Integrative Medicine Research 12 (2023) 101000

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.elsevier.com/locate/imr

Education Article

Real-world data analysis on effectiveness of integrative therapies: A practical guide to study design and data analysis using healthcare databases

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ARTICLE INFO

Keywords:
Acupuncture
Integrative medicine
Real world data
Real world evidence
Epidemiology

ABSTRACT

Real world data (RWD) is increasingly used to investigate health outcomes and treatment efficacy in the field of integrative medicine. Due to the fact that the majority of RWDs are not intended for research, their secondary use in research necessitates complex study designs to account for bias and confounding. To conduct a robust analysis of RWD in integrative medicine, a comprehensive study design process that reflects the characteristics of integrative therapies is necessary. In this paper, we present a guide for designing comparative effectiveness RWE research in integrative medicine. We discuss key factors to consider when selecting RWDs for research on integrative medicine. We provide practical steps for developing a research question, formulating the PICOT objectives (population, intervention, comparator, outcome, and time horizon), and selecting and defining covariates with a summary table. Specific study designs are depicted with corresponding diagrams. Finally, data analysis procedures are introduced. We hope this article clarifies the importance of RWE research design and related processes in order to improve the rigor of RWD studies in the field of integrative medicine research.

1. Introduction

In the field of integrative medicine, real world data (RWD) is increasingly used as a source to investigate health outcomes and treatment effectiveness.[1-3] The area of integrative medicine encompasses a form of medical practice that integrates conventional healthcare with complementary and alternative medicine,[4,5] with a focus on the integration of evidence-based methods[6] to enhance overall well-being across physical, mental, and spiritual dimensions.[7] RWD in integrative medicine refers to data collected as part of routine healthcare processes of such practice, e.g., administrative claims, electronic health records, and disease registries, that have exposure to integrative therapies and clinical outcomes.[2,8] Frequently employed RWD in integrative medicine research include national health insurance claims data from Korea,[2,9,10] Taiwan,[3,11,12] and Japan,[13-15] where integrative medicine is practiced in various formats. Application of principled database epidemiology to RWD can synthesize real world evidence (RWE) and help make decisions in healthcare policy.[16]

RWDs can provide timely and practice-based information including long-term outcomes in areas in which primary data collection may not be feasible or cost-effective through conventional randomized controlled trials (RCTs). For rare conditions which leaves little feasibility of conducting RCTs, RWD and RWE plays a pivotal role in understanding the disease progress and to support regulatory decisions.[17] In integrative medicine, RWD enables collection of data from integrative medicine providers with limited ability to engage in research. Previous studies in integrative medicine based on RWD provide information on healthcare utilization,[18-20] comparative effectiveness,[21] and long-term follow up.[22-24]

As most RWDs are not designed for research, their secondary use in research necessitates complex study designs to account for bias and confounding. Previous literature illustrates various study designs of RWE research, including the most commonly used designs such as cohort design, nested case-control design, and self-controlled case series.[25,26] Still persisting quality gaps and suspected overestimation of treatment effects in RWD studies have been attributed to variability in research question, study design, parameters, and analyses.[27,28] Appropriate research question, corresponding study design that avoids biases, rigorous statistical analysis, the quality of the data, and the fit and validity of the models are some examples of the factors that influence the quality of the evidence produced from RWD studies.[29,30]

To capture the complexity of epidemiological methods and study designs, the United States Agency for Healthcare Research and Quality published a detailed user's guide on developing a protocol for observational comparative effective research.[25] Furthermore, to ensure that the necessary components of study designs are reflected in the study and properly reported, templates for planning and reporting RWE research such as RECORD-PE,[31] STaRT-RWE,[32] and HARPER,[33] and guides for

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https://doi.org/10.1016/j.imr.2023.101000
Received 4 August 2023; Received in revised form 17 October 2023; Accepted 18 October 2023
Available online 20 October 2023

graphical depiction of longitudinal study designs[34] were developed. A recent review assessed the use of the above template in RWE studies and found low utilization of such templates,[35] implying a need for improvement of robustness of RWE studies. The observed phenomenon is not an exception within the field of integrative medicine, in which the utilization of real-world data (RWD) is increasing in research investigations. The use of these templates and instructions has the potential to enhance the reproducibility of research findings and promote more effective communication between researchers and decision makers.

In order to conduct a robust analysis of RWD in integrative medicine, a thorough process of study design reflecting the characteristics of integrative therapies and the relationships between interventions and outcomesare required. For example, the initiation date of treatment (often known as index date in observational studies),[36] the number of acupuncture sessions,[37] as well as exposure of acupuncture prior to disease diagnosis[38] are some of the factors which influence the study design and, ultimately, the results of the analysis. If acupuncture is practiced as an adjuvant treatment to conventional treatment regimen, possible differences in the characteristics of treatment and control groups have to be addressed in the study design. With little or no effort to address the above issues in RWE research in integrative medicine, possibly due to the relatively small number of studies, issues remain to be resolved.

In this paper, we present a practical guide for designing a RWE research in integrative medicine focusing on comparative effectiveness, with examples study designs using administrative data and medical records. Based on the previously reported guidelines on RWE studies,[31-34] we provide steps with graphical examples for designing an RWD-based study using the example of breast cancer.

2. Real-World Database (RWDs) in integrative medicine research

A prerequisite of study design involves selection of the source database,[31-33] from which all variables are defined. Based on the available variables in the database, operational definitions are built for each component of the study design to provide a clear and measurable criteria that researchers can apply to the database. The importance and details of operational definitions by databases, e.g., diagnosis codes, treatment codes, and hospitalization codes are also found in previous literature.[39-42]

Sources of RWD include claims database[9,11,13-15] and electronic health records which are collected during routine clinical practice.[8,26] An overview of RWDs with information on integrative therapies is provided in previous studies,[1,2,8] including the types of RWDs and their accessibility. Major advantage of RWDs such as health insurance claims data is that it is readily available and allow observation across a long-term period. However, the following issues should be discussed thoroughly among the researchers prior to and during conducting the study.

First, the information included in the database may vary by providers. The database from the two agencies in Korea, National Health Insurance Service (NHIS)[9] and Health Insurance Reassessment Agency (HIRA),[43] cover Korean population, with slight differences in the variables. Both databases contain patient's diagnosis, medical procedures, treatments, and cost; however, death records and income are only available in the NHIS database. On the other hand, HIRA provides full records of prescribed medications, while NHIS in the recent years provide limited information on brand name and exact dosage of prescribed medications.

Furthermore, information regarding integrative medicine included in the claims database is likely to be different by countries. One previous study comparing the healthcare utilization between Taiwan and Korea using health insurance claims data[19] showed that the utilization of traditional medicine in Taiwan is focused in herbal formulae, while utilization of traditional medicine in Korea is focused on acupuncture and moxibustion. Utilization of integrative therapies not covered by the national health insurance, i.e., herbal decoction in Korea, remain unknown in the administrative claims database.

Lastly, incomplete or inaccurate details of integrative therapy procedures are often found in RWDs such as administrative claims data and medical records. For example, detailed information on acupuncture treatment such as the number of needles used, exact location, duration of acupuncture treatment, and patient compliance are likely to be missing in the claims database and, in some cases of medical records as well. Lack of reported outcomes such as level of pain or discomfort is another barrier. Furthermore, inaccurate coding is often found in RWDs which limits its usability.

Nonetheless, administrative claims data and EHRs are valuable sources, and it is important to carefully consider the limitations of data source to ensure the validity and reliability of the results.

3. Practical guide to RWE research in integrative medicine

3.1. Develop a research question

As with clinical trials, the first step of conducting an RWE research involves developing a research question. The importance of a causal question in an observational study has been emphasized for more than a decade,[29] and integrative medicine should not be an exception. An appropriately designed causal question should allow an RCT design, including a randomizable intervention.[30] Randomizable intervention in integrative medicine include, but are not limited to, acupuncture, herbal medicine, and manual therapies, the goal of which may be pain control, symptom management, prevention of pathological events, and survival. Objectives and the main measure must align to a theoretical RCT designed to address the identical research question, i.e., a target trial.[44]

The following is an example of a simple research question: *"is postoperative acupuncture effective in the prevention of lymphedema among breast cancer patients?"*

3.2. The PICOT objectives and covariates

Once the causal question is defined, the primary and secondary PICOT objectives (population, intervention, comparator, outcome, and time horizon)[32] as well as the main measure of effect must be defined to reflect the research question. The PICOT framework helps ensure that the research question is specific, focused and feasible. PICOT objectives in an RWD study can be defined as follows:

1 Population: The target patient population is defined in terms of age, gender, disease, underlying health conditions, past history, and relevant clinical criteria. If the measure of effect is considered to be different by subgroups, this is also taken into consideration in the population definition and in the study design.
2 Interventions: The intervention of interest is defined by a specific drug, device, diagnostic test, or procedure.
3 Comparison: The alternative of the intervention is specified.
4 Outcome: The outcome and endpoints of interest is specified.
5 Time window: The time frame of washout period, exposure, and outcome assessment or follow up period is specified.

The rationale and context behind the study design should be conveyed through operational definitions of PICOT objectives to increase precision of the model and minimize potential bias. Similar to clinical trial designs, specific measures for each objective must be provided, but all criteria must be found within the source data. Codes for each disease, intervention, medication, and outcome during a prespecified period are used to define PICO objectives from RWD.

Reporting guidelines such as STaRT-RWE and HARPER recommends providing a table per each of the operational definitions (32, 33). This article provides a summary of each objectives with examples based on the research question drafted in the previous section (Table 1).

3.2.1. Time horizon

The first step of PICOT framework in an RWD study is defining the primary and secondary time anchors. Similar to clinical trials where re-

Table 1
Summary of exposure (treatment), outcome, and covariates.

Diagnosis	ICD-10-CM code and definition	Diagnostic definition
Inclusion criteria		
Breast cancer surgery	Mastectomy, lumpectomy, axillary dissections	Record of surgery in 01/01/2011 - 12/31/2013 [cohort entry date or Day 0]
Breast cancer	C50	Initial diagnosis during the 180-day period before cohort entry [−180, −1]
Exclusion criteria		
Cancer	C50	Diagnosis during the 10-year period prior to cohort entry [−3650, −181]
	C00 - C26, C30 - C34, C37 - C41, C43, C45 - C49, C51 - C58, C60 - C85, C88, C90 - C97	Diagnosis during the 10-year period prior to cohort entry date [−3650, -1]
Surgeries	(Intervention codes from the source data)	Breast cancer-related surgery (mastectomy, lumpectomy, axillary dissection) during one year before diagnosis of breast cancer [-3650, -1]
Lymphedema	I89.0, I97.2	Diagnosis prior to cohort entry date [-3650, -1]
Death		Reports of death before follow up window [0, +180]
Exposure		
Acupuncture	(Intervention codes from the source data)	A minimum of 5 sessions of outpatient acupuncture treatment during the 180-day period after Day 0 [+1, +180]
Baseline covariates		
Neoadjuvant therapies		
Neoadjuvant radiotherapy	(Intervention codes from the source data)	Radiotherapies between breast cancer diagnosis and cohort entry date [-180, -1]
Neoadjuvant chemotherapy	(Intervention codes from the source data) (Prescription codes from the source data)	Chemotherapies between breast cancer diagnosis and cohort entry date [-180, -1]
Comorbid conditions within one-year period before cohort entry		One year prior to breast cancer surgery [-365, -1]
Diabetes mellitus (both with and without complications)	E10, E11, E12, E13, E14	
Chronic back pain	M51, M53, M54	
Osteoarthritis	M15, M16, M17, M18, M19	
Rheumatoid	M05, M06	
Osteoporosis	M80, M81, M82	
Hyperlipidemia	E78	
Hypertension	I10, I11, I12, I13, I15	
Cardiovascular diseases	I05, I06, I07, I08, I09, I20, I21, I22, I23, I24, I25, I26, I27, I30, I31, I32, I33, I34, I35, I36, I37, I38, I39, I40, I41, I42, I43, I44, I45, I46, I47, I48, I49, I50, I51, I52	
Renal failure	N17, N18, N19	
Chronic liver diseases	K72, K73, K74, K75, K76, K77	
Cerebrovascular disease	I60, I61, I62, I63, I64, I65, I66, I67, I68, I69	
Anemia	D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64	
Demographic variables		On the day of surgery [Day 0]
Age group	<35, 35–44, 45–54, 55–64, 65–74, 75–84, ≥85	
Sex		
Type of insurance	NHIS, Medical Aid	Classified based on annual health premiums proportional to household incomes
Outcome		
Lymphedema	I89.0, I97.2	Followed up for 4 years [+181, +1460]
All-cause mortality		Followed up for 4 years[+181, +1460]

searchers determine the duration of the treatment period and follow up period to maximize treatment effects and efficiently observe treatment effectiveness, the observation period in a retrospective RWD-based study must be carefully defined. A description is provided for each element of the time horizon that will be illustrated in the following section with figures.

Cohort entry date or “day 0” is the primary time anchor that defines the study population, i.e., initial diagnosis or beginning of treatment depending on the study. Assessment windows for inclusion and exclusion criteria, baseline characteristics, and/or follow ups are defined from the cohort entry date. For example, the date of the first surgical removal of tumor can be defined as “day 0” or cohort entry date to address the research question above. The inclusion criteria of “initial breast cancer diagnosis prior to surgery within 180 days or less,” is defined based on “day 0.” The exclusion criteria of “no history of diagnosis of other types of cancer before cohort entry in the past 5 years,” and “no history of lymphedema during the 5-year period prior to cohort entry date” are also defined based on “day 0,” creating a washout window.

Depending on the study design, multiple primary time anchors are possible. In an RWD study in integrative medicine, the exposure window of integrative therapies may be defined from the definition of base cohort entry date or “day 0” using separate anchors. In the example above, “a minimum of five acupuncture treatments within 180-day period after the cohort entry date” can be used as an exposure window, with possible variations depending on the researcher’s objectives such as “a series of five consecutive acupuncture treatments with a maximum of two-weeks interval between treatments after the cohort entry date, which starts within 30 days after the surgery.”

Follow up window often starts from “day 0” until the time of censoring date, although the starting point depends on the existence of a separate exposure window. The censoring date is the day of which the earliest of the following occurs: outcome of interest, dropout from the cohort, or death. To avoid immortal time bias, the exposure or treatment window must be met prior to counting the outcomes in the follow up window.

Covariate windows should be created for baseline characteristics, accounting for the time period during which each covariates are measured.

Demographics such as age, gender, insurance type, and income are often measured on the day of the cohort entry date or “day 0” in a cohort design. For a nested case-control design, demographics can be measured on the day of the event date. Other covariates may require a longer period to measure. For certain covariates, measurements throughout all available time prior to the cohort entry date might be required, e.g., history of cancer. For others, measurements within a predefined period of time may be required, e.g., neoadjuvant chemotherapy after breast cancer diagnosis and prior to surgery.

3.2.2. Population

Detailed and specific operational definitions of population ensure homogeneity of the cohort and less bias. This encompasses demographic characteristics such as age, gender, underlying health conditions, and past history and exposures, and relevant clinical criteria, considered throughout sufficient length of time period. It is crucial to ascertain that the selected data source provides sufficient information pertaining to the population of interest.

In clinical trials, the study population comprises patients who satisfy the predetermined eligibility criteria; the target population comprises patients to whom the conclusions of the study will be applicable, and the study sample population comprises individuals who are currently enlisted as participants in the trials.[45] Recent studies showed that the target population and the study population can be identified for potential clinical trials[46,47] and to emulate pragmatic clinical trials[48] using RWDs. Using a large health care database, target population and study population can be defined in an effective and efficient approach.

In the given example concerning breast cancer patients, specification of the inclusion criteria such as neoadjuvant and adjuvant chemotherapy, chemotherapy regimen, and radiotherapy have implications about the patient’s condition. Hospital admission types may imply differences in the disease severity: for instance, stroke patients admitted through an outpatient ward might imply lighter symptoms and unimpaired cognitive symptoms, compared to those admitted through an emergency ward.[21] Similarly, time interval between disease onset and treatment may require additional attention. In the context of breast cancer, the choice to forego surgery as the primary treatment in favor of neoadjuvant chemotherapy and radiotherapy could suggest an advanced stage of the tumor.

3.2.3. Complementary and integrative therapies as intervention

Operational definition for integrative therapies requires careful consideration during the design of RWD study to convey the intended meaning. Pharmaceutical interventions categorize codes by therapeutic effect and route of administration, and health interventions categorize codes by the target, action, and means. In integrative medicine, however, professionals and decision-makers have yet to reach consensus on the classification of interventions. Due to these issues and administrative limitations, it is possible the disease codes and intervention codes contained in the claims record may not completely describe the medical encounter. In current RWDs containing data on integrative therapies, differences in the identifiers and descriptions between sources are expected.

First issue that needs to be discussed is the intervention’s scope and comparability. Generalized terms such as "integrative medicine," "traditional medicine," or "complementary and alternative medicine" encompasses a vast array of therapies. The types of therapies covered by health insurance vary by country, and as a result the RWDs of each country include different details. Importantly, the relationship between integrative therapies and target disease should be clear to address the association.

Second, integrative therapy such as acupuncture refers to a general procedure, i.e., the application of acupuncture needles to treat various symptoms. The details involved in treating specific symptoms, e.g., the combination of various acupoints, locations, and needling techniques, may not be specified in the intervention codes. Furthermore, the same codes may be used throughout diverse symptoms, and patient data with multiple symptoms may not allow identification of the target symptom that acupuncture was addressing.

To address these issues, operational definitions of treatment episodes may require multiple levels to increase specificity and precision. Depending on the research question, the definition can be specified by using medical institutional codes (clinics/hospitals/nursing hospitals/public medical centers), type of admission (inpatient/outpatient), or the main disease code for which the intervention was prescribed. Co-occurrence of other treatments may need to be assessed. Consulting a clinical expert in the field is crucial to build an operational definition that can also be interpreted into clinical practices.

The duration and frequency of the treatment must also be considered when defining a treatment episode in a RWD study of integrative medicine. Most integrative therapies are continuous, in contrast to surgeries or other one-off treatments; in addition, interval between treatments vary by patients and providers, in contrast to medications which should be repetitively taken. In the absence of a consensus regarding the minimum required number of sessions and intervals for the treatment to demonstrate clinically meaningful effect, the operational definition of the treatment episode, including the duration and number of sessions, should be carefully considered based on clinical consultations and previous literature.

Based on clinical consultations and expert consensus, the final operational definition of integrative therapies should encompass various aspects to ensure homogeneity and their causal relationship with the target disease. These include specifying the minimum number of treatment sessions within a given period, the maximum interval between consecutive treatments, permitting combinations of therapies such as physiotherapy, and adjuvant medications. Grace periods may be adopted to account for variability of treatment intervals within one episode. Details regarding the treatment regimen, including its location, duration, and specific formulations, should be included whenever feasible.

New user design was recently suggested in pharmacoepidemiology to minimize bias in estimating the association between intervention and outcomes.[49] This design involves a washout window of the exposure, which in this case is the experience of integrative therapies, prior to cohort entry date. Previous studies indicated that prevalent user designs yield a larger effect than new user designs.[50] While new user design of integrative therapies may be feasible in some countries, however, it may be extremely difficult in others, i.e., Asian nations where traditional medicine treatments are commonly practiced. Not only the users group of integrative therapies during the exposure window, but also the non-users or control group may include patients who have experience with acupuncture prior to cohort entry date. To minimize biased estimates of association, it is necessary to assess integrative therapy users prior to cohort entry. Determining the average utilization and user count will facilitate the formulation of operational definitions that mitigate this bias.

3.2.4. Comparison

Comparison group for integrative therapy intervention can be defined as non-users or users of alternative treatments. Non-users would involve patients in the base cohort who never received integrative therapies, or those who never visited medical clinics in which integrative treatment is available during the exposure window. Alternative treatments users or active comparators are patients who received other prespecified treatment during the exposure window. When defining comparison for integrative therapy, their experiences with integrative therapies prior to cohort entry and after the exposure window should be taken into account to minimize bias.

Comparison between target intervention with an active control is more recommended to non-users for two reasons.[25] First, comparison of treatments for the same indication are likely to reduce potential confounders and bias. Second, comparing a treatment to an active control allows identifying patients in similar timelines of a disease, or when the treatment decision is made. However, as there is often no standard com-

parison for integrative therapies, studies using active controls may not be feasible. In such scenarios where integrative therapies are compared to usual care, the following issues has to be considered which may inflate or reduce the association between exposure and outcome of interest.

The first pitfall is the potential disparity between the intervention and control groups, due to different timepoints of the two groups in their course of disease. This leads to potential heterogeneity in the severity or progress of the disease between the two groups, leading to biased estimates. For example, patient in the acupuncture group may have been diagnosed at an advanced stage of breast cancer than the control group, which may influence the outcome of lymphedema or survival. Furthermore, different timepoints between the intervention and control groups may cause immortal time bias, which should be correctly addressed by aligning the "day 0" as explained in the previous section.

Another pitfall is the presence of an unmeasurable confounder that constitutes the decision to utilize integrative therapies. For example, patients with higher level of pain may choose to receive acupuncture, although the level of pain is often not described in RWDs and remain unknown. Unmeasurable confounders may significantly bias the estimated results.

Examining the types of standard care in both groups and, under the presence of any difference, appropriate inclusion and exclusion criteria to remove bias can enhance the validity and reliability of the study's findings. The control group should accurately represent standard care that the target intervention is being compared against, and there should be no difference in the utilization status of care in both treatment and control groups other than the target intervention.

3.2.5. Outcomes

Obtaining data from real-world settings often presents challenges in capturing patient-reported outcomes, as the primary purpose of the data may not have been originally intended for research. Consequently, an effective approach in defining outcomes involves focusing on significant events recorded within the data source that is clearly associated to the disease and the effect of the intervention.

One such event could be mortality, a terminal state that is unambiguous and explicitly documented within a database. Some recent studies suggest operational definitions for certain outcomes that manifest over a specific period. For example, if the outcome of interest is ischemic stroke, the onset of the outcome can be defined as the date of the first hospital admission for stroke. Alternatively, another definition could be based on the date when the initial brain MRI or CT scan was conducted to rule out stroke. It is crucial to consult with clinical experts when defining outcomes, as their expertise can help identify the most critical aspects and key indicators associated with the outcome of interest.

In order to establish a causal association, it is imperative that the mechanism of the target therapy be unambiguously linked to the outcome of interest, given the expansive nature of integrative therapies. By carefully specifying the outcomes and employing relevant events or operational definitions, researchers can navigate the limitations of real-world data and effectively evaluate the impact of interventions in a variety of healthcare contexts. Collaboration with clinical experts ensures that the chosen outcomes are clinically relevant.

3.2.6. Covariates

Covariates are variables included in the study design that are neither the exposure nor the outcome of interest. In the process of study design, potential factors that may influence the outcome should be included as covariates for measurement with prespecified operational definition (e.g., continuous, binary, categorical variable). In addition to baseline demographic variables, covariates such as prespecified comorbidities, Charlson Comorbidity Index (CCI),[51] patient history, and medications may need to be measured.

Previous studies emphasized the importance of including variables to remove confounders, while avoiding inclusion of variables that may increase bias.[52,53] A directed acyclic graph (DAG) can be used to illustrate the researcher's hypothesis regarding baseline covariates that influence the treatment and the outcome. A recent study emphasized the importance of blocking all non-causal paths and none of the causal paths between the treatment and outcome based on DAG.[54] From DAG depicted in Fig. 1 which is based on the research question posed in the previous section, breast cancer and lymph dissection are included in inclusion and exclusion criteria; demographic variables, comorbidity, and adjuvant anticancer treatment are included in the study design to be adjusted using epidemiological methods.

The covariate assessment window should precede exposure and follow up windows to eliminate causal intermediates between exposure and outcome. In some cases, however, time-varying exposures and covariates during follow up may significantly influence the outcome. Previous literature suggested adopting time-varying Cox proportional hazards model and marginal structural model to adjust for time-varying covariates, e.g., HIV/AIDS medication,[55] chemotherapy,[56,57] and health behaviors such as smoking.[58]

3.3. Specify the study design

Based on the objectives and the measure of effect, several research designs can be employed to investigate the research question using RWD. Some examples of research designs are cohort design, nested case-control design, and self-controlled case series (SCCS) design.[25] Descriptions, advantages, limitations, and important considerations of each design are explained in depth in previous literature with graphical depictions and checklists.[25,26,59]

A cohort design allows the estimation of incidence and risk ratio from the temporal associations of treatment and outcome by calculating person-years and time-to-events, and allows causal inferences given that confounders and potential biases are appropriately addressed. In this design, exclusion of patients should only be applied at baseline, otherwise the exclusion process is likely to introduce selection bias.[25] The losses to follow up of the whole population enrolled must be reported in the results. In a study design investigating the effect integrative therapies, the treatment period and the assessment of outcomes must not overlap.

Nested case-control design selects patients with outcomes and compares the odds of patients who received treatment to those who did not. This allows the estimation of odds ratio which is computationally more efficient. It is important to note that the resultant odds ratio should not be readily interpreted as relative risk measures, or as measures of treatment effect.[60,61] If the outcome is rare, the odds ratio in the case-control design and the risk ratio and the incidence rate ratio in the underlying cohort design may approximate each other, a situation known as the "rare disease assumption."[62] However, such a scenario of uncommon outcomes may not be feasible in the field of integrative medicine research, as exposure to integrative therapies among patients with outcomes may be even rarer and, thus, not generalizable. Further issues have been raised regarding various case-control designs using sampling or from open cohorts, and caution is required in reporting the resultant parameters.[63]

SCCS design was suggested to estimate effect of treatment such as vaccination and requires the observed person-time to be divided into washout period, treated, and untreated person time.[64] The assumption of SCCS is that the effect of treatment is stable over time, and that the outcome has no influence on the subsequent treatment, which are often implausible in integrative medicine.

3.4. Illustrate a study design diagram

Since its introduction in 2019, study design diagrams are being actively adopted in RWD research and strongly recommended in reporting guidelines for RWE and pharmacoepidemiology studies.[31-34] Detailed guides with PowerPoint templates are provided in an article by

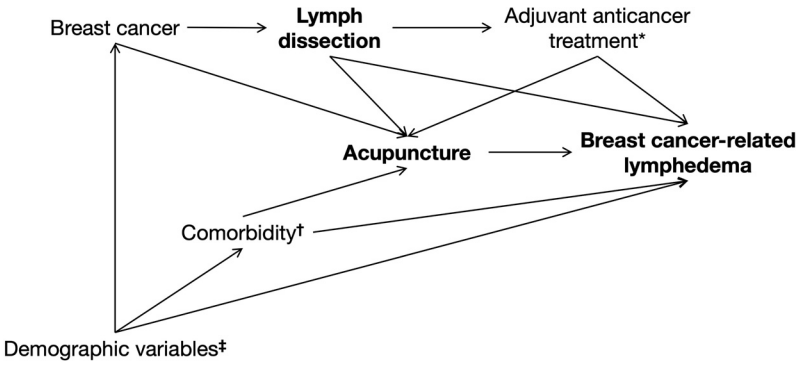

Fig. 1. Sample directed acyclic graph (DAG) illustrating the relationship between independent variable, dependent variable, and covariates.

Schneeweiss et al.[34] and in HARPER checklist.[33] In this section, we provided samples of study design diagrams with a focus on acupuncture.

Study design diagram provides an overview of how the cohort was selected and assessed through each window. Horizontal bar indicates time, which include temporal range of the source data and study period as base anchor. Vertical arrows mark the cohort entry date, and in designs where exposure and follow up are defined separately, the index date can be marked using vertical arrows. Windows are listed from top to bottom and demonstrates the sequence of actions performed to create the cohort. Washout window, exclusion assessment window, covariate assessment window, and follow up window are usually included in the study diagram. The diagram may also include footnotes that provide detailed information regarding the definitions of each assessment window.

Based on the research question posed in this article, a sample study design diagram is illustrated in Fig. 2. A cohort design was built to compare the incidence of lymphedema between breast cancer patients who received acupuncture for a minimum of five sessions and those who did

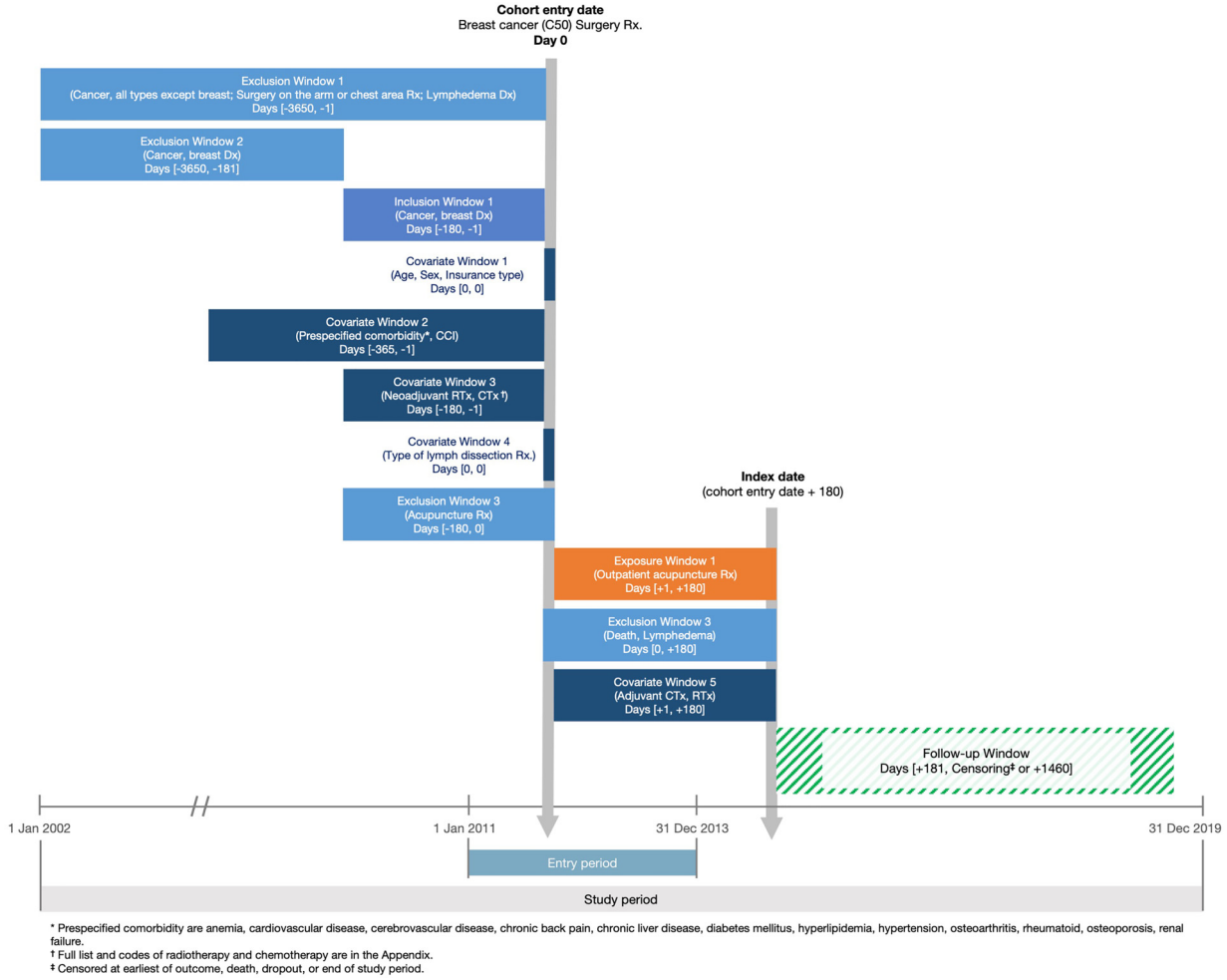

Fig. 2. Study design diagram for acupuncture research using RWD using cohort design.

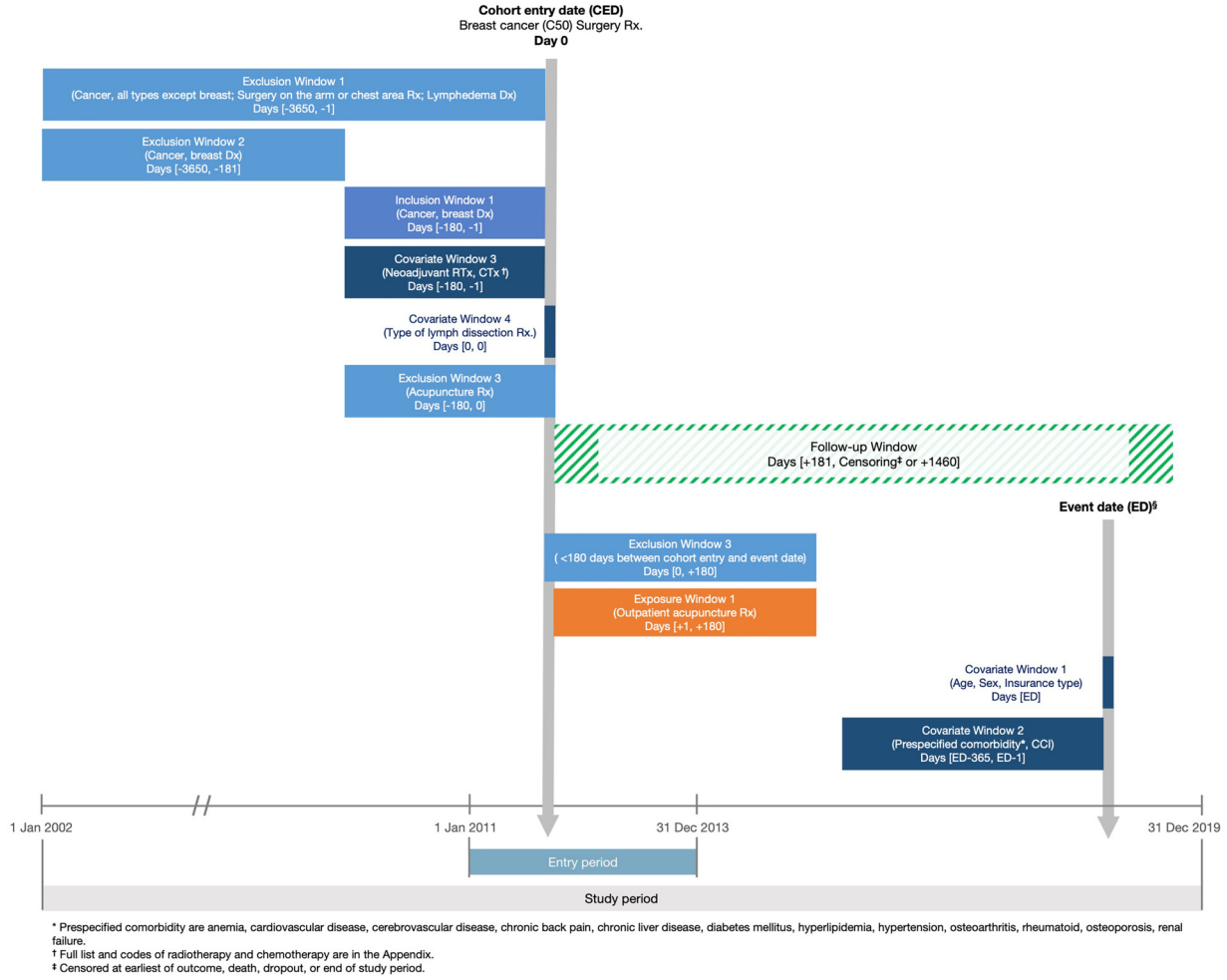

Fig. 3. Study design diagram for acupuncture research using RWD using nested case-control design.

not receive any in the 180-day period after the lymph node dissection. The cohort entry date was defined by the date of when surgical removal of tumor and lymph node dissection was performed, after diagnosis of breast cancer within 180 days prior to surgery. Index date was defined by the end of the 180-day period during which acupuncture treatment was defined. Index date in this design serves as the anchor to divide exposure window and outcome window in order to avoid immortal bias. Without a specific index date, the initiation of the follow up can be described as dependent of the exposure window, e.g., "third day of treatment" or using grace periods.

Study design diagram in Fig. 3 illustrates a nested case-cohort design, in which a group of patients with lymphedema in the follow up window was identified from the source cohort, a process called risk-set sampling. Exposure is assessed by the use of acupuncture in the postsurgical period of lymph dissection. Risk-set sampling of control patients involves matching those who are at risk for the outcome on the date of a given case patient's event, allowing matching the person-time of the controls and patients.

Some studies might find DAGs, shown in Fig. 1, more suitable to be included than the study design diagram, depending on the study design. DAGs are appropriate to illustrate conceptual hypothesis or assumption of causal relationships.[54,65]

3.5. Data analysis

RWD analysis should yield reliable and clinically relevant results with minimal bias to provide basis for causal inference. The statistical analysis plan should be complete and ready prior to data collection. In this context, the data should be preprocessed including handling missing data through imputation or deletion.[66] Controlling for confounders and mitigating for potential imbalances in covariates between groups is the next crucial step. The critical assumption underlying causal inference from RWD is that exposure or treatment is effectively randomized across all measured significant covariates of the patient cohort.[67-69] The assumption that patients were randomly assigned to treatment groups based on prespecified covariates necessitates that causal inferences for RWD studies be made after adjusting for covariates and measured confounders. Propensity score-based methods[70] such as propensity score matching (PSM) and the inverse probability of treatment weighting (IPTW) are frequently employed to achieve balance in the measured covariates across groups, thereby simulating the characteristics of an RCT.[71] Multivariable regression is an alternative method for adjusting for assessed confounders; in some studies, it has yielded comparable results to propensity score-based methods.[72]

Analytic methods of primary and secondary analysis are often decided from the study design. If the study design allows calculation of time to event from the population, i.e., cohort design, the estimation of incidence rate ratio and hazard ratio from survival analysis are possible. In other study designs, i.e., nested case-control design, odds ratio can be calculated. Sensitivity analyses are performed to assess the robustness of the findings against potential sources of bias or variations in analytical approach. In study designs where covariates after the exposure need to be adjusted to reduce bias, time-dependent survival models and marginal structural models can be employed. Current reporting guide-

lines suggest that hypothesis, software, statistical models, confounder adjustment methods, and missing data methods are listed for all of the primary and secondary analyses of RWDs.

4. Conclusion

Integrative medicine increasingly uses real-world data (RWD) such as administrative database collected from routine healthcare processes to study health outcomes and evaluate treatment efficacy. RWD provides valuable, practical information about long-term outcomes in areas where undertaking traditional randomized controlled trials (RCTs) may not be feasible or cost-effective. Utilizing healthcare database to generate real-world evidence (RWE) plays a critical role for understanding the progression of rare diseases and informing regulatory decisions.

The application of RWD analysis in integrative medicine is not without obstacles. Since the majority of RWD is not intended for research, careful study design is required to account for bias and confounding factors when repurposing this data. There is considerable variability in the quality of RWD studies due to diverse research questions, study designs, parameters, and analyses. In integrative medicine, the definition of PICOT objectives to precisely reflect the characteristics of the therapies involved is crucial.

This practical guide for RWE research design in integrative medicine illustrates concrete steps with examples from a breast cancer study using diagrams and tables. This guide primarily examined healthcare databases, specifically administrative data. We anticipate the publication of further guides in the future that cover a more extensive range of RWDs available in the field of integrative medicine. We hope that from this article, the significance of RWE research design and related steps are clarified to enhance the rigor of RWD studies in the field of integrative medicine research. Improved quality would allow evidence synthesis, regulatory decisions and policy development to be based on RWE research across a broad spectrum of integrative medicine practice.

CRediT authorship contribution statement

Ye-Seul Lee: Methodology, Writing – original draft. **Yoon Jae Lee:** Conceptualization, Writing – review & editing. **In-Hyuk Ha:** Supervision, Writing – review & editing.

Conflict of interests

The authors declare that no competing interests exist.

Funding

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (No. HF20C0222). The funders had no role in any part of this study.

Ethical statement

Not applicable.

Data availability

The data associated with this study can be made available upon reasonable request to the corresponding author.

References

1. Ahn EK. A brief introduction to research based on real-world evidence: considering the Korean National Health Insurance Service database. *Integr Med Res*. 2022;11(2):100797.
2. Cheon C, Jang BH, Ko SG. A review of major secondary data resources used for research in traditional Korean medicine. *PIM*. 2023;2(2):77–85.
3. Sung SF, Hsieh CY, Hu YH. Two decades of research using Taiwan's national health insurance claims data: bibliometric and text mining analysis on PubMed. *J Med Internet Res*. 2020;22(6):e18457.
4. Song E, Ang L, Lee MS. Increasing trends and impact of integrative medicine research: from 2012 to 2021. *Integr Med Res*. 2022;11(4):100884.
5. Locke AB, Gordon A, Guerrera MP, Gardiner P, Lebensohn P. Recommended integrative medicine competencies for family medicine residents. *Explore*. 2013;9(5):308–313.
6. Rakel D.P., Minichiello V. Integrative Medicine, E-Book: Elsevier health sciences; 2022.
7. Wolever RQ, Caldwell KL, McKernan LC, Hillinger MG. Integrative medicine strategies for changing health behaviors: support for primary care. *Prim Care*. 2017;44(2):229–245.
8. Sun X, Tan J, Tang L, Guo JJ, Li X. Real world evidence: experience and lessons from China. *BMJ*. 2018;360:j5262.
9. Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, et al. Data resource profile: the national health information database of the national health insurance service in South Korea. *Int J Epidemiol*. 2017;46(3):799–800.
10. Kim MK, Han K, Lee SH. Current trends of big data research using the Korean national health information database. *Diabetes Metab J*. 2022;46(4):552–563.
11. Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the National Health Insurance Research Database (NHIRD). *Epidemiol Health*. 2018;40:e2018062.
12. Hsieh CY, Su CC, Shao SC, Sung SF, Lin SJ, Kao Yang YH, et al. Taiwan's national health insurance research database: past and future. *Clin Epidemiol*. 2019;11:349–358.
13. Nagai K, Tanaka T, Kodaira N, Kimura S, Takahashi Y, Nakayama T. Data resource profile: JMDC claims databases sourced from Medical Institutions. *J Gen Fam Med*. 2020;21(6):211–218.
14. Nagai K, Tanaka T, Kodaira N, Kimura S, Takahashi Y, Nakayama T. Data resource profile: JMDC claims database sourced from health insurance societies. *J Gen Fam Med*. 2021;22(3):118–127.
15. Nakatani E, Tabara Y, Sato Y, Tsuchiya A, Miyachi Y. Data resource profile of Shizuoka Kokuho Database (SKDB) using integrated health- and care-insurance claims and health checkups: the Shizuoka Study. *J Epidemiol*. 2022;32(8):391–400.
16. Ball R, Robb M, Anderson SA. Dal Pan G. The FDA's sentinel initiative—a comprehensive approach to medical product surveillance. *Clin Pharmacol Ther*. 2016;99(3):265–268.
17. Wu J, Wang C, Toh S, Pisa FE, Bauer L. Use of real-world evidence in regulatory decisions for rare diseases in the United States-Current status and future directions. *Pharmacoepidemiol Drug Saf*. 2020;29(10):1213–1218.
18. Lee HJ, Lim YC, Lee YS, Kwon S, Lee YJ, Ha IH. Analysis of medical service utilization for post-stroke sequelae in Korea between 2016 and 2018: a cross-sectional study. *Sci Rep*. 2022;12(1):20501.
19. Huang CW, Hwang IH, Lee Y-s, Hwang SJ, Ko SG, Chen FP, et al. Utilization patterns of traditional medicine in Taiwan and South Korea by using national health insurance data in 2011. *PLoS One*. 2018;13(12):e0208569.
20. Min T, Yeo J, Lee YS, Kim SY, Lee D, Ha IH. Trends of medical service utilization for tinnitus: analysis using 2010-2018 health insurance review and assessment service national patient sample data. *Healthcare (Basel)*. 2022;10(8):1547.
21. Lee YS, Kwon S, Chae Y, Jang BH, Ko SG. A retrospective cohort study on the outcomes of ischemic stroke patients with adjuvant Korean Medicine treatment. *Sci Rep*. 2018;8(1):1–8.
22. Choi SR, Kim ES, Jang BH, Jung B, Ha IH. A time-dependent analysis of association between acupuncture utilization and the prognosis of ischemic stroke. *Healthcare (Basel)*. 2022;10(5):756.
23. Huang CH, Lin SK, Lin MC, Hsieh CL. Acupuncture is associated with reduced dementia risk in patients with insomnia: a propensity-score-matched cohort study of real-world data. *J Tradit Complement Med*. 2023;13(3):297–305.
24. Huang CH, Lin MC, Hsieh CL. Acupuncture treatment reduces incidence of Parkinson's disease in patients with depression: a population-based retrospective cohort study in Taiwan. *Front Aging Neurosci*. 2020;12:591640.
25. Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM. *Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide*. Developing a protocol for observational comparative effectiveness research: a user's guide Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM, editors. AHRQ Methods for Effective Health Care; 2013.
26. Liu F, Panagiotakos D. Real-world data: a brief review of the methods, applications, challenges and opportunities. *BMC Med Res Methodol*. 2022;22(1):287.
27. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JP. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. *BMJ*. 2016;352:i493.
28. Ewald H, Ioannidis JPA, Ladanie A, Mc Cord K, Bucher HC, Hemkens LG. Nonrandomized studies using causal-modeling may give different answers than RCTs: a meta-epidemiological study. *J Clin Epidemiol*. 2020;118:29–41.
29. Hernan MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes*. 2008;32(Suppl 3):S8–14.
30. Goodman SN, Schneeweiss S, Baiocchi M. Using design thinking to differentiate useful from misleading evidence in observational research. *JAMA*. 2017;317(7):705–707.
31. Langan SM, Schmidt SA, Wing K, Ehrenstein V, Nicholls SG, Filion KB, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ*. 2018;363:k3532.
32. Wang SV, Pinheiro S, Hua W, Arlett P, Uyama Y, Berlin JA, et al. STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies. *BMJ*. 2021;372:m4856.
33. Wang SV, Pottegard A, Crown W, Arlett P, Ashcroft DM, Benchimol EI, et al. Harmonized protocol template to enhance reproducibility of hypothesis evaluating re-

al-world evidence studies on treatment effects: a good practices report of a joint ISPE/ISPOR task force. *Value Health*. 2022;25(10):1663–1672.
34. Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, et al. Graphical depiction of longitudinal study designs in health care databases. *Ann Intern Med*. 2019;170(6):398–406.
35. Khambholja K, Gehani M. Use of structured template and reporting tool for real-world evidence for critical appraisal of the quality of reporting of real-world evidence studies: a systematic review. *Value Health*. 2023;26(3):427–434.
36. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11(7):437–441.
37. Gang WJ, Xiu WC, Shi LJ, Zhou Q, Jiao RM, Yang JW, et al. Factors associated with the magnitude of acupuncture treatment effects (FAMOUS): a meta-epidemiological study of acupuncture randomised controlled trials. *BMJ Open*. 2022;12(8):e060237.
38. Zhang YQ, Jiao RM, Witt CM, Lao L, Liu JP, Thabane L, et al. How to design high quality acupuncture trials-a consensus informed by evidence. *BMJ*. 2022;376:e067476.
39. Joannes C, Colineaux H, Guernec G, Castagne R, Kelly-Irving M. Toward a conceptual framework of health and its operational definition: an application in the 1958 British birth cohort. *BMC Public Health*. 2023;23(1):100.
40. Park H, Kim YR, Pyun Y, Joo H, Shin A. Operational definitions of colorectal cancer in the Korean National Health Insurance Database. *J Prev Med Public Health*. 2023;56(4):312–318.
41. Lee DH, Kim YJ, Kim H, Lee HS. Validation of operational definitions of mortality in a nationwide hemodialysis population using the health insurance review and assessment service databases of Korea. *Kidney Res Clin Pract*. 2023. doi:10.23876/j.krcp.22.077.
42. Lee YK, Park C, Won S, Park JW, Koo KH, Ha YC, et al. Validation of an operational definition to identify distal radius fractures in a national health insurance database. *J Hand Surg Am*. 2021;46(11):1026.e1–1026.e7.
43. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *JKMS*. 2017;32(5):718–728.
44. Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758–764.
45. Li Q, Guo Y, He Z, Zhang H, George Jr TJ, Bian J. Using real-world data to rationalize clinical trials eligibility criteria design: a case study of Alzheimer's disease trials. *AMIA Annu Symp Proc*. 2020;2020:717–726.
46. Belleudi V, Trotta F, Fortinguerra F, Poggi FR, Olimpieri O, Santelli E, et al. Real world data to identify target population for new CAR-T therapies. *Pharmacoepidemiol Drug Saf*. 2021;30(1):78–85.
47. Evans SR, Paraoan D, Perlmutter J, Raman SR, Sheehan JJ, Hallinan ZP. Real-world data for planning eligibility criteria and enhancing recruitment: recommendations from the clinical trials transformation initiative. *Ther Innov Regul Sci*. 2021;55(3):545–552.
48. Crown W, Dahabreh IJ, Li X, Toh S, Bierer B. Can observational analyses of routinely collected data emulate randomized trials? Design and feasibility of the observational patient evidence for regulatory approval science and understanding disease project. *Value Health*. 2023;26(2):176–184.
49. Lash TL, VanderWeele TJ, Haneuse S, Rothman KL. *Modern Epidemiology* Lippincott Williams & Wilkins (LWW; 2020:154–155.
50. Danaei G, Tavakkoli M, Hernan MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. *Am J Epidemiol*. 2012;175(4):250–262.
51. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383.
52. Sauer BC, Brookhart MA, Roy J, VanderWeele T. A review of covariate selection for non-experimental comparative effectiveness research. *Pharmacoepidemiol Drug Saf*. 2013;22(11):1139–1145.
53. van Zwieten A, Tennant PWG, Kelly-Irving M, Blyth FM, Teixeira-Pinto A, Khalatbari-Soltani S. Avoiding overadjustment bias in social epidemiology through appropriate covariate selection: a primer. *J Clin Epidemiol*. 2022;149:127–136.
54. Digitale JC, Martin JN, Glymour MM. Tutorial on directed acyclic graphs. *J Clin Epidemiol*. 2022;142:264–267.
55. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 2000;11(5):561–570.
56. Jatoi I, Bandos H, Jeong JH, Anderson WF, Romond EH, Mamounas EP, et al. Time-varying effects of breast cancer adjuvant systemic therapy. *J Natl Cancer Inst*. 2016;108(1).
57. Lee YS, Lim YC, Yeo J, Kim SY, Lee YJ, Ha IH. Risk of lymphedema and death after lymph node dissection with neoadjuvant and adjuvant treatments in patients with breast cancer: an eight-year nationwide cohort study. *Healthcare (Basel)*. 2023;11(13):1833.
58. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME. Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*. 2018;6(7):121.
59. Meyer AM, Wheeler SB, Weinberger M, Chen RC, Carpenter WR. An overview of methods for comparative effectiveness research. *Semin Radiat Oncol*. 2014;24(1):5–13.
60. Greenland S. Interpretation and choice of effect measures in epidemiologic analyses. *Am J Epidemiol*. 1987;125(5):761–768.
61. Sinclair JC, Bracken MB. Clinically useful measures of effect in binary analyses of randomized trials. *J Clin Epidemiol*. 1994;47(8):881–889.
62. Nurminen M. To use or not to use the odds ratio in epidemiologic analyses? *Eur J Epidemiol*. 1995;11(4):365–371.
63. Labrecque JA, Hunink MMG, Ikram MA, Ikram MK. Do case-control studies always estimate odds ratios? *Am J Epidemiol*. 2021;190(2):318–321.
64. Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. *Vaccine*. 2004;22(15–16):2064–2070.
65. Suzuki E, Shinozaki T, Yamamoto E. Causal diagrams: pitfalls and tips. *J Epidemiol*. 2020;30(4):153–162.
66. Little RJA, Rubin D. *Statistical Analysis with Missing Data* Wiley; 2019:95–100.
67. Rubin DB. Causal inference using potential outcomes: design, modeling, decisions. *J Am Stat Assoc*. 2005;100(469):322–331.
68. Greenland S, Robins JM. Identifiability, exchangeability, and epidemiological confounding. *Int J Epidemiol*. 1986;15(3):413–419.
69. Hernan MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health*. 2006;60(7):578–586.
70. Borah BJ, Moriarty JP, Crown WH, Doshi JA. Applications of propensity score methods in observational comparative effectiveness and safety research: where have we come and where should we go? *J Comp Eff Res*. 2014;3(1):63–78.
71. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006;98(3):253–259.
72. Biondi-Zoccai G, Romagnoli E, Agostoni P, Capodanno D, Castagno D, D'Ascenzo F, et al. Are propensity scores really superior to standard multivariable analysis? *Contemp Clin Trials*. 2011;32(5):731–740.