Access and Outcomes of Obstetric Care

To The Editor: The article by Larimore and Davis[1] is an important attempt to link access to maternity services (as measured by physician availability) to an important health outcome—infant mortality. There are several methodological and statistical problems in the study, however, that undermine the validity of the results and conclusions.

The fundamental problem of their study is that the unique biases that can affect ecologic studies such as theirs are not even addressed. First, in contrast to control of confounding in individual-level studies, attempts to control confounding in ecologic studies rarely eliminate confounding.[2,3] The inclusion of such variables as percentage of nonwhite study population, education, and income into the linear regression model does not mean that the association between INDEX (the indicator of physician availability) and infant mortality is not confounded by these variables. Second, even small errors in the measurement of covariates can result in a profound bias in an ecologic analysis, and this bias can produce effects vastly different from the effects introduced in individual-level studies.[4] Income, for instance, is probably measured with some degree of error, and this measurement error might have a substantial effect on the regression coefficient for INDEX. (It is impossible to determine the magnitude and direction of this bias without analyzing individual-level data.)

Further, the statistical considerations relevant to ecologic analyses are ignored. Correlation coefficients and, therefore R^2, are spuriously inflated in ecologic analyses relative to individual-level studies.[5] The magnitude of this difference can be profound. Morganstern,[5] for instance, offers an example in which data that were analyzed at the individual level resulted in an R^2 of 0.01, but when they were analyzed ecologically, the R^2 was 1.00.[5] Despite the hazard of using correlation coefficients (and R^2), the authors use the R^2 for their linear regression model as their primary outcome measure. The reported R^2 of 0.176 is almost certainly spuriously high. If the authors had used the regression coefficient for INDEX as their primary outcome measure (because regression coefficients are not falsely elevated in ecologic analyses), their conclusions would have been vastly different. INDEX, for instance, shows the weakest association with infant mortality rate of any variable studied, approximately 500 times weaker than the association between percentage of the nonwhite study population and infant mortality.

These criticisms are not intended as a broadside against ecologic studies in general. While ecologic studies can provide valid estimates of individual-level effects under certain very limited conditions, the effect of unique biases must be evaluated and appropriate statistical methods must be used before any conclusions can be drawn. It is difficult to draw any valid conclusions from Larimore and Davis's study because they did neither. They must be congratulated for attempting to answer a difficult and important question, but the answer must await another day.

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References

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3. Greenland S, Robins J. Invited commentary: ecologic studies—biases, misconceptions, and counterexamples. Am J Epidemiol 1994; 139:747-60.
4. Brenner H, Greenland S, Savitz DA. The effects of nondifferential confounder misclassification in ecologic studies. Epidemiology 1992; 3:456-9.
5. Morganstern H. Uses of ecologic analysis in epidemiologic research. Am J Public Health 1982; 72:1336-44.

The above letter was referred to the authors of the article in question, who offer the following reply.

To the Editor: In our article we made no inferences concerning risks to individuals based upon aggregate data; therefore, Dr. Sonis's contention that our study was ecologic and had "unique biases which can affect ecological studies" (the "Ecology Fallacy") is not, in our opinion, valid—as our basic unit of observation was the county. We had predicted that infant mortality in a county would be significantly affected by our index of physician providers of maternity care (INDEX). The statistical analysis we used revealed a necessary, but not sufficient, condition to establish cause and effect, a fact that we discussed in the paper. Nevertheless, the statistical analysis did, in our opinion, reveal a measure of truth for those with eyes to see and ears to hear.

As explained in the paper, we attempted to adjust for confounding by including only the measures of socioeconomic variables that were available to us for every county in the state. Although we feel the measures were accurate, our paper clearly stated that there could be many other covariates that were not available for our study. Of most importance, however, is that INDEX is the only real covariate the family physicians in Florida can control.

Additionally, we would point out that the regression coefficients of Table 1 were not standardized, so that each coefficient depended on the units of measurement of its corresponding independent variable; therefore, one should not use relative size of these coefficients to infer strength of association. The column for *P* values in Table 1 shows that the only significant variable, apart from total number of babies, in predicting total deaths was the INDEX.

Dr. Sonis suggests that we should have used "appropriate statistical methods." We hope our explanation will help him to see why we believe that the conclusions from our study are valid and that our answer to

the research question, although admittedly incomplete, will not have to "await another day."

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Atrial Fibrillation During Flexible Sigmoidoscopy

To the Editor: The article by Bruehlman[1] describes the occurrence of atrial fibrillation in a patient undergoing flexible sigmoidoscopy. Although this article is of great interest, the patient does not fit the high-risk criteria for which this procedure should be performed under cardiac monitoring.

Also of interest is why flexible sigmoidoscopy rather than colonoscopy was offered in the face of two episodes of bright red rectal bleeding. Flexible sigmoidoscopy is an acceptable evaluation tool provided it is followed by a barium study. In this patient the question persists as to the origin or cause of the bright red blood coming from the rectum.

That the flexible sigmoidoscope was inserted to a depth of only 50 cm, which indicates visualization of only the sigmoid colon and rectum, is unusual in a young male patient.[2] There could have been a lesion beyond the point of insertion that could have been the origin of the bright red blood.[3]

Jay R. Varma, MD
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References

1. Bruehlman RD. Atrial fibrillation during flexible sigmoidoscopy in a 36-year-old man. J Am Board Fam Pract 1995;8:403-4.
2. Varma JR, Sample L. Colorectal cancer in patients aged less than 40 years. J Am Board Fam Pract 1990;3:549.
3. Varma JR, Mills LR. Colon polyps. J Fam Pract 1992; 35:194-200.

The above letter was referred to the author of the article in question, who offers the following reply.

To the Editor: I agree with Dr. Varma that this 36-year-old man was not at high risk for sustaining a cardiac arrhythmia during sigmoidoscopy. He was placed on a cardiac monitor, not by direct physician order, but as part of a protocol applied to all patients undergoing treatment in the endoscopy suite of the hospital where the procedure was performed.

Passage of small amounts of bright red blood from the rectum is often caused by rectal conditions, such as hemorrhoids, fissures, or proctitis,[1] all of which can be diagnosed by using the fiber-optic sigmoidoscope. The patient had no evidence of anemia or fecal occult blood, making questionable the more extensive bowel preparation and expense of colonoscopy. To date, he has reported no further episodes of rectal bleeding. Given the complication of atrial fibrillation during sigmoidoscopy, further lower gastrointestinal imaging would seem to be risky business.

A future dilemma: in view of his family history (both grandfathers had colon cancer), should screening sigmoidoscopy or colonoscopy be recommended as he ages?

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Reference

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Serotonin Syndrome Cause and Treatment

To the Editor: I am delighted to see an article that details the potentially fatal interaction between selegiline (Eldepryl, also known generically outside the United States as deprenyl) and selective serotonin reuptake inhibitors.[1] Serotonin syndrome is a purely iatrogenic disorder that physicians who prescribe serotonergic drugs need to both recognize and prevent. There are, however, a few erroneous statements and conclusions in Dr. Weiss' otherwise excellent case report.

First, the article states that serotonin syndrome "results from a combination of MAOIs (monoamine oxidase inhibitors) with selective serotonin reuptake inhibitors (SSRIs), such as L-tryptophan, clomipramine, fluoxetine, and sertraline." Neither L-tryptophan nor clomipramine is an SSRI. L-Tryptophan is the precursor to endogenous serotonin production. It is not currently available as a medication in the United States because of an association with eosinophilia-myalgia syndrome. Clomipramine is a tricyclic antidepressant with potent serotonin reuptake inhibition, but it is not a selective serotonin reuptake inhibitor. Nevertheless, Dr. Weiss is correct that both L-tryptophan and clomipramine can cause serotonin syndrome in combination with MAOIs.

Serotonin syndrome causes are more complex than just an interaction between MAOIs and SSRIs, although these offenders are probably the most common. I surmise from numerous case reports that interfering simultaneously with two separate mechanisms of serotonergic neurotransmission can raise serotonin levels in the central nervous system to the point that serotonin syndrome results.[2,3] Any combination of two drugs from each of the following six classes could cause serotonin syndrome:

1. L-Tryptophan (which raises serotonin production)
2. Serotonin reuptake pump inhibitors, such as SSRIs (fluoxetine [Prozac], fluvoxamine [Luvox], paroxetine [Paxil], and sertraline [Zoloft]), tricyclic antidepressants (amitriptyline, imipramine, etc.), dextromethorphan,[3] and meperidine[3] (Demerol)
3. MAOIs, such as selegiline (Eldepryl), phenelzine (Nardil) and tranylcypromine (Parnate)
4. Amphetamines (which stimulate the release of serotonin as well as norepinephrine)
5. Direct postsynaptic serotonin agonists, such as buspirone (BuSpar)