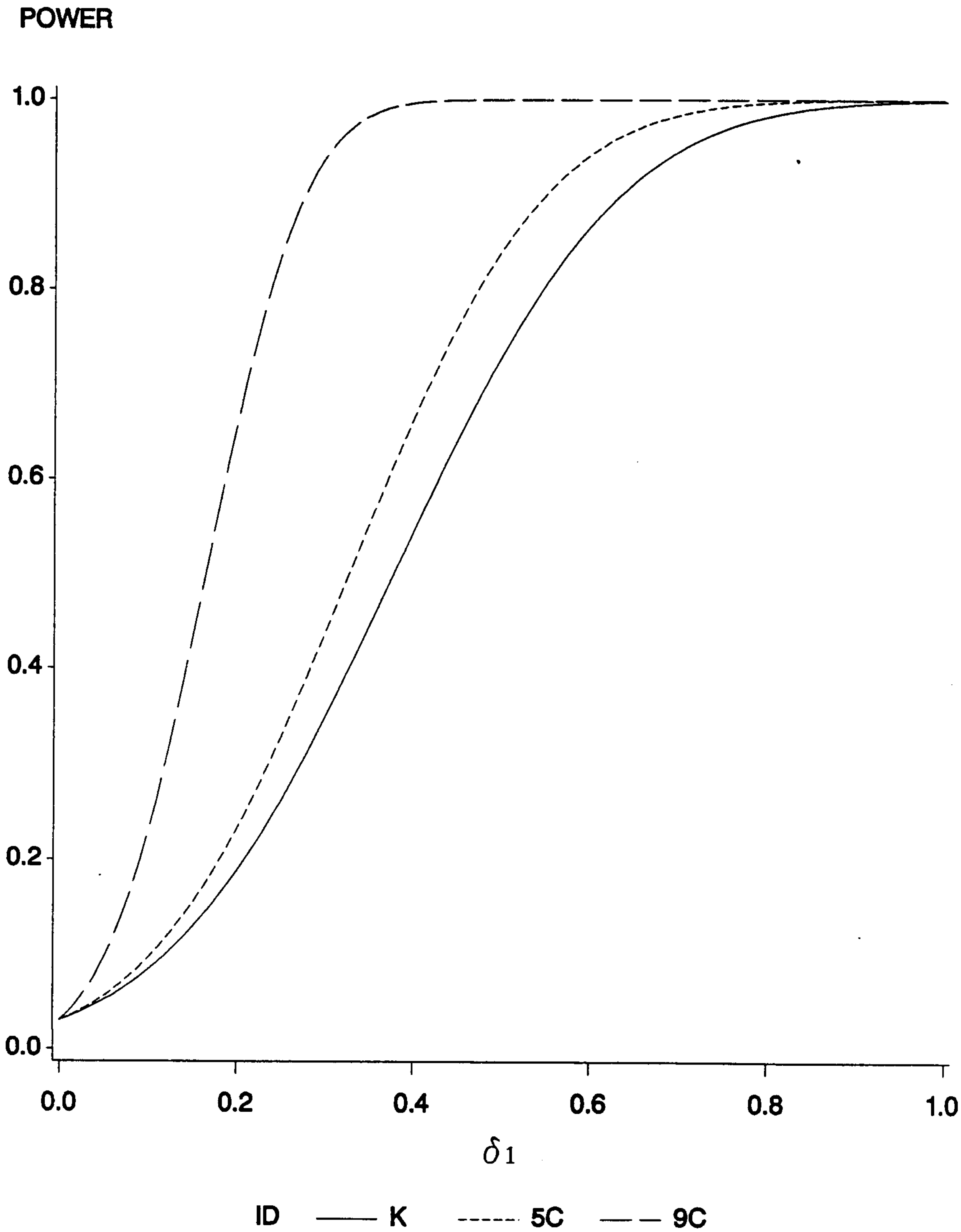
POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

$C_1=0.1 \quad C_2=1 \quad \delta_{2a}=0$



APPENDIX 2.3

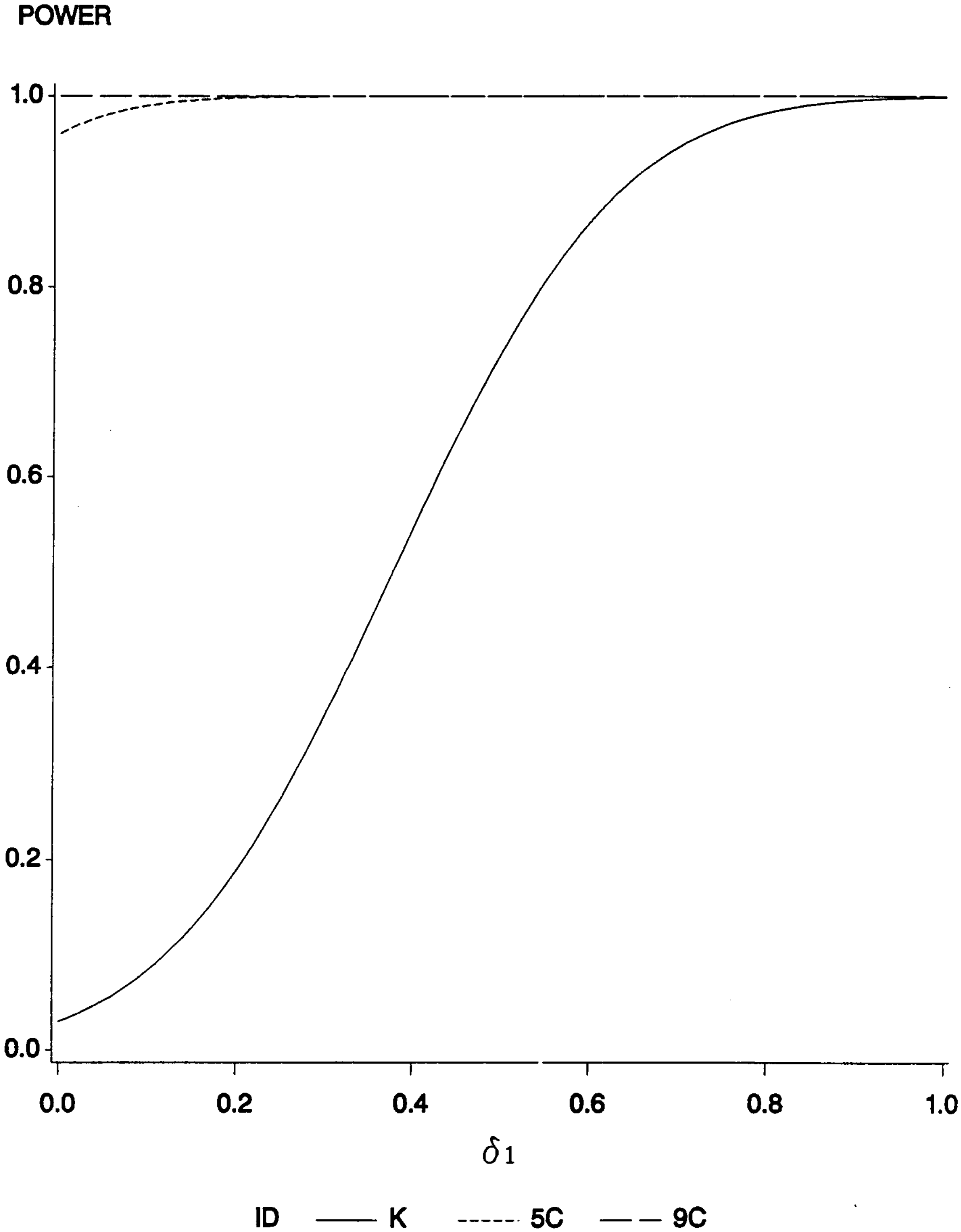
POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES
$C_1 = 0.1$ $C_2 = 10$ $\delta_{2a} = 0$



APPENDIX 2.4

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

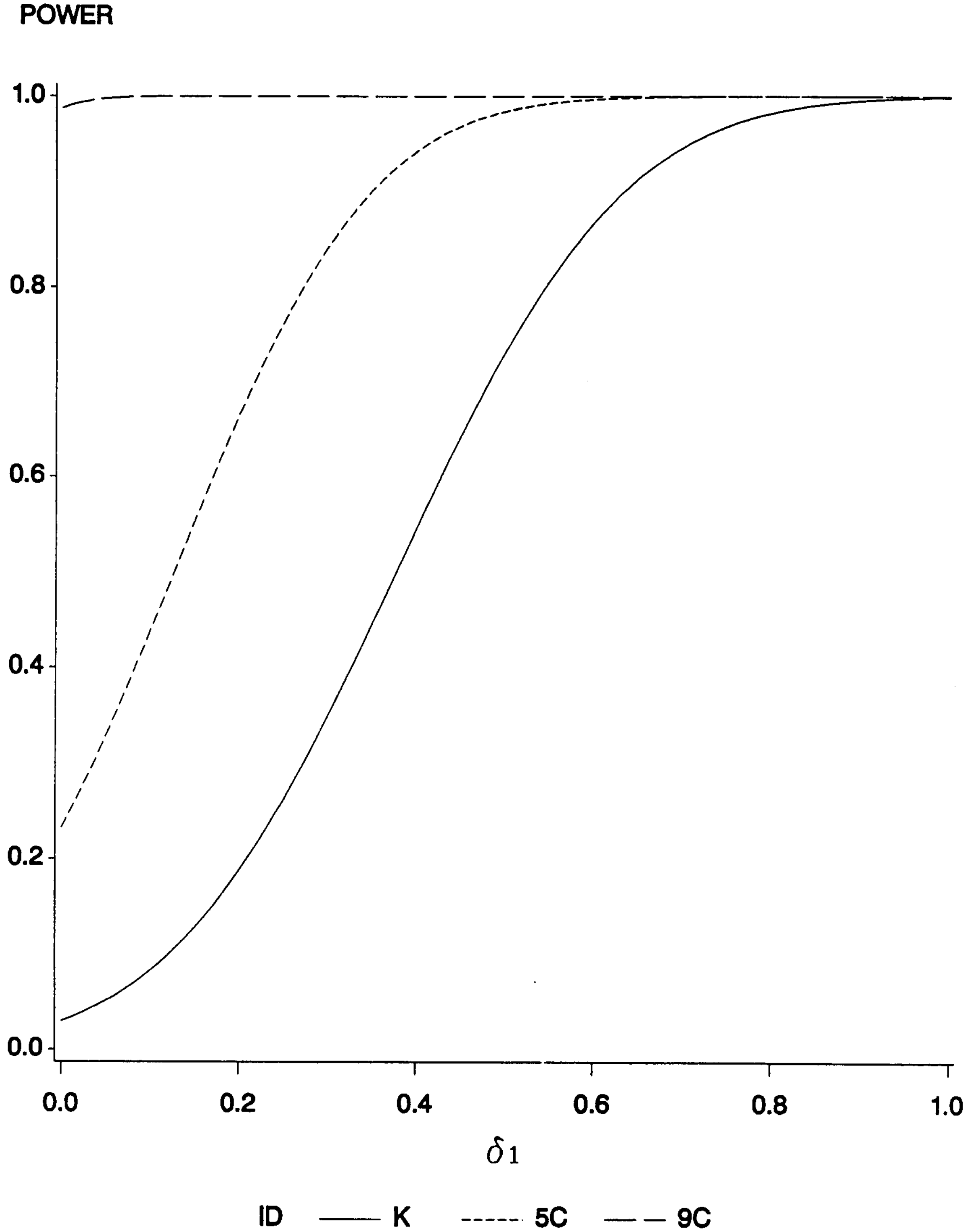
$C_1 = 0.1 \quad C_2 = 0.1 \quad \delta_{2a} = 2$



APPENDIX 2.5

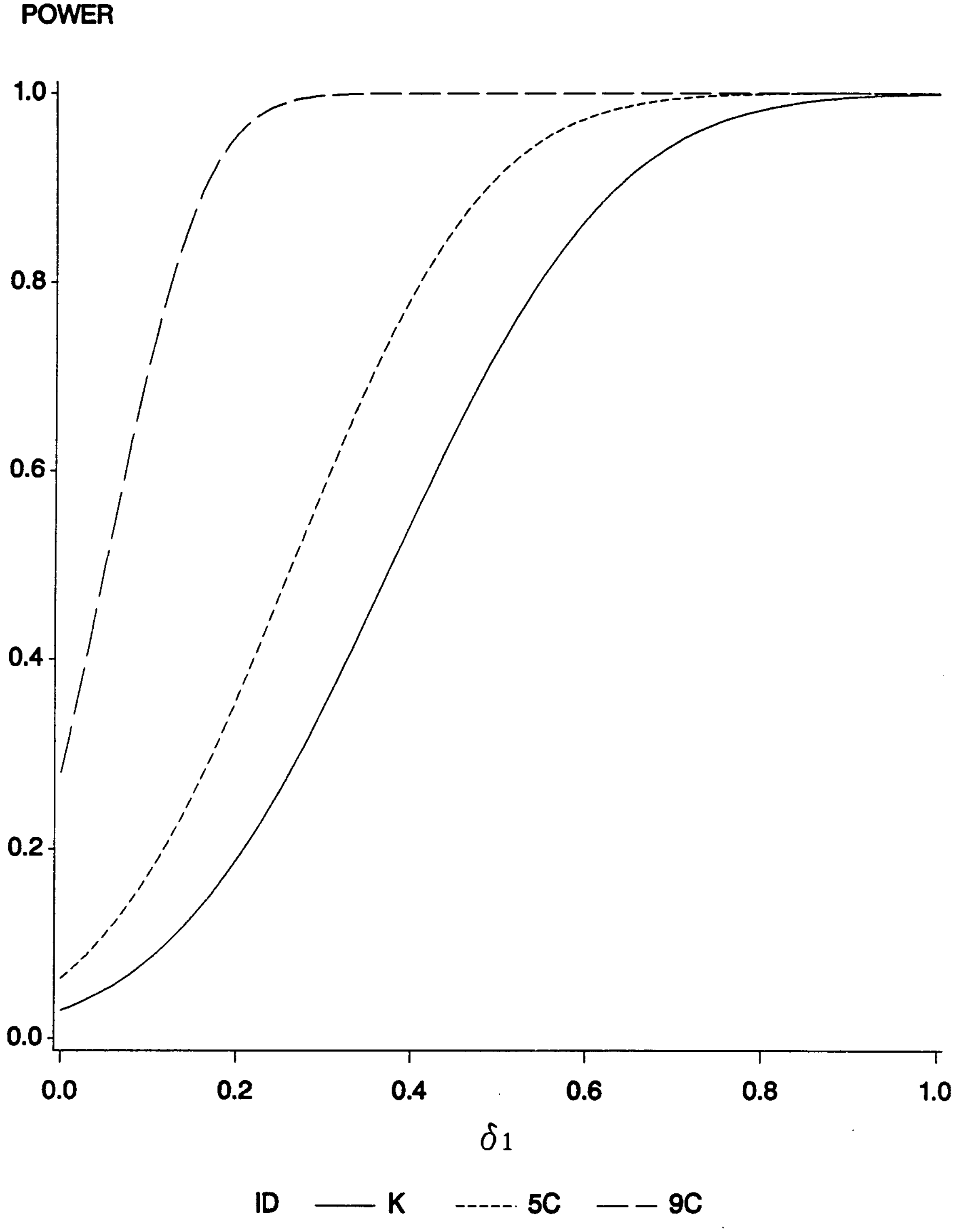
POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

$C_1 = 0.1 \quad C_2 = 1 \quad \delta_{2a} = 2$



APPENDIX 2.6

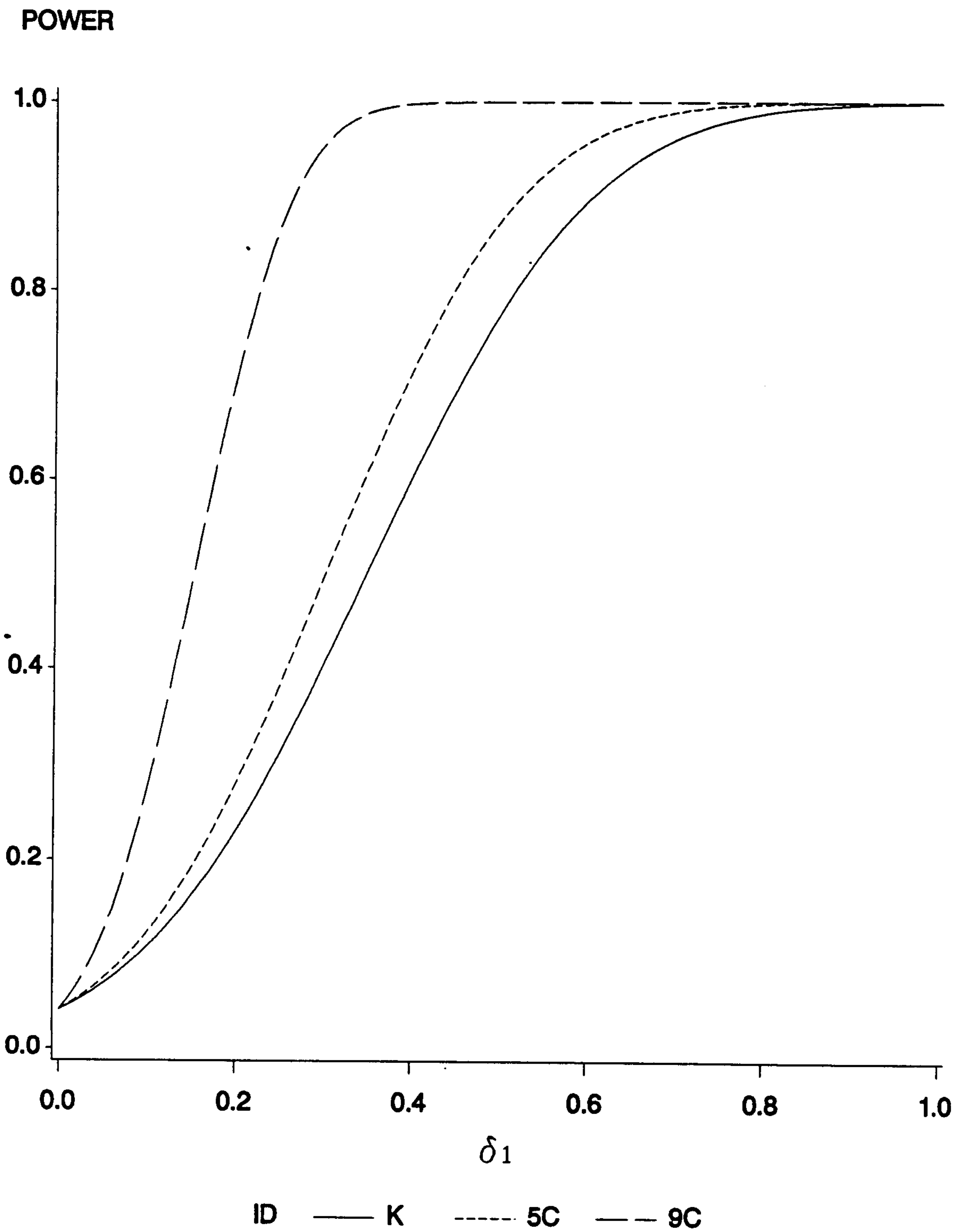
POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES
$C_1=0.1 \quad C_2=10 \quad \delta_{2a}=2$



APPENDIX 2.7

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

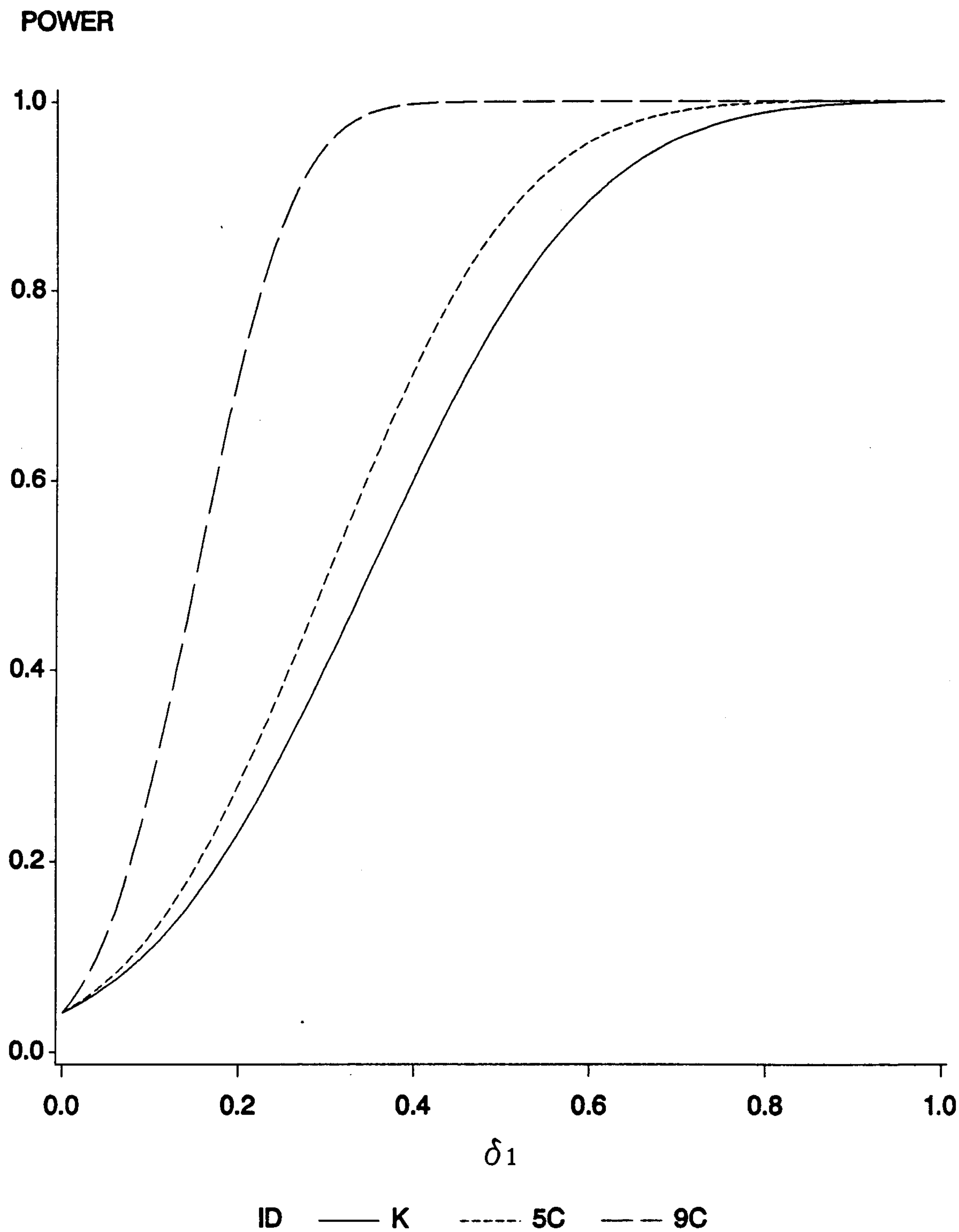
$C_1=1 \quad C_2=0.1 \quad \delta_{2a}=0$



APPENDIX 2.8

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

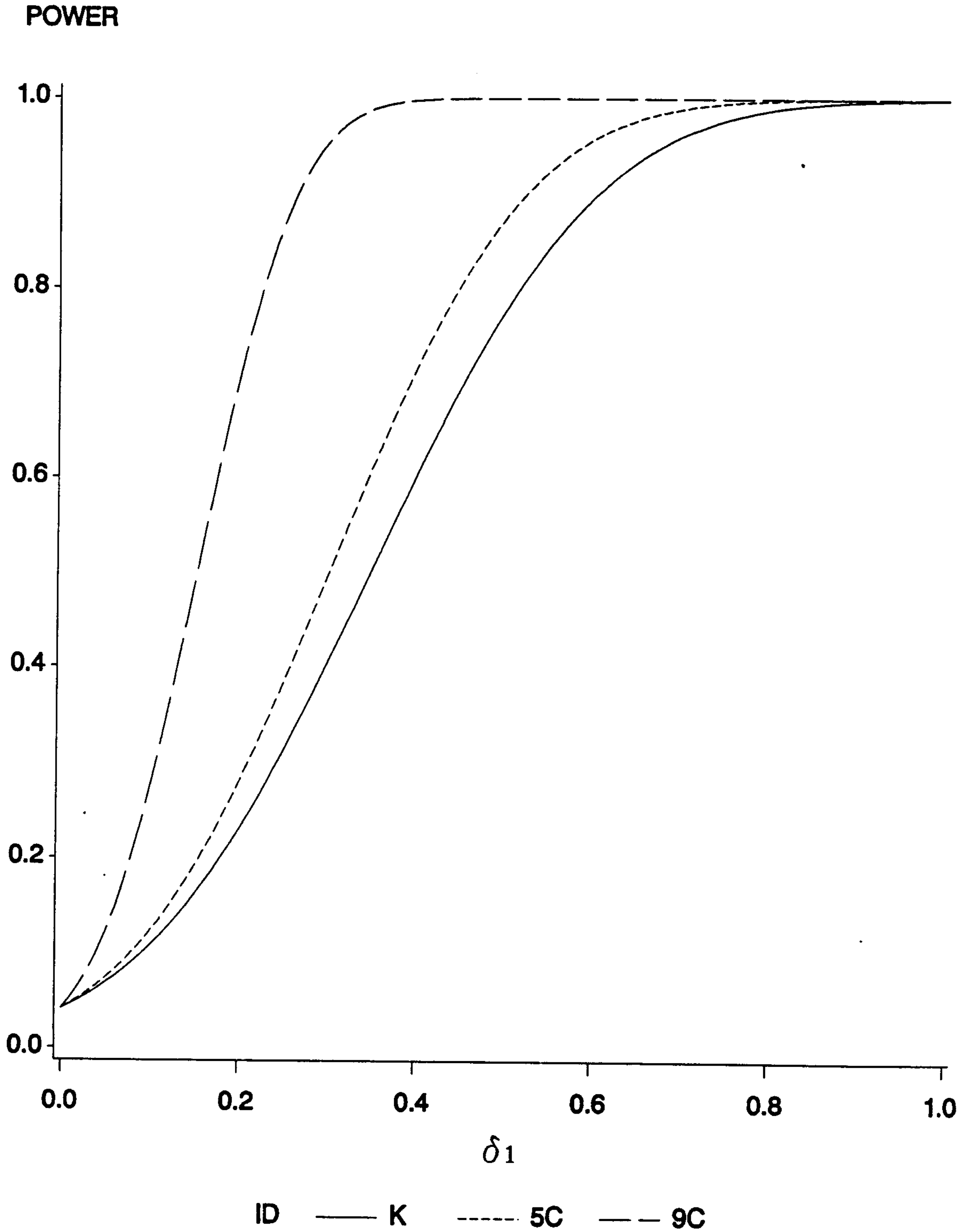
$C_1=1 \quad C_2=1 \quad \delta_{2a}=0$



APPENDIX 2.9

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

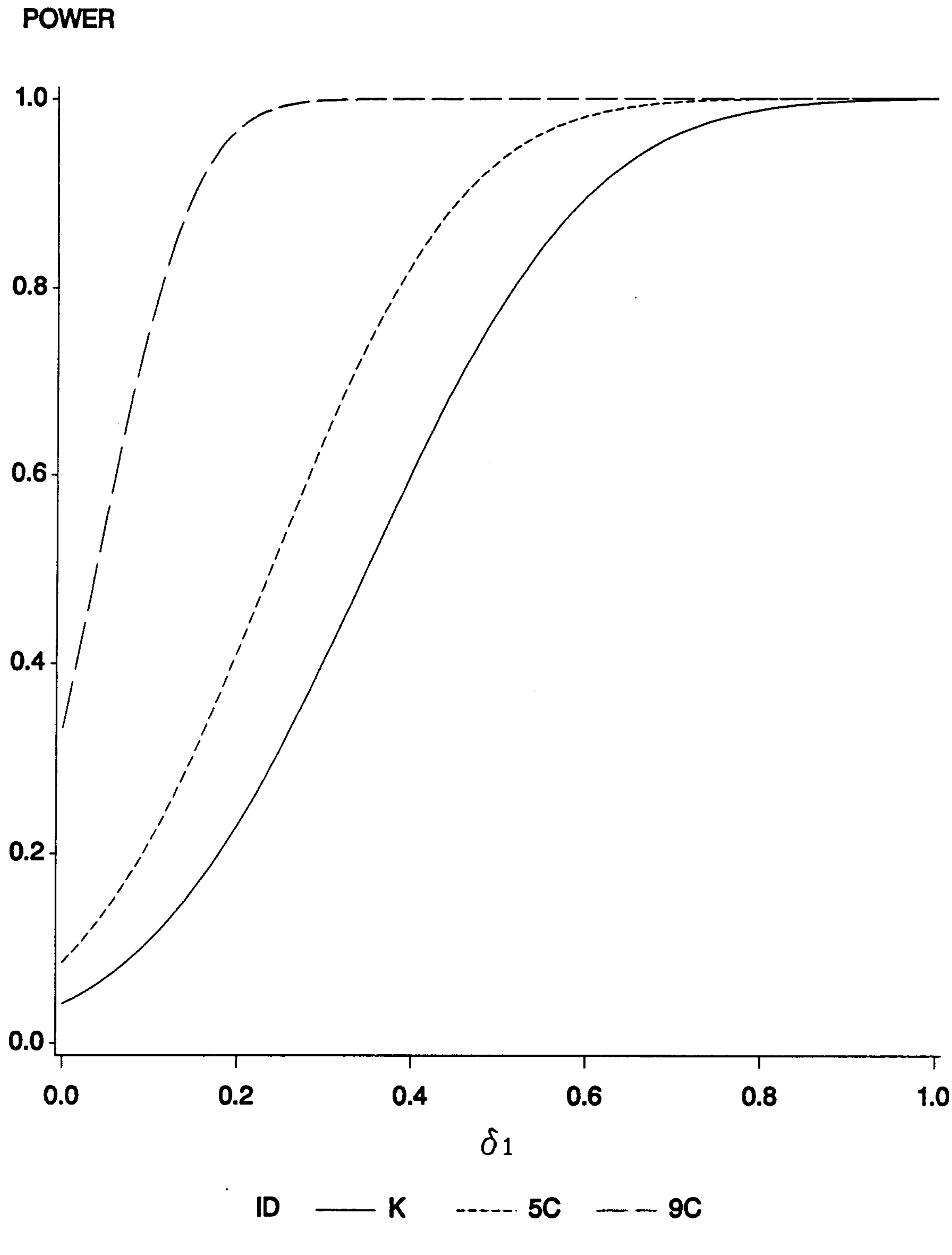
$C_1 = 1 \quad C_2 = 10 \quad \delta_{2a} = 0$



APPENDIX 2.10

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

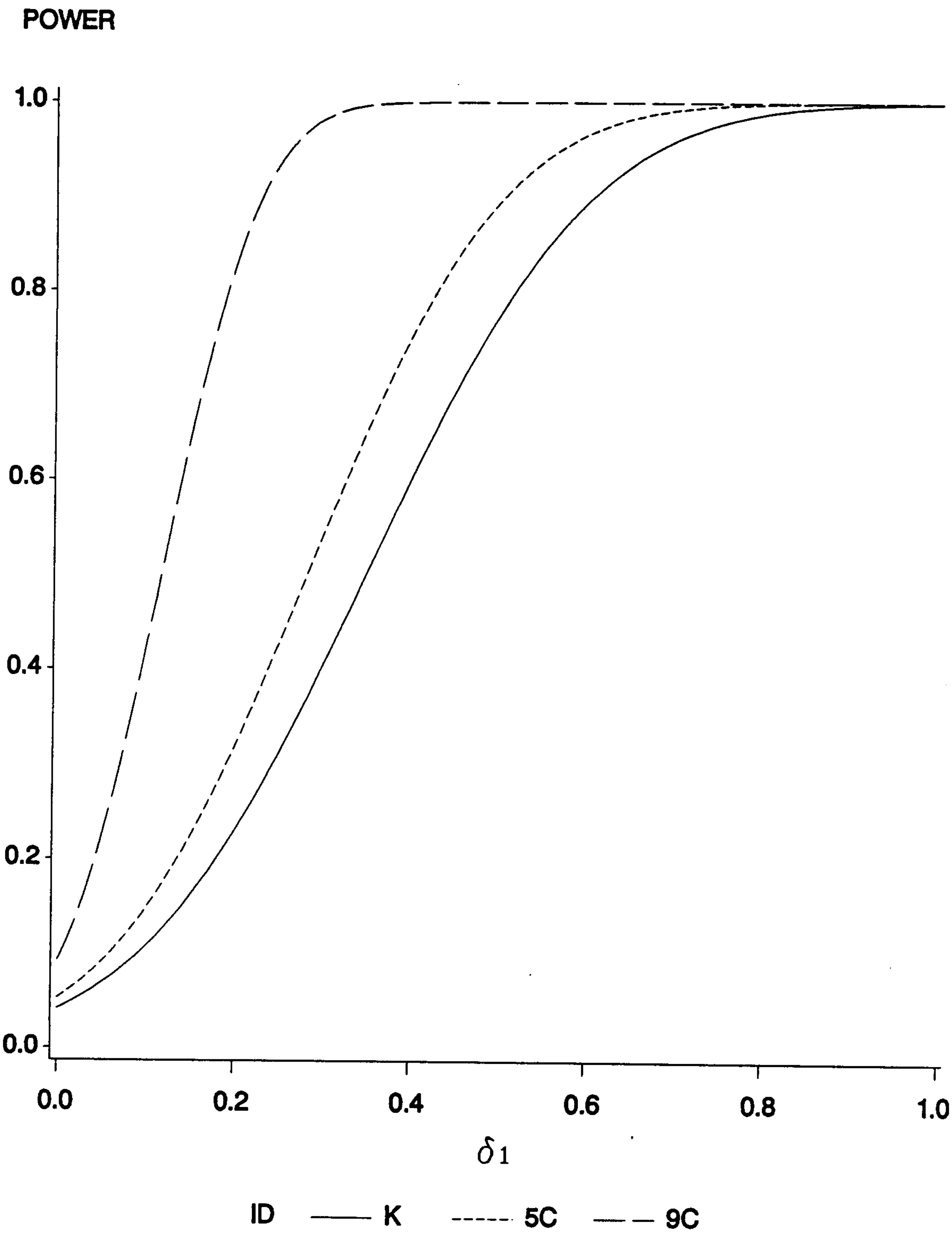
$C_1=1 \quad C_2=0.1 \quad \delta_{2a}=2$



APPENDIX 2.11

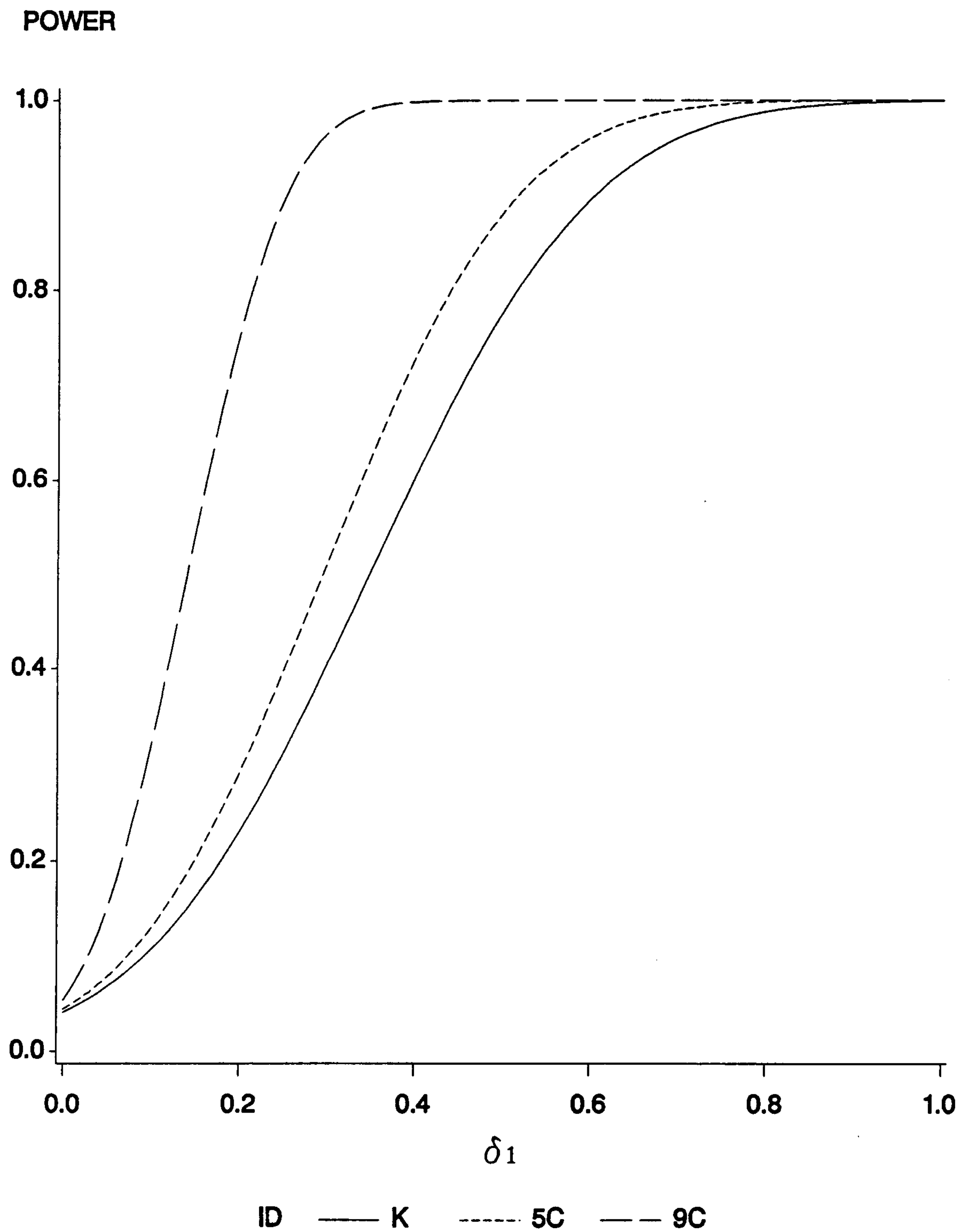
POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

$C_1 = 1 \quad C_2 = 1 \quad \delta_{2a} = 2$



APPENDIX 2.12

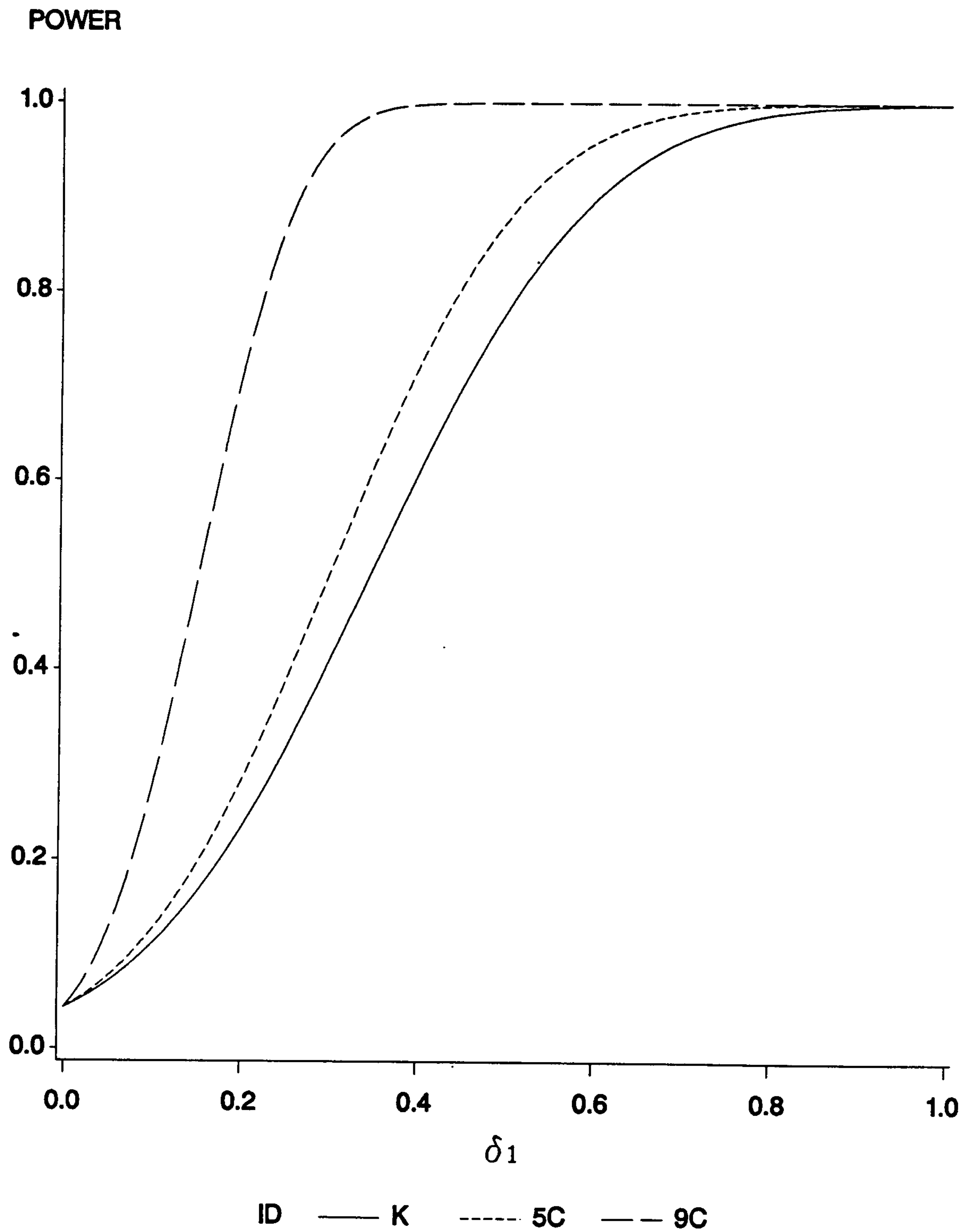
POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES
$C_1=1 \quad C_2=10 \quad \delta_{2a}=2$



APPENDIX 2.13

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

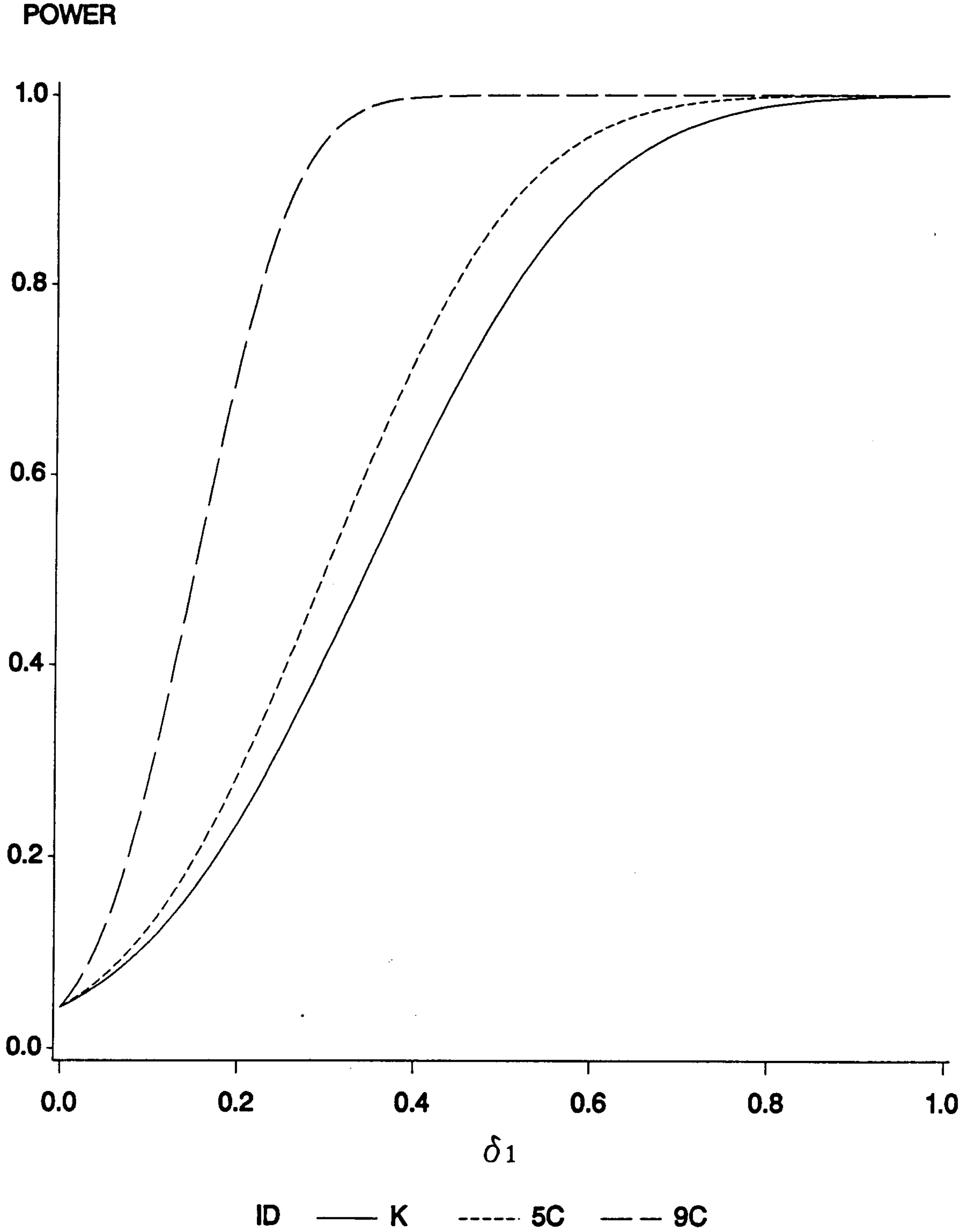
$C_1 = 10 \quad C_2 = 0.1 \quad \delta_{2a} = 0$



APPENDIX 2.14

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

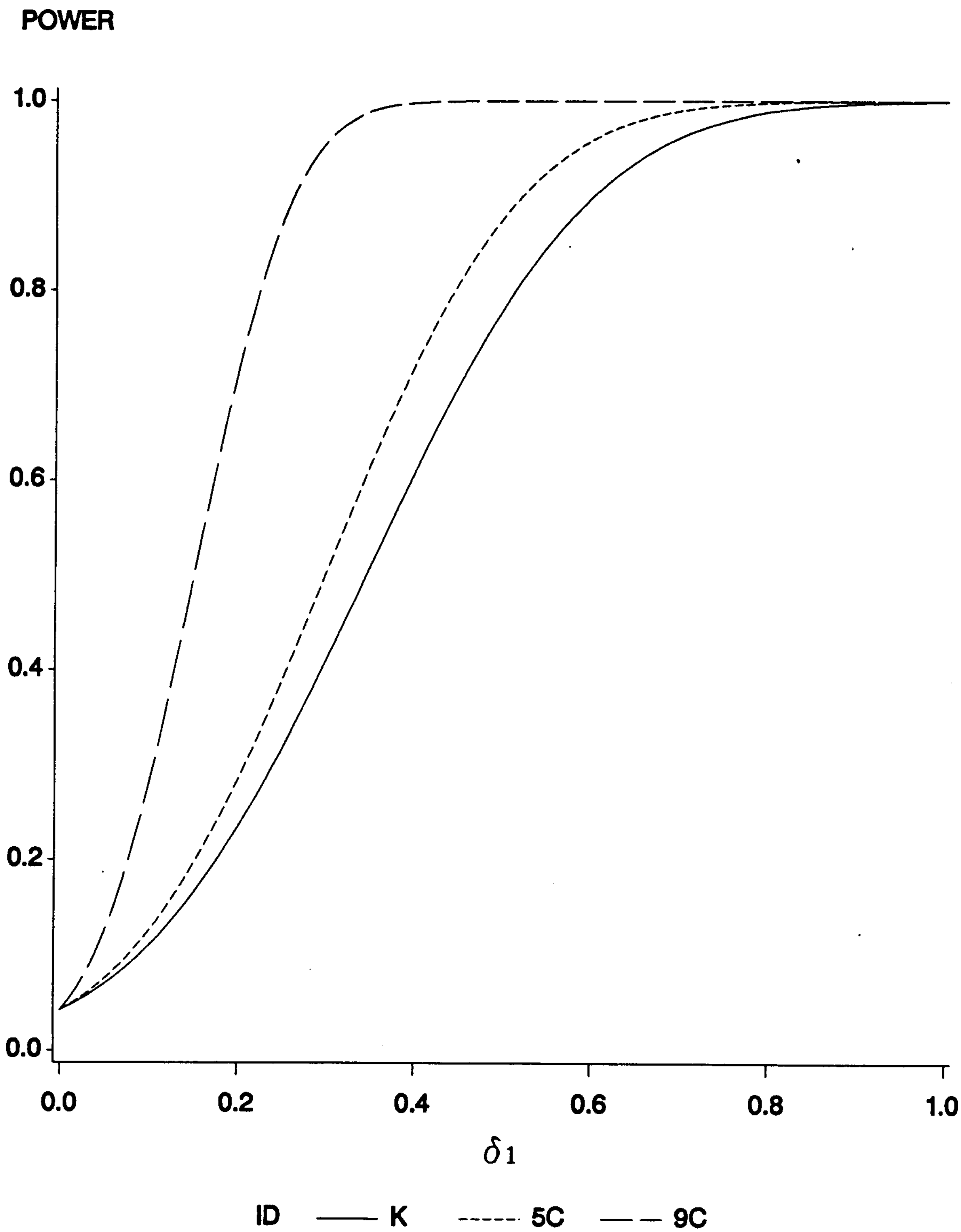
$C_1=10 \quad C_2=1 \quad \delta_{2a}=0$



APPENDIX 2.15

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

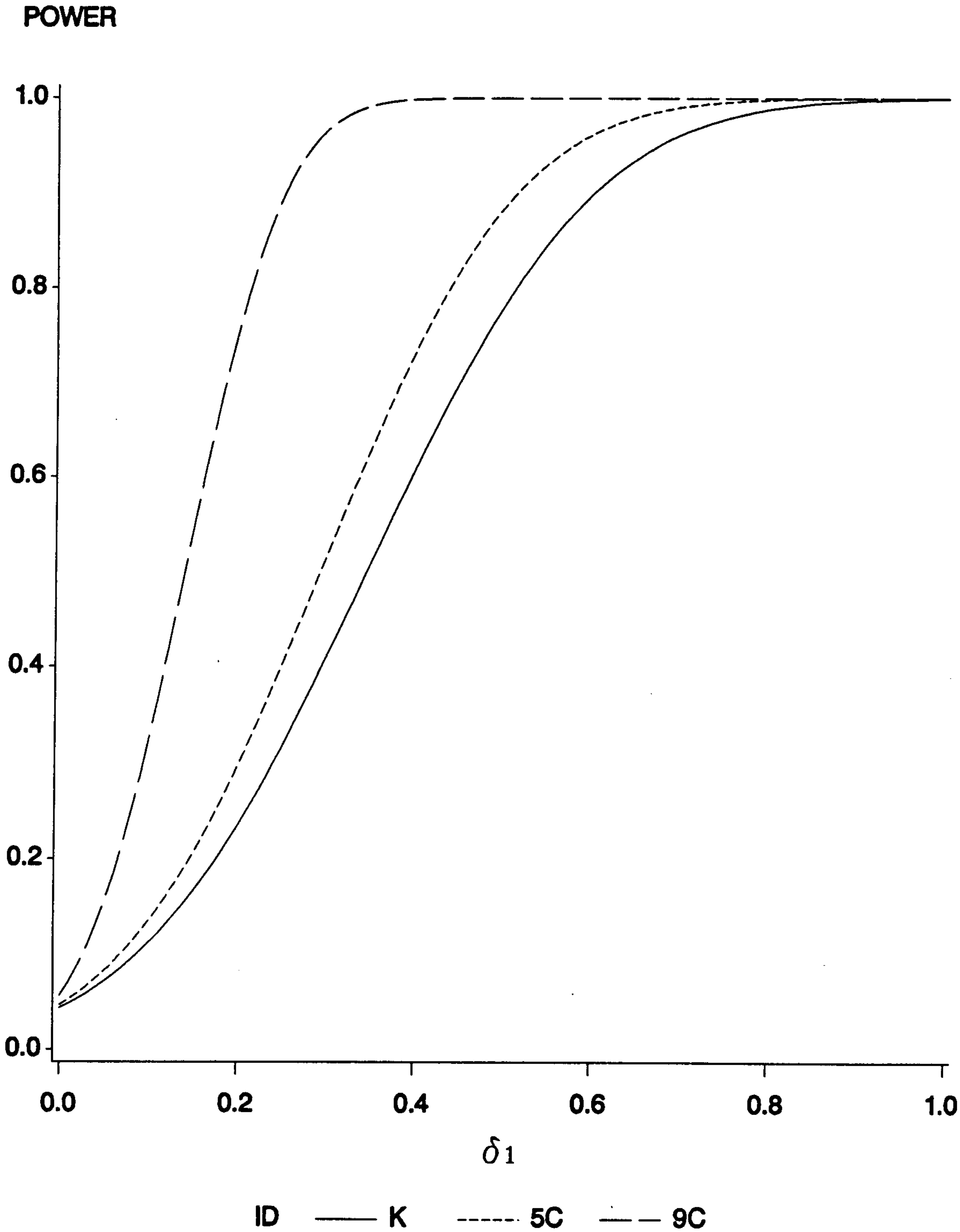
$C_1 = 10 \quad C_2 = 10 \quad \delta_{2a} = 0$



APPENDIX 2.16

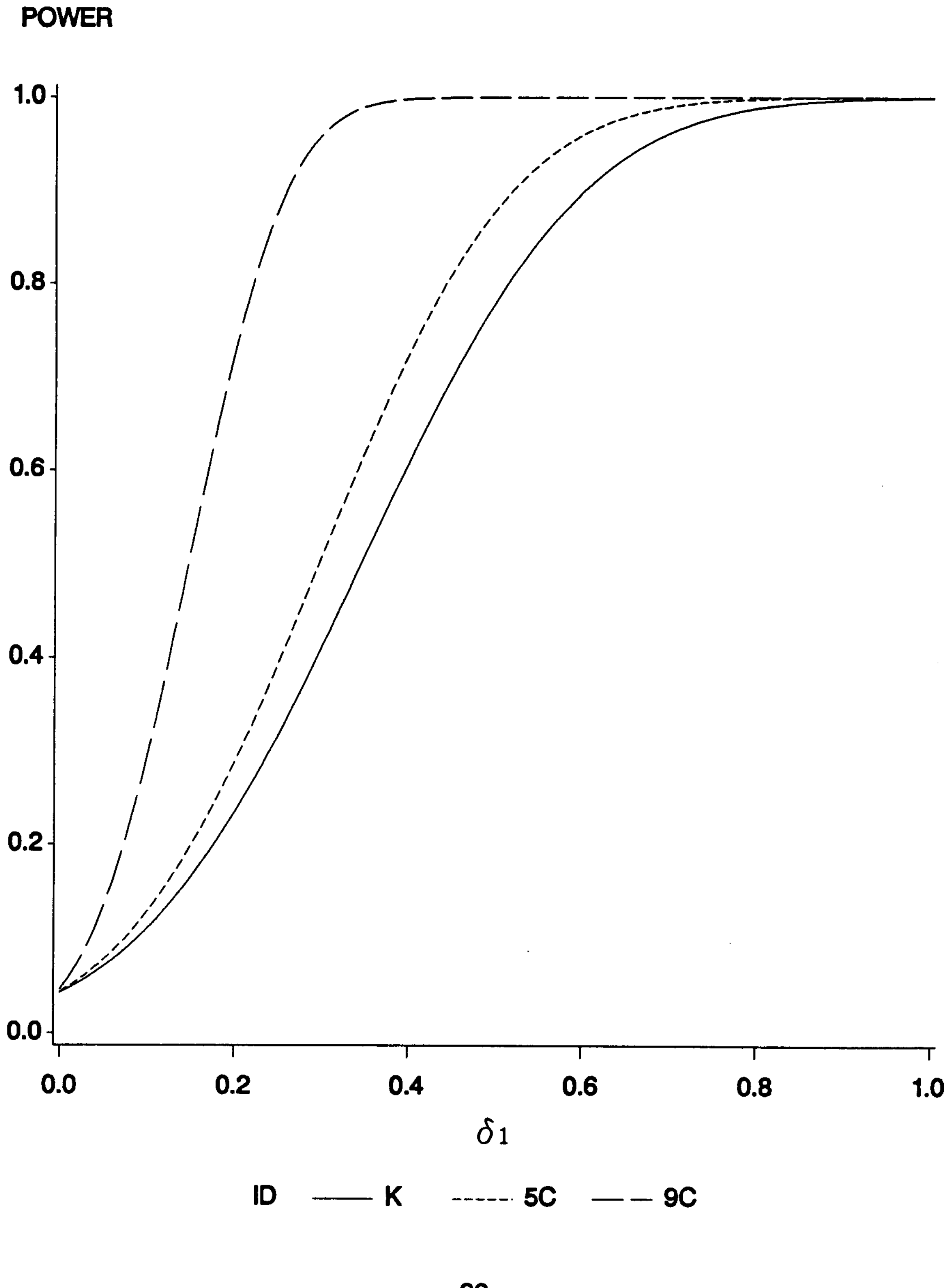
POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES

$C_1 = 10 \quad C_2 = 0.1 \quad \delta_{2a} = 2$

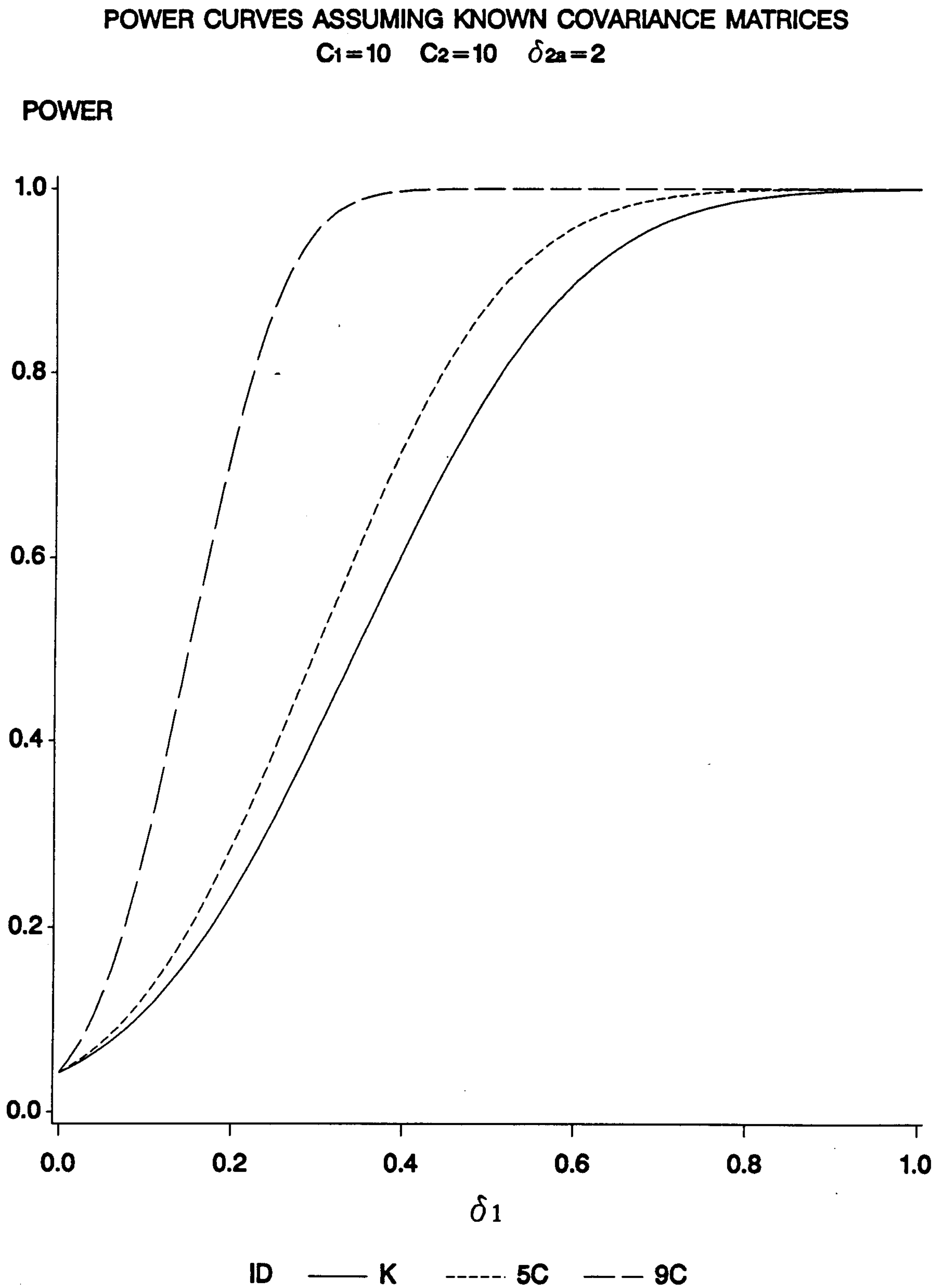


APPENDIX 2.17

POWER CURVES ASSUMING KNOWN COVARIANCE MATRICES
$C_1=10 \quad C_2=1 \quad \delta_{2a}=2$



APPENDIX 2.18



APPENDIX 3.1

SIMULATION PROGRAM FOR CHAPTER 3

```
proc iml;

****   we set up the vector of values
****          for the nuisance parameters   ;

c1=0.10; c2=1;

do l=0 to 10 by 5;
if l=5 | l=0 then rho=l/10;
else if l=10 then rho=(l-1)/10; print rho;

covar=rho*sqrt(c2);
sigma1=(1 || covar);   sigma2= (covar|| c2);
sigma_u=c1*(sigma1 // sigma2);

****  sigma_u is the covariance matrix for the mu's    ;

bu=root(sigma_u);
cu=bu`;

****  sigma_x is the covariance matrix
 ****       for the x observations;

sigma_x=(sigma1 // sigma2);
bx=root(sigma_x);
cx=bx`;

do delta1=0 to 1 by 0.2;

****   delta is the vector of alternative values
****          of delta for the power calculations;

delta=(delta1//0);


**** we now perform simulation of data
****        and resulting statistical
****        calculations 250 times          ;

do k=1 to 250  ;

****  The zij's are two normal(0,1) variates  ;

z21=normal(0);
z22=normal(0);

z2=(z21//z22);
```

SIMULATION PROGRAM FOR CHAPTER 3

```
 **** the following statement transforms z2 into u2--
 ****      bivariate normal with mean 0
 ****      and covariance matrix sigma_u;

 u2=cu*z2;

 **** We now transform u2 into mui's.
 ****     Mu1 is bivariate normal with
 ****     mean delta and mu2 is bivariate normal(0).
 ****     Each has covariance matrix sigma_u;

 mu1=u2+delta;   mu2=u2;

 **** we now generate, for a given mui,
 ****      normal samples of 50 observations
 ****      with mean mui and covariance matrix sigma_x ;

 do i=1 to 100;

 **** za and zb are n(0,1) variates  ;
 za=normal(0);   zb=normal(0);

 **** pointer equals zero for treatment group 2
 ****      and equals one for treatment group 1;

 pointer=mod(i,2);

 z=(za//zb);

 **** x_zero is a normal(0,sigma_x) bivariate vector;

 x_zero=cx*z;

 ****************************************************;

 if pointer=0 then do;
 col=i/2;

 **** x_obs, here is a normal(mu2,sigma_x) vector;

 xobs=x_zero+mu2;

if col=1 then trt2=(xobs);
else
trt2=(trt2||xobs);
end;
```

APPENDIX 3.1 (cont'd)

SIMULATION PROGRAM FOR CHAPTER 3

```
if pointer=1 then do;

col=(i+1)/2;

**** x_obs, here is a normal(mu1,sigma_x) vector;

xobs=x_zero+mu1;
if col=1 then trt1=(xobs);
else trt1=(trt1||xobs);
end;

*****************************************************;

**** TRTi is a 2 x n_obs matrix of
****      the x observations for treatment group i;

end;

n_obs=ncol(trt1);
trt1col1=trt1(|1,|);   trt1col2=trt1(|2,|);
trt2col1=trt2(|1,|);  trt2col2=trt2(|2,|);
trt1avg1=sum(trt1col1)/n_obs;
trt1avg2=sum(trt1col2)/n_obs;
trt2avg1=sum(trt2col1)/n_obs;
trt2avg2=sum(trt2col2)/n_obs;

****  TRTiMEAN is the mean vector
****       for treatment group i;

trt1mean=(trt1avg1//trt1avg2);
trt2mean=(trt2avg1//trt2avg2);

**** we now compute the sum-of-squares matrix
****      for treatment group i --
****      denoted as SSi;

do j=1 to n_obs;

mat1=trt1(|,j|);
mat2=trt2(|,j|);
ss1mat=mat1*mat1`;
ss2mat=mat2*mat2`;
if j=1 then do;
ss1=ss1mat;  ss2=ss2mat;
end;

else do;
ss1=ss1+ss1mat;   ss2=ss2+ss2mat;
end;
```

```
end;

****  COVARi is the sample sums-of-squares and
****       cross products matrix for treatment group i ;

covar1=ss1-((n_obs)*(trt1mean*trt1mean`));
covar2=ss2-((n_obs)*(trt2mean*trt2mean`));

**** COV_x is the sample covariance matrix
****      for the observations which estimates sigma_x;

cov_x=(covar1+covar2)/(n_obs+n_obs-2);

sd1=sqrt(cov_x(|1,1|));   sd2=sqrt(cov_x(|2,2|));
corr=cov_x(|2,1|)/(sd1*sd2);
corrmat=(cov_x(|1,1|)||corr)//(corr||cov_x(|2,2|));

**** COV_delt is the estimated covariance matrix
****      for the delta's which estimates 2*sigma_u   ;

cov_delt=2*c1*cov_x;

**** cov_d is the estimated covariance matrix
****      for the treatment mean differences;

cov_d=2*cov_x/n_obs;

cov_plus=cov_d+cov_delt;
cov_both=(cov_delt||cov_delt)//(cov_delt||cov_plus);

**** postmult is the 1x3 vector which is
****      the first part of the calculation of the
****      posterior mean of the distribution h;

postmult=cov_both(|1,2:4|)*inv(cov_both(|2:4,2:4|));

**** meandiff is the observed d vector -- a 2x1
****      vector of observed treatment mean differences;

meandiff=trt1mean-trt2mean;

**** postmean is the estimate of the
****      posterior mean of the distribution h ;

postmean=postmult*(0//meandiff);

****  postvar is the posterior variance
****       of the distribution h;
```

APPENDIX 3.1 (cont'd)

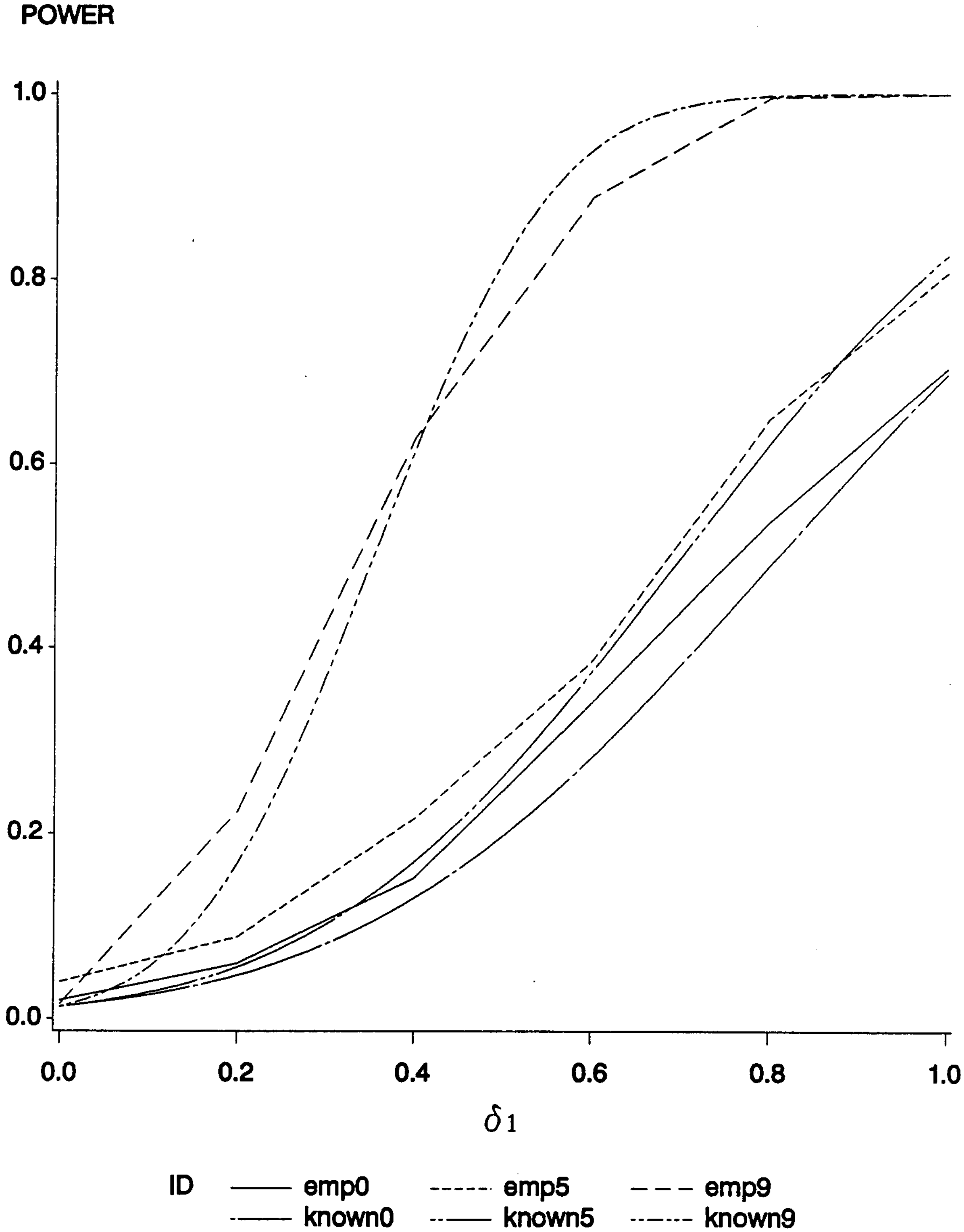
SIMULATION PROGRAM FOR CHAPTER 3

```
postvar=cov_both(|1,1|)-(postmult*cov_both(|2:4,1|));

**** var_id is a matrix to identify
****      the variable names for the output dataset;

var_id={"c1" "c2"  "delta1" "rho" "n_obs"
"postmean" "postvar" };

vector=(c1||c2||delta1||rho||n_obs||postmean||postvar);

if k=1 & delta1=0 & l=0
then create stats from vector (|colname=var_id |);

append from vector;

*****  close loop of 250 repeated simulations    ;
end;

****    close loop for differing delta1 values;
end;

****    close loop for differing rho values;
end;

data simula; set stats;
crit_val=postmean/sqrt(postvar);
if crit_val gt 1.721 then reject=1; else reject=0;
proc sort; by rho delta1;
proc means noprint;   by rho delta1;
id c1 c2 n_obs;   var reject;
output out=meands mean=power ; proc print;
libname save 'd:\lynn';
proc append base=save.simulads  data=meands;
run;
```

APPENDIX 3.2

POWER CURVE COMPARISONS FOR ESTIMATED Σx

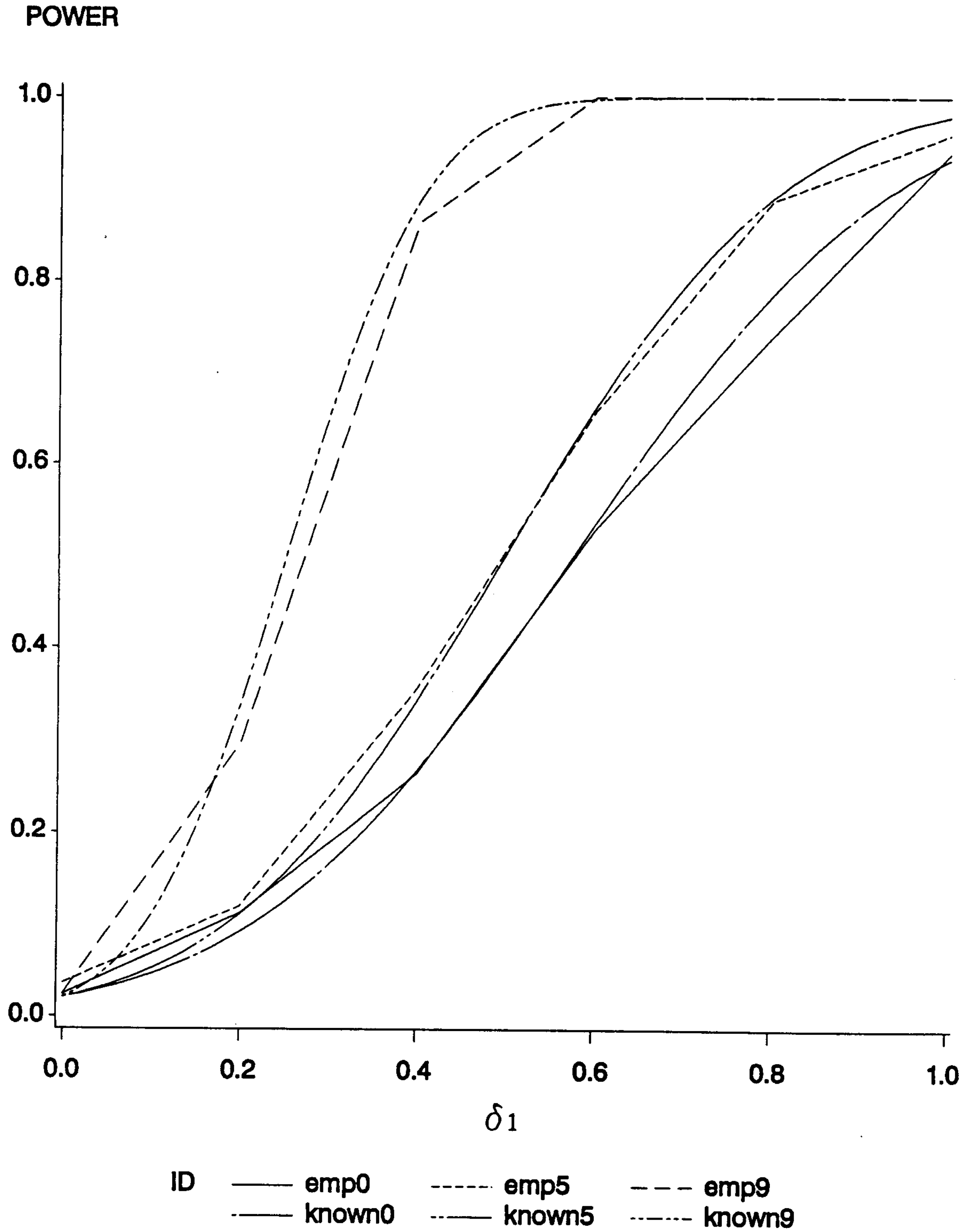
$C_1=0.1$ $C_2=0.1$ $\delta_{2a}=0$ $n=15$



APPENDIX 3.3

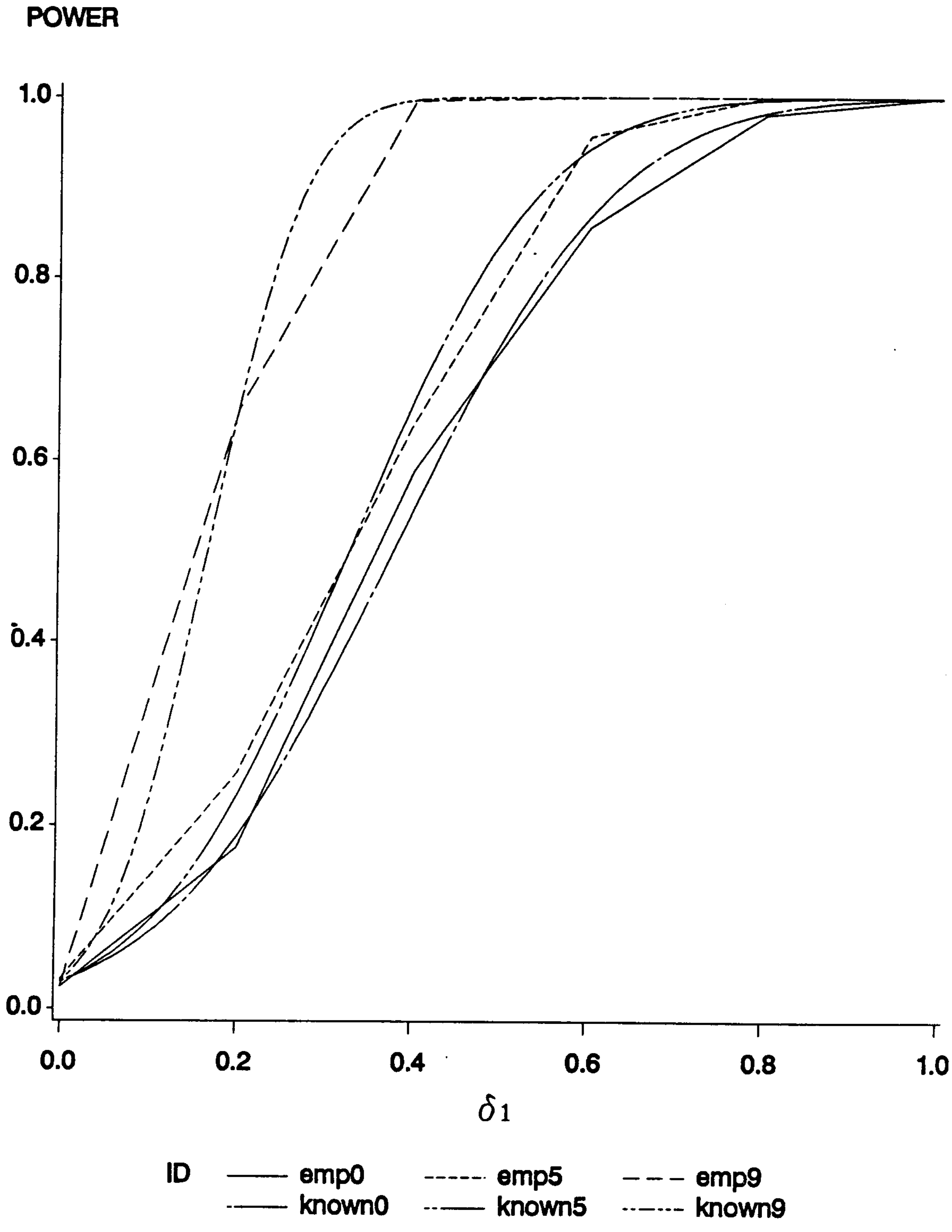
POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

$C_1 = 0.1 \quad C_2 = 0.1 \quad \delta_{2a} = 0 \quad n = 25$

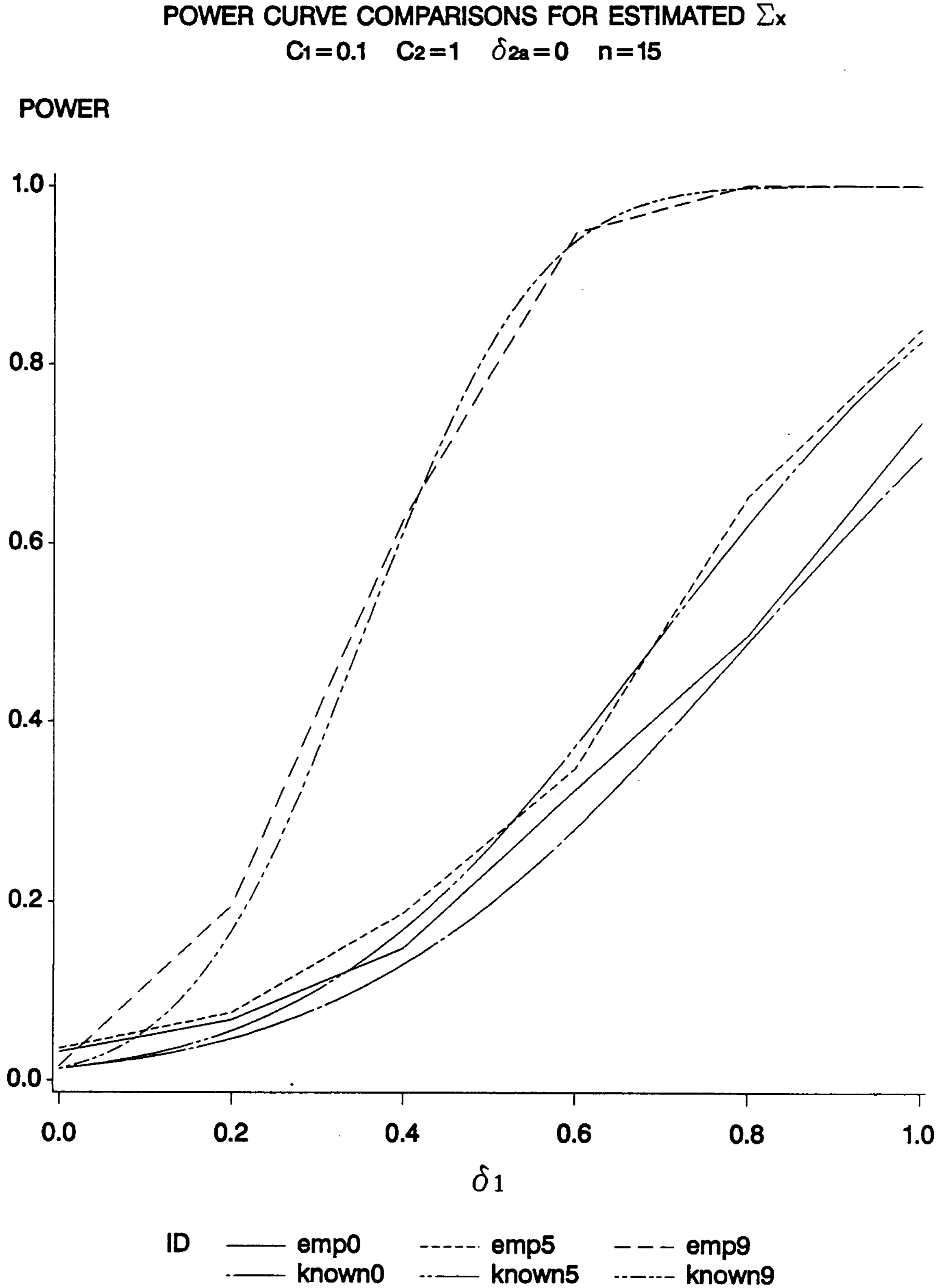


APPENDIX 3.4

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x
$C_1=0.1$ $C_2=0.1$ $\delta_{2a}=0$ $n=50$



APPENDIX 3.5

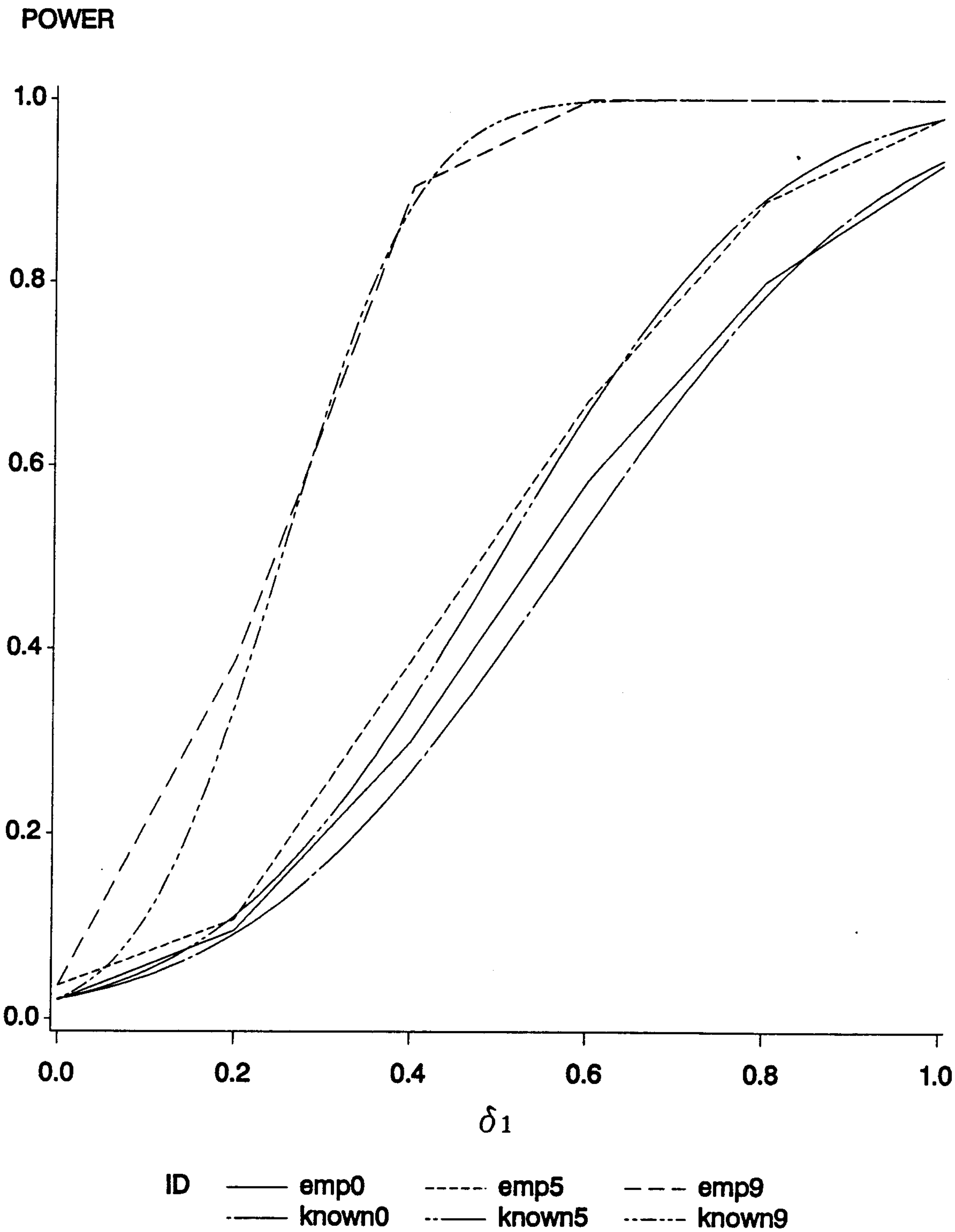


POWER CURVE COMPARISONS FOR ESTIMATED Σx
$C_1=0.1$ $C_2=1$ $\delta_{2a}=0$ $n=15$
POWER
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
δ_1
ID
emp0
emp5
emp9
known0
known5
known9

APPENDIX 3.6

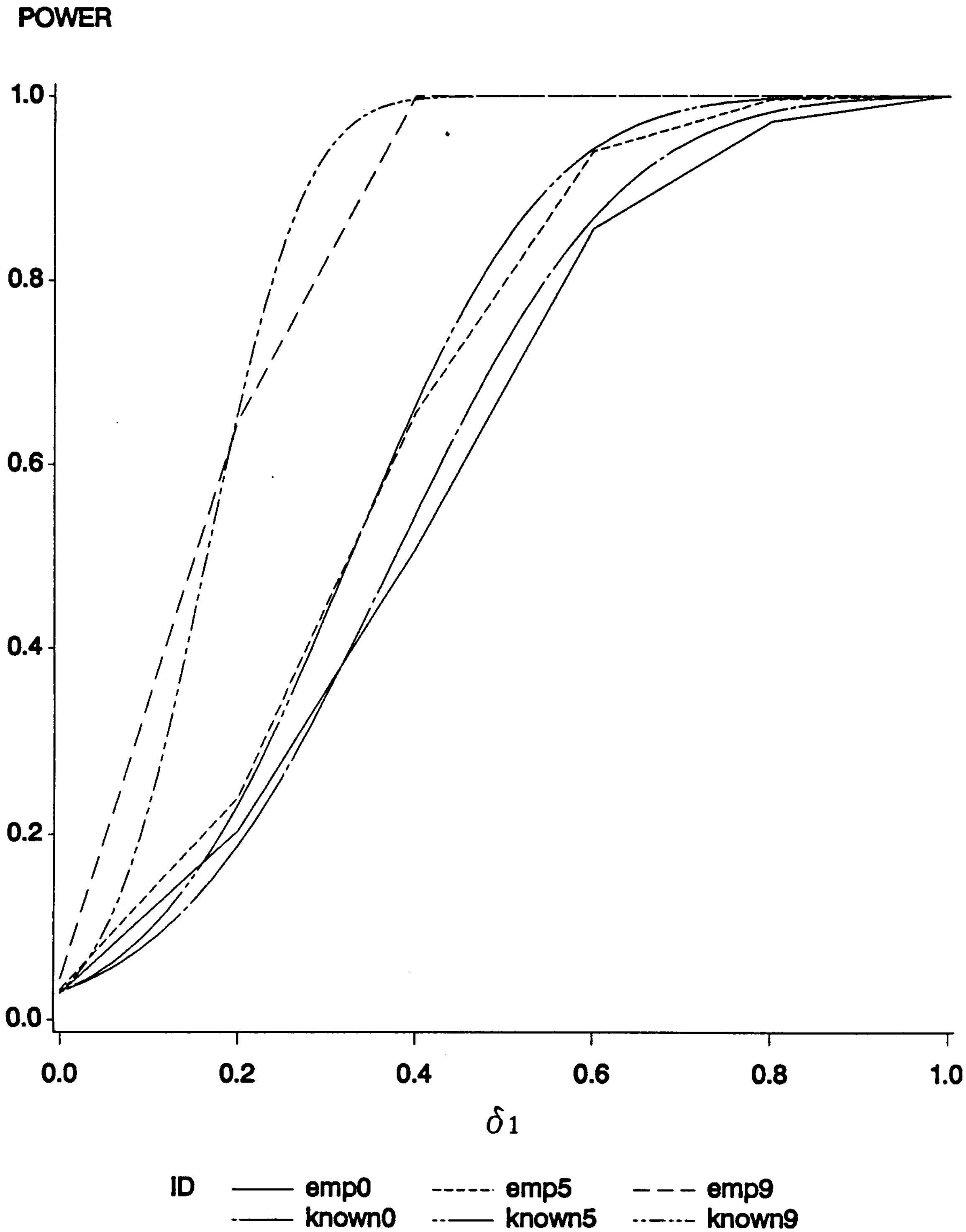
POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

$C_1 = 0.1 \quad C_2 = 1 \quad \delta_{2a} = 0 \quad n = 25$



APPENDIX 3.7

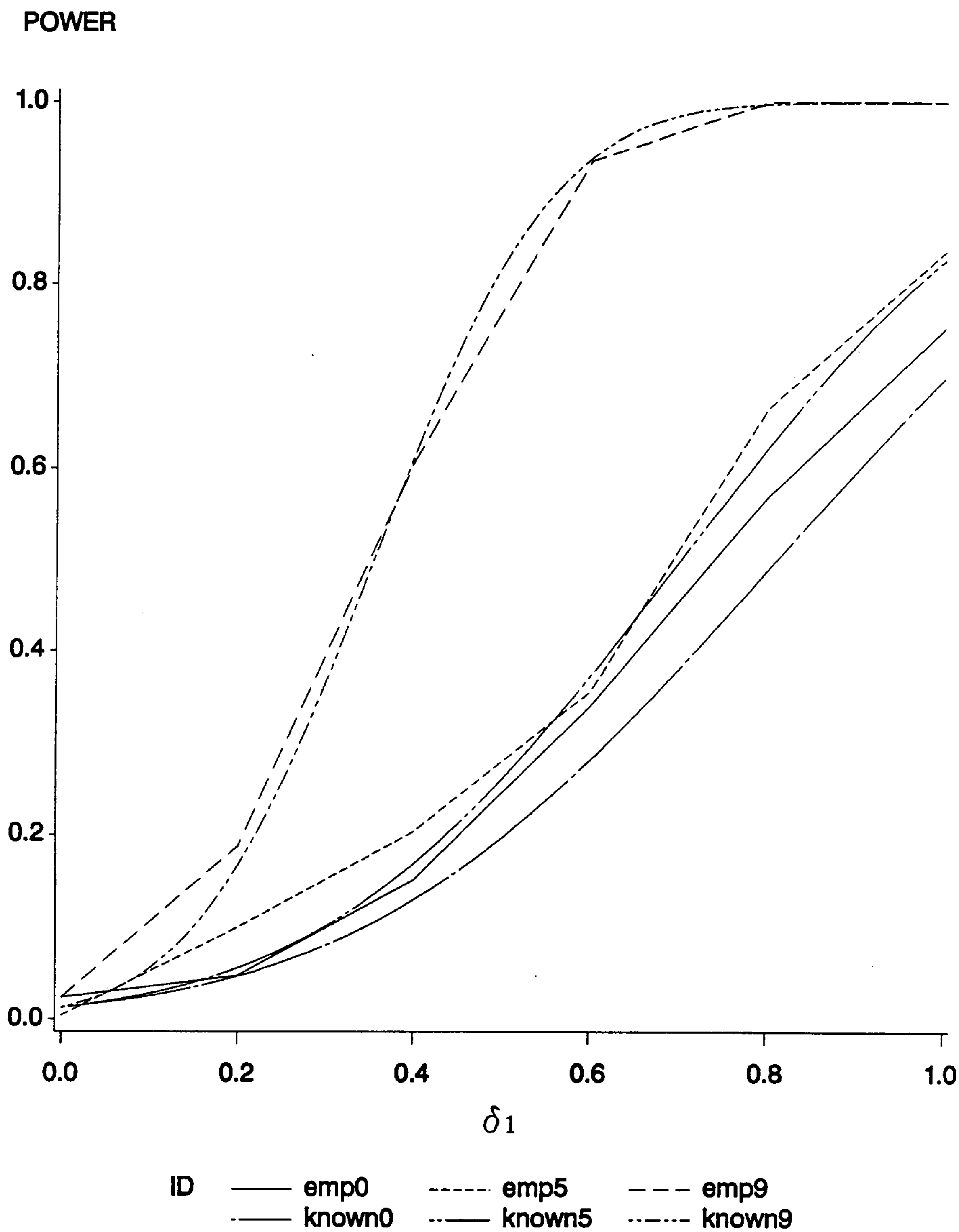
POWER CURVE COMPARISONS FOR ESTIMATED Σ_x
$C_1=0.1$ $C_2=1$ $\delta_{2a}=0$ $n=50$



APPENDIX 3.8

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

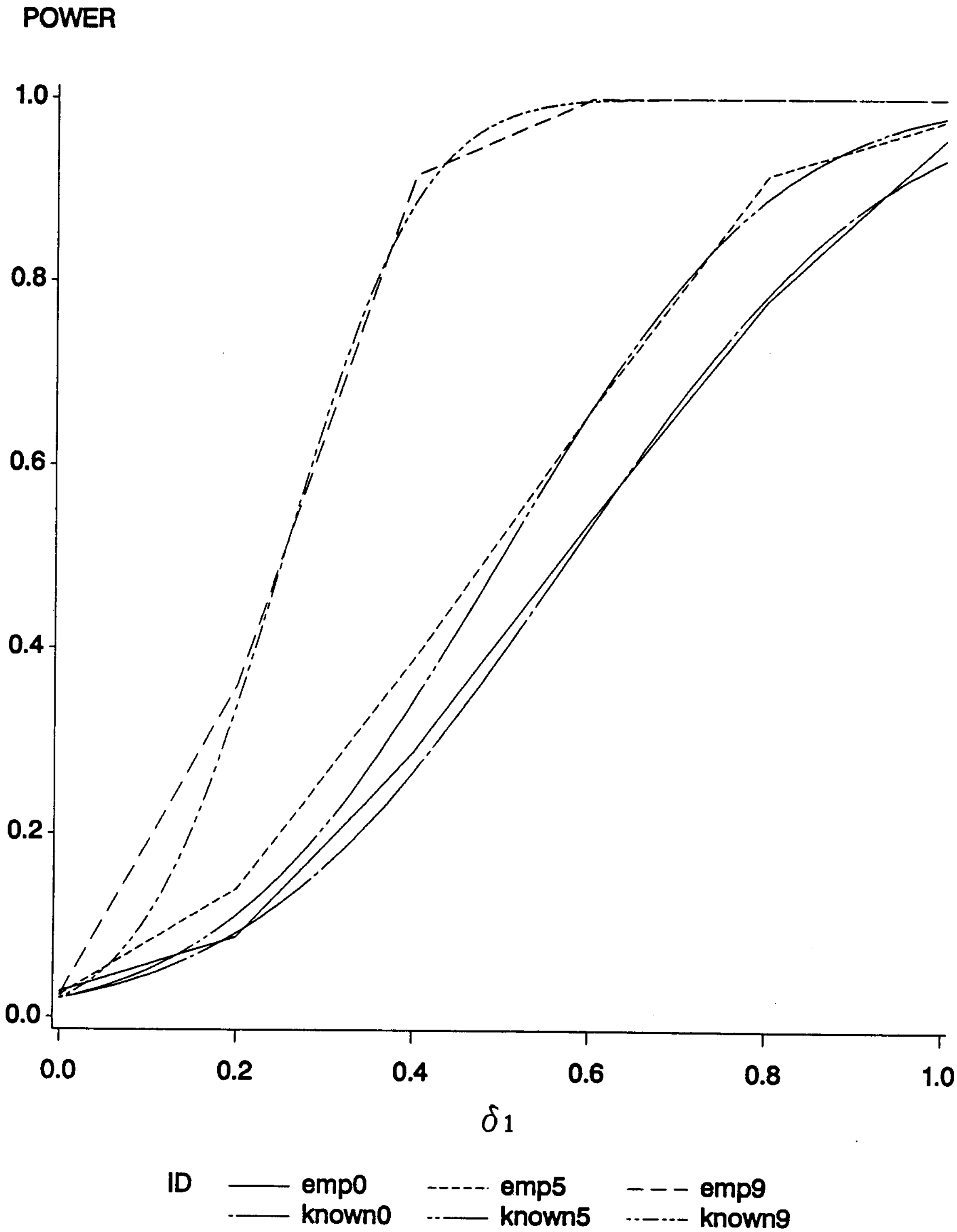
$C_1=0.1$ $C_2=10$ $\delta_{2a}=0$ $n=15$



APPENDIX 3.9

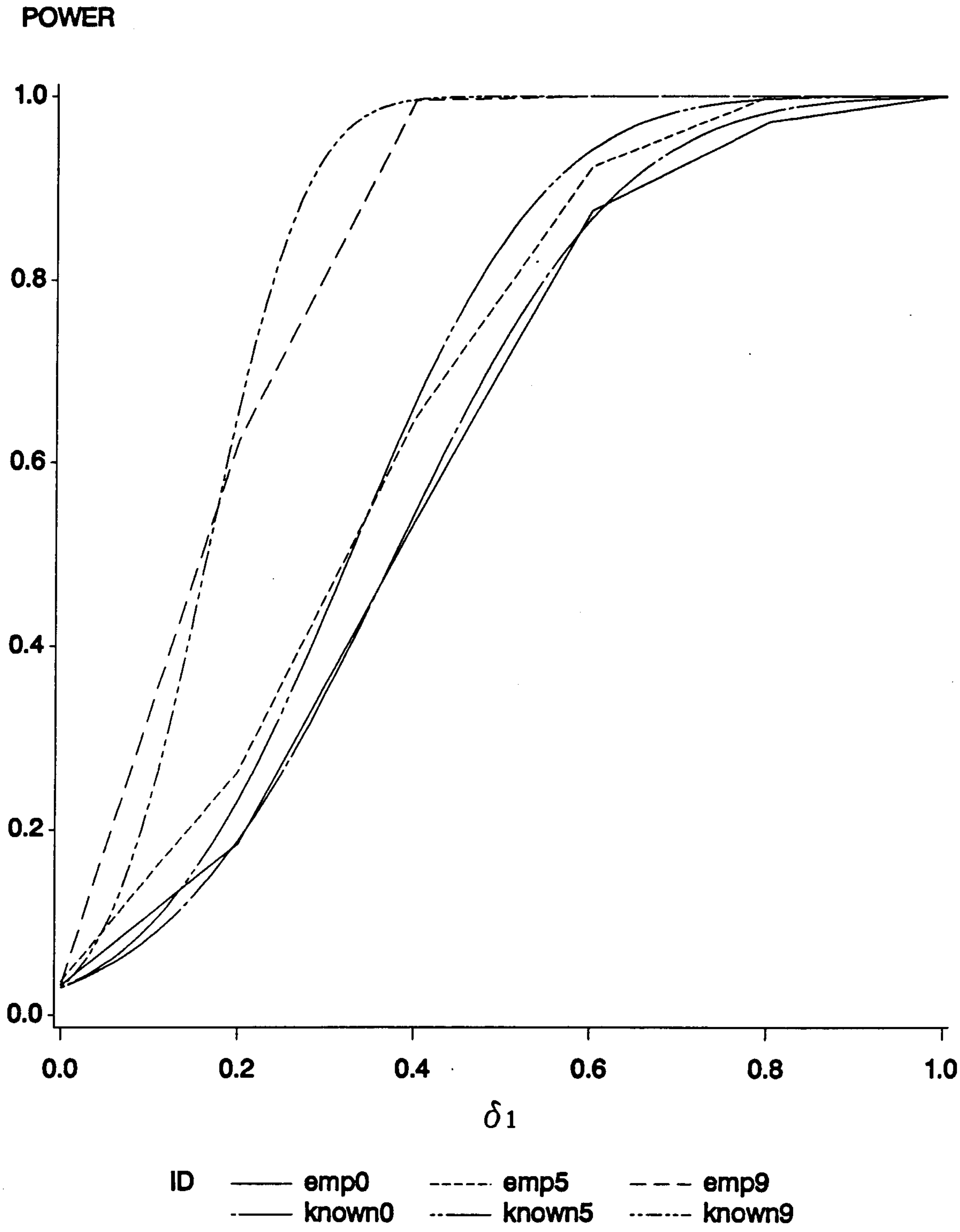
POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

$C_1 = 0.1$ $C_2 = 10$ $\delta_{2a} = 0$ $n = 25$



APPENDIX 3.10

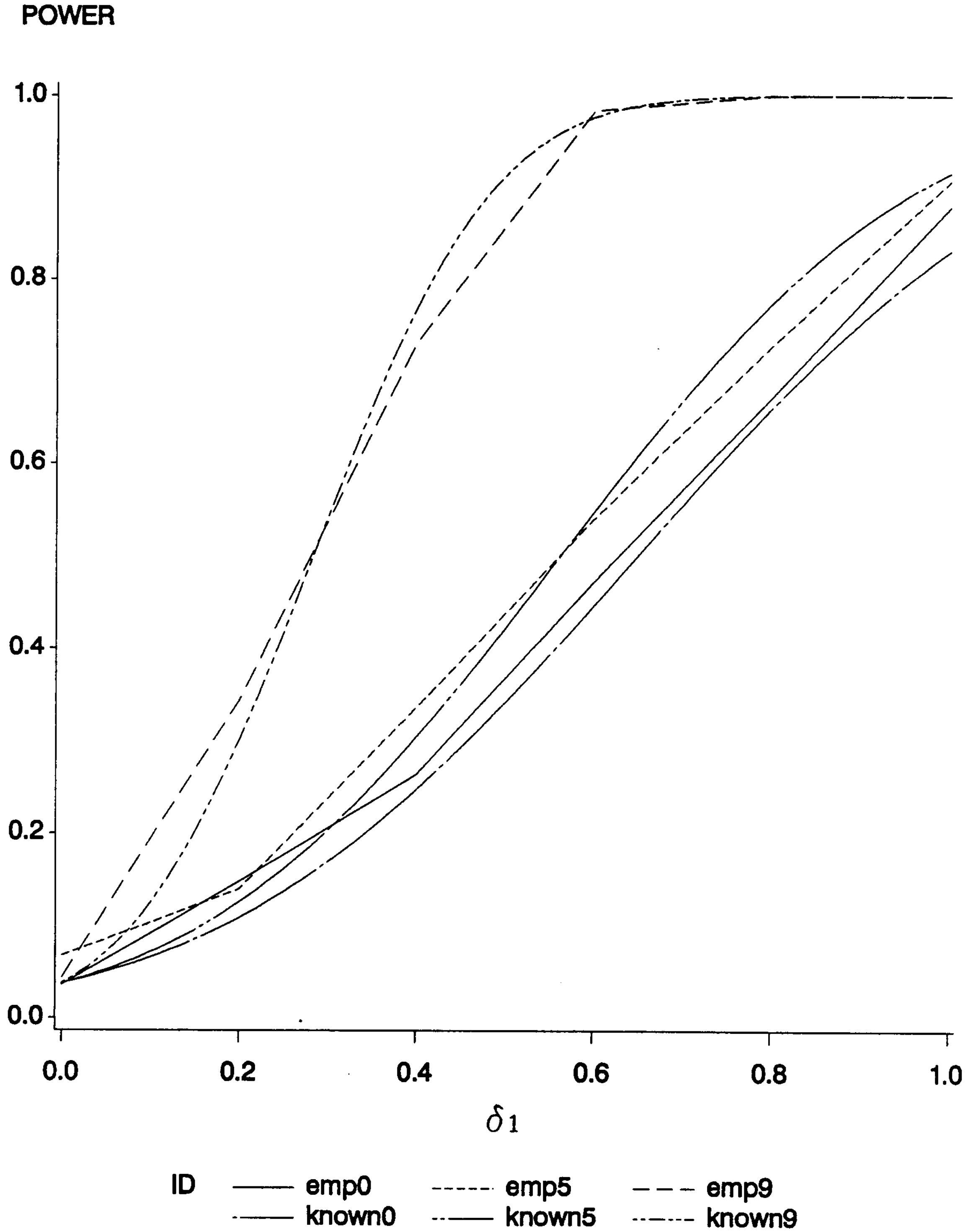
POWER CURVE COMPARISONS FOR ESTIMATED Σ_x
$C_1=0.1$ $C_2=10$ $\delta_{2a}=0$ $n=50$



APPENDIX 3.11

POWER CURVE COMPARISONS FOR ESTIMATED Σx

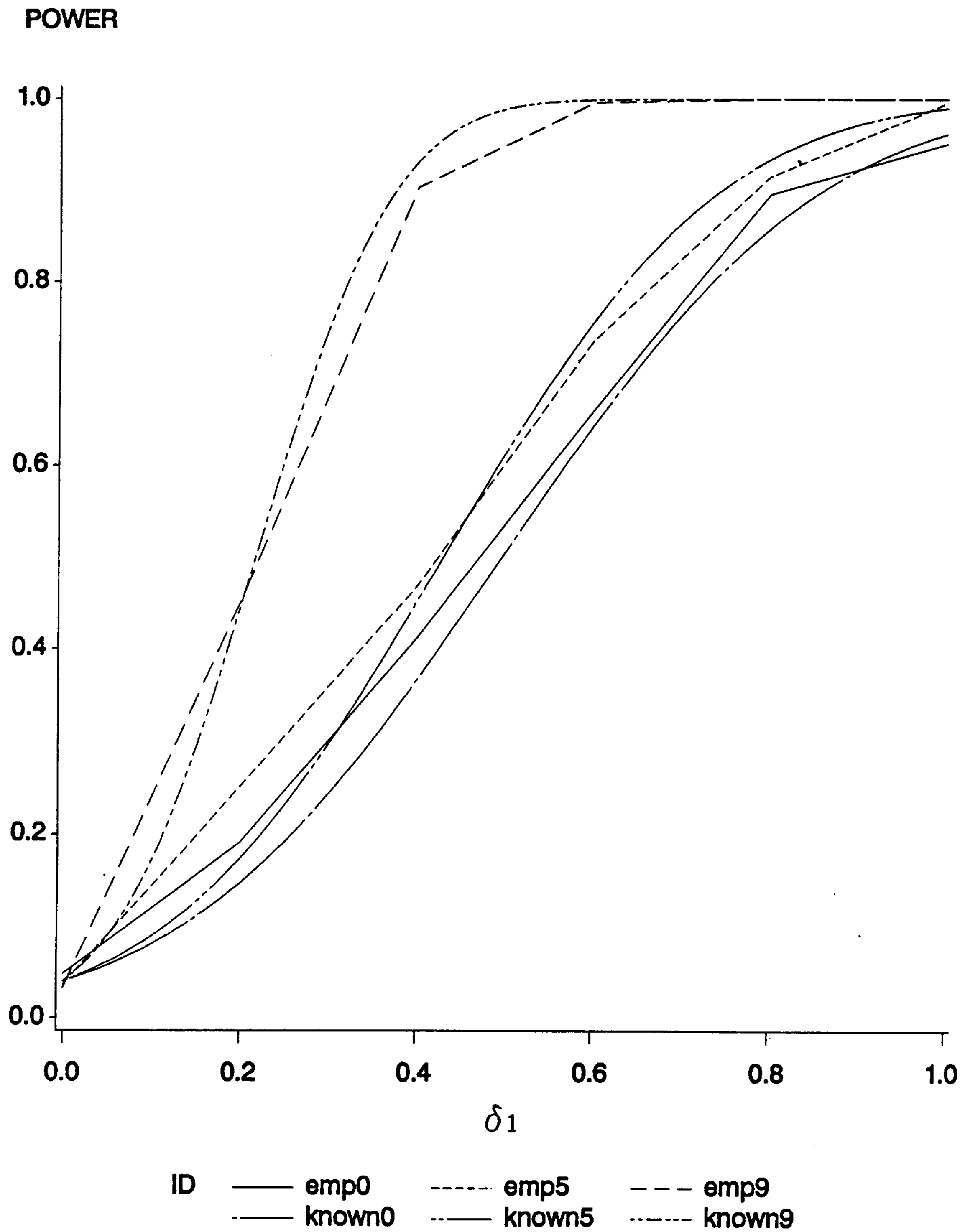
$C_1=1 \quad C_2=0.1 \quad \delta_{2a}=0 \quad n=15$



APPENDIX 3.12

POWER CURVE COMPARISONS FOR ESTIMATED Σx

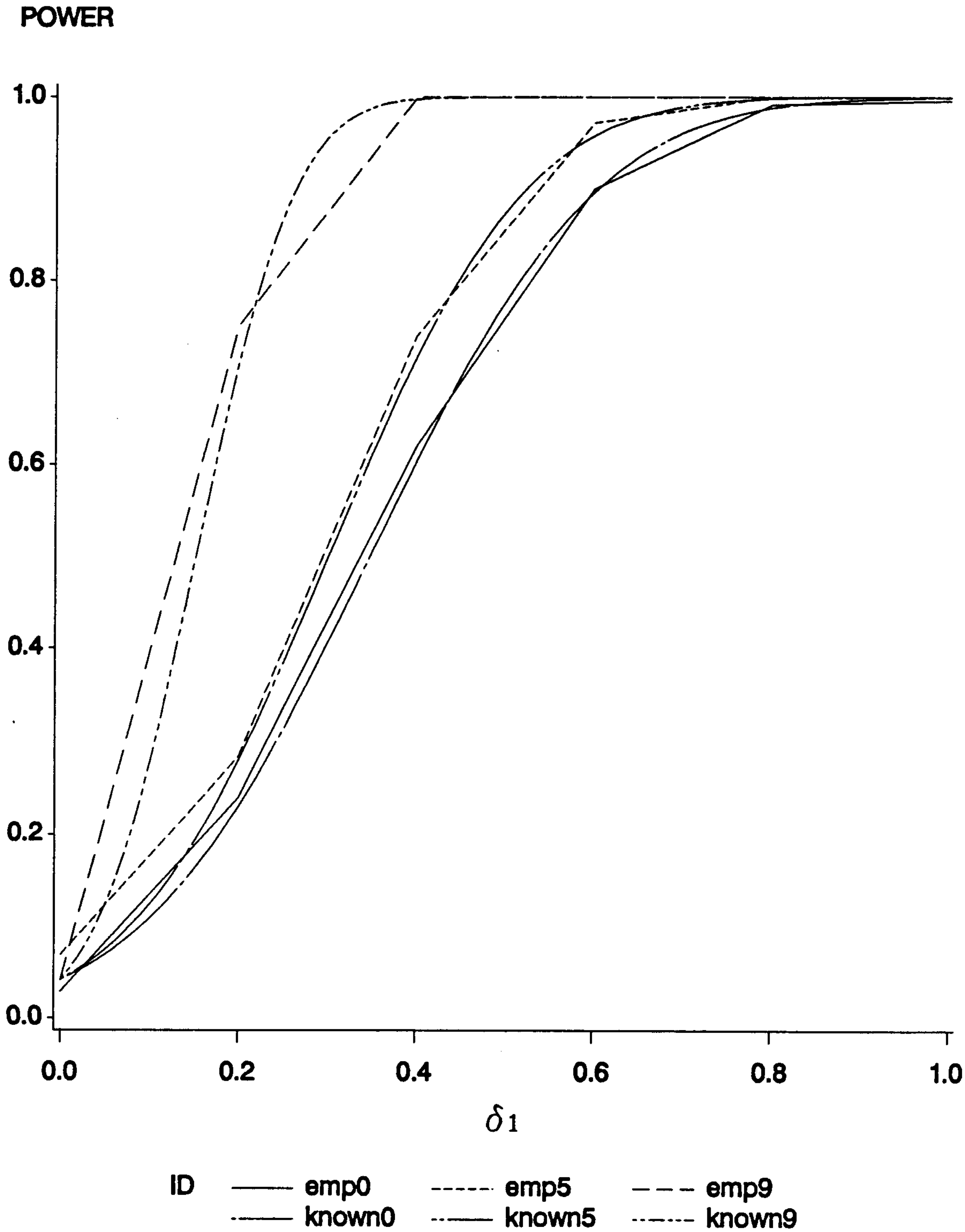
$C_1=1$ $C_2=0.1$ $\delta_{2a}=0$ $n=25$



APPENDIX 3.13

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

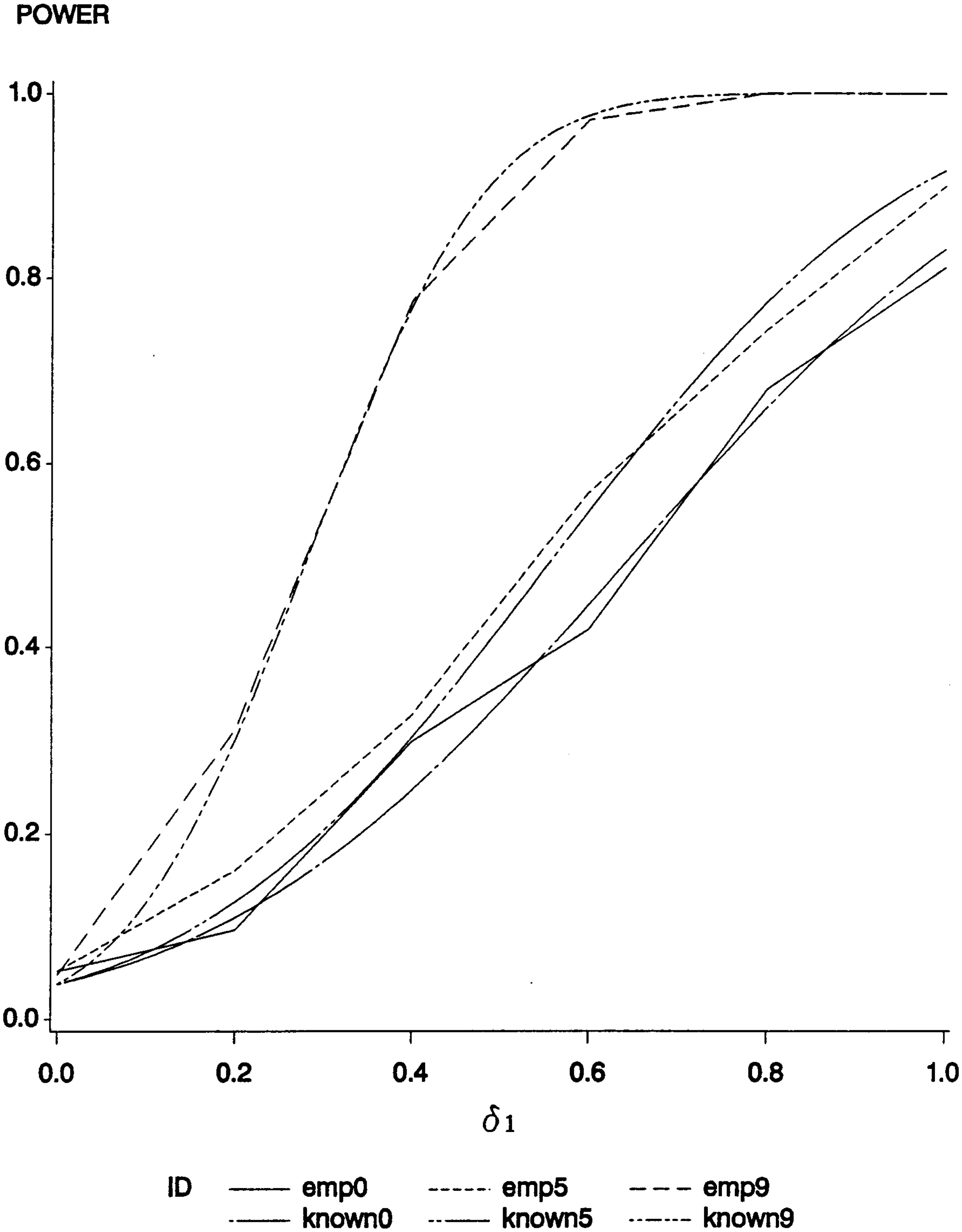
$C_1=1 \quad C_2=0.1 \quad \delta_{2a}=0 \quad n=50$



APPENDIX 3.14

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

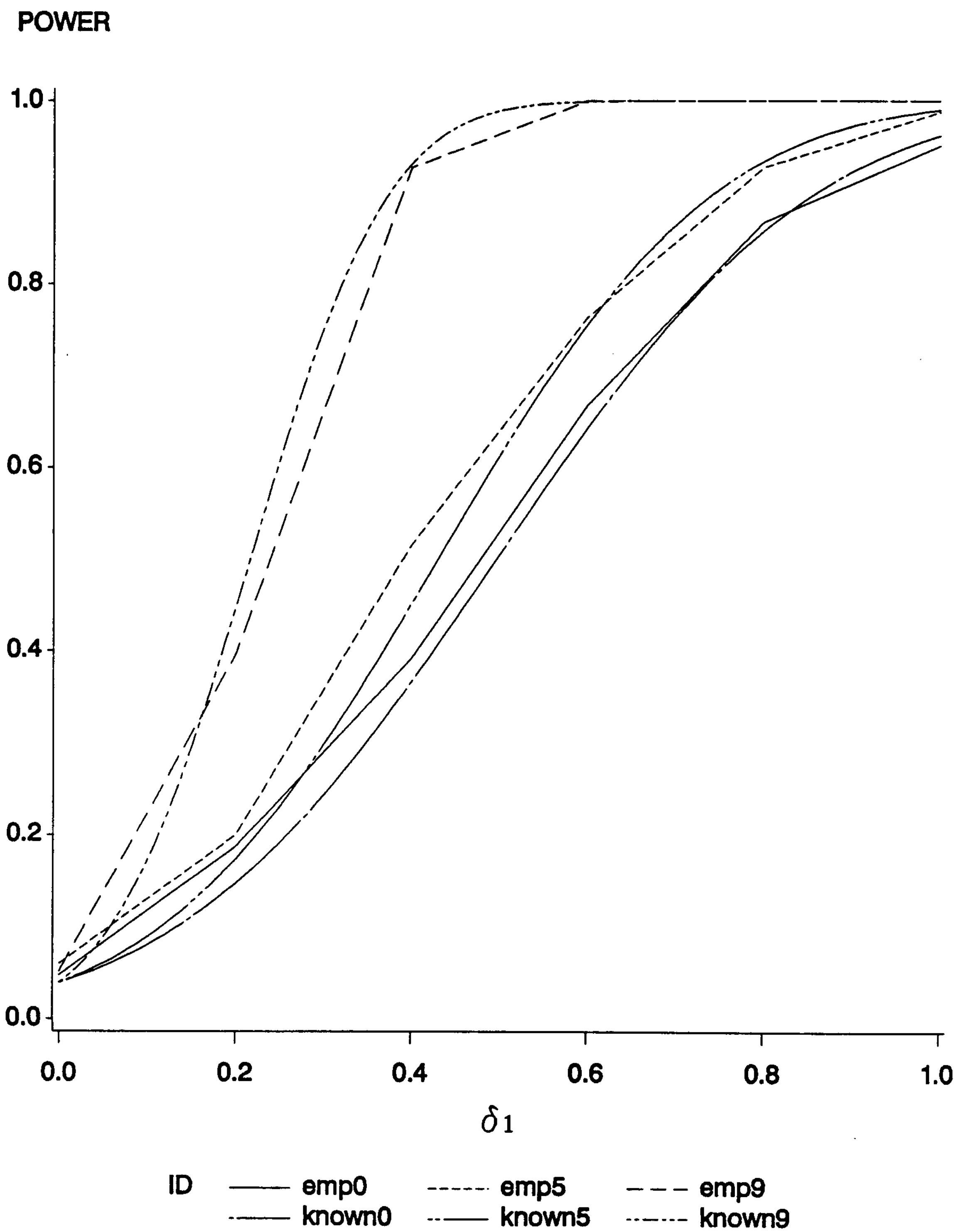
$C_1=1$ $C_2=10$ $\delta_{2a}=0$ $n=15$



APPENDIX 3.15

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

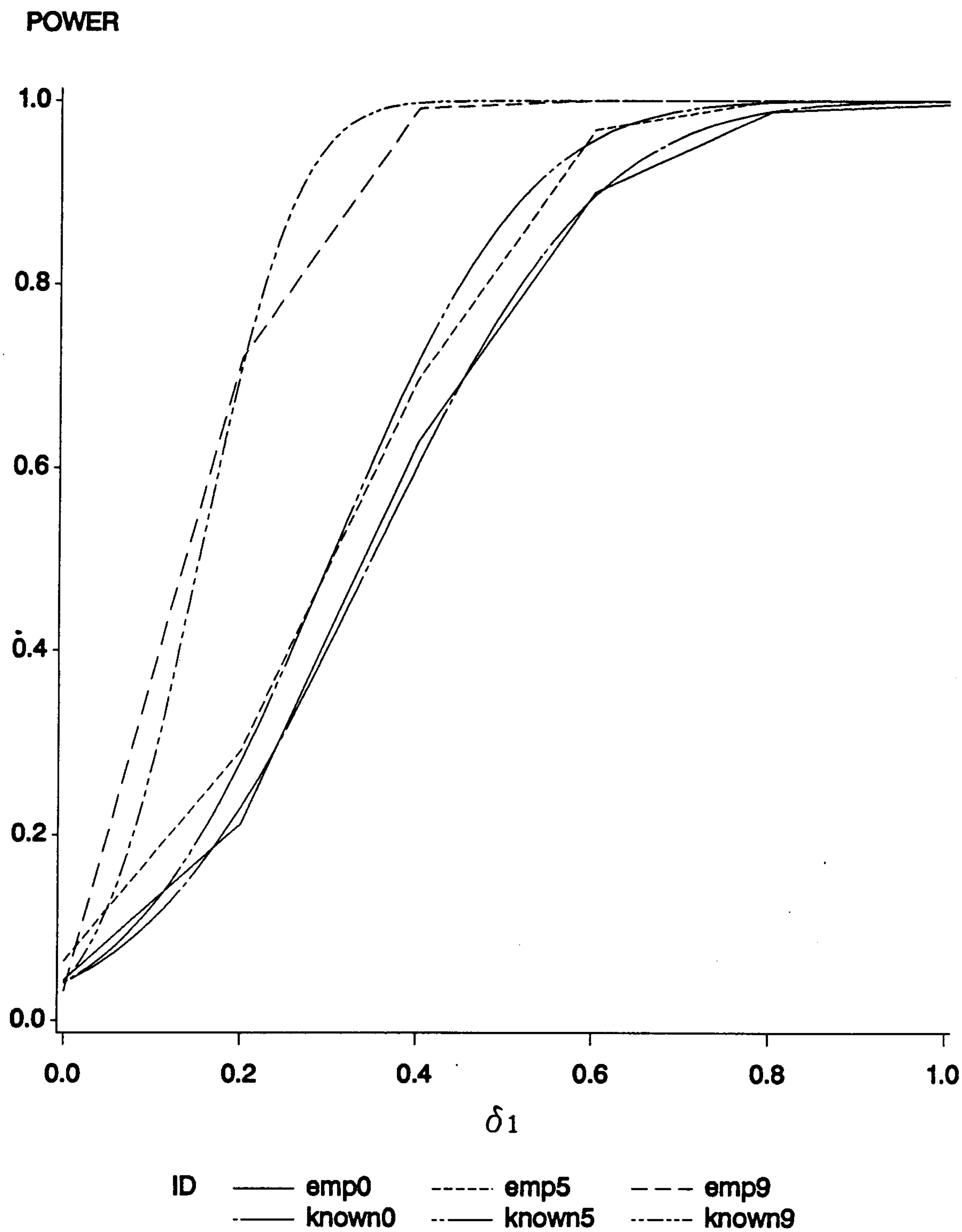
$C_1=1$ $C_2=10$ $\delta_{2a}=0$ $n=25$



APPENDIX 3.16

POWER CURVE COMPARISONS FOR ESTIMATED Σx

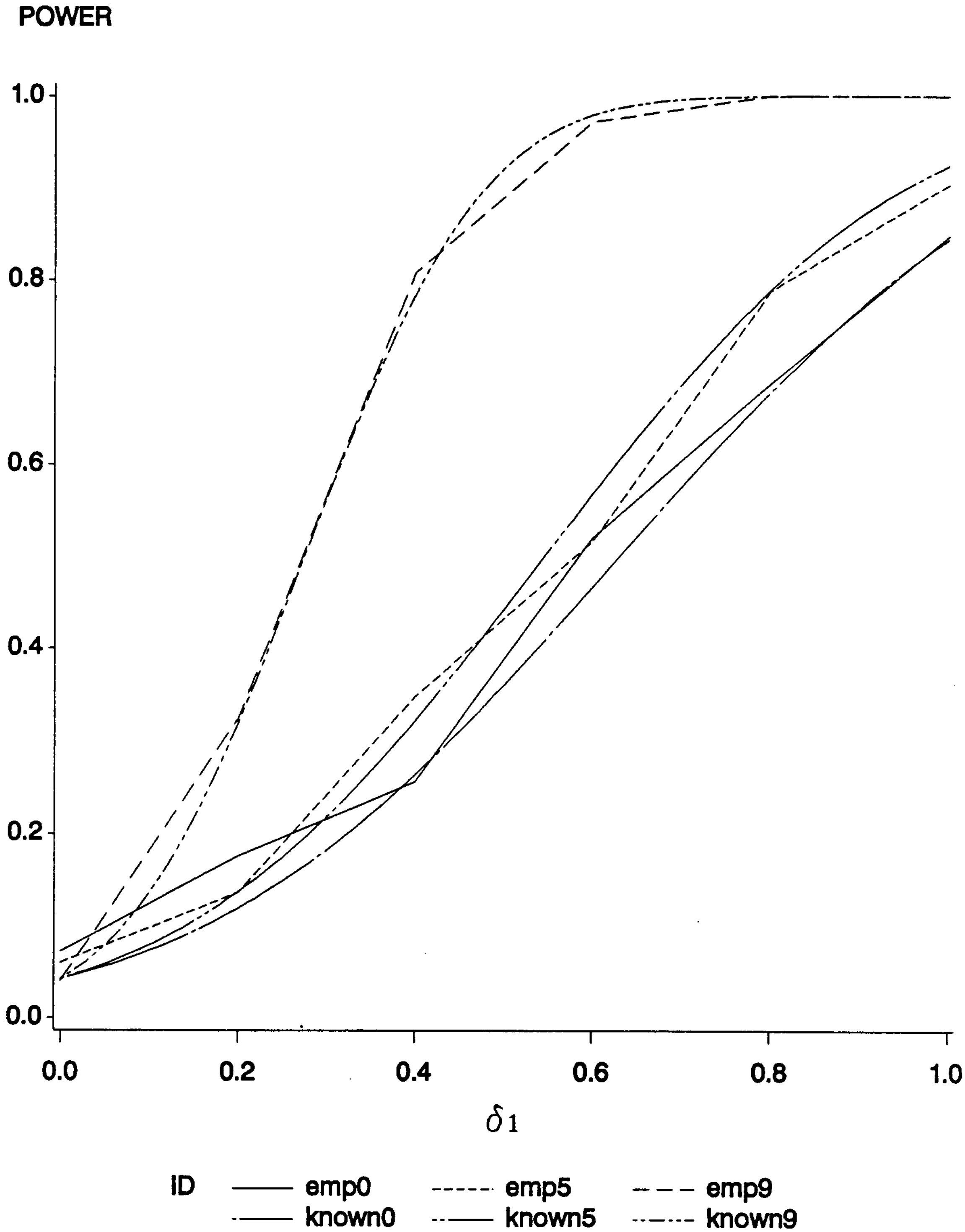
$C_1=1 \quad C_2=10 \quad \delta_{2a}=0 \quad n=50$



APPENDIX 3.17

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

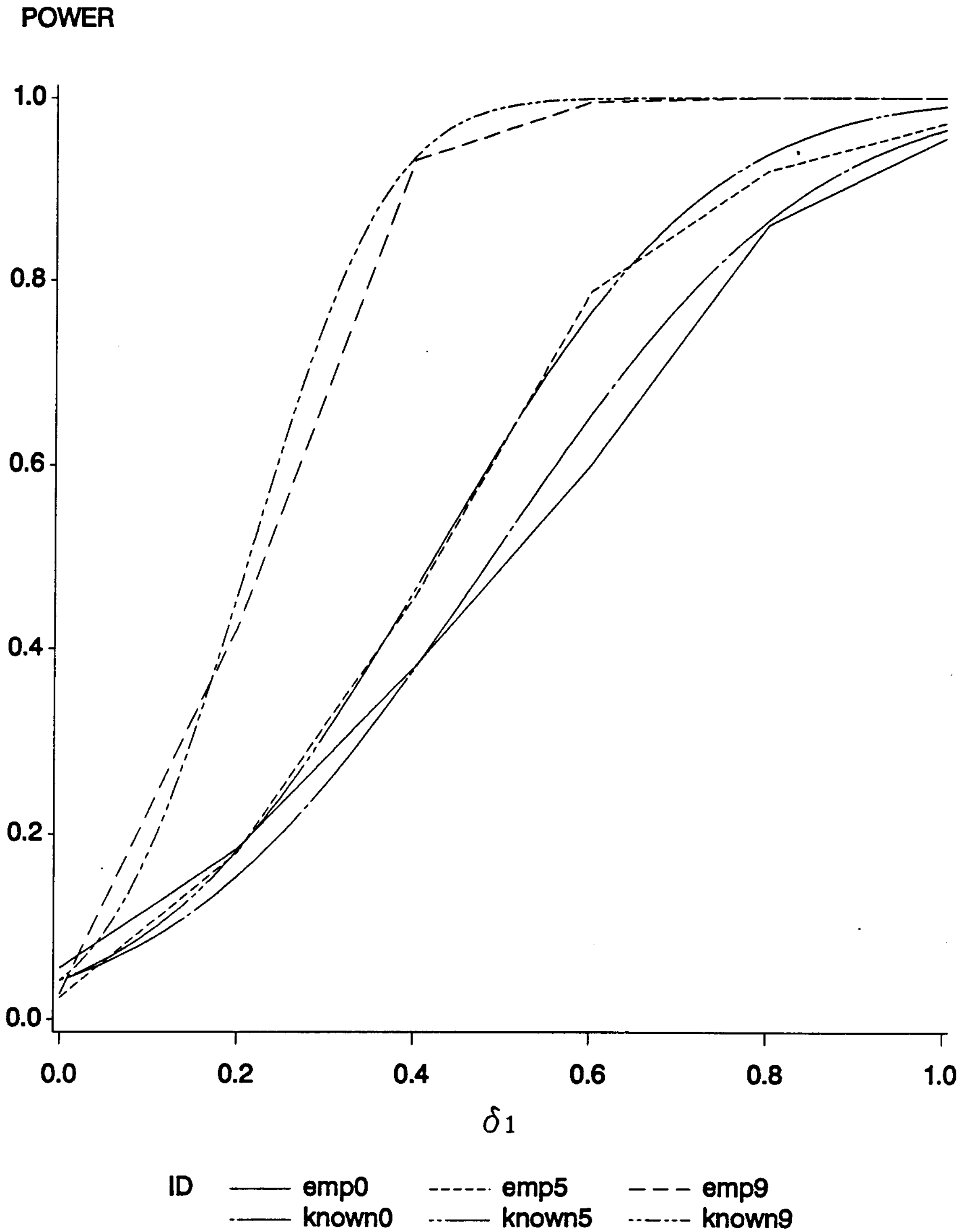
$C_1=10 \quad C_2=0.1 \quad \delta_{2a}=0 \quad n=15$



APPENDIX 3.18

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

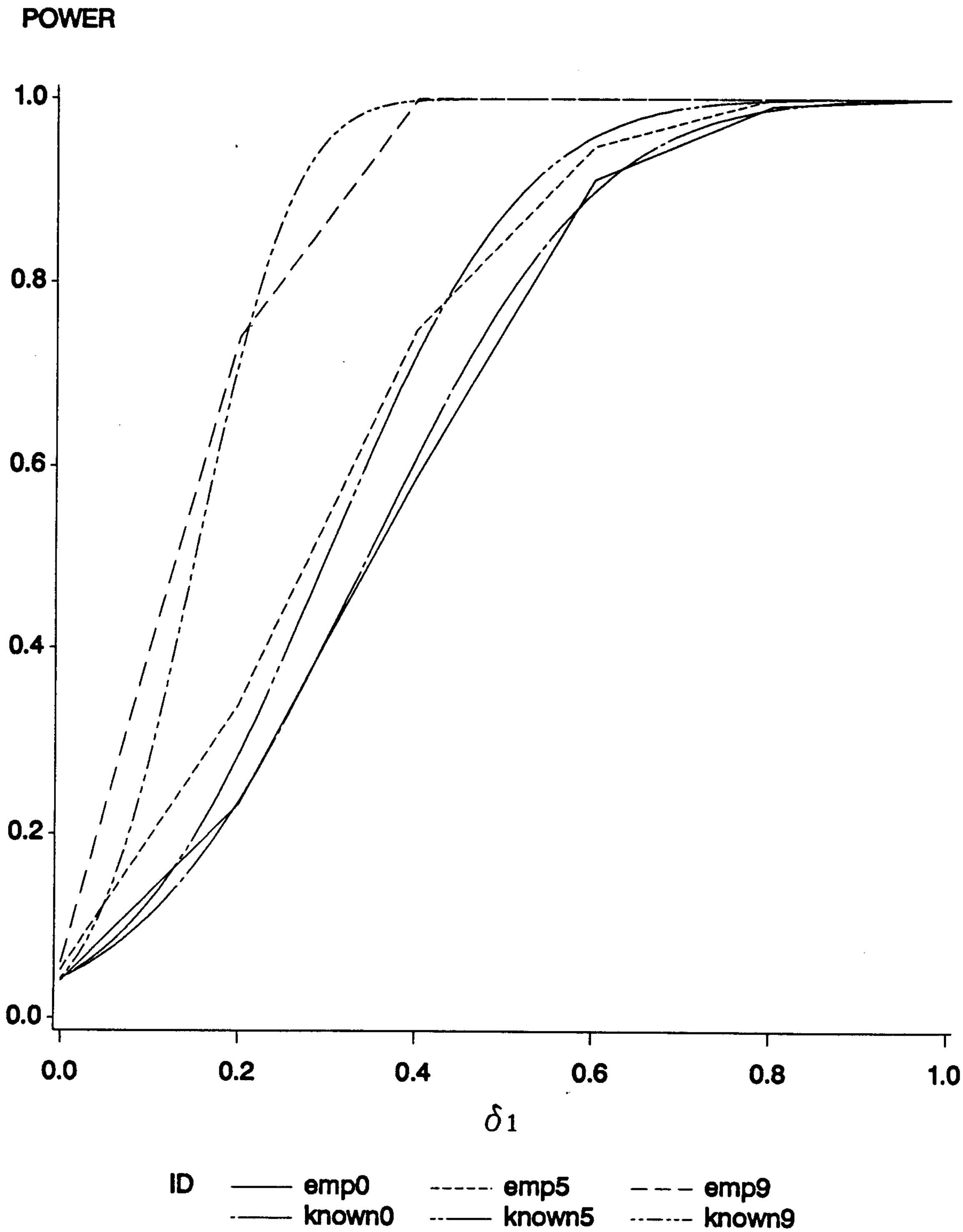
$C_1=10 \quad C_2=0.1 \quad \delta_{2a}=0 \quad n=25$



APPENDIX 3.19

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

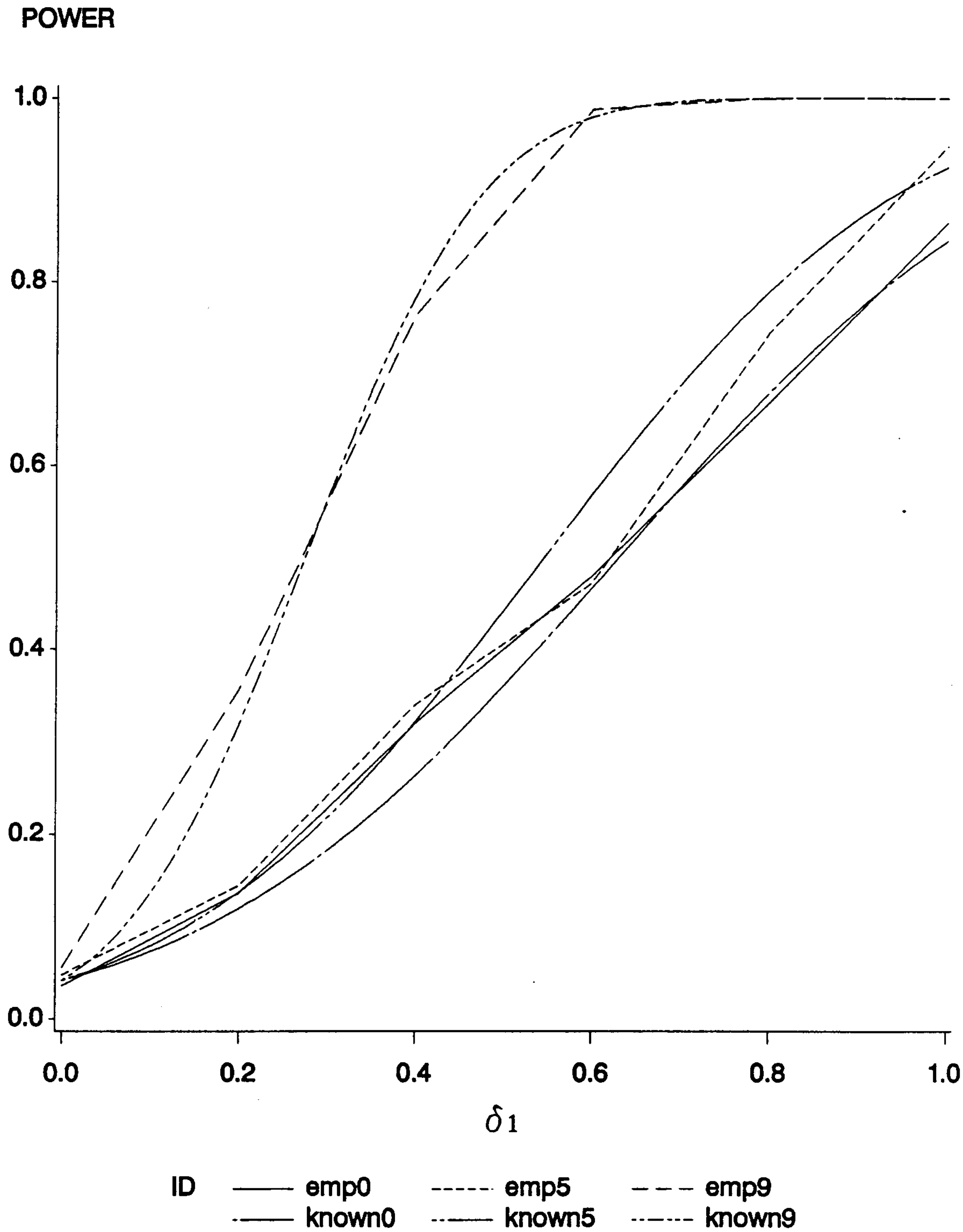
$C_1 = 10$ $C_2 = 0.1$ $\delta_{2a} = 0$ $n = 50$



APPENDIX 3.20

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

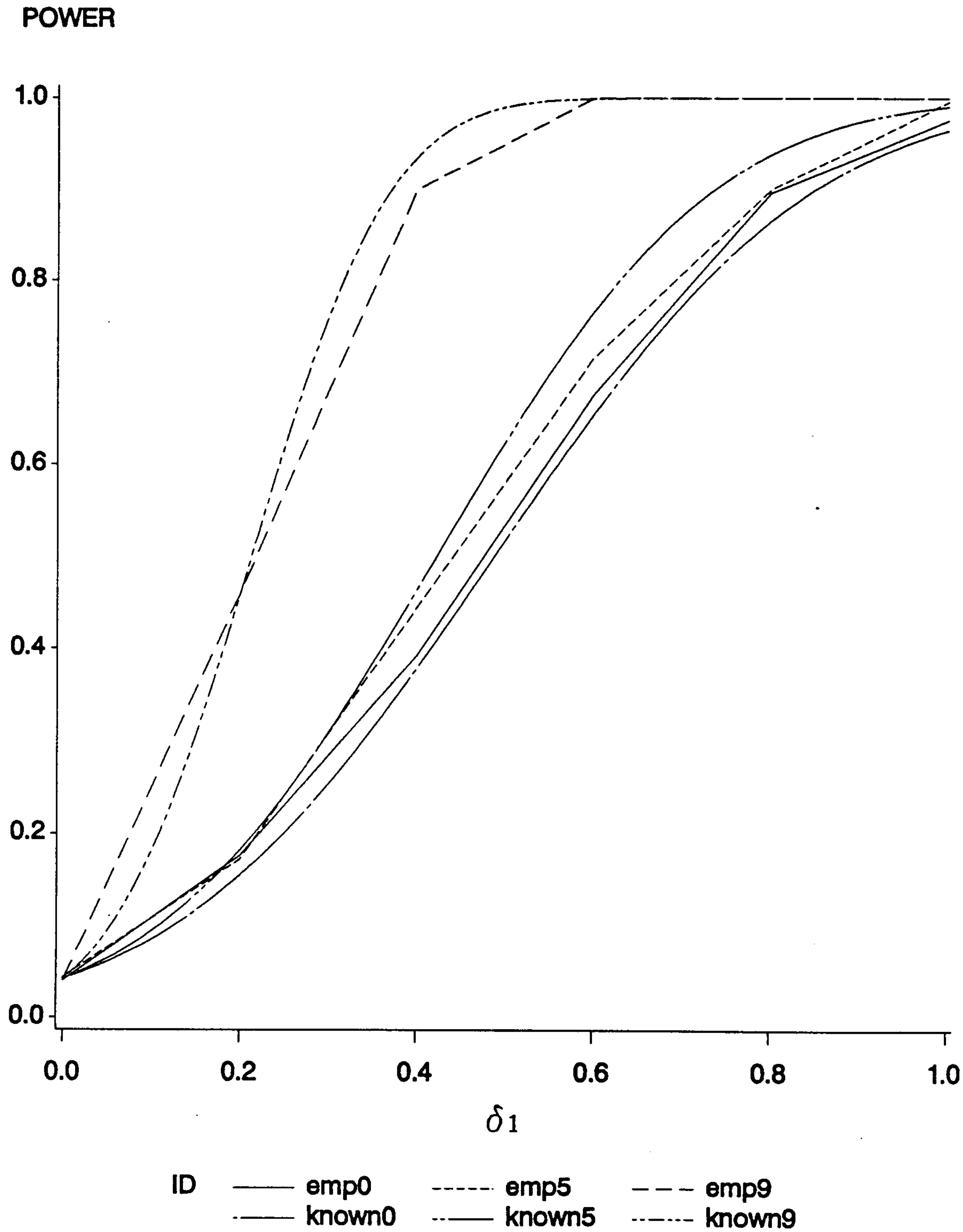
$C_1 = 10 \quad C_2 = 1 \quad \delta_{2a} = 0 \quad n = 15$



APPENDIX 3.21

POWER CURVE COMPARISONS FOR ESTIMATED Σx

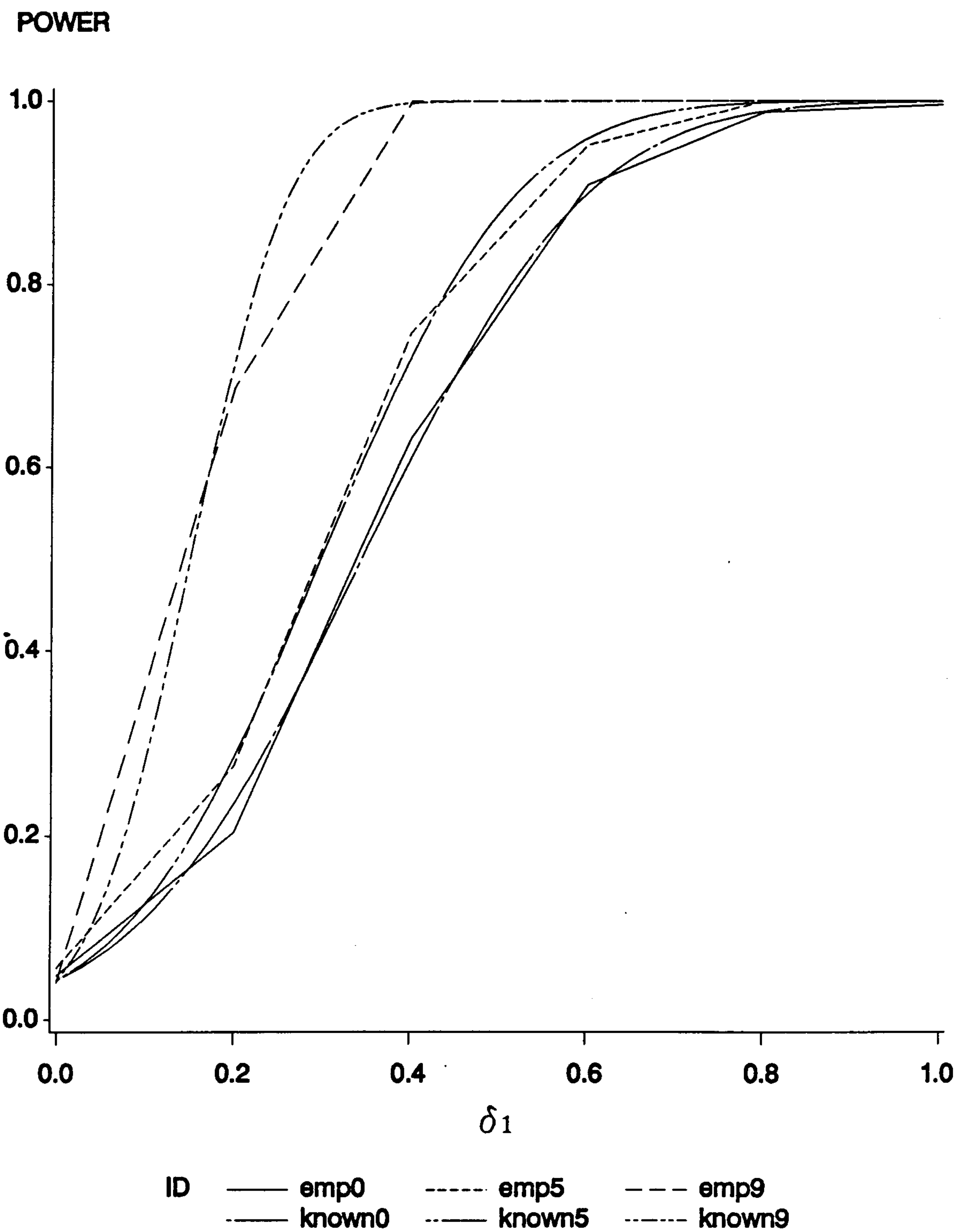
$C_1=10 \quad C_2=1 \quad \delta_{2a}=0 \quad n=25$



APPENDIX 3.22

POWER CURVE COMPARISONS FOR ESTIMATED Σx

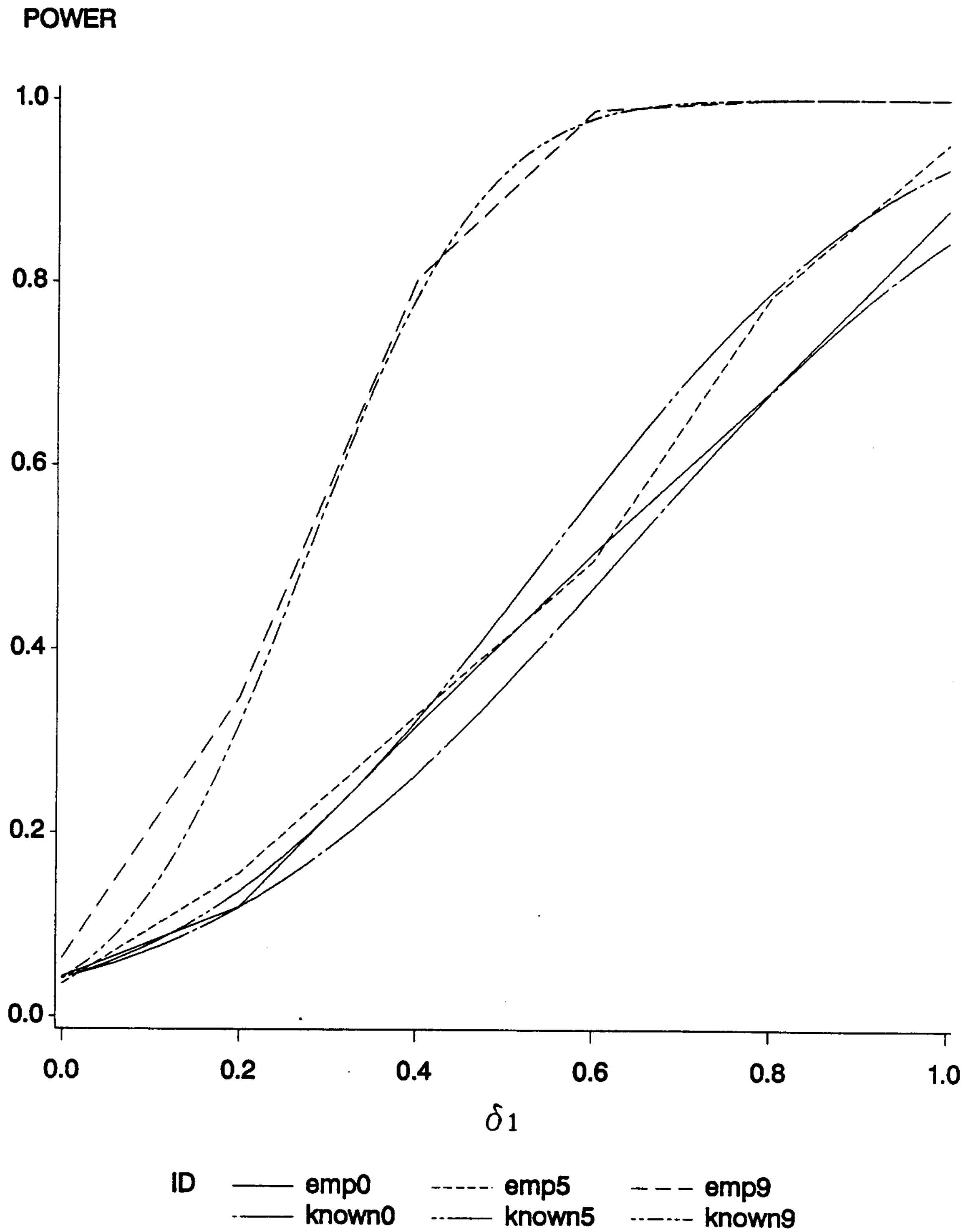
$C_1=10 \quad C_2=1 \quad \delta_{2a}=0 \quad n=50$



APPENDIX 3.23

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

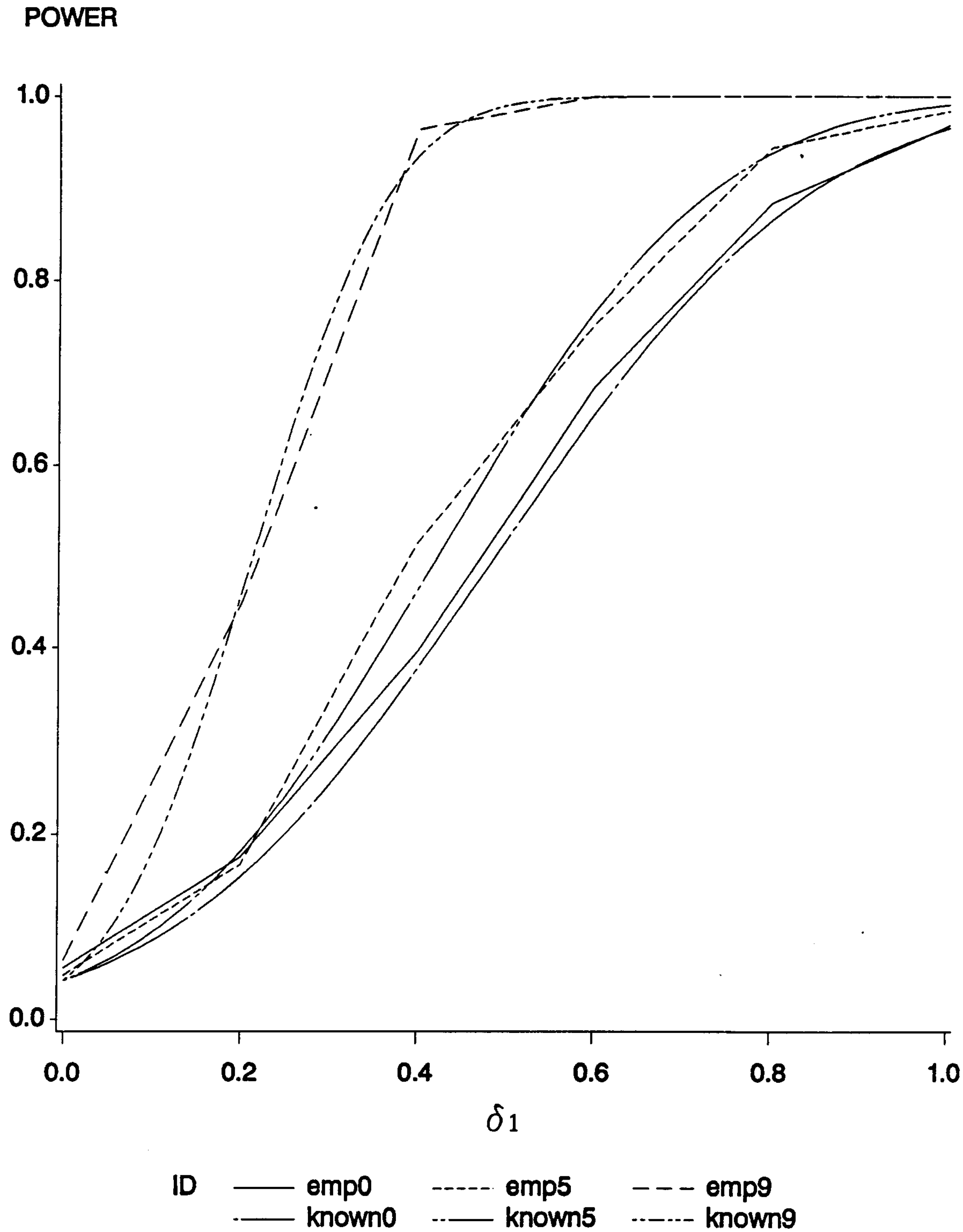
$C_1=10 \quad C_2=10 \quad \delta_{2a}=0 \quad n=15$



APPENDIX 3.24

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

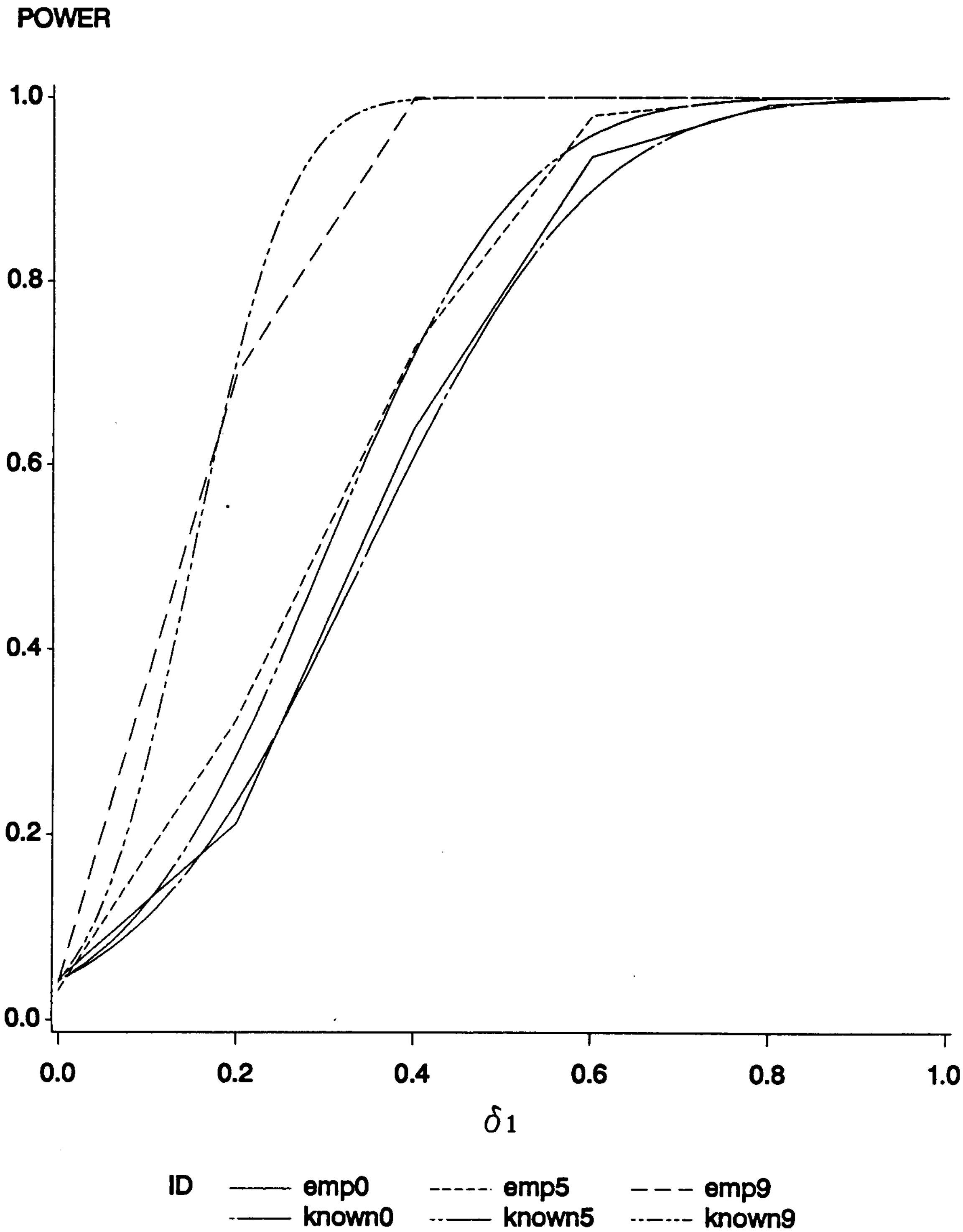
$C_1=10 \quad C_2=10 \quad \delta_{2a}=0 \quad n=25$



APPENDIX 3.25

POWER CURVE COMPARISONS FOR ESTIMATED Σ_x

$C_1=10 \quad C_2=10 \quad \delta_{2a}=0 \quad n=50$



APPENDIX 4.1

SIMULATION PROGRAM FOR CHAPTER 4

```
proc iml worksize=80;

****   we set up the vector of values
****        for the nuisance parameters  ;

c1=0.1; c2=1;

do l=0 to 10 by 5;
if l=5 | l=0 then covar=sqrt(c2)*(l/10);
else if l=10 then covar=sqrt(c2)*((l-1)/10);
rho=covar/sqrt(c2);  print rho;

****  sigma_x is the covariance matrix
****  for the x observations;

sigma_x= ( (1 || covar) //   (covar|| c2) );
cx=(root(sigma_x))`;

****  sigma_u is the covariance matrix for the mu's;

sigma_u= c1*sigma_x;   sig_delt=2*sigma_u;
cu=(root(sigma_u))`;

do delta1=0 to 1 by 0.2;

****   delta is the vector of alternative values
****        of delta for the power calculations;

delta=(delta1//0);

**** we now perform simulation of data and
****      resulting statistical calculations 250 times;

do k=1 to 250 ;

****  The zij's are two normal(0,1) variates where
****       i indexes center and j indexes treatment;

z11=normal(0);  z21=normal(0);
z12=normal(0);  z22=normal(0);
z41=normal(0);  z51=normal(0);
z42=normal(0);  z52=normal(0);
z31=normal(0);  z61=normal(0);
z32=normal(0);  z62=normal(0);
z71=normal(0);  z81=normal(0);
z72=normal(0);  z82=normal(0);
z91=normal(0);  z01=normal(0);
z92=normal(0);  z02=normal(0);
```

APPENDIX 4.1 (cont'd)

SIMULATION PROGRAM FOR CHAPTER 4

```
**** Muil is bivariate normal with mean (delta1//0)
****      and mui2 is bivariate normal with
****      mean (0). Each has covariance matrix sigma_u;

mu11=(cu*(z11//z12))+(delta1//0);
mu21=(cu*(z21//z22))+(delta1//0);
mu31=(cu*(z31//z32))+(delta1//0);
mu12=(cu*(z11//z12));
mu22=(cu*(z21//z22));
mu32=(cu*(z31//z32));

mu41=(cu*(z41//z42))+(delta1//0);
mu51=(cu*(z51//z52))+(delta1//0);
mu61=(cu*(z61//z62))+(delta1//0);
mu42=(cu*(z41//z42));
mu52=(cu*(z51//z52));
mu62=(cu*(z61//z62));

mu71=(cu*(z71//z72))+(delta1//0);
mu81=(cu*(z81//z82))+(delta1//0);
mu91=(cu*(z91//z92))+(delta1//0);
mu01=(cu*(z01//z02))+(delta1//0);
mu72=(cu*(z71//z72));
mu82=(cu*(z81//z82));
mu92=(cu*(z91//z92));
mu02=(cu*(z01//z02));

**** we concatenate the mu's for use
****      in the m (center) loop. M can be at most
****      10 for this program.  mu is 2x20;

mu=(mu11||mu12||mu21||mu22||mu31||mu32||
    mu41||mu42||mu51||mu52||mu61||mu62||
mu71||mu72||mu81||mu82||mu91||mu92||mu01||mu02);

**** we now generate, for a given muij,
****      normal samples of 10 observations with
****      mean muij and covariance matrix sigma_x ;

**** m indexes the number of centers desired;
**** i indexes the number of patients per center;

do m=1 to 5;

do i=1 to 20;

**** za and zb are n(0,1) variates  ;
za=normal(0);   zb=normal(0);
```

APPENDIX 4.1 (cont'd)

SIMULATION PROGRAM FOR CHAPTER 4

```
**** pointer equals zero for treatment group 2
****      and equals one for treatment group 1;

pointer=mod(i,2);

**********************************************;

if pointer=0 then do;
col=i/2;

**** x_obs, here is a normal(mu_m2,sigma_x) vector;

xobs=(cx*(za//zb))+mu(|,(2*m)|);

if col=1 then trt2=(xobs);
else trt2=(trt2||xobs);
end;

***********************************************;

if pointer=1 then do;

col=(i+1)/2;

**** x_obs, here is a normal(mu_m1,sigma_x) vector;

xobs=(cx*(za//zb))+mu(|,((2*m)-1)|);
if col=1 then trt1=(xobs);
  else trt1=(trt1||xobs);
 end;

***********************************************;

**** TRTj is a 2xn matrix of the x observations
****      for treatment group j in this center ;

end;

n_obs=ncol(trt1);

****  TRTjAVG is the mean vector for
****       treatment group j in this center;

trt1avg=(  (sum(trt1(|1,|))/(ncol(trt1)))  //
           (sum(trt1(|2,|))/(ncol(trt1)))   );

trt2avg=(  (sum(trt2(|1,|))/(ncol(trt2)))  //
         (sum(trt2(|2,|))/(ncol(trt2)))   );
```

```
**** diffvec is the observed d vector-- a 2x1 vector of
****       treatment mean differences for center i;

diffvec=trt1avg-trt2avg;

**** diff is the matrix of observed d vector -- a 2xm
****       vector of observed treatment mean differences;

if m=1 then do;

diff=diffvec;  matrix1=trt1avg*trt1avg`;
matrix2=trt2avg*trt2avg`;
mean1all=trt1avg;  mean2all=trt2avg;
end;

else do;

diff=diff||diffvec;
matrix1=matrix1+(trt1avg*trt1avg`);
matrix2=matrix2+(trt2avg*trt2avg`);
mean1all=mean1all||trt1avg;
mean2all=mean2all||trt2avg;
end;

**** we now compute the sum-of-squares matrix for
****       treatment group j in this center (SSj);

do j=1 to ncol(trt1);

mat1=trt1(|,j|);
mat2=trt2(|,j|);

if j=1 then do;
ss1=mat1*mat1`;  ss2=mat2*mat2`;
end;

else do;
ss1=ss1+(mat1*mat1`);   ss2=ss2+(mat2*mat2`);
end;

end;

****  COVARj is the sample sum-of-squares and cross
****        products matrix for treatment group j ;
covar1=ss1-((ncol(trt1))*(trt1avg*trt1avg`));
covar2=ss2-((ncol(trt1))*(trt2avg*trt2avg`));

if m=1 then covar=covar1+covar2;
else covar=covar+covar1+covar2;
```

APPENDIX 4.1 (cont'd)

SIMULATION PROGRAM FOR CHAPTER 4

```
**** end loop for centers indexed by m;
end;
m=m-1;

free xobs mu covar1 covar2 trt2 mat1 mat2 ss1 ss2 ;

cov_x=covar/((2*m)*(n_obs-1));


mean_d=(  sum(diff(|1,|)) //
          sum(diff(|2,|))    )  /  m;
mean_x1=(  sum(mean1all(|1,|)) //
           sum(mean1all(|2,|))    )  /  m;
mean_x2=(  sum(mean2all(|1,|)) //
           sum(mean2all(|2,|))    )  /  m;

****  we now compute the unconditional covariance
****       matrix for the observed treatment mean
****       vectors in the different centers.  This
****       matrix estimates sigma_u+(sigma_x/n);

uncond_x=(     (matrix1-(m*mean_x1*mean_x1`)) +
     (matrix2-(m*mean_x2*mean_x2`))     )  /  (2*(m-1));

**** sig_est estimates sigma_u;

sig_est=uncond_x-(cov_x/n_obs);

**** The following section is used to estimate   ;
****      c1 for the alternate multicenter covariate  ;
****      procedure ;

/*
****
**** the matrix c1_mat estimates c1*I2;

c1_mat=((uncond_x*inv(cov_x))-(I(2)/n_obs));

**** we now estimate c1 with the average of the
****      diagonal elements of the matrix c1_mat ;

c1_est=trace(c1_mat)/2;
*/

**** cov_d is the estimated covariance matrix
****      for the treatment mean differences      ;

cov_d=2*cov_x/(m*n_obs);
```

SIMULATION PROGRAM FOR CHAPTER 4

```
**** cov_delt is the estimated covariance
****      matrix for the delta's;

cov_delt=2*sig_est;

cov_both=(cov_delt||cov_delt)//
  (cov_delt||(cov_d+cov_delt));

**** postmult is the 1x3 vector which is
****      the first part of the calculation of the
****      posterior mean of the distribution h;

postmult=cov_both(|1,2:4|)*inv(cov_both(|2:4,2:4|));

**** postmean is the estimate of the posterior
****      mean of the distribution h;

postmean=postmult*(0//mean_d);

****  postvar is the posterior variance
****       of the distribution h;

postvar=cov_both(|1,1|)-(postmult*cov_both(|2:4,1|));


**** var_id is a matrix to identify the variable
****      names for the output dataset;

var_id={"m" "c1" "c2"  "delta1" "rho"
        "postmean"  "postvar"};

vector=(m||c1||c2||delta1||rho||postmean||postvar);

if k=1 & delta1=0 & l=0
  then create stats from vector (|colname=var_id |);
append from vector;

*****  close loop of 250 repeated simulations    ;
end;

****    close loop for differing delta1 values;
end;

****    close loop for differing rho values;
end;
```

APPENDIX 4.1 (cont'd)

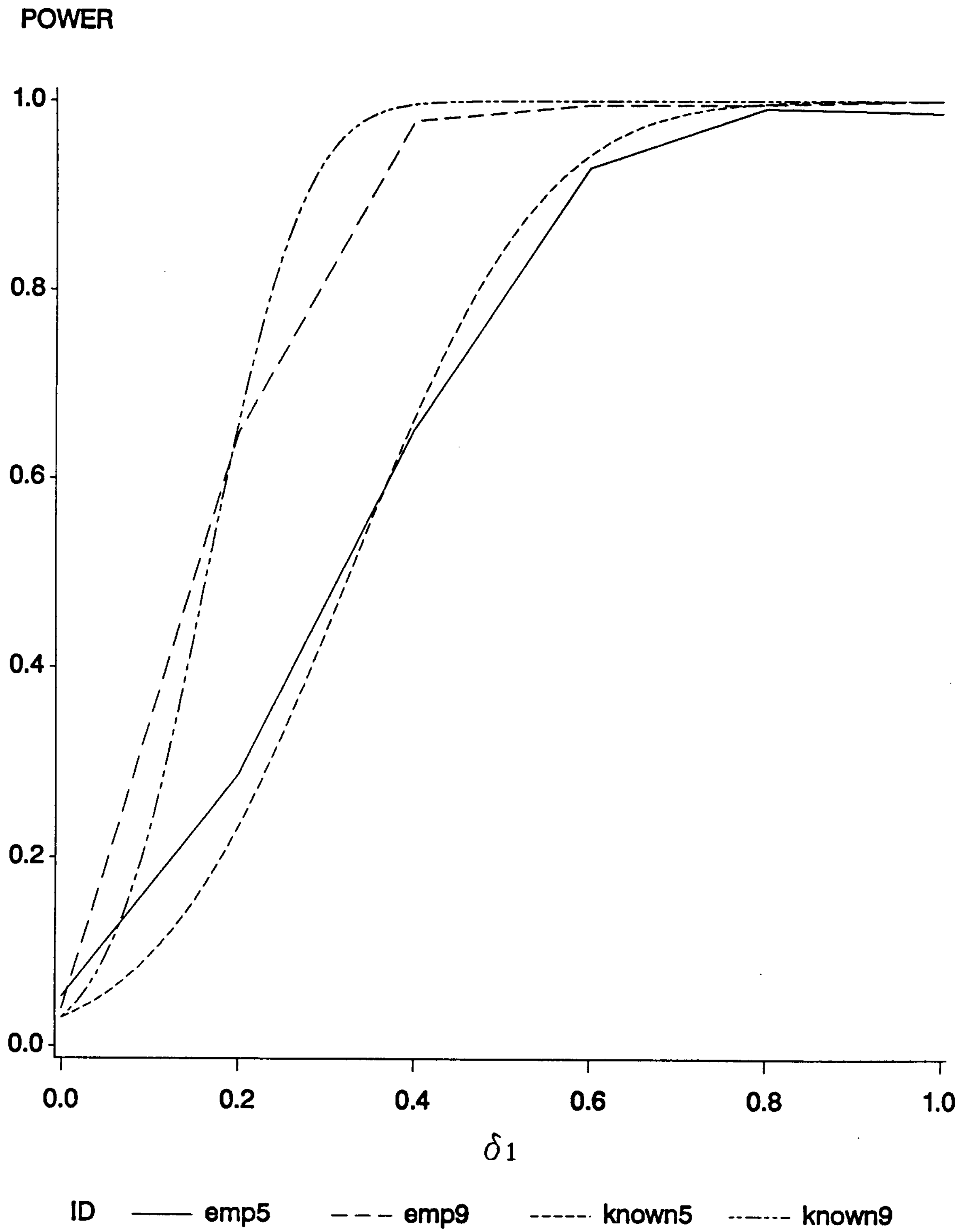
SIMULATION PROGRAM FOR CHAPTER 4

```
data simula; set stats;
if postvar le 0 then delete;
crit_val=postmean/sqrt(postvar);
if crit_val gt 1.721 then reject=1; else reject=0;
proc sort; by rho delta1;
title1 '250 simus with 5 centers using sigma_mu matrix';
proc means noprint;   by rho delta1;
id m c1 c2 ;   var reject;
output out=meands mean=power ; proc print;
libname save 'd:\lynn';

run;
```

APPENDIX 4.2

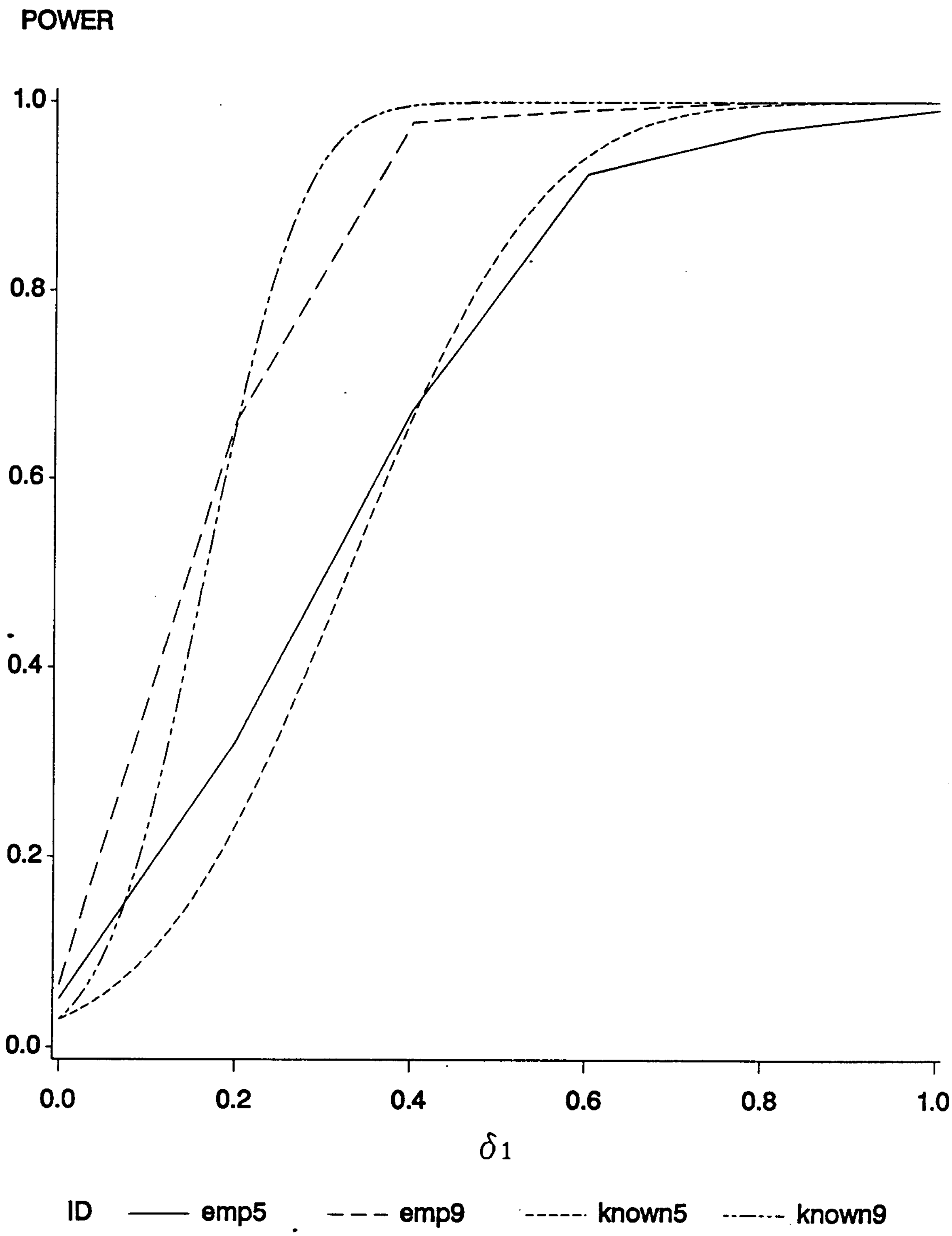
POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

$C_1=0.1$ $C_2=0.1$ $m=5$ $n=10$



APPENDIX 4.3

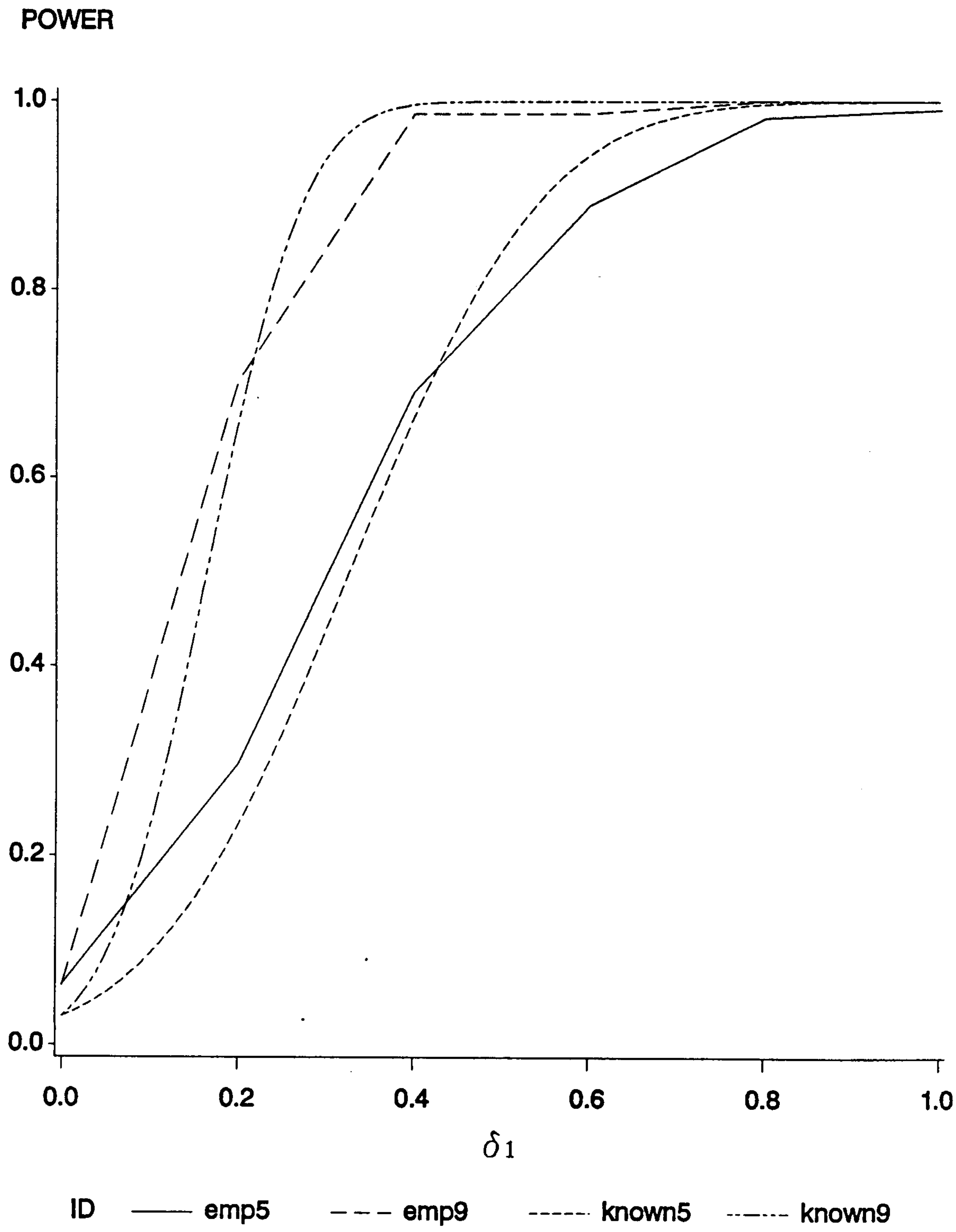
POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE
$C_1=0.1$ $C_2=1$ $m=5$ $n=10$



APPENDIX 4.4

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

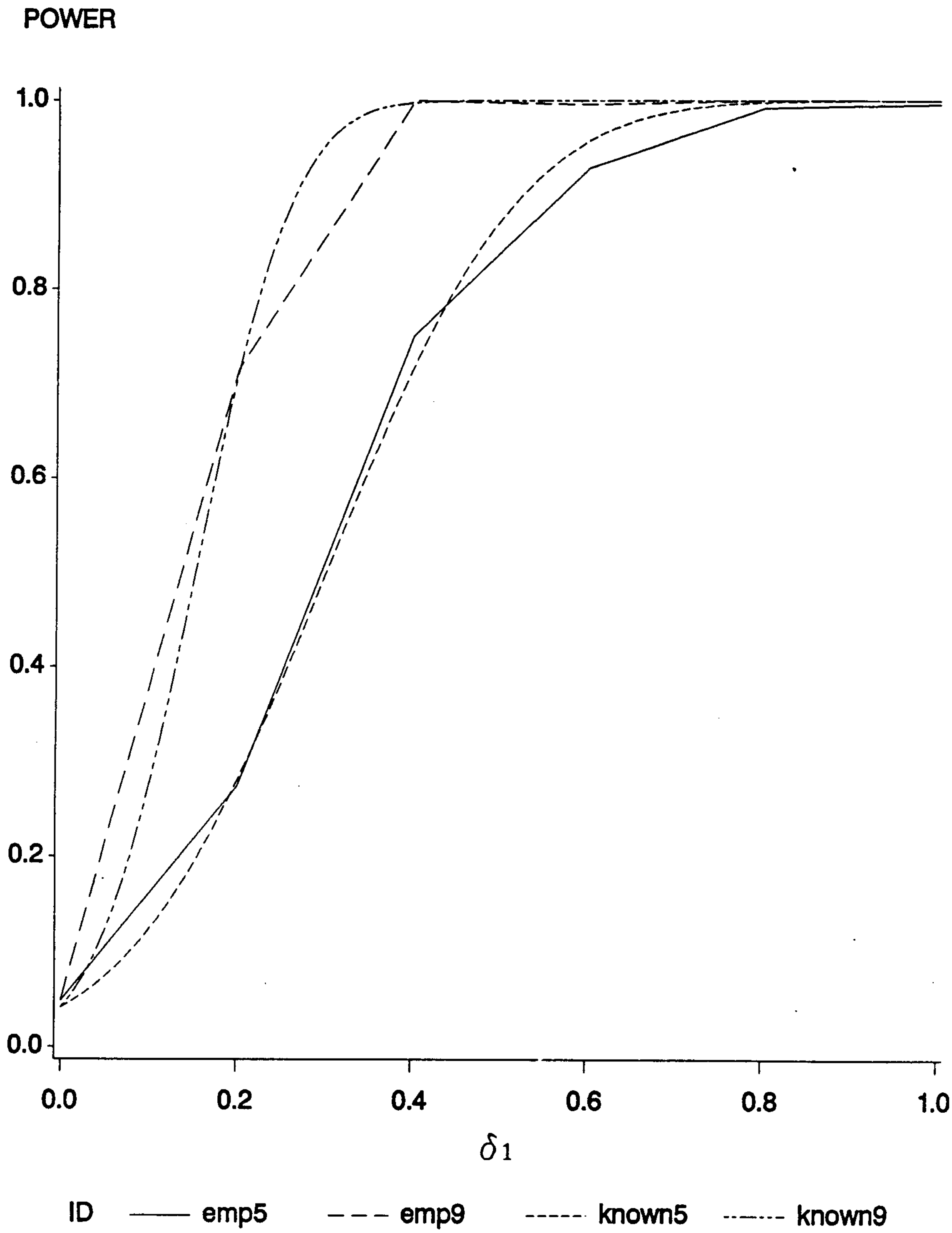
$C_1=0.1$ $C_2=10$ $m=5$ $n=10$



APPENDIX 4.5

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

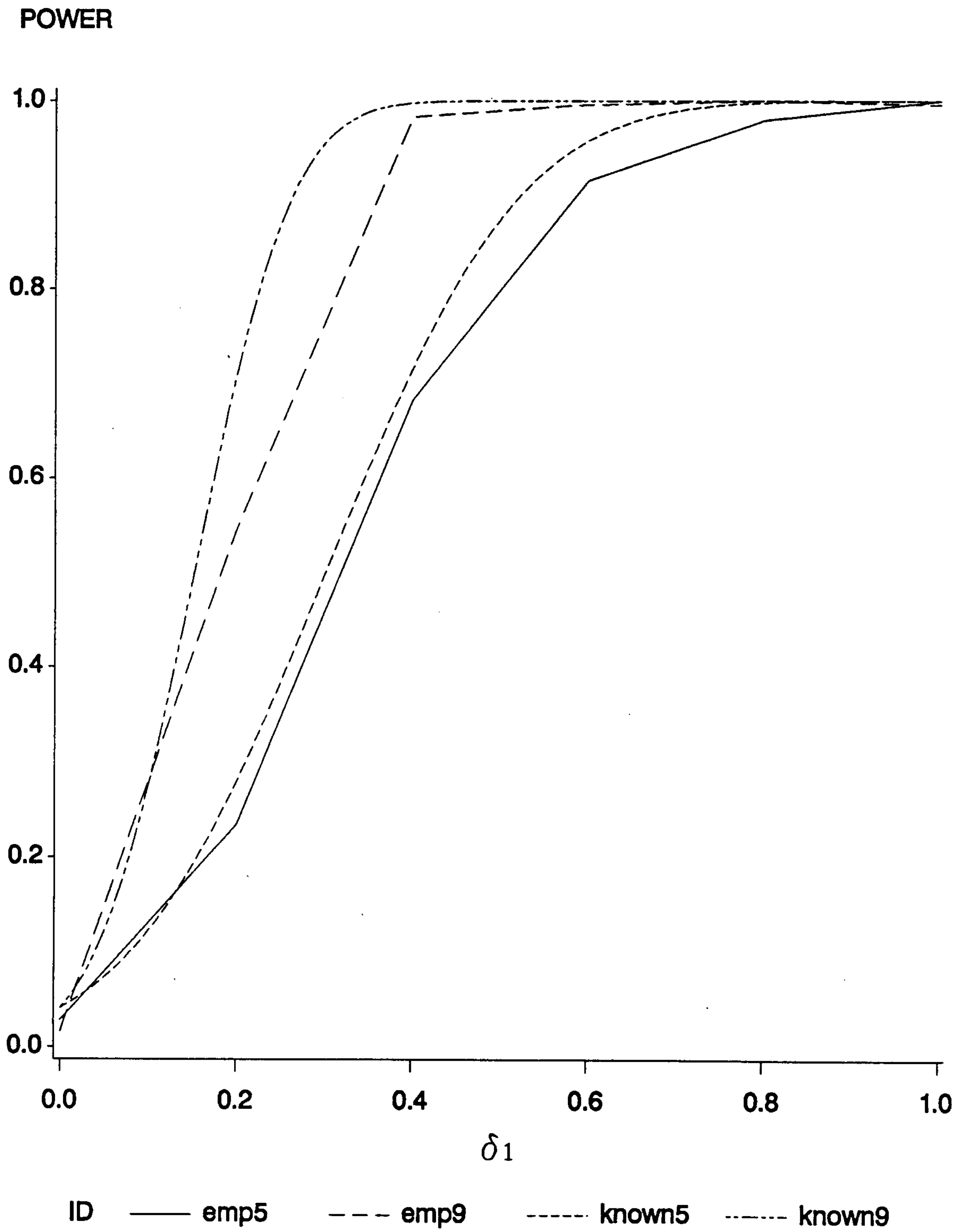
$C_1=1 \quad C_2=0.1 \quad m=5 \quad n=10$



APPENDIX 4.6

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

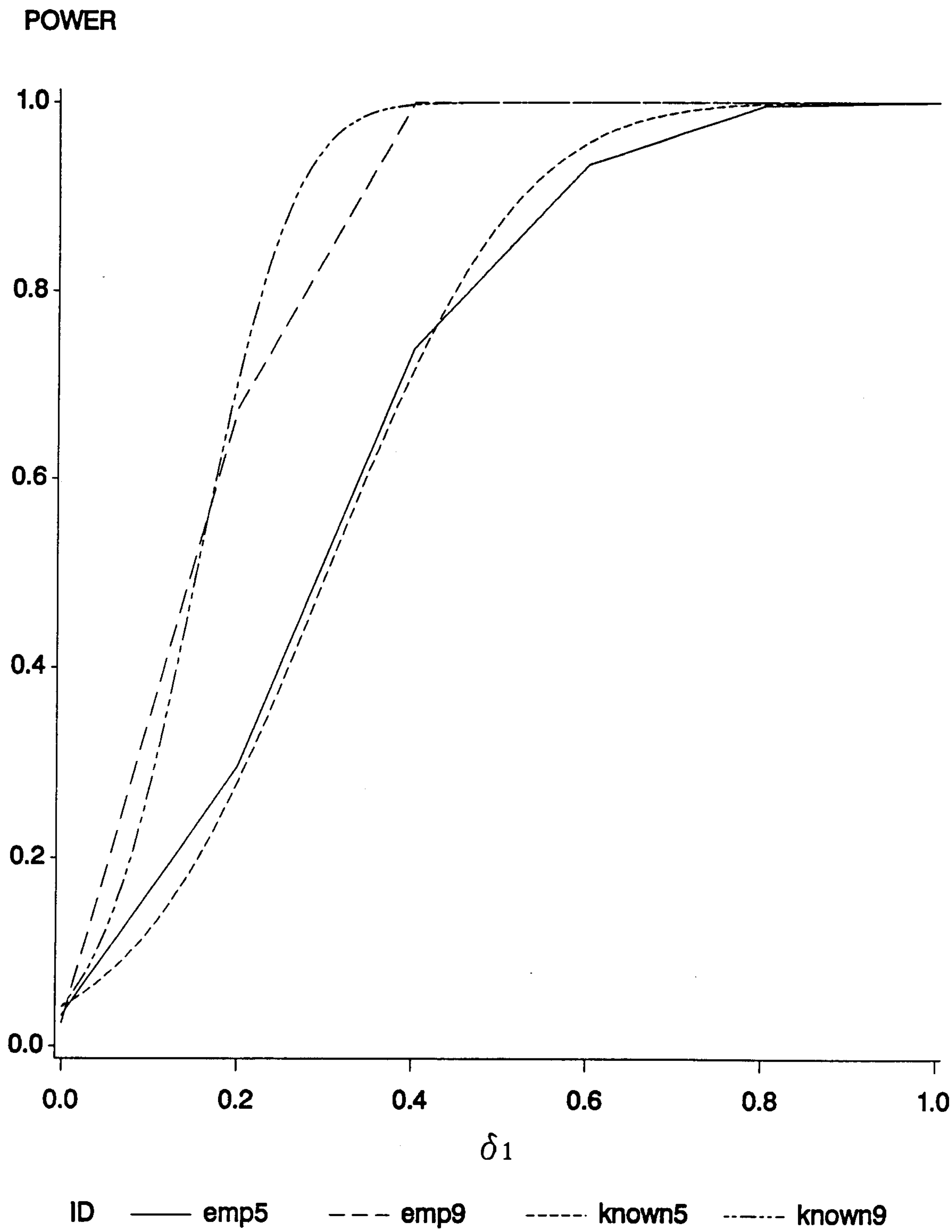
$C_1=1 \quad C_2=1 \quad m=5 \quad n=10$



APPENDIX 4.7

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

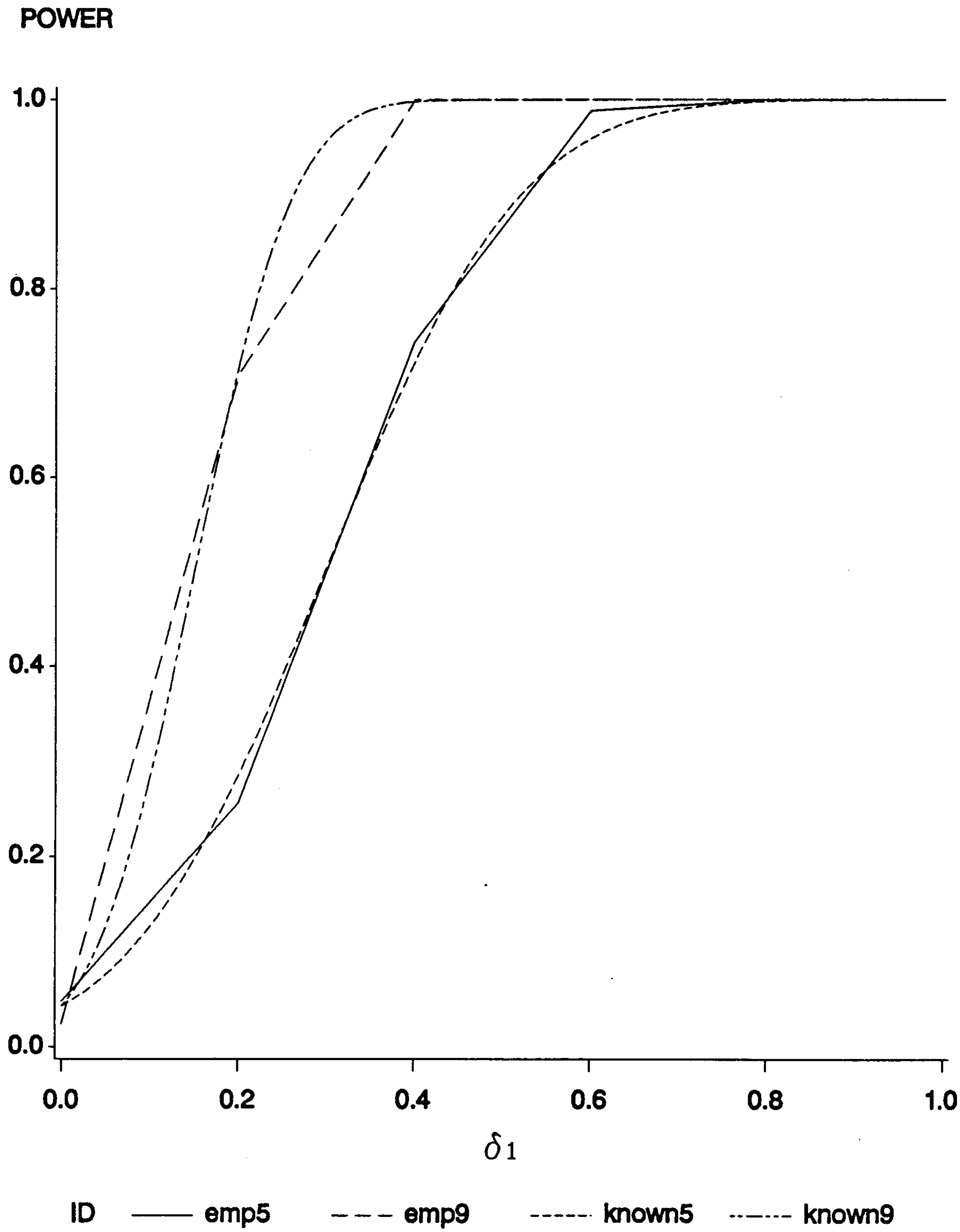
$C_1=1 \quad C_2=10 \quad m=5 \quad n=10$



APPENDIX 4.8

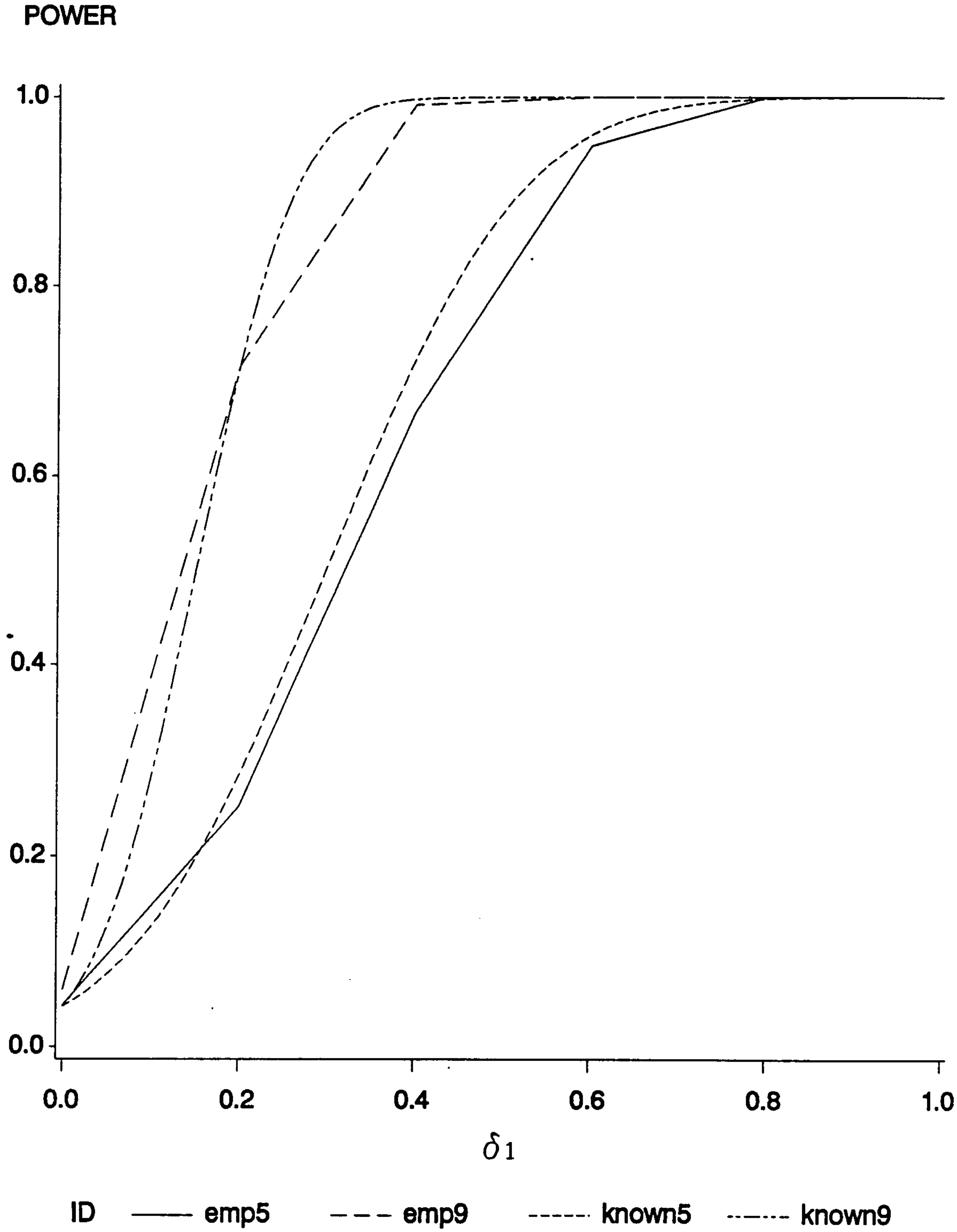
POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

$C_1=10 \quad C_2=0.1 \quad m=5 \quad n=10$



APPENDIX 4.9

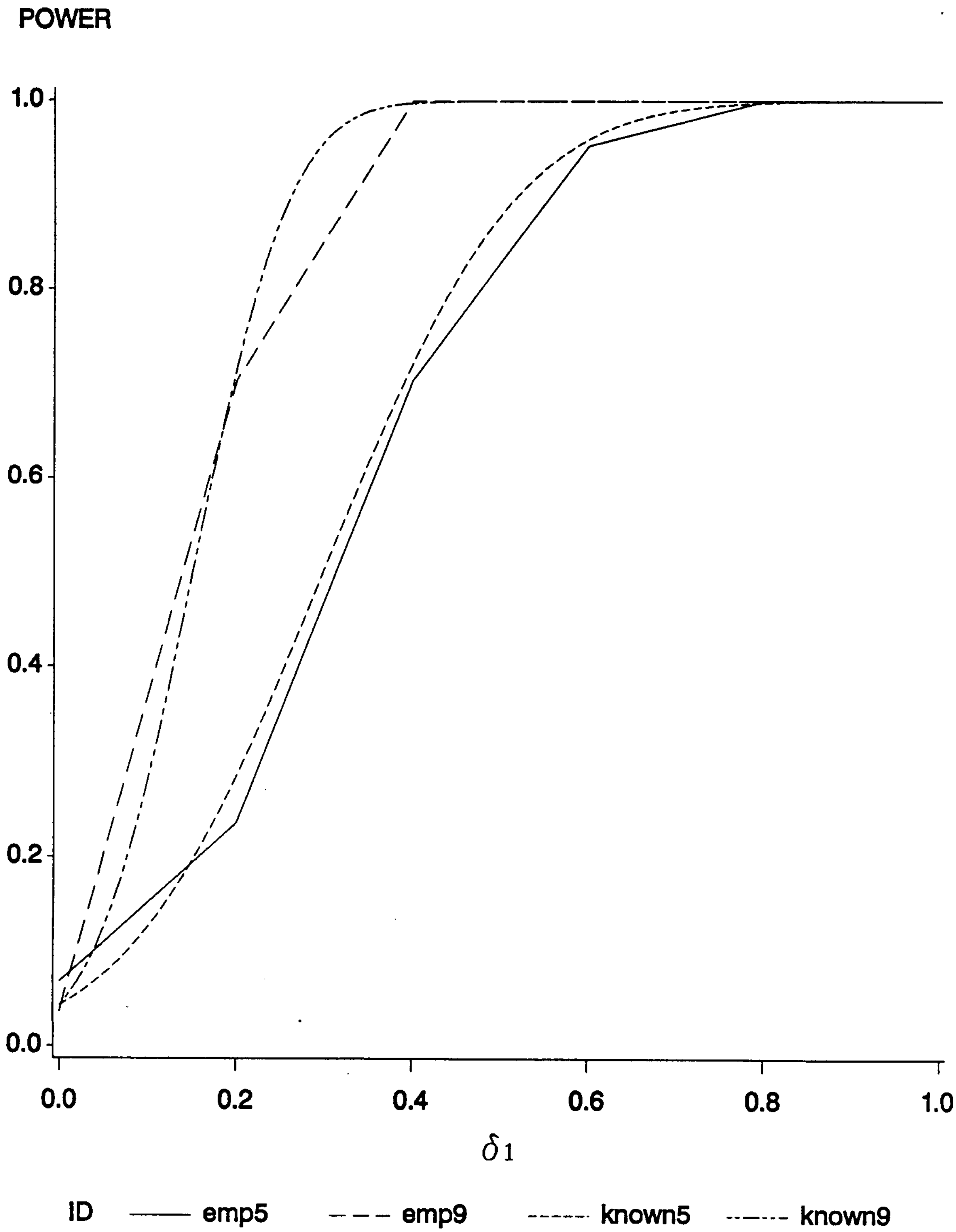
POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE
$C_1=10$ $C_2=1$ $m=5$ $n=10$



APPENDIX 4.10

POWER CURVE COMPARISONS USING MULTICENTER PROCEDURE

$C_1=10 \quad C_2=10 \quad m=5 \quad n=10$



APPENDIX 4.11

COMPARISON OF MULTICENTER PROCEDURES
m=5 n=5

C1	C2	RHO	DELTA1	KNOWN POWER	SIGMA POWER	C1 POWER
0.1	0.1	0.0	0.0	0.02086	0.07658	0.02881
0.1	0.1	0.0	0.2	0.09189	0.21525	0.18852
0.1	0.1	0.0	0.4	0.26694	0.38197	0.52917
0.1	0.1	0.0	0.6	0.53387	0.64035	0.86667
0.1	0.1	0.0	0.8	0.78585	0.83117	0.97083
0.1	0.1	0.0	1.0	0.93309	0.91703	0.98770
0.1	0.1	0.5	0.0	0.02086	0.07424	0.03347
0.1	0.1	0.5	0.2	0.11127	0.21586	0.20000
0.1	0.1	0.5	0.4	0.34336	0.48945	0.62656
0.1	0.1	0.5	0.6	0.66026	0.75983	0.92917
0.1	0.1	0.5	0.8	0.89059	0.91630	0.99145
0.1	0.1	0.5	1.0	0.97963	0.96507	1.00000
0.1	0.1	0.9	0.0	0.02086	0.02586	0.02929
0.1	0.1	0.9	0.2	0.33940	0.44541	0.62656
0.1	0.1	0.9	0.4	0.88650	0.83700	0.97107
0.1	0.1	0.9	0.6	0.99767	0.98246	0.98723
0.1	0.1	0.9	0.8	1.00000	0.99556	1.00000
0.1	0.1	0.9	1.0	1.00000	0.99558	1.00000
0.1	1.0	0.0	0.0	0.02086	0.09292	0.05394
0.1	1.0	0.0	0.2	0.09189	0.13575	0.21667
0.1	1.0	0.0	0.4	0.26694	0.44589	0.49153
0.1	1.0	0.0	0.6	0.53387	0.63063	0.81590
0.1	1.0	0.0	0.8	0.78585	0.81696	0.95816
0.1	1.0	0.0	1.0	0.93309	0.92308	0.97925
0.1	1.0	0.5	0.0	0.02086	0.05240	0.03782
0.1	1.0	0.5	0.2	0.11127	0.22072	0.21097
0.1	1.0	0.5	0.4	0.34336	0.49351	0.63025
0.1	1.0	0.5	0.6	0.66026	0.73684	0.91667
0.1	1.0	0.5	0.8	0.89059	0.90171	0.99585
0.1	1.0	0.5	1.0	0.97963	0.95279	0.99153
0.1	1.0	0.9	0.0	0.02086	0.05907	0.02479
0.1	1.0	0.9	0.2	0.33940	0.52790	0.58506
0.1	1.0	0.9	0.4	0.88650	0.90558	0.97131
0.1	1.0	0.9	0.6	0.99767	0.99561	1.00000
0.1	1.0	0.9	0.8	1.00000	0.99123	0.99163
0.1	1.0	0.9	1.0	1.00000	0.99558	0.99582
0.1	10.0	0.0	0.0	0.02086	0.07296	0.03734
0.1	10.0	0.0	0.2	0.09189	0.22174	0.18333
0.1	10.0	0.0	0.4	0.26694	0.40088	0.51230
0.1	10.0	0.0	0.6	0.53387	0.67982	0.85897
0.1	10.0	0.0	0.8	0.78585	0.82895	0.93644
0.1	10.0	0.0	1.0	0.93309	0.92140	0.98718
0.1	10.0	0.5	0.0	0.02086	0.04405	0.03404
0.1	10.0	0.5	0.2	0.11127	0.20889	0.22414
0.1	10.0	0.5	0.4	0.34336	0.49778	0.61667

APPENDIX 4.11 (cont'd)

COMPARISON OF MULTICENTER PROCEDURES
m=5 n=5

C1	C2	RHO	DELTA1	KNOWN POWER	SIGMA POWER	C1 POWER
0.1	10.0	0.5	0.6	0.66026	0.71491	0.91286
0.1	10.0	0.5	0.8	0.89059	0.91031	0.98760
0.1	10.0	0.5	1.0	0.97963	0.94323	0.99177
0.1	10.0	0.9	0.0	0.02086	0.06957	0.02083
0.1	10.0	0.9	0.2	0.33940	0.45000	0.69136
0.1	10.0	0.9	0.4	0.88650	0.85398	0.98340
0.1	10.0	0.9	0.6	0.99767	0.98305	0.99583
0.1	10.0	0.9	0.8	1.00000	0.99142	1.00000
0.1	10.0	0.9	1.0	1.00000	1.00000	1.00000
1.0	0.1	0.0	0.0	0.03962	0.05306	0.04000
1.0	0.1	0.0	0.2	0.14732	0.18852	0.20000
1.0	0.1	0.0	0.4	0.36660	0.34426	0.59600
1.0	0.1	0.0	0.6	0.64291	0.65164	0.90800
1.0	0.1	0.0	0.8	0.85844	0.82231	0.98400
1.0	0.1	0.0	1.0	0.96250	0.95161	0.99600
1.0	0.1	0.5	0.0	0.03962	0.03673	0.04800
1.0	0.1	0.5	0.2	0.17397	0.19672	0.25600
1.0	0.1	0.5	0.4	0.45141	0.42915	0.70400
1.0	0.1	0.5	0.6	0.75629	0.75918	0.96000
1.0	0.1	0.5	0.8	0.93459	0.95455	1.00000
1.0	0.1	0.5	1.0	0.99003	0.98790	1.00000
1.0	0.1	0.9	0.0	0.03962	0.03659	0.04400
1.0	0.1	0.9	0.2	0.44715	0.41296	0.69600
1.0	0.1	0.9	0.4	0.93180	0.90574	1.00000
1.0	0.1	0.9	0.6	0.99907	0.99180	1.00000
1.0	0.1	0.9	0.8	1.00000	0.99197	1.00000
1.0	0.1	0.9	1.0	1.00000	1.00000	1.00000
1.0	1.0	0.0	0.0	0.03962	0.02893	0.02400
1.0	1.0	0.0	0.2	0.14732	0.10373	0.24400
1.0	1.0	0.0	0.4	0.36660	0.36885	0.56000
1.0	1.0	0.0	0.6	0.64291	0.60081	0.91200
1.0	1.0	0.0	0.8	0.85844	0.85124	0.99200
1.0	1.0	0.0	1.0	0.96250	0.93852	1.00000
1.0	1.0	0.5	0.0	0.03962	0.04979	0.03600
1.0	1.0	0.5	0.2	0.17397	0.18257	0.29600
1.0	1.0	0.5	0.4	0.45141	0.39669	0.74400
1.0	1.0	0.5	0.6	0.75629	0.72222	0.94000
1.0	1.0	0.5	0.8	0.93459	0.91463	1.00000
1.0	1.0	0.5	1.0	0.99003	0.98770	1.00000
1.0	1.0	0.9	0.0	0.03962	0.03629	0.04000
1.0	1.0	0.9	0.2	0.44715	0.44939	0.72000
1.0	1.0	0.9	0.4	0.93180	0.93117	0.99600
1.0	1.0	0.9	0.6	0.99907	1.00000	1.00000
1.0	1.0	0.9	0.8	1.00000	1.00000	1.00000
1.0	1.0	0.9	1.0	1.00000	0.99590	1.00000

APPENDIX 4.11 (cont'd)

COMPARISON OF MULTICENTER PROCEDURES
m=5 n=5

C1	C2	RHO	DELTA1	KNOWN POWER	SIGMA POWER	C1 POWER
1.0	10.0	0.0	0.0	0.03962	0.03320	0.04800
1.0	10.0	0.0	0.2	0.14732	0.13469	0.22000
1.0	10.0	0.0	0.4	0.36660	0.42915	0.58000
1.0	10.0	0.0	0.6	0.64291	0.58197	0.91200
1.0	10.0	0.0	0.8	0.85844	0.77328	0.99200
1.0	10.0	0.0	1.0	0.96250	0.93878	1.00000
1.0	10.0	0.5	0.0	0.03962	0.06098	0.04000
1.0	10.0	0.5	0.2	0.17397	0.19328	0.33200
1.0	10.0	0.5	0.4	0.45141	0.42857	0.69600
1.0	10.0	0.5	0.6	0.75629	0.73140	0.95600
1.0	10.0	0.5	0.8	0.93459	0.90123	1.00000
1.0	10.0	0.5	1.0	0.99003	0.97177	1.00000
1.0	10.0	0.9	0.0	0.03962	0.03704	0.03200
1.0	10.0	0.9	0.2	0.44715	0.46888	0.66800
1.0	10.0	0.9	0.4	0.93180	0.91129	1.00000
1.0	10.0	0.9	0.6	0.99907	1.00000	1.00000
1.0	10.0	0.9	0.8	1.00000	1.00000	1.00000
1.0	10.0	0.9	1.0	1.00000	1.00000	1.00000
10.0	0.1	0.0	0.0	0.04231	0.03200	0.05600
10.0	0.1	0.0	0.2	0.15450	0.15600	0.27200
10.0	0.1	0.0	0.4	0.37819	0.34800	0.65200
10.0	0.1	0.0	0.6	0.65427	0.61694	0.89200
10.0	0.1	0.0	0.8	0.86520	0.86000	1.00000
10.0	0.1	0.0	1.0	0.96494	0.96000	0.99600
10.0	0.1	0.5	0.0	0.04231	0.06000	0.04400
10.0	0.1	0.5	0.2	0.18195	0.17269	0.30400
10.0	0.1	0.5	0.4	0.46357	0.44000	0.70000
10.0	0.1	0.5	0.6	0.76579	0.76800	0.95600
10.0	0.1	0.5	0.8	0.93841	0.96800	1.00000
10.0	0.1	0.5	1.0	0.99081	0.98800	1.00000
10.0	0.1	0.9	0.0	0.04231	0.04800	0.07200
10.0	0.1	0.9	0.2	0.45929	0.44800	0.72000
10.0	0.1	0.9	0.4	0.93574	0.93200	0.99200
10.0	0.1	0.9	0.6	0.99916	1.00000	1.00000
10.0	0.1	0.9	0.8	1.00000	1.00000	1.00000
10.0	0.1	0.9	1.0	1.00000	1.00000	1.00000
10.0	1.0	0.0	0.0	0.04231	0.02000	0.06000
10.0	1.0	0.0	0.2	0.15450	0.17200	0.24000
10.0	1.0	0.0	0.4	0.37819	0.37600	0.57600
10.0	1.0	0.0	0.6	0.65427	0.65200	0.90800
10.0	1.0	0.0	0.8	0.86520	0.84800	0.98400
10.0	1.0	0.0	1.0	0.96494	0.95200	1.00000
10.0	1.0	0.5	0.0	0.04231	0.02008	0.06000
10.0	1.0	0.5	0.2	0.18195	0.22984	0.26000
10.0	1.0	0.5	0.4	0.46357	0.54000	0.78000

APPENDIX 4.11 (cont'd)

COMPARISON OF MULTICENTER PROCEDURES
m=5 n=5

C1	C2	RHO	DELTA1	KNOWN POWER	SIGMA POWER	C1 POWER
10.0	1.0	0.5	0.6	0.76579	0.75200	0.93200
10.0	1.0	0.5	0.8	0.93841	0.92400	0.99200
10.0	1.0	0.5	1.0	0.99081	0.99200	1.00000
10.0	1.0	0.9	0.0	0.04231	0.05622	0.03200
10.0	1.0	0.9	0.2	0.45929	0.49200	0.69200
10.0	1.0	0.9	0.4	0.93574	0.91600	0.99600
10.0	1.0	0.9	0.6	0.99916	0.99600	1.00000
10.0	1.0	0.9	0.8	1.00000	1.00000	1.00000
10.0	1.0	0.9	1.0	1.00000	1.00000	1.00000
10.0	10.0	0.0	0.0	0.04231	0.06426	0.04400
10.0	10.0	0.0	0.2	0.15450	0.16000	0.27200
10.0	10.0	0.0	0.4	0.37819	0.42000	0.55200
10.0	10.0	0.0	0.6	0.65427	0.67339	0.90800
10.0	10.0	0.0	0.8	0.86520	0.87600	0.99200
10.0	10.0	0.0	1.0	0.96494	0.96400	0.99600
10.0	10.0	0.5	0.0	0.04231	0.03614	0.06400
10.0	10.0	0.5	0.2	0.18195	0.21600	0.29600
10.0	10.0	0.5	0.4	0.46357	0.45600	0.76400
10.0	10.0	0.5	0.6	0.76579	0.75600	0.96800
10.0	10.0	0.5	0.8	0.93841	0.93574	0.99200
10.0	10.0	0.5	1.0	0.99081	0.99600	1.00000
10.0	10.0	0.9	0.0	0.04231	0.05600	0.04000
10.0	10.0	0.9	0.2	0.45929	0.45382	0.71200
10.0	10.0	0.9	0.4	0.93574	0.91200	0.98800
10.0	10.0	0.9	0.6	0.99916	1.00000	1.00000
10.0	10.0	0.9	0.8	1.00000	1.00000	1.00000
10.0	10.0	0.9	1.0	1.00000	1.00000	1.00000

APPENDIX 4.12

COMPARISON OF MULTICENTER PROCEDURES
m=5 n=10

C1	C2	RHO	DELTA1	KNOWN POWER	SIGMA POWER	C1 POWER
0.1	0.1	0.0	0.0	0.02970	0.08850	0.02881
0.1	0.1	0.0	0.2	0.18801	0.22553	0.18852
0.1	0.1	0.0	0.4	0.54567	0.55947	0.52917
0.1	0.1	0.0	0.6	0.86752	0.81857	0.86667
0.1	0.1	0.0	0.8	0.98277	0.96639	0.97083
0.1	0.1	0.0	1.0	0.99908	0.97890	0.98770
0.1	0.1	0.5	0.0	0.02970	0.05240	0.03347
0.1	0.1	0.5	0.2	0.23252	0.28755	0.20000
0.1	0.1	0.5	0.4	0.66427	0.65236	0.62656
0.1	0.1	0.5	0.6	0.94281	0.92920	0.92917
0.1	0.1	0.5	0.8	0.99687	0.99145	0.99145
0.1	0.1	0.5	1.0	0.99995	0.98696	1.00000
0.1	0.1	0.9	0.0	0.02970	0.03896	0.02929
0.1	0.1	0.9	0.2	0.65869	0.64783	0.62656
0.1	0.1	0.9	0.4	0.99656	0.97899	0.97107
0.1	0.1	0.9	0.6	1.00000	0.99561	0.98723
0.1	0.1	0.9	0.8	1.00000	0.99578	1.00000
0.1	0.1	0.9	1.0	1.00000	1.00000	1.00000
0.1	1.0	0.0	0.0	0.02970	0.03896	0.05394
0.1	1.0	0.0	0.2	0.18801	0.28390	0.21667
0.1	1.0	0.0	0.4	0.54567	0.53947	0.49153
0.1	1.0	0.0	0.6	0.86752	0.84914	0.81590
0.1	1.0	0.0	0.8	0.98277	0.96000	0.95816
0.1	1.0	0.0	1.0	0.99908	0.98222	0.97925
0.1	1.0	0.5	0.0	0.02970	0.05106	0.03782
0.1	1.0	0.5	0.2	0.23252	0.32203	0.21097
0.1	1.0	0.5	0.4	0.66427	0.67234	0.63025
0.1	1.0	0.5	0.6	0.94281	0.92342	0.91667
0.1	1.0	0.5	0.8	0.99687	0.96875	0.99585
0.1	1.0	0.5	1.0	0.99995	0.99138	0.99153
0.1	1.0	0.9	0.0	0.02970	0.06550	0.02479
0.1	1.0	0.9	0.2	0.65869	0.66222	0.58506
0.1	1.0	0.9	0.4	0.99656	0.97854	0.97131
0.1	1.0	0.9	0.6	1.00000	0.99130	1.00000
0.1	1.0	0.9	0.8	1.00000	1.00000	0.99163
0.1	1.0	0.9	1.0	1.00000	1.00000	0.99582
0.1	10.0	0.0	0.0	0.02970	0.05508	0.03734
0.1	10.0	0.0	0.2	0.18801	0.22467	0.18333
0.1	10.0	0.0	0.4	0.54567	0.57965	0.51230
0.1	10.0	0.0	0.6	0.86752	0.80263	0.85897
0.1	10.0	0.0	0.8	0.98277	0.97309	0.93644
0.1	10.0	0.0	1.0	0.99908	0.98734	0.98718
0.1	10.0	0.5	0.0	0.02970	0.06356	0.03404
0.1	10.0	0.5	0.2	0.23252	0.29741	0.22414
0.1	10.0	0.5	0.4	0.66427	0.69130	0.61667

APPENDIX 4.12 (cont'd)

COMPARISON OF MULTICENTER PROCEDURES
m=5 n=10

C1	C2	RHO	DELTA1	KNOWN POWER	SIGMA POWER	C1 POWER
0.1	10.0	0.5	0.6	0.94281	0.88936	0.91286
0.1	10.0	0.5	0.8	0.99687	0.98276	0.98760
0.1	10.0	0.5	1.0	0.99995	0.99134	0.99177
0.1	10.0	0.9	0.0	0.02970	0.06222	0.02083
0.1	10.0	0.9	0.2	0.65869	0.70339	0.69136
0.1	10.0	0.9	0.4	0.99656	0.98734	0.98340
0.1	10.0	0.9	0.6	1.00000	0.98684	0.99583
0.1	10.0	0.9	0.8	1.00000	1.00000	1.00000
0.1	10.0	0.9	1.0	1.00000	1.00000	1.00000
1.0	0.1	0.0	0.0	0.04109	0.05645	0.04000
1.0	0.1	0.0	0.2	0.23022	0.24096	0.20000
1.0	0.1	0.0	0.4	0.60329	0.56504	0.59600
1.0	0.1	0.0	0.6	0.89650	0.89024	0.90800
1.0	0.1	0.0	0.8	0.98815	0.99194	0.98400
1.0	0.1	0.0	1.0	0.99945	1.00000	0.99600
1.0	0.1	0.5	0.0	0.04109	0.04858	0.04800
1.0	0.1	0.5	0.2	0.27980	0.27347	0.25600
1.0	0.1	0.5	0.4	0.71609	0.75000	0.70400
1.0	0.1	0.5	0.6	0.95782	0.92946	0.96000
1.0	0.1	0.5	0.8	0.99802	0.99194	1.00000
1.0	0.1	0.5	1.0	0.99997	0.99598	1.00000
1.0	0.1	0.9	0.0	0.04109	0.04839	0.04400
1.0	0.1	0.9	0.2	0.71091	0.71486	0.69600
1.0	0.1	0.9	0.4	0.99782	1.00000	1.00000
1.0	0.1	0.9	0.6	1.00000	0.99593	1.00000
1.0	0.1	0.9	0.8	1.00000	1.00000	1.00000
1.0	0.1	0.9	1.0	1.00000	1.00000	1.00000
1.0	1.0	0.0	0.0	0.04109	0.05306	0.02400
1.0	1.0	0.0	0.2	0.23022	0.08943	0.24400
1.0	1.0	0.0	0.4	0.60329	0.55285	0.56000
1.0	1.0	0.0	0.6	0.89650	0.84146	0.91200
1.0	1.0	0.0	0.8	0.98815	0.94672	0.99200
1.0	1.0	0.0	1.0	0.99945	1.00000	1.00000
1.0	1.0	0.5	0.0	0.04109	0.02834	0.03600
1.0	1.0	0.5	0.2	0.27980	0.23457	0.29600
1.0	1.0	0.5	0.4	0.71609	0.68313	0.74400
1.0	1.0	0.5	0.6	0.95782	0.91498	0.94000
1.0	1.0	0.5	0.8	0.99802	0.97959	1.00000
1.0	1.0	0.5	1.0	0.99997	1.00000	1.00000
1.0	1.0	0.9	0.0	0.04109	0.01613	0.04000
1.0	1.0	0.9	0.2	0.71091	0.54656	0.72000
1.0	1.0	0.9	0.4	0.99782	0.98367	0.99600
1.0	1.0	0.9	0.6	1.00000	0.99598	1.00000
1.0	1.0	0.9	0.8	1.00000	1.00000	1.00000
1.0	1.0	0.9	1.0	1.00000	0.99597	1.00000

APPENDIX 4.12 (cont'd)

COMPARISON OF MULTICENTER PROCEDURES
m=5 n=10

C1	C2	RHO	DELTA1	KNOWN POWER	SIGMA POWER	C1 POWER
1.0	10.0	0.0	0.0	0.04109	0.05645	0.04800
1.0	10.0	0.0	0.2	0.23022	0.18367	0.22000
1.0	10.0	0.0	0.4	0.60329	0.58400	0.58000
1.0	10.0	0.0	0.6	0.89650	0.86475	0.91200
1.0	10.0	0.0	0.8	0.98815	0.97967	0.99200
1.0	10.0	0.0	1.0	0.99945	0.99597	1.00000
1.0	10.0	0.5	0.0	0.04109	0.03200	0.04000
1.0	10.0	0.5	0.2	0.27980	0.29719	0.33200
1.0	10.0	0.5	0.4	0.71609	0.73896	0.69600
1.0	10.0	0.5	0.6	0.95782	0.93443	0.95600
1.0	10.0	0.5	0.8	0.99802	0.99597	1.00000
1.0	10.0	0.5	1.0	0.99997	1.00000	1.00000
1.0	10.0	0.9	0.0	0.04109	0.02429	0.03200
1.0	10.0	0.9	0.2	0.71091	0.67742	0.66800
1.0	10.0	0.9	0.4	0.99782	1.00000	1.00000
1.0	10.0	0.9	0.6	1.00000	1.00000	1.00000
1.0	10.0	0.9	0.8	1.00000	1.00000	1.00000
1.0	10.0	0.9	1.0	1.00000	1.00000	1.00000
10.0	0.1	0.0	0.0	0.04247	0.04400	0.05600
10.0	0.1	0.0	0.2	0.23493	0.25200	0.27200
10.0	0.1	0.0	0.4	0.60922	0.64000	0.65200
10.0	0.1	0.0	0.6	0.89925	0.87200	0.89200
10.0	0.1	0.0	0.8	0.98862	0.98400	1.00000
10.0	0.1	0.0	1.0	0.99948	1.00000	0.99600
10.0	0.1	0.5	0.0	0.04247	0.04800	0.04400
10.0	0.1	0.5	0.2	0.28501	0.25600	0.30400
10.0	0.1	0.5	0.4	0.72129	0.74400	0.70000
10.0	0.1	0.5	0.6	0.95919	0.98800	0.95600
10.0	0.1	0.5	0.8	0.99811	1.00000	1.00000
10.0	0.1	0.5	1.0	0.99997	1.00000	1.00000
10.0	0.1	0.9	0.0	0.04247	0.02400	0.07200
10.0	0.1	0.9	0.2	0.71615	0.70800	0.72000
10.0	0.1	0.9	0.4	0.99792	1.00000	0.99200
10.0	0.1	0.9	0.6	1.00000	1.00000	1.00000
10.0	0.1	0.9	0.8	1.00000	1.00000	1.00000
10.0	0.1	0.9	1.0	1.00000	1.00000	1.00000
10.0	1.0	0.0	0.0	0.04247	0.04800	0.06000
10.0	1.0	0.0	0.2	0.23493	0.23600	0.24000
10.0	1.0	0.0	0.4	0.60922	0.64257	0.57600
10.0	1.0	0.0	0.6	0.89925	0.87600	0.90800
10.0	1.0	0.0	0.8	0.98862	0.98800	0.98400
10.0	1.0	0.0	1.0	0.99948	1.00000	1.00000
10.0	1.0	0.5	0.0	0.04247	0.04400	0.06000
10.0	1.0	0.5	0.2	0.28501	0.25200	0.26000
10.0	1.0	0.5	0.4	0.72129	0.66667	0.78000

APPENDIX 4.12 (cont'd)

COMPARISON OF MULTICENTER PROCEDURES
m=5 n=10

C1	C2	RHO	DELTA1	KNOWN POWER	SIGMA POWER	C1 POWER
10.0	1.0	0.5	0.6	0.95919	0.94800	0.93200
10.0	1.0	0.5	0.8	0.99811	1.00000	0.99200
10.0	1.0	0.5	1.0	0.99997	1.00000	1.00000
10.0	1.0	0.9	0.0	0.04247	0.06024	0.03200
10.0	1.0	0.9	0.2	0.71615	0.71600	0.69200
10.0	1.0	0.9	0.4	0.99792	0.99200	0.99600
10.0	1.0	0.9	0.6	1.00000	1.00000	1.00000
10.0	1.0	0.9	0.8	1.00000	1.00000	1.00000
10.0	1.0	0.9	1.0	1.00000	1.00000	1.00000
10.0	10.0	0.0	0.0	0.04247	0.03200	0.04400
10.0	10.0	0.0	0.2	0.23493	0.22000	0.27200
10.0	10.0	0.0	0.4	0.60922	0.61200	0.55200
10.0	10.0	0.0	0.6	0.89925	0.85600	0.90800
10.0	10.0	0.0	0.8	0.98862	0.98400	0.99200
10.0	10.0	0.0	1.0	0.99948	1.00000	0.99600
10.0	10.0	0.5	0.0	0.04247	0.06800	0.06400
10.0	10.0	0.5	0.2	0.28501	0.23600	0.29600
10.0	10.0	0.5	0.4	0.72129	0.70400	0.76400
10.0	10.0	0.5	0.6	0.95919	0.95200	0.96800
10.0	10.0	0.5	0.8	0.99811	1.00000	0.99200
10.0	10.0	0.5	1.0	0.99997	1.00000	1.00000
10.0	10.0	0.9	0.0	0.04247	0.03600	0.04000
10.0	10.0	0.9	0.2	0.71615	0.70400	0.71200
10.0	10.0	0.9	0.4	0.99792	1.00000	0.98800
10.0	10.0	0.9	0.6	1.00000	1.00000	1.00000
10.0	10.0	0.9	0.8	1.00000	1.00000	1.00000
10.0	10.0	0.9	1.0	1.00000	1.00000	1.00000

APPENDIX 4.13

FREQUENCIES OF VALID RESULTS
FOR MULTICENTER PROCEDURES
m=5 n=5

C1	C2	RHO	DELTA1	SIGMA FREQ	C1 FREQ
0.1	0.1	0.0	0.0	222	221
0.1	0.1	0.0	0.2	223	230
0.1	0.1	0.0	0.4	233	232
0.1	0.1	0.0	0.6	228	224
0.1	0.1	0.0	0.8	231	228
0.1	0.1	0.0	1.0	229	235
0.1	0.1	0.5	0.0	229	232
0.1	0.1	0.5	0.2	227	230
0.1	0.1	0.5	0.4	237	231
0.1	0.1	0.5	0.6	229	226
0.1	0.1	0.5	0.8	227	222
0.1	0.1	0.5	1.0	229	234
0.1	0.1	0.9	0.0	232	219
0.1	0.1	0.9	0.2	229	230
0.1	0.1	0.9	0.4	227	221
0.1	0.1	0.9	0.6	228	219
0.1	0.1	0.9	0.8	225	224
0.1	0.1	0.9	1.0	226	222
0.1	1.0	0.0	0.0	226	227
0.1	1.0	0.0	0.2	221	230
0.1	1.0	0.0	0.4	231	229
0.1	1.0	0.0	0.6	222	226
0.1	1.0	0.0	0.8	224	228
0.1	1.0	0.0	1.0	234	226
0.1	1.0	0.5	0.0	229	229
0.1	1.0	0.5	0.2	222	227
0.1	1.0	0.5	0.4	231	219
0.1	1.0	0.5	0.6	228	228
0.1	1.0	0.5	0.8	234	201
0.1	1.0	0.5	1.0	233	224
0.1	1.0	0.9	0.0	237	232
0.1	1.0	0.9	0.2	233	230
0.1	1.0	0.9	0.4	233	225
0.1	1.0	0.9	0.6	228	220
0.1	1.0	0.9	0.8	228	231
0.1	1.0	0.9	1.0	226	220
0.1	10.0	0.0	0.0	233	234
0.1	10.0	0.0	0.2	230	229
0.1	10.0	0.0	0.4	227	219
0.1	10.0	0.0	0.6	228	237
0.1	10.0	0.0	0.8	228	225
0.1	10.0	0.0	1.0	229	236
0.1	10.0	0.5	0.0	227	224
0.1	10.0	0.5	0.2	225	227

APPENDIX 4.13 (cont'd)

FREQUENCIES OF VALID RESULTS
FOR MULTICENTER PROCEDURES
m=5 n=5

C1	C2	RHO	DELTA1	SIGMA FREQ	C1 FREQ
0.1	10.0	0.5	0.4	225	229
0.1	10.0	0.5	0.6	228	219
0.1	10.0	0.5	0.8	223	225
0.1	10.0	0.5	1.0	229	225
0.1	10.0	0.9	0.0	230	226
0.1	10.0	0.9	0.2	220	230
0.1	10.0	0.9	0.4	226	225
0.1	10.0	0.9	0.6	236	227
0.1	10.0	0.9	0.8	233	221
0.1	10.0	0.9	1.0	229	214
1.0	0.1	0.0	0.0	245	250
1.0	0.1	0.0	0.2	244	250
1.0	0.1	0.0	0.4	244	248
1.0	0.1	0.0	0.6	244	250
1.0	0.1	0.0	0.8	242	250
1.0	0.1	0.0	1.0	248	249
1.0	0.1	0.5	0.0	245	250
1.0	0.1	0.5	0.2	244	250
1.0	0.1	0.5	0.4	247	250
1.0	0.1	0.5	0.6	245	250
1.0	0.1	0.5	0.8	242	248
1.0	0.1	0.5	1.0	248	250
1.0	0.1	0.9	0.0	246	250
1.0	0.1	0.9	0.2	247	250
1.0	0.1	0.9	0.4	244	250
1.0	0.1	0.9	0.6	244	250
1.0	0.1	0.9	0.8	249	250
1.0	0.1	0.9	1.0	244	250
1.0	1.0	0.0	0.0	242	250
1.0	1.0	0.0	0.2	241	250
1.0	1.0	0.0	0.4	244	250
1.0	1.0	0.0	0.6	248	249
1.0	1.0	0.0	0.8	242	250
1.0	1.0	0.0	1.0	244	250
1.0	1.0	0.5	0.0	241	249
1.0	1.0	0.5	0.2	241	249
1.0	1.0	0.5	0.4	242	250
1.0	1.0	0.5	0.6	234	250
1.0	1.0	0.5	0.8	246	250
1.0	1.0	0.5	1.0	244	249
1.0	1.0	0.9	0.0	248	250
1.0	1.0	0.9	0.2	247	249
1.0	1.0	0.9	0.4	247	250
1.0	1.0	0.9	0.6	245	250

APPENDIX 4.13 (cont'd)

FREQUENCIES OF VALID RESULTS
FOR MULTICENTER PROCEDURES
m=5 n=5

C1	C2	RHO	DELTA1	SIGMA FREQ	C1 FREQ
1.0	1.0	0.9	0.8	247	250
1.0	1.0	0.9	1.0	244	250
1.0	10.0	0.0	0.0	241	250
1.0	10.0	0.0	0.2	245	249
1.0	10.0	0.0	0.4	247	249
1.0	10.0	0.0	0.6	244	250
1.0	10.0	0.0	0.8	247	250
1.0	10.0	0.0	1.0	245	250
1.0	10.0	0.5	0.0	246	248
1.0	10.0	0.5	0.2	238	250
1.0	10.0	0.5	0.4	245	250
1.0	10.0	0.5	0.6	242	250
1.0	10.0	0.5	0.8	243	250
1.0	10.0	0.5	1.0	248	250
1.0	10.0	0.9	0.0	243	250
1.0	10.0	0.9	0.2	241	250
1.0	10.0	0.9	0.4	248	249
1.0	10.0	0.9	0.6	241	249
1.0	10.0	0.9	0.8	247	250
1.0	10.0	0.9	1.0	245	250
10.0	0.1	0.0	0.0	250	250
10.0	0.1	0.0	0.2	250	250
10.0	0.1	0.0	0.4	250	250
10.0	0.1	0.0	0.6	248	250
10.0	0.1	0.0	0.8	250	250
10.0	0.1	0.0	1.0	250	250
10.0	0.1	0.5	0.0	250	250
10.0	0.1	0.5	0.2	249	250
10.0	0.1	0.5	0.4	250	250
10.0	0.1	0.5	0.6	250	250
10.0	0.1	0.5	0.8	250	250
10.0	0.1	0.5	1.0	250	250
10.0	0.1	0.9	0.0	250	250
10.0	0.1	0.9	0.2	250	250
10.0	0.1	0.9	0.4	250	250
10.0	0.1	0.9	0.6	250	250
10.0	0.1	0.9	0.8	250	250
10.0	0.1	0.9	1.0	250	250
10.0	1.0	0.0	0.0	250	250
10.0	1.0	0.0	0.2	250	250
10.0	1.0	0.0	0.4	250	250
10.0	1.0	0.0	0.6	250	250
10.0	1.0	0.0	0.8	250	250
10.0	1.0	0.0	1.0	250	250

APPENDIX 4.13 (cont'd)

FREQUENCIES OF VALID RESULTS
FOR MULTICENTER PROCEDURES
m=5 n=5

C1	C2	RHO	DELTA1	SIGMA FREQ	C1 FREQ
10.0	1.0	0.5	0.0	249	250
10.0	1.0	0.5	0.2	248	250
10.0	1.0	0.5	0.4	250	250
10.0	1.0	0.5	0.6	250	250
10.0	1.0	0.5	0.8	250	250
10.0	1.0	0.5	1.0	250	250
10.0	1.0	0.9	0.0	249	250
10.0	1.0	0.9	0.2	250	250
10.0	1.0	0.9	0.4	250	250
10.0	1.0	0.9	0.6	250	250
10.0	1.0	0.9	0.8	250	250
10.0	1.0	0.9	1.0	249	250
10.0	10.0	0.0	0.0	249	250
10.0	10.0	0.0	0.2	250	250
10.0	10.0	0.0	0.4	250	250
10.0	10.0	0.0	0.6	248	250
10.0	10.0	0.0	0.8	250	250
10.0	10.0	0.0	1.0	250	250
10.0	10.0	0.5	0.0	249	250
10.0	10.0	0.5	0.2	250	250
10.0	10.0	0.5	0.4	250	250
10.0	10.0	0.5	0.6	250	250
10.0	10.0	0.5	0.8	249	250
10.0	10.0	0.5	1.0	250	250
10.0	10.0	0.9	0.0	250	250
10.0	10.0	0.9	0.2	249	250
10.0	10.0	0.9	0.4	250	250
10.0	10.0	0.9	0.6	250	250
10.0	10.0	0.9	0.8	250	250
10.0	10.0	0.9	1.0	249	250

APPENDIX 4.14

FREQUENCIES OF VALID RESULTS FOR MULTICENTER PROCEDURES
m=5 n=10

C1	C2	RHO	DELTA1	SIGMA FREQ	C1 FREQ
0.1	0.1	0.0	0.0	226	243
0.1	0.1	0.0	0.2	235	244
0.1	0.1	0.0	0.4	227	240
0.1	0.1	0.0	0.6	237	240
0.1	0.1	0.0	0.8	238	240
0.1	0.1	0.0	1.0	237	244
0.1	0.1	0.5	0.0	229	239
0.1	0.1	0.5	0.2	233	240
0.1	0.1	0.5	0.4	233	241
0.1	0.1	0.5	0.6	226	240
0.1	0.1	0.5	0.8	234	234
0.1	0.1	0.5	1.0	230	236
0.1	0.1	0.9	0.0	231	239
0.1	0.1	0.9	0.2	230	241
0.1	0.1	0.9	0.4	238	242
0.1	0.1	0.9	0.6	228	235
0.1	0.1	0.9	0.8	237	237
0.1	0.1	0.9	1.0	234	241
0.1	1.0	0.0	0.0	231	241
0.1	1.0	0.0	0.2	236	240
0.1	1.0	0.0	0.4	228	236
0.1	1.0	0.0	0.6	232	239
0.1	1.0	0.0	0.8	225	239
0.1	1.0	0.0	1.0	225	241
0.1	1.0	0.5	0.0	235	238
0.1	1.0	0.5	0.2	236	237
0.1	1.0	0.5	0.4	235	238
0.1	1.0	0.5	0.6	222	240
0.1	1.0	0.5	0.8	224	241
0.1	1.0	0.5	1.0	232	236
0.1	1.0	0.9	0.0	229	242
0.1	1.0	0.9	0.2	225	241
0.1	1.0	0.9	0.4	233	244
0.1	1.0	0.9	0.6	230	233
0.1	1.0	0.9	0.8	225	239
0.1	1.0	0.9	1.0	228	239
0.1	10.0	0.0	0.0	236	241
0.1	10.0	0.0	0.2	227	240
0.1	10.0	0.0	0.4	226	244
0.1	10.0	0.0	0.6	228	234
0.1	10.0	0.0	0.8	223	236
0.1	10.0	0.0	1.0	237	234
0.1	10.0	0.5	0.0	236	235
0.1	10.0	0.5	0.2	232	232

APPENDIX 4.14 (cont'd)

FREQUENCIES OF VALID RESULTS
FOR MULTICENTER PROCEDURES
m=5 n=10

C1	C2	RHO	DELTA1	SIGMA FREQ	C1 FREQ
0.1	10.0	0.5	0.4	230	240
0.1	10.0	0.5	0.6	235	241
0.1	10.0	0.5	0.8	232	242
0.1	10.0	0.5	1.0	231	243
0.1	10.0	0.9	0.0	225	240
0.1	10.0	0.9	0.2	236	243
0.1	10.0	0.9	0.4	237	241
0.1	10.0	0.9	0.6	228	240
0.1	10.0	0.9	0.8	237	237
0.1	10.0	0.9	1.0	229	237
1.0	0.1	0.0	0.0	248	250
1.0	0.1	0.0	0.2	249	250
1.0	0.1	0.0	0.4	246	250
1.0	0.1	0.0	0.6	246	250
1.0	0.1	0.0	0.8	248	250
1.0	0.1	0.0	1.0	246	250
1.0	0.1	0.5	0.0	247	250
1.0	0.1	0.5	0.2	245	250
1.0	0.1	0.5	0.4	248	250
1.0	0.1	0.5	0.6	241	250
1.0	0.1	0.5	0.8	248	250
1.0	0.1	0.5	1.0	249	250
1.0	0.1	0.9	0.0	248	250
1.0	0.1	0.9	0.2	249	250
1.0	0.1	0.9	0.4	246	250
1.0	0.1	0.9	0.6	246	250
1.0	0.1	0.9	0.8	246	250
1.0	0.1	0.9	1.0	248	250
1.0	1.0	0.0	0.0	245	250
1.0	1.0	0.0	0.2	246	250
1.0	1.0	0.0	0.4	246	250
1.0	1.0	0.0	0.6	246	250
1.0	1.0	0.0	0.8	244	250
1.0	1.0	0.0	1.0	245	250
1.0	1.0	0.5	0.0	247	250
1.0	1.0	0.5	0.2	243	250
1.0	1.0	0.5	0.4	243	250
1.0	1.0	0.5	0.6	247	250
1.0	1.0	0.5	0.8	245	249
1.0	1.0	0.5	1.0	249	250
1.0	1.0	0.9	0.0	248	250
1.0	1.0	0.9	0.2	247	250
1.0	1.0	0.9	0.4	245	250
1.0	1.0	0.9	0.6	249	250

APPENDIX 4.14 (cont'd)

FREQUENCIES OF VALID RESULTS FOR MULTICENTER PROCEDURES
m=5 n=10

C1	C2	RHO	DELTA1	SIGMA FREQ	C1 FREQ
1.0	1.0	0.9	0.8	246	250
1.0	1.0	0.9	1.0	248	250
1.0	10.0	0.0	0.0	248	250
1.0	10.0	0.0	0.2	245	250
1.0	10.0	0.0	0.4	250	250
1.0	10.0	0.0	0.6	244	250
1.0	10.0	0.0	0.8	246	250
1.0	10.0	0.0	1.0	248	250
1.0	10.0	0.5	0.0	250	250
1.0	10.0	0.5	0.2	249	250
1.0	10.0	0.5	0.4	249	250
1.0	10.0	0.5	0.6	244	250
1.0	10.0	0.5	0.8	248	250
1.0	10.0	0.5	1.0	242	250
1.0	10.0	0.9	0.0	247	250
1.0	10.0	0.9	0.2	248	250
1.0	10.0	0.9	0.4	246	250
1.0	10.0	0.9	0.6	248	250
1.0	10.0	0.9	0.8	245	250
1.0	10.0	0.9	1.0	245	250
10.0	0.1	0.0	0.0	250	250
10.0	0.1	0.0	0.2	250	250
10.0	0.1	0.0	0.4	250	250
10.0	0.1	0.0	0.6	250	250
10.0	0.1	0.0	0.8	250	250
10.0	0.1	0.0	1.0	250	250
10.0	0.1	0.5	0.0	250	250
10.0	0.1	0.5	0.2	250	250
10.0	0.1	0.5	0.4	250	250
10.0	0.1	0.5	0.6	250	250
10.0	0.1	0.5	0.8	250	250
10.0	0.1	0.5	1.0	250	250
10.0	0.1	0.9	0.0	250	250
10.0	0.1	0.9	0.2	250	250
10.0	0.1	0.9	0.4	250	250
10.0	0.1	0.9	0.6	250	250
10.0	0.1	0.9	0.8	250	250
10.0	0.1	0.9	1.0	250	250
10.0	1.0	0.0	0.0	250	250
10.0	1.0	0.0	0.2	250	250
10.0	1.0	0.0	0.4	249	250
10.0	1.0	0.0	0.6	250	250
10.0	1.0	0.0	0.8	250	250
10.0	1.0	0.0	1.0	250	250

APPENDIX 4.14 (cont'd)

FREQUENCIES OF VALID RESULTS
FOR MULTICENTER PROCEDURES
m=5 n=10

C1	C2	RHO	DELTA1	SIGMA FREQ	C1 FREQ
10.0	1.0	0.5	0.0	250	250
10.0	1.0	0.5	0.2	250	250
10.0	1.0	0.5	0.4	249	250
10.0	1.0	0.5	0.6	250	250
10.0	1.0	0.5	0.8	249	250
10.0	1.0	0.5	1.0	250	250
10.0	1.0	0.9	0.0	249	250
10.0	1.0	0.9	0.2	250	250
10.0	1.0	0.9	0.4	250	250
10.0	1.0	0.9	0.6	250	250
10.0	1.0	0.9	0.8	250	250
10.0	1.0	0.9	1.0	249	250
10.0	10.0	0.0	0.0	250	250
10.0	10.0	0.0	0.2	250	250
10.0	10.0	0.0	0.4	250	250
10.0	10.0	0.0	0.6	250	250
10.0	10.0	0.0	0.8	250	250
10.0	10.0	0.0	1.0	250	250
10.0	10.0	0.5	0.0	250	250
10.0	10.0	0.5	0.2	250	250
10.0	10.0	0.5	0.4	250	250
10.0	10.0	0.5	0.6	250	250
10.0	10.0	0.5	0.8	250	250
10.0	10.0	0.5	1.0	250	250
10.0	10.0	0.9	0.0	250	250
10.0	10.0	0.9	0.2	250	250
10.0	10.0	0.9	0.4	250	250
10.0	10.0	0.9	0.6	250	250
10.0	10.0	0.9	0.8	250	250
10.0	10.0	0.9	1.0	250	250

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