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Author(s): Charles Poole

Source: *Epidemiology* , January 2010, Vol. 21, No. 1 (January 2010), pp. 3-9

Published by: Lippincott Williams & Wilkins

Stable URL: https://www.jstor.org/stable/25662798

Editors' note: *This series addresses topics that affect epidemiologists across a range of specialties. Commentaries start as invited talks at symposia organized by the Editors. This paper was presented at the 2009 Society for Epidemiologic Research Annual Meeting in Anaheim, CA.*

On the Origin of Risk Relativism

Charles Poole

The epidemiologic traditions that relative effect measures should be used to assess causality and that absolute measures should be used to assess impact are handed down from one generation to the next, without citation or critical reflection, as though their truth were self-evident.[1–17] Unlike other received views, these can be traced to a single source, a 1959 paper by Cornfield et al[18]:

> Both the absolute and the relative measures serve a purpose. The relative measure is helpful in (1) appraising the possible noncausal nature of an agent having an apparent effect; (2) appraising the importance of an agent with respect to other possible agents inducing the same effect; and (3) properly reflecting the effects of disease misclassification or further refinement of classification. The absolute measure would be important in appraising the public health significance of an effect known to be causal.

These general claims were embedded in a substantive controversy: the debate in the late 1950s and early 1960s over the health effects of cigarette smoking. This "landmark consensus paper"[19] was "the culminating scientific paper of the decade"[20] on the topic for some, but for others[21] it was not worth mentioning. However the paper may have influenced the debate, there is no doubt the debate influenced the paper.

CONTEXT

Until the mid-1950s, most of the epidemiologic evidence on cigarette smoking and health pertained to lung cancer. Most of that evidence came from case-control studies. Validity threats ran the gamut, from selection bias to confounding to information bias.[21] One hypothesis, "that cigarette-smoking and lung cancer, though not mutually causative, are both influenced by a common cause,"[22] achieved prominence on the authority of its chief proponent, Fisher. He could not name the completely explanatory confounder, but believed it was a feature of the genotype.

Meanwhile, considerations known today as "causal criteria" were under development. One list[23] appeared in the same year as the paper by Cornfield et al.[18] The criterion of specificity of effect was controversial from the start. Sartwell[24] flatly rejected it, but one of Cornfield's coauthors, Lilienfeld,[25] endorsed it with only mild qualification: "Generally speaking, it is difficult to quarrel with such a position, although there is a need to qualify the application of this criterion. Specificity of effect must be interpreted in terms of the degree of association of the characteristic with the disease."

Strength of association and specificity of effect thus became linked, as Susser[26,27] later noted they must be. An exposure's association becomes specific by being stronger for

From the Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC.
Editors' note: *Related articles appear on pages 13 and 10.*
Correspondence: Charles Poole, Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC 27599–7435. E-mail: cpoole@unc.edu.

ISSN: 1044-3983/10/2101-0003
DOI: 10.1097/EDE.0b013e3181c30eba

one outcome than for others. What remains, if one accepts the criteria, is to determine the scale for measuring strength.

In the mid-1950s, results from cohort studies began to appear.[21] They allowed examination of the strength, and thereby the specificity, of smoking's association with many outcomes. Berkson[28,29] took up the task enthusiastically, pointing to a lack of specificity in rate differences like those in Table 1. "For myself, I find it quite incredible that smoking should cause all these diseases. It appears to me that some other explanation must be formulated for the multiple statistical associations found with so wide a variety of categories of disease."[28] Berkson laced his skepticism with sarcasm: "The question raised by the findings is not, 'Does cigarette smoking cause cancer of the lungs?' so much as it is, 'What disease does cigarette smoking not cause?'"[29] It is easy to imagine such remarks eliciting laughter from clinicians and statisticians in the smoke-filled rooms of the day.

Opinions differed much more widely on other hypothetical smoking effects than on lung cancer. Among Cornfield's coauthors, Hammond and Horn[31] had concluded in 1954 that the association between smoking and coronary artery disease was causal, but in 1959 Lilienfeld[32] was still harboring grave doubts:

> It has been shown that smokers and nonsmokers differ with respect to emotional characteristics. Since there are clinical impressions that emotional factors may have an influence on such diseases as peptic ulcer and coronary artery disease, self-selection should be considered a possible explanation for the association of smoking with these diseases. Further investigation is necessary before a final decision can be made.

The 1964 Surgeon General's Advisory Committee[33] shared Lilienfeld's reservations: "Male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance."

This was the backdrop against which Cornfield et al[18] argued for the superiority of ratio effect measures over difference measures in assessing causality. The overall evidence was stronger and more plausible for lung cancer than for coronary artery disease and other diseases. The association seemed specific to lung cancer, or nearly so, when the rate ratio was the strength metric, but not for the rate difference. As the time had come "for planning and activating public health measures" based on lung cancer alone, the skeptics' persistence was beginning to seem like obstructionism.

TABLE 1. Death Rates, Ratios and Differences by Cigarette Smoking and Cause of Death in a Cohort Study of United States Men[30]

	Death Rate[a]			
Cause of Death	**Smokers**	**Nonsmokers**	**Ratio**	**Difference[a]**
Genitourinary system cancers	57	32	1.8	25
Oral, laryngeal and esophageal cancers	7	2	3.3	5
Other digestive system cancers	122	90	1.4	32
Lung cancer	104	10	10.7	94
Lymphatic and hematopoietic cancers	35	29	1.2	7
Cancers at other sites	24	24	1.0	0
Cancer of unknown site	16	4	3.9	12
Coronary artery disease	879	516	1.7	363
Other heart diseases	132	111	1.2	20
Cerebral vascular lesions	145	112	1.3	33
Other circulatory diseases	45	25	1.8	20
Non-neoplastic respiratory diseases	60	22	2.9	39
Cirrhosis of the liver	22	11	1.9	10
Gastric ulcer	46	0	∞	12
Duodenal ulcer	14	7	2.2	8
Other diseases	175	136	1.3	39
Accidents, violence, suicide	95	101	0.9	−6
Miscellaneous	127	118	1.1	9

[a]Deaths per 100,000 person-years.

ARGUMENT 1: THE CONFOUNDER-EXPOSURE ASSOCIATION

In their first formal argument for the risk ratio over the risk difference in assessing causality, Cornfield et al[18] showed how strong the association between a binary confounder and an exposure must be for the confounder to account for an association between the exposure and a disease. In the notation of Table 2, which differs slightly from the authors' notation, the confounder, present in both exposure groups, has a prevalence of p_0 among the unexposed and a higher prevalence of p_1 among the exposed: $0 < p_0 < p_1 < 1$. The crude risks of the disease within exposure levels may thus be written as weighted averages:

$$R_{1+} = p_1R_{11} + (1 - p_1)R_{10}$$

$$R_{0+} = p_0R_{01} + (1 - p_0)R_{00}$$

As the exposure has no effect, the risk is constant within levels of the confounder: $R_{11} = R_{01} = R_{\bullet 1}$ and $R_{10} =$

TABLE 2. Notation

Covariate (Z)	**Exposure (X)**	**Risk (R_{XZ})**
Yes (Z = 1)	Yes (X = 1)	R_{11}
	No (X = 0)	R_{01}
No (Z = 0)	Yes (X = 1)	R_{10}
	No (X = 0)	R_{00}
Total	Yes (X = 1)	R_{1+}
	No (X = 0)	R_{0+}

$R_{00} = R_{\bullet 0}$. The exposure's crude, confounded relative risk is:

$$RR_X^* = \frac{R_{1+}}{R_{0+}} = \frac{p_1 R_{\bullet 1} + (1 - p_1)R_{\bullet 0}}{p_0 R_{\bullet 1} + (1 - p_0)R_{\bullet 0}}$$

With $RR_Z = R_{\bullet 1}/R_{\bullet 0}$ denoting the unbiased relative risk for the confounder and the disease, Cornfield et al[18] rearranged this expression to form:

$$\frac{p_1}{p_0} = RR_X^* + RR_Z p_0[(1 - p_0)RR_X^* - (1 - p_1)] \quad (1)$$

Given $RR_Z > 1$, $p_0 > 0$, $RR_X^* > 1$ and $1 - p_0 > 1 - p_1$, the entire term to the right of the plus sign in expression [1] must be positive. Therefore, if a binary confounder is responsible for a spuriously elevated relative risk, the ratio of the confounder's prevalence in the exposed group to its prevalence among the unexposed must exceed that relative risk:

$$\frac{p_1}{p_0} > RR_X^* \quad (2)$$

With $RD_Z = R_{\bullet 1} - R_{\bullet 0}$ denoting the unbiased risk difference for the confounder and the disease, Cornfield et al began a parallel proof for the exposure's apparent risk difference, $RD_X^* = R_{1+} - R_{0+}$. They took it as far as the following expression:

$$RD_X^* = RD_Z(p_1 - p_0), \quad (3)$$

They left it there, asserting that expression [3] "leads to no useful conclusion about" $p_1 - p_0$.[18] It is obvious, however, given $0 < RD_Z < 1$, that expression [3] leads to:

$$p_1 - p_0 > RD_X^* \quad (4)$$

Thus, Cornfield et al stopped one step short of proving the following proposition: If a binary confounder is responsible for a spuriously elevated risk difference, the difference between the confounder's prevalence in the exposed and unexposed groups must exceed that risk difference.

Expression [2] came in handy in the discussion of smoking and lung cancer. As we shall see, expression [4], had it been recognized at the time, could have been useful in the discussion of smoking and coronary artery disease.

A LOST OPPORTUNITY

Fisher's[22] dogged promotion of his confounding hypothesis stimulated researchers, some of whom believed the association with lung cancer was causal, to compare psychological and behavioral characteristics between smokers and nonsmokers. They recognized that the burden for producing evidence relevant to a possible bias belongs not to those who suggest it,[34] but to those who would draw strong inferences and urge action from the potentially biased research.[35,36]

One such study was by Lilienfeld.[32] In this study, the "neurotic trait" most strongly associated with smoking was the response, "Very often," to the question, "Do you ever feel like smashing things for no good reason?" Bross[37] later called it "the bad temper variable" in replying to Brownlee,[38] who had continued to press Fisher's hypothesis in a critique of the 1964 Surgeon General's Advisory Committee report.[33]

The relative prevalence of bad temper in smokers and nonsmokers was $p_1/p_0 = 2.6$, which Lilienfeld[32] and Bross[37] both correctly recognized was too low for confounding by that variable to account for the reported rate ratios of 5, 10 and higher for smoking and lung cancer (eg, Table 1). It appeared quite possible, however, that such a characteristic "might be sufficient to explain the association of cigarette smoking with peptic ulcer and coronary artery disease,"[32] given their considerably smaller rate ratios in most studies.

Here is where expression [4] could have been revealing. The prevalence of bad temper in Lilienfeld's[32] study was only $p_1 = 18/903 = 0.020$ among the smokers and $p_0 = 7/903 = 0.008$ among the nonsmokers. The difference, $p_1 - p_0 = 0.012$, did not exceed the risk differences for coronary heart disease, which are estimated in Table 3 but could have been calculated directly in the cohort studies' data. The risk differences would have shown what the risk ratios could not: that confounding by such a variable could not explain the association between cigarette smoking and coronary artery disease.

I conjecture that this failure to recognize the utility of the risk difference in assessing causality delayed the formation of a consensus on the causal connection of cigarette smoking to coronary artery disease. Consider the evolving view of the Surgeon General. In 1967, it was that the evidence "strongly suggests" a causal relation.[41] In 1968, a

TABLE 3. Coronary Artery Disease Death Rates, Rate Ratios, Rate Differences, Risks, Risk Ratios, and Risk Differences by Cigarette Smoking in a Study of United States Men and a Study of Male British Physicians

	Hammond and Horn (1958)[30]		Doll and Hill (1964)[39]	
Measure	**Smokers**	**Nonsmokers**	**Smokers**	**Nonsmokers**
Rate[a]	879	516	486	361
Rate ratio	1.7	1	1.3	1
Rate difference[a]	363	0	125	0
Risk[b]	0.032	0.019	0.047	0.035
Risk ratio	1.7	1	1.3	1
Risk difference	0.013	0	0.012	0

[a]Deaths per 100,000 person-years.

[b]Estimated by $R = 1 - \exp(-It)$, where R is the risk, I is the rate, and t is the length of the follow-up period (t = 44 mo for Hammond and Horn, t = 10 years for Doll and Hill), assuming negligible competing risk and an exponential distribution of dates of coronary artery death.[40]

causal conclusion was drawn, but only in the very weak statement that smoking "can contribute to the development of" coronary artery disease.[42] Throughout most of the 1970s, the Surgeon General, while declaring smoking a "cause" of lung cancer and other cancers, was calling smoking a "risk factor" for coronary artery disease.[43–48] Not until 1979 was the unequivocal conclusion drawn that "smoking is causally related to coronary heart disease."[49]

PHANTOM ARGUMENTS: THE CONFOUNDER-DISEASE ASSOCIATION

Several authors[50–54] have attributed to Cornfield et al[18] a demonstration that for a confounder to be responsible for an exposure-disease association, the confounder's relative risk must exceed the exposure's spuriously elevated relative risk:

$$RR_Z > RR_X^* \tag{5}$$

Others have claimed that Cornfield et al conditioned their proof of expression [2] on RR_Z having a near-infinite value[55,56] or that they set statistical "nonsignificance" and not $RR_X = 1$ as the standard for the absence of an exposure effect.[56]

To the contrary, Cornfield et al proved nothing about the value of RR_Z. Their proof of expression [2] relied only on the exceedingly weak assumption, $1 < RR_Z < \infty$, and had nothing to do with statistical significance. Expression [5] was finally proved, after a fashion, by a string of infinite values along one diagonal of Table 1 in Bross's 1967 paper.[37] Later, it was proved more formally by Schlesselman.[57]

The counterpart of expression [5] for the risk difference,

$$RD_Z > RD_X^*, \tag{6}$$

appears not to have been proved formally. It follows directly from expression [3] and from $0 < p_1 - p_0 < 1$.

Expressions [2], [4], [5], and [6] must all be true for a binary confounder to be responsible for a positive exposure-disease association. If any one of them does not hold, the confounder in question is incapable of explaining the association. For rare outcomes such as lung cancer, the expressions involving the risk ratio (expressions [2] and [5]) may be more valuable. For more common outcomes, the more valuable expressions are likely to be the ones pertaining to the risk difference (expressions [4] and [6]), as in the case of smoking and coronary artery disease.

In a more extreme example, Margolis et al[58] considered the hypothesis that a single confounder might be responsible for an association based on risks of $R_{1+} = 0.88$ and $R_{0+} = 0.34$. With $RR_X^* = 2.6$ and $RD_X^* = 0.55$, expressions [4] and [6] are much more useful than expressions [2] and [5] in this application. That the difference between the exposed and unexposed groups in the prevalence of a completely explanatory confounder would have to exceed 55% would rule out a great many candidates.

ARGUMENT 2: A CAUSAL ASSOCIATION WHEN OTHER CAUSES ARE PRESENT

For this argument, Cornfield et al[18] altered 3 assumptions from their first proof. First, the exposure and the covariate both causally increase the risk of the disease. Second, the 2 causes are uncorrelated, so neither the covariate nor the exposure confounds the other's estimated effect. Third, "the risk of the disease is small" in the following, "special sense":

$$R_{00} < \frac{R_{10}R_{01}}{R_{11}} \tag{7}$$

The authors noted that under these conditions the exposure's relative risk is smaller among those exposed to the covariate than in the overall population:

$$\frac{R_{11}}{R_{01}} < RR_X^* \tag{8}$$

From this result they concluded, as though it were generally true, "The presence of other real causes thus reduces the apparent relative risk,"

Expression [8] is not generally true, in part because expression [7] is not a rare-disease assumption. Expression [7] holds, for instance, when $R_{11} = 0.99$, $R_{01} = 0.98$, $R_{10} = 0.97$ and $R_{00} = 0.95$. Expression [7] is actually an assumption of submultiplicative interaction on the risk scale[59]—that is, an assumption that the exposure's relative risk is smaller in the presence of the covariate than in its absence:

$$\frac{R_{11}}{R_{01}} < \frac{R_{10}}{R_{00}}.$$

As the covariate and the exposure are not associated with each other, the exposure's crude relative risk must be a weighted average of the relative risks in the 2 categories of the covariate[60] and, as such, must lie between them:

$$\frac{R_{11}}{R_{01}} < RR_X^* < \frac{R_{10}}{R_{00}}$$

Thus, under the stated assumptions, expression [8] is true, but trivially so.

This unremarkable result is not a good "reason for using a relative measure"[18] of effect. We could just as easily set up subadditive interaction,[59]

$$R_{00} < R_{10} + R_{01} - R_{11}, \tag{9}$$

as an ersatz rare-disease assumption. Then, noting that expression [9] and the independence of the exposure and the covariate imply

$$R_{11} - R_{01} < RD_X^* < R_{10} - R_{00},$$

we could conclude that the presence of other real causes reduces the apparent risk difference. In short, the authors'[18] second argument was circular. They proved submultiplicative interaction by assuming submultiplicative interaction.

ARGUMENT 3: SENSITIVITY TO DISEASE MISCLASSIFICATION AND AGGREGATION

In this argument, Cornfield et al[18] considered the possibility of false-positive disease classification errors or, equivalently, the aggregation of a disease the exposure affects with one or more diseases that it does not affect. Without offering a proof, the authors concluded that the relative risk is attenuated under these circumstances "while the absolute measure is unaffected."[18]

This argument requires several assumptions.[61] The specificity of disease classification must not differ between the exposed and unexposed groups and must be independent of errors in measuring other variables, including the exposure. The true-positives, or the disease affected by the exposure, must be rare. Finally, the exposure must have an effect. If all these conditions are present, the risk difference can be approximately unbiased while the risk ratio is appreciably biased toward the null.

For example, suppose $R_{1+} = 0.02$ and $R_{0+} = 0.01$ with disease classified perfectly. The unbiased effect measures are $RD_X = 0.01$ and $RR_X = 2.0$. If the sensitivity of disease classification is 1.0 and the specificity is 0.98 in both groups, the expected risks with disease misclassification are $R^*_{1+} = 0.02 + 0.02(0.98) = 0.0396$ and $R^*_{0+} = 0.01 + 0.02(0.99) = 0.0298$. The risk ratio is biased decidedly toward the null, $RR^*_X = 1.3$, but the risk difference is approximately unbiased, $RD^*_X = 0.0098$.

This is an important observation, but it is not clear why Cornfield et al called it an advantage for the risk ratio. Under conditions in which the risk difference is approximately unbiased while the risk ratio is substantially biased, the risk difference ought to be preferred.

DISCUSSION

To Cornfield et al,[18] "The evidence that tobacco is a causal agent in the development of other diseases seems weaker than the evidence for lung cancer simply because the effects are smaller." For this statement to square with the cohort studies, the rate ratio had to be superior to the rate difference for measuring strength of association or magnitude of effect.

Each argument the authors gave for that alleged superiority was specious. They showed that the risk ratio provides useful information about confounding, but overlooked the independently useful information the risk difference provides about the same question. They proved that a causally elevated risk ratio is attenuated in the presence of other real causes by assuming that a causally elevated risk ratio is attenuated in the presence of other real causes. They found conditions in which the risk ratio is substantially biased, while the risk difference is approximately unbiased, and declared them advantageous for the risk ratio.

Looking back on the writings of Fisher, Berkson, and other skeptics on smoking and lung cancer, Vandenbroucke[62] found "extremely well-written and cogent papers that might have become textbook classics for their impeccable logic and clear exposition of data and argument if only the authors had been on the right side." In the paper by Cornfield et al, we find arguments for preferring ratio effect measures over difference measures that might not have taken a half century to recognize as flawed had the authors been on the wrong side about smoking and lung cancer.

To Greenland,[63] the skeptics on smoking and lung cancer lacked "a complete epidemiologic perspective." His "impression," which conflicted with the published views[64] of at least one of the skeptics, was that they "would have opposed action against smoking on the grounds that the causal explanation of the smoking-lung cancer association had not been 'proven,'" based on "a position that action must be forestalled until all plausible noncausal explanations are refuted."

Cornfield et al[18] lacked a complete epidemiologic perspective in a different way. Given their views that unspecified public health actions were needed and that the overall evidence was strongest for lung cancer, they could not countenance the possibility that the epidemiologic association was strongest, and the hypothetical effect greatest, for coronary artery disease.

Berkson[39] was wrong about smoking and lung cancer, but he was right about the logic of the interpretation of the cohort studies. Either something was seriously amiss with these studies or smoking causes many diseases. Today we know the latter to be the case. In focusing on the rate differences, Berkson focused on the results that were giving the more accurate overall epidemiologic perspective.

This episode should have weighed in against the "causal criterion" of specificity of effect and just as strongly against the preference for ratio measures over difference measures in assessing causality. Yet, after many of smoking's effects were known, Doll[21] continued to fault Berkson for taking "no account of the great difference in the relative risks of different diseases." Given the immense nonspecificity of smoking's actual effects, the mistake was not to overlook the specificity of the relative risks, but to emphasize it. Berkson did not make that mistake. Cornfield et al did.

Rothman and I have been criticized[65–67] for suggesting that public health advocacy can adversely affect epidemiologic science.[68,69] The flawed arguments by Cornfield et al for the superiority of ratio effect measures in causal inference are a case in point. Those arguments may have served a short-term purpose with regard to smoking and lung cancer. But if they helped delay recognition of smoking's causal effect

on coronary artery disease, it is an open question whether they did more good than harm. Cornfield et al founded an era of risk relativism that continues to this day. Whether our field has benefited on balance is yet to be resolved.

ACKNOWLEDGMENTS

I thank Jay S. Kaufman and Kenneth J. Rothman for constructive comments.

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