



STANTON A. GLANTZ, PhD
Professor of Medicine
Director, Center for Tobacco Control Research and Education
Suite 366 University Library
530 Parnassus Avenue
San Francisco, California 94143-1390

Phone : 415-476-3893
Fax: 415-514-9345
E-mail: glantz@medicine.ucsf.edu

February 10, 2006

Comments on “Environmental Tobacco Smoke and Coronary Heart Disease Mortality in the United States – A Meta-Analysis and Critique” by Enstrom and Kabat, *Inhalation Toxicology* 18:199-210.

As the title indicates, this paper presents a meta-analysis of a select series of studies of the effects of secondhand smoke on heart disease. While it would seem reasonable to limit the selection of studies to cohort studies in the United States and compare “ever exposed” to “never exposed” people, doing so introduces a series of biases all of which reduce the magnitude of the risk estimate. Even with these problems, Enstrom and Kabat report an increase in risk (5%), which, albeit lower than the consensus estimate (30%), is still a substantial effect in terms of public health.

Here are some specifics:

1. Cohort studies, while generally accepted as better than case-control studies for assessing clinical interventions, are often not as accurate as case-control studies for assessing environmental toxins (like secondhand smoke) where exposures tend to change over time. Failure to get good measures of exposure – what is called nondifferential exposure missclassification bias – biases the results towards the null.
2. Including people in the “ever exposed” who are no longer exposed to SHS is inappropriate for heart disease because the risk falls off over time when the exposure ends. Doing so includes many people in the “exposed” group who are not exposed to SHS in a way that would be expected any longer to increase their heart disease risk.
3. The meta-analysis results are heavily influenced by the Enstrom/Kabat study in BMJ, which has been appropriately criticised by the American Cancer Society (and others) for inappropriate use of the ACS CPS I data set. The same issues of exposure missclassification that ACS (that bias results to the null) raised regarding cancer also apply to heart disease.
4. The meta-analysis also includes the tobacco-industry funded study by Levois and Layard that also used the ACS CPS I data set, and so suffers from the same bias due to exposure missclassification as the Enstrom/Kabat study

5. They ignore all the data from case-control studies inside the US and all studies outside the US. Doing so reduces the amount of available information and reduces the likelihood of detecting an effect, even when one exists.
6. They ignore the strong biological evidence that SHS has a big effect on the cardiovascular system at low doses. We reviewed this evidence in a paper that was published a month before the Enstrom/Kabat paper was submitted: Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation*. 2005 May 24;111(20):2684-98.
7. They use the discredited concept of "cigarette equivalents." The biology (discussed above) has shown that this simply makes no sense for heart disease, where the effects occur at very low doses, then tend to plateau at higher doses.
8. They ignore the evidence that, when using cotinine as a marker for exposure to SHS (which avoids the problems of exposure missclassification), the risk estimates for heart disease are much higher than determined from spousal studies, similar to that of light smoking. This result was published in an important paper by Whincup et al. (Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. *BMJ*. 2004 Jul 24;329(7459):200-5) and is precisely what one would expect from the biology. The Whincup paper is probably the best single study ever done on the epidemiology of passive smoking and heart disease. I suppose that they could exclude it from their meta-analysis because it was not a US study, but it should have been discussed because of the important information it includes regarding the effects of exposure missclassification bias, namely that it is a big effect.
9. The funding notice on this paper acknowledges support of Philip Morris for this project. One wonders why they also that in the past they were supported by NCI and ACS; including such a statement is unusual, since these agencies did not support this project.

The new CalEPA report has a much more complete discussion of passive smoking and heart disease, including the biology, as well as a discussion of nondifferential exposure missclassification bias. It is available at <http://www.arb.ca.gov/toxics/ets/finalreport/finalreport.htm> . Rather than getting in an argument with Enstrom and Kabat, people should rely on this definitive document prepared by a leading government scientific agency.