A Textbook of Pharmacoepidemiology and Pharmacovigilance for Pharmacy Students

# Lesson 2:
# Study Designs

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# Lesson 2: Study Designs

## Contents



## 2.1 Introduction to Study Designs

The selection of an appropriate study design is a foundational step in pharmacoepidemiologic research, as it determines the reliability, validity, and interpretability of the findings. Unlike pre-marketing clinical trials, which are typically conducted under highly controlled conditions and with carefully selected patient populations, pharmacoepidemiology is primarily concerned with the study of drug effects in real-world settings. This discipline seeks to understand not only the intended therapeutic benefits of medications but also their patterns of use, effectiveness in diverse populations, and the occurrence of rare or long-term adverse effects that may not be apparent during the initial phases of drug development.

Study designs in pharmacoepidemiology can be broadly categorized into two main types: **observational** and **experimental**. **Observational studies**, as the name suggests, involve the **passive observation of exposures and outcomes without any intervention from the researcher**. These designs are particularly valuable in the post-marketing phase, where ethical, practical, or logistical considerations often preclude the use of randomized controlled trials (RCTs). Observational studies can further be divided into descriptive studies, which aim to characterize patterns of drug use or adverse event occurrence, and analytical studies, which are designed to test specific hypotheses about associations between drug exposures and health outcomes.

**Experimental studies**, on the other hand, involve **the deliberate assignment of exposures by the investigator**, most commonly through randomization. The randomized controlled trial is considered the gold standard for establishing causal relationships between interventions and outcomes due to its ability to minimize bias and confounding. However, the stringent inclusion and exclusion criteria, limited sample sizes, and relatively short follow-up periods of RCTs often limit their generalizability to broader patient populations and their ability to detect rare or long-term adverse events.

A central concept in the evaluation of study designs is **validity**, which refers to the degree to which the results of a study accurately reflect the true association between exposure and outcome. **Internal validity** pertains to the extent to which a study is free from systematic error (bias) and confounding, ensuring that the observed associations are not due to flaws in the study's design or execution. **External validity**, or generalizability, refers to the applicability of the study findings to populations beyond the study sample. Achieving an optimal balance between internal and external validity is a persistent challenge in pharmacoepidemiologic research.

**Bias** and **confounding** are two of the most significant threats to the validity of pharmacoepidemiologic studies. **Bias** can arise at various stages of research, including during the selection of study participants (selection bias) or the measurement of exposures and outcomes (information bias). **Confounding** occurs when the observed association between a drug and an outcome is distorted by the presence of another variable that is related to both the exposure and the outcome. For example, if a new medication is preferentially prescribed to patients with more severe disease, any observed increase in adverse events may be attributable to the underlying illness rather than the drug itself - a phenomenon known as **confounding by indication**.

The choice of study design in pharmacoepidemiology is therefore guided by a careful consideration of the research question, the frequency of the exposure and outcome, the availability and quality of data, and ethical or practical constraints. For instance, rare adverse events are often best studied using **case-control designs**, while long-term safety and effectiveness are more amenable to **cohort studies**. In recent years, innovative designs such as the **self-controlled case series** and **case-crossover studies** have been developed to address specific methodological challenges, such as controlling for time-invariant confounders and assessing transient exposures.

## 2.2. Observational studies

### 2.2.1 Descriptive Studies

Descriptive studies are a fundamental component of pharmacoepidemiologic research, serving as the starting point for understanding patterns of medication use and the occurrence of health events in populations. Unlike analytical studies, which are designed to test specific hypotheses about associations between exposures and outcomes, descriptive studies are primarily concerned with the "who, what, when, and where" of drug utilization and adverse drug reactions. **Their main purpose is to generate hypotheses, quantify the burden of specific events, and provide essential background information** that can inform the design of more complex analytical investigations.

There are several types of descriptive studies commonly used in pharmacoepidemiology, including **case reports**, **case series**, and **cross-sectional studies**. Each of these designs offers unique advantages and limitations, and their appropriate use depends on the research question and the available data.

**Case Reports and Case Series**

A **case report** is a detailed account of the clinical presentation, diagnosis, treatment, and outcome of a single patient who has experienced a particular event, such as a suspected adverse

drug reaction (ADR). When multiple similar cases are described together, the report is referred to as a **case series**. These types of studies are invaluable for the early detection of rare or unexpected adverse effects, especially those that may not have been identified during pre-marketing clinical trials. For example, the initial recognition of thalidomide-induced birth defects[1] and the identification of the association between chloramphenicol and aplastic anemia were first documented through case reports and case series.

Despite their importance in signal detection, case reports and case series have significant limitations. They **lack a comparison group, making it impossible to estimate incidence rates or to establish causality**. Furthermore, they are **subject to reporting bias**, as unusual or severe cases are more likely to be published than common or mild ones. Nevertheless, regulatory agencies and pharmacovigilance systems continue to rely on these descriptive studies as a primary source for the generation of safety signals.

**Cross-Sectional Studies (Prevalence Studies)**

Cross-sectional studies, also known as **prevalence studies**, involve the collection of data on exposures and outcomes from a defined population **at a single point in time**. In pharmacoepidemiology, cross-sectional studies are frequently used to assess the prevalence of drug use, patterns of prescribing, or the frequency of adverse drug reactions within a population. For instance, a cross-sectional survey might be conducted to determine the proportion of elderly patients in a community who are taking potentially inappropriate medications.

One of the main strengths of cross-sectional studies is their efficiency; they are relatively quick and inexpensive to conduct, and they can provide a snapshot of the health status and medication use in a population. However, because **exposure and outcome are measured simultaneously, it is often difficult to establish a temporal relationship between the two**. As a result, cross-sectional studies are not suitable for studying the incidence of events or for making causal inferences.

### 2.2.2 Analytical Studies: Case-Control Studies

**Case-control** studies are fundamental analytical observational designs in pharmacoepidemiology, particularly useful for **investigating associations between drug exposures and rare or long-latency adverse events**. Case-control studies use a retrospective approach: they first identify individuals with the outcome of interest (**cases**) and compare their prior exposures to a similar group without the outcome (**controls**). This reversed temporal sequence (**from outcome to exposure**) makes case-control studies efficient tools for exploring causal hypotheses when clinical trials or prospective studies are not feasible

Proper **selection of cases and controls** is critical for the **internal validity** of a case-control study. Cases should be defined using standardized and homogeneous diagnostic criteria, while controls must come from the same source population as the cases, excluding individuals who have experienced the outcome. Exposure assessment can be conducted through medical records, electronic prescriptions, or interviews, though the latter may introduce recall bias if cases are more likely to report exposures perceived as relevant

The main strength of case-control studies lies in their **efficiency for rare events**, as they focus on a manageable number of cases and do not require prolonged follow-up of large cohorts. They

[1] Lenz W, Knapp K. Dtsch Med Wochenschr. 1962;87:1232-1242. doi:10.1055/s-0028-1111892

allow for the study of **multiple exposures** simultaneously and are generally less costly than prospective designs. However, their retrospective nature makes them susceptible to systematic biases, such as **selection bias** (if controls are not representative of the source population) and **information bias** (if exposure measurement differs between cases and controls). **Confounding by indication** is also a challenge, as the underlying risk profile of patients receiving a drug may differ from those who do not

Case-control studies have been instrumental in identifying **safety signals** that have led to regulatory actions, such as the association between aspirin and Reye's syndrome in children[2]. **Nested case-control studies**, which select cases and controls from a well-defined cohort, have enabled more precise risk estimation and adjustment for confounders using large electronic health databases and advanced analytic techniques

The primary measure of association in case-control studies is the **odds ratio** (OR), which estimates the relative odds of exposure among cases compared to controls. An OR greater than 1 suggests increased risk, while an OR less than 1 suggests a protective effect. Techniques such as **matching** and multivariable logistic regression are used to control for **confounding variables**

**Tex box: Cross-Sectional vs. Longitudinal Studies**

In pharmacoepidemiology, understanding the distinction between cross-sectional and longitudinal study designs is crucial for selecting the appropriate method to answer specific research questions. A **cross-sectional study** collects data from a population or a representative subset at a single point in time. This design offers a "snapshot" of the population, enabling researchers to estimate the prevalence of diseases, exposures, or health-related characteristics. Cross-sectional studies are efficient, relatively inexpensive, and useful for describing the current state of health or medication use within a population. However, because data on exposure and outcome are collected simultaneously, these studies cannot establish the temporal sequence of events, making it difficult to infer causality or determine the direction of associations between variables.

In contrast, a **longitudinal study** follows the same group of individuals over an extended period, collecting data at multiple time points. This repeated observation allows researchers to track changes, monitor the incidence of new outcomes, and explore the temporal relationship between exposures and effects. Longitudinal studies are particularly valuable for understanding how drug effects or health outcomes evolve over time and for identifying potential causal relationships. However, they require more resources, are time-consuming, and are susceptible to participant dropout (attrition), which can affect the validity of findings.

A fundamental difference between cross-sectional and longitudinal study designs in pharmacoepidemiology lies in how often variables are measured. In a **cross-sectional study**, each variable of interest is measured only once for each participant, at a single point in time. Conversely, a **longitudinal study** involves repeated measurements of the same variables in the same individuals over multiple time points.

[2] Halpin TJ, Holtzhauer FJ, Campbell RJ, et al. Reye's syndrome and medication use. JAMA. 1982;248(6):687-691. doi:10.1001/jama.1982.03330060027028

### 2.2.3 Analytical Studies: Cohort Studies

**Cohort studies** are analytical observational designs that start from exposure to a drug in order to evaluate its relationship with the occurrence of clinical outcomes over time. Unlike case-control studies, which reconstruct exposure retrospectively, these studies follow a natural temporal sequence (**from exposure to outcome**), allowing for the calculation of direct measures of risk, such as the **relative risk** (RR). This design is especially useful for evaluating the **effectiveness of drugs** in real-world conditions, where randomized controlled trials (RCTs) may be unfeasible due to ethical, logistical, or economic limitations (remember that RCTs evaluate efficacy).

In a cohort study, participants are divided into two groups: **exposed** (users of the drug under study) and **unexposed** (non-users or users of a comparator). Both groups are followed prospectively or retrospectively (See Text box: Clarifying Terminology for Retrospective Cohort Studies) to compare the **incidence** of outcomes.

**Measuring exposure** requires standardized criteria (dose, duration, adherence). In prospective studies, this information is collected directly from participants or through prescription records. In historical cohort studies, reliance is placed on the accuracy of administrative databases or electronic medical records. Follow-up must be sufficiently long to capture outcomes of interest, such as the development of chronic adverse effects.

The main strength of cohort studies lies in their ability to establish a clear temporal sequence and calculate **relative risks** (RR). The RR is obtained by dividing the incidence of the outcome in the exposed group by the incidence in the unexposed group. In addition, cohort studies allow for the simultaneous study of **multiple outcomes**. The WHI (Women's Health Initiative) cohort evaluated not only the risk of breast cancer associated with hormone therapy, but also its impact on bone fractures and coronary heart disease[3]. **Cox proportional hazards** models are widely used to adjust for confounding variables and analyze the impact of exposure duration.

However, these studies face significant methodological challenges. **Confounding by indication** is particularly problematic: patients who receive a drug may systematically differ from those who do not in prognostic factors. For example, in studies on SSRIs and gastrointestinal bleeding, users often have a higher prevalence of anxiety disorders, which are themselves associated with peptic ulcers[4]. To mitigate this bias, techniques such as **propensity score matching**, which balances exposed and unexposed individuals on baseline characteristics, or Cox regression models, which adjust for variables such as age, sex, and comorbidities, are employed.

Another limitation is **survival bias**, which occurs when participants who drop out of the study differ systematically from those who remain.

[3] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333. doi:10.1001/jama.288.3.321

[4] Goodwin RD, Stein MB. Generalized anxiety disorder and peptic ulcer disease among adults in the United States. Psychosom Med. 2002;64(6):862-866. doi:10.1097/01.psy.0000038935.67401.f3

**Clarifying Terminology for Retrospective Cohort Studies**

The term **"historical cohort study"** is preferred over "**retrospective cohort study**" to emphasize the prospective nature of cohort designs while distinguishing the timing of data collection. Cohort studies, by definition, involve observing a group (cohort) over time to assess outcomes relative to exposures. The critical distinction lies in whether data collection occurs prospectively (tracking events forward from the present) or retrospectively (using pre-existing records to reconstruct past exposures and outcomes).

Traditional terminology categorizes cohort studies as either *prospective* (initiated in the present with future follow-up) or *retrospective* (using historical data). However, labeling the latter as "retrospective" risks conflating the study's temporal design with its data sources. All cohort studies are inherently prospective, as they examine outcomes over time. The term **"historical cohort"** more accurately reflects that the exposure and outcome data were collected from pre-existing records (e.g., medical archives, insurance claims), avoiding ambiguity about the study's longitudinal framework.

This terminology shift aligns with methodological clarity: both prospective and historical cohorts analyze temporal relationships, but historical cohorts rely on previously recorded data.

- **Prospective cohort** (or simply cohort study): prospective follow-up from current date to the future.
- **Historical cohort**: prospective follow-up from ancient past to the recent past.

Another confusing term, **ambispective cohort**, is unnecessarily used when representing a historical cohort that continues collecting to a future date (prospective follow-up from the past to the future).

### 2.2.4 Analytical Studies: Special Designs

Case-Crossover study

The **case-crossover** design is a self-controlled observational method developed to study the **effects of transient exposures on the risk of acute events**. In this design, each subject who experiences the outcome of interest serves as their own control. The key methodological feature is the comparison of exposure status during a predefined "hazard period" immediately preceding the event (the case window) with exposure status during one or more earlier "control periods" when the event did not occur. By making **within-person comparisons**, the case-crossover design inherently **controls for all time-invariant confounders**, such as genetics, sex, and chronic health conditions, since these factors do not change between the case and control periods for the same individual

This design is particularly suited to investigating whether a brief or intermittent exposure-such as the initiation of a medication, physical exertion, or an environmental factor-acts as a trigger for a sudden-onset event, like myocardial infarction, stroke, or an adverse drug reaction. For example, a case-crossover study could compare the use of a short-acting beta-agonist in the hours before an asthma attack to use during other time windows without attacks in the same patient. The

analysis typically uses conditional logistic regression to estimate the odds ratio for the association between exposure and the acute event

However, the case-crossover design has limitations. It assumes that the exposure is transient and that the risk period is brief and well defined. It may be susceptible to bias if there are time trends in exposure, or if the selection of control periods is not appropriate. For example, if a medication is increasingly prescribed over time, control periods from earlier in the observation window may underestimate exposure, leading to biased estimates

**Example of case-crossover design**

The **case-crossover design** is a design tailored to assess transient drug exposures and acute outcomes by leveraging within-subject comparisons. In this design, each individual serves as their own control, with exposure during a **risk period** (immediately preceding the event) compared to earlier **control periods** in the same individual's history. This approach inherently adjusts for **time-invariant confounders** (e.g., genetics, chronic comorbidities), as comparisons occur within the same person. A key application illustrated in the study by Delaney and Suissa evaluated warfarin-associated gastrointestinal (GI) bleeding using the UK's General Practice Research Database. Researchers analyzed 4,028 GI bleed cases, defining exposure via warfarin prescriptions in predefined time windows (30, 90, 180 days, or 1 year). Results demonstrated significant sensitivity to window length: a 30-day window showed no association (RR = 0.98), while longer windows (90 days to 1 year) yielded inflated risk ratios (RR=1.60–3.57), likely due to exposure misclassification. Stratifying by prescription frequency revealed that **transient warfarin users** (1–3 prescriptions/year) faced a 2.59-fold increased risk, aligning with randomized trial evidence, whereas chronic users showed no elevated risk, underscoring the design's reliance on intermittent exposure assumptions.

A major strength of the case-crossover design is its ability to **eliminate confounding from stable individual factors**, such as genetic predispositions or chronic conditions, which are constant over time. This makes it particularly useful for isolating acute drug effects. Additionally, the design is **resource-efficient**, as it avoids recruiting external controls by utilizing longitudinal data. However, its validity hinges on appropriate **exposure window selection** and addressing **time-varying confounders**. For example, warfarin's variable prescription durations and clinical monitoring practices complicate exposure classification. The study highlighted these challenges: while a 30-day window underestimated risk due to mismatched prescription cycles, a 1-year window introduced bias from secular trends in warfarin use. To mitigate this, the **case-time-control extension** incorporated external controls to adjust for prescribing trends, yielding a more plausible RR of 1.72 for a 1-year window.

Case-crossover design has limitations. It is **ineffective for chronic exposures**, as continuous drug use violates the transient exposure assumption, biasing results toward the null. Autocorrelation from prolonged therapy further reduces statistical power. The design also requires careful **sensitivity analyses** to validate exposure windows and account for time-varying factors like concurrent medications or acute illnesses. In the warfarin example, stratification and lagged control periods improved accuracy, but misclassification remained a concern.

**Reference**:

Delaney JA, Suissa S. The case-crossover study design in pharmacoepidemiology. Stat Methods Med Res. 2009;18(1):53-65. doi:10.1177/0962280208092346

**Propensity Score Matched Case-Control Studies**

**Propensity score matched (PSM) case-control studies** are a cornerstone of observational research in pharmacoepidemiology, enabling researchers to approximate the balance of randomized trials while leveraging real-world data. These studies address **confounding by indication** by ensuring that **cases** (e.g., patients experiencing an adverse outcome) and **controls** (those without the outcome) **are comparable across measured baseline covariates**. The propensity score, defined as the probability of receiving a treatment or developing an outcome given observed characteristics, is estimated using logistic regression or machine learning algorithms. By matching cases to controls with similar propensity scores, researchers create balanced groups, reducing bias from confounding variables such as age, comorbidities, or concomitant medications.

The process begins with defining the study population and **identifying covariates likely to influence treatment assignment or outcome risk**. Propensity scores are calculated for each individual, often incorporating demographic, clinical, and healthcare utilization variables. Matching algorithms, such as nearest-neighbor matching with or without calipers, pair cases to controls based on these scores. For example, a 1:4 **matching ratio** (one case to four controls) is common to enhance statistical power while maintaining balance. After matching, researchers assess covariate balance using standardized mean differences or graphical methods (e.g., histograms of propensity score distributions). Statistical analyses, such as conditional logistic regression, then estimate odds ratios while accounting for the matched design.

PSM case-control studies offer several advantages. First, they improve transparency by explicitly modeling treatment assignment, making the analytical approach accessible to clinicians and regulators. Second, they enhance efficiency by reducing variability between groups, particularly in large healthcare databases where rare outcomes or exposures are studied.

However, limitations exist. PSM only adjusts for measured confounders, leaving residual bias from unobserved variables (e.g., socioeconomic status not recorded in claims data). Overly restrictive matching criteria or narrow calipers can exclude eligible participants, reducing generalizability. Additionally, model misspecification in propensity score estimation—such as omitting nonlinear effects or interactions—may compromise balance. Sensitivity analyses, including assessments of unmeasured confounding and alternative matching algorithms, are critical to validate findings.

In pharmacoepidemiology, PSM is particularly valuable for studying drug safety signals in electronic health records or insurance claims databases. This approach isolates the drug effect from confounding by underlying metabolic conditions. Recent advancements, such as machine learning-enhanced propensity scores and three-way matching for multi-drug comparisons, further refine the method’s applicability.

**Propensity score-matched case-control study on carbapenem-resistant enterobacterales**

A nationwide case-control study using Korean National Health Insurance claims data (2017–2019) investigated risk factors for carbapenem-resistant enterobacterales (CRE) infections in hospitalized patients. Researchers employed **propensity score matching (PSM)** to compare 1,619 CRE cases with 4,857 controls, adjusting for age, sex, comorbidities, healthcare utilization, and vancomycin-resistant Enterococci (VRE) history. The study identified broad-spectrum antibiotics—piperacillin/tazobactam (aOR=2.18), carbapenems (aOR=1.78), and third/fourth-generation cephalosporins (aOR=1.76) — as significant drivers of CRE risk. Comorbidities like diabetes, kidney disease, and liver disease further amplified susceptibility. CRE patients faced markedly higher mortality (8.33 vs. 3.32 deaths per 100 person-months) and healthcare costs (15.3 million vs. 5.3 million KRW per person-month), underscoring the clinical and economic burden of resistance.

The propensity score matching methodology was critical for enhancing result reliability. **By balancing baseline characteristics** (e.g., age, comorbidities, ICU exposure) between cases and controls, **PSM minimized confounding bias** inherent in observational data. This approach allowed researchers to isolate the effect of antibiotic use on CRE risk, approximating the rigor of randomized trials. For instance, the matched groups showed standardized mean differences <0.1 for most covariates, ensuring comparability. Without PSM, unmeasured differences in patient severity or healthcare access could have distorted associations, particularly given the study's reliance on retrospective claims data.

These findings highlight the importance of antimicrobial stewardship to curb broad-spectrum antibiotic use, especially in high-risk populations. The study's design — using PSM to address confounding — strengthens causal inferences about modifiable risk factors like antibiotic selection. However, residual bias from unmeasured variables (e.g., genetic predispositions, detailed clinical histories) remains a limitation. Nonetheless, this methodology provides a robust framework for evaluating drug-resistant infections in real-world settings, informing policies to mitigate CRE spread and optimize antibiotic prescribing practices.

**Reference**:

Kwon KT, Kim Y, Kim SW, et al. Antimicrobial Use and Carbapenem-Resistant Enterobacterales in Korea: A Nationwide Case-Control Study With Propensity Score Matching. J Korean Med Sci. 2024;39(14):e132. doi:10.3346/jkms.2024.39.e132

**Nested Case-Control Studies**

**Nested case-control studies** are an efficient observational design conducted within a pre-existing cohort, **combining the strengths of cohort and case-control designs**. In this approach, **cases** (individuals who develop the outcome of interest) are identified during cohort follow-up, **and controls are selected from the same cohort** who remain unaffected at the time of each case's diagnosis. Controls are often matched to cases by factors such as age, sex, and calendar time, ensuring comparability while controlling for confounding. This design is particularly valuable in pharmacoepidemiology for studying rare adverse drug reactions or complex exposures, such as biomarkers, where measuring variables for an entire cohort is impractical or costly.

A key advantage lies in its **prospective data collection within the cohort framework**. Exposure information (e.g., medication use, genetic markers) is often recorded before outcome occurrence, minimizing recall bias. The design also **allows precise time-dependent exposure assessment**, such as evaluating whether medication use precedes outcome onset, which is critical for establishing causality. Unlike traditional case-control studies, nested designs **reduce selection bias** by drawing both cases and controls from a well-defined cohort with documented follow-up.

Methodologically, nested case-control studies use risk-set sampling, where controls are selected from individuals still at risk when each case emerges. This mirrors the cohort's dynamic nature and ensures temporal alignment between exposures and outcomes. Statistical analyses typically employ conditional logistic regression to account for matching, yielding odds ratios that approximate hazard ratios from full cohort analyses.

However, limitations include potential residual confounding from unmeasured variables and reduced statistical power compared to full cohort analyses. These issues are mitigated by careful control selection and adequate sample size.

**Nested Case-Control Study on SSRIs, Oral Anticoagulants, and Major Bleeding**

A 2024 nested case-control study published in *JAMA Network Open* investigated the bleeding risks associated with concomitant use of selective serotonin reuptake inhibitors (SSRIs) and oral anticoagulants (OACs) in patients with atrial fibrillation. Using UK primary care data (1998–2021), researchers identified 42,190 major bleeding cases (e.g., gastrointestinal or intracranial hemorrhage) and matched them to 1,156,641 controls (1:30 ratio) based on age, sex, and follow-up duration. The study found that combining SSRIs with OACs increased major bleeding risk by 33% (adjusted incidence rate ratio [IRR] = 1.33; 95% CI: 1.24–1.42), with the highest risk occurring within the first 30 days of concurrent use (IRR = 1.74). Risks persisted across OAC types (direct OACs and vitamin K antagonists) and bleeding subtypes, underscoring the clinical significance of this interaction.

The **nested case-control design** was pivotal to the study's validity and efficiency. By embedding the analysis within a pre-defined cohort of 331,305 OAC users, researchers leveraged longitudinal data to retrospectively identify cases and dynamically sample controls from the same population. This approach minimized selection bias, as controls were drawn from individuals still at risk at each case's event time, ensuring temporal alignment. Matching on demographics and follow-up duration further balanced baseline characteristics, while conditional logistic regression accounted for confounding variables like comorbidities and concomitant medications. The design's efficiency was evident in its ability to analyze rare outcomes without requiring exhaustive data collection from the entire cohort.

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**(contunied) Nested Case-Control Study on SSRIs, Oral Anticoagulants, and Major Bleeding**

The study highlights the nested case-control design's strengths in pharmacoepidemiology. By using existing electronic health records, it combined the prospective cohort's rigor with the case-control method's resource efficiency. This design also enabled precise exposure timing assessments, critical for establishing causality between transient SSRI use and acute bleeding events. Additionally, stratification by OAC type and bleeding subtypes demonstrated the methodology's flexibility in exploring subgroup effects. However, limitations included potential residual confounding from unmeasured variables (e.g., adherence) and reliance on prescription records rather than actual drug intake.

These findings emphasize the importance of monitoring bleeding risks during SSRI-OAC co-therapy, particularly in early treatment phases. The nested case-control approach provided robust, real-world evidence to guide clinical decisions, illustrating how this design balances methodological rigor with practicality in large-scale drug safety research. By isolating acute drug effects while controlling for confounders, such studies inform risk mitigation strategies without the logistical challenges of randomized trials.

**Reference**:

Rahman AA, Platt RW, Beradid S, Boivin JF, Rej S, Renoux C. Concomitant Use of Selective Serotonin Reuptake Inhibitors with Oral Anticoagulants and Risk of Major Bleeding. JAMA Netw Open. 2024;7(3):e243208. doi:10.1001/jamanetworkopen.2024.3208

## 2.3. Experimental (interventional) studies

### 2.3.1 Randomized Controlled Trials (RCTs)

Randomized controlled trials (RCTs) are the gold standard for establishing causality in the evaluation of pharmacological interventions. Their internal validity stems from **randomization**, a process that assigns participants to intervention or control groups using stochastic mechanisms, balancing both known and unknown confounding factors. This design ensures that observed differences in outcomes are attributable to the treatment being evaluated rather than selection biases or external variables.

Randomization is complemented by **blinding** (double-blind, triple-blind) to minimize performance and detection biases. In a double-blind trial, neither participants nor investigators know the treatment assignment, neutralizing subjective expectations.

RCTs are structured into sequential phases:

1. **Phase I**: Evaluates safety, pharmacokinetics, and dosing in healthy volunteers (n ≈ 20–100).
2. **Phase II**: Explores preliminary efficacy and safety profiles in specific populations (n ≈ 100–300).
3. **Phase III**: Confirms efficacy and safety in large, diverse cohorts (n ≈ 1,000–30,000) and is pivotal for regulatory approval.

4. **Phase IV (Post-Marketing)**: Monitors long-term effects and rare events in real-world conditions.

Despite their rigor, RCTs have inherent limitations:

- **Reduced External Validity**: Exclusion criteria (e.g., advanced age, comorbidities, polypharmacy) create homogeneous study populations that do not reflect real-world clinical practice.
- **Limited Duration**: Most RCTs last months or a few years, insufficient to detect delayed effects.
- **Rare Events**: The typical sample size of RCTs (even Phase III) is inadequate to identify risks with incidences <1%. Thalidomide, for instance, showed safety in trials with thousands of participants, but its teratogenicity (1:10,000) was identified only after commercialization.

To address these limitations, adaptive designs have been developed:

- **Pragmatic Trials**: Integrate heterogeneous populations and clinically relevant outcomes. The **Salford Lung Study** evaluated fluticasone/vilanterol in asthma and COPD in real-world settings using electronic health records.
- **Adaptive Bayesian Designs**: Allow adjustments to sample size or hypotheses based on interim data. This approach was pivotal in the **I-SPY 2** trial for breast cancer, which evaluated multiple neoadjuvant therapies in parallel.
- **Hybrid RCTs (Phase III–IV)**: Combine pre-marketing evaluation with post-authorization monitoring. The **CANTOS** trial exemplifies this model, tracking long-term effects of canakinumab in atherosclerosis patients.

RCTs alone are insufficient for comprehensive pharmacovigilance. Their role is complemented by observational studies (cohorts, case-control) and spontaneous reporting systems.

### 2.3.2 Quasi-Experimental Studies

**Definition and Methodological Principles**

**Quasi-experimental studies** are research designs that approximate the rigor of randomized controlled trials (RCTs) but **lack random assignment** to treatment and control groups. These designs are employed when ethical, logistical, or practical constraints prevent full experimental control, such as in policy evaluations, public health interventions, or retrospective analyses of real-world data. The prefix *quasi* (Latin for "as if") reflects their hybrid nature: they mimic experimental methods while relying on observational or non-randomized assignment mechanisms.

The core strength of quasi-experiments lies in their ability to estimate causal effects in naturalistic settings. Unlike observational studies, quasi-experimental designs involve intentional manipulation of an independent variable (e.g., a drug, policy, or intervention) and include structured comparisons between groups or time periods. However, the absence of randomization introduces risks of **confounding bias**, as pre-existing differences between groups may influence outcomes. To address this, advanced statistical techniques-such as **propensity score matching**, **regression discontinuity**, or **instrumental variables**-are often applied to approximate randomization and improve internal validity.

Common Quasi-Experimental Designs

1. Non-Equivalent Control Group Design
   - Compares outcomes between a treatment group and a non-randomized control group that is "as similar as possible" to the treatment group.
   - Example: Evaluating the impact of a hospital antibiotic stewardship program by comparing infection rates in hospitals that implemented the program (treatment) versus those that did not (control), adjusting for hospital size and patient demographics.
2. Interrupted Time Series (ITS)
   - Analyzes trends in outcomes before and after an intervention within the same population.
   - Example: Assessing the effect of a vaccine mandate on measles incidence by comparing infection rates for several years pre- and post-mandate.
3. Regression Discontinuity Design (RDD)
   - Assigns treatment based on a cutoff score (e.g., blood pressure thresholds for antihypertensive therapy). Participants near the cutoff are compared to minimize confounding.
   - Example: Studying the efficacy of statin therapy by comparing cardiovascular outcomes in patients with LDL cholesterol levels just above vs. below a treatment threshold.
4. Natural Experiments
   - Leverages external events (e.g., policy changes, environmental shifts) that mimic random assignment.
   - Example: Analyzing the health effects of a sugar tax by comparing dietary behaviors and obesity rates in regions where the tax was implemented versus those where it was not.
5. Difference-in-Differences (DiD)
   - Compares changes in outcomes over time between a treatment group and a control group.

- Example: Measuring the impact of a smoking cessation campaign by comparing smoking rates in targeted cities (treatment) and non-targeted cities (control) before and after the campaign.

Strengths and Limitations

| Strengths | Limitations |
|---|---|
| - Feasible in real-world settings where RCTs are impractical or unethical. | - Risk of residual confounding due to non-random assignment. |
| - Enables evaluation of population-level interventions (e.g., laws, guidelines). | - Requires robust statistical adjustment to approximate causal inference. |
| - Cost-effective for studying long-term or rare outcomes. | - Susceptible to selection bias (e.g., healthier patients may opt into treatment). |
| - Integrates naturally occurring data (e.g., EHRs, registries). | - Limited ability to control for unmeasured confounders (e.g., socioeconomic factors). |

These study designs have different applications in pharmacoepidemiology, for example:

6. Post-Marketing Surveillance
   - Quasi-experiments are critical for evaluating drug safety signals identified in observational data. For instance, after the FDA issued a black-box warning for antidepressants and suicidality in adolescents, quasi-experimental analyses of prescription trends and hospitalization rates helped clarify the risk-benefit balance.
7. Policy Evaluations
   - Studies on opioid prescribing restrictions, cannabis legalization, or antibiotic stewardship programs often use interrupted time series or DiD designs to isolate policy effects from secular trends.
8. Comparative Effectiveness Research
   - When RCTs are unavailable, quasi-experiments compare real-world outcomes of alternative therapies. For example, RDD has been used to assess the effectiveness of GLP-1 agonists versus SGLT2 inhibitors in diabetic patients with heart failure.

**Assessing COVID-19's Impact on Antidepressant Use (Interrupted Time Series)**

The **interrupted time series (ITS)** design is a powerful tool for evaluating the causal impact of population-level events, such as pandemics, on drug consumption patterns. A 2024 study in Central Portugal demonstrated this by analyzing antidepressant dispensing data before and after the COVID-19 pandemic declaration. Using a Bayesian structural time-series model, researchers compared observed antidepressant use (N06A) to a **counterfactual series** predicted from control drugs (anti-Parkinson agents and statins) unaffected by the pandemic. This approach isolated the pandemic's effect while controlling for secular trends, seasonality, and confounding variables like demographic shifts or prescribing practices. At the regional level, antidepressant consumption showed a non-significant increase (+1.3%, 95% CI: -1.6% to 4.2%), suggesting minimal overall impact. However, finer geographical analysis revealed stark disparities: municipalities with higher elderly populations saw increases up to +37%, while densely populated areas experienced declines of -11%, highlighting heterogeneous local effects masked in aggregate data.

(continues)

**(continued) Assessing COVID-19's Impact on Antidepressant Use (Interrupted Time Series)**

The ITS design's strength lies in its ability to establish **causal inferences** by contrasting post-intervention trends with a synthetic control. By leveraging longitudinal data (2010–2021), the study accounted for pre-pandemic trajectories, reducing bias from unmeasured confounders. The Bayesian model further enhanced rigor by quantifying uncertainty through posterior probability intervals, ensuring robust estimates of the pandemic's effect. Control series (dopaminergic agents and statins) validated the method's specificity, as their consumption remained stable, confirming that observed antidepressant trends were not artifacts of broader healthcare disruptions. This design also accommodated **autocorrelation** and non-linear trends, common challenges in drug utilization studies, providing a more accurate counterfactual than traditional regression models.

The study underscores ITS's utility in pharmacoepidemiology for disentangling complex temporal relationships. By revealing subregional variations linked to demographics (e.g., elderly populations), it highlighted how ITS can identify vulnerable subgroups and inform targeted interventions. Despite limitations like residual confounding from unmeasured variables (e.g., mental health service access), the design's transparency in modeling pre-existing trends and its adaptability to multiple granularity levels make it indispensable for evaluating public health policies. For policymakers, such analyses clarify whether observed changes reflect true shifts in mental health needs or artifacts of healthcare delivery, ensuring responses are evidence-based and equitable.

**Reference**:

Negrão LG, Coelho C, Castel-Branco MM, Figueiredo IV, Fernandez-Llimos F. Impact of the COVID-19 pandemic on antidepressant consumption in the Central region of Portugal: interrupted time series. Soc Psychiatry Psychiatr Epidemiol. 2025;60(3):621-629. doi:10.1007/s00127-024-02731-0