The Impact of Prior Distributions for Uncontrolled Confounding and Response Bias: A Case Study of the Relation of Wire Codes and Magnetic Fields to Childhood Leukemia

Sander GREENLAND

This article examines the potential for misleading inferences from conventional analyses and sensitivity analyses of observational data, and describes some proposed solutions based on specifying prior distributions for uncontrolled sources of bias. The issues are illustrated in a sensitivity analysis of confounding in a study of residential wire code and childhood leukemia and in a pooled analysis of 12 studies of magnetic-field measurements and childhood leukemia. Both analyses have been interpreted as evidence in favor of a causal effect of magnetic fields on leukemia risk. This interpretation is contrasted with results from analyses based on prior distributions for the unidentified bias parameters used in the original sensitivity-analysis model. These analyses indicate that accounting for uncontrolled confounding and response bias under a reasonable prior can substantially alter inferences about the existence of a magnetic-field effect. More generally, analyses with informative priors for unidentified bias parameters can help avoid misinterpretation of conventional results and ordinary sensitivity analyses.

KEY WORDS: Bayesian statistics; Confounding; Epidemiologic methods; Leukemia; Magnetic fields; Risk assessment; Sensitivity analysis.

1. INTRODUCTION

Sensitivity analysis of bias was introduced to observational epidemiology more than 40 years ago (Cornfield et al. 1959), but since then has appeared only sporadically in analyses and textbooks in the health sciences. One reason for this may be that this analysis requires expansion of models to include bias parameters that are not identified from the analysis data (if these parameters were identified, they could simply be incorporated into conventional estimation procedures); it then "corrects" results using hypothetical values for the bias parameters. Those values must be specified from background information, which may be fragmentary or controversial. Worse, scientific interpretations of the results can themselves be very sensitive to the range of values examined and to the bias parameterization, and can be misled by too-narrow or too-broad choices for these inputs (Poole and Greenland 1997; Greenland 1998).

These problems are familiar in Bayesian analysis as the problems of prior specification and of sensitivity of posterior inferences to that specification. A Bayesian perspective, however, reveals a more subtle problem: Interpretations of sensitivity analyses tend to ignore or dismiss parameter values judged "implausible" or "unlikely"; consequently, they may seriously misrepresent coherent posterior probabilities, which integrate such values into the analysis using the appropriate probability weighting. Following probabilistic risk-analysis methodology (e.g., Morgan and Henrion 1990, chap. 8; Crouch, Lester, Lash, Armstrong, and Green 1997), it has been suggested that this problem can be addressed with analyses based on informative priors for bias parameters (Greenland 1996). For example, one may repeatedly "correct" conventional statistics using bias parameters drawn from their priors, then summarize over the resulting distribution of corrected results (e.g., Lash and Silliman 2000; Lash and Fink 2003; Phillips and Maldonado 2003). If the data provide negligible information on the bias parameters and if sampling error is properly incorporated into the final distribution, such Monte Carlo sensitivity analyses (MCSAs) can approximate Bayesian results (Robins, Rotnitzky, and Scharfstein 1999; Greenland 2001a).

The foregoing points are illustrated with a recent sensitivity analysis of possible confounding in the association of very-high-current configuration (VHCC) residential wire codes with childhood leukemia (Langholz 2001). The analysis problem is recast as one of Bayesian accounting for an unknown omitted covariate (Leamer 1974, sec. 2), and the results are contrasted with previous interpretations. The priors used for this analysis are then extended to an analysis of pooled data from 12 case-control studies of magnetic fields and childhood leukemia.

2. AN ANALYSIS OF UNCONTROLLED CONFOUNDING IN A WIRE-CODE STUDY

The Wertheimer–Leeper wire code, a four-category summary of the configuration of electrical service connection to a residence, has been used as a surrogate for magnetic-field exposure. Only the highest category, VHCC, has shown even a modestly reproducible relation to both field strength and childhood leukemia, and hence simplification to "VHCC versus other" is often used (Langholz 2001). Study results vary well beyond chance expectation (Greenland, Sheppard, Kaune, Poole, and Kelsh 2000, table 8), which renders controversial any summary or pooling across studies. Hence the present example uses data from one study (London et al. 1991) with results near average and with relatively large numbers of

Sander Greenland is Professor, Department of Epidemiology, UCLA School of Public Health and Department of Statistics, UCLA College of Letters and Science, 22333 Swenson Drive, Topanga, CA 90290 (E-mail: *lesdomes@ucla.edu*). The author thanks Babette Brumback, Thomas Richardson, James Robins, Jon Wakefield, the associate editor, and the referees for helpful comments. This research was supported by the Electric Power Research Institute and by grant 1R29-ES07986 from the National Institute of Environmental Health Sciences.

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Table 1. Marginal Case-Control Data From a Study of VHCC Wire Code and Childhood Leukemia (London et al. 1991)

	VHCC code ($X = 1$)	*Other codes* ($X = 0$)
Leukemia cases	42	169
Controls	24	181

NOTE: Marginal odds ratio, $\widehat{\text{OR}}_{\text{M}} = 1.87$; 95% confidence limits, 1.09, 2.23, lower p value = .011.

VHCC-exposed children (Table 1). The odds ratio from these data is 1.87, with a 95% confidence limits of 1.09 and 3.23; the lower one-sided p value is .011. These results change little after adjustment for measured covariates.

2.1 A Model for Uncontrolled Confounding

Let X and Y be the indicators for VHCC wire code and childhood leukemia. Following Breslow and Day (1980, sec. 3.4), Yanagawa (1984), Rothman and Greenland (1998, chap. 19), and Langholz (2001), suppose that Table 1 is the XY margin of an unobserved $2 \times 2 \times 2$ table of UXY counts where U is an unmeasured binary antecedent of X and Y and hence is a potential confounder of the XY association. This latent U may represent a specific unmeasured factor, such as a genotype, or may represent a dichotomization of a summary confounder score (such as the propensity score). Taking U as binary is not essential (see Sec. 3) but it greatly simplifies analyses by limiting the number of parameters that must be specified. Because a binary U can induce any degree of confounding [see (2)] it does not limit the degree of bias that can be modeled or simulated.

For convenience, most authors have assumed that the XY odds ratios are homogeneous across strata of U and that the disease ($Y = 1$) is uniformly rare across levels of U and X (so that one can ignore distinctions among odds ratios, risk ratios, and hazard rate ratios). Because U is by definition unmeasured (and at best speculative) neither assumption is testable with the analysis data, but each limits the number of unidentified parameters that must be specified and each has some justification; moderate violations of homogeneity have little impact on the results (see Remark 2 in Sec. 2.3) and leukemia is extremely rare in all known settings.

Let E_{uxy} be the expected cell count at $U = u$, $X = x$, and $Y = y$. The observed XY counts then have expectations $E_{+xy} \equiv E_{1xy} + E_{0xy}$ and the observed XY odds ratio is an analog estimate, $\widehat{OR}_{\text{M}}$, of the marginal XY odds ratio $OR_{\text{M}} \equiv E_{+11}E_{+00}/E_{+10}E_{+01}$ from the latent table of the E_{uxy}. Under homogeneity a log-linear model for this table is

$$E_{uxy} = \exp(\beta_0 + u\beta_U + x\beta_X + y\beta_Y + ux\beta_{UX} + uy\beta_{UY} + xy\beta_{XY}). \quad (1)$$

The following facts are important:

1. $\text{expit}(\beta_U) = P(U = 1 | X = Y = 0)$, where $\text{expit}(z)$ is the logistic transform, $e^z/(1 + e^z)$.

2. $\exp(\beta_{UX})$ is the odds ratio relating U and X within Y strata, $\exp(\beta_{UY})$ is the odds ratio relating U and Y within X strata, and $\exp(\beta_{XY})$ is the odds ratio relating X and Y within U strata.

3. The marginal XY odds ratio, OR_{M}, will equal the U-conditional odds ratio, $\exp(\beta_{XY})$, if either β_{UX} or β_{UY} is 0 (Whittemore 1978). Because the disease is rare the latter collapsibility condition implies no confounding by U (Greenland, Robins, and Pearl 1999).

4. If there is no confounding within the U strata then $\exp(\beta_{XY})$ is the unconfounded relative effect of VHCC exposure ($X = 1$) on the odds of disease ($Y = 1$); otherwise it is only a partially adjusted odds ratio. In either case, any discrepancy between the expected marginal odds ratio, OR_{M}, and the U-conditional odds ratio, $\exp(\beta_{XY})$, corresponds to confounding of OR_{M} by U; hence (absent further information) statistics on the less confounded parameter $\exp(\beta_{XY})$ rather than on OR_{M} should be used to make inferences about the effect.

5. By definition, there are no internal study data on U; consequently, no parameter in model 1 is identified by the observed (marginal) XY data and external constraints are needed to obtain inferential statistics, such as interval estimates or tail probabilities.

2.2 Sensitivity Analyses Under the Model

Sensitivity analyses attempt to address the identification problem (item 5) by repeating the analysis under numerous sharp identifying constraints, to show how β_U, β_{UX}, and β_{UY} determine the bias in the observed marginal odds ratio $\widehat{OR}_{\text{M}}$ as an estimate of $\exp(\beta_{XY})$. Let $\beta_b \equiv (\beta_U, \beta_{UX}, \beta_{UY})'$. From Yanagawa (1984, eq. 2.2), the relative bias $OR_{\text{M}}/\exp(\beta_{XY})$ is

$$B(\beta_b) \equiv \frac{\text{expit}(\beta_U + \beta_{UX} + \beta_{UY})\text{expit}(\beta_U)}{\text{expit}(\beta_U + \beta_{UX})\text{expit}(\beta_U + \beta_{UY})} \quad (2)$$

(see Flanders and Khoury 1990 for an extension to polytomous U and common diseases). Expression (2) may take on any positive value; hence a binary U can produce any degree of confounding. If $\beta_{XY} = 0$ (no X effect on Y) then the expression equals OR_{M}; thus, by solving $B(\beta_b) = \widehat{OR}_{\text{M}}$ one can see which combinations of the bias parameters β_U, β_{UX}, and β_{UY} would completely explain the observed association as a result of confounding by a binary variable.

If U represents a known but uncontrolled factor, such as a housing descriptor, then one can specify likely values for the bias parameters from external information and use these values in (2) to estimate how much bias was produced by failure to control the factor. If one has information only on the factor prevalence and its relation to exposure (β_U and β_{UX}) then one can use (2) to see how large β_{UY} would have to be for confounding by the factor to completely explain the marginal XY association. Using survey data on the prevalence of various factors and their relation to VHCC (background data on β_U and β_{UX}, for various U), Langholz (2001, table 6) showed that only three of those factors could *alone* completely explain a marginal VHCC odds ratio of 2 without requiring the factor effect $\exp(\beta_{UY})$ to exceed 10; the factor with the smallest required effect, "house built before 1920," still needed to have $\exp(\beta_{UY}) = 6$.

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As Langholz (2001) and his discussants noted, these results do not address all possibilities because they do not examine combinations of factors or take into account unmeasured factors. Nonetheless, the results do make it implausible that confounding alone could account for an association as large as that shown in Table 1. Unfortunately, later discussants went further and interpreted these sensitivity results as evidence in favor of a causal effect of magnetic fields on childhood leukemia (e.g., table 8.2.3, in "An Evaluation of the Possible Risks From Electric and Magnetic Fields From Power Lines, Internal Wiring, Electrical Occupations and Appliances," Draft 3, April 2001, formerly available at www.dhs.ca.gov/ps/deodc/ehib/emf/RiskEvaluation/riskeval.html). Although this interpretation may seem natural, it will be shown to conflict with more refined analyses based on model 1.

After checking whether U alone could plausibly explain the observed $\widehat{OR}_{\mathrm{M}}$ one could allow a role for random error. For example, to check whether confounding and random error together could plausibly explain the observed $\widehat{OR}_{\mathrm{M}}$ one might calculate the values of β_{UY} that would have produced $OR_{\mathrm{M}} = 1.09$ (the lower confidence limit), assuming that β_{UX} is as observed in the survey data and that $\beta_{XY} = 0$. For "house built before 1920," the data yield $\mathrm{expit}(\beta_U) = .144$ and $\exp(\beta_{UX}) = 5.36$ (Langholz 2001, table 6). These are of course only estimates, and a rigorous analysis would propagate the survey error through the calculations; as in the Langholz article that error is omitted here. Putting these values in (2) and equating the result to 1.09 yields $\exp(\beta_{UY}) = 1.28$, a very modest housing effect that seems even more plausible if one views U as an unmeasured-confounder summary rather than as a single factor. Based on this result one might assert that a combination of bias and random error could easily explain the results (which is indeed so), and end the analysis with that. On the other hand, the result is derived by assuming that the random error is positive and substantial (1.96 standard errors) and hence it might be dismissed as just another extreme case.

2.3 Bayesian and MCSA Analyses

The foregoing sensitivity analysis begs a key substantive question: "If the net effect X on Y is not causal, then how likely is it that random error and bias combined to produce the observed margin?" Answering this question requires consideration of every remotely plausible combination of random error and bias that would have produced the observed data if $\beta_{XY} \leq 0$. The number of such combinations is enormous and describing the plausibility of each might seem onerous. Nonetheless, this task is central to Bayesian analysis, in which random-error plausibility corresponds to data probability and parameter plausibility corresponds to prior probability. The likelihood function then restricts attention to combinations of parameters and random errors that produce the observed data.

Because there are no internal study data on U a Bayesian analysis could start with an informative prior for the vector of bias parameters, β_b. With this prior, computation can proceed using a diffuse or even improper prior over the remaining parameters, $\beta_a \equiv (\beta_0, \beta_X, \beta_Y, \beta_{XY})'$. Equation (1) then becomes a mixed model with fixed and random coefficient vectors β_a and β_b, as in "partial-Bayes" or "semi-Bayes" analyses (Bedrick, Christensen, and Johnson 1996; Greenland 2000, 2001b). Under a degenerate prior that assigns $P\{\beta_b\colon B(\beta_b) = 1\} = 1$ and is uniform (improper) for β_a, the marginal estimate and interval in Table 1 are an approximate posterior median and 95% posterior interval for $\exp(\beta_{XY})$, and the lower p value of .011 is the posterior probability that $\beta_{XY} \leq 0$. Such a prior is unreasonable, however, because it asserts that confounding is certainly absent.

A question often raised in regulatory settings (in which the .05 criterion can be found in action guidelines) is whether some reasonable prior yields a lower 95% posterior limit of 1 for $\exp(\beta_{XY})$ (or, equivalently, yields a posterior probability for $\beta_{XY} \leq 0$ of .025). Given such a "borderline" prior, one need only modify it slightly to demonstrate that some reasonable priors produce lower limits below 1 and others produce lower limits above 1, so that the data force no agreement under the criterion. One reasonable prior, back-calculated to fall on the borderline and at the same time conform to the available prior information, is contained in the following specification:

1. The UXY-specific counts are Poisson with means E_{uxy}; hence the observed marginal counts are Poisson with means E_{+xy}. This model reflects the fact that no marginal total was fixed at the observed values; if a Y margin had been fixed, rendering counts multinomial, then this Poisson model would be still yield valid likelihood-based inferences for θ provided that the Y main effect was included in the model (Lindsey 1995, chap. 6).
2. The parameters are a priori independent, because they are functionally independent and because U is unspecified. An analysis that included measured covariates or in which U represented a specific unmeasured covariate might use prior dependencies, as in Section 3.
3. The β_U prior is normal with mean 0 and variance 4, chosen to make .01 and .99 the first and 99th percentiles of the prevalence $\mathrm{expit}(\beta_U)$; the prior prevalence distribution then very roughly approximates a uniform distribution between .0025 and .9975.
4. The β_{UX} and β_{UY} priors are both normal with mean 0 and standard deviation ln(6)/1.645. These induce lognormal priors on $\exp(\beta_{UX})$ and $\exp(\beta_{UY})$ with 5th and 95th percentiles of 1/6 and 6. This specification was suggested by Langholz's findings for single factors, with minor modification to yield a lower 95th posterior limit for $\exp(\beta_{XY})$ of about 1.00.
5. The priors for $\beta_0, \beta_X, \beta_Y$, and β_{XY} are independent normals with mean 0 and variance 400 (extremely diffuse, but proper).

Let $P(\beta_b)$ denote the β_b prior from items 2–4. A Metropolis sampler (10 chains, each of length 500,000 after discarding 100,000 burn-in cycles) was used to simulate the posterior based on the above specification and the data in Table 1. The resulting 50th, 2.5th, and 97.5th percentiles of $\exp(\beta_{XY})$ were 1.89, 1.00, and 3.70. An analogous MCSA procedure generates a distribution of corrected estimates $1.87/B(\beta_b)e^{\varepsilon}$, where $B(\beta_b)$ is obtained by sampling β_b from $P(\beta_b)$ and ε is a normal $(0, v)$ variate included to account for sampling error, with $v = 1/42 + 1/24 + 1/169 + 1/181$ the estimated sampling variance of $\ln(\widehat{OR}_{\mathrm{M}})$. To approximate the Bayesian analysis, one

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should instead draw β_b from its marginal posterior $P(\beta_b|a_+)$, where a_+ is the vector of observed XY counts in Table 1; if β_b is independent of a_+, however, then the MCSA would approximate the Bayesian results (Robins et al. 1999, sec. 11). In the present example, the simulated $P(\beta_b|a_+)$ differed from $P(\beta_b)$ by less than simulation error, reflecting the lack of information on β_b (apart from its prior), and the 50th, 2.5th, and 97.5th percentiles for $\exp(\beta_{XY})$ from 500,000 MCSA draws were 1.88, .99, and 3.59.

Items 3 and 4 yield $P\{B(\beta_b) \geq 1.87\} = .005$, so the prior odds that confounding alone explains the association seen in Table 1 is miniscule, and $P\{B(\beta_b) \geq 1.09\} = .17$, so the prior odds that confounding exceeds the lower confidence limit is only 1:5. Nonetheless, the prior is sufficient to expand the posterior 95% interval to include 1 and more than double the posterior probability that $\beta_{XY} \leq 0$. Furthermore, the prior is reasonable; two covariates in table 6 of Langholz (2001) appear to have $\exp(\beta_{UX}) \geq 5$, so the β_{UX} component of the prior is quite credible. The β_{UY} component is more controversial but is defensible; there have been some intriguing proposals for possible strong confounders, including body currents arising in poorly grounded houses (Kavet and Zaffanella 2002). Furthermore, as has been pointed out (Langholz 2001, app. B), one should not disregard the possibility of strong effects by combinations of weak risk factors, given that many correlates of wire code have been found.

To summarize, the sensitivity analysis made it appear improbable that confounding alone explains the observed $\widehat{OR}_M$, yet analyses based on one reasonable prior shows that this improbability is no reason to dismiss confounding. Relative to the conventional results given in Table 1, which assume that $B(\beta_b) = 1$ when interpreted causally, allowance for uncertainty about the bias parameters in β_b can considerably expand the interval estimate for the target parameter $\exp(\beta_{XY})$ and increase the posterior probability that there is no net causal effect of X on Y ($\beta_{XY} \leq 0$).

Remark 1. As mentioned earlier, the naïve but common Bayesian interpretations of the frequentist results follow from assuming $B(\beta_b) = 1$ (no bias) and a diffuse prior on β_a (including β_{XY}). Neither assumption is correct; no one believes that bias is absent or that β_{XY} is far from 0. These two prior misspecifications have opposing effects on the posterior variance for β_{XY}; assuming $B(\beta_b) = 1$ leads to an understated posterior variance, whereas a diffuse prior for β_{XY} leads to overstatement. The foregoing analyses address only the first problem. Nonetheless, because it exerts a pull toward 0, an informative prior for β_{XY} centered at 0 can increase the posterior probability of $\beta_{XY} \leq 0$ even when it reduces the posterior variance (Greenland 2003).

Remark 2. Addition of a three-way term, $uxy\beta_{UXY}$, to the VHCC model (1) would allow heterogeneity of the XY odds ratios across U strata but would also make the analysis much more difficult. If reversal of effects of X on Y across U is implausible, then $P(|\beta_{XY}| < |\beta_{UXY}|)$ must be set low. This prior constraint would rule out a simple (e.g., bivariate normal) joint prior for β_{XY} and β_{UXY}, thus complicating prior specification and posterior sampling. Including β_{UXY} also complicates inference by requiring consideration of two target parameters (the two U-specific XY odds ratios), or some defensible average of the two. A limited number of joint prior specifications for β_{XY} and β_{UXY} were examined, using as target parameters both stratum-specific and traditional standardized odds ratios which do not assume homogeneity (see Rothman and Greenland 1998, pp. 264–265). As expected, the introduction of another unknown (β_{UXY}, an uncertainty source assumed to be 0 earlier) widened posterior intervals, but to only a minor extent for standardized odds ratios. The latter result is unsurprising in light of the close relation of summary odds ratios that assume homogeneity to those that do not (Greenland and Maldonado 1994). However, these results do not guarantee that uncertainty about heterogeneity can always be safely neglected, especially if (unlike here) effect reversal is a credible possibility.

3. UNCONTROLLED BIAS IN A POOLING PROJECT

Most studies have attempted to directly quantify magnetic-field exposure using either direct measurements or calculations from records or site features. Tables 2 and 3 present summaries from a pooled analysis of 12 case-control studies of quantitative magnetic-field measurements and childhood leukemia (Greenland et al. 2000). There seems to be no consistent association below .3 microteslas (μT), but 11 of the studies show leukemia associated with fields above .3 μT; the exception had no cases above .2 μT. There was no evidence of publication bias. Differences among studies were well within random error (homogeneity $p = .42$) and showed no relation to measurement method, study location, or system type. Results changed little on altering categories, adjusting for age and sex, or using continuous rather than categorical field measurements (Greenland et al. 2000). Virtually identical results were obtained when fields were modeled using splines or with just one indicator for fields above .3 μT. These fields are associated with VHCC code, however, and so share the same list of

Table 2. Summary of Data From 12 Case-Control Studies of Magnetic Fields and Childhood Leukemia Used in Pooled Analysis (Greenland et al. 2000)

		No. of cases		No. of controls	
First author	*Country*	*>.3 μT*	*Total*	*>.3 μT*	*Total*
Coghill (1996)	England	1	56	0	56
Dockerty (1999)	New Zealand	3	87	0	82
Feychting (1993)	Sweden[a]	6	38	22	554
Linet (1997)	United States[b]	42	638	28	620
London (1991)	United States[b]	17	162	10	143
McBride (1999)	Canada[b]	14	297	11	329
Michaelis (1998)	Germany	6	176	6	414
Olsen (1993)	Denmark[a]	3	833	3	1,666
Savitz (1988)	United States[b]	3	36	5	198
Tomenius (1986)	Sweden	3	153	9	698
Tynes (1997)	Norway[a]	0	148	31	2,004
Verkasalo (1993)	Finland[a]	1	32	5	320
Totals		99	2,656	130	7,084

[a] Calculated fields (others are direct measurement).
[b] 120 v, 60-Hz systems (others are 220 v, 50-Hz).

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Table 3. Study-Specific Odds-Ratio Estimates and Study-Adjusted Summary Estimates, With 95% Confidence Intervals From 12 Studies of Magnetic Fields and Childhood Leukemia (From Greenland et al. 2000); Reference Category, ≤ .1 μT

	Magnetic-field category (μT)		
First author	*>.1, ≤.2*	*>.2, ≤.3*	*>.3*
Coghill (1996)	.54 (.17, 1.74)	∞ (no controls)	∞ (no controls)
Dockerty (1999)	.65 (.26, 1.63)	2.83 (.29, 27.9)	∞ (no controls)
Feychting (1993)	.63 (.08, 4.77)	.90 (.12, 7.00)	4.44 (1.67,11.7)
Linet (1997)	1.07 (.82, 1.39)	1.01 (.64, 1.59)	1.51 (.92, 2.49)
London (1991)	.96 (.54, 1.73)	.75 (.22, 2.53)	1.53 (.67, 3.50)
McBride (1999)	.89 (.62, 1.29)	1.27 (.74, 2.20)	1.42 (.63, 3.21)
Michaelis (1998)	1.45 (.78, 2.72)	1.06 (.27, 4.16)	2.48 (.79, 7.81)
Olsen (1993)	.67 (.07, 6.42)	0 (no cases)	2.00 (.40, 9.93)
Savitz (1988)	1.61 (.64, 4.11)	1.29 (.27, 6.26)	3.87 (.87,17.3)
Tomenius (1986)	.57 (.33, .99)	.88 (.33, 2.36)	1.41 (.38, 5.29)
Tynes (1997)	1.06 (.25, 4.53)	0 (no cases)	0 (no cases)
Verkasalo (1993)	1.11 (.14, 9.07)	0 (no cases)	2.00 (.23,17.7)
Summaries			
MH[a], study adjusted	.95 (.80, 1.12)	1.06 (.79, 1.42)	1.69 (1.25, 2.29)
MH[b], study-age-sex adjusted	1.01 (.84, 1.21)	1.06 (.78, 1.44)	1.68 (1.23, 2.31)
Spline[b,c], study-age-sex adjusted	1.00 (.81, 1.22)	1.13 (.92, 1.39)	1.65 (1.15, 2.36)

[a] Mantel–Haenszel, study adjusted; maximum likelihood summaries differed by less than 1% from MH. Based on 2,656 cases and 7,084 controls; 3 df categorical MH summary, $p = .01$.

[b] Study-age-sex adjusted based on 2,484 cases and 6,335 controls with age, sex data (excludes Tomenius); 3 df categorical MH, $p = .01$; 1 df Mantel trend, $p = .04$ from continuous data.

[c] Estimates comparing odds at category means (.14, .24, .58 vs. .02 μT) from a quadratic logistic spline with one knot at .2 μT, plus study, age, and sex terms.

potential confounders as that of Langholz (2001). The summary odds ratio for > .3 μT is slightly less than the marginal VHCC odds ratio in Table 1; hence slightly smaller covariate associations would be needed to explain it completely.

3.1 Log-Linear Models With Bias Parameters

To extend the foregoing development to general cross-classifications, let U, X, and Y be row vectors of possible combinations of unobserved covariates, observed covariates (including study indicators), and outcomes. Taking coefficients as column vectors and UX, UY, XY, and UXY as subvectors (chosen on subject matter grounds) of the tensor products $U \otimes X$, $U \otimes Y$, $X \otimes Y$, and $U \otimes X \otimes Y$, suppose that the population distribution for the latent $U \times X \times Y$ table is

$$P_{uxy} \propto \exp(u\beta_U + x\beta_X + y\beta_Y + ux\beta_{UX} + uy\beta_{UY} + xy\beta_{XY} + uxy\beta_{UXY}) \quad (3)$$

U could include a separate component, U_k, for the maximally confounding dichotomy in study $k, k = 1, \ldots, 12$. An equivalent approach, used here, allows the bias B_k in study k due to ignoring U_k to vary across studies by allowing all of the U parameters in B_k to vary across studies; U can then be treated as a single latent variable that has interactions with observed variables. The model may be expanded to include other latent dimensions, such as the true magnetic-field level T when the observed X contains only a measurement F subject to error or coarsening.

Now suppose that the rates of response (selection) from the source populations of the studies are

$$R_{uxy} \propto \exp(u\gamma_U + x\gamma_X + y\gamma_Y + ux\gamma_{UX} + uy\gamma_{UY} + xy\gamma_{XY} + uxy\gamma_{UXY}). \quad (4)$$

Then the expected data classification is

$$E_{uxy} \propto R_{uxy}P_{uxy} \propto \exp(u\alpha_U + x\alpha_X + y\alpha_Y + ux\alpha_{UX} + uy\alpha_{UY} + xy\alpha_{XY} + uxy\alpha_{UXY}), \quad (5)$$

where for any subscript W, $\alpha_W = \beta_W + \gamma_W$, and γ_W is the response bias in α_W. Note that γ_W is not separable from β_W without information on nonresponse; separation is only needed

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when β_W is a target parameter, so specification of the response model can be limited to target interactions.

To specialize model (5) to the present example, define S to be the row vector of all 12 1,0 study indicators, and $F = 1/2$ for fields $>.3\,\mu$T and $-1/2$ for $\le .3\,\mu$T; thus $X = (S', F')'$. Also, let $Y = 1/2$ for cases, $-1/2$ for controls, and $U = 1/2, -1/2$. Then, using the full set of 12 study indicators (instead of 11), the model used here can be written as

$$E_{ufsy} = \exp(s\alpha_S + us\alpha_{US} + fs\alpha_{FS} + sy\alpha_{SY} + ufs\alpha_{UFS} + usy\alpha_{USY} + fsy\alpha_{FSY}), \quad (6)$$

with response model $\alpha_{FSY} = \beta_{FY} + \gamma_{FSY}$. Model (6) constrains the population FY odds ratio, $\exp(\beta_{FY})$, to be homogeneous across study (S) and across U. Including α_{US}, α_{UFS}, and α_{USY} allows confounding (B_k) to vary across studies, whereas including γ_{FSY} allows response bias to vary across studies. There are 85 parameters for the 96 latent cells. The 36 U parameters (12 each in α_{US}, α_{UFS}, and α_{USY}) are derived solely from the joint prior described later rather than estimated from data, and the target parameter β_{FY} is inseparable from γ_{FSY} without a constraint or prior for γ_{FSY}.

Model (6) can be rewritten as $E_{ufsy} = \exp(z_a\alpha_a + z_b\alpha_b)$, where $z_a = (s, fs, sy, fy)$, $\alpha_a = (\alpha_S', \alpha_{FS}', \alpha_{SY}', \beta_{FY}')'$, $z_b = (us, ufs, usy, fsy)$, and $\alpha_b = (\alpha_{US}', \alpha_{UFS}', \alpha_{USY}', \gamma_{FSY}')'$. A conventional analysis fits the model $E_{+fsy} = \exp(z_a\alpha_a)$ to the FSY margin of the $UFSY$ table; letting OR_{M} be the limit of the estimator from this marginal analysis, the net bias of this marginal estimator is then $B(\alpha_b) \equiv OR_{\mathrm{M}}/\exp(\beta_{FY})$. The conventional maximum likelihood estimate (MLE) and 95% confidence limits for $\exp(\beta_{FY})$ from this marginal analysis are 1.70, 1.25, and 2.30, with a lower p value of .0003. However, a causal interpretation of this result makes the highly implausible assumption that $B(\alpha_b) = 1$; that is, there is no net bias.

Model (6) can also be rewritten as a marginal-data model, $E_{+fsy} = \exp(z_a\alpha_a + g_b)$, where $g_b \equiv \ln\{\Sigma_u \exp(z_b\alpha_b)\}$ is a specially structured random effect. In essence, a sensitivity analysis specifies various α_b values, then for each value refits the model treating g_b as an offset (a known fixed term) to obtain a bias-corrected β_{FY} estimate, $\beta_{FY}(\alpha_b)$. Nonetheless, α_b has 48 components, making an ordinary sensitivity analysis unmanageable without drastic simplification. Unfortunately, most simplifications would be implausible; for example, assuming homogeneity across studies would not be credible for any parameter other than β_{FY}. One can, however, retain the full complexity of model (6) by using a prior distribution for α_b.

3.2 A Prior Distribution for the Bias Parameters

One may again ask whether some reasonable prior for the bias parameters in α_b would make the hypothesis of no net causal effect ($\beta_{FY} \le 0$) seem reasonable in light of the data given a diffuse prior for α_a. To adapt the prior from the VHCC example to the present setting let $D = 1$ for studies with direct field measurement, 0 for calculated fields, and $V = (V_1, 1 - V_1)$ where $V_1 = 1$ for studies of 120-volt, 60-Hz systems and 0 for 220-volt, 50-Hz systems. D and V are functions of S, and $V_1 = 1$ also indicates North America. A realistic bias prior would include large bias-parameter correlations among studies with similar characteristics. To create the desired prior correlations, α_b was modeled as a linear function of a vector δ_b with independent mean-0 normal components, as follows:

1. Discovering a factor associated with fields in one study would usually increase the probability of finding a similar association in another study, especially of the same system. Modeling the study-specific UF log odds ratios $s\alpha_{UFS}$ as $\delta_{UF} + v\delta_{UFV} + s\delta_{UFS}$, δ_{UF} is the portion of the UF association shared across all studies, δ_{UFV} contains the portions shared by studies of the same system, and prior correlations are simple functions of the relative prior variances of δ_{UF}, δ_{UFV}, and δ_{UFS} components. These δ were assigned variances to produce $s\alpha_{UFS}$ standard deviations of ln(6)/1.645, with cross-study correlations of .8 within systems and .6 between systems.

2. Discovering a factor associated with leukemia in one study would greatly increase the prior probability of finding a similar association in another study, especially a study of the same system type. Modeling the study-specific UY log odds ratios, $s\alpha_{USY}$, as $\delta_{UY} + v\delta_{UVY} + s\delta_{USY}$, prior correlations are functions of the relative prior variances of δ_{UY}, δ_{UVY}, and δ_{USY} components. These δ were assigned variances to produce $s\alpha_{USY}$ standard deviations of ln(6)/1.645, with cross-study correlations of .9 within systems and .8 between systems.

3. The study-specific U logits $s\alpha_{US} + fs\alpha_{UFS} + sy\alpha_{USY}$ are correlated through α_{UFS} and α_{USY}. Modeling $s\alpha_{US}$ as $\delta_U + v\delta_{UV} + s\delta_{US}$, the logit correlations are also functions of the relative prior variances of δ_U, δ_{UV}, and δ_{US} components. These δ were assigned variances to produce logit standard deviations of 2, with cross-study correlations for α_{US} of .6 within and .4 between systems. With this specification, α_{US} accounts for most of the variance of the U logits.

4. There is evidence of upward response bias in studies with direct measurements, which require entry of private property (Hatch et al. 2000), whereas such bias is not suspected in other studies. Modeling $s\gamma_{FSY}$ as $(\delta_{FY} + v\delta_{FVY} + s\delta_{FSY})\{\ln(1.1)/\ln(1.5)\}^{1-d}$, these δ were assigned variances that produced $P\{\exp(s\gamma_{FSY}) > 1.5 \mid D = 1\} = P\{\exp(s\gamma_{FSY}) > 1.1 \mid D = 0\} = .05$, with cross-study correlations of .9 within systems and .7 between systems when $D = 1$.

Denote the resulting bias prior by $P(\alpha_b)$. A Monte Carlo sensitivity analysis may repeatedly draw α_b from $P(\alpha_b)$, compute the offset g_b, and fit $E_{+fsy} = \exp(z_a\alpha_a + g_b)$ to obtain a corrected effect estimate $\beta_{FY}(\alpha_b)$. To incorporate random error into the results, one may also resample the data at each draw; a more simple approximation uses $\beta_{FY}^* = \beta_{FY}(\alpha_b) - \varepsilon$ where ε is mean-0 normal with variance equal to the estimated sampling variance of the MLE of β_{FY}. The 50th, 2.5th, and 97.5th percentiles of 500,000 such β_{FY}^* were 1.69, 1.00, and 2.86. These percentiles are much more spread out than the conventional ML limits, even though $P\{B(\alpha_b) \ge 1.70\} = .01$, so the prior odds that bias completely explains the MLE is very small. Also, $P\{B(\alpha_b) \ge 1.25\} = .14$, so the prior odds that the bias is as large as the lower ML confidence limit is only 1:6.

Remark 3. As expected with unidentified models, results are very sensitive to modest changes in the prior (Rubin 1983).

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For example, changing $P\{\exp(s\gamma_{FSY}) > 1.5 \mid D = 1\}$ in item 4 to $P\{\exp(s\gamma_{FSY}) > 1.2 \mid D = 1\}$ decreases the percentage of $\beta^*_{FY} \leq 0$ from 2.5% to 1%, whereas changing to $P\{\exp(s\gamma_{FSY}) > 1.8 \mid D = 1\}$ increases that percentage to 5%. By changing multiple features of the prior one can move results over a much wider range. Nonetheless, even one analysis with a reasonable prior for α_b can show that the conventional results are a poor guide to the uncertainty that one should have in light of the data.

Remark 4. The foregoing example does not account for errors in field measurement (which must be considerable) and so omits a major source of uncertainty. Incorporating this source would require a latent dimension for the true field T and an informative prior for its relation to F and the other variables (Gustafson, Le, and Saskin 2001). Unfortunately, there are no data for estimating this prior, nor is there even agreement as to what sort of true measure should serve as the causally relevant T. It is well known that assuming a special "random" error structure (i.e., independent nondifferential error) will usually lead to enlargement of the point estimate; this fact is often taken as evidence that the association is larger than that observed (see, e.g., the California DHS report cited earlier). Nonetheless, allowance for uncertainties about the measurement-error structure can result in an enlargement of the posterior standard deviation of β_{FY} greater than the enlargement of the posterior mean, and can decrease the posterior probability that $\beta_{FY} > 0$. Thus an analysis that ignores measurement error may overstate posterior certainty about the existence of an effect even when it understates the posterior mean of the effect.

4. DISCUSSION

One purpose for introducing unidentified bias parameters is to refine subjective uncertainty assessments, or at least to avoid misinterpretation of conventional confidence limits. Given informative priors, some authors would go further and reject the conventional limits as wholly irrelevant on philosophical grounds (DeFinetti 1975; Lindley 2000). A less abstract reason for questioning conventional statistics in observational epidemiology is the absence of any agreed-on (let alone objective) mechanism for the data-generation process, which is complex and largely unknown (e.g., the determinants of control participation are poorly understood). Others have argued that frequentist evaluations remain relevant to Bayesian applications for the purpose of model checking (e.g., Box 1980). Nonetheless, such checks can address only data constraints implied by the analysis model. Model expansion to include unidentified bias parameters is an attempt to introduce some realism into conventional sampling models. The expanded model may place no constraint on the data and hence have no associated diagnostic, in which case it can be evaluated only with subject matter arguments and external data.

In general, bias modeling may depend more on background information than on the data under analysis. Because of time and resource limitations it may also depend heavily on dictates of convenience and simplicity, although in recognizing these limitations one ought not to sanctify simplicity with a "parsimony principle" (Greenland 2000). Even when unidentifiable, the consequences of simplifications need elucidation. For example, the assumption of odds-ratio homogeneity is usually based more on convenience rather than on subject matter; however, it was argued that it should be of little consequence in the examples. It was also argued that the simplifying assumptions of binary U and disease rarity are of no practical consequence, and that ignoring measurement error has less predictable consequences than is ordinarily thought.

Although informal narrative elements are unavoidable in inference, examples like the foregoing argue that quantitative reasoning requires expansion beyond current levels. Most causal inferences from observational data seem to arise from a crude intuitive blending of conventional results (which account for only random error and measured bias sources) with feelings about uncontrolled biases. Both conventional and sensitivity analyses are prone to misinterpretation because they tend to ignore bias interactions and because narrative integration of these analyses with opinions about bias sources tends to be very incoherent. Using a credible prior for the bias parameters can show how allowance for possible uncontrolled bias can substantially increase uncertainty about the causal nature of an association, despite a very low prior probability that bias explains the association.

Of course, no analysis should be interpreted as "the" correct analysis, and most analyses of health effects based on observational data merit healthy skepticism. This is so whether or not bias parameters have been included, for elements missing from the bias model specification can reverse inferences on inclusion (Poole and Greenland 1997). But an analysis with an explicit and informative bias prior can be treated as an exercise in quantified rational skepticism rather than a definitive risk assessment. Even when it does not incorporate every subject matter detail or methodologic refinement, such an analysis can be an effective antidote to the overly precise conclusions that often flow from conventional results and traditional sensitivity analyses.

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