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Author(s): Ralf Reintjes, Annette de Boer, Wilfrid van Pelt, Joke Mintjes-de Groot
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Simpson's Paradox: An Example from Hospital Epidemiology

Ralf Reintjes,[1,2] Annette de Boer,[1] Wilfrid van Pelt,[1] and Joke Mintjes-de Groot[3]

Simpson's paradox was first recognized at the beginning of the 20th century, but few examples with real data have been presented. In this paper we present an example of this phenomenon from a multicenter study on nosocomial infections, and we try to explain intuitively this type of extreme confounding. (Epidemiology 2000;11:81–83)

Keywords: Simpson's paradox, confounding, nosocomial infections, hospital epidemiology.

Confounding is a common problem in the analysis of data. An understanding of the nature of confounding factors is essential to study design, data analysis, and interpretation of resulting estimates.[1] An extreme form of confounding is the so-called Simpson's paradox.[2] It is present when results of the data analysis in every mutually exclusive stratum or subgroup are the opposite of the crude result. This phenomenon was first recognized as a theoretical possibility at the beginning of the 20th century.[3,4] Few examples from real data have been presented.[5–7] In this paper we present an example of Simpson's paradox with data from a multicenter study on nosocomial infections. Because it may be difficult to understand how estimates can apparently shift direction, as in Simpson's paradox, we will try to give an intuitive explanation.

Methods

Severijnen *et al.* conducted a prospective multicenter study in eight hospitals to determine the feasibility of standardized surveillance of nosocomial infections in The Netherlands. Study design and data collection are described elsewhere.[8] After this study had been completed, we used the dataset from gynecologic patients to measure the influence of possible risk factors on the development of urinary tract infections (UTI). UTI are known to be associated with a variety of risk factors (host and intervention related). These factors are not independent, and confounding is an obvious problem. Antibiotic prophylaxis has been shown to be effective in randomized clinical trials and is sometimes used to prevent UTI.[9,10] In nonexperimental studies antibiotic prophylaxis has been shown to be associated positively with hospital acquired infections.[11] We studied the association between UTI and antibiotic prophylaxis using univariate and stratified analyses. Multivariate analyses were performed using conditional logistic regression.

Results

In total, 279 hospital-acquired infections were detected among 3,519 gynecology patients. Of these, 146 (52%) were UTI. The risk of UTI was 4.2 per 100 gynecological patients. The univariate analysis regarding the effect of antibiotic prophylaxis showed a relative risk (RR) of 0.7 (95% CI = 0.5–1.0) (Table 1). After stratification for hospitals with a low (<2.5%) *versus* a high percentage (>2.5%) of UTI, the RRs were 2.6 (95% CI = 1.0–6.9) and 2.0 (95% CI = 1.3–3.1) respectively (Table 2). A Mantel-Haenszel weighted RR of disease, given the eight hospitals as strata, was 3.5 (Greenland/Robins[12] 95% CI = 2.2–5.6). In a multivariate model using the eight hospitals as strata for conditional logistic regression and controlling for age and risk of procedures undergone, the OR for the effect of antibiotic prophylaxis was 5.3 (95% CI = 1.0–11.6).

Discussion

The stratified analysis of our data show that the association between antibiotic prophylaxis and UTI has an RR >1 in all strata, a result expected in a nonexperimental study, as in clinical practice the decision on prophylactic antibiotics is often made based on the patient's risk to develop UTI. The univariate analysis of the overall data, in contrast, shows that the association between antibiotic prophylaxis and UTI has an RR <1,

From the [1]Department for Infectious Diseases Epidemiology, National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [2]European Programme for Intervention Epidemiology Training (EPIET; SOC 9620258405 F01); and [3]National Organization for Quality Assurance in Hospitals (CBO), Utrecht, The Netherlands.

Address correspondence to: Ralf Reintjes, Dezernat Infektionepidemiologie, Landesinstitut für den Öffentlichen Gesundheitsdienst NRW, P.O. Box 3809, 48151 Münster, Germany.

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TABLE 1. Overall Data on Urinary Tract Infections (UTI) and Antibiotic Prophylaxis, from eight Hospitals in The Netherlands, 1992–93

	Patients from All eight Hospitals				
AB-proph.	UTI	no-UTI	Total	RR	95% CI
Yes	42 (29)	1237 (37)	1279	0.7	0.5–1.0
No	104 (71)	2136 (63)	2240		
Total	146	3373	3519		

AB-proph. = antibiotic prophylaxis.
N = 3,519 (percentages).

a result in keeping with experience in clinical trials.[9,10] Thus the stratum-specific data show the opposite effect of what is found in the complete, unstratified dataset. This phenomenon is Simpson's paradox.

How can such extreme confounding occur? It results from the fact that the variable that distinguishes the strata in Table 2, being a patient in a certain hospital, varies both with the exposure variable, antibiotic prophylaxis, and with the outcome variable, UTI.[13] Ironically, the real relation between UTI and antibiotic prophylaxis, as shown in clinical trials, is likely to be a protective effect.[14–16] This effect is consistent with the crude analysis rather than the stratified result. A possible explanation for this contrary result is that there are two or more separate confounding effects in the crude dataset that bias the effect in different directions. These effects may cancel each other out in the crude data. In the stratified data one confounding effect is removed, unmasking the other. The two tentative confounders that might explain the associations found in our study are indication severity (biasing RR upward) and some unknown factor such as general preventive measures taken by the hospital (biasing RR downward).

In the surveillance project patients were not chosen at random to receive antibiotic prophylaxis. Factors indicative of the susceptibility of the patient are likely to have influenced selection for antibiotic prophylaxis. Patients at high risk for UTI were more likely to be given prophylaxis, biasing the association positively, as observed in the stratified analysis. The question of the other confounding effect remains. It is to be expected that hospitals with a more aggressive policy of preventing UTI for a given level of risk will have lower rates of UTI.

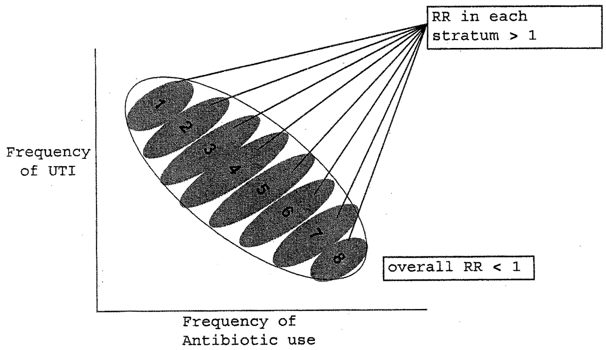

FIGURE 1. Hypothetical distribution of data in a dataset regarding antibiotic use and urinary tract infections (UTI). The complete dataset shows a negative correlation (RR < 1), while all eight independent strata (hospitals 1 to 8) show a positive correlation (RR > 1).

Stratification by hospital removes this effect. The "true" association (considering the findings of clinical trials to be the gold standard) can thus be seen in the unstratified analysis.

Comments

To support intuitive understanding of Simpson's paradox, we visualized the distribution of our data.[17,18] We abstracted the frequency of UTI in each hospital in relation to the frequency of antibiotic use per hospital. Figure 1 shows the eight hospital groups according to the frequencies in terms of UTI and antibiotic use of each hospital. Overall the data points show a negative slope, indicating a negative correlation between UTI and antibiotic prophylaxis in the total dataset, or an RR <1. Within each hospital, however, UTI and antibiotic prophylaxis are positively correlated, indicating an RR >1. This visualization shows that in each stratum the association of the variables can be the reverse of that in the overall dataset.

As indicated above, a negative association may represent the true causal relation, which may be masked by stratification for hospital. The point of stratification is to control for confounding and thus to arrive at the correct conclusion. In this study, an additional level of stratification for an unidentified confounder may be needed.

Simpson's paradox demonstrates that at first sight intuition can be unreliable as a tool for comprehending

TABLE 2. Data on Urinary Tract Infections (UTI) and Antibiotic Prophylaxis (AB-proph.) Stratified by Incidence of UTI per Hospital in Two Strata of four Hospitals in The Netherlands, 1992–93.

	Patients from four Hospitals with Low Incidence of UTI (≤2.5%)					Patients from four Hospitals with High Incidence of UTI (>2.5%)				
AB-proph.	UTI	no-UTI	Total	RR	95% CI	UTI	no-UTI	Total	RR	95% CI
Yes	20 (80)	1093 (60)	1113	2.6	1.0–6.9	22 (18)	144 (9)	166	2.0	1.3–3.1
No	5 (20)	715 (40)	720			99 (82)	1421 (91)	1520		
Total	25	1808	1833			121	1565	1686		

AB-proph. = antibiotic prophylaxis.
N = 3,519 (percentages).

statistical theory.[7] Rothman has pointed out that Simpson's paradox is the logical consequence of failing to recognize the presence of confounding variables.[19] Even if confounding is recognized, it will never be possible to identify all confounders.

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