Handling missing data, selection bias, and measurement error in observational studies

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Chapter 7

Tying research question and analytical strategy when variables are affected by medication use

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Abstract

Ill-defined research questions could be particularly problematic in an epidemiological setting where measurements fluctuate over time due to intercurrent events, such as medication use. When a research question fails to specify how medication use should be handled methodologically, arbitrary decisions may be made during the analysis phase, which likely leads to a mismatch between the intended question and the performed analysis. The mismatch can result in vastly different or meaningless interpretations of estimated effects. Thus, a research question such as 'what is the effect of X on Y?' requires further elaboration, and it should consider whether and how medication use has affected the measurements of interest.

In our study, we will discuss how well-defined questions can be formulated when medication use is involved in observational studies. We will distinguish between a situation where an exposure is affected by medication use and where the outcome of interest is affected by medication use. For each setting, we will give examples of different research questions that could be asked depending on how medication use is considered in the estimand and discuss methodological considerations under each question.

Keywords
Research question; Medication effect; Well-defined question; Estimand; Causal inference;

Key points

- An overview is given of well-defined research questions that can be formulated in an epidemiological study where the exposure or the outcome values may be affected by medication use.
- Different ways of handling medication use in the analysis can lead to vastly different estimated effects with different interpretations.
- Some commonly used approaches, such as deleting patients using medication when the outcome is affected by medication, yield estimates which do not have a meaningful interpretation
- Researchers are advised to consciously set research questions and corresponding analytic strategies for handling medication use based on the clinical aims of the study.

Introduction

A well-defined research question is the cornerstone of research. Depending on the research question, different theoretical considerations and statistical analyses are required, and most importantly, estimated effects should be interpreted differently [1, 2]. Unfortunately, researchers may start performing statistical analyses before their research question is settled with sufficient detail. Analyses are done first, and the meaning of the estimated effect remains vague [3].

Ill-defined research questions are particularly problematic in an epidemiological setting where measurements fluctuate or change over time. Medication use is one important cause for this change, as it is prescribed to target specific measures. A research question that fails to specify how medication use should be handled methodologically may lead to arbitrary decisions during the analysis phase, and a subsequent mismatch between the intended research question and the performed analysis.

Suppose that different researchers are interested in the effect of blood pressure (BP) on myocardial infarction (MI) risk. Some researchers may exclude individuals using antihypertensive drugs. The result would be interpreted as the effect of BP on MI in the subset of medication non-users, and it may not be transportable to medication users. Others may be interested in untreated BP values and take a modelling approach to reconstruct BP values without medication; for example, by using methods to account for measurement error [4]. Again, others may ignore the medication information and consider the effect of observed BP, which might have been lowered by medications in the total population. Similar problems arise when blood pressure is studied as an outcome. Thus, a research question such as ‘what is the effect of X on Y?’ requires

further elaboration, and it should consider whether and how medication use has affected the measurements of interest.

Numerous authors in causal inference have stressed that exposures should be well-defined [5-8]. Moreover, the handling of intercurrent events in causal inference has recently achieved considerable attention. Young et al. have recently proposed a causal framework where they discuss different causal estimands under competing events. In the field of randomized trials, the European Medicines Agency (EMA) released a guideline proposing several different estimands for intercurrent events such as post-randomization medication use [9].

As practical guidance, several authors [4, 10-12] discussed statistical methods that could be used when measurements are affected by medication use. However, our recent review of the handling of medication use in medical papers [13] demonstrated that a majority of studies featured vaguely formulated research questions and unclear research aims. Invalid methods were often used, and a justification for the chosen method was rarely given. Despite the efforts to raise awareness, medication use as intercurrent events was overlooked in majority of reviewed papers.

Therefore, in this paper, we emphasize the importance of further elaborating on ostensibly straightforward research questions when the exposure or the outcome variable is affected by medication use. We describe several types of research questions of interest to applied researchers; some are formulated within the framework of causal inference, and others are more explorative in nature. When considering a cause, we take a practical pluralistic perspective; not only manipulable interventions but also 'states', such as having a certain level of blood pressure, can be studied as causes [14, 15]. We discuss how medication use is incorporated into each research question and which potential design considerations or methodological challenges may occur. Additionally, we warn against some common approaches to handling medication use that generally fail to yield interpretable results.

We start this paper by discussing a situation where an exposure, possibly time-varying, is affected by medication use by considering five different research aims. Following, we consider five research aims when the outcome of interest may be affected by medication. We conclude with a general discussion.

Situation 1: The exposure is affected by medication use

Imagine a researcher interested in the effect of blood pressure (BP) on the severity of COVID-19 in patients who just tested positive for the coronavirus. The time of the positive test is indicated by *t*. The outcome, severity of COVID-19, is measured at a certain moment after *t*. Individuals' BP levels have changed over time before time t, and some people have started using antihypertensive drugs at a certain moment before time *t*. Depending on research settings, BP may have been measured repeatedly before time *t* or only at *t*.

The initial research question, 'the effect of BP on the severity of COVID-19', is not well defined; it ignores the fact that BP varies over time and does not specify which BP values are of interest. For simplicity of the further discussion, let us assume three categories of study participants (Figure 1a). In category A, individuals had a high BP for a prolonged period and never used antihypertensive drugs. Individuals in category B also had a history of high BP but started using antihypertensive drugs before *t*. Thus, at time *t*, their blood pressure is lower than before taking the medication. In category C, individuals had normal blood pressure over time without medication. We use this example to discuss different possible research questions of interest. Throughout the paper, we assume that all confounding factors are measured and dealt with appropriately. Table 1 summarizes the different research questions.

Table 1. Summary of Section 1 (the exposure is affected by medication use) and Section 2 (the outcome is affected by medication use)

Section 1		
The interest is in	**Research question example**	**When or why**
the currently observed exposure value	What is the effect of the currently observed BP value on the severity of COVID-19?	BP values observed at a certain time point reflect a patient's health status.
the exposure trajectory before time *t*	What is the effect of the history of BP on the severity of COVID-19?	Regardless of antihypertensive medication use, history of BP values manifests an accumulated effect on the outcome.
the untreated exposure value	What is the effect of untreated BP at time t on the severity of COVID-19?	Untreated BP values at time *t* better reflect the medical condition than the observed BP after medication.
the effect of an intervention on the exposure	What would have happened if no one had been treated with antihypertensive drugs?	A causal effect of intervening on BP on the relationship between BP and the outcome is of interest.

Table 1. Summary of Section 1 (the exposure is affected by medication use) and Section 2 (the outcome is affected by medication use) *(continued)*

Section 1		
The interest is in	**Research question example**	**When or why**
the untreated population only	What is the effect of BP on the severity of COVID-19 among people who did not use antihypertensive drugs?	The subpopulation of medication non-users is of interest.
Section 2		
The interest is in	**Research question example**	**When or why**
the observed value of the outcome	What is the difference in observed BP at age 40 between individuals born with and without genetic factor?	The total effect of gene A on BP that may be partly mediated by using antihypertensive drugs is of interest.
the outcome value unaffected by medication use	What is the effect of the genetic factor A on BP at age 40 if no one had used antihypertensive drugs?	The biological effect of gene A on BP is of interest, and antihypertensive drug use is considered to have altered the effect of interest.
medication use as part of the outcome	What is the effect of the genetic factor A on the risk of hypertension at age 40?	The fact that a person started using antihypertensive medication is a part of the outcome.
in the outcome values while being untreated	What is the difference in BP between individuals born with and without genetic factor A while being untreated?	Only the measurements before treatment may be of interest. More meaningful in situations where measurement after intercurrent events is undefined; i.e., quality of life between the treatment group compared over time only in those still alive.
the untreated population	What is the difference in BP between individuals born with and without genetic factor A in those untreated at age 40?	It resembles a per-protocol analysis of an RCT Questionable whether this approach corresponds to any sensible and clinically relevant estimand.

Figure 1. Visual representations of research questions 1.1 to 1.5 (: medication use) We consider three persons; person A developed high blood pressure (BP) before time t but did not start medication, person B developed high BP and started medication, and person C had low BP.

1.1 The interest is the currently observed exposure value

It may occur that BP values observed at a certain time point reflect a patient's health status. In this case, one may ask: w*hat is the effect of the currently observed BP value on the severity of COVID-19*? This question hypothesizes that the current BP value determines COVID-19 severity; for example, people with higher BP values are at a higher risk (e.g., because of inflammation or vessel wall stress), and people with lower values (whether controlled naturally or by antihypertensive medication) are at a lower risk. This is illustrated in Figure 1a, where the BP measurements as they are observed at time *t* are used as the exposure in the analysis. The analysis here is relatively straightforward. In principle, medication use does not need to be added as an extra variable in the model unless the medication affects the outcome independently of blood pressure (i.e., medication use is a confounder).

1.2 The interest is the exposure trajectory before time *t*

Researchers may hypothesize that the history of BP values may affect a certain health outcome. They may be interested in whether COVID-19 patients with a history of high BP in the last 12 months are at greater risk than comparable patients with a history of lower BP. This translates into the following research question: *what is the effect of the history of BP on the severity of COVID-19?* This implies that the history of BP values, regardless of antihypertensive medication use, manifests an accumulated effect on the outcome. To address this research question, repeated measurement of BP is required to estimate the trajectories of BP for each individual (see Figure 1b).

Still, the "effect of the history of BP" is vaguely defined and needs to be specified. For example, one could be interested in the cumulative BP values during a certain period before *t* (estimated by the area under the curve), the mean value of BP in a specific period, or the increase in BP over a certain period. In any case, the length of the period of interest before time *t* should be well defined. Notably, medication use is not added as a variable in the model, but the effect of medication use is incorporated in the analysis through its effect on subsequent BP levels. Furthermore, in this scenario, confounders should be measured at the time when the follow-up starts.

1.3 The interest is the untreated exposure value

In a third scenario, it may be hypothesized that the untreated exposure values at time *t* better reflect the medical condition of interest than the observed exposure value after medication. For example, a history of high BP may alter vessel wall conditions. While antihypertensive medication may quickly alleviate one's BP level, it takes a longer period for the damaged vessel wall to recover. If vessel wall condition affects COVID-19 severity, BP values measured shortly after treatment initiation are less informative than pre-treatment values. In this case, for those who started treatment in a certain time frame before time t, BP measurements that would have been observed under no treatment can be a proxy for the unmeasured vessel wall difference. The corresponding

research question here would be: *what is the effect of untreated BP at time t on the severity of COVID-19?* The effect of an intervention on BP, directly applicable in medical decision-making, is not under inquiry here. However, the intended research question could provide a valuable etiologic perspective [15].

Answering question 1.3 is not straightforward because the BP level without treatment at time *t* is unobserved for treated individuals. When repeated BP measurements are available, measurements before medication use could be used. For example, as depicted in Figure 1c, we may use the last BP measurement of person B before starting medication as a proxy for the untreated value at time t or extrapolate the untreated BP trajectory of B until time t (under the assumption that individual A and B are exchangeable with respect to BP trajectory). When no previous BP measurements are available, external information on the effect of medication and/or the prescription process is needed to reconstruct the untreated BP at time *t*. For instance, the mean and standard deviation of medication effect can be acquired from randomized control trials. These parameters can be used in a regression calibration method to reconstruct the untreated BP with the uncertainty around it.

If treatment started not long before *t*, such research questions seem especially sensible. Yet when there is a mixture of long-term and short-term medication users, it becomes more complicated; for example, the antihypertensive drug may have improved the vessel wall condition in long-term medication users. When this is the case, time since medication use should be incorporated into the analysis.

One simple solution to answer question 1.3 could be to remove individuals on medication from the analysis. However, when there are many medication users, the estimated effect may be less precise. Furthermore, if there is an effect modification by BP medication use or other characteristics associated with medication use, the average effect in the untreated subpopulation may differ from the average effect in the total population. Finally, one should be aware that selection bias may occur if medication users differ from non-users with high BP in terms of other characteristics and this should be properly accounted for [16].

1.4 Interest in the effect of an intervention on the exposure

The previous sections 1.2 and 1.3 are not anchored to a clear time zero, as the time of starting medication use may differ between patients. The questions are, therefore, not formulated sharply enough to fit within a causal inference framework. In this section, we consider how causal research questions can be formulated as interventions on BP before time t. For example, we may wonder *what would have happened if no one had been treated with antihypertensive drugs*. Alternatively: *what would have been the effect of BP on COVID-19 severity if we had intervened on everyone with high BP with antihypertensive drugs?* While Section 1.3 is interested in the (unobserved) untreated BP values at one particular

time point, Section 1.4 considers the effect of intervening on BP on the relationship between BP and the outcome.

These types of research questions consider hypothetical intervention scenarios as the untreated BP level at time *t,* and the corresponding untreated outcome is unobserved for treated people. Similarly, the BP level and the outcome under treatment are unobserved for people untreated for their high BP. These research questions can be formulated in a counterfactual framework using the concept of a target trial [5, 17, 18]. In a target trial, a study population would be defined at time *t*0 when the follow-up starts, and confounders would also be measured at time *t*0. In our example, *t*0 could be one year before the start of the COVID-19 epidemic. The interventions of interest may be, for example, "prescribe medication if BP is above a certain level" versus "prescribe no medication at all, even if BP is high". People are followed until they are infected by COVID-19 and experience severe or less severe symptoms of COVID-19. There are several approaches for estimating the effect of a possible time-varying intervention (see Hernan and Robins[5], chapter 21 for an overview), such as the use of inverse probability weighting [19, 20]. Ideally, all individuals should be followed from the beginning of the trajectory to the final measures; otherwise, loss to follow-up should be accounted for, for example, by using censoring weights [20, 21].

1.5 The interest is the untreated population only

Another aim may be to estimate the effect of BP on the severity of COVID-19 *among people who did not use antihypertensive drugs*. To answer this research question, one would restrict the analysis to individuals without medication use, as illustrated in Figure 1e. While previous questions are interested in the *total* population, the interest here is the subpopulation of medication non-users. Individuals in this subpopulation might be under antihypertensive treatment and may be more likely to have higher BMI. The subpopulation could therefore have different characteristics than the total population. If BMI were an effect modifier for the association between BP and the severity of COVID-19, the estimated effect would only be valid for the population untreated at time *t*.

Selection bias may occur if one does not adjust for confounding between medication use and the outcome. Individuals using antihypertensive medication could, for instance, be more health-conscious than individuals with untreated high BP. This implies that health-conscious people with high blood pressure will be underrepresented in the selected subpopulation of medication non-users. Therefore, health consciousness should be adjusted for in the analysis [16].

The appendix displays simple numerical examples of each research aim depicted in Section 1.1 to 1.5.

Situation 2: The outcome is affected by medication use

Now, let us consider a scenario where we have an exposure determined at a certain time (t_0) and a continuous outcome that could change throughout life. During follow-up, the outcome levels of some individuals may have been influenced by medication use. For this example, we pick the exposure to be genetic variant A rather than a treatment or another intervention to avoid confusion with the intercurrent medication use. The outcome is BP. In our example, the follow-up starts at adulthood (t_0), and some individuals with high BP have started using antihypertensive drugs between time t_0 and *t, t* being the end of the follow-up.

As an illustration, we consider four hypothetical individuals in Table 2 and Figure 2a. Person a1 and b1 were both born with gene A, which causes high BP. Individual b1 starts using medication. Person a0 and b0 are identical to a1 and b1, respectively, except that they both were born without the gene and did not develop high BP. Person a0 and b0 share identical characteristics, and the difference in Figure 2 only reflects random inter-variability. A summary of the research interests is given in Table 1.

Table 2. Four different hypothetical individuals under a scenario where the interest is estimating the effect of the gene A on blood pressure (BP) at time t, while some individuals started antihypertensive medication use before time t.

Individual	Genetic variant	BP before time t	Medication use
a1	Gene A	High	No
b1	Gene A	High	Yes
a0	No gene A	Low	No
b0	No gene A	Low	No

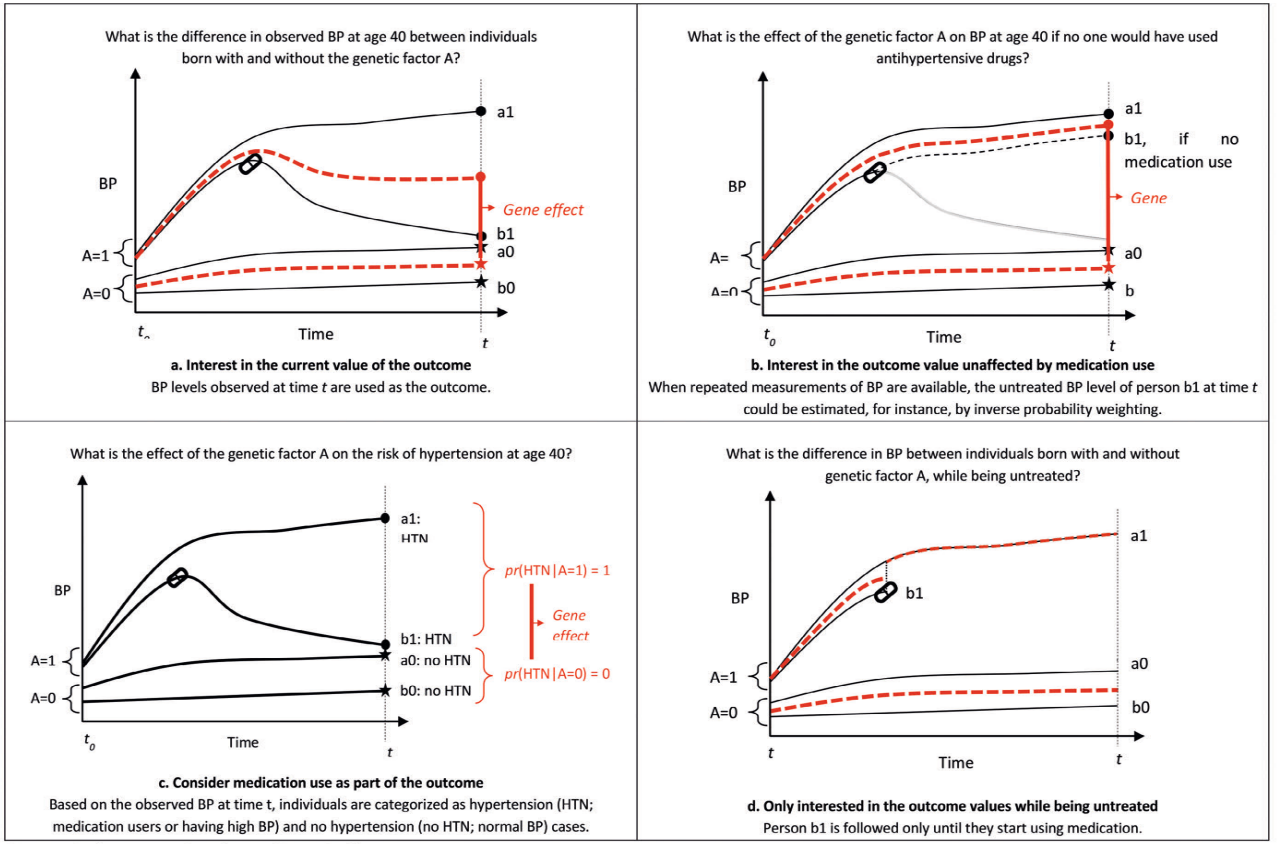

Figure 2. Visual representations of research question from 2.1 to 2.4

Four individuals are assigned to having a certain genetic factor A (A=1) or not (A=0) at time t0. The follow-up starts at time t0 and continues until time t, where t0 represents the start of adulthood and t represents the age of 40. Black lines represent the BP trajectories of the individuals in Table 2. Red dotted lines represent the average BP levels in each exposure group (the upper line for group A=1 and the lower line for group A=0). Person a0 and b0 share identical characteristics; the difference only reflects random inter-variability.

2.1 The interest is the observed value of the outcome

Firstly, the BP levels as observed can be the outcome of interest (Figure 2a). For example, we may want to compare observed BP levels at age 40 of individuals with gene A to similar individuals born without the gene. In this type of research question, one is interested in the total effect of the exposure on the outcome; that is, an effect that may be partly mediated by using antihypertensive drugs. In counterfactual notation, we are interested in the average total effect of A on the outcome: $E[Y^{A=1}] - E[Y^{A=0}]$, where $Y^{A=1}$ is the potential outcome when setting A to 1 and $Y^{A=0}$ is the potential outcome when setting A to 0. Young et al. referred to this contrast as the "effect without elimination of competing events". In the clinical trial context [9], this is referred to as "*treatment policy strategy-estimand"* [9]. The principle of such analysis corresponds to an intention-to-treat analysis in an RCT, as the data is analyzed using the observed outcomes ignoring any intercurrent event or protocol deviation. Therefore, under question 2.1, medication use would be ignored in the analysis.

2.2. The interest is the outcome value unaffected by medication use

Alternatively, the interest could be the biological effect of gene A on BP, where antihypertensive drug use may alter this effect. Here we would ask research questions such as, *what is the effect of the genetic variant A on BP at age 40 if no one would have used antihypertensive drugs?* In counterfactual notation, we are interested in the effect: $E[Y^{A=1,med=0}] - E[Y^{A=0,med=0}]$, with $Y^{A=1,med=0}$ the potential outcome of Y when A is set to 1 and no medication would have been used. This is called "the effect under elimination of competing events" [22]. In a clinical trial context, it is referred to as "*hypothetical strategy-estimand"* [9]. Figure 2b depicts this scenario.

Suppose repeated measurements of BP are available and all factors influencing medication use are measured. In that case, the estimand can be estimated using repeated measurement methods, such as linear mixed models or generalized estimation equation methods with inverse probability weighting [5, 21]. The BP levels after medication use will not be used in these analyses. If no repeated measurements of BP are available, other methods for handling an outcome variable affected by medication use, such as adding the mean medication effect to the treated measurements or fitting a censored regression model [4, 10-12, 23, 24] may be used.

2.3. Considering medication use as part of the outcome

Medication use can be incorporated into the definition of the outcome when the use of antihypertensive medication provides information about a person's condition. For example, we may use hypertension (yes/no) as a dichotomous outcome. The research question then is: *what is the effect of the genetic factor A on the risk of hypertension at age 40*? In this case, the outcome is dichotomized into *hypertension* (high BP and/or using antihypertensive medication) and *no hypertension* (normal BP and no medication use). This is illustrated in Figure 2c. In other scenarios, using an ordinal scale could be an

alternative (e.g., categorizing fasting glucose level into *normal glucose, impaired glucose,* and *diabetes*, where diabetes is defined as glucose level above a certain level or use of diabetes medication). In clinical trials, this type of scenario is called "*composite variable strategy-estimand"*.

2.4. Only interested in the outcome values while being untreated

In Section 2.2, the interest was in the effect of the gene on untreated BP measurements in the total population. In this section and Section 2.5, we consider two strategies that restrict the population based on medication use. Sometimes only the measurements before treatment may be of interest. In that case, one could compare outcomes between the exposure groups at each time point using only the individuals still untreated at that time. In other words, comparing different exposure groups conditionally on being untreated (Figure 2d). This approach may be called the "while untreated strategy", analogous to the EMA guideline where the "while on treatment-estimand" and "while alive-estimand" are discussed.

In general, this comparison will not answer a causal research question because of selection bias; the comparison only involves individuals who are still untreated at the time of comparison. Suppose people born with the genetic variant A (exposed group) are more likely to use antihypertensive drugs. As time passes, more people in the exposed group will be excluded from the comparison, and the remaining individuals in the exposed and unexposed groups are no longer comparable. This issue will arise even if the groups are exchangeable at baseline.

However, combined with comparing the percentages of individuals starting medication, this comparison may still yield valuable clinical information. It provides an answer to a combination of two questions: i) what is the effect of the genetic factor A on the probability of starting antihypertensive medication, and ii) what is the difference in blood pressure levels effect in those still untreated at the time of comparison? These types of combined questions occur, for example, in quality-of-life studies in cancer research, where the quality-of-life measurements are compared over time only in those still alive at that time because the quality of life after death is undefined [25, 26].

When persons can go on and off treatment (treatment episodes), defining a "while untreated strategy" becomes even more complicated, as also measurements in an untreated period after a period of taking the drug may be considered in some instances as "while untreated". The definition of "while untreated" should in this case, be carefully considered with the clinical context in mind.

2.5 Could the interest be only in the untreated population?

Some studies exclude all measurements of individuals who started medication during follow-up from their analysis, including the measurements before starting medication

use. A difference with Section 2.4 is that here the measurements before medication use are removed as well.

This approach resembles a per-protocol analysis of an RCT where only the participants who completed the follow-up without protocol deviation are included in the analysis [27]. Defining whether an individual belongs to a population of interest (i.e., people who are untreated at any time point) based on an event happening after the follow-up started (i.e., medication use) is risky. If the follow-up time increases, more people will start using medication and consequently be excluded from the comparisons, even for the time before using medication. Consequently, this approach can lead to substantial selection bias [28, 29]. It is questionable whether this approach corresponds to any sensible and clinically relevant estimand.

Discussion

Clinical measurements affected by medication use are commonly encountered in epidemiological research. In this paper, we discussed different research questions that could be of interest when the exposure or the outcome variable is affected by medication use. We argued that each question is driven by different assumptions and clinical aims. Concurrently, each requires a tailored strategy for handling medication use in the analysis. Even with causal inference experts emphasizing the importance of well-defined research questions, the role of medication use is often overlooked, resulting in arbitrary decisions regarding its handling in statistical analysis and vague interpretations of its estimated effects.

Some causal inference experts may argue that BP is not an *intervention* due to its nature of having multiple ways to be manipulated and, therefore, cannot be studied causally [30, 31]. In practice, however, *states* such as having a certain level of BP or glucose are frequently studied as causal risk factors, and they can provide valuable etiological knowledge. In this paper, therefore, we took a practical pluralistic perspective based in research practice and also discussed research questions that are not directly causal interventional.

Still, emulating a target trial can greatly help in crystallizing a research question and choosing a valid analytical strategy [18, 32]. A vaguely defined exposure or outcome variable would not be acceptable in RCTs. For RCTs, protocols are written in advance and demand a clear research question and a detailed statistical analysis plan. A definition of the treatment or the outcome would (and should) not change based on arbitrary decisions made during an analysis phase. Deciding how to handle medication use at the stage of formulating a research question applies equally to observational

studies. For this reason, the importance and benefits of writing a protocol and defining a target estimand prior to conducting observational studies have been stressed [33, 34]. Connecting a research question to a target trial could also contribute to identifying potential sources of bias. For instance, question 2.5 would be analogous to being interested in the effect only in the participants adhering to the protocol until the end of a randomized trial. Compared to an RCT setting, it becomes clear that this type of research question would suffer from selection bias and would rarely yield clinically meaningful results.

One of the estimands mentioned by the EMA is the "principal stratum-estimand", which is the effect in subpopulations where a particular intercurrent event would or would not occur. In our example, a principal stratum could be individuals who would not use hypertension medication when their blood pressure would be elevated (e.g., because they have an aversion to medication or are not aware that their BP is too high). We decided not to discuss this in detail as research questions using potential medication use to define a subpopulation are rarely considered. The corresponding analysis is challenging because whether a person is a medication non-user can be observed only if their BP becomes high during the follow-up.

Situations with medication use can be much more complex as multiple medications can be used simultaneously and/or switching between medications may occur. It is also possible that both the exposure and the outcome measurements are affected by medication use. In addition to medication use, behavioral changes (e.g., starting exercising regularly to regulate high BP) after the baseline could also affect measurements of interest. Needless to say, examples are not limited to blood pressure and blood pressure medication but could be other measurements, such as glucose or lipid levels, and other types of drugs. Numerous sources of potential bias outside those discussed in this paper should be critically considered as well (e.g., how to properly adjust for confounding or ill-defined time zero of follow-up: immortal time bias) [28, 35].

The complexity of the situation, however, should not discourage tackling the problem of measurements affected by medication use. Rather, it requires additional caution when defining research questions and more rigorous planning on how medication should be handled in the analysis. In any given case, we advise researchers to consciously set a research question and corresponding analytic strategy for handling medication use based on the clinical aim and underlying assumptions.

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References

1. Thabane L, Thomas T, Ye C, Paul J. Posing the research question: not so simple. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2008;56(1):71. doi:10.1007/s12630-008-9007-4
2. Bragge P. Asking good clinical research questions and choosing the right study design. Injury. 2010;41:S3-S6. doi:https://doi.org/10.1016/j.injury.2010.04.016
3. Goetghebeur E, le Cessie S, De Stavola B, Moodie EE, Waernbaum I, initiative obottgCIotS. Formulating causal questions and principled statistical answers. Statistics in Medicine. 2020;39(30):4922-48. doi:https://doi.org/10.1002/sim.8741
4. Choi J, Dekkers OM, le Cessie S. A comparison of different methods for handling measurements affected by medication use. medRxiv. 2022:2022.04.23.22273899. doi:10.1101/2022.04.23.22273899
5. Hernán M, Robins J. Causal inference: What if. Boca Raton: Chapman & Hall/CRC; 2020.
6. Maldonado G, Greenland S. Estimating causal effects. International Journal of Epidemiology. 2002;31(2):422-9. doi:10.1093/ije/31.2.422
7. VanderWeele TJ. On Well-defined Hypothetical Interventions in the Potential Outcomes Framework. Epidemiology. 2018;29(4):e24-e5. doi:10.1097/ede.0000000000000823
8. Cole SR, Frangakis CE. The Consistency Statement in Causal Inference: A Definition or an Assumption? Epidemiology. 2009;20(1):3-5. doi:10.1097/EDE.0b013e31818ef366
9. ICH E9 (R1): addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. European Medicines Agency; 2020.
10. Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. Statistics in Medicine. 2005;24(19):2911-35. doi:doi:10.1002/sim.2165
11. Spieker AJ, Delaney JAC, McClelland RL. Evaluating the treatment effects model for estimation of cross-sectional associations between risk factors and cardiovascular biomarkers influenced by medication use. Pharmacoepidemiology and drug safety. 2015;24(12):1286-96. doi:10.1002/pds.3876
12. White IR, Koupilova I, Carpenter J. The use of regression models for medians when observed outcomes may be modified by interventions. 2003;22(7):1083-96. doi:10.1002/sim.1408
13. Choi J, Dekkers OM, le Cessie S. How measurements affected by medication use are reported and handled in observational research: A literature review. Pharmacoepidemiology and Drug Safety. 2022. doi:https://doi.org/10.1002/pds.5437
14. Vandenbroucke JP, Broadbent A, Pearce N. Causality and causal inference in epidemiology: the need for a pluralistic approach. International Journal of Epidemiology. 2016;45(6):1776-86. doi:10.1093/ije/dyv341
15. Glymour C, Glymour MR. Commentary: Race and Sex Are Causes. Epidemiology. 2014;25(4):488-90. doi:10.1097/ede.0000000000000122
16. Hernán M, S H-D, Robins J. A Structural Approach to Selection Bias. Epidemiology. 2004;15(5):615-25.
17. van Geloven N, Swanson SA, Ramspek CL, et al. Prediction meets causal inference: the role of treatment in clinical prediction models. European Journal of Epidemiology. 2020;35(7):619-30. doi:10.1007/s10654-020-00636-1
18. Labrecque JA, Swanson SA. Target trial emulation: teaching epidemiology and beyond. European Journal of Epidemiology. 2017;32(6):473-5. doi:10.1007/s10654-017-0293-4

19. Mansournia MA, Etminan M, Danaei G, Kaufman JS, Collins G. Handling time varying confounding in observational research. BMJ. 2017;359:j4587. doi:10.1136/bmj.j4587

20. Cain LE, Cole SR. Inverse probability-of-censoring weights for the correction of time-varying noncompliance in the effect of randomized highly active antiretroviral therapy on incident AIDS or death. Statistics in Medicine. 2009;28(12):1725-38. doi:https://doi.org/10.1002/sim.3585

21. Robins J, Hernán M, Brumback B. Marginal Structural Models and Causal Inference in Epidemiology. Epidemiology. 2000;11(5).

22. Young JG, Stensrud MJ, Tchetgen Tchetgen EJ, Hernán MA. A causal framework for classical statistical estimands in failure-time settings with competing events. Statistics in Medicine. 2020;39(8):1199-236. doi:https://doi.org/10.1002/sim.8471

23. Spieker AJ, Delaney JA, McClelland RL. A method to account for covariate-specific treatment effects when estimating biomarker associations in the presence of endogenous medication use. Statistical Methods in Medical Research. 2018;27(8):2279-93. doi:10.1177/0962280216680240

24. Tanamas SK, Hanson RL, Nelson RG, Knowler WC. Effect of different methods of accounting for antihypertensive treatment when assessing the relationship between diabetes or obesity and systolic blood pressure. Journal of Diabetes and its Complications. 2017;31(4):693-9. doi:https://doi.org/10.1016/j.jdiacomp.2016.12.013

25. Kurland BF, Johnson LL, Egleston BL, Diehr PH. Longitudinal Data with Follow-up Truncated by Death: Match the Analysis Method to Research Aims. Stat Sci. 2009;24(2):211. doi:10.1214/09-sts293

26. Kurland BF, Heagerty PJ. Directly parameterized regression conditioning on being alive: analysis of longitudinal data truncated by deaths. Biostatistics. 2005;6(2):241-58. doi:10.1093/biostatistics/kxi006

27. ICH E9 Statistical Principles for Clinical Trials. European Medicines Agency; 1998.

28. Suissa S. Immortal Time Bias in Pharmacoepidemiology. American Journal of Epidemiology. 2007;167(4):492-9. doi:10.1093/aje/kwm324

29. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. Journal of Clinical Epidemiology. 2016;79:70-5. doi:https://doi.org/10.1016/j.jclinepi.2016.04.014

30. Hernán M. Invited Commentary: Selection Bias Without Colliders. American Journal of Epidemiology. 2017;185(11):1048-50. doi:10.1093/aje/kwx077

31. Hernán MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. International Journal of Obesity. 2008;32(3):S8-S14. doi:10.1038/ijo.2008.82

32. García-Albéniz X, Hsu J, Hernán MA. The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening. European Journal of Epidemiology. 2017;32(6):495-500. doi:10.1007/s10654-017-0287-2

33. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24. doi:10.1016/j.ijsu.2014.07.014

34. Yang W, Zilov A, Soewondo P, Bech OM, Sekkal F, Home PD. Observational studies: going beyond the boundaries of randomized controlled trials. Diabetes Research and Clinical Practice. 2010;88:S3-S9. doi:https://doi.org/10.1016/S0168-8227(10)70002-4

35. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:b5087. doi:10.1136/bmj.b5087