Research and Statistics : Case-control Studies

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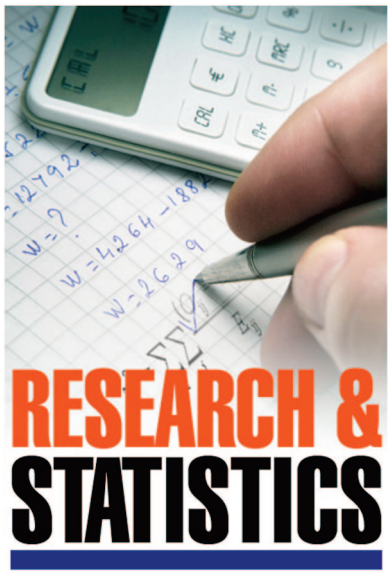

Case-control Studies

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Case Study

A 16-year-old obese girl presents to your office for evaluation of headaches. On physical examination, you document a body mass index (BMI) of 40 kg/m^2 and optic disk swelling. After negative results on head imaging, the patient undergoes a lumbar puncture that shows elevated opening pressure of 30 cm H_2O. You diagnose idiopathic intracranial hypertension (IIH). You know that the patient's weight is likely to be a major factor in this illness, but you have been working with her over several years to lose weight without success. To obtain the most up-to-date information on the link between IIH and weight gain, you conduct a literature search. You find a recent article that posed the question: How do BMI and rate of weight gain affect the risk for IIH? (1) This case-control study demonstrated that higher BMI is associated with greater risk for IIH. The authors also found that a 5% to 15% weight gain over 1 year is associated with increased risk for IIH among both obese and nonobese patients. You wonder if you can use this information to help motivate your patient to lose weight.

Introduction

Case-control studies start with a disease and compare affected patients (cases) and unaffected individuals (controls) to evaluate potential risk factors. Like cohort studies, case-control studies are observational, meaning that subjects are not assigned to a particular group by researchers but are classified by an endogenous characteristic. Unlike cohort studies, which follow subjects with and without risk factors to determine who gets a disease, case-control studies start with patients who have the disease, such as IIH in this patient, and controls are subjects who do not have the disease.

Starting with the disease makes the case-control design particularly useful for studying rare diseases, such as IIH. Because the outcome (disease) is known at the beginning of the study, a much smaller number of subjects is needed to detect differences in relative risk associated with suspected risk factors. In addition, because information usually is evaluated retrospectively, large numbers of risk factors can be examined without significant cost. The ability to review significant numbers of risk factors easily makes generation of the hypotheses another important strength of the case-control design.

Limitations

Important limitations of case-control studies must be recognized. First, it is not possible to estimate the incidence or prevalence of a disease from case-control studies because the size of the underlying population at risk is unknown. Unlike cohort studies, which may be able to evaluate risk factors for multiple outcomes, the case-control design allows study of only one outcome. Finally, case-control studies can be subject to significant bias, which may affect the validity of the findings.

Assessing Validity and Clinical Relevance

To assess the validity of a case-control study and its clinical relevance, Grimes

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and Schultz (2) propose considering the following questions.

1. **Is selection bias present?** Evaluating selection bias in a case-control study involves determining whether cases and controls are similar in all important ways other than disease status. To minimize selection bias, researchers should attempt to obtain control subjects from a population at risk for the disease that also is similar in other characteristics to the cases.

In the IIH study, cases and controls were patients examined within a 4-week period by the same neuro-ophthalmologist in a clinic. This suggests that both were drawn from the same general patient pool and that there was no significant temporal separation in their selection.

2. **Is information bias present?** Information bias refers to systematic differences in the classification of outcome or exposure status of cases and controls. One method of evaluating this criterion is to assess whether the researchers gather information about the exposures of interest similarly for cases and controls. Strategies for minimizing information bias include using validated questionnaires or tests to measure exposures, using standardized protocols for gathering information and diagnosing disease, and "blinding" those collecting the information to the case status of subjects. Attempts to use information from sources collected prior to disease diagnosis, such as from medical records, also may minimize some types of information bias that may be introduced by differential recall of information about cases and controls.

IIH was diagnosed based on a standardized clinical definition, the Modified Dandy Criteria for IIH, which suggests that patients were evaluated for the presence of disease in a similar fashion. Information regarding the primary risk factors of interest was assessed from both cases and controls via a standardized telephone interview. The interviewer was not aware of the subjects' disease status. Because the information was gathered following the diagnosis of IIH, however, the subjects being interviewed may have responded differently, based on their own knowledge of their diagnosis.

3. **Could the results be explained by confounding?** A confounder is a factor that is related to both the disease and the exposure but is not recognized by the researchers to be part of the direct causal pathway between the two. If a confounder is present in a study, researchers run the risk of attributing the presence of a disease to the variable they are studying, when that association really is due to the confounding factor. One approach to minimizing the effect of confounding is to restrict the population under study so that all participants are the same in terms of any potential confounding factors. Alternatively, researchers can match cases and controls on factors that are believed to be related to both the exposure and the disease. Finally, after a study has been conducted, researchers can analyze subjects in groups that are stratified with regard to the suspected confounding factor.

Both weight and the presence of IIH may differ by sex and age. In the IIH study, cases and controls were matched on these factors.

4. **Could the results be explained by chance?** After assessing the potential impact of bias on the results, it is important to consider whether the associations found in a study could be due to chance. If so, this phenomenon is known as a false-positive result or type I error. The *P* value of the statistical tests reported in a study give a measure of the likelihood that a difference found in the study is not a true difference in the population of interest. Another way that researchers can demonstrate that their result is not likely due to chance is to report the confidence intervals associated with their test of association.

Compared with individuals whose BMIs were less than 25, those whose BMIs were more than 35 had 26 times the chance of developing IIH, with a confidence interval of 4.9 to 135.9. Although this is not a precise estimate, the confidence interval does not cross 1, indicating a low likelihood that this association is due to chance. In addition, individuals in the study who added at least 5% to their body weight over the previous year were much more likely to have IIH than were those who did not have that weight gain.

Conclusion

Although you recognize the limitations of the case-control design, you believe that the researchers have taken steps to minimize bias and that the associations are robust. This gives you some concrete evidence of the negative health effects of your patient's continued weight gain, which you hope will provide additional motivation for her and her family to pursue weight loss.

References

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Suggested Reading

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