From Statistical Evidence to Evidence of Causality

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Abstract

Science is largely concerned with understanding the “effects of causes” (EoC), while Law is more concerned with understanding the “causes of effects” (CoE). While EoC can be addressed using experimental design and statistical analysis, it is less clear how to incorporate statistical or epidemiological evidence into CoE reasoning, as might be required for a case at Law. Some form of counterfactual reasoning, such as Rubin’s “potential outcomes” approach, appears unavoidable, but this typically yields “answers” that are sensitive to arbitrary and untestable assumptions. We must therefore recognise that a CoE question simply might not have a well-determined answer. It may nevertheless be possible to use statistical data to set bounds within any answer must lie. With less than perfect data these bounds will themselves be uncertain, leading to a novel compounding of two kinds of uncertainty. Still further care is required in the presence of possible confounding factors. In addition, even identifying the relevant “counterfactual contrast” may be a matter of Policy as much as of Science. Defining the question is as non-trivial a task as finding a route towards an answer.

This paper develops some technical elaborations of these philosophical points, and illustrates them with an analysis of a case study in child protection.

Keywords: benfluorex, causes of effects, counterfactual, child protection, effects of causes, Fréchet bound, potential outcome, probability of causation

1 Introduction

One function of a Court of Law is to attempt to assign responsibility or blame for some undesirable outcome. In many such cases there will be relevant testimony about statistical or epidemiological evidence arising from studies done on
specialized populations, but this evidence addresses the main issue only indirectly, at best. It has until now been unclear how to use such evidence to focus on the issue at hand which involves specific individuals experiencing the undesirable outcome. Although there is a considerable literature on certain aspects of this problem — see for example [Green et al., 2011], which aims to assist US judges in managing cases involving complex scientific and technical evidence — we consider that there are important logical subtleties that have not as yet been accorded the appreciation they warrant. Here we show that, even in the (very rare) case that we have the best possible and most extensive data, and can accept certain very strong but necessary conditions, there will still remain irreducible uncertainty — which we can express as interval bounds — about the relevant “probability of causation”. With less than fully perfect data, this interval uncertainty will be further compounded by statistical uncertainty. Such multiple uncertainty raises new questions of interpretation and presentation.

The structure of the paper is as follows. In §2 we consider a high-profile case where serious side-effects led to the withdrawal of a drug from the market, and, in turn, to litigation against the manufacturer. We consider how general evidence of incidence of effects might or might not be relevant to a hypothetical tort action in which an affected patient sues the manufacturer for damages, and we relate this to the important distinction we draw in §3 between “effects of causes” and “causes of effects”. After a brief consideration of inference from statistical data about effects of causes in §4, the remainder of the paper focuses on inference about causes of effects, based on a “probability of causation” defined using counterfactual logic. Although this probability is typically impossible to pinpoint on the basis of epidemiological data, however extensive, we give bounds between which it must lie—bounds which, however, will themselves be subject to statistical uncertainly. In §8 and §9 we illustrate our theory with a new analysis of a case study in child protection.

2 Epidemiological Evidence in Litigation

2.1 Epidemiological background

The drug Mediator, also known as benfluorex, was for many years marketed as an anti-diabetic drug. It was also widely used off-label as an appetite suppressant. In November 2010, however, following the publication of a popular book by Irène [Frachon, 2010], the French Health Agency CNAM announced its finding that around 500 deaths in France over a thirty year period could be attributed to Mediator (see also [Hill, 2011]). This was based on extrapolation of results in two scientific studies, published at about the same time, focusing on the effects of benfluorex on valvular heart disease. [Frachon et al., 2010] showed a significantly higher prevalence of unexplained valvular heart disease in patients taking benfluorex, as compared to controls. [Weill et al., 2010] examined the records of over a million diabetic patients in a cohort study, and reported a higher hospitalisation rate for valvular heart disease in benfluorex takers.
2.2 Litigation

As the news about Mediator reverberated through the media, the French authorities withdrew the drug from sale. At the same time, hundreds of individuals jointly filed a criminal lawsuit against the manufacturer of Mediator, the French pharmaceutical giant Servier. The trial has been under way since May 2012, with initial aspects focused on whether the company was guilty of misconduct. As of the time of preparation of this article, the issue of whether Mediator was in fact the cause of the heart disease in any of those who brought the lawsuit had yet to be addressed, and no expert scientific testimony had been presented to the court.

In the US benfluorex was removed from the marketplace in the 1990s. But the banning in 1997 of a related drug, Redux, led to a $12 billion settlement, following a class action by thousands of individuals [Anon, 2010]. Thus considerable attention both in France and elsewhere is focused on the case against Servier.

2.3 Scientific results

The matched case-control study of [Frachon et al., 2010] involved 27 cases of valvular heart disease and 54 controls. Investigators determined whether the patients had or had not used benfluorex.

We display the core data in Table 1. The face-value odds ratio in this table is $(19 \times 51) / (3 \times 8) = 40.1$, but this could be misleading because of confounding factors. A logistic regression analysis reported by [Frachon et al., 2010] adjusted for body mass index, diabetes and dexfenfluramine use, and reduced the odds ratio to 17.1, a value which is still a large and highly significant measure of positive association between benfluorex and valvular heart disease. In the same direction, [Weill et al., 2010] computed a risk ratio (though with relatively crude adjustments) of the order of 3.

<table>
<thead>
<tr>
<th>Benfluorex Use</th>
<th>Cases</th>
<th>Controls</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>19</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>No</td>
<td>8</td>
<td>51</td>
<td>59</td>
</tr>
<tr>
<td>Totals</td>
<td>27</td>
<td>54</td>
<td>81</td>
</tr>
</tbody>
</table>

Table 1: Raw results from case-control study linking benfluorex and valvular heart disease. Source: [Frachon et al., 2010]

2.3.1 Robustness of odds ratio

While the risk ratio may be a more relevant and incisive measure of the strength of an effect than the odds ratio (and it will feature importantly in our analysis of §4 below), it faces a very serious problem: it is simply not possible to compute it from a retrospective study, such as that of [Frachon et al., 2010]. In contrast, the odds ratio, whether raw or adjusted via a logistic regression, has the important property that it is simultaneously a meaningful measure of association [Bishop et al., 1975] and computable from retrospective data [Farewell, 1979].
Furthermore, it will be a good approximation to the risk ratio when the outcome is rare.

2.4 Toxic tort—A hypothetical case

Now consider a (currently purely hypothetical) case that might be brought on the basis of these scientific reports. A woman with unexplained valvular heart disease sues the manufacturer of benfluorex, claiming that it was that that caused her illness. An epidemiologist, testifying for plaintiff, claims that, on the evidence of Dr. Frachon’s and Dr. Weill’s studies, the medication can cause valvular heart disease. The defendants in turn offers their expert, who testifies that in the manufacturer’s clinical trials there was no evidence of such a side effect. How should the court rule?

The court needs to decide on the cause of this woman’s heart disease. But the plaintiff’s expert addresses something different, the general scientific question “Can benfluorex be shown to cause heart disease?” For an epidemiologist, the evidence for this would ideally be captured by the risk ratio, though, as we have seen, for the Frachon data we would have to be satisfied with the adjusted odds ratio instead. But even if we had perfect and unassailable statistical evidence in support of this general scientific hypothesis, that would still be only very indirectly relevant to the individual case at issue. We shall see below that the relationship between such a generalisation and the specific issue before the court is extremely subtle.

3 Causes of Effects and Effects of Causes

One might be tempted to assume that the “effects of causes” (henceforth EoC) and the “causes of effects” (CoE) are related probabilistically via Bayes theorem. After all, this was how [Laplace, 1986] introduced the topic: “If an event can be produced by a number \( n \) of different causes, the probabilities of these causes given the event are to each other as the probabilities of the event given the causes,...” Later authors recognized the issue to be more complex.

John Stuart Mill distinguished between inferences about “effects of causes” (henceforth EoC) and inferences about “causes of effects” (CoE), and remarked “...as a general rule, the effects of causes are far more accessible to our study than the causes of effects...” [Mill, 1843, Book 3, Chapter 10, §8]. Although a similar distinction has sometimes been expressed in statistical contexts (see e.g. [Holland, 1986]), Mill’s associated warning has largely gone unheeded. We consider that it deserves more careful attention. Though evidently related in some way, problems of CoE are distinct from problems of EoC; indeed, as Mill understood, they are considerably more subtle and difficult to handle.

In this article, which builds on and extends [Dawid, 2011] and [Fienberg et al., 2014], we attempt to delineate both the differences and the connexions between these two distinct inferential enterprises. An understanding of these issues will clearly be crucial if generic EoC evidence, such as that of the [Frachon et al., 2010] study, is to be brought to bear on an individual CoE case, such as the toxic tort case of §2.4. In particular we shall consider the possibilities of using statistical evidence to inform CoE inferences.
3.1 Aspirin trial

As a simple concrete example, we contrast the following two questions:

**Effects of Causes (EoC)** Ann has a headache. She is wondering whether to take aspirin. Would that cause her headache to disappear (within, say, 30 minutes)?

**Causes of Effects (CoE)** Ann had a headache and took aspirin. Her headache went away after 30 minutes. Was that caused by the aspirin?

Note that—in a departure from previous related treatments—in both questions we have separated out the rôles of the subject (“Ann”), on whom we have some information, and the questioner or analyst (henceforth “I”), who wants to interpret that information: these could be the same individual, but need not be. Any uncertainty about the answers to the above queries is my personal uncertainty, and is most properly regarded as a subjective probability, though informed by relevant data. This is somewhat analogous to the situation in court, where we distinguish between a witness, who supplies evidence (e.g., on epidemiology), and the trier of fact, be it a judge or a jury, who has to assess the uncertainty to associate with the question of ultimate legal interest: the cause of the effect.

What might be relevant data in the present instance? We suppose that a well-conducted (large, prospective, randomised, double-blind, . . . ) comparative clinical trial has indicated the following recovery rates:

\[
\Pr(R = 1 | E = 1) = 30\% \quad (1) \\
\Pr(R = 1 | E = 0) = 12\% \quad (2)
\]

where \(E = 1\) [resp., 0] denotes “exposure to” ( = treatment with) aspirin [resp., no aspirin], and \(R = 1\) [resp., 0] denotes that the headache does [resp., does not] disappear (within 30 minutes). Here and throughout, we use \(\Pr(\cdot)\) to denote probabilities (henceforth termed chances) underlying a population data-generating process.

4 Statistical Evidence for EoC

Ann has a headache. She is wondering whether to take aspirin. Would that cause her headache to disappear (within, say, 30 minutes)?

Most of classical statistical experimental design and inference is geared to elucidating the effects of causes, and much careful attention over many years has gone into clarifying and improving methods for doing this, for example by the use of randomised comparative experiments [Fisher, 1935, Hill, 1951] to control for potential confounding factors. Even when emphasis is specifically targeted on statistical causality [Rubin, 1974, Pearl, 2009] this still mostly addresses EoC problems, albeit in observational rather than experimental settings.

In order to highlight the major issue, we confine attention here to data from a study, such as the aspirin trial of §3.1, that can be regarded as supporting
genuinely causal inferences.\footnote{Some considerations relevant to the possibilities for causal inference in various data-collection settings can be found in \cite{Dawid2011}.} In particular, for the aspirin trial this would mean that—so long as I can regard Ann as being comparable with the patients in the trial—if she takes aspirin I can expect her headache to disappear within 30 minutes with probability 30%, but with probability only 12% if she does not. If I myself am Ann, then (other things being equal) taking the aspirin is my preferred option.

In this case, the EoC causal inference is based on a simple contrast between the two “prospective” conditional probabilities, $\Pr(R = 1 \mid E = 1)$ and $\Pr(R = 1 \mid E = 0)$. In particular, the information needed for making EoC causal inferences—and so for guiding future decisions—is subsumed in the joint probability distribution of the exposure $E$ and the response $R$. In more complex situations we may have to make various modifications, e.g. adjustment for confounders, but the essential point remains that purely probabilistic knowledge, properly conditioned on known facts, is sufficient to address EoC-type questions.

5 How to Understand “Causes of Effects”?\footnote{The observed response $R$ is determined by these three variables as $R = R_E$.}

Addressing a CoE-type question is much more problematic—indeed, even to formulate the question clearly is a nontrivial enterprise. We can no longer base our approach purely on the probability distribution of $E$ and $R$ conditioned on known facts, since we know the values of both variables ($E = 1$, $R = 1$), and after conditioning on that knowledge there is no probabilistic uncertainty left to work with.

One possible approach, popular in statistical circles, is based on the concept of the “counterfactual contrast”, which in turn rests on the introduction of “potential responses” \cite{Rubin1974}. We proceed by splitting the response variable $R$ into two variables, $R_0$ and $R_1$, where we conceive of $R_1$ [resp., $R_0$] as a potential value of $R$, that will eventuate if in fact $E = 1$ [resp., 0]. These potential responses are regarded as existing prior to the determination of $E$. We thus now need to model the three variables $(E, R_0, R_1)$ together, rather than (as previously) just the two variables $(E, R)$.

We might now cast the CoE question as enquiring about the relationship between $R_0$ and $R_1$. Thus “$R_1 = 1, R_0 = 0$” describes the situation where Ann’s headache disappears if she takes the aspirin, but does not if she does not—a state of affairs that might reasonably be described as the disappearance of Ann’s headache being caused by taking the aspirin. In particular, if Ann has taken the aspirin and her headache disappeared (thus $R_1 = 1$), these two events can be regarded as causally connected just in the case that $R_0 = 0$.

5.1 Science and Policy

Although we shall follow through with the above formulation in the remainder of this article, we here turn aside to consider an objection to it: it simply might not be appropriate to regard, as the “counterfactual foil” to the factual response ($R_1$), what would have happened ($R_0$) if the exposure had not occurred ($E = 0$) but all other prior circumstances were the same. For example, there has
been a series of legal cases in which various administrations have sued tobacco companies on the basis that they had not properly informed the public of the dangers of smoking when they first had that evidence, and should therefore be liable for the increased costs that fell on health services due to that act of omission. But it could be argued that, since smokers tend to die earlier than non-smokers, encouraging (or at least not discouraging) smoking would in fact reduce the total burden on the health services. Such an attempted defence has, however, usually been ruled inadmissible. Instead, as a matter of policy, the relevant counterfactual comparator is taken to be a hypothetical universe in which every one lives just as long as they do in fact, but they are healthier because they smoke less. Here we see Science and Policy as inextricably intertwined in formulating the appropriate CoE question. And the conceptual and implementational difficulties that we discuss below, that beset even the simplest case of inference about causes of effects, will be hugely magnified when we wish to take additional account of such policy considerations.

6 Statistical Evidence for CoE

Ann had a headache and took aspirin. Her headache went away after 30 minutes. Was that caused by the aspirin?

After the above detour, we return to our formulation of the CoE question, in terms of a contrast between $R_1$, the actually observed response (in this case, $R_1 = 1$) to the treatment actually taken ($E = 1$), and $R_0$, the (necessarily unknown) counterfactual response, that would have been observed had Ann in fact not taken the aspirin. If “in counterfact” $R_0 = 1$, then Ann’s headache would have disappeared even if she had not taken the aspirin, so I must conclude that it was not the aspirin that cured her. Conversely, if $R_0 = 0$ then I can indeed attribute her cure to having taken the aspirin. In this way, we formulate the CoE causal question in terms of the contrast between the factual outcome $R_1$ and the counterfactual outcome $R_0$.

To address the CoE question I thus need to query $R_0$. Since $R_0$ has not been observed, it retains a degree of uncertainty, which I could try to express probabilistically. However, not only have I not observed $R_0$, there is, now, no way I could ever observe it, since once I have observed $R_1$, $R_0$ has becomes a counterfactual quantity, predicated on a condition ($E = 0$) that is counter to known facts ($E = 1$). This logical difficulty leads to a degree of unavoidable ambiguity affecting our ability to address the CoE question.

In evaluating my probabilistic uncertainty, I should condition on all I know. My full knowledge about Ann can be expressed as $(E = 1, R_1 = 1, H)$, where $H$ denotes all the background knowledge I have about Ann, and the other variables are likewise individualised to her. With this understanding, we formally define my PROBABILITY OF CAUSATION$^3$ as the conditional probability:

$$PC_A = P_A(R_0 = 0 | H, E = 1, R_1 = 1)$$

where $P_A$ denotes my probability distribution over attributes of Ann.

$^3$This is similar to what [Pearl, 2009, Chapter 9] terms the “Probability of Necessity” (PN)—which however does not account for the conditioning on $H$. See also [Tian and Pearl, 2000].
But how can I go about evaluating $PC_A$, and what other evidence could be used, and how, to inform this evaluation? In particular, how—if at all—could I make use of EoC probabilities such as (1) and (2) to assist my evaluation of the CoE probability (3)?

6.1 Bounding the probability of causation

We note that (3) involves a joint distribution of $(R_0, R_1)$. Since, as a matter of definition, it is never possible to observe both $R_0$ and $R_1$ on the same individual, it is problematic to estimate such a joint distribution. We might however have a hope of assessing separate marginal probabilities for $R_0$ and $R_1$; and this information can be used to set bounds on $PC$. Indeed it is straightforward to show (cf. [Dawid, 2011]):

$$
\min \left\{1, \frac{1}{P_A(R_1 = 1 \mid H, E = 1)} - \frac{1}{RR_A} \right\} \geq PC_A \geq \max \left\{0, 1 - \frac{1}{RR_A} \right\},
$$

(4)

where

$$
RR_A := \frac{P_A(R_1 = 1 \mid H, E = 1)}{P_A(R_0 = 1 \mid H, E = 1)}.
$$

Readers will recognize (4) as a version of the Bonferroni-Fréchet-Hoeffding bounds [Bonferroni, 1936, Fréchet, 1940, Hoeffding, 1940] that play important rôles in other areas of statistics.

The inequality (4) will yield a non-trivial lower bound so long as $RR_A > 1$, which we can interpret as saying that there is a positive causal effect of exposure on outcome: cf. the related argument in [Robins and Greenland, 1989]. Whenever $RR_A$ exceeds 2, we can deduce from (8), without making any further assumptions, that $PC_A$ must exceed 50%. In a civil legal case such as that of §2.4, causality might then be concluded “on the balance of probabilities”. It is however important to note that, when $RR_A < 2$, it would not be correct to conclude from this that $PC_A < 50\%$ (which would lead to the case failing); rather, we can only say that we can not be sure that the probability of causation exceeds 50\%.

The upper bound in (4) is more subtle. It is less than 1 when $P_A(R_0 = 1 \mid H, E = 1) + P_A(R_1 = 1 \mid H, E = 1) > 1$. This happens in general only when both Ann’s potential outcomes are “highly likely.” If $P_A(R_1 = 1 \mid H, E = 1) = P_A(R = 1 \mid H, E = 1)$ is only modest in size, e.g., less than 1/2 and $RR_A > 1$, then the upper bound is 1. If $RR_A$ is large, e.g., $RR_A > 10$, the upper bound will again be 1 unless $P_A(R = 1 \mid H, E = 1)$ is close to 1. For the remainder of the paper, for simplicity we proceed using an upper bound of 1. Thus we work with the bounds

$$
1 \geq PC_A \geq \max \left\{0, 1 - \frac{1}{RR_A} \right\},
$$

(6)

with $RR_A$ given by (5).

6.2 The risk ratio

The denominator of (5) involves a counterfactual consideration: of $R_0$, Ann’s potential response were she not to have taken the aspirin, in the situation that she is known to have taken aspirin ($E = 1$). So it would seem problematic to
estimate it from data. However, if my background knowledge $H$ of Ann (on which my distribution $P_A$ is being conditioned) is sufficiently detailed, then, at the point before Ann has decided whether or not to take the aspirin, it might seem appropriate to consider that my uncertainty, conditional on $H$, about the way her treatment decision $E$ will be made would not further depend on the (so far entirely unobserved) potential responses $(R_0, R_1)$. That is, in this case we might assume

$$(R_0, R_1) \perp_A E \mid H$$

(7)

where $\perp_A$ denotes conditional independence [Dawid, 1979] in my distribution $P_A$ for Ann’s characteristics. When (7) holds we will term the background information $H$ sufficient. Then we can replace (5) by

$$RR_A = \frac{P_A(R_1 = 1 \mid H)}{P_A(R_0 = 1 \mid H)}.$$  

(8)

my causal risk ratio for Ann.

Sufficiency is a kind of “no confounding” requirement on my distribution $P_A$ for Ann. It would fail if, for example, I thought that Ann might take the treatment if she felt really poorly, and not otherwise; but I did not initially have information as to how she felt. Then observing that she took the treatment ($E = 1$) would inform me that she was feeling poorly, so decreasing the probability of a good response (whether actual, $R_1$, or counterfactual, $R_0$). Now if I myself am Ann, my $H$ will already include my own knowledge of my perceived state of health, so this argument does not apply, and sufficiency is an acceptable condition. If I am an external observer, however, the sufficiency condition is much more problematic, since I must be able to satisfy myself that my knowledge $H$ of Ann is complete enough to avoid the above possibility of confounding. If I can not assume sufficiency, I can not replace the counterfactual denominator of (5) by anything even potentially estimable from data.

Note that the “no confounding” property of sufficiency relates solely to Ann and my knowledge of her. It should not be confused with the superficially similar no confounding property of exogeneity described in §6.3 below, which refers, not to Ann, but to the process whereby possibly relevant data on other individuals have been gathered.

### 6.3 Estimating the risk ratio

Henceforth we assume sufficiency, which at least gets us started, and aim to see what further progress can be made, and under what conditions, to get a handle on the bounds on $PC_A$ supplied by $RR_A$. It is important to be explicit about the assumptions required, which can be very strong and not easy to justify!

It would be valuable if the probabilities featuring in (5) could be related in some way to chances such as (1) and (2) that are estimable from data. Consider first the numerator, the Ann-specific probability $P_A(R_1 = 1 \mid H, E = 1) = P_A(R = 1 \mid H, E = 1)$. It is tempting to replace this by the analogous chance, $Pr(R = 1 \mid H, E = 1)$, which could be estimated from data as for (1), based on the subset of treated trial subjects sharing the same $H$-value as Ann.

Alternatively, the estimate might be constructed from a model for the dependence of the response $R$ on $H$ and $E = 1$, fitted to all the data, and applied with Ann’s value of $H$. We might also be able to reduce to a smaller information set $H$, if that is all that is relevant for prediction of the responses.
This would be justified if we could make the following bold assumption (where Bayesians can replace the intuitive term “comparable” with the more precise term “exchangeable”):

**Condition 1** *Conditional on my knowledge of the pre-treatment characteristics of Ann and the trial subjects, I regard Ann’s potential responses as comparable with those of the treated subjects having characteristic $H$.*

Up to this point we have not needed the assumption that $H$ is sufficient. But consider now the denominator of (4). Because of its counterfactual nature, we can not argue directly as above. However, with sufficiency of $H$ we have $P_A(R_0 = 1 | H, E = 1) = P_A(R_0 = 1 | H, E = 0) = P_A(R = 1 | H, E = 0)$; and we can estimate this from the trial data, e.g. as the estimated chance $\Pr(R = 1 | H, E = 0)$, if we can assume:

**Condition 2** *Conditional on my knowledge of the pre-treatment characteristics of Ann and the trial subjects, I regard Ann’s potential responses as comparable with those of the untreated subjects having characteristic $H$.*

Now if both Condition 1 and Condition 2 are to hold, then (by Euclid’s first axiom, “Two things that are equal to the same thing are also equal to each other”), the groups of trial subjects with Ann’s characteristics $H$ in both arms must be comparable with each other. This requires that $H$ be exogenous, in the sense that, conditional on $H$, the potential outcomes $(R_0, R_1)$ have the same distribution among treated and untreated study subjects. This will hold for a suitably randomised study, and also in certain observational studies where the possibility of further confounding factors can be discounted.

Note however that we can not take, as $H$, just any exogenous set of variables. The full set of required conditions is:

1. $H$ is exogenous.
2. $H$ is sufficient for Ann’s response.
3. Conditional on $H$, Ann’s potential responses are comparable with those of the trial subjects.

Only when we can make good arguments for the acceptability of all these strong conditions can we justify estimating $\text{RR}_A$ by the population counterpart of (8), the observational risk ratio:

$$\text{ORR} = \frac{\Pr(R = 1 | H, E = 1)}{\Pr(R = 1 | H, E = 0)}.$$  \hfill (9)

### 6.4 Uncertain exposure

Above we have supposed we know both the fact of exposure ($E = 1$) and the fact of response ($R = 1$), the only uncertainty being about whether there was a causal link between these two facts. There are other situations where we might observe the response, and wonder whether it was caused by exposure, without knowing with certainty whether or not that exposure had in fact taken place. In such cases we have to multiply the probability of causation $\text{PC}_A$ by the
probability of exposure, conditional on the known fact of a positive response, yielding a modified probability of causation:

$$PC_A^* = PC_A \times P_A(E = 1 \mid H, R = 1).$$

(10)

In particular, when the strong conditions of §6.3, justifying the use of population chances $Pr(\cdot)$ in place of Ann-specific probabilities $P_A(\cdot)$, can be assumed, combining this with (10) (and using the upper bound 1 of (6)) delivers the inequalities

$$Pr(E = 1 \mid H, R = 1) \geq PC^* \geq \max\left\{0, 1 - \frac{Pr(E = 0 \mid H, R = 1)}{Pr(E = 0 \mid H)}\right\}. \quad (11)$$

(Here and henceforth we drop the identifier $A$ on $PC^*$: these bounds will apply to any individual for which the required conditions hold.)

7 Statistical Uncertainty

Our discussion so far has treated estimates, such as those in (1) and (2), as if they were the true values of the chances. Even so, we found that we obtain, at best, only partial CoE information, which confines PC or $PC^*$ to an interval but does not yield a point value. In real applications our data will not be extensive enough to give us pinpoint estimates even of the bounds featuring in these inequality formulae, and so we have to take additional account of the resulting statistical uncertainty. The result of our inference is thus an uncertain interval within which a probability (PC or $PC^*$) must lie—thus compounding three different kinds of uncertainty. This is a novel form of inferential output, and it is far from clear how best to express and display it, and what use to make of it.

Statistical uncertainty, at least, is well studied, and can be expressed and understood in a variety of different ways, as touted and debated by the various competing schools of statistical inference. We consider it most straightforward here to take a Bayesian approach, which delivers a joint probability distribution (which, following the helpful terminology of [Best et al., 2013], we henceforth term a credence distribution) for all the unknown chances in the problem, conditional on observed data.

One possible tactic would be to work with a joint credence distribution for the chances assigned to the four configurations of $(R_0, R_1)$. While this would deliver a seemingly comprehensible inference, in the form of a posterior credence distribution for $PC^*$, this is problematic: because $R_0$ and $R_1$ are never simultaneously observable, these joint chances can not be consistently estimated from data, so that this “inference” remains highly sensitive to the specific prior assumptions made, however extensive the data. Instead, we prefer to work with a joint credence distribution for the (estimable) marginal chances: given sufficient data, of sufficiently good quality, these will be well estimated and insensitive to prior assumptions. The price of this increased statistical precision, however, is logical imprecision, since from these chances we can at best derive inequalities for PC or $PC^*$. Thus our inference has the form of a random interval asserted to contain PC or $PC^*$. 

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7.1 Additional issues

The above analysis is predicated on the causal relevance of the epidemiological data, assuming that we can use the study to obtain a sound estimate of the causal risk ratio $RR$ that features in (5). For example, in a simple fully randomised study we could use $\text{ORR}$, as given by (9), as a proxy for $RR$. But such studies are the exception in epidemiology, so that the issues in real world settings where interest is focused on the causes of effects are typically much more complex. Thus in the benfluorex example of §2, using the frequencies in Table 1 for this purpose, by plugging them into the formula for $\text{ORR}$ and interpreting this as $RR$, would be totally misleading, even if we attempted to account for statistical uncertainty as described above. Indeed, as the discussion in Section 2 noted, there are additional problems in this case: because the study of [Frachon et al., 2010] was retrospective, the frequencies in Table 1 could not even be used to estimate $\text{ORR}$, even in the absence of confounding. And this problem remains when, admitting the likely existence of confounding, we conduct a more sophisticated analysis—such as the multiple logistic regression that produced the adjusted odds ratio—to try and account for it. Even when this ploy can be regarded as successful, still the best we can ever do with retrospective data is to estimate the causal odds ratio—which will approximate the desired causal risk ratio, as required for setting the lower bound on PC, only when the outcome is rare.

The judge in the hypothetical case we pose should therefore be doubly wary of the relevance of the epidemiological evidence when trying to assess whether the drug caused the plaintiff’s heart disease.

There are even more complex situations where the data are of a retrospective sort and where there are multiple outcomes of interest and multiple time points for their assessment. A notable example comes from a continuing effort in the United States to examine the long-term health effects of exposure to Agent Orange among US Vietnam veterans. From 1962 to 1971, the US military sprayed herbicides over Vietnam. In 1991 the US Congress passed the Agent Orange Act, requiring a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used in Vietnam. [of Medicine, 2011] is the eighth biennial update implementing this Congressional mandate. The report examines epidemiological studies of the health status of veterans considering a multiplicity of deleterious effects, e.g., different forms of cancer and early-onset peripheral neuropathy, and with limited information on exposure, both at the aggregate and individual level. A standard tool in the studies incorporated into this regularly-updated assessment is the use of adjusted odds-ratios from retrospective logistic regression analyses. Identification of a substantial $RR$ triggers compensation to veterans for health and disability outcomes associated with putative exposure.

8 Case Study

We illustrate our analysis with an example taken from [Best et al., 2013]. The motivating real life case was the diagnosis of abuse in an infant child, $c$, presenting with an acute life threatening event (“ALTE”) and nosebleed (“bleed”). So now we take exposure, $E = 1$, to denote abuse, and response, $R = 1$ to denote
the combination of ALTE and bleed.

8.1 Three tasks

We can distinguish three tasks that we might wish to address probabilistically concerning the relationship between exposure and response in this individual case; these are quite distinct and should not be confused—although there are of course relationships (far from trivial) between them. We use $P_c$ to indicate my probabilities, individuated to this child (and implicitly conditioned on the background information $H$ I have about the child).

**Forecasting** If the child is abused, what is the probability the child will suffer ALTE and nosebleed? — $P_c(\text{ALTE} \& \text{nosebleed} | \text{abuse})$?

**Backcasting** If the child suffers ALTE and nosebleed, what is the probability the child was abused? — $P_c(\text{abuse} | \text{ALTE} \& \text{nosebleed})$?

**Attribution** If the child suffers ALTE and nosebleed, what is the probability these were caused by abuse?

8.2 Attribution analysis

[Best et al., 2013] focused on the backcasting task: of assessing whether or not abuse has in fact taken place, based on the data on the individual case and on relevant statistical studies. Their analysis directly addressed the main substantive concern, since it was the occurrence of abuse—whether or not it in fact caused the observed signs—that was at issue. They did not need to enquire whether or not the observed signs were caused by abuse. That attribution question however will be our focus here. We note that, since the very fact of abuse is itself uncertain, we also need to consider the backcasting issue. This is done by taking, as the relevant probabilistic target of our inference, the modified probability of causation $PC^*$, as given by (10).

We have described in §6 the many very strong assumptions that have to be made in order to justify using data to estimate even the weak interval bounds of (11) for $PC^*$. In the present example, the data used by [Best et al., 2013] were gleaned from a search for relevant published studies. Those identified were of varying design and quality, and the data extracted from them can in no sense be regarded as supporting genuine causal inferences — indeed, it is not easy to find real examples where the conditions supporting causal inference of this type could be regardeds as satisfied. Nevertheless, purely for illustration we shall proceed as if they are, so that we can use the inequalities of (11). As a further highly unrealistic assumption, we take the sufficient information $H$ to be trivial.

Using a Gibbs sampler implemented in the WinBUGS software [Lunn et al., 2012], [Best et al., 2013] find the posterior credence distributions for various conditional chances, based on the data. In particular, they obtain the posterior

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5[Best et al., 2013] conduct several alternative analyses, with some of the less reliable data values being either included or excluded. Our own analysis is based on the predictive model and data in the combined WinBUGS code of Appendices B and D of their paper, as for their own Table 4. This analysis targets a case-specific chance, having greater relevance, but also more uncertainty, than the overall population-based chance.
credence distribution for the conditional chance $\Pr(E = 1 \mid R = 1)$, and thus for $\Pr(E = 0 \mid R = 1) = 1 - \Pr(E = 1 \mid R = 1)$, as needed on both sides of (11).

For our purposes, however, we need more: the lower bound for PC* in (11) also involves the marginal prior chance $\Pr(E = 0)$—or, essentially equivalently, $\theta := \Pr(E = 1)$, the chance of abuse having taken place (in this individual case), before the evidence of ALTE and bleed is taken into consideration. And there is no available statistical evidence relevant to this quantity.

We therefore proceed by introducing our own prior credence distribution for $\theta$, and treating this chance as independent of all the others in the problem. We can expect considerable sensitivity to the specific choice made. To begin to explore this, we try two different prior credence distributions for $\theta$, both beta distributions for simplicity and tractability:

**Prior 1:** $\theta \sim \beta(0.1, 0.1)$.

This has mean 0.5 and standard deviation 0.46. It can be regarded as representing very substantial prior uncertainty about $\theta$.

**Prior 2:** $\theta \sim \beta(1, 9)$.

This has mean 0.1 and standard deviation 0.09. While still admitting uncertainty, it attempts to take into account the prior unlikelihood of abuse: its mean 0.1 is the unconditional probability assigned to this event.

Density functions of these two prior credence distributions are displayed in Figure 1.

![Figure 1: Two prior credence distributions for $\theta$](image)

**9 Data Analysis**

We have conducted our own analysis of the data, based on the WinBUGS code of [Best et al., 2013] elaborated so as to incorporate $\theta$. A chain of length 500000 was generated after a burn-in phase of 500000 iterations. Interpreting the
generated chain as an independent sample of size 500000 would give potentially misleading density estimates: for this reason we have based the estimates on thinned samples taking every 10th elements of the chain, as suggested by an analysis (not reported) of autocorrelation estimates.

9.1 Bivariate distribution

A complete inference would describe the posterior credence distribution of the interval (11) for PC*, whose end-points are functions of random chances, and hence themselves have a bivariate distribution.

Note that, whenever the inequality $\Pr(E = 1 \mid R = 1) \leq \Pr(E = 1)$ between chances holds, which corresponds to negative association between exposure and outcome and will happen with positive probability in the posterior credence distribution, the lower bound of the interval is 0 and is thus entirely uninformative. Thus the posterior credence distribution is a mixture of a continuous bivariate distribution, and (with positive probability) a distribution for the upper bound alone. The probability that the lower bound of the interval is 0 is estimated as 0.627 for Prior 1, and 0.677 for Prior 2.

Figure 2 displays, for the two different priors, samples from the bivariate posterior credence distribution (ordered by lower bound). In the plots are reported 100 intervals obtained by selecting one iteration of the chain every 5000.

![Figure 2: Intervals are ordered in increasing value of lower bound](image)

In Figure 3 are shown bivariate contour plots, for Priors 1 and 2, of the end-points of the random interval, excluding those cases where the lower bound is equal to zero. The full joint distribution is completed by specifying the distribution of the upper bound for these cases: these are shown in Figure 4.

9.2 Univariate summaries

Useful univariate summaries of the overall bivariate inference are the marginal posterior credence distributions of the upper and lower bounds, and of the length
Figure 3: Contour plot of the joint posterior distribution of lower and upper bounds (for lower bound > 0)

Figure 4: Posterior density of upper bound (for lower bound = 0)
of the interval.

9.2.1 Upper bound

The upper bound $\Pr(E = 1 \mid R = 1)$ in (11) is the chance of abuse given the case evidence, as already considered by [Best et al., 2013]. Its posterior credence distribution (which is unaffected by the choice of prior for $\theta$) is summarised in the first row of Table 4 of [Best et al., 2013]. We compute the posterior mean and standard deviation for this upper bound to be 0.043 and 0.013, respectively. Its posterior density is shown in Figure 5.

![Figure 5: Posterior credence density for upper bound for PC*](image)

9.2.2 Lower bound

The lower bound on $PC^*$ in (11), $\max\{0, 1 - \Pr(E = 0 \mid R = 1)/\Pr(E = 0)\}$, depends also on $\theta = \Pr(E = 1)$, and its posterior credence distribution could be sensitive to the prior credence distribution chosen for $\theta$. We have already noted that the posterior credence probability that the lower bound is 0 is 0.627 for Prior 1, and 0.677 for Prior 2. Figure 6 displays the posterior densities for the lower bound, conditional on its being strictly positive, for these two priors; the means are 0.039 and 0.025, and the standard deviations are 0.015 and 0.016, respectively. We see that the effects of the differences between the priors are relatively minor.
9.2.3 Length of interval

Another useful summary of the full inference is the posterior credence distribution of the length of the interval between the lower and upper bounds on PC*, as displayed in Figure 7.

The posterior mean and standard deviation based on Prior 1 are, respectively, 0.028 and 0.022, while for Prior 2 these quantities are 0.035 and 0.016. We see high sensitivity to the prior assumptions. This is particularly apparent when we exclude data with lower bound equal to zero (see Figure 8). For cases with lower bound equal to 0, the interval length is identical with the upper...
bound, as displayed in Figure 4, where the two priors give very similar results. These features are also clearly visible in Figure 2.

![Figure 8: Posterior credence density of length of interval for PC$^*$, for data with lower bound different from zero](image)

9.2.4 Coverage probability

Finally, for any probability value $p$, we can compute the posterior credence that this is included in the random interval (11)—and thus is at least a candidate as a value for PC$^*$. We graph this coverage measure, as a function of $p$, in Figure 9 for both priors.

![Figure 9: Posterior credence probability that the interval covers a specific value](image)
10 Conclusions

We have seen that statistical inference about “causes of effects” is particularly problematic from many points of view, and difficult to justify even in ideal circumstances.

First, in order merely to formalise the question, we need to carefully specify, separately, both who is making the inference (in §6 we called that person “I”) and who (there called “Ann”) the inference relates to. Next, we need to be satisfied that my information $H$ about Ann is sufficient, in the sense of there being no confounding that could make Ann’s treatment choice informative (for me) about her potential outcome variables. When all these conditions are satisfied we can begin to try and learn from relevant data about the two versions, PC and PC$, of the probability of causation. For that purpose we should have good experimental data from which we can get good estimates of the distribution of the outcome, conditional on exposure $E$ and $H$. And even with such ideal estimated probabilities, the resulting inferences are complex, compounding as they do three different kinds of uncertainty: interval bounds, for a probability, that are themselves random. We have made a start at exploring ways of understanding, describing and displaying such triple uncertainty (in an example that admittedly falls far short of the ideal situation), but much remains to be done.

In the case study of §9 we addressed the question whether the ALTE and bleed were together caused by abuse. But we can formulate other CoE questions, such as whether the ALTE alone was caused by abuse. Since we have observed bleed, this would involve replacing the denominator of the lower bound in (11) by $1 - Pr(abuse|bleed)$. Again, we have no data directly relevant to $Pr(abuse|bleed)$, and would need to assess a prior credence distribution for it. This might reasonably be taken to be higher and tighter than that for $Pr(abuse)$ alone, but it would again be important to investigate sensitivity to a range of reasonable choices.

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References


