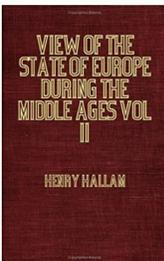
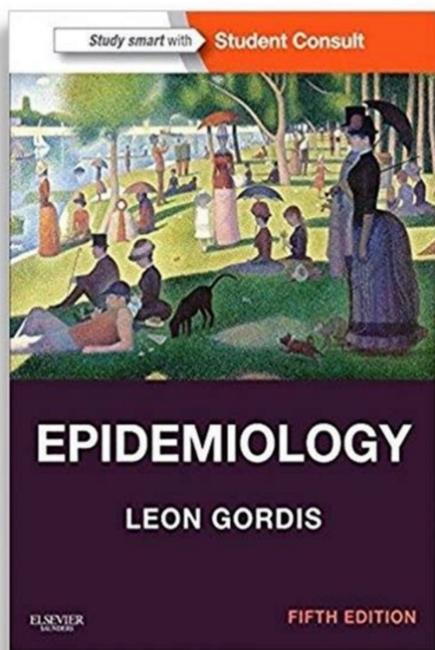


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Reasoning

Descriptive; association on group level
development of broad hypotheses

Descriptive; individual association ma
and specification of hypotheses

Increased prevalence of risk factor amo
causal relationship

Increased risk of disease among expos
relationship

Modification (reduction) of the inciden
confirms a causal relationship

This discrepancy between the crude rate ratio and the rate ratios for each of the two age categories is a result of the strong age effect and the fact that female patients tend to be older than male patients. Mothers who have given birth to a baby with a serious birth defect are thought to be able to recall accurate many exposures during early pregnancy, such as taking non-prescription drugs or experiencing a fever, because the adverse pregnancy outcome serves as a stimulus for the mother to consider potential causes. As stated above, the p value is a statistic that can be viewed as a measure of the compatibility between the data in hand and the null hypothesis. The brothers of the cases are not part of the source population. The incidence rate among those exposed to radiation is 14.6/10,000 yr compared with 7.9/10,000 yr among those unexposed. If the time period over which a risk is calculated approaches 0, the risk itself also approaches 0; thus, the risk of a given person having a myocardial infarction may be 10% in a decade, but in the next 10 seconds it will be extremely small, its value shrinking along with the length of the time interval. For these studies, it is appropriate to consider drawing a control series comprising patients from the same hospitals or clinics as the cases. To measure a causal effect, we have to contrast the experience of exposed people with what would have happened in the absence of exposure. Nevertheless, when a retrospective cohort study is feasible, it offers the advantage of providing information that is usually much less costly than that from a prospective cohort study, and it may produce results much sooner because there is no need to wait for the disease to occur. Similarly, an incidence rate is the momentary rate at which cases are occurring within a group of people. Some diseases occur only once in a person, whereas others can recur. Would the study be more informative if (1) the study participants had the same distribution of socioeconomic factors as the general population or (2) the study participants were recruited so that there were equal numbers in each category of the socioeconomic variable(s)? This person's time at risk ended with his or her death from leukemia. In a study of factory workers, an investigator inferred that the factory work was dangerous because the average age at onset of a particular kind of cancer was lower in these workers than among the general population. Calculation of p Values Although the reader is better off relying on estimation rather than tests of statistical significance for inference, for completeness we give here the basic formulas from which traditional p values can be derived that test the null hypothesis that exposure is not related to disease. Induction Since the rise of modern science in the seventeenth century, scientists and philosophers alike have puzzled over the question of how to determine the truth about assertions that deal with the empirical world. If so, why should the denominators for the risks not change no matter what disease is studied whereas the denominators for the rates change from studying one disease to another? In many studies, the second onset of breast cancer would not be counted as a new case, despite all biologic indications that it represents a separate cancer rather than the spread of the first cancer. The information for the study is obtainable in its entirety from a series of cases. This question leads directly to the philosophy of science, a

Often, proportionately fewer of the smokers died during the ensuing 20 years than nonsmokers. What is the rate ratio that corresponds to this level of? If the risk difference reflects a causal effect that is not distorted by any bias, then the attributable fraction is a measure that quantifies the proportion of the disease burden among exposed people that is caused by the exposure. The goal is to find an unexposed population that would give a result close, if not identical, to that from a counterfactual comparison. Thus, even if smoking did not lead to emphysema, smokers would appear to have a greater incidence rate of emphysema than nonsmokers because of the greater likelihood that emphysema would not be diagnosed in a nonsmoker. What is missing from this measure? Death is the clearest example of a disease outcome that can occur but once to a given person. Given enough time, this curve gradually flattens out so that the total number of deaths approaches the total number of people in the population. To what time does the reciprocal of an incidence rate correspond? The age-specific data show that in the youngest and oldest age categories there was little difference between smokers and nonsmokers in risk of death. Typically, a cohort comprises persons with a common characteristic, such as an exposure or ethnic identity. The way to do that is to make the essential comparisons within each stratum and then to aggregate the information from these comparisons over all strata. Consequently, taking the reciprocal of the mortality rate for a population is not a practical method for estimating the expectation of life. What would be the pros and cons of using statistical significance to judge whether an exposure or a therapy has an effect? Instead of show- pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. Thus, the female experience is older than the male experience. Thus, the 120% is a description of the relative effect that subtracts the 1 from the RR. Similarly, misclassification of disease is non differential if it is unrelated exposure; otherwise, it is differential. One cannot study the effect of blood type in a case-crossover study. If there is no effect to begin with, then non differential misclassification of the exposure will not bias the effect estimate. Clin Endocrinol 1995; 43:55–69. Thus, a person who has already developed the disease or has died is no longer eligible to be selected as a control. For people of the same age in the two countries, the death rate among Swedes is indeed lower than that of Panamanians, but in both places older people die at a greater rate than younger people. For risks, the relative effect is 1 [RD is the risk difference, and R0 is the risk among the unexposed. In a risk calculation, every person in The numerator (that is, every case) is also a person in the denominator (a person in the source Population). Snow, J. On the Mode of Communication of Cholera, 2nd ed. Get yours now! Confidence Intervals for Measures of Effect Studies that measure the effect of an exposure involve comparison of two or more groups. Sometimes epidemiologists refer to the percentage increase in risk to convey the magnitude of relative effect. A closed cohort is one with a fixed membership. As induction became popular, it was seen to differ considerably from deduction. The research process of learning about and controlling for confounding can be thought of as a walk through a maze toward a central goal. Explain his error. Can we attribute 75% of the cases to smoking and 67% to alcohol drinking among those who are exposed to both? This comparison is biased because the general population contains many people who cannot work because of ill health. From the biologic perspective, the causal role of a factor in producing disease is neither strong nor weak: the biology of causation corresponds simply to the identity of the component causes in a causal mechanism. A newspaper article states that a disease has increased by 1200% in the past decade. Thus, the often- pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. It presents a quantitative visual message about the estimated size of the effect. Because the cases in such a study are those who have the disease at a given point in time, the study is more heavily weighted with cases of long duration than any series of incident cases would be. In this chapter, we discuss several measures of disease frequency: risk, incidence rate, and prevalence. The average pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. Chapter 7 introduces the basic analytic methods for estimat- pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. Clearly, disease occurrence affects prevalence. * STATA * Students and scholars who pursue epidemiology as a career should find this book a useful addition to their library ... Nevertheless, because of an inappropriate reliance on statistical significance testing, the data were incorrectly interpreted as refuting earlier studies and indicating no effect of flu amide, despite the fact that they replicated previous results.4 (Reproduced with permission, The Lancet, copyright 1999, Elsevier Science, all rights reserved.) pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. Consider the above example of studying the effect of radiation exposure from the atomic bomb blasts on the development of leukemia. Perhaps the most straightforward way to get both messages is from the two numbers that form the boundaries to a confidence interval. One way to avert the bias would be to compare the workers in a specific job with workers in other jobs that differ in occupational exposures or hazards. Generalization in Epidemiology A useful way to think of scientific generalization is to consider a generalization to be the elaboration of a scientific theory. When the female offspring of women who took diethylstilbestrol were assembled for a special-exposure cohort study, defining their exposure was comparatively clear-cut, based on whether or not their mothers took diethylstilbestrol while they were pregnant.1* For other exposures, however, such as second-hand smoke or dietary intake of saturated fat, nearly everyone is exposed to some extent; and the pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. In contrast, the population pyramid of Sweden is more rectangular, with roughly the same number of people in each of the age categories up to about age 60 and some tapering above that age. This process describes an endless cycle of conjecture and refutation. Interaction between Causes The causal pie model posits that several causal components act in concert to produce an effect. The focus is on estimating epidemiologic measures of Table 6–4. Risk difference has no dimensionality (that is, it has no units and is measured as a pure number) because the underlying measure, risk, is also dimensionless and the dimensionality of a difference is the same as that of the underlying measure. They based their conclusion solely on a test of statistical significance, which gave a result of p = 0.14. Individuals in the control group are then classified into exposed and unexposed categories. In an actual experiment, the investigator assigns the study participants to the exposed and unexposed groups. The switch, however, is often pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. The statistical inference that such sampling allows is only superficially similar to the scientific inference that is the goal of epidemiologic research. Get yours now! order, however, is a blend of whatever effect birth order has by itself and the effect of another variable that is closely correlated with birth order. In this expression, the minus sign is used to obtain the lower confidence limit and the plus signisused to obtain the upper confidence limit. Even if we matched people who were exposed with similar people who were not exposed, they might still differ in unapparent ways. It is the theory that is the real target of inference. Get yours now! Introduction to Epidemiologic Thinking This book presents the basic concepts and methods of epidemiology. Get yours now! 32 Epidemiology: An Introduction ter gives you a continuous measure of the current speed. Get yours now! 50 Epidemiology: An Introduction We can also measure the effect of breast-feeding on diarrhea risk in relative terms. You can note the speed for a given instant from the speedometer (which continuously calculates the ratio of distance to time over a recent finite short interval of time). Get yours now! Analyzing Simple Epidemiologic Data 135 Cohort Studies with Risk Data (or Prevalence Data) Consider a cohort study of a dichotomous exposure with the categories exposed and unexposed. Suppose that the official tape used in the measurements was a cloth tape that had been laundered before the project began. This type of epidemiologic application relates more to administrative areas of public health than to causal research. The longer the duration of disease once it occurs, the higher the prevalence. In this type of study, the exposure is assigned to groups of people rather than singly. Dawber, TR, Moore, FE, Mann, GV: Coronary heart disease in the Framingham study. This equivalence of the two types of ratio for short time intervals has resulted in some confusion of terminology; often, the phrase relative risk is used to refer to either an incidence rate ratio or a risk ratio and more general term relative risk has some justification. Suppose that the average time it takes before causal mechanisms that involve radiation are completed and leukemia occurs is 5 years and that few causal mechanisms are completed until 3 years have passed. In this case, the toltbutamide group comprised subjects who were older on average than the placebo group. Suppose that you were interested in the case fatality rate among patients undergoing bypass cardiac surgery in a new cardiac surgery unit. One need look no further than the confidence interval given in Table 6– 4 to appreciate the location and spread of the underlying p value function. The second person died from another cause, an auto- mobile crash, after which he or she was no longer at risk of dying from leukemia. This substitution is the crucial concern in many epidemiologic studies: does the experience of the unexposed group actually simulate what would have happened to the exposed group had they been unexposed? What effect would this error have on the reported results (be specific)? 5–2 to Fig. 6. Get yours now! 86 Epidemiology: An Introduction Numerator and the denominator of a risk. Of 98 who received St. John's wort, 26 responded positively, whereas 19 of the 102 who received placebo responded positively. Systematic error, or bias, is treated first, in Chapter 5, and random error in Chapter 6. On the left are hypothetical data that presume no misclassification with respect to a high-fat diet. Get yours now! 44 Epidemiology: An Introduction associated with the prevalence of ventricular septal defect at birth could be a cause of ventricular septal defect, but it could also be a factor that does not cause the defect but instead enables embryos that develop the defect to survive until birth. Dead people Dead people are not in the source population for cases, since death will preclude the occurrence of any further disease. But just as for the nursery school students and the military commandos, if these workers were young, the cancers that occurred among them would have to be occurring in young people. Incidence rates range from zero to infinity and have the dimensionality of 1/time. Although Hill did not propose these criteria as a checklist for evaluating whether a reported association might be interpreted as causal, many others have applied them in that way. The minus sign indicates that the rate is lower among the group with total blindness, which is here considered the "exposed" group. Because age is strongly related to the risk of death, this imbalance in age introduced confounding. You might decide to measure the height of 100 women sampled randomly from the population of all women in the city. We first obtain an absolute measure of effect, which would be either the risk difference or the incidence rate difference, and then we divide that by the measure of occurrence of disease among the unexposed. It may appear puzzling that restriction is not used more often in epidemiologic research. The attributable fraction for the group with no exposure is 0. To measure an incidence rate takes a finite amount of time, just as it does to measure speed; but the concepts of speed and incidence rate can be thought of as applying at a given instant. Lancet 1999; 353:1641–1648. 1) In experiments where the investigator assigns the exposure to study subjects, randomization confers powerful benefits. Suppose a case-control study could be expanded to be infinitely large. If a population has N people and A people out of the N develop disease during a period of time, the proportion A/N represents the average risk of disease in the population during that period. Instead, they could be attributable to other factors that differ between exposed and unexposed people. A nested case-control study is then more efficient. Number of expected deaths over 20 years among 1000 people Experiencing a mortality rate of 11 deaths per 1000 person-years 1000 people being followed at the start of the year? Did it lead to confounding by age? The crude data overestimate the adverse effect of toltbutamide by nearly 30% (4.5% is nearly 30% greater than 3.5%). To apply formulas 6–1 and 6–2 to obtain confidence intervals for the risk difference and the risk ratio, we need formulas for the standard error of RD and the in (RR): Example: Confidence Limits for Risk Difference and Risk Ratio As an example of risk data, consider Table 7–1, which describes recurrence risks among women with breast cancer treated with either tamoxifen or a combination of tamoxifen and radiotherapy. The population studied in the Connecticut cancer registry may be considered a dynamic cohort that comprises the people of Connecticut. What sources of error affect your estimate? The result is a strikingly different age distribution for the female smokers and non- smokers of Wickham. Over a short period of time, the influence of competing risks is generally small, and it is not unusual for studies to ignore competing risks if the follow-up is short. The incidence rate among the exposed is a/PT1 and that among the unexposed is b/PT0. Such information is often referred to as being misclassified if the variable is measured on a categorical scale and the error leads to a person being placed in an incorrect category. This hypothesis predicted that women who changed tampons more frequently would have a higher risk of toxic shock syndrome than women who changed tampons infrequently. The induction itself involves an inference beyond the observations to a general statement that describes the nature of boiling water. Random Error and the Role of Statistics, 113 7. 4. Case-Cohort Study Design Recall that in density case-control studies, the control series represents the person-time distribution of exposure in the source population. For example, a study may be based entirely on a series of deaths. In the example of sexual intercourse and myocardial infarction, the average frequency of sexual intercourse would be ascertained for each case during a period, say 1 year, before the myocardial infarction occurred. While possible, this scenario is implausible, and without evidence for these changes in smoking behavior, this implausible scenario is not a reasonable criticism of the study findings. The data are reproduced in Table 1-1. Thus, the 90% confidence interval for the risk ratio estimate of 0.78 is 0.720-85.Inother words, the 90% confidence interval for this benefit of combined treatment rangesfroma28%lower risk to a 15% lower risk. This product has no dimensionality either, so the equation holds as far as dimensionality is concerned. Put age on the horizontal axis and the 20- year risk of death on the vertical axis. * European Journal of Public Health * Epidemiology: An Introduction is a superb addition to other publications that have appeared in the past decade. Could such a study have a control series comprising the brothers of the female cases? The method of induction starts with observations on nature. Another example would be blood type. Because it remains constant, cross-sectional information on blood type is a perfect proxy for past information about blood type. Their interpretation that flu amide was ineffective which gave a result of p = 0.14. Individuals in the control group are then classified into exposed and unexposed categories. In an actual experiment, the investigator assigns the study participants to the exposed and unexposed groups. The switch, however, is often pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. Example: Confidence Limits for a Risk or Prevalence Using this formula with the example of 20 cases of influenza in 100 people, we can calculate the lower bound of a 90% confidence interval for the risk as follows. Sometimes random error stems from a random process, but it might not. Each of the time intervals should be short enough so that the incidence rate applied to it can be considered approximately constant. To be at risk of disease implies that everyone in the population at risk must be alive at the start of follow-up; dead people are not at risk of getting any disease. In addition, the disease must have an abrupt onset. Nevertheless, even with this simple age stratification, the estimate of effect is lower than the estimate from the crude data. Get yours now! Types of Epidemiologic Study 93 be possible to study the effect of cigarette smoking on sudden death from arrhythmia using that design. The calculation of effects from incidence rate data is analogous to the calculation of effects from risk data. The curve for a propagated epidemic tends to show a more gradual initial rise and a more symmetrical shape than that for a point-source epidemic because the causes spread gradually through the population. Common sense suggests that if the people in an occupation tend to live long lives, the occupation must be good for health. Hypothetical data giving 1-year disease risks for people at three levels of exposure high-exposure group, the attributable fraction is 0.75 because the risk ratio is 4. One solution is to distinguish male and female breast cancer as different diseases. After the exposure, disease does not occur until the induction period has passed (see Chapter 2). Also, any person who dies during the follow-up period, for whatever reason, would no longer be part of a population at risk. The fundamental observations in epidemiology are measures of the occurrence of illness. Epidemic curve of fatal cholera cases during the Broad Street outbreak, London 1854 Bomb blasts in Hiroshima and Nagasaki. For example, in the experiment in 1954 in which the Salk vaccine was tested, hundreds of thousands of schoolchildren were given either the Salk vaccine or a placebo. This time period may be short or long, but without identifying it, risk values are not meaningful. The curve in Figure 6–1 plots the p value testing the compatibility of the data in Table 6–1 with every possible value of RR. Rather, it amounted to an assumption that what had been observed in the past would continue to occur in the future. On the Mode of Communication of Cholera, 2nd ed. The p value function pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. N Eng J. Randomization tends pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. There is more to the causal mechanism for getting the light to shine than turning the light switch to the "on" position, however. In the calculations of rates for the data in Figure 4–2, the rate in the exposed group declined after taking the induction period into account. Explain the difference between a confounding factor and a potential confounding factor. In non experimental epidemiologic studies, the formal definition of a confidence interval is a fiction that at best provides a rough estimate of the statistical variability in a set of data. People may enter and leave a population at risk depending on their health and other possible eligibility criteria (such as age or geography). Cumulative number of deaths in 1000 people experiencing a mortality rate of 11 deaths per 1000 person-years, presuming no population shrinkage (equation 3–1) and taking the population shrinkage into account (exponential decay). Prevalence at birth is easier to assess and often used as a substitute for incidence measures. This approach was used to calculate the risk for cholera in Snow's analysis depicted in Table 4–1. Risk of recurrence of breast cancer in a randomized trial of Women treated with tamoxifen and radiotherapy or tamoxifen alone* pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. Clearly, we cannot use equation 3–1 to calculate risks that are large because it is a poor approximation in such situations. The value of 3.5% obtained after the age stratification may not be completely unconfounded by age. Equation 3–1 calculates risk as directly proportional to both the incidence rate and the time period, so as the time period is extended, the risk becomes proportionately greater. If we wish to calculate a 95% confidence interval, we would add and subtract 1.96 x SD to the point estimate to get the 95% confidence limits. To obtain a 90% confidence interval for this estimate of rate difference, we use formula 6–1 in combination with formula 7–4, as follows. Age was one of the possible confounding factors. The same approach could be applied to a closed cohort, thus addressing the problem of competing risks. Milunsky, A, Jick, H, Jick, SS, et al: Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. In this respect. Typically, the two primary variables in an epidemiologic study relate to exposure and disease. It is usually pointless, however, to measure risk in a single person, since for most diseases we would say that the person either did or did not get the disease. It is common to see confidence intervals reported for an epidemiologic measure, but it is uncommon to see a full p value function or confidence interval function. Thus, although unlikely in typical studies, the same person may appear in the control group two or more times. P value function for the data in Table 6–1 and the hypothetical case- control data in Table 6–2. The prevalence proportion of hypertension among women in the town on that date is 1200/10,000 0.12, or 12%. Get yours now! 98 Epidemiology: An Introduction Table 5–1. If a geographic roster of residences is not available, some scheme must be devised to sample residences without enumerating them all. The refutationist view is that the repeated experiments showing that water boils at 100°C corroborate the hypothesis that water boils at this temperature, but do not prove it.6 A colleague of the New York researcher who works in Denver, a city at high altitude, might find that water there boils at a much lower temperature. Pettitt, DB, Sidney, S. Therefore, the follow-up times for the exposed cohort would be 9, 17, 12, 0, and 7 years, for a total of 45 years, with only two disease events occurring during this follow-up experience. Analogously, the denominators of risk for a set of several different diseases occurring in the cohort would have the same denominator. Commonly, the arbitrary level of confidence is set at either 95% or 90%, although any level in the interval 0%–100% is possible. One approach is to frame the questions to aid accurate recall. Thus, with 20 influenza cases in a population of 100 at risk, the 90% confidence interval for the risk estimate of 0.2 is 0.13–0.27. For the low-exposure group, the attributable fraction is 0.50 because the risk ratio is 2. If the exposure is not dichotomous, there may be bias toward the null value; but there may also be bias away from the null value, depending on the categories to which individuals are misclassified. We can also compute the risk ratio and its confidence interval from the same data. Some people may be hard to track, to assess whether they have developed disease. The key difference comes in obtaining the control "series." Instead of obtaining information from other people, in the case- crossover study, the control information is obtained from the cases themselves. Since the person in question did develop disease during the study period, many investigators would be tempted to count the person as a case, not as a control. Another possible point-source epidemic that occurred over decades was an apparent outbreak of multiple sclerosis in the Faroe Islands, which followed the occupation of those islands by British troops during the Second World War.4 Furthermore, propagated epidemics, can occur over extremely short time spans. The actual data reported by Eisenberger et al.2 are given in Table 6–3. This difference reflects the rate of breast cancer among exposed women that can be attributed to radiation exposure, under the assumption that exposed women would have had a rate equal to that among unexposed women if not for the exposure. The primary estimate of effect that we can derive from these data is the incidence rate ratio, which in case-control studies is estimated from the odds ratio (OR), ad/bc. When one looks at the average age at death, one looks only at those who actually die and ignores all those who survive. For example, in a case-control study nested within an occupational cohort, workers on an employee roster will have been followed for varying lengths of time, and our random sampling scheme should reflect these varying times.the intermixing of the water supply of the Southwark and Vauxhall Company with that of the Lambeth Company, over an extensive part of London, admitted of the subject being sifted in such a way as to yield the most incontrovertible proof on one side or the other. An Introduction to Karl Popper. For example, RR of 3 represents twice as great an effect as RR of 2. AFI is the attributable fraction for exposure level i. P. Represents the proportion of all cases that falls in exposure category 1, and Z indicates the sum of each of the exposure-specific attributable fractions. Last, JM: A Dictionary of Epidemiology, 3rd Ed. New York: Oxford University Press, 1995. In epidemiology, a study is considered to pdfMachine Is a pdf writer that produces quality PDF files with ease! Produce quality PDF files in seconds and preserve the integrity of your original documents. The prevalence proportion will be P/N. Get yours now! Prospective and Retrospective Case-Control Studies Case-control studies, like cohort studies, can also be either prospective or retrospective. These factors may not have been measured among these women, or perhaps not even discovered. Are confidence intervals always symmetrical around the point estimate? This calculation is strictly hypothetical because the number at risk is reduced only by deaths from motor-vehicle injury. Suppose that the differences in the rates reflect causal effects. This approach would avoid relying on hand-picked examples, but it still suffers from an important problem that would lead to an incorrect answer. In many instances, this population may be identifiable, for example, all residents of Rio de Janeiro during the year 2001, but in other instances, the members of the source population might be hard to identify. It is certainly not true that a typical 60-year-old woman has a 2% chance of dying from cardiovascular disease within the next 24 hours or in the next week or month. What are the two main messages that should come with a statistical estimate? Over a very short time period, the risk of any particular disease is usually extremely low. In short, the strength of a cause does not equate with the biology of causation. It can be applied to nonfatal risks as well as to death but the approach originated from data that related to deaths. Get yours now! Types of Epidemiologic Study 63 Being alive and free of the disease are straightforward eligibility conditions, but other eligibility conditions may not be as simple.

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