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REGULATION was first published in July 1977 "because the extension of regulation is piecemeal, the sources and targets diverse, the language complex and often opaque, and the volume overwhelming."

REGULATION is devoted to analyzing the implications of government regulatory policy and the effects on our public and private endeavors.

For the Record

Our "Damned Lies" Spark Another Exchange

A Critical Assessment

IN "LIES, DAMNED LIES, & 400,000 Smoking-Related Deaths" (Regulation, Vol. 21, No. 4), Robert Levy and Rosalind Marimont contend that the government's estimate that cigarette smoking causes 400,000 premature deaths a year is scientifically unsound and substantially inflated. The authors assert: "The war on smoking... has grown into a monster of deceit and greed, eroding the credibility of government and subverting the rule of law."

In May 1999, Levy and Marimont's arguments resurfaced in an article by *Boston Globe* columnist Jeff Jacoby. Mr. Jacoby's column has been circulated widely and cited in op-ed pages nationwide.

Levy and Marimont's article also served in the defense of U.S. tobacco companies in the recent Florida "Engle case," the largest class action lawsuit filed against the tobacco industry.

For more than 20 years, the American Council on Science and Health (ACSH) has relied on sound science to educate the public about risks to health. ACSH has paid particular attention to well-established and preventable causes of disease and death, especially cigarette smoking.

In this letter, we evaluate the plausibility of the estimate that smoking causes 400,000 premature deaths a year, review the confirmed health problems caused by smoking, explain the scientific methods used to establish those risks, and evaluate the key arguments used by Levy and Marimont to

discount the fatalities caused by cigarette smoking.

THE HEALTH HAZARDS OF SMOKING

CIGARETTE SMOKING HAS BEEN RECOGNIZED as a leading cause of disease and death for at least 40 years. Few subjects have received such thorough and extensive scientific scrutiny by both governmental and independent bodies. Thousands of scientific studies have confirmed that smoking is a major health hazard. Besides the relationship between smoking and disease, many studies have found that the overall death rate among smokers is two to three times greater than that of nonsmokers. Cigarettes also contain nicotine, a chemical proven to be highly addictive (which internal tobacco-industry documents have acknowledged).

Despite overwhelming evidence to the contrary, Levy and Marimont state that the hazards of smoking remain largely speculative. They allege that the "war on smoking started with a kernel of truth—that cigarettes are a high risk factor for lung cancer." Ironically, it is Levy and Marimont's article that contains only a kernel of truth about the risks of smoking. In fact, active cigarette smoking has been causally linked to lung cancer and associated with an array of other diseases; specifically:

- Cigarette smoking is a principal cause of cancer of the esophagus, larynx, lip, mouth, pharynx, tongue, kidney, pancreas, urinary bladder, and uterine cervix.

We welcome notes about current regulatory topics, letters that challenge or expand upon material we have published, and replies from authors. The writer's name, affiliation, address, and telephone number should be included. We cannot publish all the letters we receive, and we may reject any letter at our discretion. We may edit letters for length, clarity, and conformity to our editorial style.

- Cigarette smoking has been identified as a major cause of cardiovascular disease, including atherosclerosis, coronary heart disease (angina and heart attack), stroke, sudden death, and aortic aneurysm.

- Cigarette smoking causes chronic obstructive lung disease (emphysema, chronic bronchitis, and related conditions). Smokers have been found to suffer more respiratory problems (such as colds, pneumonia, influenza, and bronchitis) and their recovery from those illnesses is slower.

- For men under age 65, smoking has been shown to be an independent risk factor for impotence, including erectile dysfunction. For women, smoking can impair fertility, induce premature menopause and spontaneous abortion, and lead to a host of complications of pregnancy and childbirth.

- Cigarette smoking increases the risk for osteoporosis (a reduction in bone mass) and periodontal (gum) disease.

- Smoking precipitates vision problems, including blindness secondary to cataracts and macular degeneration, and premature hearing loss.

- Smokers face a significantly greater chance than do nonsmokers of suffering complications during and after surgery.

Evidence suggests that smoking also increases the risk for other diseases, such as rheumatoid arthritis, and cancers of the prostate and stomach. Those relationships, however, have not yet been scientifically established.

Preliminary research also indicates that cigarette smoking may be associated with reduced risk for endometrial cancer and Parkinson's disease. Yet the harmful effects of cigarette smoking dramatically outweigh any of its potential benefits.

ENVIRONMENTAL TOBACCO SMOKE

A MOUNTING BODY OF SCIENTIFIC research reveals that exposure to environmental tobacco smoke (ETS) also

poses health risks. The most common and firmly established adverse health effects associated with exposure to ETS are irritation of the eyes, nose, and respiratory tract; exacerbation of asthma and emphysema; and increased susceptibility to respiratory infections. Furthermore, studies have consistently shown that ETS contributes to lung cancer and heart disease. (See *Environmental Tobacco Smoke, Health Risk or Health Hype?*, a 1999 report by the American Council on Science and Health.)

As Levy and Marimont's article itself illustrates, concerns about secondhand smoke extend far beyond public health. The political implications of finding a causal association between ETS and disease have fueled long and bitter struggles between pro- and anti-tobacco organizations and individuals. In an effort to resist the trend toward indoor-smoking restrictions and to allay public fears, some parties, including the tobacco industry, have argued that ETS does not pose a "meaningful" lung cancer risk—and therefore does not present a threat to public health.

Similarly, authors Levy and Marimont focus their arguments about secondhand smoke exclusively on lung cancer in an attempt to dismiss all of the health effects associated with ETS. Their argument is simplistic, as it ignores ETS-related health risks other than lung cancer—heart disease and respiratory illnesses, for example—that should also be considered when developing public health policy.

ESTABLISHING CAUSE AND EFFECT

SCIENTISTS RELY ON EPIDEMIOLOGY—the study of the distribution and determinants of disease frequency—to determine whether a factor, such as cigarette smoking, causes a particular health outcome, that is, disease or death. They begin by suggesting and then establishing an association.

The best way to evaluate the effect of smoking on health is to compare groups of smokers with groups of nonsmokers to assess the differences between them (if any) in health outcomes. Researchers try to ensure that, aside from smoking, the smokers and

nonsmokers have similar characteristics, so that differences in health outcomes are more likely attributable to smoking than to other factors. Statistical analysis of the research data can help to explain differences in health outcomes attributable to smoking, even where there are dissimilarities between the groups.

When an association is found between smoking and disease or death, researchers must determine whether the apparent association is valid. A valid association is unlikely to be the result of chance, bias on the part of researchers or study participants, or confounders—other factors that caused the disease and are independently associated with smoking.

Statistical tests are routinely applied to research findings to assess the probability that the results are "statistically significant" and not merely coincidental. A test for statistical significance takes into account such factors as the number of persons examined (sample size) and the strength of the association between the exposure and the health outcome. Generally, the larger the sample size and the stronger the association, the more likely it is that the results will be found to be significant.

Even if a result is statistically significant, bias and potential confounders must be addressed to demonstrate a valid association. Furthermore, a statistically significant finding does not alone confirm a causal relationship. To conclude that smoking causes a particular disease, researchers must assess the relationship against five criteria:

Strength of the association found between smoking and disease. Relative risk is the ratio of disease among smokers to disease among nonsmokers. A relative risk of 1 indicates that there is no association between the exposure and the outcome. The closer relative risk is to 1, the smaller or weaker the association.

A relative risk of 2, for example, would indicate that smokers are twice as likely as nonsmokers to develop the health outcome under study (e.g., death from heart disease). The larger the relative risk, the less likely an association can be attributed solely to bias or con-

founders. But a small relative risk does not exclude the possibility of a causal relationship, nor does it preclude the possibility that the relative risk is statistically significant.

Consistency of the finding across studies. If several well-designed studies replicate a finding, the more likely it that the relationship being studied is real. As stated previously, the enormous body of research on the health effects of smoking corroborates the relationship between smoking and disease.

Biological plausibility of the hypothesis. The relationship between an exposure and a disease must be consistent with what is known about biology and the disease. Much is understood about the biological mechanisms by which smoking causes disease, though more remains to be learned. It is known that cigarette smoke contains approximately 4,000 chemical components, many of which are toxins and some of which are human carcinogens.

Presence of a dose-response relationship. In a dose-response relationship, risk increases with the degree of exposure. Many studies have shown that increases in the duration of cigarette use and number of cigarettes smoked increase the risk for smoking-related disease and death.

Sequence of cause and effect. The exposure or hypothesized cause must precede the effect. There is ample research to affirm that cigarette use precedes adverse health outcomes.

We will apply these five principles below, when we assess Levy and Marimont's claims.

CALCULATING PREMATURE DEATHS CAUSED BY CIGARETTE SMOKING

THE NUMBER OF DEATHS ATTRIBUTABLE to cigarette smoking may be thought of as the reduction in the number of deaths that would obtain if no one had ever smoked. That reduction is essentially estimated in the following way:

1. Apply death rates for smoking-

related diseases among representative nonsmokers to the entire population. That gives the number of deaths expected if everyone were a nonsmoker.

2. Subtract the expected number of deaths from the actual number of deaths.

The calculation is complicated by the fact that the many people who have smoked and quit have a greater risk of smoking-related disease than do people who have never smoked. Therefore, some formulas, such as that used by the Centers for Disease Control and Prevention (CDC), distinguish between current smokers, former smokers, and "never-smokers" in estimating the incidence of smoking-related deaths.

Estimates of the death toll from smoking can vary widely, depending on what diseases are considered smoking-related, the data sources used, the control for confounding variables (e.g., age), and variations in formulas.

For more than two decades, the U.S. government has been estimating the number of Americans who die prematurely from smoking. The government currently estimates that about 430,000 deaths occur each year in the United States as a result of cigarette smoking. (Higher estimates fall in the range of 600,000 to 700,000 annual deaths.)

ASSESSMENT OF LEVY AND MARIMONT'S CHARGES

IN "LIES, DAMNED LIES, & 400,000 SMOKING-Related Deaths," Levy and Marimont challenge the reality of the associations found between smoking and disease and, ultimately, the veracity of the estimate that smoking causes 400,000 premature deaths a year. The authors try to minimize smoking's death toll by using largely haphazard and unscientific methods. Here, we assess Levy and Marimont's key arguments.

Argument 1 *Relative risks less than 2 are "statistically insignificant" and "insufficiently reliable to conclude that a particular agent (e.g., tobacco) caused a particular disease." Based on that claim, Levy and Marimont subtract more than 160,000 of the 400,000 annual deaths caused by smoking.*

A relative risk less than 2, although small, can be statistically significant and can reflect a causal relationship. Given the pervasiveness of a risk factor, such as smoking, and the prevalence of some of the diseases it causes, small relative risks can, and do, represent a serious threat to public health. For example, cigarette smoking is a much greater risk factor for mortality from lung cancer than from heart disease. But because heart disease affects many more people than lung cancer, the number of smoking-related deaths from heart disease rivals those from lung cancer.

Levy and Marimont's assumptions regarding small relative risks violate basic principles of epidemiology. The authors confuse two distinct concepts, that of relative risk and that of statistical significance.

The size of a relative risk, alone, does not signify its statistical significance. Rather, as explained earlier, a research finding must undergo statistical tests to assess its "significance." A small relative risk suggests a weak association (or risk factor), not necessarily an insignificant finding. Again, a small relative risk may have a substantial effect on public health if the exposure affects a large proportion of the population.

Moreover, the value of a relative risk, in itself, does not imply a causal relationship between risk factor and disease. As discussed above, relative risk is one of several factors that must be considered when judging causality. Judged in that light, a small relative risk may reflect a causal relationship.

Levy and Marimont offer a good illustration of this point. In their derision of the risks associated with ETS, Levy and Marimont claim that "the relative risk of lung cancer for persons who drink whole milk is 2.4." Even if we accept this highly dubious association, the other criteria necessary to judge causality (biological plausibility, consistency of findings, etc.) are not fulfilled. Thus, whole milk cannot legitimately be judged a cause of lung cancer on relative risk alone.

The authors mislead readers by misrepresenting a quotation from the National Cancer Institute (NCI), which qualifies relative risks, as the agency's

“own guideline.” In fact, NCI has no such guideline about relative risks, and the quotation cited is taken from a 1994 NCI press release on abortion and the risk of breast cancer. Taken in context, the so-called guideline makes a much different point than the one suggested by the authors.

In sum, Levy and Marimont arbitrarily, and without scientific justification, reduce CDC’s estimate of smoking deaths by 163,071 by asserting that a relative risk less than 2 is statistically insignificant. But, as we have argued, their logic is fundamentally flawed.

Argument 2 The American Cancer Society’s Cancer Prevention Survey (CPS)—a widely used data set for the calculation of public health statistics—is unrepresentative of the general population and is therefore “the wrong sample [to use] as a standard of comparison” when estimating smoking-related deaths in the United States.

It is true that the American Cancer Society’s CPS has greater proportions of white, older, more educated, married, and middle-class people than the entire U.S. population. That, alone, does not invalidate findings derived from CPS. It has a uniquely strong study design, from which valid estimations have been drawn.

Moreover—and perhaps more important—the relative risks of dying from smoking-related diseases, as estimated from CPS, are within the range of estimates from other studies. That consistency lends credence to CDC’s estimate of smoking-related deaths, which is based on relative risks drawn from CPS.

The important issue whether a particular study’s results are applicable to other populations should be considered only after determining the study’s validity. Levy and Marimont overlook the overriding strengths of CPS: its excellent study design and valid findings. With more than one million participants, CPS is the largest U.S. study that collects data over an extensive period of time on the relationship between smoking and mortality.

After accepting that the results of CPS

reflect valid cause and effect relationships, the next important question is how the results for a mostly white, middle-class population would differ, if at all, from those for the entire United States. The answer depends on how the data are used. The absolute mortality rates are lower in CPS than in the general population, but CDC’s estimation of smoking-related deaths relies on ratios from CPS—relative risks for smokers and former smokers. Those relative risk estimates are close to relative risk estimates from other studies, which corroborates the reliability of CDC’s estimate.

Levy and Marimont advocate sub-

Levy and Marimont fail to present a sound argument that the estimate of 400,000 annual smoking-related deaths is a gimmick.

stituting data from the National Center for Health Statistics (specifically, the National Mortality Followback Survey and the National Health Interview Survey) for data from CPS, as does long-time tobacco industry consultant T.D. Sterling. However, Sterling’s work has been criticized, justly, for its implausible findings (e.g., previous smoking was found to be protective against coronary heart disease and cerebrovascular disease among males over age 65), and for combining data from two surveys with largely dissimilar, and thus incompatible, study designs.

By contrast, CPS uses an appropriate study design to derive valid estimates of relative risk: following large cohorts of smokers and nonsmokers over an appropriate length of time to observe health outcomes.

Argument 3 cdc fails “to control for obvious confounding variables” in its estimation of smoking-related deaths. Levy and Marimont argue that after accounting for other factors that may contribute to deaths among smokers, cdc’s estimate should be greatly reduced.

CDC’s estimate of annual smoking-related deaths does control for age, the confounding variable that has the great-

est effect on the association of smoking with disease and death. Analyses that have controlled for several factors (e.g., exercise and alcohol intake) indicate a minimal effect of potential confounders on the age-adjusted risk of disease or death from smoking.

According to Levy and Marimont, “if a smoker who is obese, has a family history of high cholesterol, diabetes, and heart problems, and never exercises dies of a heart attack, the government attributes his death to smoking alone.” What the authors are reasonably questioning here is the effect of potential confounders—other factors that may explain some of the deaths attributed to smoking—on estimates of smoking-related deaths. For some diseases, the influence of confounders is trivial—smoking causes approximately 87 percent of lung cancers, for example. But for diseases that have sev-

eral significant risk factors, such as cardiovascular disease, the effect of confounders may indeed be significant.

As Levy and Marimont point out, failing to account for confounders can cause inaccurate estimates of smoking-related deaths. But the authors incorrectly assume that CDC’s age-adjusted estimate would be reduced significantly by controlling for potential confounders. In fact, it has been shown that controlling for confounders can cause increases in attributable risk, which suggests that CDC’s estimate might be conservative.

When assessing the effect of confounding variables on CDC’s estimate, it is important to consider the results of studies that have examined the effects of confounders on smoking risk. The Nurses’ Health Study (NHS)—a well-designed, prospective cohort study, with 12 years of followup on registered nurses in the United States—controlled for many potential confounders, including hypertension, diabetes, high serum cholesterol, weight, parental history of heart attack before age 60, past use of oral contraceptives, postmenopausal estrogen use, and age at which smoking started. NHS found a multivariate relative risk of 1.87 for death of current

smokers compared with “never-smokers,” almost the same as their age-adjusted estimate of 1.86. NHS also found a slight strengthening of the association between current smoking and mortality from cardiovascular disease, after adjusting for alcohol and exercise.

In a 1997 analysis of the CPS data used by CDC, Battelle controlled for risk factors—including age, education, alcohol intake, diabetes and hypertension—and found smoking-related mortality estimates for the combined disease categories of lung cancer, ischemic heart disease, bronchitis/emphysema, chronic airway obstruction, and cerebrovascular disease to be 2 percent higher than CDC’s age-adjusted estimates.

Thus, contrary to Levy and Marimont’s claim, the available data strongly suggest that further adjustment for potential confounders other than age would have little effect on CDC’s estimate of roughly 400,000 smoking-related deaths a year.

Argument 4 Smoking-related mortality is overstated, particularly with respect to children, given that the majority of smoking-related deaths occur late in life.

In fact, it has been estimated that more than half of all smoking-related deaths occur between ages 35 and 69, which translates into an average loss of roughly 23 years of life. Cigarette smoking also accounts for approximately 30 percent of all deaths among those 35–69 years of age. That the majority of deaths from smoking occur among adults does not mitigate the real risks that cigarettes pose to children.

Levy and Marimont aver that smoking “kill[s] people at an average age of roughly 72—far closer to 99 than to childhood or even young adulthood.” This unreferenced assertion is inconsistent with studies suggesting that the average age of death among smokers is much less than 72 years.

It is important to consider that what the authors are reporting is an average age of death. Cigarette smoking kills people at ages much less than 72, as well as at ages much greater than 72. Long-term, followup studies have found that smokers are three times more likely to die between the ages of 45 and 64,

and two times more likely to die between the ages of 65 and 84, than are nonsmokers. Thirty-three percent of nonsmokers live to age 85, while only 12 percent of smokers live that long.

Levy and Marimont insinuate that the deaths of older adults should not be considered premature or preventable. But many adults remain healthy into their eighties and nineties. It is inappropriate to set an arbitrary age limit on premature death. A premature, preventable death is a premature, preventable death at any age. The authors’ underlying assumption is that deaths among the elderly are less consequential than deaths among the young, a “modest proposal” that controverts the fundamental, humanitarian principle of medicine and public health: all human lives are valuable.

In an effort to minimize the impact of smoking-related mortality, Levy and Marimont present smoking-related deaths in terms of years of potential life lost (YPLL). The authors, however, rely on an outdated way of calculating YPLL, by considering only those years under age 65. YPLL is more accurately calculated from life expectancy, which extends well beyond age 65.

After inappropriately comparing smoking-attributed mortality with immediate deaths from motor vehicle accidents, suicide, and homicide, the authors state that “measured by YPLL, tobacco was... not ‘the number one killer in America’ as alarmists have exclaimed.” Some premature, preventable deaths with causes other than smoking do occur at a much younger age than deaths caused by smoking. But given the vast number of deaths caused by cigarette use, smoking remains the leading cause of preventable death.

It is important to note that YPLL is just one of many measures representing the public health effect of a risk factor. Aside from mortality due to smoking, the authors fail to take into account smoking-related morbidity and the poor quality of life that often accompanies the chronic illnesses caused by cigarette smoking.

The authors assert that the concern about smoking among young people is unfounded because the majority of

cigarette-related deaths occur later in life. They suggest that alcohol and drug abuse are more legitimate threats to the young. However, the dangers from alcohol and drug abuse do not preclude the dangers of cigarette smoking.

Cigarettes and cigarette smoke contain nicotine, a powerfully addictive drug. People who begin smoking as children are more likely to become lifetime smokers and, therefore, to die from smoking-caused disease. Smoking at a young age (or any age) causes irreversible genetic and cellular damage that may take years to emerge as disease. Furthermore, studies have found that cigarette smoking is associated with, and tends to precede, alcohol and illicit drug use—the very behaviors Levy and Marimont deem most threatening to children.

Levy and Marimont’s arguments obscure the real risks associated with cigarette smoking—effects that may not be immediately observed, but are harmful nonetheless.

CONCLUSION

Levy and Marimont fail to present a scientifically sound and convincing argument that the estimate of 400,000 annual smoking-related deaths is a specious, statistical gimmick. In an effort to minimize smoking’s death toll, they make unsupported assumptions about the effects of potential confounders and inappropriately dismiss relative risks less than 2. Moreover, their criticisms of the CPS data and their disregard for the long-term effects of cigarette smoking are misguided. We conclude that the estimate of 400,000 annual deaths from cigarette smoking is indeed reliable and may even be an underestimate.

“Lies, Damned Lies, & 400,000 Smoking-Related Deaths” does, however, bring to light some reasonable questions that the public may share about the methods used to determine smoking-related deaths. The article clearly illustrates the importance of educating nonscientists about basic epidemiological and biostatistical concepts.

In their conclusion, the authors make further misleading and unscientific claims, stating, for example, that “the actual damage from smoking is neither

known nor knowable with precision.” But as we have said, smoking and tobacco use is the most-studied health risk factor in the history of human health research. In fact, the first report of diminished life span among smokers appeared in 1938. The pathological effects of chronic tobacco use in individuals are well documented. Using rigorous study designs and analytical methods, scientists have established with a high degree of certainty the causal role of tobacco in disease and death.

Levy and Marimont suggest that the “correctly calculated number of smoking-related deaths” is about 100,000 a year. Even if one were to accept the authors’ gross miscalculation, is not the premature, debilitating, and often painful death of “only” 100,000 Americans (of any age) worthy of being addressed as a significant public health problem?

The authors might well heed their own advice when they criticize federal officials for “tainting science to advance predetermined ends.” By straying from basic epidemiological principles in their arguments, and by touting opinions that masquerade as facts, the authors have themselves strayed far from science.

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The Authors Respond

OUR REGULATION ARTICLE “LIES, Damned Lies, & 400,000 Smoking-Related Deaths” exposes the pseudo-scientific, antismoking emissions of the Centers for Disease Control and Prevention (CDC). For that service, we stand accused by Ms. Lukachko and Dr. Whelan of “straying from basic epidemiological principles” and “touting opinions that masquerade as facts.” In response, we examine Lukachko and Whelan’s four specific charges, then offer some concluding comments.

RELATIVE RISK

LUKACHKO AND WHELAN CLAIM THAT we erroneously omit certain diseases on

the ground that relative risks of less than 2 (a 100 percent increase) are “insufficiently reliable to conclude that a particular agent (e.g., tobacco) caused a particular disease.” Well, consider this cautionary statement: “Relative risks less than 2 are considered small.... Such increases may be due to chance, statistical bias, or effects of confounding factors that are sometimes not evident.” That statement comes not from us, but from a 1994 release by the National Cancer Institute (NCI), referring to a study of abortion and breast cancer.

As Lukachko and Whelan point out, epidemiological principles are not dependent on the specific variables under investigation. If a relative risk of less than 2 confirms the politically correct view that an association between abortion and breast cancer has not been demonstrated, then the same relative risk supports the politically incorrect view that an association between smoking and various diseases is likewise suspect. Not surprisingly—at least to those of us who have followed both the tobacco wars and the abortion debate—NCI goes to great lengths to dispute the potentially harmful effects of abortions while it trumpets the harmful effects of cigarettes, applying equally dubious evidence.

But do not take our word. A special report from *Science* magazine illuminates the real world of epidemiology in practice. From Gary Taubes’s article, “Epidemiology Faces Its Limits” (*Science* 269, July 14, 1995: 164), here is what respected scientists from both the public and private sector, within the United States and without, have said about low relative risks.

- Sir Richard Doll of Oxford University: “No single epidemiological study is persuasive unless one can be statistically confident of at least a threefold increase in risk.”

- Harvard researcher Dimitrio Trichopoulos: “A fourfold risk increase is the lower limit.”

- Marcia Angell, editor of the *New England Journal of Medicine*: “As a general

rule of thumb, we are looking for a relative risk of three or more before accepting a paper for publication.”

- Robert Temple, director of drug evaluation at the U.S. Food and Drug Administration: “If the relative risk isn’t at least three or four, forget it.”

- And from interviews conducted by *Science* magazine: “Most epidemiologists...said they would not take seriously a single study reporting a new potential cause of cancer unless... exposure to the agent in question increased a person’s risk by at least a factor of three.” Even then, interviewees warn, “skepticism is in order.”

Yet Lukachko and Whelan assure us that “a relative risk less than 2, although small, can indeed be statistically significant.” Well, yes, that is certainly true—and completely irrelevant, as even they concede. Statistical significance measures chance error, which depends in part on risk levels for smokers and nonsmokers, and in part on sample size.

All else equal, given a specified background risk among nonsmokers, the smaller the relative risk, the less likely that the difference in risk between smokers and nonsmokers is statistically significant. Still, large samples can produce statistically significant results even when the relative risk is low. But that is not the point at all.

A relative risk less than 2 means that it is less probable, though not impossible, that a relationship is statistically significant. (In an unrelated section of our article, we imprecisely said that “the relationship between parental smoking and pediatric diseases carries a risk ratio of less than 2, and thus is statistically insignificant.” We should have said “epidemiologically unsubstantiated” rather than “statistically insignificant.” Except for that inconsequential lapse, we were quite careful throughout the article not to equate low relative risk and statistical insignificance, although the two are often linked.)

Low relative risk may indicate that a study did not adequately control for confounding variables or that it was

affected by bias on the part of researchers or participants. Thus, statistical significance is necessary to demonstrate that a study is valid—it denotes low probability of sampling error—but it is not sufficient. The potential problems associated with confounders and bias do not disappear merely because of a large sample size.

Lukachko and Whelan understand that concept quite well. As they correctly state, “Even if a result is statistically significant, *bias* and potential *confounders* must be addressed to demonstrate a valid association.” Astonishingly, having acknowledged that principle, they wholly disregard its implications. Relative risk is an indicator not only of statistical significance but also of possible confounders and bias. That is why epidemiologists uniformly hold that a low relative risk goes hand in hand with suspect validity.

Inexplicably, Lukachko and Whelan persist in arguing that a small relative risk can represent a serious threat to public health. In support, they point to the relationship between smoking and heart disease. The relative risk of smoking for many types of heart disease is less than 2. But heart disease kills many more people than lung cancer. Therefore, according to Lukachko and Whelan, “the number of smoking-related deaths from heart disease rivals those from lung cancer.” Verbal gymnastics, but manifestly untrue. The missing link is obvious: low relative risks mean that deaths from various types of heart disease have not been shown to be smoking-related. To characterize those deaths as “smoking-related” simply begs the question.

SAMPLE BIAS

NEXT, LUKACHKO AND WHELAN SAY that we incorrectly characterize the American Cancer Society’s Cancer Prevention Survey (CPS), on which CDC relies, as “the wrong sample [to use] as a standard of comparison.” They assert that the CPS database is perfectly acceptable as a standard of comparison even though it has “greater proportions of white, older, more educated, married, and middle-class participants than the

entire U.S. population.” In fact, the mortality rate for *smokers* in the CPS database is lower than that for *nonsmokers* in the general population. That is because CPS excludes most persons of lower socioeconomic status, who are comparatively less healthy whether or not they smoke, as we discuss more fully below.

In condoning the use of a thoroughly biased sample, Lukachko and Whelan ignore their own tutorial on calculating the number of smoking-related deaths. That calculation, they tell us, involves applying “death rates for smoking-related diseases among *representative* nonsmokers to the entire population [emphasis added].” By their own admission, the CPS database is far from representative. How then can Lukachko and Whelan square the use of that database with their directive to start the calculations with a representative sample of nonsmokers?

They offer three answers to that question. First, Lukachko and Whelan remind us that “the relative risks of dying from smoking-related diseases, as estimated from CPS, are within the range of estimates from other studies.” But that proves nothing if those “other studies” also rely on the CPS database. As Oxford epidemiologist David Sackett observed in Gary Taubes’s *Science* article, if the studies have the same design and “if there’s an inherent bias, it wouldn’t make any difference how many times it’s replicated. Bias times 12 is still bias.”

Second, Lukachko and Whelan justify CPS because of its large sample size. “With more than one million participants, CPS is the largest U.S. study that collects data over an extensive period of time on the relationship between smoking and mortality.” So what? As a leading text tells us, “When a selection procedure is biased, taking a large sample does not help. This just repeats the basic mistake on a larger scale” (David Freedman, Roger Pisani, and Roger Purves. *Statistics* [3d. ed.]. New York: W.W. Norton & Co., 1998, p. 335).

Put somewhat differently, large databases give us more reliable information about how closely sample statistics are likely to approach the average or other characteristic of the group that the sam-

ple *actually represents*. But increasing the sample size has absolutely no effect on how far off we may be because of a biased sample—that is, a sample that is not a fair selection from the universe we wish to study.

Third, Lukachko and Whelan volunteer this rationalization for CPS: Although “*absolute* mortality rates are lower in CPS than in the general population...CDC’s estimation of smoking-related deaths relies on ratios from CPS—relative risks for smokers and nonsmokers [emphasis in original].” That is, we are to assume that the relative risk between smokers and nonsmokers for, say, heart disease is the same no matter whether the database is disproportionately white, old, and better educated—like CPS—or non-white, young, and less well educated—like many of the persons omitted from CPS. Lukachko and Whelan do not try to justify that heroic assumption, nor could they. If there are reliable data for the people excluded by CPS, why were the data excluded? Rather than accept unverified pronouncements by Lukachko and Whelan, we would be better advised to heed this warning from the *Reference Manual on Scientific Evidence* (New York: Matthew Bender & Co., 1994): “If the sample is drawn from an underinclusive universe, there is no way to know how the unrepresented members would have responded” (p. 237).

CONFOUNDING VARIABLES

LUKACHKO AND WHELAN’S THIRD major criticism is that we overstate the problem of CDC’s failure “to control for obvious confounding variables.” Let us begin by specifying the problem.

A confounding variable is one that is correlated with both the outcome (e.g., heart disease) and the variable under investigation (e.g., tobacco use). To illustrate, there seems to be a close association between math scores and shoe size. Yet no one would suggest that big feet enhance mathematical ability, nor that math skills cause one’s feet to grow. The obvious confounding variable is age. As people grow older, they learn more about math and they wear larger shoes.

Similarly, in assessing the correla-

tion between smoking and various diseases, it is essential to control for a long list of factors: income, education, diet, exercise, family medical history, and occupation, to name a few. If those variables are omitted, a disparity in disease rates may mistakenly be attributed to cigarettes when the real problem may be elsewhere. For example, smokers, who are disproportionately lower-income blue collar workers, are exposed more often to other disease-causing agents.

Lukachko and Whelan unveil two studies that supposedly prove that estimates of the harmful effects of smoking are little affected by adjusting for potential confounders. First, there is the Nurse's Health Study (NHS). It relies on a database of registered nurses that is even less representative of the general population than is CPS. Participants in NHS had the same or very similar occupations, education, income, access to medical care, and working conditions—each of which can have a profound effect on health. After adjusting for hypertension, diabetes, high serum cholesterol, weight, parental history of heart attack before age 60, and a few other variables, NHS found “a multivariate relative risk of 1.87 for death of current smokers compared with ‘never-smokers,’ almost the same as CDC’s age-adjusted estimate of 1.86.”

Pardon us for belaboring the point, but a relative risk of 1.87 is an unsubstantiated risk. We understand that principle. Epidemiologists around the globe understand it. The National Cancer Institute understands it—at least when the agency conducts itself less like an anti-tobacco zealot and more like the sponsor of dispassionate science it is supposed to be. In short, everyone with the apparent exception of Lukachko and Whelan knows that relative risks below 2 are insufficient to substantiate an epidemiological association.

Then there is the 1997 Battelle report, which claims to have controlled for education, alcohol, diabetes, and hypertension. Battelle’s estimates of

smoking-related deaths for various diseases are *higher* than CDC’s estimates. But Lukachko and Whelan neglect to disclose that the Battelle report was prepared specifically for CDC; it was not peer reviewed; and it did not control for potential confounders like diet, exercise, income, and occupational exposure. By comparison, the Sterling study, which we cite, was published in the *American Journal of Epidemiology*; it found that smoking-attributable death counts declined by 55 percent after simultaneous adjustments for alcohol consumption and income.

Lukachko and Whelan dismiss the

Clearly, the evidence demands that any respectable analysis of the ill effects of smoking must control for socioeconomic status.

Sterling article, citing criticism that appeared in two letters to the editor. To dismiss a peer-reviewed article in a respected publication like the *American Journal of Epidemiology* on the basis of two letters to the editor is rather peculiar.

Most important, neither the NHS study nor the Battelle study takes into account the single confounding variable that nearly every researcher regards as key: socioeconomic status (SES). Indeed, the databases used in both studies entirely exclude persons in the lower strata of SES. Yet, SES—typically determined from household income, educational level, and occupational status—is closely associated with both smoking and health. The National Institutes of Health thought the subject important enough to hold a two-day conference on SES and cardiovascular disease in 1995. The conference report (available at www.nhlbi.nih.gov/resources/docs/ses.txt) concluded that low SES is correlated with (1) a higher prevalence of smoking and (2) an unfavorable pattern of “major lifestyle and biomedical risk factors” for cardiovascular disease. Both propositions have been con-

firmed independently.

For example, economist W. Kip Viscusi determined that lower income families consume a larger amount of tobacco—unlike most commodities—than higher income families. Based on 1990 data, Viscusi reports that smoking prevalence was 31.6 percent among adults having annual family income below \$10,000. By contrast, only 19.3 percent of adults smoked in the \$50,000 and over income class. (Viscusi’s findings are cited in a Congressional Research Service study available at www.senate.gov/~dpc/crs/reports/ascii/97-995.)

In 1998, the U.S. Department of Health and Human Services (HHS) released, for the first time, statistics on the effect of income inequality on the health of the U.S. population. The HHS report found that white men who were 45 years of age dur-

ing any year from 1979 to 1989, and who had a family income of at least \$25,000, could expect to live 6.6 years longer than white men with a family income less than \$10,000. For black men, the effect of higher income was an increase of 7.4 years in life expectancy. (HHS’s “National Longitudinal Mortality Study” is available at www.wsws.org/news/1998/oct1998/hhs-o02.shtml.)

As we reported in our article, a 1991 RAND Corporation study concluded that smoking “reduces the life expectancy of a 20-year-old by about 4.3 years.” Clearly, the evidence demands that any respectable analysis of the ill effects of smoking must control for SES, among other factors.

According to the *New York Times*, in the past five years 193 papers addressing aspects of SES and health have appeared in scientific journals. (See “For Good Health, It Helps to Be Rich and Important,” by Erica Goode, June 1, 1999.) Has that focus on SES somehow eluded Lukachko and Whelan? We do not know. But the literature is both pervasive and unambiguous. From the *Times* piece, we learn that “an explosion of research is demonstrating that social class... is one of the most pow-

erful predictors of health, more powerful than genetics, exposure to carcinogens, even smoking... The higher the rung on the socioeconomic ladder, the lower the risk" for many diseases, including cardiovascular disease and some types of cancer.

Yes, one explanation could be that less affluent people engage in more risky behavior, such as smoking. But the *Times* also reports that "the same health disparity from pay grade to pay grade...held for nonsmokers, too." Thus, low income affects health in a manner that, in part, is independent of smoking. Smokers, who disproportionately have lower incomes, may therefore contract various diseases not because they smoke but because they are relatively poor. Failure to control for SES renders any study of tobacco-related deaths not only incomplete but also positively misleading.

AGE AT DEATH

FINALLY, LUKACHKO AND WHELAN RAISE a series of objections to our data on the age distribution of smoking-related deaths. First, they characterize as "unreferenced" our statement that "smoking kills people at an average age of roughly 72." That is just careless reading on their part. The statistic appears in our Table 2, which is quite clearly referenced to CDC. Elsewhere in the article, we indicate that CDC provided age distribution data to us in a private communication, which we will make available to Lukachko and Whelan and anyone else who is interested.

Second, we are admonished that the statistics are a lot worse than we say they are. For instance, Lukachko and Whelan write that "more than half of all smoking-related deaths occur between ages 35 and 69, which translates into an average loss of roughly 23 years of life." Evidently, they arrive at a loss of 23 years by subtracting the simple average of 35 and 69 (52) from 75. That calculation is disingenuous, at best, because the distribution of deaths between ages 35 and 69 is heavily tilted toward the lat-

ter years. Here are the actual statistics, as provided by CDC:

age at death	number of deaths
35-39	3,519
40-44	6,733
45-49	11,742
50-54	18,623
55-59	29,562
60-64	48,670
65-69	52,367

Using the midpoint of each age group, the *weighted* average age at death is not 52 as calculated by Lukachko and Whelan, but 59. Therefore, the loss of

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life to age 75 is not 23 years but a more modest 16 years. Bear in mind that the calculation—for reasons known only to Lukachko and Whelan—excludes the 59.5 percent of smokers who die at age 70 or greater and thus lose far fewer, if any, years of expected life.

Third, Lukachko and Whelan quarrel with our reference to the 72,000 smokers who die at age 85 and greater. They do not dispute the number but, rather, our criticism of public health officials who call those deaths "premature"—as if we were all destined to live eternally. Lukachko and Whelan remind us that "many adults remain healthy into their eighties and nineties. It is inappropriate to set an arbitrary age limit on premature death."

That exercise in polemics corrupts the language and robs "premature" of its meaning. By Lukachko and Whelan's logic, all deaths are premature. If, as the dictionary suggests, premature deaths are those "occurring prior to the customary time," then deaths at age 85 are not premature. On the other hand, if all deaths are premature, the term "premature death" is mere tautology and ought to be purged from CDC's lexicon.

Fourth, alas, we have been indicted

for assuming "that deaths among the elderly are less consequential than deaths among the young." Predictably outraged, Lukachko and Whelan trot out the "fundamental, humanitarian principle of medicine and public health: all human lives are valuable." We are tempted to say, "Give us a break," and leave it at that. But perhaps a few words are in order.

In Washington, D.C., there is a tried-and-true—but utterly cynical—maxim: Any policy initiative can be sold if it is pitched as being for the benefit of children. That is why we hear ad nauseam about the number of kids who start smoking each day and how many of them will die from a tobacco-related illness. Never mind that the statistics are bogus; where there is a political objective, science be damned. When the public health community abandons demagoguery in favor of

science, perhaps we can engage in substantive debate. Meanwhile, there can be no greater hypocrisy than for Lukachko or Whelan or any of their allies in the tobacco wars to criticize us for distinguishing between deaths among the old and deaths among the young.

The plain truth, as we reported, is that children do not die of tobacco-related illnesses, correctly determined. Children who become heavy smokers in their teens may die of lung cancer in their old age, fifty or sixty years later, assuming lung cancer is still a threat then. If that sounds Pollyanna-ish, consider this, from a page-one story in the *New York Times* (July 8, 1999): "Death rates from lung cancer could be greatly reduced if smokers and former smokers were routinely given CAT scans of their lungs." According to the *Times*, CAT scans are now available for as low as \$300; they could change the lung cancer survival rate from its current level of 12-15 percent to an astounding 80 percent. That is a difference of more than 65 percentage points—an annual reduction of more than 100,000 deaths. The estimated economic benefit is \$1.5 billion a year, which would more than cover the cost of screening.

Advances in medicine are occurring at an incredible rate. Only recently was the map of human chromosome number 22 completed. In a few years, the complete genome will be known. Imagine, if you can, the extent of medical progress in the next half-century. It is rather extraordinary that our public policy seems centered almost exclusively on tobacco-related illnesses, which may affect our children 50 years from now, even as we assign relatively fewer resources to tackling problems like homicides, suicides, and alcohol and drug abuse, which are destroying young lives here and now.

CONCLUDING COMMENTS

THAT BRINGS US, FINALLY, TO A FEW loose ends we would like to tie up. First, on a personal note, one of us—Rosalind B. Marimont—retired after 37 years at the Bureau of Standards and the National Institutes of Health (NIH). Although that fact was noted conspicuously in our article, Lukachko and Whelan somehow omitted any reference to NIH in their biographical sketch of Marimont. Yet they mentioned that she had testified against a Maryland antitobacco ordinance. That (unpaid) testimony lasted all of five minutes, in contrast to the 19 years she spent at NIH. The inclusion of one item and the exclusion of the other is most curious.

Second, we are wrongly censured for stating that “the hazards of smoking remain largely speculative.” What we actually said is quite different, indeed mostly contrary: “Evidence does suggest that cigarettes substantially increase the risk of lung cancer, bronchitis, and emphysema. The relationship between smoking and other diseases is not nearly so clear.”

Third, we are rebuked for focusing our arguments about secondhand smoke on lung cancer, thus ignoring “irritation of the eyes, nose, and respiratory tract; exacerbation of asthma and emphysema; and increased susceptibility to respiratory infections.” In fact, we mentioned secondhand smoke in but two contexts: (1) a study by the World Health Organization (WHO), which WHO fraudulently promoted by proclaiming that “Passive Smoking

Does Cause Lung Cancer,” and (2) an Environmental Protection Agency (EPA) report entitled “Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders,” which asserted without justification that secondhand smoke “is a Group A carcinogen that causes approximately 3,000 lung cancer deaths per year among non-smokers.” So it was WHO and EPA, not we, that framed the secondhand smoke issue. As to “irritation of the eyes,” etc., we were, after all, writing about the calculation of smoking-related deaths, not about every comparatively minor ailment that might somehow be connected to tobacco.

Fourth, Lukachko and Whelan contend that we “fail to take into account smoking-related morbidity and the poor quality of life that often accompanies the chronic illnesses caused by cigarette smoking.” Again, our article was directed at the number of deaths, not the number of chronic illnesses, not the financial costs, not the addictive nature of nicotine, not any of a myriad of other problems that we elected not to address.

That said, we did cite, in passing, a study in the *American Journal of Preventive Medicine* that looked at medical treatment measured by days of hospital care—a fairly good proxy for poor quality of life. On that basis as well, smoking is not the number one health problem in America, as alarmists would have us believe. For example, both nonalcohol-related injuries and nutrition-related diseases are considerably more burdensome than tobacco.

Fifth and last, Lukachko and Whelan ask rhetorically, “is not the premature, debilitating, often painful death of ‘only’ 100,000 Americans (of any age) worthy of being addressed as a significant public health problem?” The answer is self-evident, but the question is intended to generate more heat than light. Let us be unmistakably clear: Smoking is a public health problem; 100,000 deaths or some lesser number is a public health problem; we are against premature, debilitating, and painful deaths—yes, even of old people. But none of that has much to do with our original article.

We started that article with this declaration: “Truth was an early victim in the battle against tobacco.” We ended the article with this admonition: “When that goal [i.e., truth] yields to politics, tainting science in order to advance predetermined ends, we are all at risk. Sadly, that is exactly what has transpired as our public officials fabricate evidence to promote their crusade against big tobacco.” Our essential points are that government has lied to us, junk science has replaced honest science, and we have been propagandized by an avalanche of misinformation—much of it from those who should know better, some of it from those who do know better. Those problems are every bit as troublesome as the harmful health effects of a legal product that 45 million Americans consume with full knowledge of its risks, that 45 million other Americans have elected no longer to consume, and that, unhappily, will kill members of both groups—but far fewer than 400,000 per year—at an average age of 72, until we find cures for their diseases.

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Addendum to a Book Review

IN MY REVIEW OF *Why People Don't Trust Government*, edited by Nye, Zelikow, and King (*Regulation*, Vol. 22, No. 3), I claimed (among other things) that “Nowhere can be found the libertarian perspective.” That claim is factually untrue. There are at least four clear mentions, and some discussion, of the argument that people might fear government because it is worth fearing.

I am still ready to defend the position that the argument is not taken seriously enough, but that is my own subjective assessment, and it is very different from “never mentioned.”

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