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LETTERS TO THE EDITOR

RE: "USE OF TWO-SEGMENTED LOGISTIC REGRESSION TO ESTIMATE CHANGE-POINTS IN EPIDEMIOLOGIC STUDIES"

We thank Ulm and Küchenhoff (1) for their valuable comments on our paper (2) about the estimation of change-points in epidemiologic studies. We agree with them that several methods for change-point estimation in generalized linear models have already been described in the statistical literature (3–6). However, it is equally important to recognize that their epidemiologic application to dose-response assessment has been limited by the lack of an algorithm to simultaneously estimate the change-point and the other parameters of effect. In the above approaches, the maximum likelihood estimates are obtained from the profile log-likelihood of sequential models at different fixed change-points, and hence, this estimation procedure does not provide appropriate error estimates for model parameters, except for the change-point (see the Discussion section of our paper (2) for a detailed description). To overcome this problem, the algorithm proposed in our article (2) provides simultaneous estimation of all model parameters and realistic measurements of statistical error. An alternative method recently proposed by Daniels et al. (7) is now also available.

As stated in our paper (2), all inferences presented, such as confidence intervals or tests of hypothesis, were based on the assumption of existence of the change-point. Although we did not explicitly address the problem of testing for this assumption, we recognized, as stated in the Discussion section of our paper, that further research is needed in this area. Ulm (3) suggested a test procedure based on a quasi one-sided χ^2_1 distribution. The justification of this method was supported by a simulation study, but it would be desirable to have a more rigorous theoretical justification. In our opinion, alternative methods to test formally for the existence of change-points are still needed.

With respect to the example of alcohol intake and risk of myocardial infarction, several points need to be clarified. This example illustrates the applicability of two-segmented logistic models to estimate and provide inferences about the location of the change-point and the magnitude of other parameters of effect, when the change-point actually exists. If there is no change-point (i.e., $\beta_2 = 0$), the model reduces to a standard logistic regression, and hence, the change-point is not well defined. In such circumstances, the standard asymptotic properties of Wald and likelihood ratio statistics do not hold (8). Finally, we would like to stress that, although several models are used to display the dose-response relation of alcohol with the risk of myocardial infarction, only the quadratic-linear model provides a statistical estimation of the change-point.

We concur with Ulm and Küchenhoff (1) on the importance of careful modeling and interpretation in assessing change-points and, as already discussed in our article (2), we suggest using nonparametric regression to check the appropriate parameterization of segmented models. Alternative parametric change-point models, which can accommodate many epidemiologic dose-response relations, are also described in the Discussion section of our paper. In conclusion, we believe that the two-segmented logistic regression model provides valuable inference procedures when threshold effects are anticipated and that it deserves wider use in epidemiologic dose-response analyses.

References

1. Ulm K, Küchenhoff H. Re: "Use of two-segmented logistic regression to estimate change-points in epidemiologic studies." (Letter). Am J Epidemiol 2000;152:289.
2. Pastor R, Guallar E. Use of two-segmented logistic regression to estimate change-points in epidemiologic studies. Am J Epidemiol 1998;148:631–42.
3. Ulm K. A statistical method for assessing a threshold in epidemiological studies. Stat Med 1991;10:341–9.
4. Stasinopoulos DM, Rigby RA. Detecting break points in generalized linear models. Comput Stat Data Anal 1992;13:461–71.
5. Goetghebeur E, Pocock SJ. Detection and estimation of J-shaped risk-response relationships. J R Stat Soc (A) 1995;158:107–21.
6. Küchenhoff H. An exact algorithm for estimating breakpoints in segmented generalized linear models. Comput Stat 1997; 12:235–47.
7. Daniels MJ, Dominici F, Samet JM, et al. Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am J Epidemiol 2000;152:397–406.
8. Feder PI. The log likelihood ratio in segmented regression. Ann Stat 1975;3:84–97.

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RE: "ARE CHILDREN LIVING NEAR HIGH-VOLTAGE POWER LINES AT INCREASED RISK OF ACUTE LYMPHOBLASTIC LEUKEMIA?"

A recent article by Kleinerman et al. (1) uses an "exposure index" similar to a model for residential magnetic field exposures that we developed (2). Magnetic fields predicted by our model were associated with childhood leukemia

(odds ratio = 2.00 in the highest exposure group, 95 percent confidence interval: 1.03, 3.89, p for trend = 0.02) (3), while Kleinerman et al. were unable to find an association (odds ratio for a continuous exposure variable = 0.95, 95 percent confidence interval: 0.78, 1.16).

Potential explanations for these conflicting results are worth discussing because the carcinogenicity of electric and magnetic fields (EMF) is unresolved (4). This letter focuses on two possible reasons: 1) differences in the two methods for assessing residential magnetic field exposures; and 2) unmeasured EMF characteristics, which could be effect modifiers or confounders. Epidemiologic biases that might explain these discrepancies are discussed elsewhere (3, 5).

Compared with the diverse methods used in the EMF epidemiologic literature (5), these two studies have much in common: Both reanalyzed case-control datasets, but from different regions (6, 7). Both measured residential magnetic fields and collected wiring configuration data. The wiring data were inputs for both exposure models, whose mathematical forms were derived from the same physical principles (8, 9).

The most striking difference between the two studies is their exposure model. In the paper by Kleinerman et al., the foremost independent variable of the exposure index is the horizontal distance from the subject's residence to nearby power lines. Parameters representing the average currents in different kinds of transmission and primary distribution lines were "based on [their] experience and best judgment" (1, p. 513).

In our exposure model, current parameters were calibrated by regression against magnetic fields measured in a subset of residences. Our regression model used additional wiring variables, such as secondary distribution lines, number of transformers, service drops between lines and homes, etc., and the term for each line had $1/r$ or$1/r^2$ dependence with distance in keeping with theory (8). Stepwise regressions were conducted for both electric utilities servicing our study region. Since the current parameters vary greatly with the location of the home in the distribution system, their calibration for nearby wire configurations improved the accuracy of our magnetic field model. Having separate models for the two utilities reflects their different methods of grounding and transformer wiring, which further increased the correlation with measurements from 0.35 to 0.43 (2).

In contrast, Kleinerman et al. used the same exposure formula for all homes and utilities in a study covering nine states. Although their paper did not report correlations with measurements, the simplicity of their index would seem to create greater exposure assessment errors, increasing chances for a false-negative result.

Another explanation for inconsistent findings from EMF epidemiology is unmeasured field characteristics that may be effect modifiers. To date, epidemiologic studies have mostly assessed exposures to one magnetic field property, the root-mean-squared vector magnitude with frequencies of alternating-current electricity (5). The field's frequency spectrum, polarization, spatial orientation, and high-frequency transients have never been measured in human health studies, even though these characteristics are reported to affect biologic processes in laboratory and/or theoretic studies (10). Since magnetic field characteristics vary widely between homes (11), these unmeasured exposure variables could be modifying the cancer risks associated with the root-mean-squared magnetic field magnitude, producing seemingly inconsistent results in different populations. Most recently, residential magnetic fields have been associated with contact currents (or "microshocks") from the electrical grounding system of a house, which could adversely affect a child's hemopoiesis (12). Until such potential confounders and effect modifiers in the EMF environment are measured, epidemiologic studies will have trouble clarifying EMF's unsatisfactory status as a "possible carcinogen" (4, 5).

References

1. Kleinerman RA, Kaune WT, Hatch EE, et al. Are children living near high-voltage power lines at increased risk of acute lymphoblastic leukemia? Am J Epidemiol 2000;151:512–15.
2. Bowman JD, Thomas DC, Liangzhong J, et al. Residential magnetic fields predicted from wiring configurations. I. Exposure model. Bioelectromagnetics 1999;20:399–413.
3. Thomas DC, Bowman JD, Liangzhong J, et al. Residential magnetic fields predicted from wiring configurations. II. Relationship to childhood leukemia. Bioelectromagnetics 1999;20:414–22.
4. National Institute of Environmental Health Sciences. Health effects from exposure to power-line frequency electric and magnetic fields. Research Triangle Park, NC: National Institute of Environmental Health Sciences, 1999. (NIH publication no. 99–4493).
5. National Institute of Environmental Health Sciences Working Group. Assessment of health effects from exposure to power-line frequency electric and magnetic fields. Research Triangle Park, NC: National Institute of Environmental Health Sciences, National Institutes of Health, 1998:9–78, 167–89. (NIH publication no. 98–3981).
6. Linet MS, Hatch EE, Kleinerman RA, et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia. N Engl J Med 1997:337:1–7.
7. London SJ, Thomas DC, Bowman JD, et al. Exposure to residential electric and magnetic fields and risk of childhood leukemia. Am J Epidemiol 1991;134:923–37.
8. Kaune WT, Zaffanella LE. Analysis of magnetic fields produced far from power lines. IEEE Trans Power Deliv 1994; 2:149–70.
9. Kaune WT, Stevens RG, Callahan NJ, et al. Residential magnetic and electric fields. Bioelectromagnetics 1987;8:315–35.
10. Bowman JD, Gailey PC, Gillette L, et al., eds. Proceedings of a Joint NIOSH/DOE Workshop on "EMF Exposure Assessment and Epidemiology: Hypotheses, Metrics, and Measurements". Report PB-2000–101086. Arlington, VA: National Technical Information Service, 1999.
11. Bracken TD, Rankin RF, Senior RS, et al. Association of wire code configuration with long-term average 60-Hz magnetic field exposure. Report TR-111767. Palo Alto, CA: Electric Power Research Institute, 1998.
12. Kavet R, Zaffanella LE, Daigle JP, et al. The possible role of contact current in cancer risk associated with residential magnetic fields. Bioelectromagnetics 2000;21:538–53.

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SIX OF THE AUTHORS REPLY

Bowman and Thomas (1) cite two concerns about a residential magnetic field exposure index based on distance from homes to overhead transmission and three-phase primary distribution power lines that we used to evaluate childhood leukemia risk: 1) the simplicity of our model, and 2) the possible importance of unmeasured magnetic field characteristics. In our study conducted in nine Midwestern and mid-Atlantic States, we found no evidence of a positive association between leukemia risk and a magnetic field exposure index based on distance (2). In a reanalysis of data from a study in Los Angeles, Bowman et al. previously found a twofold risk for childhood leukemia in a high exposure group defined by a magnetic field exposure index based on distance (3) that was more complex than the one we used. Bowman and Thomas suggest that the different epidemiologic results in Los Angeles and the nine-state study might be explained by the models used or differences in unmeasured magnetic field characteristics between the two studies.

As Bowman and Thomas point out, the mathematical forms of both models were derived from the same general physical principles (4). Our exposure model was simpler than theirs because we chose to focus solely on transmission and distribution lines, the types of lines that generally emit the strongest magnetic fields (5). Along with these types of power lines, Bowman et al. also included secondary distribution lines and service drops in their model.

Bowman and Thomas used residential magnetic field measurements from their dataset to determine the values of several parameters incorporated in their model, that is, to essentially "tune" their model for the homes in their study. We did not follow this course, but instead utilized an "expert estimate" of the relative strengths of the magnetic fields produced by the average transmission and three-phase primary lines to select the key parameter in our model. We used this approach based on simplicity and experience with an earlier model developed by one of us (4). The earlier, more complex model did not predict magnetic fields for residences other than the original 43 homes in Seattle, Washington, for which the model was developed. Furthermore, it was not feasible for us to separately tune our model for the geographic regions within the nine-state area that were served by more than 100 different utility companies.

Unmeasured magnetic field characteristics may be effect modifiers, as Bowman and Thomas suggest, but any notable influence on the risk of childhood leukemia from any postulated effect modifier has yet to be demonstrated (6). We recently reanalyzed the nine-state study results on field measurements (7) by using a variety of magnetic field metrics, including rate of change, peak exposures, and measures of short-term variability (8). We oncluded (7, 8) that there is little evidence of an association between any measure of magnetic fields and risk of childhood acute lymphoblastic leukemia (8).

REFERENCES

1. Bowman JD, Thomas DC. Re: "Are children living near high-voltage power lines at increased risk of acute lymphoblastic leukemia?" (Letter). Am J Epidemiol 2000:153:615–16.
2. Kleinerman RA, Kaune WT, Hatch EE, et al. Are children living near high-voltage power lines at increased risk of acute lymphoblastic leukemia? Am J Epidemiol 2000;151:512–15.
3. Bowman JD, Thomas DC, Liangzhong J, et al. Residential magnetic fields predicted from wiring configurations. I. Exposure model. Bioelectromagnetics 1999;20:399–413.
4. Kaune WT, Stevens RG, Callahan NJ, et al. Residential magnetic and electric fields. Bioelectromagnetics 1987;8:315–35.
5. Zafanella LE. Survey of residential magnetic field sources. Vol. 1. Goals, results, and conclusions. Report TR-102759-VI. Palo Alto, CA: Electric Power Research Institute, 1993.
6. Ahlbom A, Day N, Feychting M, et al. A pooled analysis of magnetic fields and childhood leukemia. Br J Cancer 2000; 83:692–8.
7. Linet MS, Hatch EE, Kleinerman RA, et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. N Engl J Med 1997;337:1–7.
8. Auvinen A, Linet MS, Hatch EE, et al. Extremely low-frequency magnetic fields and childhood acute lymphoblastic leukemia: an exploratory analysis of alternative exposure metrics. Am J Epidemiol 2000;152:20–31.

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