Likelihood-Based Inference on Haplotype Effects in Genetic Association Studies

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A haplotype is a specific sequence of nucleotides on a single chromosome. The population associations between haplotypes and disease phenotypes provide critical information about the genetic basis of complex human diseases. Standard genotyping techniques cannot distinguish the two homologous chromosomes of an individual, so only the unphased genotype (i.e., the combination of the two homologous haplotypes) is directly observable. Statistical inference about haplotype–phenotype associations based on unphased genotype data presents an intriguing missing-data problem, especially when the sampling depends on the disease status. The objective of this article is to provide a systematic and rigorous treatment of this problem. All commonly used study designs, including cross-sectional, case-control, and cohort studies, are considered. The phenotype can be a disease indicator, a quantitative trait, or a potentially censored time-to-disease variable. The effects of haplotypes on the phenotype are formulated through flexible regression models, which can accommodate various genetic mechanisms and gene–environment interactions. Appropriate likelihoods are constructed that may involve high-dimensional parameters. The identifiability of the parameters and the consistency, asymptotic normality, and efficiency of the maximum likelihood estimators are established. Efficient and reliable numerical algorithms are developed. Simulation studies show that the likelihood-based procedures perform well in practical settings. An application to the Finland–United States Investigation of NIDDM Genetics Study is provided. Areas in need of further development are discussed.

KEY WORDS: Case-control study; Gene–environment interaction; Hardy–Weinberg equilibrium; Missing data; Single nucleotide polymorphism; Unphased genotype.

1. INTRODUCTION

In the early 1900s there was a fierce debate between Gregor Mendel's followers and the biometrical school led by Francis Galton and Karl Pearson as to whether the patterns of inheritance were consistent with Mendel's law of segregation or with a "blending"-type theory. Fisher (1918) reconciled the two conflicting schools by recognizing the difference in the genetic basis for the variation in the trait being studied. For the traits that the Mendelists studied, the observed variation was due to a simple difference at a single gene; for the traits studied by the biometrical school, individual differences were attributed to many different genes, with no particular gene having a singly large effect.

Like the traits studied by Mendel, many genetic disorders, such as Huntington disease and cystic fibrosis, are caused by mutations of single genes. The genes underlying a number of these Mendelian syndromes have been discovered over the last 20 years through linkage analysis and positional cloning (Risch 2000). The same approach, however, is failing to unravel the genetic basis of complex human diseases (e.g., hypertension, bipolar disorder, diabetes, schizophrenia), which are influenced by a variety of genetic and environmental factors, just like the traits studied by the biometrical school a century ago. It is widely recognized that genetic dissection of complex human disorders requires large-scale association studies, which relate disease phenotypes to genetic variants, especially single nucleotide polymorphisms (SNPs) (Risch 2000; Botstein and Risch 2003).

SNPs are DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. SNPs make up about 90% of all human genetic variation and are believed to have a major impact on disease susceptibility. Aided by the sequencing of the human genome (International Human Genome Sequencing Consortium 2001; Venter et al. 2001), geneticists have identified several million SNPs (International SNP Map Working Group 2001). With current technology, it is economically feasible to genotype thousands of subjects for thousands of SNPs. These remarkable scientific and technological advances offer unprecedented opportunities to conduct SNPs-based association studies aimed at unraveling the genetic basis of complex diseases.

There is one of three possible genotypes at each SNP site: homozygous with allele A, homozygous with allele a, or heterozygous with one allele A and one allele a. Thus assessing the association between a SNP and a disease phenotype is a trivial three-sample problem. It is, however, desirable to deal with multiple SNPs simultaneously. One appealing approach is to consider the haplotypes for multiple SNPs within candidate genes (Hallman, Groenemeijer, Jukema, and Boerwinkle 1999; International SNP Map Working Group 2001; Patil et al. 2001; Stephens, Smith, and Donnelly 2001).

The haplotype (i.e., a specific combination of nucleotides at a series of closely linked SNPs on the same chromosome of an individual) contains information about the protein products. Because the actual number of haplotypes within a candidate gene is much smaller than the number of all possible haplotypes, haplotyping serves as an effective data-reduction strategy. Using SNP-based haplotypes may yield more powerful tests of genetic associations than using individual, unorganized SNPs, especially when the causal variants are not measured directly or when there are strong interactions of multiple mutations on the same chromosome (Akey, Jin, and Xiong 2001; Fallin et al. 2001; Li 2001; Morris and Kaplan 2002; Schaid, Rowland, Tines, Jacobson, and Poland 2002; Zaykin et al. 2002; Schaid 2004).

Determining haplotype requires the parental origin or gametic phase information, which cannot be easily obtained with the current genotyping technology. As a result, only the unphased genotype (i.e., the combination of the two homologous

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Journal of the American Statistical Association
March 2006, Vol. 101, No. 473, Theory and Methods
DOI 10.1198/016214505000000808

haplotypes) can be determined. Statistically speaking, this is a missing-data problem in which the variable of interest pertains to two ordered sequences of 0's and 1's but only the summation of the two sequences is observed. This type of missing-data problem has not been studied in the statistical literature.

Many authors (e.g., Clark 1990; Excoffier and Slatkin 1995; Stephens et al. 2001; Zhang, Pakstis, Kidd, and Zhao 2001; Niu, Qin, Xu, and Liu 2002; Qin, Niu, and Liu 2002) have proposed methods to infer haplotypes or estimate haplotype frequencies from unphased genotype data. To make inference about haplotype effects, one may then relate the probabilistically inferred haplotypes to the phenotype through a regression model (e.g., Zaykin et al. 2002). This approach does not account for the variation due to haplotype estimation, and does not yield consistent estimators of regression parameters.

A growing number of articles have been published in genetic journals on making proper inference about the effects of haplotypes on disease phenotypes. Most of these articles have dealt with case-control studies. Specifically, Zhao, Li, and Khalid (2003) developed an estimating function that approximates the expectation of the complete-data prospective-likelihood score function given the observable data. This method assumes that the disease is rare and that haplotypes are independent of environmental variables, and it is not statistically efficient. Epstein and Satten (2003) derived a retrospective likelihood for the relative risk that does not accommodate environmental variables. Stram et al. (2003) proposed a conditional likelihood for the odds ratio assuming that cases and controls are chosen randomly with known probabilities from the target population, but did not consider environmental variables or investigate the properties of the estimator. Building on the earlier work of Schaid et al. (2002), Lake et al. (2003) discussed likelihood-based inference for cross-sectional studies under generalized linear models. Seltman, Roeder, and Devlin (2003) provided a similar discussion based on the cladistic approach. Recently, Lin (2004) showed how to perform Cox's (1972) regression when potentially censored age at onset of the disease observations are collected in cohort studies. All of the aforementioned work assumes Hardy–Weinberg equilibrium (Weir 1996, p. 40). Simulation studies (Epstein and Satten 2003; Lake et al. 2003; Satten and Epstein 2004) revealed that violation of this assumption can adversely affect the validity of the inference.

The aim of this article is to address statistical issues in estimating haplotype effects in a systematic and rigorous manner. For case-control studies, we allow environmental variables and derive efficient inference procedures. For cross-sectional and cohort studies, we consider more versatile models than those in the existing literature. For all study designs, we accommodate Hardy–Weinberg disequilibrium. We construct appropriate likelihoods for a variety of models. Under case-control sampling, the likelihood pertains to the distribution of genotypes and environmental variables conditional on the case-control status, which involves infinite-dimensional nuisance parameters if environmental variables are continuous. In cohort studies, it is desirable to not parameterize the distribution of time to disease, so that the likelihood also involves infinite-dimensional parameters. The presence of infinite-dimensional parameters entails considerable theoretical and computational challenges. We establish the theoretical properties of the maximum likelihood estimators (MLEs) by appealing to modern asymptotic techniques, and develop efficient and stable algorithms to implement the corresponding inference procedures. We assess the performance of the proposed methods through simulation studies, and provide an application to a major genetic study of type 2 diabetes mellitus.

2. INFERENCE PROCEDURES

2.1 Preliminaries

We consider SNP-based association studies of unrelated individuals. Suppose that each individual is genotyped at M biallelic SNPs within a candidate gene. At each SNP site, we indicate the two possible alleles by the values 0 and 1. Thus each haplotype h is a unique sequence of M numbers from $\{0, 1\}$. The total number of possible haplotypes is $K \equiv 2^M$; the actual number of haplotypes consistent with the data is usually much smaller. For $k = 1, \ldots, K$, let h_k denote the kth possible haplotype. Figure 1 shows the eight possible haplotypes for three SNPs.

Our human chromosomes come in pairs, one member of each pair inherited from our mother and the other member inherited from our father. These pairs are called homologous chromosomes. Thus each individual has a pair of homologous haplotypes that may or may not be identical. Routine genotyping procedures cannot separate the two homologous chromosomes, so only the (unphased) genotypes (i.e., the combinations of the two homologous haplotypes) are directly observable. For each individual, the multi-SNP genotype is an ordered sequence of M numbers from $\{0, 1, 2\}$.

Let H and G denote the pair of haplotypes and the genotype for an individual. We write $H = (h_k, h_l)$ if the individual's haplotypes are h_k and h_l, in which case $G = h_k + h_l$. The ordering of the two homologous haplotypes within an individual is considered arbitrary. By allowing genotypes to include missing SNP information, we may assume that G is known for each individual. Given G, the value of H is unknown if the individual is heterozygous at more than one SNP or if any SNP genotype is missing. For the case of $M = 3$ shown in Figure 1, if $G = (0, 2, 1)$, then $H = (h_3, h_4)$, and if $G = (0, 1, 1)$, then $H = (h_1, h_4)$ or $H = (h_2, h_3)$.

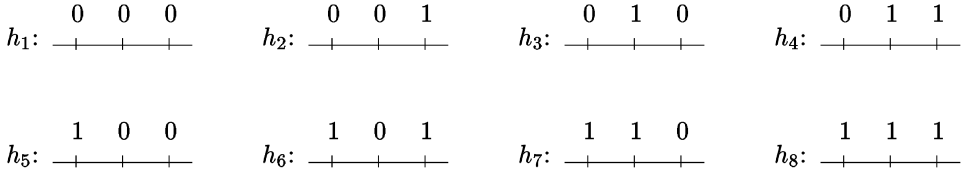

Figure 1. Possible Haplotype Configurations With Three SNPs.

The goal of the association studies is to relate the pair of haplotypes to disease phenotypes or traits. The simplest phenotype is the binary indicator for the disease status, which takes the value 1 if the individual is diseased and 0 otherwise. The diseased individuals may be further classified into several categories corresponding to different types of disease or varying degrees of disease severity. If the age of onset is likely to be genetically mediated, then it is desirable to use the age of onset as the phenotype. One may also be interested in disease-related traits, such as blood pressure.

The data on the disease phenotype may be gathered in various ways. The simplest approach is to obtain a random sample from the target population and measure the phenotype of interest on every individual in the sample. Such studies are referred to as cross-sectional studies, which are feasible if the disease is relatively frequent or if one is interested only in some readily measured traits that are related to the disease. If one is interested in the age at the onset of a disease, however, then it is necessary to follow a cohort of individuals forward in time, in which case the phenotype (i.e., time to disease occurrence) may be censored. When the disease is relatively rare, it is more cost-effective to use the case-control design, which collects data retrospectively on a sample of diseased individuals and on a separate sample of disease-free individuals. It is often desirable to collect data on environmental variables or covariates so as to investigate gene–environment interactions.

Let $\mathbf{Y}$ be the phenotype of interest, and let $\mathbf{X}$ be the covariates. For cross-sectional and case-control studies, the association between $\mathbf{Y}$ and $(\mathbf{X}, H)$ is characterized by the conditional density of $\mathbf{Y} = \mathbf{y}$ given $H = (h_k, h_l)$ and $\mathbf{X} = \mathbf{x}$, denoted by $P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{y}|\mathbf{x}, (h_k, h_l))$, where $\boldsymbol{\alpha}$ denotes the intercept(s), $\boldsymbol{\beta}$ denotes the regression effects, and $\boldsymbol{\xi}$ denotes the nuisance parameters (e.g., variance and overdispersion parameters). There is considerable flexibility in specifying the regression relationship. Suppose that h^* is the target haplotype of interest and that there are no covariates. Then a linear predictor in the form of $\alpha + \beta I(h_k = h_l = h^*)$ pertains to a recessive model, $\alpha + \beta\{I(h_k = h^*) + I(h_l = h^*) - I(h_k = h_l = h^*)\}$ pertains to a dominant model, $\alpha + \beta\{I(h_k = h^*) + I(h_l = h^*)\}$ pertains to an additive model, and $\alpha + \beta_1\{I(h_k = h^*) + I(h_l = h^*)\} + \beta_2 I(h_k = h_l = h^*)$ pertains to a codominant model, where $I(\cdot)$ is the indicator function. Clearly, the codominant model contains the other three models as special cases. A codominant model with gene–environment interactions has the following linear predictor:

$$\begin{aligned}\alpha &+ \beta_1\{I(h_k = h^*) + I(h_l = h^*)\} + \beta_2 I(h_k = h_l = h^*) \\ &+ \boldsymbol{\beta}_3^T\mathbf{x} + \boldsymbol{\beta}_4^T\{I(h_k = h^*) + I(h_l = h^*)\}\mathbf{x} \\ &+ \boldsymbol{\beta}_5^T I(h_k = h_l = h^*)\mathbf{x}. \qquad (1)\end{aligned}$$

Additional terms may be included so as to examine the effects of several haplotype configurations or to investigate the joint effects of multiple candidate genes.

Although we are interested in the effects of H and $\mathbf{X}$ on $\mathbf{Y}$, we observe G instead of H. As mentioned earlier, G is the summation of the paired sequences in H. Thus we have a regression problem with missing data in which the primary explanatory variable pertains to two ordered sequences of numbers from $\{0, 1\}$, but only the summation of the two sequences is observed. We assume that $\mathbf{X}$ is independent of H conditional on G and that $(1, \mathbf{X}^T)$ is linearly independent with positive probability.

Write $\pi_{kl} = P\{H = (h_k, h_l)\}$ and $\pi_k = P(h = h_k)$, $k, l = 1, \ldots, K$. As we demonstrate in this article, it is sometimes possible to make inference about haplotype effects without imposing any structures on $\{\pi_{kl}\}$, although estimating $\{\pi_k\}$ and testing for no haplotype effects require some restrictions on $\{\pi_{kl}\}$. Under Hardy–Weinberg equilibrium,

$$\pi_{kl} = \pi_k\pi_l, \qquad k, l = 1, \ldots, K. \qquad (2)$$

We consider two specific forms of departure from Hardy–Weinberg equilibrium,

$$\pi_{kl} = (1 - \rho)\pi_k\pi_l + \delta_{kl}\rho\pi_k \qquad (3)$$

and

$$\pi_{kl} = \frac{(1 - \rho + \delta_{kl}\rho)\pi_k\pi_l}{1 - \rho + \rho\sum_{j=1}^K \pi_j^2}, \qquad (4)$$

where $0 \le \pi_k \le 1$, $\sum_{k=1}^K \pi_k = 1$, $\delta_{kk} = 1$, and $\delta_{kl} = 0$ $(k \ne l)$. In (3), ρ is called the inbreeding coefficient or fixation index (Weir 1996, p. 93) and corresponds to Cohen's (1960) kappa measure of agreement. Equation (4) creates disequilibrium by giving different fitness values to the homozygous and heterozygous pairs (Niu et al. 2002). The denominator is a normalizing constant. Both (3) and (4) reduce to (2) if $\rho = 0$. Excess homozygosity (i.e., $\pi_{kk} > \pi_k^2, k = 1, \ldots, K$) arises when $\rho > 0$, and excess heterozygosity (i.e., $\pi_{kk} < \pi_k^2, k = 1, \ldots, K$) arises when $\rho < 0$. Recently, Satten and Epstein (2004) considered (3) for the control population under the case-control design. We abuse the notation slightly in that the $\{\pi_k\}$ in (4) do not pertain to the marginal distribution of H unless $\rho = 0$.

Let $\widetilde{h}$ denote a haplotype that differs from h at only one SNP. Write $\nabla_{\mathbf{u}} f(\mathbf{u}, \mathbf{v}) = \partial f(\mathbf{u}, \mathbf{v})/\partial\mathbf{u}$. The following lemma states that under (3) or (4), $\{\pi_k\}$ and ρ are identifiable from the data on G, and the data on G provide positive information about these parameters.

Lemma 1. Assume that either (3) or (4) holds. The parameters $\{\pi_k\}$ and ρ are uniquely determined by the distribution of G. For nondegenerate distribution $\{\pi_k\}$, if there exist a constant μ and a vector $\boldsymbol{\nu} = (\nu_1, \ldots, \nu_K)^T$ such that $\sum_{k=1}^K \nu_k = 0$ and $\mu\nabla_\rho \log P(G = g) + \sum_{k=1}^K \nu_k \nabla_{\pi_k} \log P(G = g) = 0$ for $g = 2h$, then $\mu = 0$ and $\boldsymbol{\nu} = \mathbf{0}$.

In the sequel, $\mathcal{G}$ denotes the set of all possible genotypes and $\mathcal{S}(G)$ denotes the set of haplotype pairs that are consistent with genotype G. We suppose that $\pi_k > 0$ for all $k = 1, \ldots, K$, where K is now interpreted as the total number of haplotypes that exist in the population. For any parameter $\boldsymbol{\theta}$, we use $\boldsymbol{\theta}_0$ to denote its true value if the distinction is necessary. We assume that the true value of any Euclidean parameter $\boldsymbol{\theta}$ belongs to the interior of a known compact set within the domain of $\boldsymbol{\theta}$. Proofs of Lemma 1 and all of the theorems are provided in the Appendix.

2.2 Cross-Sectional Studies

There is a random sample of n individuals from the underlying population. The observable data consist of $(\mathbf{Y}_i, \mathbf{X}_i, G_i)$, $i = 1, \ldots, n$. The trait $\mathbf{Y}$ can be discrete or continuous, univariate or multivariate. As stated in Section 2.1, the conditional density of $\mathbf{Y}$ given $\mathbf{X}$ and H is given by $P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{Y}|\mathbf{X}, H)$. For a univariate trait, this regression model may take the form of a generalized linear model (McCullagh and Nelder 1989) with the linear predictor given in (1). If the trait is measured repeatedly in a longitudinal study, then generalized linear mixed models (Diggle, Heagerty, Liang, and Zeger 2002, chap. 9) may be used. The following conditions are required for estimating $(\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\xi})$.

Condition 1. If $P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{Y}|\mathbf{X}, H) = P_{\widetilde{\boldsymbol{\alpha}},\widetilde{\boldsymbol{\beta}},\widetilde{\boldsymbol{\xi}}}(\mathbf{Y}|\mathbf{X}, H)$ for any $H = (h_k, h_k)$ and $H = (h_k, \widetilde{h}_k)$, $k = 1, \ldots, K$, then $\boldsymbol{\alpha} = \widetilde{\boldsymbol{\alpha}}$, $\boldsymbol{\beta} = \widetilde{\boldsymbol{\beta}}$, and $\boldsymbol{\xi} = \widetilde{\boldsymbol{\xi}}$.

Condition 2. If there exists a constant vector $\boldsymbol{\nu}$ such that $\boldsymbol{\nu}^T \nabla_{\underset{\sim}{\boldsymbol{\alpha}},\boldsymbol{\beta},\boldsymbol{\xi}} \log P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{Y}|\mathbf{X}, H) = 0$ for $H = (h_k, h_k)$ and $H = (h_k, \widetilde{h}_k)$, then $\boldsymbol{\nu} = \mathbf{0}$.

Remark 1. Condition 1 ensures that the parameters of interest are identifiable from the genotype data. The linear independence of the score function stated in Condition 2 ensures nonsingularity of the information matrix. The reason for considering $H = (h_k, h_k)$ and $H = (h_k, \widetilde{h}_k)$ is that these haplotype pairs can be inferred with certainty because of the unique decompositions of the corresponding genotypes $g = 2h_k$ and $g = h_k + \widetilde{h}_k$. All of the commonly used regression models, particularly generalized linear (mixed) models with linear predictors in the form of (1), satisfy Conditions 1 and 2.

We show in Section A.2.1 that it is possible to estimate the regression parameters without imposing any structure on the joint distribution of H. But this estimation requires knowledge of whether or not the dominant effects exist. Specifically, if there are no dominant effects, then only $(\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\xi})$ and $P(G = g)$ are identifiable; otherwise, $(\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\xi})$, $P(G = g)$, and $P(H = (h^*, g - h^*))$ are identifiable. If either (3) or (4) holds, then it follows from Lemma 1 and Condition 1 that all of the parameters are identifiable regardless of the genetic mechanism. Denote the joint distribution of H by $P_{\boldsymbol{\gamma}}(H = (h_k, h_l))$, where $\boldsymbol{\gamma}$ consists of the identifiable parameters in the distribution of H. Under (3) or (4), $\boldsymbol{\gamma} = (\rho, \pi_1, \ldots, \pi_K)^T$. When the distribution of H is unspecified, $\boldsymbol{\gamma}$ pertains to the aspects of the distribution of H that are identifiable.

Write $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\xi})$. The likelihood for $\boldsymbol{\theta}$ based on the cross-sectional data is proportional to

$$L_n(\boldsymbol{\theta}) \equiv \prod_{i=1}^{n} \prod_{g \in \mathcal{G}} \{m_g(\mathbf{Y}_i, \mathbf{X}_i; \boldsymbol{\theta})\}^{I(G_i = g)}, \tag{5}$$

where

$$m_g(\mathbf{y}, \mathbf{x}; \boldsymbol{\theta}) = \sum_{(h_k, h_l) \in \mathcal{S}(g)} P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}\big(\mathbf{y}|\mathbf{x}, (h_k, h_l)\big) P_{\boldsymbol{\gamma}}(h_k, h_l).$$

The MLE $\widehat{\boldsymbol{\theta}}$ can be obtained by maximizing (5) via the Newton–Raphson algorithm or an optimization algorithm. It is generally more efficient to use the expectation–maximization (EM) algorithm (Dempster, Laird, and Rubin 1977), especially when the distribution of H satisfies (3) with $\rho \geq 0$; see Section A.2.2 for details.

By the classical likelihood theory, we can show that $\widehat{\boldsymbol{\theta}}$ is consistent, asymptotically normal, and asymptotically efficient under Conditions 1 and 2 and the following condition.

Condition 3. If there exists a constant vector $\boldsymbol{\nu}$ such that $\boldsymbol{\nu}^T \nabla_{\boldsymbol{\theta}} \log m_g(\mathbf{Y}, \mathbf{X}; \boldsymbol{\theta}_0) = 0$, then $\boldsymbol{\nu} = \mathbf{0}$.

Remark 2. Condition 3 ensures the nonsingularity of the information matrix. This condition can be easily verified when the joint distribution of H is unspecified and is implied by Lemma 1 and Condition 2 when the distribution satisfies (3) or (4).

2.3 Case-Control Studies With Known Population Totals

We consider case-control data supplemented by information on population totals (Scott and Wild 1997). There is a finite population of N individuals that is considered a random sample from the joint distribution of $(Y, \mathbf{X}, H)$, where Y is a categorical response variable. All that is known about this finite population is the total number of individuals in each category of $Y = y$. A sample of size n stratified on the disease status is drawn from the finite population, and the values of $\mathbf{X}$ and G are recorded for each sampled individual. The supplementary information on population totals is often available from hospital records, cancer registries, and official statistics. If a case-control sample is drawn from a cohort study, then the cohort serves as the finite population. The observable data consist of $(Y_i, R_i, R_i\mathbf{X}_i, R_iG_i)$, $i = 1, \ldots, N$, where R_i indicates, by the values 1 versus 0, whether or not the ith individual in the finite population is selected into the case-control sample.

The association between Y and $(\mathbf{X}, H)$ is characterized by $P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(Y|\mathbf{X}, H)$, where $\boldsymbol{\alpha}$, $\boldsymbol{\beta}$, and $\boldsymbol{\xi}$ pertain to the intercept(s), regression effects, and overdispersion parameters (McCullagh and Nelder 1989). In the case of a binary response variable, important examples of $P_{\alpha,\boldsymbol{\beta},\xi}(Y|\mathbf{X}, H)$ include the logistic, probit, and complementary log–log regression models. When there are more than two categories, examples include the proportional odds, multivariate probit, and multivariate logistic regression models. Because the data associated with $R_i = 1$ yield the same form of likelihood as that of a cross-sectional study and the data associated $R_i = 0$ yield a missing-data likelihood, all of the identifiability results stated in Section 2.2 apply to the current setting. We again write $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\xi}, \boldsymbol{\gamma})$, where $\boldsymbol{\gamma}$ consists of the identifiable parameters in the distribution of H.

Let $F_g(\cdot)$ be the cumulative distribution function of $\mathbf{X}$ given $G = g$, and let $f_g(\mathbf{x})$ be the density of $F_g(\mathbf{x})$ with respect to a dominating measure $\mu(\mathbf{x})$. Note that $F_g(\cdot)$ is infinite-dimensional if $\mathbf{X}$ has continuous components. The joint density of $(Y = y, G = g, \mathbf{X} = \mathbf{x})$ is $m_g(y, \mathbf{x}; \boldsymbol{\theta}) f_g(\mathbf{x})$. The likelihood concerning $\boldsymbol{\theta}$ and $\{F_g\}$ takes the form

$$L_n(\boldsymbol{\theta}, \{F_g\}) = \prod_{i=1}^{N} \left[\prod_{g \in \mathcal{G}} \{m_g(Y_i, \mathbf{X}_i; \boldsymbol{\theta}) f_g(\mathbf{X}_i)\}^{I(G_i = g)} \right]^{R_i} \times \left[\sum_{g \in \mathcal{G}} \int m_g(Y_i, \mathbf{x}; \boldsymbol{\theta})\, dF_g(\mathbf{x}) \right]^{1 - R_i}. \tag{6}$$

Unlike the likelihood for the cross-sectional design given in (5), the density functions of $\mathbf{X}$ given G cannot be factored out of the likelihood given in (6) and thus cannot be omitted from the likelihood.

We maximize (6) to obtain the MLEs $\widehat{\boldsymbol{\theta}}$ and $\{\widehat{F}_g(\cdot)\}$. The latter is an empirical function with point masses at the observed $\mathbf{X}_i$ such that $G_i = g$ and $R_i = 1$. The maximization can be carried out via the Newton–Raphson, profile-likelihood, or large-scale optimization methods. An alternative way to calculate the MLEs is through the EM algorithm described in Section A.3.1.

We impose the following regularity condition, and then state the asymptotic results in Theorem 1.

Condition 4. For any $g \in \mathcal{G}$, $f_g(\mathbf{x})$ is positive in its support and continuously differentiable with respect to a suitable measure.

Theorem 1. Under Conditions 1–4, $\widehat{\boldsymbol{\theta}}$ and $\{\widehat{F}_g(\cdot)\}$ are consistent in that $|\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0| + \sup_{\mathbf{x},g} |\widehat{F}_g(\mathbf{x}) - F_g(\mathbf{x})| \to 0$ almost surely. In addition, $n^{1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)$ converges in distribution to a mean 0 normal random vector whose covariance matrix attains the semiparametric efficiency bound.

Let $pl_n(\boldsymbol{\theta})$ be the profile log-likelihood for $\boldsymbol{\theta}$, that is, $pl_n(\boldsymbol{\theta}) = \max_{\{F_g\}} \log L_n(\boldsymbol{\theta}, \{F_g\})$. Then the (s,t)th element of the inverse covariance matrix of $\widehat{\boldsymbol{\theta}}$ can be estimated by $-\epsilon_n^{-2}\{pl_n(\widehat{\boldsymbol{\theta}} + \epsilon_n\mathbf{e}_s + \epsilon_n\mathbf{e}_t) - pl_n(\widehat{\boldsymbol{\theta}} + \epsilon_n\mathbf{e}_s - \epsilon_n\mathbf{e}_t) - pl_n(\widehat{\boldsymbol{\theta}} - \epsilon_n\mathbf{e}_s + \epsilon_n\mathbf{e}_t) + pl_n(\widehat{\boldsymbol{\theta}})\}$, where ϵ_n is a constant of the order $n^{-1/2}$ and $\mathbf{e}_s$ and $\mathbf{e}_t$ are the sth and tth canonical vectors. The function $pl_n(\boldsymbol{\theta})$ can be calculated via the EM algorithm by holding $\boldsymbol{\theta}$ constant in both the E-step and the M-step.

Remark 3. If N is much larger than n or if the population frequencies rather than the totals are known, then we maximize $\prod_{i=1}^n \prod_{g\in\mathcal{G}}\{m_g(Y_i, \mathbf{X}_i; \boldsymbol{\theta}) f_g(\mathbf{X}_i)\}^{I(G_i=g)}$ subject to the constraints that $\sum_{g\in\mathcal{G}} \int m_g(y, \mathbf{x}; \boldsymbol{\theta})\, dF_g(\mathbf{x}) = p_y$, where p_y is the population frequency of $Y = y$. The resultant estimator of $\boldsymbol{\theta}_0$ is consistent, asymptotically normal, and asymptotically efficient. The results in this section can be extended straightforwardly to accommodate stratifications on covariates.

2.4 Case-Control Studies With Unknown Population Totals

We consider the classical case-control design, which measures $\mathbf{X}$ and G on n_1 cases ($Y = 1$) and n_0 controls ($Y = 0$) and requires no knowledge about the finite population. With the notation introduced in the previous section, the likelihood contribution from one individual takes the form

$$RL(\boldsymbol{\theta}, \{F_g\}) = \frac{\prod_{g\in\mathcal{G}}\{m_g(y, \mathbf{X}; \boldsymbol{\theta}) f_g(\mathbf{X})\}^{I(G=g)}}{\sum_{g\in\mathcal{G}} \int m_g(y, \mathbf{x}; \boldsymbol{\theta})\, dF_g(\mathbf{x})}, \qquad (7)$$

where we use y instead of Y to emphasize that y is not random.

Define

$$f_g^\dagger(\mathbf{x}) = \frac{m_g(0, \mathbf{x}; \boldsymbol{\theta}) f_g(\mathbf{x})}{\int m_g(0, \mathbf{x}; \boldsymbol{\theta})\, dF_g(\mathbf{x})},$$

$$q_g = \frac{\int m_g(0, \mathbf{x}; \boldsymbol{\theta})\, dF_g(\mathbf{x})}{\sum_{\tilde{g}\in\mathcal{G}} \int m_{\tilde{g}}(0, \mathbf{x}; \boldsymbol{\theta})\, dF_{\tilde{g}}(\mathbf{x})}.$$

Clearly, $f_g^\dagger(\mathbf{x})$ is the conditional density of $\mathbf{X}$ given $G = g$ and $Y = 0$, and q_g is the conditional probability of $G = g$ given $Y = 0$. Let g_0 and $\mathbf{x}_0$ be some specific values of G and $\mathbf{X}$. Write $F_g^\dagger(\mathbf{x}) = \int_0^{\mathbf{x}} f_g^\dagger(\mathbf{s})\, d\mu(\mathbf{s})$. We can express (7) as

$$RL(\boldsymbol{\theta}, \{F_g^\dagger\}, \{q_g\}) = \frac{\prod_{g\in\mathcal{G}}\{\eta(y, \mathbf{X}, g; \boldsymbol{\theta}) f_g^\dagger(\mathbf{x}) q_g\}^{I(G=g)}}{\sum_{g\in\mathcal{G}} q_g\{\int \eta(y, \mathbf{x}, g; \boldsymbol{\theta})\, dF_g^\dagger(\mathbf{x})\}}, \qquad (8)$$

where

$$\eta(y, \mathbf{x}, g; \boldsymbol{\theta}) = \frac{m_g(y, \mathbf{x}; \boldsymbol{\theta}) m_{g_0}(0, \mathbf{x}_0; \boldsymbol{\theta})}{m_g(0, \mathbf{x}; \boldsymbol{\theta}) m_{g_0}(y, \mathbf{x}_0; \boldsymbol{\theta})}.$$

We call η the generalized odds ratio (Liang and Qin 2000), which reduces to the ordinary odds ratio when $\mathcal{S}(g)$ is a singleton.

Remark 4. The parameter q_g is a functional of $f_g^\dagger$ and $\boldsymbol{\theta}$ because $\int m_g(0, \mathbf{x}; \boldsymbol{\theta})\, dF_g(\mathbf{x}) = \{\int m_g^{-1}(0, \mathbf{x}; \boldsymbol{\theta})\, dF_g^\dagger(\mathbf{x})\}^{-1}$. This constraint makes it very difficult to study the identifiability of the parameters. Thus we treat q_g as a free parameter in our development.

For traditional case-control data, the odds ratio is identifiable (whereas the intercept is not), and its MLE can be obtained by maximizing the prospective likelihood (Prentice and Pyke 1979). Similar results hold when the exposure is measured with error (Roeder, Carroll, and Lindsay 1996); however, the distribution of the measurement error needs to be estimated from a validation set or an external source. With unphased genotype data, identifiability is much more delicate. We show in Section A.4.1 that the components of $\boldsymbol{\theta}$ that are identifiable from the retrospective likelihood are exactly those that are identifiable from the generalized odds ratio. Thus we assume that the generalized odds ratio depends only on a set of identifiable parameters, still denoted by $\boldsymbol{\theta}$; otherwise, the inference is not tractable. For the logistic link function with linear predictor (1), we show in Section A.4.2 that if there are no dominant effects, then $\boldsymbol{\theta}$ consists only of $\boldsymbol{\beta}$; if there are no covariate effects but there exists a dominant main effect, then $\boldsymbol{\beta}$ is identifiable and $P(H = (h^*, g - h^*))/P(G = g)$ is identifiable up to a scalar constant; and if the dominant effect depends on a continuous covariate or if the dominant main effect and the main effect of a continuous covariate are nonzero, then $\boldsymbol{\theta}$ consists of α, $\boldsymbol{\beta}$, and $P(H = (h^*, g - h^*))/P(G = g)$. For the probit and complementary log–log link functions, we show in Section A.4.3 that if there are dominant effects and at least one continuous covariate has an effect, then $\boldsymbol{\theta}$ consists of α, $\boldsymbol{\beta}$, and $P(H = (h^*, g - h^*))/P(G = g)$.

We maximize the product of (8) over the $n \equiv n_1 + n_0$ individuals in the case-control sample to produce the MLEs $\widehat{\boldsymbol{\theta}}$, $\{\widehat{F}_g^\dagger(\cdot)\}$, and $\{\widehat{q}_g\}$. Although the $\{F_g^\dagger(\cdot)\}$ are high-dimensional, we show in Section A.4.4 that $\widehat{\boldsymbol{\theta}}$ can be obtained by profiling a likelihood function over a scalar nuisance parameter.

To state the asymptotic properties of the MLEs, we impose the following conditions.

Condition 5. If there exists a vector $\mathbf{v}$ such that $\mathbf{v}^T \nabla_{\boldsymbol{\theta}} \log \eta(1, \mathbf{x}, g; \boldsymbol{\theta})$ is a constant with probability 1, then $\mathbf{v} = \mathbf{0}$.

Condition 6. The function $f_g^\dagger$ is positive in its support and continuously differentiable.

Condition 7. The fraction $n_1/n \to \varrho \in (0, 1)$.

Remark 5. Condition 5 implies nonsingularity of the information matrix for $\boldsymbol{\theta}_0$ and can be shown to hold for the logistic, probit, and complementary log–log link functions. Condition 7 ensures that there are both cases and controls in the sample.

Theorem 2. Under Conditions 5–7, $|\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0| + \sup_g |\widehat{q}_g - q_g| + \sup_{\mathbf{x},g} |\widehat{F}_g^{\dagger}(\mathbf{x}) - F_g^{\dagger}(\mathbf{x})| \to 0$ almost surely. In addition, $n^{1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)$ converges in distribution to a normal random vector whose covariance matrix attains the semiparametric efficiency bound.

In most case-control studies, the disease is (relatively) rare. When the disease is rare, considerable simplicity arises because of the following approximation for the logistic regression model:

$$P_{\alpha,\boldsymbol{\beta}}(Y|\mathbf{X}, H) \approx \exp\{Y(\alpha + \boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X}, H))\},$$

where $\mathcal{Z}(\mathbf{X}, H)$ is a specific function of $\mathbf{X}$ and H. We assume that either (3) or (4) holds. The likelihood based on $(\mathbf{X}_i, G_i, y_i)$, $i = 1, \ldots, n$, can be approximated by

$$\begin{aligned}\widetilde{L}_n(\boldsymbol{\theta}, \{F_g\}) &= \prod_{i=1}^{n} \left(\frac{\prod_{g\in\mathcal{G}} [f_g(\mathbf{X}_i) \sum_{(h_k,h_l)\in\mathcal{S}(g)} e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X}_i,h_k,h_l)} P_{\boldsymbol{\gamma}}(h_k,h_l)]^{I(G_i=g)}}{\sum_{g\in\mathcal{G}} \int_{\mathbf{x}} \sum_{(h_k,h_l)\in\mathcal{S}(g)} e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{x},h_k,h_l)} P_{\boldsymbol{\gamma}}(h_k,h_l)\, dF_g(\mathbf{x})} \right)^{y_i} \\ &\quad \times \left[\prod_{g\in\mathcal{G}} \left\{ f_g(\mathbf{X}_i) \sum_{(h_k,h_l)\in\mathcal{S}(g)} P_{\boldsymbol{\gamma}}(h_k,h_l) \right\}^{I(G_i=g)} \right]^{1-y_i}. \end{aligned} \tag{9}$$

We impose the following condition.

Condition 8. If $\alpha + \boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X}, H) = \widetilde{\alpha} + \widetilde{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X}, H)$ for $H = (h_k, h_k)$ and $H = (h_k, \widetilde{h}_k)$, then $\alpha = \widetilde{\alpha}$ and $\boldsymbol{\beta} = \widetilde{\boldsymbol{\beta}}$.

This condition is similar to Condition 1 stated in Section 2.2, and it holds for the codominant model. Under this condition, it follows from Lemma 1 that no two sets of parameters can give the same likelihood with probability 1. Thus the maximizer of (9), denoted by $(\widehat{\boldsymbol{\theta}}, \{\widehat{F}_g\})$, is locally unique. We show in Section A.4.5 that $\widehat{\boldsymbol{\theta}}$ can be easily obtained by profiling over a small number of parameters.

To derive the asymptotic properties, we provide a mathematical definition of rare disease.

Condition 9. For $i = 1, \ldots, n$, the conditional distribution of Y_i given $(\mathbf{X}_i, H_i)$ satisfies that $P(Y_i = 1|\mathbf{X}_i, H_i) = a_n \exp\{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X}_i, H_i)\}/[1 + a_n \exp\{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X}_i, H_i)\}]$, where $a_n = o(n^{-1/2})$.

Theorem 3. Under Conditions 6–9, $|\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0| + \sup_{\mathbf{x},g} |\widehat{F}_g(\mathbf{x}) - F_g(\mathbf{x})| \to^{P_n} 0$, where P_n is the probability measure given by Condition 9. Furthermore, $n^{1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)$ converges in distribution to a normal random vector whose covariance matrix achieves the semiparametric efficiency bound.

2.5 Cohort Studies

In a cohort study, Y represents the time to disease occurrence, which is subject to right-censorship by C. The data consist of $(\widetilde{Y}_i, \Delta_i, \mathbf{X}_i, G_i)$, $i = 1, \ldots, n$, where $\widetilde{Y}_i = \min(Y_i, C_i)$ and $\Delta_i = I(Y_i \le C_i)$. We relate Y_i to $(\mathbf{X}_i, H_i)$ through a class of semiparametric linear transformation models,

$$\Gamma(Y_i) = -\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X}_i, H_i) + \epsilon_i, \qquad i = 1, \ldots, n, \tag{10}$$

where Γ is an unknown increasing function, $\mathcal{Z}(\mathbf{X}, H)$ is a known function of $\mathbf{X}$ and H, and the ϵ_i's are independent errors with known distribution function F. We may rewrite (10) as

$$P(Y_i \le t|\mathbf{X}_i, H_i) = Q\big(\Lambda(t) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X}_i,H_i)}\big),$$

where $\Lambda(t) = e^{\Gamma(t)}$ and $Q(x) = F(\log x)$ $(x > 0)$. The choices of the extreme-value and standard logistic distributions for F, or equivalently, $Q(x) = 1 - e^{-x}$ and $Q(x) = 1 - (1+x)^{-1}$, yield the proportional hazards model and the proportional odds model (Pettitt 1984).

We impose Condition 8. Under this condition, $\boldsymbol{\beta}$ and $\Lambda(\cdot)$ are identifiable from the observable data. The identifiability of the distribution of H is the same here as in the case of cross-sectional studies. Under (3) or (4) and Condition 8, all of the parameters, including $\boldsymbol{\beta}$, $\Lambda(\cdot)$, and $\boldsymbol{\gamma}$, are identifiable. This is shown in Section A.5.1.

The following assumption on censoring is required in constructing the likelihood.

Condition 10. Conditional on $\mathbf{X}$ and G, the censoring time C is independent of Y and H.

Let $\boldsymbol{\theta} = (\boldsymbol{\beta}, \boldsymbol{\gamma})$. The likelihood concerning $\boldsymbol{\theta}$ and Λ takes the form

$$\begin{aligned} L_n(\boldsymbol{\theta}, \Lambda) &= \prod_{i=1}^{n} \Bigg[\sum_{(h_k,h_l)\in\mathcal{S}(G_i)} \{\dot{\Lambda}(\widetilde{Y}_i) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X}_i,(h_k,h_l))} \\ &\qquad \times \dot{Q}\big(\Lambda(\widetilde{Y}_i) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X}_i,(h_k,h_l))}\big)\}^{\Delta_i} \\ &\quad \times \{1 - Q\big(\Lambda(\widetilde{Y}_i) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X}_i,(h_k,h_l))}\big)\}^{1-\Delta_i} P_{\boldsymbol{\gamma}}(h_k,h_l) \Bigg]. \end{aligned} \tag{11}$$

Here and in the sequel, $\dot{f}(x) = df(x)/dx$ and $\ddot{f}(x) = d^2 f(x)/dx^2$. Like (6), (8), and (9), this likelihood involves infinite-dimensional parameters. If Λ is restricted to be absolutely continuous, then, as in the case of density estimation, there is no maximizer of this likelihood. Thus we relax Λ to be right-continuous and replace $\dot{\Lambda}(\widetilde{Y}_i)$ in (11) by the jump size of Λ at $\widetilde{Y}_i$. By the arguments of Zeng, Lin, and Lin (2005), the resultant MLE, denoted by $(\widehat{\boldsymbol{\theta}}, \widehat{\Lambda})$, exists, and $\widehat{\Lambda}$ is a step function with jumps only at the observed $\widetilde{Y}_i$ for which $\Delta_i = 1$. The maximization can be carried out through an optimization algorithm. Furthermore, the covariance matrix of $\widehat{\boldsymbol{\theta}}$ can be estimated by the profile likelihood method, as discussed by Zeng et al. (2005).

Lin (2004) considered the special case of the proportional hazards model under condition (2) and provided an EM algorithm for obtaining the MLEs. We can modify that algorithm to accommodate Hardy–Weinberg disequilibrium along the lines of Section A.2.2. In addition, the EM algorithm can be used to evaluate the profile likelihood.

We assume the following regularity conditions for the asymptotic results.

Condition 11. There exists some positive constant δ_0 such that $P(C_i \geq \tau | \mathbf{X}_i, G_i) = P(C_i = \tau | \mathbf{X}_i, G_i) \geq \delta_0$ almost surely, where τ corresponds to the end of the study.

Condition 12. The true value $\Lambda_0(t)$ of $\Lambda(t)$ is a strictly increasing function in $[0, \tau]$ and is continuously differentiable. In addition, $\Lambda_0(0) = 0$, $\Lambda_0(\tau) < \infty$, and $\dot{\Lambda}_0(0) > 0$.

Theorem 4. Under Conditions 8 and 10–12, $n^{1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0, \widehat{\Lambda} - \Lambda_0)$ converges weakly to a Gaussian process in $\mathbb{R}^d \times l^\infty([0, \tau])$, where d is the dimension of $\boldsymbol{\theta}_0$, and $l^\infty([0, \tau])$ is the space of all bounded functions on $[0, \tau]$ equipped with the supremum norm. Furthermore, $\widehat{\boldsymbol{\theta}}$ is asymptotically efficient.

3. SIMULATION STUDIES

We used Monte Carlo simulation to evaluate the proposed methods in realistic settings. We considered the five SNPs on chromosome 22 from the Finland–United States Investigation of NIDDM Genetics (FUSION) Study described in the next section. We obtained the π_k's from the frequencies shown in Table 1 by assuming a 7% disease rate, and generated haplotypes under (3) with $\rho = .05$. The R_h^2 in Table 1 is the measure of haplotype certainty of Stram et al. (2003). We focused on $h^* = (0, 1, 1, 0, 0)$ and considered case-control and cohort studies.

For the cohort studies, we generated ages of onset from the proportional hazards model,

$$\lambda\{t|x, (h_k, h_l)\} = 2t \exp\big[\beta_1\{I(h_k = h^*) + I(h_l = h^*)\} + \beta_2 x + \beta_3\{I(h_k = h^*) + I(h_l = h^*)\}x\big],$$

where X is a Bernoulli variable with $P(X = 1) = .2$ that is independent of H. We generated the censoring times from the uniform $(0, \tau)$ distribution, where τ was chosen to yield approximately 250, 500, and 1,000 cases under $n = 5{,}000$. We let $\beta_1 = \beta_2 = .25$ and varied β_3 from $-.5$ to .5.

As shown in Table 2, the MLE is virtually unbiased, the likelihood ratio test has proper type I error, and the confidence interval has reasonable coverage. Additional simulation studies revealed that the proposed methods also perform well for making inference about other parameters and under other genetic models.

Table 1. Observed Haplotype Frequencies in the FUSION Study

	Frequencies		
Haplotype	Controls	Cases	R_h^2
00011	.0042	.0066	.388
00100	.0035	.0034	.336
00110	.0018	.0007	.377
01011	.1292	.1344	.592
01100	.2514	.3183	.738
01101	.0012	$<10^{-4}$	.450
01110	$<10^{-4}$	.0045	.499
01111	.0019	$<10^{-4}$	.325
10000	.0136	.0114	.456
10010	$<10^{-4}$	.0012	.500
10011	.3573	.2883	.727
10100	.0521	.0597	.402
10110	.0317	.0318	.554
11011	.1392	.1290	.560
11100	.0109	.0092	.266
11110	$<10^{-4}$	.0014	$<10^{-4}$
11111	.0020	$<10^{-4}$	.338

Table 2. Simulation Results for the Haplotype–Environment Interactions in Cohort Studies

β_3	Cases	Bias	SE	CP	Power
0	250	−.010	.232	.949	.051
	500	−.005	.157	.953	.047
	1,000	−.003	.114	.954	.046
−.25	250	−.014	.256	.950	.190
	500	−.008	.172	.949	.334
	1,000	−.004	.122	.952	.554
−.5	250	−.022	.281	.950	.505
	500	−.011	.190	.950	.806
	1,000	−.006	.132	.952	.976
.25	250	−.007	.216	.947	.207
	500	−.002	.146	.953	.395
	1,000	−.001	.109	.954	.614
.5	250	−.003	.204	.943	.693
	500	−.001	.140	.951	.940
	1,000	−.001	.105	.952	.998

NOTE: Bias and SE are the bias and standard error of $\widehat{\beta}_3$. CP is the coverage probability of the 95% confidence interval for β_3. Power pertains to the .05-level likelihood ratio test of $H_0 : \beta_3 = 0$. Each entry is based on 5,000 replicates.

For the case-control studies, we used the same distributions of H and X and considered the same h^* as in the cohort studies. We generated disease incidence from the logistic regression model,

$$\begin{aligned}\operatorname{logit} P\{Y = 1|x, (h_k, h_l)\} &= \alpha + \beta_1\{I(h_k = h^*) + I(h_l = h^*)\} \\ &\quad + \beta_2 x + \beta_3\{I(h_k = h^*) + I(h_l = h^*)\}x. \qquad (12)\end{aligned}$$

For making inference on β_1, we set $\beta_2 = \beta_3 = .25$ and varied β_1 from $-.5$ to .5; for making inference on β_3, we set $\beta_1 = \beta_2 = .25$ and varied β_3 from $-.5$ to .5. We chose $\alpha = -3$ or -4, yielding disease rates between 1.6% and 7%. We let $n_1 = n_0 = 500$ or 1,000. We considered the situations of known and unknown population totals, with N being 15 and 30 times of n under $\alpha = -3$ and -4. For known population totals, we used the EM algorithm described in Section A.3.1 and evaluated the inference procedures based on the likelihood ratio statistic. For unknown population totals, we used the profile-likelihood method for rare diseases described in Section A.4.5 and set the $\widehat{\pi}_k$ less than $2/n$ to 0 to improve numerical stability. The results for β_1 and β_3 are displayed in Tables 3 and 4.

For known population totals, the proposed estimators are virtually unbiased, and the likelihood ratio statistics yield proper tests and confidence intervals. For unknown population totals, $\widehat{\beta}_1$ has little bias, especially for large n, whereas $\widehat{\beta}_3$ tends to be slightly biased downward; the variance estimators are fairly accurate, and the corresponding confidence intervals have reasonable coverage probabilities except for $\{\alpha = -3, \beta_3 = .5\}$. The method with known population totals yields slightly higher power than the method with unknown population totals.

All the aforementioned results pertain to haplotype 01100, which has a relatively high frequency and a large value of R_h^2; the covariate is binary, and ρ is .05, which is relatively large. Additional simulation studies showed that the foregoing conclusions continue to hold for other haplotypes, other values of ρ, and continuous covariates. Table 5 reports some results for haplotype 10100, which has a frequency of about 5% and

Table 3. Simulation Results for the Main Effects of the Haplotype in Case-Control Studies

			Known totals				Unknown totals				
$n_1 = n_0$	α	β_1	Bias	SE	CP	Power	Bias	SE	SEE	CP	Power
500	−3	−.5	−.003	.117	.952	.987	.019	.121	.124	.951	.979
		−.25	−.002	.109	.954	.587	.014	.112	.117	.960	.525
		0	−.001	.104	.951	.049	.009	.109	.112	.955	.045
		.25	−.001	.102	.950	.641	.002	.105	.108	.961	.646
		.5	.000	.099	.948	.996	−.005	.103	.106	.958	.998
	−4	−.5	.001	.112	.954	.987	.022	.119	.124	.951	.977
		−.25	−.002	.104	.955	.574	.013	.114	.117	.952	.529
		0	−.002	.100	.953	.047	.004	.109	.112	.953	.047
		.25	−.001	.095	.956	.636	−.003	.103	.108	.959	.640
		.5	−.000	.094	.950	.999	−.009	.102	.105	.956	.997
1,000	−3	−.5	−.003	.082	.953	1.00	.005	.087	.087	.949	1.00
		−.25	−.002	.076	.952	.874	.005	.081	.082	.948	.853
		0	−.001	.073	.951	.049	.005	.077	.077	.954	.046
		.25	−.001	.071	.953	.898	.004	.075	.076	.948	.920
		.5	−.001	.070	.953	1.00	.003	.075	.075	.946	1.00
	−4	−.5	.000	.079	.952	1.00	.005	.087	.088	.947	1.00
		−.25	−.000	.074	.959	.867	.005	.081	.083	.954	.847
		0	−.001	.070	.955	.045	.002	.079	.079	.949	.051
		.25	−.001	.067	.956	.904	.000	.074	.076	.955	.909
		.5	−.001	.066	.956	1.00	−.002	.073	.074	.954	1.00

NOTE: Bias and SE are the bias and standard error of $\widehat{\beta}_1$. SEE is the mean of the standard error estimator for $\widehat{\beta}_1$. CP is the coverage probability of the 95% confidence interval for β_1. Power pertains to the .05-level test of $H_0 : \beta_1 = 0$. Each entry is based on 5,000 replicates.

an R_h^2 of .4. We generated disease incidence from the logistic regression model

$$\begin{aligned}&\operatorname{logit} P\{Y = 1|X_1, X_2, (h_k, h_l)\}\\ &\quad = \alpha + \beta_h\{I(h_k = h^*) + I(h_l = h^*)\}\\ &\qquad + \beta_{x_1}X_1 + \beta_{x_2}X_2 + \beta_{hx_2}\{I(h_k = h^*) + I(h_l = h^*)\}X_2,\end{aligned}$$

where $h^* = (10100)$, X_1 is Bernoulli with .2 success probability, and X_2 is uniform(0, 1). We set $\rho = .01$, $\alpha = -3.7$, $\beta_h = 0$, and $\beta_{x_1} = \beta_{x_2} = -\beta_{x_2h} = .5$, yielding an overall disease rate of 7%. We assumed unknown population totals and used the profile-likelihood method for rare diseases described in Section A.4.5. The method performed remarkably well.

4. APPLICATION TO THE FUSION STUDY

Type 2 diabetes mellitus or non–insulin-dependent diabetes mellitus is a complex disease characterized by resistance of peripheral tissues to insulin and a deficiency of insulin secretion. Approximately 7% of adults in developed countries suffer from the disease. The FUSION study is a major effort to map and clone genetic variants that predispose to type 2 diabetes (Valle et al. 1998). We consider a subset of data from this study.

Table 4. Simulation Results for the Haplotype–Environment Interactions in Case-Control Studies

			Known totals				Unknown totals				
$n_1 = n_0$	α	β_3	Bias	SE	CP	Power	Bias	SE	SEE	CP	Power
500	−3	−.5	−.008	.205	.949	.729	.030	.187	.195	.953	.692
		−.25	−.002	.186	.949	.271	.016	.169	.176	.961	.244
		0	−.001	.173	.946	.054	−.006	.155	.162	.963	.037
		.25	.002	.165	.949	.334	−.038	.144	.151	.958	.287
		.5	.006	.161	.947	.885	−.088	.138	.143	.915	.831
	−4	−.5	−.009	.198	.950	.763	.012	.194	.195	.950	.720
		−.25	−.005	.181	.949	.309	.006	.172	.176	.953	.264
		0	−.002	.168	.945	.055	−.007	.156	.161	.956	.044
		.25	−.001	.157	.944	.370	−.022	.146	.149	.948	.333
		.5	.001	.148	.945	.926	−.047	.136	.141	.945	.904
1,000	−3	−.5	−.004	.147	.943	.953	.027	.134	.136	.950	.953
		−.25	−.003	.133	.946	.493	.013	.122	.123	.949	.477
		0	−.001	.123	.951	.049	−.005	.114	.113	.948	.052
		.25	.000	.119	.945	.580	−.034	.107	.106	.934	.535
		.5	.002	.117	.947	.994	−.080	.102	.101	.870	.986
	−4	−.5	−.005	.140	.945	.965	.010	.137	.136	.949	.965
		−.25	−.002	.128	.945	.529	.005	.124	.123	.951	.505
		0	−.001	.119	.946	.054	−.004	.113	.113	.947	.053
		.25	−.000	.110	.947	.633	−.016	.104	.105	.952	.601
		.5	.002	.105	.949	.998	−.037	.099	.099	.937	.995

NOTE: Bias and SE are the bias and standard error of $\widehat{\beta}_3$. SEE is the mean of the standard error estimator for $\widehat{\beta}_3$. CP is the coverage probability of the 95% confidence interval for β_3. Power pertains to the .05-level test of $H_0 : \beta_3 = 0$. Each entry is based on 5,000 replicates.

Table 5. Simulation Results for Haplotype 10100 in Case-Control Studies

$n_1 = n_0$	Parameter	True value	Bias	SE	SEE	CP	Power
500	β_h	0	−.030	.400	.401	.957	.043
	β_{x_1}	.5	.002	.151	.152	.951	.917
	β_{x_2}	.5	.001	.228	.230	.953	.584
	β_{hx_2}	−.5	.015	.641	.644	.956	.118
1,000	β_h	0	−.017	.275	.277	.953	.047
	β_{x_1}	.5	.002	.107	.107	.954	.997
	β_{x_2}	.5	.000	.162	.161	.950	.871
	β_{hx_2}	−.5	.012	.441	.443	.950	.198

NOTE: Bias and SE are the bias and standard error of the parameter estimator. SEE is the mean of the standard error estimator. CP is the coverage probability of the 95% confidence interval. Power pertains to the .05-level test of zero parameter value. Each entry is based on 5,000 replicates.

A total of 796 cases and 415 controls were genotyped at 5 SNPs in a putative susceptibility region on chromosome 22, with 131 cases and 82 controls having missing genotype information for at least one SNP. If G_i is missing, then the set $\mathcal{S}(G_i)$ is enlarged accordingly in the analysis. Table 1 displays the estimated haplotype frequencies under (3) separated by the cases and controls, along with the values of R_h^2 (Stram et al. 2003) for the controls. We estimated ρ at .000 for controls and .002 for cases.

We use the method based on (9) to estimate the effects of the haplotypes whose observed frequencies in the controls are greater than 2%. As shown in Table 6, the results are significant for the two most common haplotypes; haplotype 01100 increases the risk of disease, whereas haplotype 10011 is protective against diabetes. Epstein and Satten (2003) also reported the estimates for these two haplotypes, which agree with our numbers. Although they did not report standard error estimates, their confidence intervals are similar to those based on Table 6. The results under the codominant model as well as the calculations of the Akaike information criterion (AIC) (Akaike 1985) suggest that the additive model fits the data the best for both haplotypes 01100 and 10011.

The FUSION investigators are currently exploring gene–environment interactions on chromosome 22, so the covariate information is confidential at this stage. To illustrate our method for detecting gene–environment interactions, we artificially created a binary covariate X by setting $X = 1$ for the first 600 individuals in the dataset. Under the additive genetic model for haplotype 01100, the estimate of the interaction is .043 with an estimated standard error of .110. For further illustration, we generated a binary covariate from the conditional distribution of X given Y and G under model (12) with $\alpha = -3.7$, $\beta_1 = .32$, and $\beta_2 = .25$. Based on 5,000 replicates, the power for testing $H_0 : \beta_3 = 0$ is estimated at .053, .479, or .974 under $\beta_3 = 0, .25$, or .5.

5. DISCUSSION

Inferring haplotype–disease associations is an interesting and difficult statistical problem. The presence of infinite-dimensional nuisance parameters in the likelihoods for case-control and cohort studies entails considerable theoretical and computational challenges. Although we have conducted a systematic and rigorous investigation, providing powerful new methods, there remain substantial open problems. Here we discuss some directions for future research.

Case-Control Studies. It is numerically difficult to maximize (6) when N is much larger than n, and algorithms for implementing the constrained maximization mentioned in Remark 3 have yet to be developed. For case-control studies with unknown population totals, identifiability is a thorny issue. We have provided a simple and efficient method under the rare disease assumption, which appears to work well even when the disease is not rare. But can we do better?

Model Selection and Model Assessment. Because our approach is built on likelihood, we can apply likelihood-based model selection criteria, such as the AIC used in Section 4. Lin (2004) showed that the AIC performs well for the proportional hazards model. It is unclear how to apply the traditional residual-based methods for assessing model adequacy, because the haplotypes are not directly observable.

Other Genetic Variants. We have focused on SNPs-based haplotypes. The proposed inference procedures are potentially applicable to microsatellite loci and other genotype data, although the identifiability of parameters needs to be verified for each kind of genotype data.

Other Study Designs. It is sometimes desirable to use the matched case-control design in which one or more controls are individually matched to each case. In large cohort studies with rare diseases, it is cost-effective to adopt the case-cohort design or nested case-control design, so that only a subset of the cohort members needs to be genotyped. We are currently developing efficient inference procedures for such designs.

Population Substructure. The presence of latent population substructure can cause bias in association studies of unrelated individuals. There exist several statistical methods to adjust for the effects of population substructure with the aid of genomic markers. It should be possible to extend the proposed methods so as to accommodate potential population substructure.

Table 6. Estimates of Haplotype Effects Under Various Genetic Models for the FUSION Study

Haplotype	Recessive model	Dominant model	Additive model	Codominant model	
				Additive	Recessive
01011	$.327_{(.270)}$	$-.027_{(.140)}$	$.049_{(.135)}$	$.005_{(.143)}$	$.331_{(.289)}$
01100	$.316_{(.146)}$	$.274_{(.109)}$	$.355_{(.099)}$	$.334_{(.114)}$	$.063_{(.167)}$
10011	$-.206_{(.155)}$	$-.323_{(.112)}$	$-.320_{(.095)}$	$-.344_{(.111)}$	$.076_{(.183)}$
10100	$-1.019_{(1.020)}$	$.196_{(.219)}$	$.116_{(.213)}$	$.169_{(.217)}$	$-1.131_{(1.029)}$
10110	$.903_{(.746)}$	$-.007_{(.248)}$	$.063_{(.249)}$	$.016_{(.254)}$	$.892_{(.765)}$
11011	$-.222_{(.328)}$	$-.096_{(.140)}$	$-.127_{(.133)}$	$-.108_{(.140)}$	$-.143_{(.344)}$

NOTE: Standard error estimates are shown in parentheses.

Studies of Related Individuals. This article is concerned with studies of unrelated individuals. Many genetic studies involve multiple family members or relatives. Haplotype ambiguity possibly can be reduced by using the genotype information from related individuals. Inference on haplotype effects needs to account for the intraclass correlation.

Genotyping Error and DNA Pooling. Laboratory genotyping is prone to error. It is sometimes necessary to pool DNA samples rather than genotyping individual samples (Wang, Kidd, and Zhao 2003). Such data create additional complexity in haplotype analysis (Zeng and Lin 2005).

Many SNPs. The traditional EM algorithm works well for a small number of SNPs. When the number of SNPs is large, the partition–ligation method of Niu et al. (2002) and Qin et al. (2002) and other modifications potentially can be adapted to reduce the computational burden. However, the haplotype analysis may not be very useful if the SNPs are weakly linked.

Many Haplotypes and Rare Haplotypes. The approach taken in this article assumes that we are interested in a small number of haplotype configurations that are relatively frequent. If there are many haplotypes, then we are confronted with the problem of multiple comparisons and sparse data. Schaid (2004) discussed some possible solutions.

Large-Scale Studies. There is an increasing interest in genome-wide association studies. With a large number of SNPs, one possible approach is to use sliding windows of 5–10 SNPs and test for the haplotype–disease association in each window. Because most of the SNPs are common between adjacent windows, the test statistics tend to be highly correlated, so that the Bonferroni-type correction for multiple comparisons would be extremely conservative. To properly adjust for multiple comparisons, one needs to ascertain the joint distribution of the test statistics. This can be done by permuting the data or by evaluating the asymptotic joint normal distribution of the test statistics (Lin 2005).

We hope that other statisticians will join us in tackling the foregoing problems and other challenges in genetic association studies.

APPENDIX: TECHNICAL AND COMPUTATIONAL DETAILS

A.1 Proof of Lemma 1

We provide a proof under (3); the proof under (4) is simpler and is omitted here. To prove the first part of the lemma, we suppose that two sets of parameters, $(\{\pi_k\}, \rho)$ and $(\{\widetilde{\pi}_k\}, \widetilde{\rho})$, yield the same distribution of G. We wish to show that these two sets are identical. Consider $g = 2h_k$. For such a choice of g, the set $\mathcal{S}(g)$ is a singleton. Clearly, $(1-\rho)\pi_k^2 + \rho\pi_k = (1-\widetilde{\rho})\widetilde{\pi}_k^2 + \widetilde{\rho}\widetilde{\pi}_k$. We denote this constant by c_k. Then $0 \le c_k \le 1$ for all k, and $0 < c_k < 1$ for at least one k. Because $\pi_k \ge 0$, we have $\pi_k = [-\rho + \{\rho^2 + 4c_k(1-\rho)\}^{1/2}]/2(1-\rho)$. Thus $(1-\rho)^{-1}$ satisfies the equation $\sum_k[(1-x) + \{(x-1)^2 + 4c_k x\}^{1/2}] = 2$, and $(1-\widetilde{\rho})^{-1}$ satisfies the same equation. It can be shown that the first derivative of $(1-x) + \{(x-1)^2 + 4c_k x\}^{1/2}$ is nonpositive and is strictly negative for at least one k. Thus the foregoing equation has a unique solution for $x > 1$, which implies that $\rho = \widetilde{\rho}$. It follows immediately that $\pi_k = \widetilde{\pi}_k$ for all k. To prove the second part of the lemma, we choose $g = 2h_k$ to obtain $\nu_k\{2\pi_k(1-\rho) + \rho\} + \mu\pi_k(1-\pi_k) = 0$. Because $\sum_k \nu_k = 0$, we have $\sum_k\{\mu\pi_k(1-\pi_k)\}/\{2\pi_k(1-\rho) + \rho\} = 0$. Therefore, $\mu = 0$ and $\boldsymbol{\nu} = \mathbf{0}$.

A.2 Cross-Sectional Studies

A.2.1 Identifiability Under Arbitrary Distributions of H. Under Condition 1, $(\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\xi})$ is identifiable. The identifiability of the distribution of H depends on the structure of $P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}$. For concreteness, we consider the codominant logistic regression model for a binary trait. We divide $\mathcal{G}$ into three categories: $\mathcal{G}_1 = \{g \in \mathcal{G} : g = h + h \text{ or } g = h + \widetilde{h}\}$, $\mathcal{G}_2 = \{g \in \mathcal{G} - \mathcal{G}_1 : g \text{ is not } \ge h^*\}$, and $\mathcal{G}_3 = \mathcal{G} - \mathcal{G}_1 - \mathcal{G}_2$. We derive the expression for $m_g(y, \mathbf{x}; \boldsymbol{\theta})$ when g belongs to each of the three categories.

For $g \in \mathcal{G}_1$, $\mathcal{S}(g) = \{(h,h)\}$ or $\{(h,\widetilde{h})\}$, so that $m_g(y, \mathbf{x}; \boldsymbol{\theta}) = P_{\alpha,\boldsymbol{\beta},\xi}(Y = y|\mathbf{X} = \mathbf{x}, H = (h,h))P(H = (h,h))$ or $m_g(y, \mathbf{x}; \boldsymbol{\theta}) = P_{\alpha,\boldsymbol{\beta},\xi}(Y = y|\mathbf{X} = \mathbf{x}, H = (h,\widetilde{h}))P(H = (h,\widetilde{h}))$. For $g \in \mathcal{G}_2$, $P_{\alpha,\boldsymbol{\beta},\xi}(Y = y|\mathbf{X} = \mathbf{x}, H = (h_k, h_l))$ does not depend on $(h_k, h_l) \in \mathcal{S}(g)$, so that $m_g(y, \mathbf{x}; \boldsymbol{\theta}) = P_{\alpha,\boldsymbol{\beta},\xi}(Y = y|\mathbf{X} = \mathbf{x}, H = (h_k, h_l))P(G = g)$, where $(h_k, h_l) \in \mathcal{S}(g)$. For $g \in \mathcal{G}_3$,

$$m_g(y, \mathbf{x}; \boldsymbol{\theta}) = \frac{\exp\{y(\alpha + \beta_1 + \boldsymbol{\beta}_3^T\mathbf{x} + \boldsymbol{\beta}_4^T\mathbf{x})\}}{1 + \exp(\alpha + \beta_1 + \boldsymbol{\beta}_3^T\mathbf{x} + \boldsymbol{\beta}_4^T\mathbf{x})}\pi_1(g) + \frac{\exp\{y(\alpha + \boldsymbol{\beta}_3^T\mathbf{x})\}}{1 + \exp(\alpha + \boldsymbol{\beta}_3^T\mathbf{x})}\pi_2(g),$$

where $\pi_1(g) = 2P(H = (h^*, g - h^*))$ and $\pi_2(g) = P(H = (h_k, h_l) : h_k + h_l = g, h_k \ne h^*, h_l \ne h^*)$.

Let $\boldsymbol{\theta}_0$ denote the true value of $\boldsymbol{\theta}$, $P_0(G = g)$ denote the true value of $P(G = g)$, and $\pi_{0j}(g)$ denote the true values $\pi_j(g)$, $j = 1, 2$. We then can draw the following conclusions: (1) When $\beta_{01} = 0$ and $\boldsymbol{\beta}_{04} = \mathbf{0}$, $m_g(y, \mathbf{x}; \boldsymbol{\theta}) = m_g(y, \mathbf{x}; \boldsymbol{\theta}_0)$ if and only if $\alpha = \alpha_0$, $\boldsymbol{\beta} = \boldsymbol{\beta}_0$, and $P(G = g) = P_0(G = g)$ for any $g \in \mathcal{G}$; and (2) when either β_{01} or $\boldsymbol{\beta}_{04}$ is nonzero, $m_g(y, \mathbf{x}; \boldsymbol{\theta}) = m_g(y, \mathbf{x}; \boldsymbol{\theta}_0)$ if and only if $\alpha = \alpha_0$, $\boldsymbol{\beta} = \boldsymbol{\beta}_0$, $P(G = g) = P_0(G = g)$ for $g \in \mathcal{G}_1 \cup \mathcal{G}_2$, and $\pi_j(g) = \pi_{0j}(g)$ for $g \in \mathcal{G}_3$ and $j = 1, 2$. These conclusions hold for any generalized linear model with the linear predictor given in (1).

A.2.2 EM Algorithm. The complete-data likelihood is proportional to $\prod_{i=1}^n\{P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{Y}_i|\mathbf{X}_i, H_i)P_{\boldsymbol{\gamma}}(H_i)\}$. The expectation of the logarithm of this function conditional on the observable data $(\mathbf{Y}_i, \mathbf{X}_i, G_i)$, $i = 1, \ldots, n$, is

$$\sum_{i=1}^n \sum_{(h_k,h_l)\in\mathcal{S}(G_i)} p_{ikl}(\boldsymbol{\theta})\{\log P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{Y}_i|\mathbf{X}_i, (h_k,h_l)) + \log P_{\boldsymbol{\gamma}}(h_k,h_l)\},$$

where

$$p_{ikl}(\boldsymbol{\theta}) = \frac{P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{Y}_i|\mathbf{X}_i, (h_k,h_l))P_{\boldsymbol{\gamma}}(h_k,h_l)}{\sum_{(h_k,h_l)\in\mathcal{S}(G_i)} P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{Y}_i|\mathbf{X}_i, (h_k,h_l))P_{\boldsymbol{\gamma}}(h_k,h_l)}.$$

Thus, in the $(m+1)$st iteration of the EM algorithm, we evaluate $p_{ikl}(\boldsymbol{\theta})$ at the current estimate $\widehat{\boldsymbol{\theta}}^{(m)}$, and obtain $\widehat{\boldsymbol{\theta}}^{(m+1)}$ by solving the following equations through the Newton–Raphson algorithm:

$$\sum_{i=1}^n \sum_{(h_k,h_l)\in\mathcal{S}(G_i)} p_{ikl}\big(\widehat{\boldsymbol{\theta}}^{(m)}\big) \times \nabla_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}} \log P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}\big(\mathbf{Y}_i|\mathbf{X}_i, (h_k,h_l)\big) = \mathbf{0},$$

$$\sum_{i=1}^n \sum_{(h_k,h_l)\in\mathcal{S}(G_i)} p_{ikl}\big(\widehat{\boldsymbol{\theta}}^{(m)}\big)\nabla_{\boldsymbol{\gamma}} \log P_{\boldsymbol{\gamma}}(h_k,h_l) = \mathbf{0}. \tag{A.1}$$

Under (3) with $\rho \ge 0$, the estimate of $\boldsymbol{\gamma} \equiv (\rho, \{\pi_k\})$ can be obtained in a closed form rather than by solving (A.1). Let B be a Bernoulli variable with success probability ρ, let Q_1 be a discrete random variable taking values in H with $P(Q_1 = (h_k, h_l)) = \delta_{kl}\pi_k$, and let Q_2 be another discrete random variable taking values in H

with $P(Q_2 = (h_k, h_l)) = \pi_k\pi_l$. Then H has the same distribution as $BQ_1 + (1-B)Q_2$. The complete-data likelihood can be represented by

$$\prod_{i=1}^{n}\Big\{P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(\mathbf{Y}_i|\mathbf{X}_i, H_i)\prod_k \pi_k^{I(Q_{1i}=(h_k,h_k))B_i} \times \prod_{k,l}(\pi_k\pi_l)^{I(Q_{2i}=(h_k,h_l))(1-B_i)}\rho^{B_i}(1-\rho)^{1-B_i}\Big\}.$$

The corresponding score equations for $\{\pi_k\}$ and ρ satisfy

$$\pi_k = c^{-1}\left[\sum_{i=1}^{n} B_i I\big(Q_{1i} = (h_k, h_k)\big) + \sum_{i=1}^{n}\sum_{l=1}^{K}(1-B_i)\big\{I\big(Q_{2i} = (h_k, h_l)\big) + I\big(Q_{2i} = (h_l, h_k)\big)\big\}\right]$$

and $\rho = n^{-1}\sum_{i=1}^{n} B_i$, where c is a normalizing constant such that $\sum_k \pi_k = 1$. Define

$$\begin{aligned}
&E\{\omega(B_i, Q_{1i}, Q_{2i})|\mathbf{Y}_i, \mathbf{X}_i, G_i\}\\
&\quad= \sum_{bq_1+(1-b)q_2\in\mathcal{S}(G_i)} P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}\big(\mathbf{Y}_i|\mathbf{X}_i, bq_1 + (1-b)q_2\big) \times p(b, q_1, q_2)\omega(b, q_1, q_2)\\
&\qquad\times\left[\sum_{bq_1+(1-b)q_2\in\mathcal{S}(G_i)} P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}\big(\mathbf{Y}_i|\mathbf{X}_i, bq_1 + (1-b)q_2\big) \times p(b, q_1, q_2)\right]^{-1},
\end{aligned}$$

where $\omega(B, Q_1, Q_2) = BI(Q_1 = (h_k, h_k))$, $(1-B)I(Q_2 = (h_k, h_l))$ or B, and

$$p(b, q_1, q_2) = \prod_k \pi_k^{bI(q_1=(h_k,h_k))} \times \prod_{k,l}(\pi_k\pi_l)^{(1-b)I(q_2=(h_k,h_l))}\rho^b(1-\rho)^{1-b}.$$

In the $(m+1)$st iteration, the estimates of π_k and ρ are obtained in closed form,

$$\pi_k^{(m+1)} = \frac{1}{c^{(m+1)}}\left[\sum_{i=1}^{n} E^{(m)}\big\{B_i I\big(Q_{1i} = (h_k, h_k)\big)\big\} + 2\sum_{i=1}^{n}\sum_{l=1}^{K} E^{(m)}\big\{(1-B_i)I\big(Q_{2i} = (h_k, h_l)\big)\big\}\right],$$

and $\rho^{(m+1)} = n^{-1}\sum_{i=1}^{n} E^{(m)}(B_i)$, where $E^{(m)}\{\omega(B_i, Q_{1i}, Q_{2i})\}$ is $E\{\omega(B_i, Q_{1i}, Q_{2i})|\mathbf{Y}_i, \mathbf{X}_i, G_i\}$ evaluated at $\boldsymbol{\theta} = \widehat{\boldsymbol{\theta}}^{(m)}$ and $c^{(m+1)}$ is the constant such that $\sum_k \pi_k^{(m+1)} = 1$.

A.3 Case-Control Studies With Known Population Totals

A.3.1 EM Algorithm. This is similar to the EM algorithm for cross-sectional studies, except that in addition to unknown H on all individuals, $\mathbf{X}$ is missing for the individuals not selected into the case-control sample and there are nonparametric components $\{F_g(\cdot)\}$. The complete-data likelihood is

$$\prod_{i=1}^{N} P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(Y_i|\mathbf{X}_i, H_i)P_{\boldsymbol{\gamma}}(H_i)\prod_g\{f_g(\mathbf{X}_i)\}^{I(G_i=g)}.$$

The M-step solves the following equations for $\boldsymbol{\theta}$:

$$\begin{aligned}
&\sum_{i=1}^{N} I(R_i = 1)E\big\{\nabla_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}\log P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(Y_i|\mathbf{X}_i, H_i)|Y_i, \mathbf{X}_i, G_i\big\}\\
&\qquad+\sum_{i=1}^{N} I(R_i = 0)E\big\{\nabla_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}\log P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(Y_i|\mathbf{X}_i, H_i)|Y_i\big\} = \mathbf{0},\\
&\sum_{i=1}^{N} I(R_i = 1)E\{\nabla_{\boldsymbol{\gamma}}\log P_{\boldsymbol{\gamma}}(H_i)|Y_i, \mathbf{X}_i, G_i\}\\
&\qquad+\sum_{i=1}^{N} I(R_i = 0)E\{\nabla_{\boldsymbol{\gamma}}\log P_{\boldsymbol{\gamma}}(H_i)|Y_i\} = \mathbf{0}, \quad \text{(A.2)}
\end{aligned}$$

and also estimates F_g by an empirical function with the following point mass at the $\mathbf{X}_i$ for which $(G_i = g, R_i = 1)$:

$$\begin{aligned}
&F_g\{\mathbf{X}_i\}\\
&\quad=\left[\sum_{j=1}^{N} I(\mathbf{X}_j = \mathbf{X}_i, G_j = g, R_j = 1) + \sum_{j=1}^{N} I(R_j = 0)E\{I(\mathbf{X}_j = \mathbf{X}_i, G_j = g)|Y_j\}\right]\\
&\qquad\times\left[\sum_{j=1}^{N} I(G_j = g, R_j = 1) + \sum_{j=1}^{N} I(R_j = 0)E\{I(G_j = g)|Y_j\}\right]^{-1},
\end{aligned}$$

where the conditional expectations are evaluated at the current estimates of $\boldsymbol{\theta}$ and $\{F_g\}$ in the E-step. For a random function $\omega(Y_i, \mathbf{X}_i, H_i)$, the conditional expectation takes the form

$$\frac{\sum_{(h_k,h_l)\in\mathcal{S}(G_i)} w(Y_i, \mathbf{X}_i, (h_k, h_l))P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(Y_i|\mathbf{X}_i, (h_k, h_l))P_{\boldsymbol{\gamma}}(h_k, h_l)}{\sum_{(h_k,h_l)\in\mathcal{S}(G_i)} P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(Y_i|\mathbf{X}_i, (h_k, h_l))P_{\boldsymbol{\gamma}}(h_k, h_l)}$$

for $R_i = 1$ and

$$\begin{aligned}
&\sum_{g\in\mathcal{G}}\sum_{\mathbf{x}\in\{\mathbf{X}_i:\, G_i=g, R_i=1\}}\sum_{(h_k,h_l)\in\mathcal{S}(g)} \omega(Y_i, \mathbf{x}, (h_k, h_l)) \times P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(Y_i|\mathbf{x}, (h_k, h_l)) \times P_{\boldsymbol{\gamma}}(h_k, h_l)F_g\{\mathbf{x}\}\\
&\quad\times\left(\sum_{g\in\mathcal{G}}\sum_{\mathbf{x}\in\{\mathbf{X}_i:\, G_i=g, R_i=1\}}\sum_{(h_k,h_l)\in\mathcal{S}(g)} P_{\boldsymbol{\alpha},\boldsymbol{\beta},\boldsymbol{\xi}}(Y_i|\mathbf{x}, (h_k, h_l)) \times P_{\boldsymbol{\gamma}}(h_k, h_l)F_g\{\mathbf{x}\}\right)^{-1}
\end{aligned}$$

for $R_i = 0$. Under (3) with $\rho \geq 0$, the idea described in Section A.2.2 can be applied to (A.2) to obtain a closed-form estimate of $\boldsymbol{\gamma}$.

A.3.2 Proof of Theorem 1. The case-control design with known population totals is a special case of the two-phase designs studied by Breslow, McNeney, and Wellner (2003). The likelihood given in (6) resembles (2.3) of Breslow et al. The key difference is that the former involves several nonparametric components $\{F_g(\cdot)\}$, whereas the latter involves only a single nonparametric function. Despite this difference, the arguments of Breslow et al. can be used to prove Theorem 1 with minor modifications. Specifically, the regularity conditions of Breslow et al. hold under our Conditions 1–4. Thus, the consistency of $(\widehat{\boldsymbol{\theta}}, \{\widehat{F}_g(\cdot)\})$ follows from the results of van der Vaart and Wellner (2001), whereas the weak convergence and asymptotic efficiency can be established by applying the results of Murphy and van der Vaart (2000) through a least favorable submodel, which can be constructed as done by Breslow et al. (2003, sec. 3).

A.4 Case-Control Studies With Unknown Population Totals

A.4.1 Equivalence Class. Suppose that two sets of parameters, $(\boldsymbol{\theta}, \{F_g^\dagger\}, \{q_g\})$ and $(\widetilde{\boldsymbol{\theta}}, \{\widetilde{F}_g^\dagger\}, \{\widetilde{q}_g\})$, yield the same likelihood,

$$RL(\boldsymbol{\theta}, \{F_g^\dagger\}, \{q_g\}) = RL(\widetilde{\boldsymbol{\theta}}, \{\widetilde{F}_g^\dagger\}, \{\widetilde{q}_g\}). \tag{A.3}$$

Because $\eta(0, \mathbf{x}, g; \boldsymbol{\theta}) = 1$, (A.3) with $y = 0$ implies that $f_g^\dagger(\mathbf{x}) q_g / \sum_{\widetilde{g}\in\mathcal{G}} q_{\widetilde{g}} = \widetilde{f}_g^\dagger(\mathbf{x}) \widetilde{q}_g / \sum_{\widetilde{g}\in\mathcal{G}} \widetilde{q}_{\widetilde{g}}$. Thus $f_g^\dagger(\mathbf{x}) = \widetilde{f}_g^\dagger(\mathbf{x})$ and $q_g = \widetilde{q}_g$. It then follows from (A.3) that

$$\eta(y, \mathbf{x}, g; \boldsymbol{\theta}) = C(y)\eta(y, \mathbf{x}, g; \widetilde{\boldsymbol{\theta}}), \tag{A.4}$$

where $C(y)$ depends only on y. By setting $\mathbf{x} = \mathbf{x}_0$ and $g = g_0$ in (A.4) and noting that $\eta(y, \mathbf{x}_0, g_0; \boldsymbol{\theta}) = 1$, we conclude that $C(y) = 1$. Hence the equivalence class for $(\boldsymbol{\theta}, \{F_g^\dagger\}, \{q_g\})$ is $\{(\widetilde{\boldsymbol{\theta}}, \{F_g^\dagger\}, \{q_g\}) : \eta(y, \mathbf{x}, g; \widetilde{\boldsymbol{\theta}}) = \eta(y, \mathbf{x}, g; \boldsymbol{\theta})\}$.

A.4.2 Identifiability for the Logistic Link Function. Suppose that

$$\eta(y, \mathbf{x}, g; \widetilde{\boldsymbol{\theta}}) = \eta(y, \mathbf{x}, g; \boldsymbol{\theta}) \tag{A.5}$$

for two sets of parameters $\widetilde{\boldsymbol{\theta}}$ and $\boldsymbol{\theta}$. Let $g_0 = 0$. As in Section A.2.1, we partition $\mathcal{G}$ into $(\mathcal{G}_1, \mathcal{G}_2, \mathcal{G}_3)$. For $g \in \mathcal{G}_1$, $\mathcal{S}(g)$ is a singleton, so the generalized odds ratio reduces to the ordinary odds ratio of Y given $\mathbf{X}$ and H. Thus (A.5) is equivalent to $\boldsymbol{\beta} = \widetilde{\boldsymbol{\beta}}$ under Condition 8. For $g \in \mathcal{G}_2$, $P(Y = 0|\mathbf{X} = \mathbf{x}, H = (h_k, h_l)) = \{1 + \exp(\alpha + \boldsymbol{\beta}_3^T \mathbf{x})\}^{-1}$. Thus (A.5) holds if and only if $\widetilde{\boldsymbol{\beta}}_3 = \boldsymbol{\beta}_3$. For $g \in \mathcal{G}_3$, both $\pi_1(g)$ and $\pi_2(g)$ are nonzero. Then (A.5) becomes

$$\frac{\widetilde{\pi}_1(g)(1 + e^{\widetilde{\alpha}+\psi_2(\mathbf{x})})/\widetilde{\pi}_2(g)(1 + e^{\widetilde{\alpha}+\psi_1(\mathbf{x})}) + e^{\psi_2(\mathbf{x})-\psi_1(\mathbf{x})}}{\widetilde{\pi}_1(g)(1 + e^{\widetilde{\alpha}+\psi_2(\mathbf{x})})/\widetilde{\pi}_2(g)(1 + e^{\widetilde{\alpha}+\psi_1(\mathbf{x})}) + 1}$$
$$= \frac{\pi_1(g)(1 + e^{\alpha+\psi_2(\mathbf{x})})/\pi_2(g)(1 + e^{\alpha+\psi_1(\mathbf{x})}) + e^{\psi_2(\mathbf{x})-\psi_1(\mathbf{x})}}{\pi_1(g)(1 + e^{\alpha+\psi_2(\mathbf{x})})/\pi_2(g)(1 + e^{\alpha+\psi_1(\mathbf{x})}) + 1}, \tag{A.6}$$

where $\psi_1(\mathbf{x}) = \beta_1 + \boldsymbol{\beta}_3^T \mathbf{x} + \boldsymbol{\beta}_4^T \mathbf{x}$ and $\psi_2(\mathbf{x}) = \boldsymbol{\beta}_3^T \mathbf{x}$.

Without loss of generality, assume that $\mathbf{0}$ is in the support of $\mathbf{X}$. We then have the following results:

1. $\beta_1 = 0$ and $\boldsymbol{\beta}_4 = \mathbf{0}$. Then (A.6) holds naturally.
2. $\beta_1 \neq 0, \boldsymbol{\beta}_4 = \mathbf{0}$, and $\boldsymbol{\beta}_3 = \mathbf{0}$. Then, because the function $(\lambda + c)/(\lambda + 1)$ is strictly monotone in λ for $c \neq 1$, (A.6) yields

$$\frac{\widetilde{\pi}_1(g)}{\widetilde{\pi}_2(g)} \frac{1 + e^{\widetilde{\alpha}}}{1 + e^{\widetilde{\alpha}+\beta_1}} = \frac{\pi_1(g)}{\pi_2(g)} \frac{1 + e^{\alpha}}{1 + e^{\alpha+\beta_1}}.$$

   Thus (A.6) is equivalent to

$$\frac{\widetilde{\pi}_1(g)/\widetilde{\pi}_2(g)}{\widetilde{\pi}_1(\widetilde{g})/\widetilde{\pi}_2(\widetilde{g})} = \frac{\pi_1(g)/\pi_2(g)}{\pi_1(\widetilde{g})/\pi_2(\widetilde{g})} \quad \text{for all } g, \widetilde{g} \in \mathcal{G}_3.$$

3. $\beta_1 \neq 0, \boldsymbol{\beta}_4 = \mathbf{0}$, and $\beta_{3,z} \neq 0$, where $\beta_{3,z}$ is the component of $\boldsymbol{\beta}_3$ associated with a continuous covariate Z. For $\mathbf{x}$ such that $\beta_{3,z} z \neq 0$, (A.6) yields

$$\frac{\widetilde{\pi}_1(g)}{\widetilde{\pi}_2(g)} \frac{1 + e^{\widetilde{\alpha}+\beta_{3,z}z}}{1 + e^{\widetilde{\alpha}+\beta_1+\beta_{3,z}z}} = \frac{\pi_1(g)}{\pi_2(g)} \frac{1 + e^{\alpha+\beta_{3,z}z}}{1 + e^{\alpha+\beta_1+\beta_{3,z}z}}.$$

   The foregoing equation holds for any $z \in (-\infty, \infty)$ because the functions on the two sides are analytic in z and z is continuous. Without loss of generality, assume that $\beta_{3,z} > 0$. By letting $z = -\infty$, we have $\widetilde{\pi}_1(g)/\widetilde{\pi}_2(g) = \pi_1(g)/\pi_2(g)$. Then by letting $z = 0$, we have $\widetilde{\alpha} = \alpha$. Thus (A.6) is equivalent to $\{\widetilde{\alpha} = \alpha, \widetilde{\pi}_1(g)/\widetilde{\pi}_2(g) = \pi_1(g)/\pi_2(g)\}$.
4. $\beta_{4,z} \neq 0$, where $\beta_{4,z}$ is the component of $\boldsymbol{\beta}_4$ pertaining to z. Then (A.6) is equivalent to

$$\frac{\widetilde{\pi}_1(g)}{\widetilde{\pi}_2(g)} \frac{1 + e^{\widetilde{\alpha}+\psi_2(\mathbf{x})}}{1 + e^{\widetilde{\alpha}+\psi_1(\mathbf{x})}} = \frac{\pi_1(g)}{\pi_2(g)} \frac{1 + e^{\alpha+\psi_2(\mathbf{x})}}{1 + e^{\alpha+\psi_1(\mathbf{x})}} \tag{A.7}$$

   for any $\mathbf{x}$ such that $\beta_1 + \boldsymbol{\beta}_4^T \mathbf{x} \neq 0$. We set $\mathbf{x}$ except the component z to $\mathbf{0}$. By letting $z \to -\beta_1/\beta_{4,z}$, we have $\widetilde{\pi}_1(g)/\widetilde{\pi}_2(g) = \pi_1(g)/\pi_2(g)$. Then by differentiating both sides of (A.7) with respect to z and letting $z \to -\beta_1/\beta_{4,z}$, we obtain $\alpha = \widetilde{\alpha}$. Thus (A.6) is equivalent to $\{\widetilde{\alpha} = \alpha, \widetilde{\pi}_1(g)/\widetilde{\pi}_2(g) = \pi_1(g)/\pi_2(g)\}$.

A.4.3 Identifiability for Probit and Complementary Log–Log Link Functions. Assume that $|\beta_1| + |\boldsymbol{\beta}_4| \neq 0$. Also assume that there exists a continuous covariate in $\mathbf{X}$, denoted by Z, such that the corresponding regression parameter β_z is nonzero. Let $\mathbf{x}_0 = \mathbf{0}$ and $g_0 = 0$. We claim that under the probit and complementary log–log regression models, $\eta(1, \mathbf{x}, g; \boldsymbol{\theta}) = \eta(1, \mathbf{x}, g; \widetilde{\boldsymbol{\theta}})$ for two sets of parameters $\boldsymbol{\theta}$ and $\widetilde{\boldsymbol{\theta}}$ if and only if $\alpha = \widetilde{\alpha}$, $\boldsymbol{\beta} = \widetilde{\boldsymbol{\beta}}$, and $\pi_1(g)/\pi_2(g) = \widetilde{\pi}_1(g)/\widetilde{\pi}_2(g)$ for $g \in \mathcal{G}_3$.

We first prove the foregoing claim for the probit model. Suppose that $\eta(1, \mathbf{x}, g; \boldsymbol{\theta}) = \eta(1, \mathbf{x}, g; \widetilde{\boldsymbol{\theta}})$. Without loss of generality, assume that h^* is a nonzero sequence. Let $g = 2h^*, h^* + \widetilde{h}^*$, and 0 in turn. Because $\mathcal{S}(g)$ has a single element for such g, we obtain

$$\frac{\Phi(\alpha)}{1 - \Phi(\alpha)} \left\{ \frac{1}{\Phi(\alpha + 2\beta_1 + \beta_2 + \boldsymbol{\beta}_3^T \mathbf{x} + 2\boldsymbol{\beta}_4^T \mathbf{x} + \boldsymbol{\beta}_5^T \mathbf{x})} - 1 \right\}$$
$$= \frac{\Phi(\widetilde{\alpha})}{1 - \Phi(\widetilde{\alpha})} \left\{ \frac{1}{\Phi(\widetilde{\alpha} + 2\widetilde{\beta}_1 + \widetilde{\beta}_2 + \widetilde{\boldsymbol{\beta}}_3^T \mathbf{x} + 2\widetilde{\boldsymbol{\beta}}_4^T \mathbf{x} + \widetilde{\boldsymbol{\beta}}_5^T \mathbf{x})} - 1 \right\}, \tag{A.8}$$

$$\frac{\Phi(\alpha)}{1 - \Phi(\alpha)} \left\{ \frac{1}{\Phi(\alpha + \beta_1 + \boldsymbol{\beta}_3^T \mathbf{x} + \boldsymbol{\beta}_4^T \mathbf{x})} - 1 \right\}$$
$$= \frac{\Phi(\widetilde{\alpha})}{1 - \Phi(\widetilde{\alpha})} \left\{ \frac{1}{\Phi(\widetilde{\alpha} + \widetilde{\beta}_1 + \widetilde{\boldsymbol{\beta}}_3^T \mathbf{x} + \widetilde{\boldsymbol{\beta}}_4^T \mathbf{x})} - 1 \right\}, \tag{A.9}$$

and

$$\frac{\Phi(\alpha)}{1 - \Phi(\alpha)} \left\{ \frac{1}{\Phi(\alpha + \boldsymbol{\beta}_3^T \mathbf{x})} - 1 \right\}$$
$$= \frac{\Phi(\widetilde{\alpha})}{1 - \Phi(\widetilde{\alpha})} \left\{ \frac{1}{\Phi(\widetilde{\alpha} + \widetilde{\boldsymbol{\beta}}_3^T \mathbf{x})} - 1 \right\}, \tag{A.10}$$

where Φ is the standard normal distribution function. In (A.10), we let $\mathbf{x}$ except the component z be $\mathbf{0}$. Then

$$\frac{\Phi(\alpha)}{1 - \Phi(\alpha)} \left\{ \frac{1}{\Phi(\alpha + \beta_z z)} - 1 \right\} = \frac{\Phi(\widetilde{\alpha})}{1 - \Phi(\widetilde{\alpha})} \left\{ \frac{1}{\Phi(\widetilde{\alpha} + \widetilde{\beta}_z z)} - 1 \right\}.$$

By letting $z \to \infty$ or $-\infty$, we conclude that β_z and $\widetilde{\beta}_z$ must have the same sign. Without loss of generality, assume that $\beta_z > \widetilde{\beta}_z > 0$. Then the left side divided by the right side goes to 0 as $z \to \infty$. This is a contradiction. Therefore, $\beta_z = \widetilde{\beta}_z$. We differentiate both sides to obtain

$$\frac{\Phi(\alpha)}{1 - \Phi(\alpha)} \frac{\phi(\alpha + \beta_z z)}{\Phi(\alpha + \beta_z z)^2} = \frac{\Phi(\widetilde{\alpha})}{1 - \Phi(\widetilde{\alpha})} \frac{\phi(\widetilde{\alpha} + \beta_z z)}{\Phi(\widetilde{\alpha} + \beta_z z)^2}.$$

By taking the ratio of the two sides and letting $z \to \operatorname{sgn}(\beta_z)\infty$, we immediately conclude that $\alpha = \widetilde{\alpha}$. Applying this result to (A.8)–(A.10), we obtain $2\beta_1 + \beta_2 + \boldsymbol{\beta}_3^T \mathbf{x} + 2\boldsymbol{\beta}_4^T \mathbf{x} + \boldsymbol{\beta}_5^T \mathbf{x} = 2\widetilde{\beta}_1 + \widetilde{\beta}_2 + \widetilde{\boldsymbol{\beta}}_3^T \mathbf{x} + 2\widetilde{\boldsymbol{\beta}}_4^T \mathbf{x} + \widetilde{\boldsymbol{\beta}}_5^T \mathbf{x}$, $\beta_1 + \boldsymbol{\beta}_3^T \mathbf{x} + \boldsymbol{\beta}_4^T \mathbf{x} = \widetilde{\beta}_1 + \widetilde{\boldsymbol{\beta}}_3^T \mathbf{x} + \widetilde{\boldsymbol{\beta}}_4^T \mathbf{x}$, and $\boldsymbol{\beta}_3^T \mathbf{x} = \widetilde{\boldsymbol{\beta}}_3^T \mathbf{x}$. Therefore, $\boldsymbol{\beta} = \widetilde{\boldsymbol{\beta}}$. For $g \in \mathcal{G}_3$,

$$\begin{aligned}
&\eta(1, \mathbf{x}, g; \boldsymbol{\theta}) \\
&\quad = \frac{1 - \Phi(\alpha)}{\Phi(\alpha)} \{\Phi(\alpha + \beta_1 + \boldsymbol{\beta}_3^T \mathbf{x} + \boldsymbol{\beta}_4^T \mathbf{x})\pi_1(g)/\pi_2(g) \\
&\qquad + \Phi(\alpha + \boldsymbol{\beta}_3^T \mathbf{x})\} \\
&\qquad \times \left[\{1 - \Phi(\alpha + \beta_1 + \boldsymbol{\beta}_3^T \mathbf{x} + \boldsymbol{\beta}_4^T \mathbf{x})\}\pi_1(g)/\pi_2(g) \right. \\
&\qquad \left. + 1 - \Phi(\alpha + \boldsymbol{\beta}_3^T \mathbf{x})\right]^{-1}.
\end{aligned} \tag{A.11}$$

It follows that $\pi_1(g)/\pi_2(g) = \widetilde{\pi}_1(g)/\widetilde{\pi}_2(g)$. The other direction of the claim is obvious in view of (A.11) and the expressions of $\eta(1, \mathbf{x}, g)$ for $g \in \mathcal{G}_1$ and $g \in \mathcal{G}_2$.

For the complementary log–log model, we obtain the same equations as (A.8)–(A.11) with $\Phi(x)$ replaced by $1 - \exp(-e^x)$. In particular, $e^{-e^\alpha}(e^{e^{\alpha+\beta_z z}} - 1)/(1 - e^{-e^\alpha}) = e^{-e^{\widetilde{\alpha}}}(e^{e^{\widetilde{\alpha}+\widetilde{\beta}_z z}} - 1)/(1 - e^{-e^{\widetilde{\alpha}}})$. Taking the first and second derivatives of the two sides with respect to z and forming the ratio of them, we obtain $\beta_z(e^{\alpha+\beta_z z} + 1) = \widetilde{\beta}_z(e^{\widetilde{\alpha}+\widetilde{\beta}_z z} + 1)$. Thus $\alpha = \widetilde{\alpha}$ and $\beta_z = \widetilde{\beta}_z$. The rest of the proof is the same as that of the probit model.

A.4.4 Profile Likelihood of $\boldsymbol{\theta}$ Based on (8). Suppose that there are J distinct observed values of $(\mathbf{X}, G)$, denoted by $(\mathbf{x}_1, g_1), \ldots, (\mathbf{x}_J, g_J)$. Let n_{1j} and n_{0j} be the number of times that $(\mathbf{x}_j, g_j)$ is observed in the cases and controls, and let δ_j be the jump size of the estimated distribution of $(\mathbf{X}, G)$ at $(\mathbf{x}_j, g_j)$. Then the log-likelihood based on (8) can be written as

$$l_n(\boldsymbol{\theta}, \{\delta_j\}) = \sum_{j=1}^{J} n_{1j} \log \eta(1, \mathbf{x}_j, g_j; \boldsymbol{\theta}) - n_1 \log\left\{\sum_{j=1}^{J} \eta(1, \mathbf{x}_j, g_j; \boldsymbol{\theta})\delta_j\right\} + \sum_{j=1}^{J} n_{+j} \log \delta_j,$$

where $n_{+j} = n_{0j} + n_{1j}$. Following Scott and Wild (1997), we introduce a Lagrange multiplier λ for the constraint $\sum_j \delta_j = 1$ and set the derivative with respect to δ_j to 0. We then obtain

$$\frac{n_{+j}}{\delta_j} - \frac{n_1 \eta(1, \mathbf{x}_j, g_j; \boldsymbol{\theta})}{\sum_{j=1}^{J} \eta(1, \mathbf{x}_j, g_j; \boldsymbol{\theta})\delta_j} + \lambda = 0.$$

Multiplying both sides by δ_j and summing over j, we see that $\lambda = n_1 - n$. Thus

$$\delta_j = \frac{n_{+j}}{n - n_1 + n_1 \eta(1, \mathbf{x}_j, g_j; \boldsymbol{\theta})/\mu}, \tag{A.12}$$

where $\mu = \sum_{j=1}^{J} \eta(1, \mathbf{x}_j, g_j; \boldsymbol{\theta})\delta_j$. Plugging (A.12) into $l_n(\boldsymbol{\theta}, \{\delta_j\})$, we see that the objective function to be maximized is, up to a constant C_n, equal to

$$l_n^*(\boldsymbol{\theta}, \mu) = \sum_{j=1}^{J} n_{1j} \log \eta(1, \mathbf{x}_j, g_j; \boldsymbol{\theta}) - \sum_{j=1}^{J} n_{+j} \log\left\{\frac{n_1}{n}\eta(1, \mathbf{x}_j, g_j; \boldsymbol{\theta}) + \left(1 - \frac{n_1}{n}\right)\mu\right\} + (n - n_1)\log \mu.$$

Thus $\max_{\{\delta_j\}} l_n(\boldsymbol{\theta}, \{\delta_j\}) \le \max_\mu l_n^*(\boldsymbol{\theta}, \mu) + C_n$. If μ maximizes $l_n^*(\boldsymbol{\theta}, \mu)$, then $\partial l_n^*(\boldsymbol{\theta}, \mu)/\partial \mu = 0$, and the δ_j given in (A.12) satisfy $\sum_{j=1}^{J} \delta_j = 1$. Thus $\max_\mu l_n^*(\boldsymbol{\theta}, \mu) + C_n \le \max_{\{\delta_j\}} l_n(\boldsymbol{\theta}, \{\delta_j\})$. Therefore, the profile log-likelihood function for $\boldsymbol{\theta}$ based on $l_n(\boldsymbol{\theta}, \{\delta_j\})$ equals the profile function based on $l_n^*(\boldsymbol{\theta}, \mu)$, up to a constant C_n. We maximize $l_n^*(\boldsymbol{\theta}, \mu)$ via Newton–Raphson to yield $\widehat{\boldsymbol{\theta}}$ and $\widehat{\mu}$, where $\widehat{\boldsymbol{\theta}}$ is the MLE of $\boldsymbol{\theta}$. It can be shown that up to a constant, $l_n^*(\boldsymbol{\theta}, \mu)$ is the log-likelihood based on a random sample of size n from a conditional distribution of Y given $\mathbf{X}$ and G. Hence the covariance matrix of $(\widehat{\boldsymbol{\theta}}, \widehat{\mu})$ can be estimated by the inverse information matrix of $l_n^*(\boldsymbol{\theta}, \mu)$.

A.4.5 Profile Likelihood of $\boldsymbol{\theta}$ Based on (9). Suppose that (3) holds. Write $\boldsymbol{\theta} = (\boldsymbol{\beta}, \{\pi_k\}, \rho)$. Also define

$$\zeta_1(\mathbf{x}, g; \boldsymbol{\theta}) = \sum_{(h_k, h_l) \in \mathcal{S}(g)} e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{x}, h_k, h_l)}\{\rho \pi_k \delta_{kl} + (1 - \rho)\pi_k \pi_l\},$$

$$\zeta_0(g; \boldsymbol{\theta}) = \sum_{(h_k, h_l) \in \mathcal{S}(g)} \{\rho \pi_k \delta_{kl} + (1 - \rho)\pi_k \pi_l\}.$$

By a derivation similar to that of Section A.4.4, profiling (9) over $\{F_g(\cdot)\}$ is equivalent to profiling the following function over $\{\mu_g\}$:

$$\widetilde{l}_n^*(\boldsymbol{\theta}, \{\mu_g\}) = \sum_{i=1}^{n}\{y_i \log \zeta_1(\mathbf{X}_i, G_i; \boldsymbol{\theta}) + (1 - y_i)\log \zeta_0(G_i; \boldsymbol{\theta})\} - \sum_{i=1}^{n}\sum_{g} I(G_i = g)\log\left\{\zeta_1(\mathbf{X}_i, G_i; \boldsymbol{\theta}) + n_1^{-1}\widetilde{n}_g \sum_{\widetilde{g}} \mu_{\widetilde{g}} - \mu_g\right\} + \sum_{i=1}^{n}(1 - y_i)\log\left\{\sum_g \mu_g\right\},$$

where $\widetilde{n}_g$ is the number of times $G = g$ in the sample. The covariance matrix of $\widehat{\boldsymbol{\theta}}$ can be estimated by the sandwich estimator or the profile likelihood method.

If $\mathbf{X}$ is independent of G, then we obtain the MLE $\widehat{\boldsymbol{\theta}}$ by maximizing the following function:

$$\widetilde{l}_n^*(\boldsymbol{\theta}, \mu) = \sum_{i=1}^{n} y_i \log \zeta_1(\mathbf{X}_i, G_i; \boldsymbol{\theta}) + \sum_{i=1}^{n}(1 - y_i)\log \zeta_0(G_i; \boldsymbol{\theta}) + \sum_{i=1}^{n}(1 - y_i)\log \mu - \sum_{i=1}^{n}\log\left\{(1 - r)\mu + r\sum_g \zeta_1(\mathbf{X}_i, g; \boldsymbol{\theta})\right\},$$

where $r = n_1/n$. Let $H = BQ_1 + (1 - B)Q_2$, where B is a Bernoulli variable, Q_1 takes values in $\{(h_k, h_k); k = 1, \ldots, K\}$, and Q_2 takes values in $\{(h_k, h_l); k, l = 1, \ldots, K\}$. Suppose that Y is a binary variable and that the conditional distribution of (B, Q_1, Q_2, Y) given $\mathbf{X}$ is characterized by

$$P(B, Q_1, Q_2, Y|\mathbf{X}) = \frac{\exp\{\boldsymbol{\vartheta}^T \mathcal{W}(B, Q_1, Q_2, Y, \mathbf{X})\}}{\sum_{B, Q_1, Q_2, Y} \exp\{\boldsymbol{\vartheta}^T \mathcal{W}(B, Q_1, Q_2, Y, \mathbf{X})\}},$$

where $\boldsymbol{\vartheta} = (-\log \mu + \log r/(1 - r), \boldsymbol{\beta}^T, \log \pi_1 - \log \rho/(1 - \rho), \ldots, \log \pi_K - \log \rho/(1 - \rho))^T$ and $\mathcal{W}(B, Q_1, Q_2, Y, \mathbf{X}) = (Y, Y\mathcal{Z}^T(\mathbf{X}, H), BI(Q_1 = (h_1, h_1)) + (1 - B)\sum_l\{I(Q_2 = (h_1, h_l)) + I(Q_2 = (h_l, h_1))\}, \ldots, BI(Q_1 = (h_K, h_K)) + (1 - B)\sum_l\{I(Q_2 = (h_K, h_l)) + I(Q_2 = (h_l, h_K))\}^T$. We can show that $\widetilde{l}_n^*(\boldsymbol{\theta}, \mu)$ is equivalent to the log-likelihood

$$\widetilde{l}_n^*(\boldsymbol{\vartheta}) = \sum_{i=1}^{n} \log\left[\sum_{BQ_1 + (1-B)Q_2 \in \mathcal{S}(G_i)} \frac{e^{\boldsymbol{\vartheta}^T \mathcal{W}(B, Q_1, Q_2, Y_i, \mathbf{X}_i)}}{\sum_{b, q_1, q_2, y} e^{\boldsymbol{\vartheta}^T \mathcal{W}(b, q_1, q_2, y, \mathbf{X}_i)}}\right].$$

We maximize $\widetilde{l}_n^*(\boldsymbol{\vartheta})$ through the EM algorithm, in which (B, Q_1, Q_2) is treated as missing. The estimation of the covariance matrix of $\widehat{\boldsymbol{\theta}}$ is based on the information matrix of $\widetilde{l}_n^*(\boldsymbol{\vartheta})$.

The complete-data score function is

$$\sum_{i=1}^{n}\left[\mathcal{W}(B_i, Q_{1i}, Q_{2i}, Y_i, \mathbf{X}_i) - \frac{\sum_{b, q_1, q_2, y} \mathcal{W}(b, q_1, q_2, y, \mathbf{X}_i)\exp\{\boldsymbol{\vartheta}^T \mathcal{W}(b, q_1, q_2, y, \mathbf{X}_i)\}}{\sum_{b, q_1, q_2, y} \exp\{\boldsymbol{\vartheta}^T \mathcal{W}(b, q_1, q_2, y, \mathbf{X}_i)\}}\right].$$

Thus in the E-step we calculate the conditional expectation of $\mathcal{W}(B_i, Q_{1i}, Q_{2i}, Y_i, \mathbf{X}_i)$ given $(Y_i, \mathbf{X}_i, G_i)$ and the current parameter estimates,

$$E[\mathcal{W}(B_i, Q_{1i}, Q_{2i}, Y_i, \mathbf{X}_i)|Y_i, \mathbf{X}_i, G_i] = \frac{\sum_{b, q_1, q_2} I(bq_1 + (1-b)q_2 \in \mathcal{S}(G_i))e^{\boldsymbol{\vartheta}^T \mathcal{W}(b, q_1, q_2, Y_i, \mathbf{X}_i)}\mathcal{W}(b, q_1, q_2, Y_i, \mathbf{X}_i)}{\sum_{b, q_1, q_2} I(bq_1 + (1-b)q_2 \in \mathcal{S}(G_i))e^{\boldsymbol{\vartheta}^T \mathcal{W}(b, q_1, q_2, Y_i, \mathbf{X}_i)}}.$$

In the M-step we use the one-step Newton–Raphson iteration to update the parameter estimates,

$$\begin{aligned}\boldsymbol{\vartheta}^{(k+1)} &= \boldsymbol{\vartheta}^{(k)} - \boldsymbol{\Sigma}^{-1} \times \sum_{i=1}^{n}\Bigg[E[\mathcal{W}(B, Q_1, Q_2, Y_i, \mathbf{X}_i)|Y_i, \mathbf{X}_i, G_i] \\ &\quad - \frac{\sum_{b,q_1,q_2,y} \mathcal{W}(b, q_1, q_2, y, \mathbf{X}_i)\exp\{\boldsymbol{\vartheta}^T\mathcal{W}(b, q_1, q_2, y, \mathbf{X}_i)\}}{\sum_{b,q_1,q_2,y}\exp\{\boldsymbol{\vartheta}^T\mathcal{W}(b, q_1, q_2, y, \mathbf{X}_i)\}}\Bigg],\end{aligned}$$

where

$$\begin{aligned}\boldsymbol{\Sigma} &= -\Bigg[\sum_{i=1}^{n}\frac{\sum_{b,q_1,q_2,y}\mathcal{W}^{\otimes 2}(b, q_1, q_2, y, \mathbf{X}_i)e^{\boldsymbol{\vartheta}^T\mathcal{W}(b,q_1,q_2,y,\mathbf{X}_i)}}{\sum_{b,q_1,q_2,y}e^{\boldsymbol{\vartheta}^T\mathcal{W}(b,q_1,q_2,y,\mathbf{X}_i)}}\Bigg] \\ &\quad + \sum_{i=1}^{n}\Bigg[\frac{\{\sum_{b,q_1,q_2,y}\mathcal{W}(b, q_1, q_2, y, \mathbf{X}_i)e^{\boldsymbol{\vartheta}^T\mathcal{W}(b,q_1,q_2,y,\mathbf{X}_i)}\}^{\otimes 2}}{\{\sum_{b,q_1,q_2,y}e^{\boldsymbol{\vartheta}^T\mathcal{W}(b,q_1,q_2,y,\mathbf{X}_i)}\}^2}\Bigg]\end{aligned}$$

and $\mathbf{a}^{\otimes 2} = \mathbf{a}\mathbf{a}^T$.

A.4.6 Proof of Theorem 2. Write $F_{\mathbf{x},g}(\mathbf{x}, g) = F_g^\dagger(\mathbf{x})q_g$ and $\widehat{F}_{\mathbf{x},g}(\mathbf{x}, g) = \widehat{F}_g^\dagger(\mathbf{x})\widehat{q}_g$. Because $\widehat{\boldsymbol{\theta}}$ is bounded and $\widehat{F}_{\mathbf{x},g}$ is a probability distribution, we can choose a subsequence such that $\widehat{\boldsymbol{\theta}} \to \boldsymbol{\theta}^*$ and $\widehat{F}_{\mathbf{x},g}(\mathbf{x}, g) \to F^*_{\mathbf{x},g}(\mathbf{x}, g) \equiv F^*_g(\mathbf{x})q^*_g$, where $q^*_g > 0$ for any g.

Because $\widehat{F}_g^\dagger$ maximizes the likelihood, there exists some Lagrange multiplier $\widehat{\lambda}_g$ such that

$$\frac{I(G_i = g)}{\widehat{F}_g^\dagger\{\mathbf{X}_i\}} - \frac{n_1\eta(1, \mathbf{X}_i, g; \widehat{\boldsymbol{\theta}})\widehat{q}_g}{\int_{\mathbf{x},\widetilde{g}}\eta(1, \mathbf{x}, \widetilde{g}; \widehat{\boldsymbol{\theta}})\,d\widehat{F}_{\mathbf{x},g}(\mathbf{x}, \widetilde{g})} - n\widehat{\lambda}_g = 0,$$

where $\widehat{F}_g^\dagger\{\mathbf{X}_i\}$ denotes the point mass of $\widehat{F}_g^\dagger$ at $\mathbf{X}_i$ and the integral is interpreted as integration over $\mathbf{x}$ and summation over g. Because $\sum_{i=1}^n \widehat{F}_g^\dagger\{\mathbf{X}_i\} = 1$, $\widehat{\lambda}_g$ satisfies the equation

$$n^{-1}\sum_{i=1}^{n}\frac{I(G_i = g)}{\widehat{\lambda}_g + n_1\eta(1, \mathbf{X}_i, g; \widehat{\boldsymbol{\theta}})\widehat{q}_g\{n\int_{\mathbf{x},\widetilde{g}}\eta(1, \mathbf{x}, \widetilde{g}; \widehat{\boldsymbol{\theta}})\,d\widehat{F}_{\mathbf{x},g}(\mathbf{x}, \widetilde{g})\}^{-1}} = 1 \quad \text{(A.13)}$$

and

$$\min_{1\le i\le n}\left\{\widehat{\lambda}_g + \frac{n_1\eta(1, \mathbf{X}_i, g; \widehat{\boldsymbol{\theta}})\widehat{q}_g}{n\int_{\mathbf{x},\widetilde{g}}\eta(1, \mathbf{x}, \widetilde{g}; \widehat{\boldsymbol{\theta}})\,d\widehat{F}_{\mathbf{x},g}(\mathbf{x}, \widetilde{g})}\right\} > 0.$$

Clearly, $\widehat{\lambda}_g$ must be bounded asymptotically. Thus, by choosing a subsequence, we assume that $\widehat{\lambda}_g \to \lambda^*_g$.

By (A.13) and the Lipschitz continuity of $\eta(1, \mathbf{x}, g; \boldsymbol{\theta}^*)$ in the continuous components of $\mathbf{x}$, we can show that there exists a positive constant δ such that

$$\min_{g,\mathbf{x}}\left\{\left|\lambda^*_g + \frac{\varrho\eta(1, \mathbf{x}, g; \boldsymbol{\theta}^*)q^*_g}{\int_{\mathbf{x},\widetilde{g}}\eta(1, \mathbf{x}, \widetilde{g}; \boldsymbol{\theta}^*)\,dF^*_{\mathbf{x},g}(\mathbf{x}, \widetilde{g})}\right|\right\} > \delta.$$

Consequently, when n is sufficiently large,

$$\begin{aligned}\widehat{F}_g^\dagger(\mathbf{x}) &= n^{-1}\sum_{i=1}^{n}I(G_i = g, \mathbf{X}_i \le \mathbf{x}) \\ &\quad \times \Bigg(\max\Bigg[\Bigg|\widehat{\lambda}_g + \eta(1, \mathbf{X}_i, g; \widehat{\boldsymbol{\theta}})\widehat{q}_g n_1 \\ &\quad \times \left\{n\int_{\mathbf{x},\widetilde{g}}\eta(1, \mathbf{x}, \widetilde{g}; \widehat{\boldsymbol{\theta}})\,d\widehat{F}_{\mathbf{x},g}(\mathbf{x}, \widetilde{g})\right\}^{-1}\Bigg|, \delta\Bigg]\Bigg)^{-1}.\end{aligned}$$

We define an empirical function $\widetilde{F}_g^\dagger$ whose jump size at $\mathbf{X}_i$ is proportional to

$$\begin{aligned}n^{-1}I(G_i = g)\Bigg(&P(G = g, Y = 0) + \eta(1, \mathbf{X}_i, g; \boldsymbol{\theta}_0)q_g\varrho \\ &\times \left\{\int_{\mathbf{x},\widetilde{g}}\eta(1, \mathbf{x}, \widetilde{g}; \boldsymbol{\theta}_0)\,dF_{\mathbf{x},g}(\mathbf{x}, \widetilde{g})\right\}^{-1}\Bigg)^{-1}.\end{aligned}$$

Then it can be verified that $\widetilde{F}_g^\dagger$ converges uniformly to $F_g^\dagger$. In addition, $\widehat{F}_g^\dagger$ is absolutely continuous with respect to $\widetilde{F}_g^\dagger$, and the Radon–Nikodym derivative $d\widehat{F}_g^\dagger(\mathbf{x})/d\widetilde{F}_g^\dagger(\mathbf{x})$ is bounded and converges uniformly to $dF^*_g(\mathbf{x})/dF^\dagger_g(\mathbf{x})$. Let $\widetilde{F}_{\mathbf{x},g}(\mathbf{x}, g) = \widetilde{F}_g^\dagger(\mathbf{x})q_g$, and let $l_n(\boldsymbol{\theta}, \{F_g^\dagger\}, \{q_g\})$ be the log-likelihood based on (8). By the definition of the MLE, $n^{-1}l_n(\widehat{\boldsymbol{\theta}}, \{\widehat{F}_g^\dagger\}, \{\widehat{q}_g\}) - n^{-1}l_n(\boldsymbol{\theta}_0, \{\widetilde{F}_g^\dagger\}, \{q_g\}) \ge 0$. The limit of this difference is the negative Kullback–Leibler information of the distribution for $(\boldsymbol{\theta}^*, \{F^*_g\}, \{q^*_g\})$ with respect to $(\boldsymbol{\theta}_0, \{F_g^\dagger\}, \{q_g\})$ under $P(Y = 1) = \varrho$. The identifiability conditions then yield $\boldsymbol{\theta}^* = \boldsymbol{\theta}_0$, $F^*_g = F_g^\dagger$ and $q^*_g = q_g$. Thus the consistency of $\widehat{\boldsymbol{\theta}}$ is established. Because $F_{\mathbf{x},g}$ is continuous, $\sup_{\mathbf{x},g}|\widehat{F}_{\mathbf{x},g}(\mathbf{x}, g) - F_{\mathbf{x},g}(\mathbf{x}, g)| \to 0$ almost surely.

The derivation of the asymptotic distribution is similar to the proof of theorem 1.2 of Murphy and van der Vaart (2001). We first obtain a score function by differentiating $l_n(\boldsymbol{\theta}, \{F_g^\dagger\}, \{q_g\})$ with respect to $\widehat{\boldsymbol{\theta}}$ along the direction $\mathbf{v}$ and with respect to $\widehat{F}_{\mathbf{x},g}$ along the path $\widehat{F}_\epsilon = \widehat{F}_{\mathbf{x},g} + \epsilon\int\psi(\mathbf{x}, g)\,d\widehat{F}_{\mathbf{x},g}$, where $\mathbf{v}$ has a unit norm and $\psi(\cdot, g)$ is any function whose total variation is bounded by 1. The linearization of the score function around the true parameter value yields

$$\begin{aligned}&n^{1/2}\Bigg\{(\mathbf{v}^T\boldsymbol{\Omega}_{11} + \boldsymbol{\Omega}_{21}[\psi]^T)(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0) \\ &\qquad + \int(\mathbf{v}^T\boldsymbol{\Omega}_{12} + \Omega_{22}[\psi])\,d(\widehat{F}_{\mathbf{x},g} - F_{\mathbf{x},g})\Bigg\} \\ &\quad = n^{-1/2}\sum_{i=1}^{n}y_i\Bigg\{\mathbf{v}^T l_{\boldsymbol{\theta}}(1, \mathbf{X}_i, G_i; \boldsymbol{\theta}_0, F_{\mathbf{x},g}) \\ &\qquad\qquad + l_F(1, \mathbf{X}_i, G_i; \boldsymbol{\theta}_0, F_{\mathbf{x},g})\Bigg[\int\psi\,dF_{\mathbf{x},g}\Bigg]\Bigg\} \\ &\qquad + n^{-1/2}\sum_{i=1}^{n}(1 - y_i)\Bigg\{\mathbf{v}^T l_{\boldsymbol{\theta}}(0, \mathbf{X}_i, G_i; \boldsymbol{\theta}_0, F_{\mathbf{x},g}) \\ &\qquad\qquad + l_F(0, \mathbf{X}_i, G_i; \boldsymbol{\theta}_0, F_{\mathbf{x},g})\Bigg[\int\psi\,dF_{\mathbf{x},g}\Bigg]\Bigg\} \\ &\qquad + o_p(1),\end{aligned}$$

where $\boldsymbol{\Omega}_{11}$ is a constant matrix, $\boldsymbol{\Omega}_{12}$ is a vector function of $\mathbf{x}$, $\boldsymbol{\Omega}_{21}[\psi]$ and $\Omega_{22}[\psi]$ are linear operators of ψ, and $l_{\boldsymbol{\theta}}$ and l_F are the scores with respect to $\boldsymbol{\theta}$ and $F_{\mathbf{x},g}$. The right side of the foregoing equation converges weakly to a Gaussian process, which depends on $(y_1, y_2, \dots)$ only through ϱ. We can show that the operator $\mathcal{B}[\mathbf{v}, \psi] \equiv \{\mathbf{v}^T\boldsymbol{\Omega}_{11} + \boldsymbol{\Omega}_{21}[\psi]^T, \mathbf{v}^T\boldsymbol{\Omega}_{12} + \Omega_{22}[\psi]\}^T$ is invertible along the lines of Murphy and van der Vaart (2001). It then follows from theorem 3.3.1 of van der Vaart and Wellner (1996) that $n^{1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0, \widehat{F}_{\mathbf{x},g} - F_{\mathbf{x},g})$ converges weakly to a Gaussian process.

Because the asymptotic distribution depends on $(y_1, y_2, \dots)$ only via ϱ, we assume that $(y_1, y_2, \dots)$ are independent realizations from a Bernoulli distribution with mean ϱ. By choosing some ψ such that $\mathcal{B}[\mathbf{v}, \psi] = (\mathbf{v}^T, 0)^T$ for all $\mathbf{v}$, we see that $\widehat{\boldsymbol{\theta}}$ is an asymptotically linear estimator for $\boldsymbol{\theta}_0$ with the influence function in the score space. It follows from proposition 3.3.1 of Bickel, Klaassen, Ritov, and Wellner (1993) that the limiting covariance matrix of $n^{1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)$ attains the semiparametric efficiency bound.

A.4.7 Proof of Theorem 3. We call the probability distribution induced by (9) the pseudoprobability law, denoted by $\widetilde{P}_n$. Let $f(y, \mathbf{x}, g; \boldsymbol{\theta}, \{F_g\}, a_n)$ be the density function under the true probability law P_n. Because $a_n = o(n^{-1/2})$,

$$\frac{dP_n}{d\widetilde{P}_n} = \exp\left\{ a_n \sum_{i=1}^{n} \frac{\partial \log f(y_i, \mathbf{X}_i, G_i; \boldsymbol{\theta}, \{F_g\}, a)}{\partial a}\bigg|_{a=0} + o(1) \right\} \to^{\widetilde{P}_n} 1.$$

Thus any weak convergence under $\widetilde{P}_n$ also holds for P_n. In addition, by the arguments in the proof of Theorem 2, we can easily verify the results of Theorem 3 when the data are generated from $\widetilde{P}_n$. Thus Theorem 3 holds when the data are generated from P_n.

A.5 Cohort Studies

A.5.1 Identifiability. We show that if two sets of parameters $(\boldsymbol{\theta}, \Lambda)$ and $(\widetilde{\boldsymbol{\theta}}, \widetilde{\Lambda})$ yield the same joint distribution, then $\boldsymbol{\theta} = \widetilde{\boldsymbol{\theta}}$ and $\Lambda = \widetilde{\Lambda}$. First, it follows from Lemma 1 that $\boldsymbol{\gamma} = \widetilde{\boldsymbol{\gamma}}$. Suppose that

$$\begin{aligned}
&\sum_{H\in\mathcal{S}(G)} \{\widetilde{\Lambda}(\widetilde{Y}) e^{\widetilde{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X},H)} \dot{Q}(\widetilde{\Lambda}(\widetilde{Y}) e^{\widetilde{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X},H)})\}^{\Delta} \\
&\qquad \times \{1 - Q(\widetilde{\Lambda}(\widetilde{Y}) e^{\widetilde{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X},H)})\}^{1-\Delta} P_{\boldsymbol{\gamma}}(H) \\
&= \sum_{H\in\mathcal{S}(G)} \{\dot{\Lambda}(\widetilde{Y}) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X},H)} \dot{Q}(\Lambda(\widetilde{Y}) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X},H)})\}^{\Delta} \\
&\qquad \times \{1 - Q(\Lambda(\widetilde{Y}) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X},H)})\}^{1-\Delta} P_{\boldsymbol{\gamma}}(H).
\end{aligned}$$

By choosing $\Delta = 1$ and integrating Y from 0 to τ on both sides, we obtain

$$\begin{aligned}
&\sum_{H\in\mathcal{S}(G)} Q(\widetilde{\Lambda}(\tau) e^{\widetilde{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X},H)}) P_{\boldsymbol{\gamma}}(H) \\
&\qquad = \sum_{H\in\mathcal{S}(G)} Q(\Lambda(\tau) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X},H)}) P_{\boldsymbol{\gamma}}(H).
\end{aligned}$$

Because $Q(\cdot)$ is strictly increasing, the foregoing equation implies that $\widetilde{\Lambda}(\widetilde{Y}) e^{\widetilde{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X},H)} = \Lambda(\widetilde{Y}) e^{\boldsymbol{\beta}^T \mathcal{Z}(\mathbf{X},H)}$ for $H = (h, h)$ and $H = (h, \widetilde{h})$. It then follows from Condition 8 that $\widetilde{\boldsymbol{\beta}} = \boldsymbol{\beta}$ and $\widetilde{\Lambda} = \Lambda$.

A.5.2 Proof of Theorem 4. Our problem is the same as that of Zeng et al. (2005), except replacing the integration over random effects in that article by the sum over $H \in \mathcal{S}(G)$. The asymptotic properties stated in the theorem follow from the identifiability shown in Section A.5.1 and the proofs of Zeng et al. (2005), provided that we can verify the following result: If there exist a vector $\boldsymbol{\mu} = (\boldsymbol{\mu}_{\boldsymbol{\beta}}^T, \boldsymbol{\mu}_{\boldsymbol{\gamma}}^T)^T$ and a function $\psi(t)$ such that

$$\boldsymbol{\mu}^T l_{\boldsymbol{\theta}}(\boldsymbol{\theta}_0, \Lambda_0) + l_{\Lambda}(\boldsymbol{\theta}_0, \Lambda_0)\left[\int \psi \, d\Lambda_0\right] = 0, \tag{A.14}$$

where $l_{\boldsymbol{\theta}}$ is the score function for $\boldsymbol{\theta}$ and $l_{\Lambda}[\int \psi \, d\Lambda_0]$ is the score function for Λ along the submodel $\Lambda_0 + \epsilon \int \psi \, d\Lambda_0$, then $\boldsymbol{\mu} = \mathbf{0}$ and $\psi = 0$.

To prove the desired result, we write out (A.14). We then let $\Delta = 1$ and integrate Y from 0 to τ to obtain

$$\begin{aligned}
&\sum_{H\in\mathcal{S}(G)} \{Q(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)})\} P_{\boldsymbol{\gamma}}(H) \\
&\quad \times \left\{ \frac{\dot{Q}(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)}) \Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)} \boldsymbol{\mu}_{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X}, H)}{Q(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)})} \right. \\
&\qquad + \frac{\dot{Q}(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)}) \int_0^{\tau} \psi(t) \, d\Lambda_0(t) \, e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)}}{Q(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)})} \\
&\qquad \left. + \boldsymbol{\mu}_{\boldsymbol{\gamma}}^T \nabla_{\boldsymbol{\gamma}} \log P_{\boldsymbol{\gamma}}(H) \right\} = 0.
\end{aligned} \tag{A.15}$$

In contrast, by letting $\Delta = 0$ and $Y = \tau$ in (A.14), we have

$$\begin{aligned}
&\sum_{H\in\mathcal{S}(G)} \{1 - Q(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)})\} P_{\boldsymbol{\gamma}}(H) \\
&\quad \times \left\{ - \frac{\dot{Q}(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)}) \Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)} \boldsymbol{\mu}_{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X}, H)}{1 - Q(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)})} \right. \\
&\qquad - \frac{\dot{Q}(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)}) \int_0^{\tau} \psi(t) \, d\Lambda_0(t) \, e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)}}{1 - Q(\Lambda_0(\tau) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)})} \\
&\qquad \left. + \boldsymbol{\mu}_{\boldsymbol{\gamma}}^T \nabla_{\boldsymbol{\gamma}} \log P_{\boldsymbol{\gamma}}(H) \right\} = 0.
\end{aligned} \tag{A.16}$$

The summation of (A.15) and (A.16) entails $\boldsymbol{\mu}_{\boldsymbol{\gamma}}^T \nabla_{\boldsymbol{\gamma}} \log P_{\boldsymbol{\gamma}}(H) = 0$. From the proof of Lemma 1, $\boldsymbol{\mu}_{\boldsymbol{\gamma}} = \mathbf{0}$. We choose $G = 2h$ or $h + \widetilde{h}$ and let $\Delta = 1$ and $Y = 0$ in (A.14) to obtain $\boldsymbol{\mu}_{\boldsymbol{\beta}}^T \mathcal{Z}(\mathbf{X}, H) + \psi(0) = 0$ for $H = (h, h)$ and $(h, \widetilde{h})$. Thus, $\boldsymbol{\mu}_{\boldsymbol{\beta}} = \mathbf{0}$ and $\psi(0) = 0$ under Condition 8. Finally, (A.14) with $\Delta = 1$ implies that

$$\psi(\widetilde{Y}) + \frac{\ddot{Q}(\Lambda_0(\widetilde{Y}) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)}) \int_0^{\widetilde{Y}} \psi(t) \, d\Lambda_0(t) \, e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)}}{\dot{Q}(\Lambda_0(\widetilde{Y}) e^{\boldsymbol{\beta}_0^T \mathcal{Z}(\mathbf{X},H)})} = 0$$

for $H = (h, h)$. Therefore, $\psi = 0$.

[Received September 2004. Revised February 2005.]

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Comment

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The detailed and careful article by Lin and Zeng deals with the estimation of haplotype effects. It is perhaps useful to give a little more genetical background on the problem at hand. Through epidemiological studies (where, e.g., one compares risk of siblings or twins of affected individuals with population prevalence) we can identify that some diseases have a clear genetic component. That is, there are modifications in the DNA sequence that predispose carriers to develop the disease. These modifications have varied nature; there may be mutations, insertions, or deletions in the gene sequence that lead to the synthesis of a different protein, or these variations may take place in noncoding portions of DNA, affecting slicing patterns or expression levels. Understanding the nature of these mutations and their functional effects is of considerable importance; it leads to

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Journal of the American Statistical Association
March 2006, Vol. 101, No. 473, Theory and Methods
DOI 10.1198/016214505000000817