



Published in final edited form as:

Curr Epidemiol Rep. 2018 September ; 5(3): 272–283. doi:10.1007/s40471-018-0155-y.

The importance and implications of comparator selection in pharmacoepidemiologic research

Monica D’Arcy, PhD¹, Til Stürmer, MD, PhD¹, and Jennifer L. Lund, PhD¹

¹Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

Purpose of review: Pharmacoepidemiologic studies employing large databases are critical to evaluating the effectiveness and safety of drug exposures in large and diverse populations. Because treatment is not randomized, researchers must select a relevant comparison group for the treatment of interest. The comparator group can consist of individuals initiating: (1) a similarly indicated treatment (active comparator), (2) a treatment used for a different indication (inactive comparator) or (3) no particular treatment (non-initiators). Herein we review recent literature and describe considerations and implications of comparator selection in pharmacoepidemiologic studies.

Recent findings: Comparator selection depends on the scientific question and feasibility constraints. Because pharmacoepidemiologic studies rely on the choice to initiate or not initiate a specific treatment, rather than randomization, they are at-risk for confounding related to the comparator choice including: by indication, disease severity and frailty. We describe forms of confounding specific to pharmacoepidemiologic studies and discuss each comparator along with informative examples and a case study. We provide commentary on potential issues relevant to comparator selection in each study, highlighting the importance of understanding the population in whom the treatment is given and how patient characteristics are associated with the outcome.

Summary: Advanced statistical techniques may be insufficient for reducing confounding in observational studies. Evaluating the extent to which comparator selection may mitigate or induce systematic bias is a critical component of pharmacoepidemiologic studies.

Keywords

pharmacoepidemiology; comparator selection; new user; confounding; detection bias

Corresponding author: Monica D’Arcy, PhD, National Cancer Institute, 9609 Medical Center Drive, 6E228, Rockville MD 20850, mdarcy@email.unc.edu; monica.d’arcy@nih.gov, Phone: 240-276-5757.

Compliance with Ethical Standards

Conflict of Interest

Monica D’Arcy declares no conflicts of interest; Til Stürmer reports grants from the National Institute on Aging, during the conduct of the study, grants from AstraZeneca and Amgen, outside the submitted work, membership (Center for Pharmacoepidemiology) of GlaxoSmithKline, UCB BioSciences, Merck, and Shire, outside the submitted work, and stock in Novartis, Roche, BASF, AstraZeneca, and NovoNordisk; Jennifer L. Lund reports grants from PhRMA Foundation, outside the submitted work; Dr. Lund’s husband is a full-time, paid employee of GlaxoSmithKline.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Randomized clinical trials (RCTs) are considered the gold standard to assess the effects of a treatment on a specific outcome because randomization and blinding remove many potential sources of bias. However, observational studies are often better positioned to evaluate the effectiveness and safety of drug exposures with respect to rare outcomes of interest (e.g., cancer) because they can include large and diverse study populations with extended follow-up. They are also critical to describing drug effects in real-world settings, as RCTs are often restricted to highly select populations with tightly controlled treatment monitoring. Large administrative databases with drug reimbursement and dispensing information are particularly useful, because they capture longitudinal exposure information for individuals across healthcare settings.

Robust study design reduces the potential for estimating biased treatment effects. When observational studies add the concept of a hypothetical intervention, usually resulting in a new user study design[1], the choice of a comparator is one of the most critical components of study design. Three comparison choices are possible: the active comparator[2], the inactive comparator[3], and the non-initiator comparator with the choice of the comparator depending on the research question and feasibility considerations. An active comparator is a specific drug or class of drugs with a similar indication and formulation as the treatment of interest. The choice of an active comparator depends upon the question of interest and whether class-level or drug-specific effects are known or hypothesized[4, 5]. An inactive comparator is a drug or class of drugs not indicated or used in the same way as the treatment of interest. Yet, an inactive comparator can help to “synchronize” cohorts on a variety of factors, including healthcare utilization and the start of study follow-up. The simplest comparator, in name but often not in implementation, is the non-initiator comparator. In this scenario, the comparator group is comprised of individuals not initiating a particular treatment. Non-initiator comparisons are often employed in the setting where an inactive or active comparator does not exist.

Several biases can arise in observational studies of drug effects, including: (1) time-related biases (e.g., immortal time bias, time-window bias, immeasurable time bias)[6–9], (2) confounding by frailty, (3) confounding by indication or derivations thereof, and (4) outcome detection bias. The potential for these biases depends, in large part, on the comparator selected. In the following sections, we will provide an overview of each of these biases and discuss how comparator selection (i.e., active comparator, inactive comparator, or non-initiator comparator) influences the likelihood of these biases. To contextualize these design decisions, we draw upon several contemporary examples from the pharmacoepidemiology literature to highlight considerations for comparator selection (summarized in Table 1) and close with a case study that walks through a structured decision-making process for selecting a comparator in a pharmacoepidemiologic study.

Overview of biases relevant to comparator selection

Several factors can influence treatment choice and may also be related to the outcome of interest, and thus confound observed estimates of treatment effects. In the simplest case

when the comparison is no treatment (i.e., a non-initiator comparator), time-related biases such as immortal time bias can result from requiring no use of the drug of interest after cohort entry[6, 7]. This bias occurs because a natural synchronization between treatment initiation and non-initiation does not exist. Because time-related biases have been extensively described in the pharmacoepidemiologic literature[6, 7, 10, 8, 9], we will not provide further examples in this review.

Confounding by frailty[11] occurs when certain therapies are differentially withheld from individuals in poor health, because there may be little to no benefit. This bias can lead to exaggerated beneficial treatment effects[12]. When the reason (or indication) for the treatment is also a risk factor for the outcome, confounding by indication[13–15] can occur. A variation of confounding by indication is confounding by disease severity. This occurs when disease severity is associated with the outcome, and also influences treatment choice. This type of bias can make a treatment appear more harmful than it is. A derivative of confounding by indication occurs when behaviors or characteristics associated with the primary indication for treatment are also risk factors for the outcome. Studies examining the effect of psychiatric medications may be particularly prone to this type of confounding because individuals with certain conditions, particularly if untreated, may be more likely to engage in unhealthy behaviors compared to the general population[16–21].

Outcome detection bias occurs when there is differential outcome ascertainment by treatment group[22, 23]. This bias can occur if overall health status or health seeking behavior influences if and when a person is diagnosed with the outcome. Although outcome detection bias is possible for many outcomes, cancers for which screening exists (e.g., prostate, colorectal, breast) may be particularly prone to detection bias. The likelihood of being diagnosed with cancer is influenced by: 1) being healthy enough to be screened (diagnostic or routine), 2) adhering to screening guidelines, and 3) being engaged with the medical system. The same set of factors can also influence whether or not the same person will visit a physician and initiate certain types of medications. This form of bias can move in both directions. For example, statins may appear to increase cancer risk[24], whereas Alzheimer's medications may appear to reduce cancer risk.

Active comparators

Although active comparator studies have less potential for confounding than other studies (i.e., inactive and non-initiator comparators) because they restrict comparisons to patients initiating medications with similar indications, they can still suffer from confounding by disease severity and frailty.

Glargine and cancer risk

Because of concerns that the long-acting insulin analog glargine could increase the risk of cancer, Stürmer et al[25] conducted a new user, active comparator study examining the association between insulin glargine versus human NPH insulin initiation and cancer. This study was performed within the Medical Outcomes Research for Effectiveness and Economics registry between January 2003-December 2010.

Body mass index (BMI) is associated with cancer risk and with diabetes but was unmeasurable in the study dataset. BMI could therefore have been an important confounder. To address this issue, the authors examined the association between BMI and treatment choice in two external datasets and found that after controlling for other covariates, there was no association (adjusted odds ratio (aOR) 1.00, 95%CI 0.98, 1.02; 0.99 0.96–1.03). The authors concluded that there was no short-term association between glargine use and cancer incidence overall (aHR 1.11, 0.95–1.32), or breast, prostate or colon cancer incidence. When important potential confounders are unavailable in an observational study, it may be possible to investigate the potential for residual bias based on an external validation dataset.

Nicotine replacement therapy and cardiovascular disease (CVD)

A study by Døllnerup[26] et al examined the association between nicotine replacement therapy (NRT) and cardiovascular disease in comparison to individuals receiving smoking cessation counseling (SCC) alone. Although the authors reported no association with cardiovascular disease after 4 weeks of treatment, the time to ischemic heart disease (aHR 1.35, 95%CI: 1.03–1.77) or cerebrovascular disease (aHR 1.54, 1.08–2.19) among the NRT group was increased at 52 weeks compared with the smoking cessation counseling treatment group. Smoking intensity may have confounded the association, as physicians may be more likely to prescribe NRT to individuals who are longer and heavier smokers. Smoking is a strong risk factor for cardiovascular disease, and individuals prescribed NRT may have had more heart damage attributable to smoking compared to the counseling only group. Yet, this information was unavailable in the dataset. There are other medications with smoking cessation indications (among others) that could have potentially been used as comparators[27]. Comparison with these medications may have reduced confounding by smoking severity, although this design is contingent on accurate identification of the smoking cessation indication.

Postoperative chemotherapy in older adults with rectal cancer

A study by Lund et al[28] examined the association between postoperative chemotherapy and rectal cancer survival following preoperative chemoradiation or chemotherapy among older patients. Using the cancer registry data linked with Medicare claims, the authors examined mortality differences between individuals who had received postoperative 5-fluorouracil (5-FU) or capecitabine, 5-FU/capecitabine plus oxaliplatin, or no chemotherapy. Compared to patients not receiving postoperative chemotherapy, postoperative 5-FU/capecitabine alone was associated with reduced mortality (aHR 0.46, 95%CI: 0.30–0.72) among patients aged 66–74. There was no observed effect among individuals older than 74 years. Although the authors controlled for measured confounding using propensity score weighting incorporating a wide array of clinical variables, they speculated that their study overestimated the benefits of post-operative chemotherapy. Even though this study was restricted to individuals healthy enough to initiate preoperative therapy and surgery, it is possible that individuals receiving postoperative chemotherapy were more robust than individuals not receiving chemotherapy. It may be impossible to fully control this bias, as has been shown previously in influenza studies[29–31].

Inactive comparators

An alternative to non-users when the goal is to obtain a causal contrast[3] between treatment and no treatment is a comparator for which there is no known association with the outcome. The use of an inactive treatment comparator helps reduce time-related biases by synchronizing the start of follow-up at medication initiation. However, identifying an appropriate comparator is challenging, because it has its own indications, and could be associated with the outcome. This approach has been previously referred to as an active comparator[32–35], a negative exposure control[36], and an inactive comparator[3].

There are a few key considerations when identifying an inactive comparator. First, the association between the inactive comparator and the outcome should be well-described. In practice it can be difficult to identify a treatment with a known association with the outcome, because it requires a treatment for which there is sufficient evidence. If the desired contrast is between use and non-use, then the inactive comparator should have evidence of no association with the outcome. Note that it is important to understand the association between an active comparator and an outcome to make proper inferences. For example, in a study evaluating the association between a new anti-hypertensive drug and angioedema with an active comparator of angiotensin-converting enzyme inhibitors (ACEIs). Any inferences would have to account for the well-known association between ACEIs and angioedema risk[37] or identify a different comparator with no known association with angioedema.

The inactive treatment should also be used in a similar way to the active treatment. For example, if the active treatment is indicated for the long-term management of a chronic disease, the inactive comparator should be used similarly and not used only for the treatment of acute symptoms. There should be a sufficient number of anticipated users to allow precise estimation, with another consideration being the projected number of concomitant users, who would be ineligible for analysis. Finally, the risk factors for the outcome should be well-known, with the most important being directly measurable in the data.

Benzodiazepines and mortality

A recent study examined the association between benzodiazepines and mortality[35], with the primary comparison group consisting of randomly selected high-dimensional propensity score matched non-users who had visited a physician within 14 days of the matched benzodiazepine initiator. To minimize access to healthcare differences, they required that both non-users and benzodiazepine users filled at least one non-benzodiazepine prescription in the 0–90 and 91–180 days prior to the index date. They reported no association between benzodiazepine initiation and non-initiation. In a sensitivity analysis, they compared benzodiazepine initiators to selective serotonin reuptake inhibitors (SSRI) initiators, because with the exception of a small increased risk of suicide among adolescents and young adults[38], SSRIs are not associated with increased mortality. This analysis represents an inactive comparison, because the medications lack similarity in indication. Additionally, how these medications are taken varies substantially. SSRIs are used for the long-term management of various conditions including depression, anxiety, sleep disorders and chronic pain[39, 40]. They are taken daily over months and years, and it can take few weeks to notice symptom reduction. In contrast, benzodiazepines are used for the acute treatment of

anxiety, panic and sleep disorders. They are controlled substances with the potential for abuse, with prescribers potentially being more hesitant to prescribe these medications for long periods of time. Benzodiazepines are commonly prescribed on an “as-needed” basis, whereas SSRIs are taken daily. These differences in the two underlying populations may explain the small, albeit increased risk of death associated with the benzodiazepine initiators (aHR 1.09, 95%CI 1.03–1.16). Because of the risk for abuse, it could be reasoned that individuals who take benzodiazepines regularly instead of SSRIs may have a higher propensity for substance abuse and other related but unmeasurable factors that differentially increase mortality.

Non-user comparators

When there is no clear alternative to the treatment of interest, many studies employ non-initiator comparisons, whereby individuals initiating a treatment of interest are compared to individuals not initiating that treatment. Although, non-initiator comparisons are particularly prone to immortal time bias, there are strategies to reduce this bias[41]. There are also more advanced adjustment techniques such as propensity scores and a special case, high-dimensional propensity scores,[42] to reduce the risk of *measured* confounding (see example 4 above). Unmeasured confounding, especially with respect to drug indication and frailty remain since these are difficult to measure.

Influenza vaccine and mortality

Although numerous studies[43–48] have documented the strong inverse association between receiving the flu vaccine and mortality, there is sound evidence that a substantial proportion of these associations are due to the underlying differences in the populations that received or did not receive the vaccine. Individuals who were close to death and were thus not expected to survive the flu season, may have been less likely to get vaccinated. In contrast, individuals who received the vaccine were perceived as healthy enough to benefit from the vaccine. In a classic example, Jackson et al[29] addressed this hypothesis by examining the association between influenza vaccination versus no vaccination and death prior to the influenza season, a negative control outcome that should not be affected by influenza vaccination. The authors found that vaccine receipt was associated with a substantial reduction in mortality (risk ratio (RR) = 0.39, 0.33–0.47). Moreover, adjustment for important diagnosis codes did not materially alter the association, underscoring the challenge of controlling for frailty by adjustment for measured variables contained within administrative data. A contemporary study[31] attempted to reduce confounding by frailty in similar setting, by adjustment for markers of independent living, as a proxy for health status. The association with mortality was attenuated compared with the previous study (HR 0.68, 0.67–0.70), but the authors concluded that substantial confounding remained despite more rigorous health status measurement.

Statins, antibiotics, and breast cancer outcomes

A study by Wirtz et al[49] aimed to understand why previous studies within the same parent study had reported increased risks of second breast cancers associated with antibiotic use[50, 51], and decreased risk of recurrent breast cancer associated with statin use[52]. All studies

compared medication users to non-users. In the follow-up study, they examined screening practices of the antibiotic or statin users. Adherent statin use was associated with more surveillance mammography (odds ratio (OR): 1.11, 95% CI 1.01–1.25) compared to non-users, whereas heavy antibiotic use was associated with less surveillance mammography (OR: 0.90, 95% CI 0.82–0.99). Although adjustment for screening behaviors did not qualitatively impact inferences, this study highlights how screening practices can vary among initiators of various medication classes.

Lithium and pregnancy outcomes

Lithium is one of the primary treatments of bipolar disorder, a condition that affects ~1–2.5% of the population[53]. Untreated, individuals with bipolar disorder may engage in dangerous behaviors (e.g. substance abuse)[54, 19, 18, 53] that could negatively impact fetal development. Untreated women may also be more likely to forgo early prenatal care. Concerns over the safety of lithium in early pregnancy[55, 56] prompted Paterno et al[57] to examine the association between lithium use in the first trimester of pregnancy and the risk of fetal cardiac malformations. This important question is challenging because it is difficult to disentangle bipolar-associated behaviors and medications on fetal outcomes. A woman who was untreated at conception may have been engaging in behaviors, that on their own, could have negatively impacted fetal development.

In the primary analysis, the authors compared women who used lithium (without requiring a bipolar diagnosis) in the first trimester of their pregnancy with women who did not use lithium based on Medicaid data. The authors controlled for measured confounding using a matched propensity score approach containing a rich set of variables. The study reported an increased risk associated with lithium (adjusted hazard ratio (aHR) 1.65, 95% CI 1.02–2.68) in this population. It is however possible that untreated bipolar women appearing in the non-user group may have biased the relative association towards the null. Although the proportion of women with a bipolar diagnosis was relatively small in the non-user group, untreated women could have obscured the risk in the non-user group.

To address potential confounding by indication, the authors performed an analysis restricted to women with a bipolar diagnosis, where individuals using lithium were compared to individuals using lamotrigine, also indicated for bipolar disorder (i.e., an active comparator). Lamotrigine is not associated with the risk of cardiac malformations. Both the comparison to lamotrigine exposed women and the restriction to individuals with a bipolar diagnosis may have reduced confounding by unhealthy behaviors in bipolar women. Characteristics of lamotrigine and lithium exposed women were similar with respect to mental health diagnoses and other comorbidities before propensity score weighting. The association in this comparison was similar (aHR 2.25, 95% CI 1.17–4.34), albeit higher than the other comparison.

Case study: Antidepressants and colorectal cancer

As a case study, we explored designing a study to evaluate the association between SSRI use and incident colorectal cancer (CRC). We were also interested in two other classes: serotonin norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs).

Here, we will walk through the process of selecting a comparator and the considerations, such as important covariate availability, that could influence study results (see Table 1 for summary).

Comparator choice considerations

An active comparator, if it exists, is generally ideal to minimize the risk of bias. As noted earlier, psychiatric drugs may be particularly prone to confounding because of behaviors associated with the indication. However, we could not identify a comparator with a similar indication without evidence of an association with CRC risk[58–61]. We next considered other psychotropic drugs, but there was insufficient evidence to state with certainty that they were not associated with CRC risk. Additionally, some anti-psychotics are also differentially given to individuals with late stage dementia to improve behavior[62, 63] even without a history of psychosis. Those individuals are less likely to be screened and diagnosed with a cancer, which could lead to outcome detection bias.

Given that we could not identify an active comparator, we preferred to select a group of individuals initiating a medication taken daily for the management of a chronic disease. We sought to identify a comparator that was commonly prescribed by a primary care physician, because they also commonly prescribe SSRIs, except in the case of more severe mental illness. For these reasons, we ruled out selection of non-initiators. Practically, it is also more straightforward to the start follow-up at medication initiation.

We briefly considered selecting anti-glaucoma drugs as an inactive comparator, because it has been previously used in the published literature[33, 34, 64, 32]. We were, however, concerned that these drugs are generally prescribed by an ophthalmologist. This provider may not be aware of the patients' overall health issues, as a primary care physician would. These medications may not be given in for “long-term” use, in a prophylactic manner, but more for symptom abatement. We were also not convinced that there would be a sufficient number of initiators in the data. Statins were excluded because there is ongoing debate as to whether they are associated with cancer risk[65, 66]. There is a substantial body of evidence on anti-hypertensives (AHT), enough to state with some certainty that they do not dramatically alter CRC risk, and limited evidence that some may reduce risk[67], with the exception of beta-blockers where evidence suggests a reduced cancer risk[68]. Additionally, primary care physicians generally treat hypertension.

Identifying risk factors in administrative data

We thus moved forward with a new user[69] study design with an AHT inactive comparator using a Medicare beneficiary population[70]. We a-priori hypothesized that all three antidepressant (AD) classes had “late-acting” effects on CRC risk such that the medications were acting close to the adenoma-carcinoma transition. We therefore hypothesized that we could detect associations with only a few years of follow-up data. The natural history of CRC has been fairly well documented[71–74], with major risk factors generally identified[75]. We were thus aware of which risk factors were measurable. Age, male sex, history of inflammatory conditions and black race are all strong risk factors for which we had information. Family history and genetics[75] are strong risk factors that were

unmeasurable. We used diagnoses for all non-CRC prior to initiation as a proxy for upstream genetic predisposition to cancer generally. We had information or proxies for hormone replacement therapy, non-steroidal anti-inflammatory use, diabetes, alcohol consumption, smoking and obesity, all of which modestly affect CRC risk[75]. We lacked information on diet, exercise, BMI, or aspirin (generally unavailable) use.

Potential for confounding by indication derivative.

Limited evidence suggests that depressed individuals, for which antidepressants are indicated, may be less like to adhere to screening guidelines[76, 77] and would be less likely to be screened or visit a physician. In turn, they may be less likely to be diagnosed with CRC. This could lead to outcome detection bias if we did not have information on screening behaviors. Administrative data do however contain information on CRC screening and diagnostic events, because Medicare pays for these services[78]. We therefore would be able to control for recent screening behavior that may be influenced by depression status. Finally, if antidepressants improve depressive symptoms, then screening may not be a concern after a few months of follow-up.

Antidepressants and CRC results

We identified 530,304 SSRI, SNRI, TCA, or AHT initiators with a second prescription meeting age, enrollment and CRC-free status criteria. Substantially more individuals exclusively initiated an AHT (n=417,491) class than an AD (SSRI: n=87,401 SNRIs: n=12,211; TCAs: n=13,201). The median days of continuous medication class use after the second prescription (overall=332 days) varied across classes [AHT=363; SSRI= 252; TCA=172; SNRI=238 days].

We observed 1,728 CRC events in 631,920 person years (PY), with incidence varying from 214 per 100,000 PY for TCA initiators to 281 cases per 100,000 PY for AHT initiators. SSRI initiators had a reduced rate of CRC compared with AHT initiators: (aHR 0.85 95%CI 0.71–1.00). TCA and SNRI initiators had lower adjusted CRC rates compared with AHT initiators [0.83, 0.52–1.31; 0.91, 0.59, 1.41], respectively. In sensitivity analyses, we observed a reduced rate (5%–20%) of CRC among SSRI users compared with AHT initiators. These associations fell within the range of previously reported estimates[79–84].

Our comparator was not perfect. Limitations included a large reduction in sample size due to concomitant AD and AHT users, and differences in follow-up time. Because we lacked absolute proof that our AHT comparator was not associated with CRC, it may have been informative to perform sensitivity analyses with additional inactive comparators that we hypothesized had no association with the outcome. A similar strategy was used in a study of immune-related conditions and the risk of keratinocyte cancers[85]. However, the data we used contained information on key variables, proxies for other factors, and managed to perfectly balance these factors. We also compared drug classes that required somewhat regular physician interaction. As such, our analysis provides some evidence that SSRIs do not increase the risk of CRC compared to AHT in a Medicare population.

Conclusions

Comparator selection in observational pharmacoepidemiologic studies is infrequently straightforward. In general, systematic bias is always a threat because of the potential for unmeasured confounding. However, it is possible to carefully design and select a comparator that may reduce the potential for bias, weighing each of the considerations mentioned in Table 1. It is critical to understand (1) the population in whom the treatment is given, to (2) how patient characteristics are associated with the outcome, and (3) the natural history and risk factors for the outcome. Advanced statistical techniques may be insufficient for reducing confounding in observational studies. Thus, complementary strategies such as the use of active comparators or addressing the extent to which bias may impact estimated treatment effects (e.g., via validation studies and multiple bias modeling) represent promising directions for future studies.

References

1. Johnson ES, Bartman BA, Briesacher BA, Fleming NS, Gerhard T, Kornegay CJ et al. The incident user design in comparative effectiveness research. *Pharmacoepidemiol Drug Saf.* 2013;22(1):1–6. doi:10.1002/pds.3334.
2. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep.* 2015;2(4):221–8. doi:10.1007/s40471-015-0053-5. [PubMed: 26954351]
3. Huitfeldt A, Hernan MA, Kalager M, Robins JM. Comparative Effectiveness Research Using Observational Data: Active Comparators to Emulate Target Trials with Inactive Comparators. *EGEMS (Wash DC).* 2016;4(1):1234. doi:10.13063/2327-9214.1234. [PubMed: 27891526] ** Clearly describes how to think about and design a study using observational data to emulate a target trial. There are very intuitive diagrams in this paper.
4. Gokhale M, Buse JB, Gray CL, Pate V, Marquis MA, Sturmer T. Dipeptidyl-peptidase-4 inhibitors and pancreatic cancer: a cohort study. *Diabetes Obes Metab.* 2014;16(12):1247–56. doi:10.1111/dom.12379. [PubMed: 25109825]
5. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA.* 2010;304(4):411–8. doi:10.1001/jama.2010.920. [PubMed: 20584880]
6. Suissa S Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf.* 2007;16(3):241–9. doi:10.1002/pds.1357. [PubMed: 17252614]
7. Suissa S Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol.* 2008;167(4):492–9. doi:10.1093/aje/kwm324. [PubMed: 18056625]
8. Suissa S Immeasurable time bias in observational studies of drug effects on mortality. *Am J Epidemiol.* 2008;168(3):329–35. doi:10.1093/aje/kwn135. [PubMed: 18515793]
9. Suissa S, Dell'aniello S, Vahey S, Renoux C. Time-window bias in case-control studies: statins and lung cancer. *Epidemiology.* 2011;22(2):228–31. doi:10.1097/EDE.0b013e3182093a0f. [PubMed: 21228697]
10. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. *Diabetes Care.* 2012;35(12):2665–73. doi:10.2337/dc12-0788. [PubMed: 23173135]
11. Glynn RJ, Knight EL, Levin R, Avorn J Paradoxical relations of drug treatment with mortality in older persons. *Epidemiology.* 2001;12(6):682–9. doi:10.1097/00001648-200111000-00017. [PubMed: 11679797] ** Shows how a series of medications that should not affect mortality are associated with mortality. Factors such as proximity to death and overall health status drive the associations.
12. Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a

- simulation study. *Am J Epidemiol.* 2010;172(7):843–54. doi:10.1093/aje/kwq198. [PubMed: 20716704]
13. Garrett JE, Lanes SF, Kolbe J, Rea HH. Risk of severe life threatening asthma and beta agonist type: an example of confounding by severity. *Thorax.* 1996;51(11):1093–9. [PubMed: 8958891]
 14. Ernst P, Habbick B, Suissa S, Hemmelgarn B, Cockcroft D, Buist AS et al. Is the association between inhaled beta-agonist use and life-threatening asthma because of confounding by severity? *Am Rev Respir Dis.* 1993;148(1):75–9. doi:10.1164/ajrccm/148.1.75. [PubMed: 8100409]
 15. Harrold LR, Patterson MK, Andrade SE, Dube T, Go AS, Buist AS et al. Asthma drug use and the development of Churg-Strauss syndrome (CSS). *Pharmacoepidemiol Drug Saf.* 2007;16(6):620–6. doi:10.1002/pds.1353. [PubMed: 17192840]
 16. Roche MW, Boyle DJ, Cheng CC, Del Pozzo J, Cherneski L, Pascarella J et al. Prevalence and Risk of Violent Ideation and Behavior in Serious Mental Illnesses: An Analysis of 63,572 Patient Records. *J Interpers Violence.* 2018;886260518759976. doi:10.1177/0886260518759976. [PubMed: 29534632]
 17. Thoma P, Daum I. Comorbid substance use disorder in schizophrenia: a selective overview of neurobiological and cognitive underpinnings. *Psychiatry Clin Neurosci.* 2013;67(6):367–83. doi: 10.1111/pcn.12072. [PubMed: 23890122]
 18. Stokes PRA, Kalk NJ, Young AH. Bipolar disorder and addictions: the elephant in the room. *Br J Psychiatry.* 2017;211(3):132–4. doi:10.1192/bjp.bp.116.193912. [PubMed: 28864753]
 19. Bobo WV, Na PJ, Geske JR, McElroy SL, Frye MA, Biernacka JM. The relative influence of individual risk factors for attempted suicide in patients with bipolar I versus bipolar II disorder. *J Affect Disord.* 2018;225:489–94. doi:10.1016/j.jad.2017.08.076. [PubMed: 28865370]
 20. Regnart J, Truter I, Meyer A. Critical exploration of co-occurring Attention-Deficit/Hyperactivity Disorder, mood disorder and Substance Use Disorder. *Expert Rev Pharmacoecon Outcomes Res.* 2017;17(3):275–82. doi:10.1080/14737167.2017.1351878. [PubMed: 28686107]
 21. Zulauf CA, Sprich SE, Safren SA, Wilens TE. The complicated relationship between attention deficit/hyperactivity disorder and substance use disorders. *Curr Psychiatry Rep.* 2014;16(3):436. doi:10.1007/s11920-013-0436-6. [PubMed: 24526271]
 22. Gokhale M, Girman C, Chen Y, Pate V, Funk MJ, Sturmer T. Comparison of diagnostic evaluations for cough among initiators of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf.* 2016;25(5):512–20. doi:10.1002/pds.3977. [PubMed: 26860956]
 23. Hong JL, Henderson LM, Jonsson Funk M, Lund JL, Buse JB, Pate V et al. Differential Use of Screening Mammography in Older Women Initiating Metformin versus Sulfonylurea. *Pharmacoepidemiol Drug Saf.* 2017;26(6):666–75. doi:10.1002/pds.4195. [PubMed: 28370798]
 24. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol.* 2007;166(3):348–54. doi:10.1093/aje/kwm070. [PubMed: 17504779]
 25. Sturmer T, Marquis MA, Zhou H, Meigs JB, Lim S, Blonde L et al. Cancer incidence among those initiating insulin therapy with glargine versus human NPH insulin. *Diabetes Care.* 2013;36(11):3517–25. doi:10.2337/dc13-0263. [PubMed: 23877991]
 26. Dollerup J, Vestbo J, Murray-Thomas T, Kaplan A, Martin RJ, Pizzichini E et al. Cardiovascular risks in smokers treated with nicotine replacement therapy: a historical cohort study. *Clin Epidemiol.* 2017;9:231–43. doi:10.2147/CLEP.S127775. [PubMed: 28490903]
 27. Toh S, Baker MA, Brown JS, Kornegay C, Platt R, Mini-Sentinel I. Rapid assessment of cardiovascular risk among users of smoking cessation drugs within the US Food and Drug Administration's Mini-Sentinel program. *JAMA Intern Med.* 2013;173(9):817–9. doi:10.1001/jamainternmed.2013.3004. [PubMed: 23529063]
 28. Lund JL, Sturmer T, Sanoff HK. Comparative effectiveness of postoperative chemotherapy among older patients with non-metastatic rectal cancer treated with preoperative chemoradiotherapy. *J Geriatr Oncol.* 2016;7(3):176–86. doi:10.1016/j.jgo.2016.01.011. [PubMed: 26926829]
 29. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol.* 2006;35(2):337–44. doi:10.1093/ije/dyi274. [PubMed: 16368725] ** Elegantly demonstrates how much of the observed association

between receipt of the influenza vaccine and reduced mortality likely resulted from the differential receipt of the vaccine whereby individuals not expected to survive to the influenza season did not receive the vaccine.

30. Jackson ML, Yu O, Nelson JC, Naleway A, Belongia EA, Baxter R et al. Further evidence for bias in observational studies of influenza vaccine effectiveness: the 2009 influenza A(H1N1) pandemic. *Am J Epidemiol*. 2013;178(8):1327–36. doi:10.1093/aje/kwt124. [PubMed: 23978527]
31. Zhang HT, McGrath LJ, Wyss R, Ellis AR, Sturmer T. Controlling confounding by frailty when estimating influenza vaccine effectiveness using predictors of dependency in activities of daily living. *Pharmacoepidemiol Drug Saf*. 2017;26(12):1500–6. doi:10.1002/pds.4298. [PubMed: 28840621]
32. Patrick AR, Schneeweiss S, Brookhart MA, Glynn RJ, Rothman KJ, Avorn J et al. The implications of propensity score variable selection strategies in pharmacoepidemiology: an empirical illustration. *Pharmacoepidem Dr S*. 2011;20(6):551–9. doi:10.1002/pds.2098.
33. Schneeweiss S, Patrick AR, Sturmer T, Brookhart MA, Avorn J, Maclure M et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Medical Care*. 2007;45(10):S131–S42. doi:DOI 10.1097/MLR.0b013e318070c08e. [PubMed: 17909372]
34. Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation*. 2007;115(1):27–33. doi:10.1161/CIRCULATIONAHA.106.650176. [PubMed: 17179016]
35. Patorno E, Glynn RJ, Levin R, Lee MP, Huybrechts KF. Benzodiazepines and risk of all cause mortality in adults: cohort study. *BMJ*. 2017;358:j2941. doi:10.1136/bmj.j2941. [PubMed: 28684397]
36. Dusetzina SB, Brookhart MA, Maciejewski ML. Control Outcomes and Exposures for Improving Internal Validity of Nonrandomized Studies. *Health Serv Res*. 2015;50(5):1432–51. doi:10.1111/1475-6773.12279. [PubMed: 25598384]
37. Knecht SE, Dunn SP, Macaulay TE. Angioedema related to Angiotensin inhibitors. *J Pharm Pract*. 2014;27(5):461–5. doi:10.1177/0897190014546101. [PubMed: 25124378]
38. Mann JJ, Emslie G, Baldessarini RJ, Beardslee W, Fawcett JA, Goodwin FK et al. ACNP Task Force report on SSRIs and suicidal behavior in youth. *Neuropsychopharmacology*. 2006;31(3):473–92. doi:10.1038/sj.npp.1300958. [PubMed: 16319919]
39. Patetsos E, Horjales-Araujo E. Treating Chronic Pain with SSRIs: What Do We Know? *Pain Res Manag*. 2016;2016:2020915. doi:10.1155/2016/2020915. [PubMed: 27445601]
40. Sansone RA, Sansone LA. Pain, pain, go away: antidepressants and pain management. *Psychiatry (Edgmont)*. 2008;5(12):16–9.
41. Lund JL, Horvath-Puho E, Komjathine Szepligeti S, Sorensen HT, Pedersen L, Ehrenstein V et al. Conditioning on future exposure to define study cohorts can induce bias: the case of low-dose acetylsalicylic acid and risk of major bleeding. *Clin Epidemiol*. 2017;9:611–26. doi:10.2147/CLEP.S147175. [PubMed: 29200891]
42. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20(4):512–22. doi:10.1097/EDE.0b013e3181a663cc. [PubMed: 19487948]
43. Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet*. 2005;366(9492):1165–74. doi:10.1016/S0140-6736(05)67339-4. [PubMed: 16198765]
44. Nordin J, Mullooly J, Poblete S, Strikas R, Petrucci R, Wei F et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis*. 2001;184(6):665–70. doi:10.1086/323085. [PubMed: 11517426]
45. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med*. 2003;348(14):1322–32. doi:10.1056/NEJMoa025028. [PubMed: 12672859]

46. Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med*. 2007;357(14):1373–81. doi:10.1056/NEJMoa070844. [PubMed: 17914038]
47. Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. *Clin Infect Dis*. 2002;35(4):370–7. doi:10.1086/341403. [PubMed: 12145718]
48. Spaude KA, Abrutyn E, Kirchner C, Kim A, Daley J, Fisman DN. Influenza vaccination and risk of mortality among adults hospitalized with community-acquired pneumonia. *Arch Intern Med*. 2007;167(1):53–9. doi:10.1001/archinte.167.1.53. [PubMed: 17210878]
49. Wirtz HS, Calip GS, Buist DSM, Gralow JR, Barlow WE, Gray S et al. Evidence for Detection Bias by Medication Use in a Cohort Study of Breast Cancer Survivors. *Am J Epidemiol*. 2017;185(8):661–72. doi:10.1093/aje/kww242. [PubMed: 28338879] * Demonstrates how individuals at the extremes of health status (very sick/very healthy) are more/less likely to obtain certain medications and/or be adherent. Individuals at both extremes may differentially utilize cancer screening and may therefore be differentially diagnosed with cancer potentially leading to spurious associations.
50. Velicer CM, Heckbert SR, Lampe JW, Potter JD, Robertson CA, Taplin SH. Antibiotic use in relation to the risk of breast cancer. *JAMA*. 2004;291(7):827–35. doi:10.1001/jama.291.7.827. [PubMed: 14970061]
51. Wirtz HS, Buist DS, Gralow JR, Barlow WE, Gray S, Chubak J et al. Frequent antibiotic use and second breast cancer events. *Cancer Epidemiol Biomarkers Prev*. 2013;22(9):1588–99. doi:10.1158/1055-9965.EPI-13-0454. [PubMed: 23833124]
52. Boudreau DM, Yu O, Chubak J, Wirtz HS, Bowles EJ, Fujii M et al. Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. *Breast Cancer Res Treat*. 2014;144(2):405–16. doi:10.1007/s10549-014-2870-5. [PubMed: 24557337]
53. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007;64(5):543–52. doi:10.1001/archpsyc.64.5.543. [PubMed: 17485606]
54. Blanco C, Compton WM, Saha TD, Goldstein BI, Ruan WJ, Huang B et al. Epidemiology of DSM-5 bipolar I disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions - III. *J Psychiatr Res*. 2017;84:310–7. doi:10.1016/j.jpsychires.2016.10.003. [PubMed: 27814503]
55. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. A reevaluation of risk of in utero exposure to lithium. *JAMA*. 1994;271(2):146–50. [PubMed: 8031346]
56. Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L et al. Management of bipolar disorder during pregnancy and the postpartum period. *Am J Psychiatry*. 2004;161(4):608–20. doi:10.1176/appi.ajp.161.4.608. [PubMed: 15056503]
57. Paterno E, Huybrechts KF, Bateman BT, Cohen JM, Desai RJ, Mogun H et al. Lithium Use in Pregnancy and the Risk of Cardiac Malformations. *N Engl J Med*. 2017;376(23):2245–54. doi:10.1056/NEJMoa1612222. [PubMed: 28591541]
58. Cloonan SM, Williams DC. The antidepressants maprotiline and fluoxetine induce Type II autophagic cell death in drug-resistant Burkitt's lymphoma. *International journal of cancer*. 2011;128(7):1712–23. doi:10.1002/ijc.25477. [PubMed: 20503272]
59. Levkovitz Y, Gil-Ad I, Zeldich E, Dayag M, Weizman A. Differential induction of apoptosis by antidepressants in glioma and neuroblastoma cell lines: evidence for p-c-Jun, cytochrome c, and caspase-3 involvement. *Journal of molecular neuroscience : MN*. 2005;27(1):29–42. doi:10.1385/JMN:27:1:029. [PubMed: 16055945]
60. Reddy KK, Lefkove B, Chen LB, Govindarajan B, Carracedo A, Velasco G et al. The antidepressant sertraline downregulates Akt and has activity against melanoma cells. *Pigment cell & melanoma research*. 2008;21(4):451–6. doi:10.1111/j.1755-148X.2008.00481.x. [PubMed: 18710373]

61. Xia Z, Bergstrand A, DePierre JW, Nassberger L. The antidepressants imipramine, clomipramine, and citalopram induce apoptosis in human acute myeloid leukemia HL-60 cells via caspase-3 activation. *Journal of Biochemical and Molecular Toxicology*. 1999;13(6):338–47. [PubMed: 10487422]
62. Barnes TR, Banerjee S, Collins N, Treloar A, McIntyre SM, Paton C. Antipsychotics in dementia: prevalence and quality of antipsychotic drug prescribing in UK mental health services. *Br J Psychiatry*. 2012;201(3):221–6. doi:10.1192/bjp.bp.111.107631. [PubMed: 22790679]
63. Corbett A, Burns A, Ballard C. Don't use antipsychotics routinely to treat agitation and aggression in people with dementia. *BMJ*. 2014;349:g6420. doi:10.1136/bmj.g6420. [PubMed: 25368388]
64. Kerr SJ, Rowett DS, Sayer GP, Whicker SD, Saltman DC, Mant A. All-cause mortality of elderly Australian veterans using COX-2 selective or non-selective NSAIDs: a longitudinal study. *Br J Clin Pharmacol*. 2011;71(6):936–42. doi:10.1111/j.1365-2125.2010.03702.x. [PubMed: 21276041]
65. Liu Y, Tang W, Wang J, Xie L, Li T, He Y et al. Association between statin use and colorectal cancer risk: a meta-analysis of 42 studies. *Cancer Causes Control*. 2014;25(2):237–49. doi: 10.1007/s10552-013-0326-6. [PubMed: 24265089]
66. Lochhead P, Chan AT. Statins and colorectal cancer. *Clin Gastroenterol Hepatol*. 2013;11(2):109–18; quiz e13–4. doi:10.1016/j.cgh.2012.08.037. [PubMed: 22982096]
67. Makar GA, Holmes JH, Yang YX. Angiotensin-converting enzyme inhibitor therapy and colorectal cancer risk. *J Natl Cancer Inst*. 2014;106(2):djt374. doi:10.1093/jnci/djt374. [PubMed: 24431411]
68. Fitzgerald PJ. Beta blockers, norepinephrine, and cancer: an epidemiological viewpoint. *Clin Epidemiol*. 2012;4:151–6. doi:10.2147/CLEP.S33695. [PubMed: 22807646]
69. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915–20. [PubMed: 14585769]
70. D'Arcy ME, Sturmer T, Funk MJ, Baron JA, Sandler RS, Pate V et al. Abstracts 618. Antidepressants (AD) and Colorectal Cancer (CRC). *Pharmacoepidemiol Drug Saf*. 2015;24(Supplemental S1):1–587. doi:10.1002/pds.3838. [PubMed: 26395592]
71. Fearon ER. Molecular genetics of colorectal cancer. *Annual review of pathology*. 2011;6:479–507. doi:10.1146/annurev-pathol-011110-130235.
72. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990;61(5):759–67. [PubMed: 2188735]
73. Jass JR. Molecular heterogeneity of colorectal cancer: Implications for cancer control. *Surgical oncology*. 2007;16 Suppl 1:S7–9. doi:10.1016/j.suronc.2007.10.039. [PubMed: 18023574]
74. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology*. 2007;50(1):113–30. doi:10.1111/j.1365-2559.2006.02549.x. [PubMed: 17204026]
75. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet*. 2013. doi:10.1016/S0140-6736(13)61649-9.
76. Rogers CR, Robinson CD, Arroyo C, Obidike OJ, Sewali B, Okuyemi KS. Colorectal Cancer Screening Uptake's Association With Psychosocial and Sociodemographic Factors Among Homeless Blacks and Whites. *Health Educ Behav*. 2017;44(6):928–36. doi: 10.1177/1090198117734284. [PubMed: 28978252]
77. Owusu D, Quinn M, Wang KS. Alcohol Consumption, Depression, Insomnia and Colorectal Cancer Screening: Racial Differences. *Int J High Risk Behav Addict*. 2015;4(2):e23424. doi: 10.5812/ijhrba.4(2)2015.23424. [PubMed: 26097837]
78. Centers for M, Medicaid Services HHS. Medicare program; revisions to payment policies and five-year review of and adjustments to the relative value units under the physician fee schedule for calendar year 2002. Final rule with comment period. *Fed Regist*. 2001;66(212):55245–503. [PubMed: 11760761]
79. Chubak J, Boudreau DM, Rulyak SJ, Mandelson MT. Colorectal cancer risk in relation to antidepressant medication use. *International journal of cancer* *Journal international du cancer*. 2011;128(1):227–32. doi:10.1002/ijc.25322. [PubMed: 20232382]

80. Coogan PF, Strom BL, Rosenberg L. Antidepressant use and colorectal cancer risk. *Pharmacoepidemiology and drug safety*. 2009;18(11):1111–4. doi:10.1002/pds.1808. [PubMed: 19623565]
81. Cronin-Fenton DP, Riis AH, Lash TL, Dalton SO, Friis S, Robertson D et al. Antidepressant use and colorectal cancer risk: a Danish population-based case-control study. *British journal of cancer*. 2011;104(1):188–92. doi:10.1038/sj.bjc.6605911. [PubMed: 20877356]
82. Haukka J, Sankila R, Klaukka T, Lonnqvist J, Niskanen L, Tanskanen A et al. Incidence of cancer and antidepressant medication: record linkage study. *International journal of cancer*. 2010;126(1):285–96. doi:10.1002/ijc.24537. [PubMed: 19739257]
83. Walker AJ, Card T, Bates TE, Muir K. Tricyclic antidepressants and the incidence of certain cancers: a study using the GPRD. *British journal of cancer*. 2011;104(1):193–7. doi:10.1038/sj.bjc.6605996. [PubMed: 21081933]
84. Xu W, Tamim H, Shapiro S, Stang MR, Collet JP. Use of antidepressants and risk of colorectal cancer: a nested case-control study. *The lancet oncology*. 2006;7(4):301–8. doi:10.1016/S1470-2045(06)70622-2. [PubMed: 16574545]
85. Yanik EL, Pfeiffer RM, Freedman DM, Weinstock MA, Cahoon EK, Arron ST et al. Spectrum of Immune-Related Conditions Associated with Risk of Keratinocyte Cancers among Elderly Adults in the United States. *Cancer Epidemiol Biomarkers Prev*. 2017;26(7):998–1007. doi: 10.1158/1055-9965.EPI-17-0003. [PubMed: 28377416]

Table 1.

Review of comparator selection considerations and implications for selected pharmacoepidemiologic studies.

#	Topic	Author, Year	Considerations for comparator selection	Comparator selected	Rationale/Potential for bias remaining	Approach used to address remaining bias
1	Glargine and the risk of cancer among diabetics	Stürmer, 2013	High body mass index (BMI) is the main driver of (indication for) the need to add insulin in patients with type 2 diabetes and a risk factor for several cancers; no information on BMI in claims data.	Active comparator: long-acting human (NPH) insulin	By comparing to a medication with the same indication, the authors hope to reduce the risk of unmeasured confounders (e.g. BMI). If the choice to initiate a specific drug was associated with BMI, then confounding by BMI status could exist.	Examined the association between BMI and choice of insulin using 2 external electronic medical record databases; result: no effect of BMI on choice of insulin.
2	The effect of nicotine replacement therapy (NRT) on cardiovascular disease in smokers	Dollerup, 2017	Smoking is a strong risk factor for heart disease, so the authors wanted a comparison group consisting of smokers. This would reduce the risk of confounding by smoking status.	Active comparator: smoking cessation counseling	By comparing to NRT to smoking cessation treatment, study is restricted to smokers who want to quit smoking. It is possible that the prescribing physician preferentially referred heavy smokers with substantial existing heart damage to NRT. Therefore, confounding by disease severity could exist.	The authors acknowledged limitations in the discussion.
3	The effect of postoperative chemotherapy on mortality among stage II-III rectal cancer patients	Lund, 2016	Individuals receiving postoperative chemotherapy may be healthier than those not receiving postoperative chemotherapy. The authors wanted to identify a group of patients who were similarly "healthy" to those receiving postoperative chemotherapy.	Non-initiator: compared postoperative 5-fluorouracil (5-FU) or capecitabine to no chemotherapy. Active comparator: compared individuals receiving 5-FU or capecitabine to individuals receiving 5-FU/capecitabine + oxaliplatin	They restricted their study population to non-metastatic rectal cancer patients who had received preoperative chemoradiation or radiotherapy. Non-user comparison: physician may preferentially give healthier patients chemotherapy post-surgery (confounding by frailty). Active comparison: residual confounding by disease severity and frailty.	The authors stratified into clinically meaningful age groups. They acknowledged limitations and estimated the direction of bias. They used active and non-initiator comparisons.
4	Benzodiazepines and mortality	Patorno, 2017	Non-initiators may have lower disease burden and therefore	Primary analysis: non-initiators. Sensitivity analysis:	Non-user comparison: By requiring the non-users and users to	The authors used high dimensional propensity

			lower mortality or perhaps less access to care/surveillance and higher mortality.	inactive comparator (SSRIs)	have filled 1+ non-benzodiazepine prescription in the 0–90 and 91–180 days prior to index date, they restricted to individuals utilizing the healthcare system.	score models with many variables. They stratified into clinically meaningful age groups. They performed a sensitivity analysis with a comparator with overlapping indications.
5	Influenza vaccine and mortality	Jackson, 2005	Individuals close to death and not expected to live to flu season may have had the vaccine withheld. individuals receiving the vaccine may be healthier and at lower risk of death	Non-user comparison in time periods where influenza vaccine should have no effect on mortality	The authors examined the effect of vaccine receipt on mortality in the time before, during and after influenza. They examined patterns of relative mortality risk over the three intervals to try and disentangle the true vaccine from bias attributable to health differences.	The authors incorporated many variables associated with health status into the models. They acknowledged that despite comprehensive variable selection, confounding by health status still exists.
6	Influenza vaccine and mortality	Zhang, 2017	Individuals close to death and not expected to live to flu season may have had the vaccine withheld. individuals receiving the vaccine may be healthier and at lower risk of death	Non-user comparison in time period where influenza vaccine should have no effect on mortality	Examining the effect of vaccine receipt on mortality in a non-influenza time period aids in estimating the amount of confounding by frailty that exists.	The authors added variables related to independent living to their propensity score model. They acknowledged that residual confounding likely still exists.

7	Antibiotic use and recurrent breast cancer	Wirtz, 2017	Individuals with many antibiotic events may be sicker than non-users and therefore differentially screened compared with non-users	Non-user comparison	The authors examined the association between antibiotic use and surveillance mammography.	The authors adjusted for screening in overall analysis. They acknowledged that ongoing surveillance is difficult to model and there may be residual confounding.
8	Statin use and recurrent breast cancer	Wirtz, 2017	Adherent statin users may be healthier than non-users and therefore differentially screened compared with non-users	Non-user comparison	The authors examined the association between statin use and surveillance mammography.	The authors adjusted for screening in overall analysis. They acknowledged that ongoing surveillance is difficult to model and there may be residual confounding.
9	Lithium and fetal outcomes	Patorno, 2017	Individuals with bipolar disorder are much more likely to engage in unhealthy behaviors and to have more comorbidities.	Primary analysis: non-initiator Sensitivity analysis: active comparator (lamotrigine)	Non-user analysis: The non-user comparison group had a small percentage of individuals with a bipolar disorder diagnosis. They may have been untreated and as such may have distorted the non-user group. Sensitivity analysis: By restricting to an active comparator in individuals with a bipolar diagnosis, they the authors reduced confounding by bipolar behaviors.	The authors used rich propensity score model with many variables. They performed multiple sensitivity analyses including one with an active comparator.
10	Case study: Antidepressants and colorectal cancer (CRC)		Antidepressants, SSRIs in particular are commonly prescribed by a primary care physician. The prescribing physician generally wants to see the patient more frequently shortly after initiation to evaluate drug effects and titrate dosage. SSRIs are given for the long-term management of many diseases. It frequently takes a	Primary analysis: inactive comparator - antihypertensive initiators excluding beta-blockers	The authors chose a comparison group 1) with little known association with the outcome 2) that must be engaged with the healthcare system 3) that regularly takes a medication given for the long-term management of chronic disease and that is commonly prescribed by a primary care physician 5) with a large number of anticipated initiators.	The authors had a strong understanding of the pathogenesis of CRC and used a wide set of clinically important covariates (including screening/diagnostic events) associated with CRC in the propensity score model. It was well-balanced. They performed several

couple of weeks to observe symptom abatement. They are commonly used drugs and we expected a large number of initiators.

sensitivity analyses where they varied latency and lag assumptions. They acknowledged that there could still be some residual confounding.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript