**Chapter 9: Matched Case Control and Comparative Effectiveness**

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**Learning Objectives**

After reading this chapter, students will be able to:

* Identify data in electronic health records that can be used to evaluate the comparative effectiveness of different interventions
* Define a case that has received an intervention and matched controls who have not received an intervention
* Contrast outcomes for cases that have received an intervention to matched controls
* Test if the difference of cases and matched controls is statistically significant
* Visually display data for outcomes of cases and matched controls over time
* Discuss the variables that can be used to match controls to intervention cases.

**Key Concepts**

* Cases
* Matched controls
* Observation period
* Enrollment event
* Follow-up period
* Exposure to treatment
* Time to event
* Days in range
* Probability of adverse events
* Odds ratio
* Verification of matching
* Confidence interval
* Normal distribution
* Standard error.

**Chapter in a Glance**

 Managers often need to compare the effectiveness of different interventions. One method of doing so is using matched case controls. This retrospective approach can be used in a variety of settings, including evaluating the impact of a program, the productivity of employees, or the market penetration of varying initiatives. Cases are selected from those who have received an intervention; controls are selected from those who have not. Cases are matched to controls based on relevant characteristics, after which the outcome of specific interventions is assessed. Data on which the analysis is based often come from electronic health records.

This chapter describes a nested, matched, case-control design using retrospective data. It defines the enrollment, observation and follow-up time periods, as well as how cases and controls are matched. Finally, it describes statistical procedures for verifying that matching was done correctly, and evaluating the statistical significance of an intervention.

**Widespread Application**

 Managers are often called upon to make judgments on the comparative effectiveness of various interventions. Here are some examples:

* **Marketing Decisions:** In marketing, cases and matched controls are needed to examine the effectiveness of competing marketing initiatives. For example, Hollon and colleagues used this technique to evaluate the effectiveness of direct-to-consumer marketing efforts.[[1]](#endnote-1)
* **Strategic Planning:** In strategic planning, this method can be used to assess the likelihood of success of different plans. For example, Mattes and colleagues used this method to evaluate the likelihood of commercial success of new inventions.[[2]](#endnote-2)
* **Quality Control and Process Improvement:** Case control studies are often used to assess quality of care. Consider the situation where there is a change in a clinical process: cases represent patient experience after a change is made; matched controls represent patients who were treated before the change was put in place. For example, Sundberg et al. contrasted the cost and effectiveness of integrated pain management. They identified pain patients who had received integrated management and contrasted them to pain patients who had received conventional care but had the same pain diagnosis, age, gender and socio-demographics.[[3]](#endnote-3) Others have used matched case control approaches to study quality factors that lead to unplanned readmissions.[[4]](#endnote-4) In another study, Danielsen and Rosenberg showed how patient education could reduce the cost of care using a matched case control study.[[5]](#endnote-5) In still another study, Grammatico-Guillon and colleagues used matched case control to monitor a hospital discharge database for hip and knee arthroplasty-related infections.[[6]](#endnote-6) Anantha and colleagues used matched case control to examine the cost and timing of care (day time or night time) for emergency general surgery.[[7]](#endnote-7) Dykes and colleagues used it to improve patient safety.[[8]](#endnote-8)
* **Health Information System Evaluation:** Case control approaches can be used to evaluate the effectiveness of electronic health record systems. For example, the relationship between computerized provider order entry and pediatric adverse drug events can be assessed,[[9]](#endnote-9) as can the effectiveness of care received remotely via telemedicine compared with that received in a typical hospital or physician office setting.[[10]](#endnote-10) Matched case controls have also been used to evaluate public health and occupational health programs.[[11]](#endnote-11)
* **Finance and Cost Effectiveness:** The use of case control studies to conduct cost effectiveness analysis is common.[[12]](#endnote-12),[[13]](#endnote-13),[[14]](#endnote-14) A retrospective matched case-control study was conducted to assess the financial impact of treating ventilator-associated pneumonia. The analysis provided the first demonstration of significant, sustained reductions in pediatric ventilator-associated pneumonia rates following the implementation of a costly prevention bundle.[[15]](#endnote-15) Others have used this method to examine the profitability of business operations,[[16]](#endnote-16) to examine hospital closure,[[17]](#endnote-17) to examine the cost effectiveness of robotic surgery, [[18]](#endnote-18) and to examine expenditures before and after surgical interventions.[[19]](#endnote-19)
* **Predictive Medicine:** A novel application was made in predictive medicine using the matched case control approach. Data from an electronic health record were used to select cases from Geisinger Clinical primary care patients with a diagnosis of heart failure. Controls were randomly selected matched based on sex, age, and clinic. The study demonstrated that it was possible to predict heart failure six months before a clinical diagnosis was made.
* **Human Resource Decisions**: The U.S. Army used the matched case control method to assess risk factors for disability retirement among its personnel.[[20]](#endnote-20) Matched case controls have also been used to evaluate the effectiveness of pre-employment screening.[[21]](#endnote-21)

As this demonstrates, the matched case control approach has broad application. Learning this method can lay a strong foundation for effective managerial decisions.

**Comparative Effectiveness Studies**

In recent years there has been growing interest in comparative effectiveness studies, partially due to the increased use of electronic health records which have made these techniques more accessible to a wider group of practitioners and researchers. The gold standard for medical research is the prospective randomized clinical trial (RCT), a rigorous approach that provides unbiased information about the impact of an intervention. The RCT does, however, have several drawbacks: (1) it involves costly data collection, (2) it restricts study to pre-defined eligible populations such as those without comorbidities, and (3) it denies access to some level of care for patients in the control group. By comparison, comparative effectiveness research (CER) allows use of data collected in the course of caring for patients. Although CER provides less rigorous conclusions, its retrospective approach enables all patients to be considered for inclusion in the study. Data from electronic medical records (EMR) and other electronic data sources are used to evaluate the impact of interventions with statistical methods. Although there are limitations, these techniques have yielded surprising and important insights into clinical care. Moreover, studies based on use of electronic and administrative data are generally less expensive and can be completed more quickly than studies based on randomized clinical trials.

Many different techniques have been developed to conduct comparative effectiveness studies, [[22]](#endnote-22) and none is without its critics.[[23]](#endnote-23) The chief complaint is often that different comparative effectiveness methods can lead to contradictory conclusions.[[24]](#endnote-24) Contradictions can occur because conclusions are based on nonrandom data and observations drawn from a wide variety of disparate sources including databases for insurance claims, prescription histories, national registries, and patient treatment records. This illustrates both the problem and its solution: lacking true random sampling, studies must be carefully designed to ensure that data are representative of the larger population for the characteristics being assessed; moreover, it must be possible to measure outcomes with variables available in the database.[[25]](#endnote-25) This chapter describes procedures for conducting a retrospective matched case control comparative effectiveness study.

**Source of Data**

Data for retrospective comparative effectiveness research (CER) is usually obtained from electronic health records. These data may include prescriptions, diagnoses, records from hospitalizations and outpatient care, clinician’s notes and dates of encounters. Data are usually obtained for a well-defined number of recent years that exceed both the planned observation prior to enrollment in the program, and the follow-up years after enrollment.

**Figure 1: Example of a Relational Database**[[26]](#endnote-26)



Statisticians are used to matrix data structures with cases in rows of a table and variables in columns. These types of data structures have sparse entries since many variables are not relevant in every case. In contrast, data in electronic health records are distributed in numerous smaller but dense tables. For example, all information about patient characteristics (e.g. date of birth, date of death) is available in one table (see left side of Table 1); information about encounters is available in other tables (see right side of Table 1), and yet another table provides information about laboratory findings. In modern electronic health record systems, millions of data elements can be distributed in thousands of tables. The analysis of data starts with becoming familiar with the data structure. The first challenge in performing a comparative effectiveness study is to aggregate data in a format that can be used for statistical analysis.[[27]](#endnote-27)

**Table 1: Patient Data & Visit Data Are in Two Different Tables**



 In a relational database, each table is a set of information about a specific variable or primary key. As an example, for a table of diagnosis codes the primary key is DIAGNOSIS\_CODE, and the information in the table are possible values for the variable. In another example, a table on patients lists the patient’s medical record number as the primary key and patient’s name and birthday as other variables (see left side of Table 1). A table on visits (see right side of Table 1) has encounter ID and diagnoses ID but not the description of the diagnosis, a patient ID but not the patient characteristics, a provider ID but no other information about the provider.

 Standard Query Language, (SQL) is used to prepare the data for analysis. Using SQL, the investigator uses the JOIN command to include data from multiple tables using each table’s primary key. This allows the investigator to connect the visit table to the patient table and thus be able to read the date of birth of the patient. It also enables joining the visit table to the diagnoses table, allowing the description of the patient’s diagnoses to be read. Knowledge of SQL is needed for preparing data electronic health records for statistical analysis.

Besides the JOIN function, SQL provides other functions to filter, count and average data. These commands can be learned quickly, and enable preparation of complex data in formats suitable for statistical analysis. Detailed instructions on use of SQL can be found at different locations including <http://openonlinecourses.com/databases>. Moreover, almost all common errors and methods of combining data can be found on-line, and there are many sites where experienced SQL programmers will help novices solve data transformation problems.

**Study Design and Methods**

In observational studies there is no random assignment of patients to groups. Consequently, observed outcomes may be due to a patient’s condition and not related to treatment. A matched case control study provides a comparison group for patients who have received the treatment, and thus reduces the possibility of erroneous attribution of findings.

The approach taken in case control studies has a long history. One of the earliest examples comes from the famous 1854 cholera epidemic in London in which it was demonstrated that most of those who died drew water from the same Broad Street pump.[[28]](#endnote-28) Case control studies also were used in many important studies in the 1920s, but truly came to prominence in the 1950s with studies that demonstrated the unexpectedly strong relationships between smoking and cancer.[[29]](#endnote-29) Use of matched case control studies in the analysis of data from electronic health records is common, and considerable advances in theory, methods, and practice of case control designs have been and are being made in epidemiology and biostatistics.[[30]](#endnote-30)

**Definition of Cases and Controls**

Patients who receive an intervention are referred to as “cases”. Patients who do not receive an intervention are referred to as “controls.” For example, patients who were admitted to the Veteran Administration’s Medical Foster Home (MFH) program (an alternative to nursing home care) may be considered cases and patients in the traditional nursing home program may be considered controls. MFH allows patients to rent their own room in a community home while receiving medical and social services from the VA in this community setting.

The identification of cases in the medical record can be difficult as these databases typically record utilization of services and not necessarily participation in a program or a need for care. There are at least two methods of identifying a case. First, a case can be identified by examining the medical record for a unique clinical event of interest. A clinical event can be a physician office visit, inpatient admission, or emergency room visit. For a study of heart failure, for example, a clinical event could be an initial diagnosis of congestive heart failure. Typically these events are defined using codified nomenclatures such as the International Classification of Diseases (ICD-9/10). The Healthcare Cost & Utilization Project of the Agency for Healthcare Research and Quality has defined how various diagnoses codes correspond to common disease categories.[[31]](#endnote-31). For example, heart failure can have one of the following ICD-9 codes: 402.01, 402.11, 402.91, 425.1, 425.4, 425.5, 425.7, 425.8, 425.9, 428.0, 428.1, 428.2, 428.21, 428.22, 428.23, 428.3, 428.31, 428.32, 428.33, 428.4, 428.41, 428.42, 428.43, or 428.9. Other examples include falls,[[32]](#endnote-32) injuries,[[33]](#endnote-33) medication errors,[[34]](#endnote-34) mood and anxiety problems,[[35]](#endnote-35) and hospitalization encounters.

Second, a case can be identified by examining admission to a program. For example, in the MFH project, the providers listed patients for whom they provided care. Patient’s scrambled social security numbers were used to identify them within the electronic health record. These patients were compared to patients in nursing homes, as MFH is an alternative to nursing home care. Nursing home patients were identified through admission and discharge dates for the nursing home information available in the medical record of the patients.

**Measurement of Exposure to Treatment**

In defining cases and controls, consideration should be given to the extent of “exposure” to an intervention. A sufficient exposure should be allowed so that a change in the outcome being evaluated can be expected. For example, the day after enrollment in MFH care, no change in patient outcome is expected since a person enrolled for one day is not considered to have received the full benefit of enrollment. Sometimes, patients enroll and dis-enroll shortly afterwards. In an on-going VA study, it was assumed that three months of enrollment is needed before a patient can be considered an MFH patient. A similar timeframe is used for controls in nursing homes. This excludes short stays – those that reside in nursing homes for less than three months.

Some patients receive both the intervention and the control programs. For example, a patient may enroll for MFH at first but after months of enrollment leave it for care in a nursing home. A patient’s enrollment in a case or control group is for a specific period. Since the same patient has spent time in both groups, they may appear to be an ideal match for themselves. The case and control match many features, with one exception - the case and control are examined in different timeframes. Unfortunately, transition from one intervention to another is almost always accompanied with a major crisis that affects patient’s health. In these situations, the same patient before and after has a different health status. For example, in Figure 2, we see information on the blood pressure of one patient. For seven years, this patient was in a nursing home. At end of the seventh year there was a hospitalization, shown as a circle. Following this hospitalization, the patient was discharged to the Medical Foster Home. The blood pressure values during year eight show the patient’s condition in the Medical Foster Home program. The conditions immediately prior year eight show blood pressure when the patient was in a nursing home. The patient’s condition worsened right before the transfer from nursing home to medical foster home program. Blood pressure can be compared before and after transfer if these data exist; without them, the patient’s experience in the two timeframes cannot be compared.

When patients are classified into cases or controls over different time periods the analytical methods for assessing treatment effects become statistically and conceptually complex. Analysis must explicitly consider “person-time”; that is, the amount of time that each patient spends as a case or control. Additionally, matching patients over time is often difficult, since time can be an important covariate with treatment results, and matching eliminates opportunities for statistical analyses of this variable.

**Figure 2: Patient Transitions among Care Venues**



**Enrollment and Observation Period**

It is important to choose an enrollment period that allows selection of a large group of patients. On the left side of Figure 3, patients arrive at different times during the enrollment period. Each patient is followed for an amount of time and their outcomes noted. The enrollment period is defined relative to the enrollment event. The left side of Figure 3 shows a graph of data based on date of visits. The right side of Figure 3 shows the same data based on time since first visit, demonstrating that patients are followed for different intervals until the outcome of interest occurs.

**Figure 3: Enrollment on Specific Dates**Numbers in the graph show patient IDs. Letter “O” indicates timing of measurement of outcome.



The observation period is typically set to one year prior to the enrollment event. During this period, no difference between cases and controls is expected. In fact, by design, controls are selected so that there is no significant difference between cases and controls prior to enrollment.

 As an example, consider the data in Table 2. Dates of various events are given as well as the calculated time since enrollment in the program. Suppose enrollment is any diabetic visit after January 1; the follow up period is any relevant event within one year of enrollment. The patient depicted in Table 2 visits the physician on January 9. This is the first diabetic visit during the enrollment period, so this becomes the enrollment event. Over the next thirteen months, the patient has several encounters with their physician as well as two ED visits. On both occasions, the ED visits were the results of falls. The time since enrollment in the study is the number of days between these fall events and the enrollment date. As Table 2 shows, one of these fall events was within one year of enrollment and therefore during the follow-up period. In analyzing data from electronic health records, it is important specify the enrollment event and follow up and observation periods as these time intervals change the data.

**Table 2: A Sample Patient and His Encounters**



**Matching Criteria**

Controls differ from cases in distinct ways. For example, controls may be older or have different comorbidities - differences that could change outcomes. Consequently, it is important to match controls to cases to ensure that such differences are not attributed to the intervention. The variables used to match controls to cases differ from study to study, but often involve one or more of the following:

1. Same observation period. Controls are often selected from the same enrollment period. When this is not done, the differences in case and controls could be due to changes that have occurred over time in the environment, or provider’s learning.
2. Same age on admission. Controls are often randomly selected so that patient ages are the same as that for cases.
3. Same gender on admission. The gender of the control and the case is often set to match.
4. Same comorbidities. Controls are randomly selected so that comorbidities match those of cases.

Another way of controlling for differences prior to enrollment is to choose controls so that they match cases in outcomes observed in the period prior to enrollment. In this fashion, case and controls have the same history. The variables typically used in this fashion include history of hospitalization, medical errors, falls, and use of mental health services. Matching by history, however, can be difficult when all relevant medical conditions data are not in the EMR and cannot be easily found in other sources.

For continuous variables, a control can be said to match the case if controls are within one standard deviation of the case. This general rule may not apply when the literature or previous research indicates absolute differences or other criteria that should be used for matching. For discrete variables, the two match if the control and the case have the same value. For each case, three matching controls may be selected, because literature and research show that the statistical power is not improved beyond a ratio of three controls to each case.[[36]](#endnote-36) If more than three controls are available, the decision on which three should be selected can be done randomly. To illustrate an example of how matching occurs, examine the data in Table 3. This table shows data for two cases who received an intervention and seven who did not. These patients are to be matched based on age, identifying as potential controls patients within one standard deviation. Control patients whose age is within one standard deviation for each case patient are eligible; selection of specific control patients is accomplished by choosing those with the lowest random number.

**Table 3: A Procedure for Matching Controls to Cases**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Patient ID** | **Received Intervention** | **Age** | **Months to Fall** | **Random Number** | **Case or control?** |
| **Observation Period** | **Follow-up Period** |
| 1 | Yes | 65 |  | 3 | 0.24 | Case |
| 2 | No | 60 |  | 2 | 0.85 |  |
| 3 | Yes | 84 | 2 |  | 0.64 | Case |
| 4 | No | 82 | 4 |  | 0.7 | Control |
| 5 | No | 78 |  |  | 0.87 |  |
| 6 | No | 80 | 3 |  | 0.72 | Control |
| 7 | No | 79 |  |  | 0.86 |  |
| 8 | No | 64 |  |  | 0.16 | Control |
| 9 | No | 70 |  | 2 | 0.17 | Control |
|  |
| **Standard Deviation** | 8.89 |  |

Suppose we need to randomly select two controls for each case. For case 1, we choose patients 8 and 9. For case 2, we also choose patients 4 and 6. Let’s look at the calculations for this example step-by-step.

**Step 1**: Calculate the standard deviation for age across all nine patients. The average age in Table 2 is 73.6 years. The standard deviation, S, can be calculated using the formula:

$$S=\sqrt{\frac{\sum\_{1}^{n}(x\_{i}-\overbar{x})^{2}}{n-1}}$$

 Where $x\_{i}$ is the ith observation from n observations $\overbar{x}$ is the average of the observations.

$$S=\sqrt{\frac{(65-73.6)^{2}+(60-73.6)^{2}+…+(70-73.6)^{2}}{9-1}}=8.89$$

 **Step 2**: For each patient that received the intervention, calculate a one standard deviation interval based on age (see Table 4).

**Table 4: Sample Calculations of Matching Controls to Age of Cases**

|  |  |  |  |
| --- | --- | --- | --- |
| Case Patients | Control Case Age | Age – One Std. Deviation | Age + One Std. Deviation |
| Patient 1 | 65 | 65 – 8.89 = 56.1 | 65 + 8.89 = 73.9 |
| Patient 3 | 84 | 84 – 8.89 = 75.1 | 84 + 8.89 = 92.9 |

**Step 3**: Identify eligible controls that fall within one standard deviation of the age of the case. Select two from among the eligible controls for each case with the lowest random numbers.

* Patient 1 is the first Case Patient with an age of 65. Patients 2, 8, and 9 fall within one standard deviation of this age. Patients 8 and 9 have the lowest random numbers, and are selected as controls.

* Patient 3 is the second Case patient with an age of 84. Patients 4, 5, 6 and 7 fall within one standard deviation of this age. Patients 4 and 6 have the lowest random numbers, and are selected as controls.

These selections provide us with assignments of controls to cases matched on age. Other variables could also be used for matching, and the decision of which matching variables should be used is a crucial decision. One common method to reduce uncertainty about the appropriate variable to match is to rely on the outcomes observed during the observation period. In this fashion, cases are matched to the control on history of the outcomes that are being monitored.

**Measurement of Outcomes**

Outcomes are typically defined over a range of values over time. Patients may be in and out of the therapeutic range on several days; consequently, it is important to calculate the percent of time patients are within the therapeutic range; this procedure was first proposed by Rosendaal.[[37]](#endnote-37) Figure 5 shows an example of a patient going in and out of range for blood pressure. In Figure 5, times when systolic blood pressures are within the range of 120 mmHG to 140 mmHG are indicated.

**Figure 5: Examples of Blood Pressures in and out of Therapeutic Range**

For two consecutive values that are in the range, the calculation is straightforward. For two consecutive values where one is in the range and another is out of range a linear extrapolation is made to determine the day the patient moved out of range. A preset maximum (e.g. 60 days) is used to reduce the influence of the linear extrapolation for two values that are very far apart. The percent of days the patient is in the therapeutic range is calculated as the sum of all estimated days in range divided by the number of days from first to last measure. For two values at two consecutive measurements, the extrapolation is based on the following formula:

$$Days in Range=\frac{Upper or lower Range-Starting Value}{Ending value-Starting Value}\*\left(Ending day-Starting day\right)$$

“Unknown days” refer to the difference of “days in range” and the maximum number of days that can be estimated from two measures. These are days that are neither in nor out of range. The percent of days in range is then calculated using the following approximation:

$$Percent Days in Range=\frac{Days in Range-Unknown Days}{Days between Last and First Measure-Unknown Days}$$

For example, in Table 5 we see six blood pressures, some in and some out of range. In the first two measurements, the patient goes from blood pressure of 125 to out of range pressure of 150. These two measures are 20 days apart; this patient is estimated to be in the range for 12 of these 20 days. Similar estimates are made for every two consecutive blood pressure. For thesecond and third measurement the estimate of days in the range is 20 days. If we assume that days more than 2 weeks away from the measurement are “unknown days”, then 6 out of these 20 days are unknown days. In the last two measurements, both measures are within range; there are 30 days between these measures, 16 of which are unknown days. The total number of days the patient is in the range is 77 days, the total number of unknown days is 22 and the percent of days in the therapeutic range are 56%.

**Table 5: Calculation of Percent Days in Therapeutic Range**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Days Since Enrollment** | **BP** | **Therapeutic Range** | **In range** | **Days in Range** | **Unknown Days > Max of 14 Days** |
|
| **Lower** | **Upper**  |
| 0 | 125 | 120 | 140 | Yes | 12 | 0 |
| 20 | 150 | 120 | 140 | No | 20 | 6 |
| 60 | 130 | 120 | 140 | Yes | 5 | 0 |
| 70 | 110 | 120 | 140 | No | 10 | 0 |
| 90 | 130 | 120 | 140 | Yes | 30 | 16 |
| 120 | 135 | 120 | 140 | Yes |  |  |
|  |  | **Total Days in Range** | 77 | 22 |
|  | **Percent Days in Therapeutic Range** | 56% |  |

At least two observations over time are needed before the “Percent Days in Therapeutic Range” can be calculated. A detailed example of these calculations is provided in Appendix A.

**Verification of Matching**

Cases and controls are compared before cases are enrolled to verify that matching was successful. The null hypothesis is that the cases and the matched controls have the same rate for outcomes during the pre-enrollment period. The alternative hypothesis is that there is a statistically significant difference between these two groups. First, the difference between each case and the mean of the controls that match the case are calculated; then the average and the standard deviation of the differences are calculated. The t-statistic is used to test if the mean of the differences is significantly different from zero. If so, the null hypothesis is rejected, and the matching process has not led to equivalent groups. If equivalent groups are not available, the procedure is repeated until two statistically equivalent groups are identified.

In many studies, the calculation of the statistics is made in error.[[38]](#endnote-38) A paired t-test can be done when cases have 1:1 match to controls and have a symmetrical distribution, the Wilcoxon, signed ranks test is used for measured non-parametric results with 1:1 matching, linear or logistic regression is used to handle matched sets other than 1:1 matching.[[39]](#endnote-39) The section below shows how to test the statistical significant of results when many controls have been matched to one case. Applying the same procedures to pre-intervention period is one way of testing that the method for matching controls to cases has been effective.

**Analysis of Outcomes**

Outcomes of case and control patients can be analyzed using the odds ratio of observed outcomes.  First, the number of outcomes in cases and controls during the follow-up period are counted.  Table 6 shows the presence of these outcomes with positive and absence with negative symbols.   So $n\_{case,+} $and $n\_{control, +}$ is the number of cases and controls that had positive outcome.  Likewise, $n\_{case, -}$ and  $n\_{control,-}$ are the number of cases and controls that had negative outcomes.

**Table 6:  Contingency Table for Adverse Outcomes**

|  |  |  |
| --- | --- | --- |
| **Outcome =Fall** | **Cases** | **Controls** |
| **Yes** | $n\_{case,+} $= 1 | $n\_{control, +} $= 1 |
| **No** | $n\_{case, -} $= 1 | $n\_{control,-} $= 3 |
| **Total** | $n\_{case}$ = 2 | $n\_{control} $= 4 |

The probability of the outcomes among the cases is calculated as the ratio of the number of observed outcomes divided by the number of possible outcomes:

$$Probability of Outcome in Cases=\frac{n\_{case,+}}{n\_{case}}$$

$$Probability of Outcome in Controls=\frac{n\_{control,+}}{n\_{control}}$$

The odds ratio of positive outcomes is calculated as the ratio of these two probabilities and is written as:

$$Odds Ratio= \frac{Probability of Outcome in Cases}{Probability of Outcome in Controls}= \frac{n\_{case,+} n\_{control,-}}{n\_{control, +}n\_{case, -}}$$

An odds ratio greater than 1 suggests more positive outcomes among the cases than controls; an odds ratio less than one suggests the reverse. An odds ratio of 1 suggests that the probability of the positive outcomes in Cases and Controls is the same.

The odds ratio is a point estimate.  A more useful concept is to a have a confidence interval around this ratio.  Confidence intervals are created so that the probability of the true odds ratio falling outside of the interval is very small, say less than 5%.  If there are a large number of cases in the study, the distribution of the natural log odds ratio, shown below as L, is approximately Normal.

$$L=Ln⁡\left(\frac{n\_{case,+} n\_{control,-}}{n\_{control, +}n\_{case, -}}\right)$$

In a Normal distribution, 95% of the data would fall within 1.96 standard deviation of the mean.  The standard deviation of the log of the odds ratio can be calculated as:

$$Standard deviation of L=\sqrt{\frac{1}{n\_{Case, +}}+\frac{1}{n\_{Case,-}}+\frac{1}{n\_{Control, +}}+\frac{1}{n\_{Control, -}}}$$

In a Normal distribution, values that are more than 1.96 standard deviations away from the mean are relatively rare and occur less than 5% of time. Therefore, the approximate 95% confidence interval for the population log odds ratio was estimated as:[[40]](#endnote-40)

$$C\_{\pm }=L \pm 1.96 \sqrt{\frac{1}{n\_{Case, +}}+\frac{1}{n\_{Case,-}}+\frac{1}{n\_{Control, +}}+\frac{1}{n\_{Control, -}}}$$

The above confidence limits are for the natural log of the odds ratio.  The confidence limit for the odds ratio, itself, is then given by:

$$Limits for Odds Ratio=e^{C\_{\pm }}$$

If this confidence interval does not include 1, then the hypothesis that cases and controls have the same outcomes has less than 5% chance of occurrence.  Then, one could reject the hypothesis with relative confidence.  The above procedure shows how the statistical significance of the difference between cases and controls are examined.

 Table 7 applies these concepts to our data. Clearly, we have very few cases and controls and one would not expect the findings to be significant nor appropriate for test of confidence interval. We apply the proposed method to these data only to explain the use of the formulas. We can examine the outcomes during the follow-up period among cases (i.e. 1 and 3) and controls (i.e. 2, 4, 8, and 9). From Table 5, the test statistic L is calculated as:

$$L=Ln⁡\left(\frac{1÷1}{1÷3}\right)=1.1$$

$Confidence Interval for natural log=1.1 \pm 1.96 \sqrt{\frac{1}{1}+\frac{1}{1}+\frac{1}{1}+\frac{1}{3}}$ = (-2.5, 4.7)

This confidence interval must now be translated back into the original units:

Confidence interface = ($e^{-2.5}$, $e^{4.7})$ = (0.1, 107.4)

The confidence interval for the ratio excludes 1. Therefore, the hypothesis of significant difference between cases and controls can be rejected.

**Table 7: Calculation of Odds Ratio for Example Cases and Controls**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Cases** | **Controls** |
| **Yes** | 1 | 1 |
| **No** | 1 | 3 |
| **Total** | 2 | 4 |
|  |  |  |
| **L=** | 1.1 |  |
| **Variance=** | 2.08 |  |
| **Std Dev.**  | 1.44 |  |
| **1.96 Std. Dev. P** | 3.58 |  |
| **Upper Limit=** | 107.45 |  |
| **Lower Limit=** | 0.08 |  |

Many policymakers prefer visual displays. Typically one plots the data using the probability of the outcome before and after enrollment. Before enrollment in the program, the rate is 50% positive for cases and 50% positive for controls. This is the overlapping point in Figure 6 and shows that before enrollment in the program cases and controls had the same rate of falls. In the follow-up period, the percent of patients with fall changes. Both groups have a decline in the rate of falls but the decline is more in the cases than controls.

**Figure 6: Impact of Enrollment in Program on Patient Falls**

The problem with Figure 6 is that it does not show the period of time that elapses before a fall occurs. Since adverse outcomes often happen eventually it is important to trace the time to the event.

**Analysis of Time to Event**

Sometimes the outcome of interest is not a count of events (e.g. falls), but days, or in our case, months to the event (person-time in epidemiology). The analysis of outcomes over time is made using a Kaplan-Meier estimator.[[41]](#endnote-41) It is used to report the time until adverse outcomes occur. The advantage of using this estimator is that it can accommodate changes in patients available to the study. For example, if patients die before the outcome of interest is measured, they can be left out of the calculation for periods that they were not available. For another example, if patients change their place of care, then they can be excluded from the study from the time that they changed providers. During each period, one can recalculate the number of patients at risk and therefore patients who drop out of the study do not affect the calculations.

During each period, the number of patients at risk of falling (number of patients in the study minus the patients that are censored) and the number of patients that do not fall (number at risk minus number that have fallen) is calculated. This is the conditional probability of falling given that the patient has not fallen in previous time periods. The probability of falling in the period is calculated as the probability of falling in the past time period times the conditional probability of not falling. Table 8 shows the calculation of these probabilities for our data. Among the 2 cases, there was one fall in the 3rd month. Among the 4 controls, there was 1 fall in the 2nd month. There was one patient in the control group that died in the 1st month and therefore was not available to the study for the following months.

**Table 8: Probability of Falling at Different Time Periods**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Period** | **Number at risk** | **Number censored** | **Number Fell** | **Number No Fall** | **No Fall Probability** |
| **Cases** | 1 | 2 | 0 | 0 | 2 | 1 |
| 2 | 2 | 0 | 0 | 2 | 1 |
| 3 | 2 | 0 | 1 | 1 | 0.5 |
| **Controls** | 1 | 4 | 1 | 0 | 4 | 1 |
| 2 | 3 | 0 | 1 | 2 | 0.67 |
| 3 | 2 | 0 | 0 | 2 | 0.67 |

Figure 7 shows the resulting percent of patients having no falls at different time intervals. Cases had a fall sooner than the controls. The statistical significance of differences in rates of falls over time can be established by using the variance for Kaplan Meier statistic.[[42]](#endnote-42)

**Figure 7: Impact of Enrollment on Months to Falls**

**Measurement of Severity**

In comparative effectiveness research it is important to statistically control for differences among severity of illness of cases and controls. Without adequate control for severity of illness, one may mistakenly attribute differences in cases and controls during the follow-up period to the intervention, as opposed to initial differences in severity of illness. The matched case control tries to control for possible differences in the two groups prior to the intervention. It is reasonable to include severity as one of the variables on which cases and controls are matched. Using the history of patient outcomes is another way of also measuring severity as these two variables are often related. Unfortunately, measures of severity can differ in terms of reliability, and reliability is often ignored in such analyses when it should be specifically modeled or adjusted when known measures of reliability exist. It has already been suggested above that uses of patient history can have its own problems. No matter what is used for matching, it is important to verify as best as possible that the cases and controls did not differ at start in their severity of illness.

There are many approaches to measuring severity of illness from patient information available in medical records. One method uses patient laboratory findings, and another method uses patient diagnoses as coded in the International Classification of Diseases.[[43]](#endnote-43),[[44]](#endnote-44) Since data warehouses have a large number of cases, it is often possible to statistically derive relationships between the patient characteristics and outcomes from the data. In these circumstances, the features and the statistical model can be used as a measure of severity of illness. Also, if difficulties arise in the analyses, simulations, bootstrapping, or other techniques might be used to assess potential effects of the reliability of severity measures.

**Propensity Scoring**

 We have shown how matched case control studies are organized. An alternative to matching is to use all data but weight the control patients to match the proportion of the cases on specific variables. Propensity scoring allows one to use all of the data while matching discards patients that do not match to cases, but the appropriateness of propensity scoring and its uses is still being debated in the literature.

**Summary**

This chapter has described how matched case controls can be organized and applied to data within electronic health records. These types of studies control for a number of possible ways in which observational studies may lead to erroneous conclusions. Like a quasi-experimental study, the matched case control protects against variables that affect both cases and controls, and the effect of time and enrollment period can be appropriately handled. There are a number of ways in which these methods could lead to erroneous conclusions. These include:

1. Poor selection of variables on which cases and controls are matched,
2. Inadequate measurement of severity of illness of patients,
3. Incomplete medical records, when patients visits outside the healthcare system is not reflected in the record,
4. Inadequate measurement of outcomes over time.

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