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Do We Really Know What Makes Us Healthy? Part III

The Bias of Health Users and Compliance

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Your Life Your Health

The Examiner

October 11, 2007

This continues our four-part review of the *New York Times Magazine's* feature article about science and health recommendations. The first part was published in the September 27, 2007 *Examiner*.

“The Bias of Healthy Users

“The Nurses’ Health Study was founded at Harvard in 1976 by Frank Speizer, an epidemiologist who wanted to study the long-term effects of oral contraceptive use. It was expanded to include postmenopausal estrogen therapy because both treatments involved long-term hormone use by millions of women, and nobody knew the consequences. Speizer’s assistants in this endeavor, who would go on to become the most influential epidemiologists in the country, were young physicians — Charles Hennekens, Walter Willett, Meir Stampfer and Graham Colditz — all interested in the laudable goal of preventing disease more than curing it after the fact.

“When the Nurses’ Health Study first published its observations on estrogen and heart disease in 1985, it showed that women taking estrogen therapy had only a third the risk of having a heart attack as had women who had never taken it; the association seemed compelling evidence for a cause and effect. Only 90 heart attacks had been reported among the 32,000 postmenopausal nurses in the study, and Stampfer, who had done the bulk of the analysis, and his colleagues “considered the possibility that the apparent protective effect of estrogen could be attributed to some other factor associated with its use.” They decided, though, as they have ever since, that this was unlikely. The paper’s ultimate conclusion was that “further work is needed to define the optimal type, dose and duration of postmenopausal hormone use” for maximizing the protective benefit.

“Only after Stampfer and his colleagues published their initial report on estrogen therapy did other investigators begin to understand the nature of the other factors that might explain the association. In 1987, Diana Petitti, an epidemiologist now at the University of Southern California, reported that she, too, had detected a reduced risk of heart-disease deaths among women taking H.R.T. in the Walnut Creek Study, a population of 16,500 women. When Petitti looked at all the data, however, she “found an even more dramatic reduction in death from homicide, suicide and accidents.” With little reason to believe that estrogen would ward off homicides or accidents, Petitti concluded that something else appeared to be “confounding” the association she had observed. “The same thing causing this obvious spurious association might also be contributing to the lower risk of coronary heart disease,” Petitti says today.

“That mysterious something is encapsulated in what epidemiologists call the healthy-user bias, and some of the most fascinating research in observational epidemiology is now aimed at understanding this phenomenon in all its insidious subtlety. Only then can epidemiologists learn how to filter out the effect of this healthy-user bias from what might otherwise appear in their studies to be real causal relationships. One complication is that it encompasses a host of different and complex issues, many or most of which might be impossible to quantify. As Jerry Avorn of Harvard puts it, the effect of healthy-user bias has the potential for “big mischief” throughout these large epidemiologic studies.

“At its simplest, the problem is that people who faithfully engage in activities that are good for them — taking a drug as prescribed, for instance, or eating what they believe is a healthy diet — are fundamentally different from those who don’t. One thing epidemiologists have established with certainty, for example, is that women who take H.R.T. differ from those who don’t in many ways, virtually all of which associate with lower heart-disease risk: they’re thinner; they have fewer risk factors for heart disease to begin with; they tend to be more educated and wealthier; to exercise more; and to be generally more health conscious.

“Considering all these factors, is it possible to isolate one factor — hormone-replacement therapy — as the legitimate cause of the small association observed or even part of it? In one large population studied by Elizabeth Barrett-Connor, an epidemiologist at the University of California, San Diego, having gone to college was associated with a 50 percent lower risk of heart disease. So if women who take H.R.T. tend to be more

educated than women who don't, this confounds the association between hormone therapy and heart disease. It can give the appearance of cause and effect where none exists.

“Another thing that epidemiologic studies have established convincingly is that wealth associates with less heart disease and better health, at least in developed countries. The studies have been unable to establish why this is so, but this, too, is part of the healthy-user problem and a possible confounder of the hormone-therapy story and many of the other associations these epidemiologists try to study. George Davey Smith, who began his career studying how socioeconomic status associates with health, says one thing this research teaches is that misfortunes “cluster” together. Poverty is a misfortune, and the poor are less educated than the wealthy; they smoke more and weigh more; they're more likely to have hypertension and other heart-disease risk factors, to eat what's affordable rather than what the experts tell them is healthful, to have poor medical care and to live in environments with more pollutants, noise and stress. Ideally, epidemiologists will carefully measure the wealth and education of their subjects and then use statistical methods to adjust for the effect of these influences — multiple regression analysis, for instance, as one such method is called — but, as Avorn says, it “doesn't always work as well as we'd like it to.”

“The Nurses' investigators have argued that differences in socioeconomic status cannot explain the associations they observe with H.R.T. because all their subjects are registered nurses and so this “controls” for variations in wealth and education. The skeptics respond that even if all registered nurses had identical educations and income, which isn't necessarily the case, then their socioeconomic status will be determined by whether they're married, how many children they have and their husbands' income. “All you have to do is look at nurses,” Petitti says. “Some are married to C.E.O.'s of corporations and some are not married and still living with their parents. It cannot be true that there is no socioeconomic distribution among nurses.” Stampfer says that since the Women's Health Initiative results came out in 2002, the Nurses' Health Study investigators went back into their data to examine socioeconomic status “to the extent that we could” — looking at measures that might indirectly reflect wealth and social class. “It doesn't seem plausible” that socioeconomic status can explain the association they observed, he says. But the Nurses' investigators never published that analysis, and so the skeptics have remained unconvinced.

“The Bias of Compliance

“A still more subtle component of healthy-user bias has to be confronted. This is the compliance or adherer effect. Quite simply, people who comply with their doctors’ orders when given a prescription are different and healthier than people who don’t. This difference may be ultimately unquantifiable. The compliance effect is another plausible explanation for many of the beneficial associations that epidemiologists commonly report, which means this alone is a reason to wonder if much of what we hear about what constitutes a healthful diet and lifestyle is misconceived.

“The lesson comes from an ambitious clinical trial called the Coronary Drug Project that set out in the 1970s to test whether any of five different drugs might prevent heart attacks. The subjects were some 8,500 middle-aged men with established heart problems. Two-thirds of them were randomly assigned to take one of the five drugs and the other third a placebo. Because one of the drugs, clofibrate, lowered cholesterol levels, the researchers had high hopes that it would ward off heart disease. But when the results were tabulated after five years, clofibrate showed no beneficial effect. The researchers then considered the possibility that clofibrate appeared to fail only because the subjects failed to faithfully take their prescriptions.

“As it turned out, those men who said they took more than 80 percent of the pills prescribed fared substantially better than those who didn’t. Only 15 percent of these faithful “adherers” died, compared with almost 25 percent of what the project researchers called “poor adherers.” This might have been taken as reason to believe that clofibrate actually did cut heart-disease deaths almost by half, but then the researchers looked at those men who faithfully took their placebos. And those men, too, seemed to benefit from adhering closely to their prescription: only 15 percent of them died compared with 28 percent who were less conscientious. “So faithfully taking the placebo cuts the death rate by a factor of two,” says David Freedman, a professor of statistics at the University of California, Berkeley. “How can this be? Well, people who take their placebo regularly are just different than the others. The rest is a little speculative. Maybe they take better care of themselves in general. But this compliance effect is quite a big effect.”

“The moral of the story, says Freedman, is that whenever epidemiologists compare people who faithfully engage in some activity with those who don’t — whether taking prescription pills or vitamins or exercising regularly or eating what they consider a

healthful diet — the researchers need to account for this compliance effect or they will most likely infer the wrong answer. They'll conclude that this behavior, whatever it is, prevents disease and saves lives, when all they're really doing is comparing two different types of people who are, in effect, incomparable.

“This phenomenon is a particularly compelling explanation for why the Nurses' Health Study and other cohort studies saw a benefit of H.R.T. in current users of the drugs, but not necessarily in past users. By distinguishing among women who never used H.R.T., those who used it but then stopped and current users (who were the only ones for which a consistent benefit appeared), these observational studies may have inadvertently focused their attention specifically on, as Jerry Avorn says, the “Girl Scouts in the group, the compliant ongoing users, who are probably doing a lot of other preventive things as well.”