Web Material

The State of Use and Utility of Negative Controls in Pharmacoepidemiologic Studies

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Web Appendix 1. Search Strategy and Selection Criteria

Search strategy

Our search strategy was built for each database as follows:
('negative control*':ti,ab OR 'negative outcome control*':ti,ab OR 'negative exposure control*':ti,ab OR 'bias indicator*':ti,ab OR 'probe variable*':ti,ab OR 'negatively control*':ti,ab OR 'proxy outcome*':ti,ab) AND ('confounding variable'/exp OR confound*:ti,ab OR 'statistical bias'/exp OR bias*:ti,ab OR misclassification*:ti,ab OR 'measurement error*':ti,ab OR 'measurement error'/exp OR 'internal validity'/exp OR 'internal validity':ti,ab OR 'epidemiology'/exp OR epidemiolog*:ti,ab OR pharmacoepidemiolog*:ti,ab OR 'p value calibration':ti,ab OR 'confidence interval calibration':ti,ab).

MeSH terms were utilized for the MEDLINE/PubMed search, and Emtree was used for the EMBASE search.

Details of the electronic databases used

- EMBASE (Elsevier interface)
- CINAHL (EBSCOhost interface)
- Cochrane Library (includes the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Cochrane Methodology Register)
- Scopus (Elsevier interface)
- Dissertations and Theses Global (ProQuest interface)

Key studies utilized for the manual search for citing articles

We utilized following articles in the manual search as key papers on negative controls that are often cited by epidemiologic studies using negative control methods. We identified these studies based on the review of articles from a pilot search for developing search strategies.

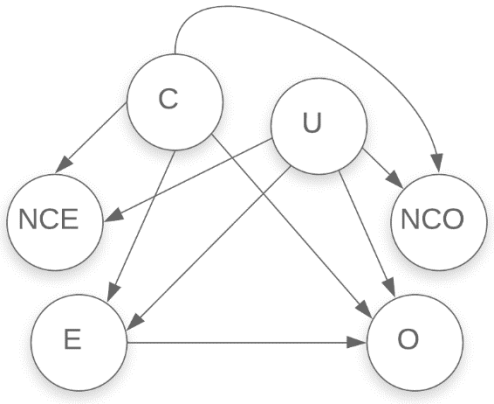
1. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiol Camb Mass. 2010 May;21(3):383–8.
2. Arnold BF, Ercumen A. Negative Control Outcomes: A Tool to Detect Bias in Randomized Trials. JAMA. 2016 27;316(24):2597–8.
3. Arnold BF, Ercumen A, Benjamin-Chung J, Colford JM. Brief Report: Negative Controls to Detect Selection Bias and Measurement Bias in Epidemiologic Studies. Epidemiol Camb Mass. 2016;27(5):637–41.
4. Tchetgen Tchetgen E. The Control Outcome Calibration Approach for Causal Inference With Unobserved Confounding. Am J Epidemiol. 2014 Mar 1;179(5):633–40.

Selection criteria

1. The study is on a topic of pharmacoepidemiology which is the study of safety, effectiveness, and utilization of drugs in human population.
2. The study is of an observational nature, either using an observational study design or studying methods for observational studies.
3. The study uses a negative control method or discusses a novel utility of negative control methods for observational studies.
4. The primary effect measure for the exposure-outcome of interest in the study can be estimated without a negative control, and the negative control is not used primarily as a comparator for the causal question of interest in the study (e.g., an active comparator).
5. The study is published in a peer-reviewed journal, not grey literature such as dissertation, thesis, or conference abstracts.
6. The study is published in English.

Web Appendix 2. Graphical and Mathematical Representations of the Key Assumptions of Negative Controls

In this section, we provide a directed acyclic graph (DAG) diagram for the causal model for a negative control analysis. We also provide the mathematical representation of the assumptions of negative controls as well as the assumptions needed for proximal causal inference, detection, and identification of bias.[1]



Web Figure 1. Directed acyclic graph for causal associations between variables in a negative control analysis. E represents exposure of interest; O, outcome of interest; C, measured confounders; U, unmeasured confounders; NCE, negative control exposure; NCO, negative control outcome.

Assumptions needed for proximal causal inference, which are described in more details by Shi et. al.[1]:

Consistency assumption: $O(e) = O \; when \; E = e$, where O represents the observed outcome and $O(e)$ represents the counterfactual or potential outcome if the exposure level was e, $E = e$.

Latent ignorability: $O(e) \perp\!\!\!\perp \mathrm{E} \mid \mathrm{C}, \mathrm{U}$; which indicates that the exposure and outcome of interest are independent given measured and unmeasured confounders. $O(e)$ represents the potential outcome if the exposure level was e, $E = e$.

Assumptions for valid negative control exposure and outcome[1]:

Negative control exposure and outcome: $O(e, nce) = O(e) \mid C, U$ and $NCE \perp\!\!\!\perp \mathrm{O(e)} \mid \mathrm{C}, \mathrm{U}$; $NCO(e, nce) = NCO \mid C, U$ and $NCO \perp\!\!\!\perp \mathrm{E} \mid \mathrm{C}, \mathrm{U}$. $O(e, nce)$ represents the counterfactual or potential outcome value for exposure level e, $E = e$, and negative control exposure level nce, $NCE = nce$. Similarly, $NCO(e, nce)$ represents the counterfactual or potential negative control outcome value for exposure level e, $E = e$, and negative control exposure level nce, $NCE = nce$.

Assumption for bias detection[1]:

U-comparability assumption: $NCE \perp\!\!\!\perp U \mid C, E$ and $NCO \perp\!\!\!\perp U \mid C$.

Additional assumptions for identification of the causal effect[1]:

Positivity assumption: $0 < P(E = e,\ NCE = nce) \mid C) < 1$, for all levels of C, E and NCE.

Completeness assumption: For all e, $NCE \perp\!\!\!\perp NCO \mid E = e,\ C$. Also, for any square integrable function g, if $E[g(NCO) \mid NCE = nce, E = e,\ C] = 0$ for all e and nce, then $g(NCO) = 0$.

Web Table 1. Data Extraction Table for Studies Included in the Review

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
1	Abrahami, 2018a[2]	Cohort study	EHR (UK Clinical Practice Research Datalink)	E: Use of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (vs. other second or third line antidiabetic drugs) O: Cholangiocarcinoma NCE: Use of insulin, long-acting insulin analogues	HR	Exposure	2	Confounding bias by disease severity	Detection of bias	No	NA
2	Abrahami, 2018b[3]	Cohort study	EHR (UK Clinical Practice Research Datalink)	E: Use of dipeptidyl peptidase-4 inhibitors (vs. other antidiabetic drugs) O: Inflammatory bowel disease NCE: Use of insulin	HR	Exposure	1	Confounding bias by disease severity	Detection of bias	No	NA
3	Ajrouch, 2019[4]	Cohort study	Healthcare administrative data (French Healthcare administrative data: Système National des Données de Santé (SNDS))	E: Chronic use of low dose aspirin (LDA) O: Overall cancer incidence NCE: Clopidogrel use	Sub-distribution hazard ratio	Exposure	1	NR	Detection of bias	Yes	NA
4	Arfè, 2015[5]	Cohort study	Healthcare administrative data (Healthcare administrative data of Italian Lombardy Region)	E: High adherence to statins (vs. low adherence to statins) O: Diabetes NCE: High adherence to bisphosphonate (vs. low adherence to bisphosphonate) NCO: Hypertension	HR	Exposure and outcome	1 exposure and 1 outcome	Information bias (Detection bias)	Detection of bias	No	NA
5	Aronson, 2020[6]	Other design (Database review)	Passive surveillance data (Drug safety surveillance data: List of reports of suspected adverse drug reactions published by the Medicines and Healthcare products Regulatory Agency (MHRA))	E: Nine commonly used non-enzyme-inducing antibacterial drugs (amoxicillin, ampicillin, cephalexin, ciprofloxacin, erythromycin, metronidazole, nitrofurantoin, oxytetracycline, trimethoprim) (vs. nine control medications, not expected to alter the efficacy of oral contraceptives (citalopram, ibuprofen, lansoprazole, loperamide, loratadine, paracetamol, propranolol, theophylline, zolpidem)) O: Unintended pregnancy NCO: Cardiac arrhythmias, headache	OR	Outcome	2	NR	Detection of bias	No	NA
6	Backenroth, 2016[7]	Case-control study	EHR (EHR at New York-Presbyterian (NYP)/Columbia University Medical Center)	O: Acute kidney injury (AKI), acute liver injury (ALI), acute myocardial infarction (AMI) and gastrointestinal ulcer hospitalization (GIU) PCE: Positive controls drugs (refer to study text for entire list)	AUC	Exposure-Outcome pair (Combinations of outcomes and NCEs)	234 negative control-outcome pairs	Confounding bias	Evaluation of performance of different methods	Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				NCE: Negative control drugs (refer to study text for entire list)							
7	Bedson, 2019[8]	Cohort study	EHR (UK Clinical Practice Research Datalink)	E: Prescription of long-term opioids O: Primary outcomes - major trauma and intentional overdose (any); Secondary outcomes - addiction (any), falls, accidental poisoning, attempted suicide/self-harm, gastrointestinal pathology and bleeding, iron deficiency anemia NCO: Incident eczema and psoriasis	HR	Outcome	2	Bias in general	Detection of bias	No	NA
8	Bijlsma, 2016[9]	Cohort study	Healthcare administrative data (University of Groningen prescription database, Statistics Netherlands)	E: Adherence to statin therapy O: Cardiovascular mortality NCO: Mortality due to diseases of the respiratory system and endocrine, nutritional and metabolic diseases (composite outcome)	HR	Outcome	1	Large model: Confounding bias (Healthy adherer bias); Small model: Overadjustment bias, bias due to competing risk	Detection of bias	Large model: Yes; Small model: No	NA
9	Brassard, 2017[10]	Cohort study	EHR (UK Clinical Practice Research Datalink)	E: Statin use O: Influenza-like illness morbidity and mortality NCO: Motor vehicle accidents (MTVAs) and burns	Cumulative incidence ratio	Outcome	2	Bias in general, Confounding bias (Healthy user bias)	Detection of bias	Yes, though not statistically significant	NA
10	Brauchli Pernus, 2016[11]	Reference set identification	NA	NA	NA	Exposure-Outcome pair	NA	NA	Reference set identification	NA	NA
11	Brookhart, 2007[12]	Cohort study	Healthcare administrative database (Administrative claims data - Medicare and Pennsylvania Pharmaceutical Assistance Contract for Elderly (PACE))	E: Adherence to statin therapy O: NA NCO: Utilization of preventive medical services and tests (bone mineral density testing and screening mammography for women, prostate-specific antigen testing for men, and fecal occult blood tests, influenza vaccinations, and pneumococcal vaccinations for both women and men)	HR	Outcome	6	Confounding bias (Healthy user bias)	Detection of bias	Yes	NA
12	Brookhart, 2012[13]	Cohort study	Healthcare administrative data (Administrative claims database - HealthCore Integrated Research Database)	E: MMR (Measles, mumps, and rubella) or MMRV (measles, mumps, rubella, and varicella) vaccine O: NA NCO: Injuries, urinary tract infections, and congenital malformations	Excess cumulative incidence	Outcome	3	NR	Detection of bias, Evaluation of performance of different methods	Yes (congenital malformation), No (injuries, urinary tract infections)	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
13	Brown, 2007[14]	Pharmacovigilance method (Sequential statistical testing)	EHR (Electronic healthcare data from 9 participating health plans in the HMO Research Network's Center for Education and Research on Therapeutics (CERT))	PC: 5 drug-comparator-outcome combinations with known associations (refer to study text for entire list) NC: 2 drug-comparator-outcome combinations without suspected associations (refer to study text for entire list)	Number of drug-outcome combinations that generated alerts based on a maximized sequential probability ratio test (max SPRT)	Exposure-Outcome pair	6	NR	Evaluation of performance of different methods	NA	NA
14	Brown, 2009[15]	Pharmacovigilance method (Sequential statistical testing)	EHR (Electronic healthcare data from 9 participating health plans in the HMO Research Network's Center for Education and Research on Therapeutics (CERT))	PC: 5 drug-comparator-outcome combinations with known associations (refer to study text for entire list) NC: 2 drug-comparator-outcome combinations without suspected associations (refer to study text for entire list)	Number of drug-outcome combinations that generated alerts based on a maximized sequential probability ratio test (max SPRT)	Exposure-Outcome pair	6	NR	Evaluation of performance of different methods	NA	NA
15	Burkard, 2018[16]	Cohort study	EHR (UK Clinical Practice Research Datalink)	E: Statin therapy initiation O: Incident hand osteoarthritis (OA) NCO: Cataract, peptic ulcer, psoriasis, tinnitus	HR	Outcome	4	Information bias (Surveillance bias due to differential health seeking behavior)	Detection of bias	No	NA
16	Busby, 2018a[17]	Cohort study	EHR, Disease registry, Census, Vital records (English National Cancer Data Repository (NCDR), UK Clinical Practice Research Datalink (CPRD), Census information, and Office for National Statistics (ONS))	E: Angiotensin receptor blocker use O: Gastro-esophageal cancer survival NCE: Use of angiotensin converting enzyme (ACE) inhibitors	HR	Exposure	1	Confounding bias	Detection of bias	No	NA
17	Busby, 2018b[18]	Cohort study	EHR, Disease registry, Census, Vital records (English National Cancer Data Repository (NCDR), UK Clinical Practice Research Datalink (CPRD), Census information, and Office for National Statistics (ONS))	E: Selective serotonin reuptake inhibitor (SSRI) use O: Breast cancer survival NCE: Use of tricyclic antidepressants (TCA) and venlafaxine	HR	Exposure	2	Confounding bias	Detection of bias	Yes	NA
18	Butler, 2019[19]	Cohort study	Disease registry linked with healthcare administrative data (United States end-stage renal disease program)	E: Dose of influenza vaccine received O: All-cause mortality NCO: Pre-influenza season mortality	Risk ratio	Outcome	1	Confounding bias (Healthy user bias)	Detection of bias	Yes	NA
19	Casula, 2018[20]	Nested case-control study	Healthcare administrative data (Healthcare administrative data of Lombardy Region NHS)	E: Incident proton pump inhibitor (PPI) use O: Hospitalization for cardio/cerebrovascular event	OR	Exposure	1	Confounding bias	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				NCE: H2 histamine antagonists							
20	Casula, 2020[21]	Cohort study	Healthcare administrative data (Healthcare administrative data of Lombardy Region NHS)	E: Incident Bisphosphonate use O: Hospitalization for atherosclerotic/ cardiovascular events NCE: Incident raloxifene use	HR	Exposure	1	Confounding bias (Healthy user bias)	Detection of bias	No	NA
21	Cheung, 2018[22]	Cohort study	Healthcare administrative data (Clinical Data Analysis and Reporting System (CDARS) of Hong Kong Hospital Authority)	E: Long-term use of proton pump inhibitors O: Gastric cancer development NCE: H2 histamine receptor blocker use	HR	Exposure	1	Protopathic bias	Detection of bias	No	NA
22	Chien, 2016[23]	Nested case-control study	Healthcare administrative data, Disease registry, Vital records (Taiwan's National Health Insurance Research Database, Taiwan Cancer registry, National Death Registry)	E: Proton pump inhibitor (PPI) use O: Periampullary cancers NCO: Lung cancer case	OR	Outcome	1	Confounding bias	Detection of bias	No	NA
23	Chou, 2020[24]	Cohort study	Disease Registry linked with healthcare utilization data (Surveillance, Epidemiology and End Results (SEER)-Medicare data)	E: Low-Income Subsidy (LIS) program O: Time to initiate orally administered anticancer drugs (Part D medication) NCO: Time to initiate Part B medication	HR	Outcome	1	Confounding bias (Confounding due to financial status of individuals)	Detection of bias	Yes	NA
24	Christiansen, 2019[25]	Cohort study	Healthcare administrative data, Vital records (Danish Intensive Care Database data and other Danish registries)	E: Influenza vaccination O: 1-year risk of hospitalization for myocardial infarction, stroke, heart failure, pneumonia, and mortality NCO: 1-year risk of hospitalization for injury	HR	Outcome	1	Confounding bias (Healthy user bias)	Detection of bias	No	NA
25	Cohen, 2017[26]	Cohort study	Healthcare administrative data (Administrative claims database - Medicaid Analytic eXtract database)	E: Use of amphetamine-dextroamphetamine or methylphenidate monotherapy in the first half of pregnancy O: Adverse placental-associated pregnancy outcomes including preeclampsia, placental abruption, growth restriction, and preterm birth NCE: Use of atomoxetine	Risk ratio	Exposure	1	Confounding bias (Confounding by indication)	Detection of bias	No	NA
26	Cohen, 2019[27]	Cohort study	Research data (Norwegian Mother and Child Cohort Study (MoBa) - data from questionnaires, data from biospecimens)	E: Maternal antidepressant use in pregnancy O: Shorter gestational length and child anxiety NCE: Paternal antidepressant use	OR	Exposure	1	Confounding bias	Detection of bias	Yes (anxiety), No (gestational age at birth)	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
27	Coloma, 2013[28]	Reference set identification	NA	NA	NA	Exposure-Outcome pair	NA	NA	Reference set identification	NA	NA
28	Danaei, 2013[29]	Cohort study	EHR (Health Improvement Network (THIN))	E: Use of statins O: Incident type 2 diabetes NCO: Incidence peptic ulcer	HR	Outcome	1	Information bias, Selection bias	Detection of bias	No	NA
29	Dave, 2019[30]	Cohort study	Healthcare administrative data (Administrative claims database - Optum, IBM Market Scan, Medicare fee-for service data)	E: Initiation of SGLT-2 inhibitor treatment O: Hospitalization for Fournier gangrene NCO: Hospitalization for necrotizing fasciitis	HR, Rate difference	Outcome	1	NR	Detection of bias	No	NA
30	Davies, 2017[31]	Cohort study	EHR (Clinical Practice Research Datalink (CPRD))	E: Use of varenicline (vs. nicotine replacement products) O: Suicide and self-harm, and depression NCE: Negative control population - individuals prescribed an antidepressant who consulted with a physician on the same day that the physician issued a smoking cessation medication to another patient NCO: Negative control outcome - urinary tract infection	Absolute risk difference in incidence	Exposure and Outcome	1 exposure (population) and 1 outcome	Confounding bias (Healthy user bias)	Evaluation of methods, Detection of bias	Negative control population: No association with outcomes Negative control outcome (urinary tract infection): Yes, with the conventional regression analysis, No with Instrumental variable	NA
31	de Groot, 2014[32]	Case-control study	Healthcare administrative data, Research data, EHR (Administrative claims data, pharmacy dispensing data, prospective cohort data, hospital EHR data - Data from Dutch Mondriaan project, Netherlands Primary Care Database coordinated by NIVEL (NPCD), PHARMO Record Linkage System, a prospective cohort of community acquired pneumonia patients, Hospital data from St. Antonius hospital, Nieuwegein and Gelderse Vallei Hospital, Ede (ANT))	E: Use of ACE inhibitor, statins, and proton pump inhibitors (PPIs) O: Pneumonia NCE: Use of selective serotonin reuptake inhibitors (SSRIs)	OR	Exposure	1	Selection bias; Information bias (Bias due to outcome and exposure ascertainment)	Detection of bias	By data used: NPCD: Yes PHARMO: Yes	NA
32	Desai, 2019[33]	Cohort study	Healthcare administrative data (Administrative claims database - Optum, Truven)	For 8 drug compounds (alendronate, amlodipine, amlodipine-benazepril, calcitonin salmon, escitalopram, glipizide, quinapril, sertraline)	HR	Exposure	8 (total of 8 analyses in the study, one NC for each analysis)	Confounding bias (Bias due to one's perception of generic drugs)	Detection of bias	Yes (significant association between AG and brand-name initiators for 2 drug compounds among 8 (higher psychiatric	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				E: Use of generic drugs (as opposed to brand name drugs) O: Effectiveness outcome corresponding to each drug compound (fracture, cardiovascular endpoint, cardiovascular endpoint, fracture, psychiatric hospitalization, insulin initiation, cardiovascular endpoint, psychiatric hospitalization) NCE: Use of authorized generics (AG)						hospitalization rates for escitalopram, sertraline))	
33	Dillon, 2019[34]	Cohort study	Healthcare administrative data, Research data (Pharmacy dispensing data, survey for self-reported outcomes)	E: Gaps in antihypertensive medication adherence O: Injurious fall NCE: Gaps in antithrombotic medication adherence	Relative risk	Exposure	1	Confounding bias (Healthy adherer bias)	Detection of bias	No	NA
34	Dormuth, 2009[35]	Cohort study	Healthcare administrative data (Administrative claims database - British Columbia PharmaNet database)	E: Adherence to statin therapy O: Events that were possibly expected to be associated with statin exposure (4 + 1 composite) (refer to study text for entire list) NCO: Accident events (7 +1 composite), screening events (7 + 2 composite), other events for which no possible association with statin exposure was expected (16 +1 composite) (refer to study text for entire list)	HR	Outcome	34	Confounding bias	Detection of bias	Yes	NA
35	Douros, 2018a[36]	Cohort study	EHR (UK Clinical Practice Research Datalink linked to Hospital Episode Statistics (HES) repository).	E: Adding or switching to sulfonylureas O: Increased risk of myocardial infarction, ischemic stroke, cardiovascular death, all-cause mortality, and severe hypoglycemia NCO: Risk of diabetic retinopathy	HR	Outcome	1	Confounding bias	Detection of bias	No	NA
36	Douros, 2018b[37]	Cohort study	EHR (UK Clinical Practice Research Datalink linked to Hospital Episode Statistics (HES) repository).	E: Use of glucagon-like peptide 1 receptor agonists O: Incident diabetic retinopathy NCE: Current use of dipeptidyl peptidase-4 inhibitor (DPP-4)	HR	Exposure	1	NR	Detection of bias	No	NA
37	Duke, 2017[38]	Cohort study	Healthcare administrative data, EHR (EMRs from Columbia University Medical Center/New York-Presbyterian Hospital, IMS Ambulatory EMR, IMS French EMR, Stanford Clinical Data Warehouse, and University of Texas	E: Levetiracetam use O: Angioedema risk NCO: 100 negative control outcomes not related to the primary exposure (refer to study text for entire list)	HR	Outcome	100	Any residual bias	Detection of bias, Calibration of p-value	Yes	The study used Schuemie's empirical *p*-value calibration method.[39]

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
			Cerner Health Facts Database. Claims datasets from OptumIn-sight's Clinformatics Datamart, IMS Pharmetrics Plus, Truven MarketScan Commercial Claims and Encounters (CCAE), Truven MarketScan Multistate Medicaid (MDCD), and Truven MarketScan Medicare Supplemental Beneficiaries (MDCR))								
38	DuMouchel, 2013[40]	Pharmacovigilance method (Disproportionality analysis)	Healthcare administrative data, EHR, Simulated datasets (MarketScan Lab Supplemental, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database, OSIM datasets)	PCE: Positive controls (refer to study text for entire list) O: Acute liver failure, acute myocardial infarction, acute renal failure, upper GI bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Bias (Relative risk), Coverage probability	Exposure-Outcome pair	234	NR	Evaluation of methods	Yes	NA
39	Etminan 2017[41]	Nested case-control study	Healthcare administrative data (Administrative claims database - LifeLink (IMS, Danbury, CT) health claims databases)	E: Use of macrolide antibiotics (erythromycin, azithromycin, clarithromycin, and telithromycin) O: Sensorineural hearing loss (SNHL) NCE: Use of albuterol	Rate ratio	Exposure	1	Confounding bias	Detection of bias	No	NA
40	Farhat 2020[42]	Nested case-control study	EHR (Cerner Health Facts® database)	E: Combined clopidogrel–proton pump inhibitor (PPI) treatment O: Primary outcome - recurrent MI; Secondary outcome - stroke, all-cause mortality, and the composite outcome (stroke, MI, and all-cause mortality) NCE: Combined use of PPI and prasugrel or ticagrelor, combined use of H2 receptor antagonists (H2RA) and clopidogrel	OR	Exposure	3	Confounding bias (Confounding by indication)	Detection of bias	No	NA
41	Gagne 2014a[43]	Cohort study	Healthcare administrative data (Administrative claims database - Medicare)	E: Generic/Brand name statin initiation O: Adherence to statin therapy and a composite outcome comprising hospitalization for an acute coronary syndrome or stroke and all-cause mortality NCO: Cancer	HR, Absolute rate differences	Outcome	1	Confounding bias, Information bias (differential surveillance)	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
42	Gagne, 2014b[44]	Cohort study	Healthcare administrative data (Administrative claims database - Medicare)	Uncertain combinations: 2 Drug-comparator-outcome combination with unknown association (refer to study text for entire list) PC: 5 drug-comparator-outcome combinations with known associations (refer to study text for entire list) NC: 2 drug-comparator-outcome combinations without suspected associations (refer to study text for entire list)	HR, number of drug-outcome combinations that generated alerts based on a maximized sequential probability ratio test (max SPRT)	Exposure-Outcome pair	2	NR	Evaluation of methods	No	NA
43	Gandhi, 2017[45]	Cohort study	Healthcare administrative data, Healthcare utilization data, Vital records (9 linked databases: Ontario Registered Persons Database, Ontario Drug Benefit Program, Canadian Institute for Health Information (CIHI) Discharge Abstract Database, CIHI National Ambulatory Care Reporting System database, Ontario Mental Health Reporting System database, Ontario Health Insurance Plan database, ICES Physician Database, Cerner (a medical laboratory service provider), Gamma-Dynacare Medical Laboratories)	E: Initiation of a second-generation antidepressant drug O: Hospitalization with hyponatremia, hospitalization with both hyponatremia and delirium NCO: Hospitalization with bowel obstruction	Relative risk	Outcome	1	NR	Detection of bias	No	NA
44	Gerhard, 2015[46]	Cohort study	Healthcare administrative data (Administrative claims database - Medicare)	E: Lithium treatment in adults with bipolar disorder O: Risk for dementia NCE: Anticonvulsants commonly used as mood stabilizers	HR	Exposure	1	Confounding bias (Healthy adherer bias)	Detection of bias	No	NA
45	Gidaya, 2014[47]	Case-control study	Vital records, Healthcare administrative data (Danish Civil Registration System (DCRS), Danish National Hospital Register (DNHR), Danish Psychiatric Central Register (DPCR), Danish Drug Prescription Register (DDPR))	E: In utero exposure to selective serotonin reuptake inhibitors (SSRI) O: Risk for autism spectrum disorder NCE: Pre-conception SSRI use	OR	Exposure	1	Confounding bias	Detection of bias	Yes	NA
46	Gokhale, 2016[48]	Cohort study	Healthcare administrative data (Administrative claims database - Medicare)	E: Initiators of angiotensin converting enzyme inhibitors and angiotensin receptor blockers O: Diagnostic evaluations for cough	HR	Outcome	1	Confounding bias	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				NCO: Lung cancer							
47	Gottlieb, 2017[49]	Cohort study	EHR (Explorys database (IBM))	E: Utilization of a second-line drug belonging to any of four classes: sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 agonists O: HbA1c and BMI NCO: Patient height and pretreatment HbA1C	Absolute difference	Outcome	2	Confounding bias	Detection of bias	Yes (pretreatment HbA1c), No (patient height)	NA
48	Greene, 2013[50]	Cohort study	EHR (Vaccine Safety Datalink (VSD))	E: Use of oseltamivir O: Adverse events NCO: Cellulitis, anemia, injury/trauma in prior year	OR, Risk difference	Outcome	3	NR	Detection of bias, Correction for bias	Yes	To reduce bias, history of NCOs was included in the propensity score matching model.
49	Gruber, 2018[51]	Cohort study	Research data (Clinical trials - RV1 (Clinical Trial Number: NCT00241644) and RV5 (Clinical Trial Number: NCT00362648))	E: Vaccine dose timing O: Severe rotavirus gastroenteritis incidence NCE: Placebo arm	Risk difference	Exposure	1	Confounding bias; Administrative censoring	Detection of bias, Correction for bias	Yes	To correct for bias in the estimated risk difference, the effect estimate for the placebo arm was subtracted from the effect estimate for the vaccination arm (for the ratio outcomes, these estimates were divided). A nonparametric bootstrap with 2000 sample draws with replacement was used to obtain the point estimates and empirical 95% CIs.
50	Hamad, 2020[52]	Cohort study	Vital records, Healthcare administrative data, Research data (Manitoba Population Research Data Repository (survey data, utilization, other data linked))	E: Prenatal use of antibiotics O: Attention deficit/hyperactivity disorder in offspring NCE: Maternal use of antibiotics in the year before conception and the year after birth	HR	Exposure	2	Confounding bias	Detection of bias	Yes	NA
51	Han, 2017[53]	Self-controlled case series	Healthcare administrative data (Administrative claims database - Clinformatics Data Mart Database)	E: Concomitant use of a precipitant of interest (vs. not receiving a precipitant) with secretagogues O: Hypoglycemia NCE: Concomitant use of a precipitant of interest with metformin	Rate ratio	Exposure	1	Confounding bias (Confounding by inherent hypoglycemic effects of the precipitants)	Detection of bias, Correction for bias	Yes	The ratio of the semi-Bayes-adjusted rate ratio associated with the exposure to the semi-Bayes-adjusted rate ratio associated with the corresponding NCE was estimated. The delta method was used for 95% CI calibration.[54]
52	Harpaz, 2017[55]	Self-controlled case series	Healthcare administrative data (Administrative claims database - Truven MarketScan)	E: Personal zoster awareness O: Zoster vaccine uptake NCO: Pneumococcal vaccination	Relative incidence	Outcome	1	NR	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
53	Harrison, 2020[56]	Cohort study	EHR (TriNetX)	E: Use of calcium channel blockers (vs. diuretics, renin-angiotensin system agents and beta-blockers) O: Delirium NCO: Benign colonic polyp, Ganglion, Hallux valgus, Hernia, Ingrowing nail, Sebaceous cyst, Senile keratosis, Trigger finger, Otalgia, Onycholysis, Viral warts, Cutaneous abscess	OR	Outcome	12	Confounding bias	Detection of bias	Yes	NA
54	Hauben, 2017[57]	Pharmacovigilance method (Disproportionality analysis)	Passive surveillance data (Data from US FDA Adverse Event Reporting System (FAERS))	PCE: Positive control drugs (refer to study text for entire list) O: Adverse events in the reporting system (refer to study text for entire list) NCE: Negative control drugs (refer to study text for entire list)	Sensitivity, specificity, positive predictive value, negative predictive value, Matthews correlation coefficient, signal-to-noise ratio	Exposure-Outcome pair	67	NR	Evaluation of methods	Yes	NA
55	Hripcsak, 2020[58]	Cohort study	Healthcare administrative data, EHR (MarketScan Commercial Claims and Encounters database (CCAE), Clinformatics Data Mart Database (ie, Optum), Optum deidentified Electronic Health Record Dataset (ie, PanTEHR))	E: Use of chlorthalidone (vs. Hydrochlorothiazide) O: Acute myocardial infarction, hospitalization for heart failure, ischemic or hemorrhagic stroke, and a composite cardiovascular disease outcome including the first 3 outcomes and sudden cardiac death, Fifty-one safety outcomes (refer to study text for entire list) NCO: 76 negative control outcomes (refer to study text for entire list)	HR	Outcome	76	Any residual bias	Detection of bias, Calibration of point estimate and CI	Yes	The study used Schuemie's empirical CI calibration method.[59]
56	Huang, 2019[60]	Cohort study	Healthcare administrative data (Swedish Hospital Discharge Register)	E: Use of phosphodiesterase-5 Inhibitors O: Colorectal Cancer NCO: Accidents	HR	Outcome	1	Confounding bias	Detection of bias	No	NA
57	Imfeld, 2018[61]	Case-control study	EHR (UK Clinical Practice Research Datalink)	E: Proton Pump Inhibitor Use O: Risk of Developing Alzheimer's Disease or Vascular Dementia NCE: Histamine-2 receptor antagonists (H2Ras)	OR	Exposure	1	NR	Detection of bias	No	NA
58	Ing, 2020[62]	Cohort study	Healthcare administrative data (Administrative claims database - Texas and New York Medicaid)	E: Exposure to surgery and anesthesia in early childhood O: Subsequent use of attention deficit hyperactivity disorder medication	HR	Outcome	3	Any residual bias; Confounding bias	Detection of bias	Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				NCO: Use of non-psychotropic medications (amoxicillin, azithromycin, diphenhydramine)							
59	Ivers, 2015[63]	Case-control study	Research data (Prospective cohort study data)	E: Receipt of oral inactivated bivalent whole-cell vaccine O: Acute watery diarrhea with a stool sample positive for cholera NCO: Acute watery diarrhea with a stool sample that tested negative for cholera	Relative risk	Outcome	1	Bias in general	Detection of bias	No	NA
60	Izurieta, 2017[64]	Cohort study	Healthcare administrative data, public health survey data (Administrative claims database – Medicare, Medicare Current Beneficiary Survey)	E: Herpes zoster vaccine O: Incident herpes zoster cases NCO: Hip fracture, Thrombosis, Cholelithiasis and cholecystitis, Renal stone, Wrist fracture, Gout, Epistaxis, Wound of hand or finger, Ingrown nail, Hemorrhoids, Cataract, Lipomas, Eyelid disorder	Vaccine effectiveness (VE) VE (%)= (1 − HR) × 100	Outcome	13	Confounding bias (health-seeking behavior), Selection bias, Information bias (Ascertainment bias)	Detection of bias	No	NA
61	Izurieta, 2018[65]	Cohort study	Healthcare administrative data (Administrative claims database – Medicare)	E: Statin Use O: Risk of influenza-related outcomes (influenza-related office visits & influenza-related hospital visits) NCE: Use of hydrochlorothiazide medications (HCTZs) not combined with another drug in a single pill and use of proton pump inhibitors (PPIs)	Relative risk	Exposure	2	Any residual bias; Confounding bias	Detection of bias	No (HCTZ), Yes (PPI)	NA
62	Izurieta, 2019[66]	Cohort study	Healthcare administrative data, public health survey data (Administrative claims database – Medicare, Medicare Current Beneficiary Survey)	E: Herpes zoster vaccine O: Incident herpes zoster cases NCO: Hip fracture, Thrombosis, Cholelithiasis and cholecystitis, Renal stone, Wrist fracture, Gout, Epistaxis, Wound of hand or finger, Ingrown nail, Hemorrhoids, Cataract, Lipomas, Eyelid disorder	Vaccine effectiveness (VE) VE (%)= (1 − HR) × 100	Outcome	13	Confounding bias (health-seeking behavior), Selection bias, Information bias (Ascertainment bias)	Detection of bias, Evaluation of methods	No	NA
63	Jackson, 2006[67]	Cohort study	Healthcare administrative data (Integrated Health System data - Group Health Cooperative data)	E: Influenza vaccination O: All-cause mortality, Pneumonia or influenza hospitalization, ischemic heart disease hospitalization, Congestive heart failure hospitalization, Cerebrovascular disease hospitalization, Injury or trauma hospitalization during and post influenza season NCO: Outcomes in pre-influenza season	Relative risk	Outcome	6 (1 for each primary outcome)	Confounding bias (Confounding by health status)	Detection of bias	Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
64	Jensen, 2019[68]	Cohort study	Vital records, Healthcare administrative data (National Patient Register, Register of Medicinal Product Statistics, Medical Birth Registry, Danish National Health Service Register (NHSR))	E: Childhood vaccination O: Mortality, hospitalization for infection and asthma NCO: Hospitalizations due to accidents	HR	Outcome	1	Confounding bias	Detection of bias	Yes	NA
65	Johanson, 2012[69]	Ecological study	Healthcare utilization data, public health surveillance data, research data (primary data) (Applicant surveys, Physician survey, National Poison Control Data System, Publicly available surveillance data information related to diversion and abuse (National Forensic Laboratory Information System, Drug Abuse Warning Network(DAWN)), Insurance claims data (IMS Health))	E: Buprenorphine/naloxone O: Diversion (The percentage of applicants who reported knowing that buprenorphine/naloxone was sold on the street) and abuse (the percentage who reported knowing that it was used to get high) NCE: Amitriptyline	Proportion	Exposure	1	Measurement error	Detection of bias, Correction for bias	Yes	To correct for the point estimate, the following formula was used: Relative abuse of buprenorphine/naloxone = (abuse of buprenorphine or naloxone – abuse of NCE) / (abuse of PCE – abuse of NCE)).
66	Kaiser, 2018[70]	Cohort study	Research data (Cohort study - Cardiovascular Health Study (CHS))	E: Statin use (either prevalent use or new use depending on the design) O: Incident Myocardial Infarction (MI) NCO: Non-Cardiovascular disease (CVD) mortality	HR	Outcome	1	Confounding bias (Healthy user bias; Early adopter bias)	Detection of bias, Evaluation of methods	Yes	N/A (Method evaluation)
67	Kim, 2020 [71]	Cohort study	EHR, Healthcare administrative data (EHR: University of Texas Cerner Health Facts Database, Columbia University Medical Center/NewYork-Presbyterian Hospital, Stanford University Hospital; Administrative claims: OptumInsight's Clinformatics Datamart, Truven MarketScan Commercial Claims and Encounters, Truven MarketScan Multi-State Medicaid, Truven MarketScan Medicare Supplemental Beneficiaries, IQVIA PharMetrics Plus, Korean National Health Insurance Service - National Sample Cohort)	E: Use of alendronate (vs. Raloxifene) O: Hip fracture, vertebral fracture, esophageal cancer, osteonecrosis of the jaw NCO: NCOs identified by data-rich algorithms (refer to study text for entire list)	HR	Outcome	147	Confounding bias, any residual bias	Detection of bias, p-value calibration	Yes	The study used Schuemie's empirical p-value calibration method to construct the empirical null distribution and compare it to the theoretical null distribution to check the presence of bias.[39]
68	Kioumourtzoglou, 2018[72]	Cohort study	Research data (Longitudinal cohort data (Nurses' Health Study II (NHSII) - data from	E: Exposure to diethylstilbestrol in utero for mothers (when mother's mother (1st	OR	Exposure	2	Confounding bias (Confounding by indication)	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
			survey using questionnaires, biospecimens))	generation) was pregnant) in the first trimester O: Attention-deficit/hyperactivity disorder (ADHD) in the child (the 3rd generation) NCE: Exposure to diethylstilbestrol in utero for mothers in the 2nd and 3rd trimester							
69	Kipp, 2019[73]	Cohort study	Research data (TREAT-AF (The Retrospective Evaluation and Assessment of Therapies in AF) cohort)	E: Use of class IC Antiarrhythmic Drugs (AAD) (vs. Use of class III AAD) O: Hospitalization for atrial fibrillation (AF)/atrial flutter (AFL), heart failure, ischemic stroke NCO: Urinary tract infection, pneumonia, and hip fracture	HR	Outcome	3	Confounding bias	Detection of bias	No	NA
70	Kjerpeseth, 2019[74]	Cohort study	Vital records, Healthcare administrative data (Pharmacy dispensing data, Public healthcare database (country level), Norwegian Prescription Database, Norwegian Patient Registry, Norwegian Cause of Death Registry and National Registry)	E: Direct oral anti-coagulants (DOACs, Dabigatran, Rivaroxaban, Apixaban) (vs. warfarin) O: Primary effectiveness outcome - composite of hospitalizations with Ischemic stroke, transient ischemic attack (TIA), systemic embolism or death from ischemic stroke or systemic embolism; Secondary effectiveness outcomes - hospitalization or death from ischemic stroke or systemic embolism; Primary safety outcome - major or clinically relevant non-major bleeding (composite of intracranial bleeding, gastrointestinal bleeding and other bleeding); Secondary safety outcomes - intracranial bleeding, gastrointestinal bleeding and other bleeding NCO: Hospitalization or death from pneumonia	HR	Outcome	1	Confounding bias	Detection of bias	No	NA
71	Kürüm, 2017[75]	Ecological study (Time-series analysis)	Healthcare administrative data (US: Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases (SID) / Brazil: Brazil Unified Health System (Sistema Único de Saúde; SUS) / Chile: Chilean Ministry of Health, Department of Statistics and Health (Departamento de Estadísticas e información de Salud; DEIS))	E: Pneumococcal conjugate vaccines (PCVs) O: Invasive pneumococcal disease and pneumonia NCO: UTI and rotaviral enteritis	Percentage change	Outcome	2	NR	Detection of bias	Yes (UTI- US)	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
72	Lane, 2020[76]	Cohort study	EHR, Healthcare administrative data	E: Initiation of hydroxychloroquine (vs. initiation of sulfasalazine) O: 16 severe adverse events (gastrointestinal bleeding, acute renal failure, acute pancreatitis, myocardial infarction, stroke, transient ischaemic attack, cardiovascular events (composite), angina or chest pain, heart failure, cardiac arrhythmia, bradycardia, venous thromboembolism, end-stage renal disease, and hepatic failure, all-cause mortality, cardiovascular mortality) NCO: 67 conditions identified by a semi-autonomous method (refer to study text for entire list)	HR	Outcome	67	Systematic error; Confounding bias	Detection of bias, Calibration of point estimate and CI	Yes	The study used Schuemie's empirical CI calibration method.[39,29]
73	Lavikainen, 2016[77]	Cohort study	Vital records, Healthcare administrative data (The Finnish Prescription Register, The Special Reimbursement Register, The Finnish Care Register, Statistics Finland)	E: High adherence to statin therapy (vs. low adherence) O: Composite of an acute cardiovascular event defined as a hospitalization for an acute coronary syndrome (ACS) or an acute ischemic stroke NCO: Low-energy fracture	HR	Outcome	1	Confounding bias	Detection of bias	Yes	NA
74	Lazarus, 2016[78]	Cohort study	ARIC cohort: Research data (Longitudinal cohort data and registry- Atherosclerosis Risk in Communities - which collects data from clinical examinations, telephone surveys, local hospital discharge data, Vital records and other publicly available data) Replication cohort: Healthcare administrative data and EHR linked with disease registry (Geisinger Health System data; United States Renal Data System registry)	E: Use of proton pump inhibitors (PPI) O: Chronic kidney disease (CKD) NCE: Use of H2 receptor antagonist	HR	Exposure	1	Residual bias	Detection of bias	No	NA
75	Leonard, 2017[79]	Self-controlled case series	Healthcare administrative data (Administrative claims database - United States Medicaid programs of California, Florida, New York, Ohio, and Pennsylvania)	E: Discontinuation of the antihyperlipidemic drug (one of atorvastatin, cerivastatin, fenofibrate, fluvastatin, gemfibrozil, lovastatin, pitavastatin, rosuvastatin, and simvastatin) initially defining concomitancy in the presence of warfarin O: Composite of hospitalization for venous thromboembolism or ischemic stroke	IRR	Exposure	1	Confounding bias (Confounding by inherent effects on the outcome of the precipitants)	Detection of bias, Correction for bias	Yes	To correct for the point estimate and 95% CI, ratio of IRR for the exposure vs. IRR for the NCE was calculated.

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				NCE: Discontinuation of pravastatin in the presence of warfarin							
76	Leonard, 2019[80]	Self-controlled case series	Healthcare administrative data (Optum Clinformatics Data Mart)	E: Concomitantly use of clopidogrel and a precipitant drug of interest O: Gastrointestinal bleeding or intracranial hemorrhage NCE: Concomitantly use of pravastatin and a precipitant drug of interest	Rate ratio	Exposure	1	Confounding bias (Confounding by inherent effects on the outcome of the precipitants)	Detection of bias, Correction for bias	Yes	The ratio of the semi-Bayes-adjusted rate ratio associated with the exposure to the semi-Bayes-adjusted rate ratio associated with the corresponding NCE was estimated. The delta method was used for 95% CI calibration.[54]
77	Leung, 2011[81]	Cohort study	Healthcare administrative data (Administrative claims database -MarketScan databases)	E: Introduction of the varicella vaccination program in 1995 O: Herpes Zoster incidence NCO: Cerumen, acute pharyngitis, kidney/ureter calculus, urinary tract infection not otherwise specified, cellulitis of the leg, ingrowing nail, lipoma, wrist/hand sprain, blepharitis, and unilateral inguinal hernia	Incidence	Outcome	10	Confounding bias (Secular changes in health care access, health seeking behavior, the composition of the enrolled population, or the databases themselves)	Detection of bias	No	NA
78	Levine, 2018[82]	Case-control study	Healthcare administrative data (Family Relations Register, Diagnostic Classification Register, Prescription Register from Meuhedet health care organization)	E: Prenatal use of folic acid (vitamin B9), multivitamin supplements, or any combinations of folic acid and multivitamin supplement O: Autism spectrum disorder (ASD) in offspring NCE: Pre-pregnancy (2 years before pregnancy) use of folic acid (vitamin B9), multivitamin supplements (Anatomical Therapeutic Chemical A11 codes vitamins A, B, C, and D), or any combinations of folic acid and multivitamin supplement	Relative risk	Exposure	1	Confounding bias	Detection of bias	Yes	NA
79	Liew, 2019[83]	Cohort study	Research data (Longitudinal cohort data - Nurses' Health Study II (NHSII) - data from questionnaires, biospecimens)	E: Acetaminophen Exposure during pregnancy O: Attention-Deficit/Hyperactivity Disorder in children NCE: Maternal acetaminophen use before and after pregnancy	OR	Exposure	2	Confounding bias (Confounding by time-invariant factors)	Detection of bias	No	NA
80	Lin, 2018 [84]	Cohort study	Healthcare administrative data (Longitudinal Health Insurance Database, subsets of NHIRD (National Health Insurance Research Database))	E: Post-stroke statin use (vs. pre-stroke use) O: Poststroke epilepsy (PSE) NCE: Use of oral proton pump inhibitors (PPIs) NCO: Acute gastroenteritis	HR	Exposure and Outcome	1 exposure and 1 outcome	NR	Detection of bias	No	NA

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81	Lip, 2017 [85]	Cohort study	Healthcare administrative data, Vital records data (Danish National Patient Registry, Danish National Prescription Registry, Danish Civil Registration System)	E: Nonvitamin K Antagonist Oral Anticoagulants (NCOACs, apixaban, dabigatran, rivaroxaban) (vs. warfarin) O: Ischemic stroke/systemic embolism, death, and bleeding NCO: Pneumonia, hip fractures, cancer, urinary tract infection	HR	Outcome	4	Confounding bias	Detection of bias	Yes	NA
82	Liu, 2020[86]	Self-controlled risk interval study	Healthcare administrative data (Taiwan National Immunization Information System (NIIS) linked with Taiwan National Health Insurance (NHI) system data)	E: Varicella vaccine O: Pneumonia, ITP, meningitis, encephalitis, and ischemia stroke NCO: Fracture	IRR	Outcome	1	NR	Detection of bias	No	NA
83	Madigan, 2013a[87]	Multiple designs (New user cohort, Self-controlled case series)	EHR, Healthcare administrative data (General Electric Healthcare, Truven Health Analytics, Inc., Humana, Inc., Partners HealthCare, Regenstrief Institute, Indiana Network for Patient Care, Regenstrief Institute, Indiana Network for Patient Care, SDI Health, LLC, Department of Veterans Affairs)	PCE: Positive control drugs (in relation to outcomes) (refer to study text for entire list) O: Angioedema, Aplastic anemia, Bleeding, Hip fracture, Hospitalization, Liver failure (acute), Mortality after myocardial infarction, Myocardial infarction (acute), Renal failure (acute), Upper gastrointestinal ulcer (requiring hospitalization) NCE: Negative control drugs in relation to outcomes) (refer to study text for entire list)	Relative risk	Exposure-Outcome pair	44	Any residual bias	Detection of bias	Yes	NA
84	Madigan, 2013b [88]	Case-control study	Healthcare administrative data, EHR, Simulated datasets (MarketScan Lab Supplemental, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database, OSIM datasets)	PCE: Positive controls (refer to study text for entire list) O: Acute liver injury, acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Bias (Odds ratio), Coverage probability	Exposure-Outcome pair	234	NA	Evaluation of methods	Yes	NA
85	Man, 2020[89]	Self-controlled case series	EHR (Clinical Data Analysis and Reporting System (CDARS))	E: Use of methylphenidate O: Incident seizure NCO: Skin infection	IRR	Outcome	1	Confounding bias	Detection of bias	No	NA
86	Marbac, 2016[90]	Multiple designs (Disproportionality-based methods, Lasso-based logistic regressions, Model-based	Passive surveillance data (French pharmacovigilance data)	PCE: Positive control drugs (in relation to outcomes) (refer to study text for entire list) O: Acute myocardial infarction (AMI), Acute kidney injury (AKI), Acute liver injury (ALI), Upper gastro-intestinal bleeding (GIB)	Measure of performance: Number of signals (NS), Rate of positive controls (RPC), Rate of negative controls (RNC),	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	NR	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
		logistic regressions)		NCE: Negative control drugs in relation to outcomes) (refer to study text for entire list)	Rate of unknown signals (RUS)						
87	Markovic, 2019[91]	Cohort study	Research data (Longitudinal cohort data - Generation R study (data from physical examinations, questionnaires, biospecimens))	E: Maternal exposure to NSAIDS during pregnancy O: Neurodevelopmental outcomes (attention problem score) in children NCE: Maternal NSAIDs use before pregnancy NCO: Somatic complaints in children	Mean difference	Exposure and Outcome	1 Exposure and 1 Outcome	Confounding bias	Detection of bias	No	NA
88	Matthews, 2016[92]	Cohort study	EHR (UK Clinical Practice Research Datalink)	E: Phosphodiesterase Type 5 Inhibitors O: Malignant Melanoma NCO: Basal cell carcinoma, colorectal cancer, and solar keratosis	HR	Outcome	3	Confounding bias	Detection of bias	Yes (Basal cell carcinoma and solar keratosis)	NA
89	McGrath, 2015[93]	Cohort study	Disease registry linked with Healthcare administrative data (United States end-stage renal disease program)	E: Influenza vaccine O: All-cause mortality NCO: Outcome measured in pre-influenza vaccine period	HR	Outcome	1	Confounding bias (Healthy user bias)	Detection of bias, Evaluation of methods	Yes (under certain restrictions)	NA
90	McGrath 2020[94]	Cohort study	Healthcare administrative data (Administrative claims data - MarketScan Commercial and Supplemental claims)	E: Initiation of an oral bisphosphonate (BP) (risedronate, alendronate, or ibandronate), denosumab (an injected biologic), or intravenous zoledronic acid (ZA) O/NCO: decubitus ulcer, dementia diagnosis, transfusion, accident, wellness visit, Mohs surgery, visual test, influenza vaccine, herpes zoster vaccine, pelvic screening, and colon cancer screening	Risk difference	Outcome	11	Confounding bias	Detection of bias	Yes (certain comparisons)	NA
91	Moon, 2020[95]	Cohort study	Healthcare administrative data (Administrative claims database - IQVIA Pharmetrics (Durham, NC) database)	E: Opioid prescription O: Hepatic encephalopathy NCE: Use of statins and levothyroxine	HR	Exposure	2	Confounding bias (Healthy user bias or confounding by selective prescribing)	Detection of bias	No	NA
92	Morales, 2019a[96]	Nested-case control study	EHR (Health Improvement Network database, a large primary care population database)	E: Use of fluoroquinolone O: Peripheral neuropathy NCE: Use of oral amoxicillin-clavulanate exposure	Incidence rate ratio	Exposure	1	Confounding bias (Confounding by indication or by severity)	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
93	Morales, 2019b[97]	Nested-case control study	EHR (Health Improvement Network database, a large primary care population database)	E: Use of fluoroquinolone O: Tendon rupture NCE: Use of oral amoxicillin-clavulanate exposure	Incidence rate ratio	Exposure	1	Confounding bias (Confounding by indication or by severity)	Detection of bias	No	NA
94	Morales, 2020[98]	Nested-case control study	EHR (Health Improvement Network database)	E: Ever use of HCTZ (Hydrochlorothiazide) O: Squamous cell carcinoma (SCC), basal cell carcinoma (BCC), melanoma, lip cancer NCO: Oral cavity cancer	Incidence rate ratio	Outcome	1	Confounding bias	Detection of bias	No	NA
95	Morales, 2021[99]	Cohort study	EHR, Healthcare administrative data (Columbia University Irving Medical Center (New York, NY, USA) data warehouse (CUIMC), Information Systems for Research in Primary Care (SIDIAP) database, and US Department of Veterans Affairs OMOP (VA-OMOP) database)	E: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) (vs. calcium channel blockers (CCBs) and thiazide or thiazide-like diuretics (THZs)) O: COVID-19 diagnosis; hospital admission with COVID-19; hospital admission with pneumonia; and hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis NCO: Up to 123 possible controls (refer to study text for entire list)	HR	Outcome	123	Confounding bias	Detection of bias, Calibration of p-value and CI	Yes	The study used Schuemie's empirical CI and p-value calibration method.[39 39]
96	Moran, 2019[100]	Cohort study	Healthcare administrative data (Administrative claims databases - Optum Clinformatics and IBM MarketScan)	E: Use of methylphenidate and amphetamine O: Psychosis NCO: Emergency department visits or inpatient hospitalizations for alcohol use disorder, all other substance use disorders combined, cannabis use disorders, opioid use disorders, and major depressive disorder without psychotic features at 100 days of follow-up	HR	Outcome	5	Confounding bias	Detection of bias	No	NA
97	Moulis, 2014[101]	Disproportionality design	Passive surveillance data (Spontaneous reporting database: French pharmacovigilance database (FPVD))	PCE: Isoniazid E: Monoclonal antibodies and soluble receptor O: Tumor necrosis factor inhibitor-induced lupus or lupus-like syndrome NCE: Acetaminophen	Reporting odds ratio	Exposure	1	Information bias (Event-related, drug related competition biases)	Detection of bias	NR-but results seem to indicate, Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
98	Muanda, 2019[102]	Cohort study	Healthcare administrative data (province-wide)	E: Prescription for oral baclofen greater than or equal to 20mg per day (vs. less than 20mg per day) O: Hospitalization with encephalopathy NCE: The index date defined to be 90 days before the baclofen start date NCO: Hospitalization with heart failure	Risk ratio, risk difference	Exposure and Outcome	1 Exposure and 1 Outcome	NR	Detection of bias	No	NA
99	Nishtala, 2017[103]	Prescription sequence symmetry analysis	Healthcare administrative data (Pharmacy dispensing data - NZ pharmaceutical collections)	PCE-O pair: Use of positive control outcome drugs in response to adverse events from an exposure drugs (6 E-PCO pairs) (refer to study text for entire list) NCE-O: Use of negative control outcome drugs in response to adverse events from an exposure drugs (6 E-NCO pairs) (refer to study text for entire list)	Sequence ratio (SR)	Exposure-Outcome pair	6	NA	Evaluation of methods	Yes	NA
100	Norén, 2013[104]	Self-controlled cohort study	Healthcare administrative data, EHR (MarketScan Lab Supplemental, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database)	PCE: Positive controls (refer to study text for entire list) O: Acute liver injury, acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), bias (relative rate) and coverage probability	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	Yes	NA
101	O'Grady, 2020[105]	Case-control study	Healthcare administrative data and EHR (a prospectively maintained database containing all adult patients aged 20 years or over assessed at the Christchurch Hospital, and drug utilization data from the Pharmaceutical Management Agency of New Zealand)	E: Use of statins O: Diverticulitis NCE: Use of selective serotonin reuptake inhibitors (SSRIs) PCE: Use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs)	Relative risk	Exposure-outcome pair	1	NR	Detection of bias	Yes	NA
102	Osokogu, 2015	Reference set identification	NA	NA	NA	Exposure-outcome pair	Reference set identification	NA	NA	NA	NA
103	Osokogu, 2016[106]	Disproportionality design	Passive surveillance data (Data from US FDA Adverse Event Reporting System (FAERS))	PC: Positive drug-event combinations (DECs) (refer to study text for entire list) NC: Negative drug-event combinations (DECs) (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC)	Exposure-outcome pair	90	NR	Evaluation of methods	Yes	

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
104	Ospina-Romero, 2020[107]	Cohort study	Research data (Longitudinal panel data (US Health and Retirement Study (HRS) - data from questionnaire)	E: Cancer diagnosis O: Long term memory NCO: Spouse's memory	Rate	Outcome	1	Confounding bias	Detection of bias	No	
105	Ou, 2015[108]	Cohort study	Healthcare administrative data (National Health Insurance Research Database)	E: Dipeptidyl peptidase-4 (DPP-4) inhibitor use (vs. sulfonylurea use as a control group) O: All-cause mortality, risk of cardiovascular events (ischemic stroke, myocardial infarction, etc.) NCO: Cancer	HR	Outcome	1	Confounding bias	Detection of bias	No	NA
106	Ou, 2017 [109]	Cohort study	Healthcare administrative data (National Health Insurance Research Database)	E: Dipeptidyl peptidase-4 (DPP-4) inhibitor use (vs. DPP-4 non-user as a control group) O: All-cause mortality, risk of cardiovascular events (ischemic stroke, myocardial infarction, etc.) NCO: Cancer	HR	Outcome	1	Confounding bias	Detection of bias	No	NA
107	Pan, 2020 [110]	Cohort study	Healthcare administrative data (National Health Insurance Research Database)	E: Statin use (vs. non-user as a control group) O: Tuberculosis and herpes zoster infections NCO: Pyogenic liver abscess	HR	Outcome	1	NR	Detection of bias	No	NA
108	Paul, 2020[111]	Cohort study	EHR	E: Immune checkpoint inhibitors (ICIs) O: Engraftment, GVHD incidence, non-relapse mortality, progression-free survival (PFS), and overall survival (OS) NCE: Brentuximab vedotin (BV)	OR	Exposure	1	NR	Detection of bias	No	NA
109	Pierce, 2017[112]	Other design	Social media data	PC: 6 drug outcome pairs recently identified as safety signals (refer to study text for entire list) NC: 6 drug-outcome pairs with no suspected causal association (refer to study text for entire list)	Number of drug-outcome associations appeared in the social media data	Exposure-Outcome pair	6	NR	Evaluation of methods	NA	NA
110	Pottegård, 2018[113]	Case-crossover study	Healthcare administrative data (Register of Legally Induced Abortions, Medical Birth Registry, Danish National Prescription Registry, and Danish Patient Registry)	E: Use of dicloxacillin at the time of conception O: Unintended pregnancy NCE: Use of phenoxymethyl penicillin, amoxicillin and macrolides (antibiotic drugs with no suspected CYP-inducing potential)	OR	Exposure	3	NR	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
111	Pratt, 2015[114]	Prescription sequence symmetry analysis	Healthcare administrative data, EHR (Australian Government Department of Veterans' Affairs healthcare claims database, Korea Health Insurance Review and Assessment Service database, National Health Insurance Research Database, Clinical Data Analysis and Reporting System)	E: Amiodarone PCO: Use of thyroxine (Positive control outcome) NCO: Use of allopurinol (Negative control outcome)	Sequence ratio (SR)	Outcome	1	NR	Evaluation of methods	No	NA
112	Quinn, 2017[115]	Self-controlled case series	Healthcare administrative data (Administrative claims database)	E: Use of stimulant medications O: Substance-related events NCE: Use of selective serotonin reuptake inhibitor (SSRIs)	OR	Exposure	1	NR	Detection of bias	No	NA
113	Rai, 2017[116]	Cohort study	Healthcare administrative data, research data (Stockholm youth cohort)	E: Antidepressant use during pregnancy in mothers O: Autism spectrum disorders in offspring NCE: Antidepressant use in fathers during the mothers' pregnancy	OR	Exposure	1	NR	Detection of bias	No	NA
114	Ray, 2019 [117]	Case-control study	EHR	E: Inactive influenza vaccine O: Positive test result for any influenza NCO: Positive test result for respiratory syncytial virus (RSV)	OR	Outcome	1	Confounding bias	Detection of bias	No	NA
115	Raymakers, 2020[118]	Cohort study	Healthcare administrative data (province-wide) (Administrative data from Medical Services Paln (MSP) data file, Discharge Abstract Database (DAD), PharmaNet datafile, BC Cancer Registry file)	E: Statin use O: Lung cancer diagnosis NCE: Calcium channel blockers (CB) use	HR	Exposure	1	Residual bias; Confounding bias	Detection of bias	No	NA
116	Reich, 2013a[119]	Multiple designs (new user cohort design (CM), case control design (CC), the self-controlled case series (SCCS), a self-controlled cohort design (SCC), temporal pattern discovery (ICTPD), a disproportionality analysis (DP) and a longitudinal	Healthcare administrative data, EHR (MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database)	PCE: Positive controls (refer to study text for entire list) O: Acute liver failure, acute myocardial infarction, acute renal failure, upper GI bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Bias (Relative risk), Minimal Detectable Relative Risk (MDRR)	Exposure-Outcome pair	Varies depending on outcome and its definition	Residual bias, Information bias (misclassification)	Evaluation of methods	Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
		gamma Poisson shrinker (LGPS))									
117	Reich, 2013b[120]	Multiple designs (new user cohort design (CM), case control design (CC), the self-controlled case series (SCCS), a self-controlled cohort design (SCC), temporal pattern discovery (ICTPD), a disproportionality analysis (DP) and a longitudinal gamma Poisson shrinker (LGPS))	Healthcare administrative data (MarketScan Lab Supplement, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters)	PCE: Positive controls (refer to study text for entire list) O: Acute liver failure, acute myocardial infarction, acute renal failure, upper GI bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Minimal Detectable Relative Risk (MDRR)	Exposure-Outcome pair	Varies depending on outcome and its definition	NA	Evaluation of methods	Yes	NA
118	Ridenhour, 2013[121]	Cohort study	Healthcare administrative data (province-wide) (Administrative data from public health insurance plan of Ontario)	E: Influenza vaccination O: Influenza-associated mortality, deaths occurring 30 days after an influenza-associated pneumonia/influenza hospitalization, influenza-associated pneumonia/influenza hospitalizations NCO: Hospitalizations for urinary tract infection	Vaccine effectiveness (VE)	Outcome	1	NR	Detection of bias	No	NA
119	Rodgers, 2020[122]	Cohort study	EHR (Clinical Practice Research Datalink (CPRD))	E: Use of thiazolidinediones (TZDs) (vs. sulfonylureas (SUs)) O: Edema, weight gain NCO: Outcomes measured in the prior period (period before exposure), Gastrointestinal side effects	HR	Outcome	1 outcome, 1 Negative control period	Confounding bias	Detection of bias, Point estimate and CI calibration	Yes	To correct for bias, the ratio of the HR for the post period vs. the HR of the prior period was calculated. They verified the removal of bias by replicating the same bias correction method for the NCO (ratio of the HRs for the post vs. prior periods for the NCO). The standard error for the estimates was obtained by bootstrapping.
120	Rodríguez, 2020[123]	Cohort study	Research data (Prospective cohort data - Odense Bisphosphonate Safety Study (OBSS))	E: Use of oral bisphosphonates O: Hospitalization for cardiovascular (CV) events (composite and specific CV events) NCO: Inguinal hernia and ingrown toenail	HR	Outcome	2	Confounding bias	Detection of bias	No	NA
121	Roshanov, 2017[124]	Cohort study	Research data (Prospective cohort study data)	E: Use of Angiotensin-converting-enzyme inhibitors (ACEI)/ Angiotensin II receptor blocker (ARB) 24 hours before surgery	RR	Outcome	1	Confounding bias	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				O: 30-day composite outcome of all-cause death, myocardial injury after noncardiac surgery (MINS), and stroke NCO: Intraoperative blood transfusion and significant bleeding within 30 days that require transfusion of blood products or reoperation							
122	Ryan, 2012[125]	Multiple designs (Incident user design, Case-control surveillance, Case-crossover, Observational screening, High-dimensional propensity score, Self-controlled case series, Temporal pattern discovery, Disproportionality analysis)	Healthcare administrative data and EHR (GE Centricity Electronic Health Record, MarketScan Research Databases from Thomson Reuters, Humana Inc., Partners HealthCare System, Regenstrief Institute/Indiana Network for Patient Care, SDI Health (IMS Health Inc.), National Patient Care Database/Veterans Health Administration)	PCE: Positive controls (refer to study text for entire list) O: Angioedema, Aplastic anemia, Acute liver injury, Bleeding, Myocardial infarction (MI), Mortality after MI, Renal failure, Hip fracture, Upper gastrointestinal ulcer NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Partial area under ROC curve at 30% false positive rate (PAUC30), Average precision (AP), Recall at 5% false positive (RECALL5), Sensitivity, Specificity, Positive predictive value, Bias (relative risk)	Exposure-Outcome pair	44	Residual bias	Evaluation of methods	Yes	NA
123	Ryan, 2013a[126]	Cohort study	Healthcare administrative data, EHR, Simulated datasets (MarketScan Lab Supplemental, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database, OSIM datasets)	PCE: Positive controls (refer to study text for entire list) O: Acute liver injury, acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Bias (Relative risk), Coverage probability	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	Yes	NA
124	Ryan, 2013b[127]	Self-Controlled Cohort study	Healthcare administrative data, EHR, Simulated datasets (MarketScan Lab Supplemental, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database, OSIM datasets)	PCE: Positive controls (refer to study text for entire list) O: Acute liver injury, acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Bias (Relative risk), Coverage probability	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
125	Ryan, 2013c[128]	Reference set identification	NA	NA	NA	NA	NA	NA	NA	NA	NA
126	Ryan, 2013d[129]	Multiple designs (new user cohort design (CM), case control design (CC), the self-controlled case series (SCCS), a self-controlled cohort design (SCC), temporal pattern discovery (ICTPD), a disproportionality analysis (DP) and a longitudinal gamma Poisson shrinker (LGPS))	Healthcare administrative data, EHR (MarketScan Lab Supplemental, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database)	PCE: Positive controls (refer to study text for entire list) O: Acute liver injury, acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), bias (relative risk) and coverage probability	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	Yes	NA
127	Ryan, 2013e[130]	Multiple designs (new user cohort design (CM), case control design (CC), the self-controlled case series (SCCS), a self-controlled cohort design (SCC), temporal pattern discovery (ICTPD), a disproportionality analysis (DP) and a longitudinal gamma Poisson shrinker (LGPS))	Simulated datasets	PCE: Positive controls (refer to study text for entire list) O: Acute liver injury, acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Bias (Relative risk) and coverage probability	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	Yes	NA
128	Sarvet, 2018[131]	Cross-sectional study	Public health survey data (National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Wave 2)	E: Presence of a state-level medical marijuana law (MML) O: Prevalence of self-medication with drugs NCO: Prevalence of self-medication with alcohol	Prevalence difference	Outcome	1	NR	Detection of bias	No	NA
129	Schuemie, 2012[132]	Multiple designs (SRS Methods: Proportional reporting ratio (PRR), Reporting odds ratio (ROR), Gamma poisson shrinker (GPS),	Healthcare administrative data, EHR, Healthcare administrative data (Aarhus - Denmark, Health Search - Italy, IPCI - Netherlands, Pedianet - Italy, ARS - Italy, PHARMO - Netherlands)	PCE: Drug-event associations that are well recognized (known associations) (refer to study text for entire list) O: 10 select outcomes (bullous eruptions (BE), acute renal failure (ARF), anaphylactic shock (AS), acute myocardial infarction (AMI), rhabdomyolysis (RHABD),	Measure of performance: Area under the receiver operating curve (AUC)	Exposure-Outcome pair	50	Residual bias	Evaluation of methods	Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
		also, Bayesian confidence propagation neural network (BCPNN)); Cohort methods (Incidence rate ratio (IRR), Longitudinal gamma poisson shrinker (LGPS), Bayesian hierarchical model (BHM)); Case-based Methods (Matched case control (CC), Self-controlled case series (SCCS)); Longitudinal evaluation of observational profiles of adverse events related to drugs (LEOPARD)		pancytopenia (PANCYTOP), neutropenia (NCEUTROP), cardiac valve fibrosis (CARDFIB), acute liver injury (ALI), and upper gastrointestinal bleeding (UGIB)) NCE: Negative control drug-event pairs (refer to study text for entire list)							
130	Schuemie, 2013a[133]	Multiple designs (self-controlled case series (SCCS), case-control (CC) and case-population (CP) design variants)	Healthcare administrative data, EHR, Healthcare administrative data (Aarhus - Denmark, Health Search - Italy, IPCI - Netherlands, Pedianet - Italy, ARS - Italy, PHARMO - Netherlands)	PCE: Positive controls (refer to study text for entire list) O: Acute liver failure, acute myocardial infarction, acute renal failure, upper GI bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Bias (relative risk)	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	Yes	NA
131	Schuemie 2013b[134]	Longitudinal Gamma Poisson Shrinker (LGPS) and Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs (LEOPARD) methods	Healthcare administrative data, EHR, Simulated datasets (MarketScan Lab Supplemental, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database, OSIM datasets)	PCE: Positive controls (refer to study text for entire list) O: Acute liver injury, acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), Bias (Incidence rate ratio), Coverage probability	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	Yes	NA
132	Schuemie, 2014[39]	Multiple designs (Example 1: Cohort design; Example 2: Case-control study; Example 3: Self-	Example 1: Healthcare administrative data (Administrative claims - Thomson MarketScan Medicare Supplemental Beneficiaries database)	Example 1: E: Use of isoniazid O: Acute liver injury	OR	Exposure	Example 1: 37 Example 2 and 3: 67	Any residual bias (most forms of bias, including residual confounding, misclassification, selection bias)	Detection of bias, p-value calibration	Example 1: No Example 2: Yes Example 3: Yes	This study developed a methodology for calibrating the p-value of the effect estimate when a set of negative controls were used to account for bias. The method first derived an empirical null distribution from the observed effect estimates for the

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
		controlled case series)	Example 2 and 3: EHR (General Electric (GE) Centricity database)	NCE: Drugs not related to the outcome (refer to study text for entire list) Example 2 and 3: E: Use of selective serotonin reuptake inhibitors (SSRIs) O: Upper GI bleeding NCE: Drugs not related to the outcome (refer to study text for entire list)							negative controls, then generated calibrated p-values assuming Gaussian distribution to the estimates and taking into account the sampling error of each estimate. We refer to this method 'Schuemie's empirical p-value calibration method' throughout.
133	Schuemie, 2018a[39]	Multiple designs (Southworth replication: Cohort study; Graham replication: Cohort study; Tata case-control replication: Case-control study; Tata SCCS replication: Self-controlled case series)	Southworth replication: Healthcare administrative data (Administrative claims database - OptumInsight's deidentified Clinformatics Datamart (Optum)) Graham replication: Healthcare administrative data (Administrative claims database - Truven MarketScan Medicare Supplementary Beneficiaries database) Tata case-control replication, Tata SCCS replication: EHR (Clinical Practice Research Datalink (CPRD) database)	Southworth replication: E: Use of dabigatran (vs. warfarin) O: GI hemorrhage NCE: Drugs not related to the outcome (refer to study text for entire list) Graham replication: Patients aged 65 or older initiating oral anticoagulant therapy E: Use of dabigatran (vs. warfarin) O: GI hemorrhage NCE: Drugs not related to the outcome (refer to study text for entire list) Tata case-control replication: E: Use of selective serotonin reuptake inhibitors (SSRIs) O: Upper GI bleeding NCE: Drugs not related to the outcome (refer to study text for entire list) Tata SCCS replication E: Use of selective serotonin reuptake inhibitors (SSRIs) O: Upper GI bleeding	Southworth replication: IRR Graham replication: HR Tata case-control replication: OR Tata SCCS replication: IRR	Exposure	50 for each replication	Any residual bias	Detection of bias, point estimate and CI calibration	Yes	This study developed a methodology for empirical calibration of 95% CI of the effect estimate when a set of negative controls were used in observational studies. The calibration procedure first estimated the distribution of systematic error using the observed estimates for negative and positive controls, then generated calibrated 95% CIs considering both random and systematic error and assuming Gaussian distribution with a mean and log standard deviation linearly related to the true effect size. We refer to this method 'Schuemie's empirical CI calibration method' throughout.

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				NCE: Drugs not related to the outcome (refer to study text for entire list)							
134	Schuemie, 2018b[135]	Cohort study	Healthcare administrative data (Truven MarketScan Commercial Claims and Encounters (CCAE), Truven MarketScan Medicare Supplemental Beneficiaries (MDCR), Truven MarketScan Multi-state Medicaid (MDCD), OptumInsight's de-identified Clinformatics™ Datamart (Optum))	E: Use of duloxetine (vs. sertraline) O: Stroke NCO: 52 outcomes not related to antidepressants (refer to study text for entire list)	HR	Outcome	52	Any residual bias	Detection of bias, point estimate and CI calibration	Yes	The study used Schuemie's empirical CI calibration method.[39]
135	Schuemie, 2019[136]	Case-control study	Healthcare administrative data (IBM® MarketScan® Commercial Claims and Encounters Database (CCAE))	Crockett study replication: E: Use of isotretinoin O: Ulcerative colitis (UC) NCE: Drugs not related to the outcome (refer to study text for entire list) Chou study replication: E: Use of dipeptidyl peptidase-4 (DPP-4) inhibitors O: Acute pancreatitis NCE: Drugs not related to the outcome (refer to study text for entire list)	OR	Exposure	Crockett study replication: 33 Chou study replication: 78	Any residual bias	Detection of bias, p-value calibration	Crockett study replication: Yes Chou study replication: Yes	The study used Schuemie's empirical p-value calibration method.[39]
136	Shao, 2019[137]	Cohort study	EHR (Chang Gung Research Database (CGRD))	E: Use of Dapagliflozin (vs. empagliflozin) O: Cardiovascular events (primary outcome: the composite event of cardiovascular mortality, myocardial infarction, ischemic stroke and heart failure in the diagnosis of hospitalization and outpatient data /secondary outcome: individual events of the CV outcomes in the composite measure) NCO: Incident atrial fibrillation	HR	Outcome	1	NR	Detection of bias	No	NA
137	Shi, 2020[138]	Cohort study	Healthcare administrative data (Integrated Health System data - Kaiser Permanente Washington)	E: DTaP-IPV-Hib vaccine (vs. DTaP containing comparator vaccine) O: Fever NCO: Injury or trauma	Relative risk	Exposure and Outcome	1 exposure, 1 outcome	Confounding bias	Detection of bias, Point estimate and CI calibration	No	The study develops a methodology for correcting for categorical unmeasured confounding. The methodology uses a NCE and a NCO to build a semiparametric model and propose multiply robust estimator for the average treatment effect. The study demonstrated the application of

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				NCE: Ringworm							their method in a pharmacoepidemiologic vaccine safety study and showed that the multiply robust estimator provided a smaller bias and protected against the model misspecification.
138	Shoag, 2019[139]	Cohort study	Public health survey data (National Health and Nutrition Examination Survey (NHANES))	E: Kidney stone history O: Current use of opioid NCO: Current use of benzodiazepines and antihyperlipidemic agents	OR	Outcome	2	NR	Detection of bias	No	NA
139	Simonov, 2020[140]	Cohort study	Research data (Prospective cohort study data (Women's Veterans Cohort Study cohort)	E: Use of proton pump inhibitors (PPIs) O: Nephrolithiasis NCE: Use of levothyroxine	HR	Exposure	1	NR	Detection of bias	No	NA
140	Simonsen, 2014[141]	Ecological study	Healthcare administrative data (IMS Charge Data Master hospital database)	E: Introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) O: Number of pneumococcus-related admissions to hospital NCO: Number of urinary tract infection-related admissions to hospital	Rate reduction	Outcome	1	NR	Detection of bias	No	NA
141	Sinnott, 2019[142]	Cohort study	EHR (Clinical Practice Research Datalink)	E: Fourth-line anti-hypertensive drugs (aldosterone, antagonist, beta-blocker, or alpha-blocker; compared to one another for comparative effectiveness) O: Cardiovascular events (composite of all-cause mortality, stroke, and myocardial infarction as a primary outcome, and each outcome separately for secondary outcomes) NCO: Herpes zoster	HR	Outcome	1	NR	Detection of bias	Yes	NA
142	Sköldberg, 2016[143]	Case-control study	Healthcare administrative data, Vital records (National Patient Register, Prescribed Drug Register, Swedish Register of Total Population, Swedish Cancer Register, Causes of Death Register, National Education Register)	E: Statin use (former and current use) O: First-time diagnosis of diverticular disease of the colon NCE: Anti-glaucoma preparations and miotics, vitamin B12	OR	Exposure	2	NR	Detection of bias	No	NA
143	Sørup, 2016[144]	Cohort study	Healthcare administrative data, Vital records (Danish Civil Registration System, Danish National Health	E: Simultaneous administration of MMR and DTaP-IPV-Hib vaccines (vs. MMR vaccine alone)	IRR	Outcome	1	NR	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
			Service Register, Danish National Patient Register)	O: Infectious disease admissions NCO: Emergency room visits due to unintentional accidents							
144	Spoendlin, 2018[145]	Cohort study	Healthcare administrative data (Administrative claims database)	E: Prasugrel vs clopidogrel, ticagrelor vs clopidogrel, and prasugrel vs ticagrelor O: (1) Composite effectiveness endpoint including myocardial infarction, ischemic stroke, or inpatient mortality; (2) Composite safety endpoint including major bleeding events requiring hospitalization NCE: Pneumonia hospitalization	HR	Outcome	1	NR	Detection of bias	No	NA
145	Stolfo, 2020[146]	Cohort study	Healthcare administrative data, Disease registry (Swedish Heart Failure Registry, National Patient Registry)	E: Beta-blocker use O: 5-year all-cause mortality, 5-year composite of cardiovascular (CV) mortality, first HF hospitalization NCO: Hospitalization for cancer	HR	Outcome	1	NR	Detection of bias	No	NA
146	Suchard, 2013[147]	Self-controlled case series	Healthcare administrative data, EHR (MarketScan Lab Supplemental, MarketScan Medicare Supplemental Beneficiaries, MarketScan Multi-State Medicaid, MarketScan Commercial Claims and Encounters, General Electric Centricit database)	PCE: Positive controls (refer to study text for entire list) O: Acute liver injury, acute myocardial infarction, acute renal failure, upper gastrointestinal bleeding NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC), bias (relative risk) and coverage probability	Exposure-Outcome pair	234	Residual bias	Evaluation of methods	Yes	NA
147	Sundbakk, 2019[148]	Cohort study	Research data (Prospective cohort study data - MoBa study)	E: Use of benzodiazepine and z-hypnotics during pregnancy O: Externalizing and internalizing behaviors of the child at age of 5 NCE: Use of benzodiazepine and z-hypnotics before pregnancy	Risk ratio	Exposure	1	Confounding bias	Detection of bias	No	NA
148	Symes, 2015[149]	Cohort study	Healthcare administrative data (Administrative claims database - LifeLink)	E: Use of bupropion, topiramate O: Incident angle-closure glaucoma (ACG) NCO: Use of esomeprazole	Rate ratio	Exposure	1	NR	Detection of bias	No	NA
149	Tate, 2009[150]	Cohort study	Healthcare administrative data (Vaccine Safety Datalink (VSD))	E: Receipt of Rotashield vaccine O: Hospitalizations and emergency department (ED) Visits for All-Cause Acute Gastroenteritis	Vaccine effectiveness (VE)	Exposure and outcome	1 exposure and 1 outcome	Confounding bias (Confounding by health-seeking behavior, socioeconomic status)	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				NCE: Acute gastroenteritis hospitalizations and ED visits that occurred during the non-rotavirus season NCO: Hospitalizations and ED visits for acute respiratory illness	VE(%)=(1-risk ratio)*100						
150	Thomsen, 2020[151]	Multiple designs (Cohort study, Self-controlled case-series (SCCS))	Healthcare administrative data (Danish Civil Registration System, Danish National Health Service Register, which includes data on primary-care services, Danish National Patient Registry, Psychiatric Central Research Register, Danish National Prescription Registry, socioeconomic registries maintained by Statistics Denmark)	E: Human papilloma virus (HPV) vaccination O: Pain, fatigue, circulatory symptoms NCO: Trauma, diabetes mellitus, cancer, pneumonia, asthma, appendicitis, all-cause death	IRR	Outcome	7	NR	Detection of bias	No	NA
151	Thorrington, 2018[152]	Ecological study	Healthcare administrative data (Hospital admission data - Hospital Episodes Statistics (HES))	E: 24-month pre-pneumococcal conjugate vaccine (PCV) period O: Hospital-diagnosed pneumonia, sepsis, and otitis media NCO: Urinary tract infections, infections of the skin and subcutaneous tissue, disorders of the thyroid gland, diseases of the blood, and fractures	IRR	Outcome	5	Confounding bias (Biases arising from a potential secular trend)	Detection of bias, Point estimate and CI calibration	Yes	For each outcome of interest: The age-specific ratio of the IRR for the outcome of interest vs. the geometric mean of the IRR for the NCOs was calculated. The minimum and maximum incidence rate ratio across all NCOs were used to represent uncertainty.
152	Thurin, 2020[153]	Multiple designs (Self-controlled case series (SCCS), Case-control (CC), Case-population (CP) design variants)	Healthcare administrative data (French National Healthcare System database (SNDS))	PCE: Positive controls (refer to study text for entire list) O: Upper gastrointestinal bleeding (UGIB) NCE: Negative controls (refer to study text for entire list)	Measure of performance: Area under the receiver operating curve (AUC)	Exposure	42	Residual bias	Evaluation of methods	Yes	NA
153	Tielemans, 2017[154]	Cohort study	Healthcare administrative data (Præventis, a national immunization register; National medical register)	E: Measles, mumps, and rubella (MMR) + meningococcal C (MenC) as the most recent vaccination (vs. diphtheria, tetanus, pertussis, polio, and Haemophilus influenzae type b (DTaP-IPV-Hib) + pneumococcal vaccination (PCV) as the most recent vaccination) O: Hospital Admissions for infection NCO: Hospital admission for injuries or poisoning (composite)	HR	Outcome	1	Confounding bias	Detection of bias	Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
154	Tien, 2020[155]	Cohort study	Research data (Prospective cohort study)	E: Chlorhexidine (CHG) bathing (vs. usual care (bathing over-the-counter non–CHG-based antibacterial soap or cleansing lotion)) O: Gram-positive cocci–related, skin flora–related, or central line–associated bloodstream infection NCO: Gut-origin bacteremia	HR	Outcome	1	Confounding bias; Selection bias (Participation bias)	Detection of bias	No	NA
155	Totterdell, 2020[156]	Self-controlled case series	EHR (MedicineInsight data)	E: Receiving ZVL, 23vPPV or influenza vaccine (all three vaccines analyzed jointly and also separately analyzed compared to those who did not receive the vaccine) O: Injection site reaction, myocardial infarction (MI), stroke, clinical attendance NCO: Burn	Relative incidence (RI)	Outcome	1	NR	Detection of bias	No	NA
156	Toulis, 2017[157]	Cohort study	EHR (Health Improvement Network(THIN) database)	E: New use of dapagliflozin (vs. non-use) O: Primary outcome - all-cause mortality; secondary outcomes - CVD outcomes (myocardial infarction and ischemic heart disease, stroke or TIA, and heart failure or left ventricular dysfunction) NCE: Use of dipeptidyl peptidase-4 inhibitor	Incidence rate ratio	Exposure	1	Residual bias	Detection of bias	No	NA
157	Trinh, 2019[158]	Sequential statistical testing	Passive surveillance data (Base Nationale de Pharmacovigilance (BNPV), EudraVigilance (EV))	PC: 62 drug-comparator-outcome combinations with known associations from the OMOP reference set (refer to study text for entire list) NC: 128 drug-comparator-outcome combinations without suspected associations from the OMOP reference set (refer to study text for entire list)	Number of drug-outcome pairs satisfying the change point analysis (CPA) hypothesis	Exposure-Outcome pair	128	NR	Evaluation of methods	Yes	NA
158	Trønnes, 2019[159]	Cohort study	Research data (Prospective cohort data - Norwegian Mother and Child Cohort Study (MoBa))	E: Prenatal paracetamol use O: Neurodevelopment outcomes of the child at age 5 (communication skills, child's behavior, temperament) NCE: Paracetamol use prior to pregnancy	Relative risk, regression coefficient	Exposure	1	Confounding bias	Detection of bias	Yes	NA
159	Tseng, 2011[160]	Cohort study	Healthcare administrative data (Integrated Health System data - Kaiser Permanente Southern California)	E: Herpes zoster vaccine O: Risk of herpes zoster NCO: Hip fracture, Thrombosis, Gout, Cholelithiasis and cholecystitis, Wrist fracture, Renal stone, Epistaxis, Lipomas,	HR	Outcome	13	Confounding bias (Confounding by underlying risk for herpes zoster, ability and desire to access care for herpes zoster)	Detection of bias	Yes	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
				Eyelid disorders, Cataracts, Ingrown nail, Wound of hand or finger, Hemorrhoids							
160	Tsujimoto, 2019[161]	Cohort study	Research data (Clinical trial - Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist trial)	E: Nitrate use O: A major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) or heart failure hospitalization NCO: Hyperkalemia	HR	Outcome	1	NR	Detection of bias	No	NA
161	van Rein, 2014[162]	Case-control study	Research data (Data used in "factors in oral anticoagulation safety (FACTORS)" case-control study)	E: Use of statins O: Major bleedings during treatment with vitamin K antagonists NCE: Blood group non-O	OR	Exposure	1	Selection bias (Survivor bias)	Detection of bias	No	NA
162	Vonesh, 2018[163]	Cohort study	Healthcare administrative data linked with EHR (Optum claims database were integrated with Humedica primary care EHR data)	E: Initiation of mirabegron (vs. antimuscarinics) O: Cardiovascular risk profiles at baseline NCO: Shingles, Hepatitis C, Community-acquired pneumonia (CAP)	OR	Outcome	3	Residual bias	Detection of bias	No	NA
163	Voss, 2017[164]	Reference set identification	NA	NA	NA	Exposure-Outcome pair	NA	NA	NA	NA	NA
164	Vouri, 2019[165]	Prescription sequence symmetry analysis	Healthcare administrative data (MarketScan Commercial and Medicare Supplemental Claims databases (IBM Corp))	E: Initiation of dihydropyridine calcium channel blockers (DH CCBs) O: Initiation of a loop diuretic before or after the initial DH CCB claim NCE: Initiation of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), levothyroxine, tiotropium, nonbenzodiazepine hypnotics	Sequence ratio	Exposure	4	Confounding bias (Influence of natural disease progression that may warrant the use of a loop diuretic for hypertension control)	Detection of bias	Yes	NA
165	Walsh, 2019[166]	Cohort study	Healthcare administrative data (province-wide), Vital records (Better Outcomes Registry & Network (BORN), Ontario birth registry, health administrative databases)	E: Receipt of the monovalent 2009 pH1N1 influenza vaccine during pregnancy O: Immune related (infectious diseases, asthma), non-immune related (neoplasms, sensory disorders), and non-specific morbidity outcomes (urgent or inpatient health services use, pediatric complex chronic conditions), under-5 childhood mortality NCO: All-cause injuries	HR	Outcome	1	NR	Detection of bias	Yes	NA
166	Wei, 2019[167]	Cohort study	Healthcare administrative data (Longitudinal Cohort of Diabetes Patients data, a	E: Concomitant use of clopidogrel with repaglinide	OR	Exposure	2	NR	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
			subset of NHIRD (National Health Insurance program in Taiwan))	O: Hypoglycemia NCE: Concomitant use of aspirin with repaglinide / Concomitant use of clopidogrel and nateglinide							
167	Weinstein, 2016[168]	Ecological study	Healthcare administrative data (Truven MarketScan® Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MDCR) databases)	E: Cold/influenza season O: Acute liver injury (ALI) NCO: Breast cancer, diabetes mellitus	Ratio of peak-to-low occurrence rates	Outcome	2	NR	Detection of bias	No	NA
168	Weinstein, 2017[169]	Cohort study	EHR (Clinical Practice Research Datalink (CPRD) database)	E: Use of any paracetamol (alone or combination with ibuprofen) (vs. use of ibuprofen alone) O: Gastrointestinal (GI) bleeding, Myocardial Infarction (MI), ischemic or hemorrhagic stroke, or acute or chronic renal disease NCO: 31 conditions not related to the primary exposure (refer to study text for entire list)	OR	Outcome	31	Confounding bias (Channeling bias)	Detection of bias, Evaluation of methods	Model 1, 2, 3, 4: Yes Model 5,6: No	NA
169	Weinstein, 2020[170]	Cohort study	EHR (Clinical Practice Research Datalink (CPRD) database)	E: Use of any paracetamol (vs. use of ibuprofen) O: Gastrointestinal (GI) bleeding, Myocardial Infarction (MI), ischemic or hemorrhagic stroke, or acute or chronic renal disease NCO: 39 conditions not related to the primary exposure (refer to study text for entire list)	HR	Outcome	39	Confounding bias (Channeling bias)	Detection of bias, p-value calibration, Point estimate and CI calibration	Yes	The study used Schuemie's empirical CI and p-value calibration method.[39,59]
170	Welk, 2020[171]	Cohort study	Healthcare administrative data, Vital records (Canadian Institute for Health Information Discharge Abstract Database and Same Day Surgery, Ontario Mental Health Reporting System, and National Ambulatory Care Reporting System, Ontario Health Insurance Plan, Registered Persons Database, Ontario Cancer Registry)	E: Filling an opioid prescription within 5 days of the index urologic surgery O: New persistent opioid use (two prescriptions filled between 9 and 15 months after the index surgery) NCO: Shingles and cancer	OR	Outcome	2	Confounding bias	Detection of bias	No	NA
171	Whitlock, 2020[172]	Cohort study	Healthcare administrative data (Canadian Institute for Health Information Hospital Discharge Abstracts, Diagnostic Services of	E: Initiation of monotherapy with metformin (vs. sulfonylurea)	HR	Outcome	3	Confounding bias	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
			Manitoba, Drug Program Information Network, Emergency Admission, Discharge, and Transfer Emergency Department Information System, Manitoba Health Insurance Registry, Medical Claims/Services databases)	O: All-cause mortality, cardiovascular events, and major hypoglycemic episodes NCO: Cataract surgery, gastrointestinal bleeding, major osteoporotic fractures							
172	Xian, 2019[173]	Cohort study	Disease registry, Healthcare administrative data (Get With The Guidelines–Stroke (GWTG-Stroke) clinical registry, Medicare claims)	E: Direct oral anticoagulants (DOACs) (vs. warfarin) O: Primary outcomes - Home time, major adverse cardiovascular events (MACE, a composite measure of all-cause mortality, cardiovascular, or cerebrovascular readmission); Secondary outcomes - all-cause mortality, fatal bleeding (readmission for bleeding with in-hospital mortality), all-cause readmission, cardiovascular readmission, ischemic stroke readmission, systemic embolism readmission, hemorrhagic stroke readmission, gastrointestinal bleeding, and any bleeding requiring hospitalization NCO: Hospital readmission with pneumonia or readmission with sepsis	HR	Outcome	2	Selection bias	Detection of bias	No	NA
173	Xie, 2019[174]	Cohort study	Healthcare administrative data (Department of Veterans Affairs databases)	E: Intention to treat with Proton pump inhibitors (PPIs) (prescription of more than 90-day supply of PPI in the 180-day period since the first prescription) (vs. Intention to treat with H2 blockers) O: All-cause mortality, cause-specific mortality (circulatory system diseases; neoplasms; respiratory system diseases; external causes; endocrine, nutritional, and metabolism diseases; nervous system diseases; digestive system diseases; mental and behavioral disorders; genitourinary system diseases; infectious and parasitic diseases; and other causes) NCO: Transportation related death, death due to peptic ulcer disease	Estimated excess burden associated with new use PPI per 1000 people based on estimated cumulative incidence rate probability at 10 years	Outcome	2	Residual bias, Confounding bias (Confounding by indication)	Detection of bias	No	NA
174	Yates, 2017[175]	Cohort study	EHR (United Kingdom Clinical Practice Research Datalink)	E: New use of lansoprazole (vs. new use of omeprazole or pantoprazole) O: Incident tuberculosis NCO: Myocardial infarction (MI) and herpes zoster	HR	Outcome	2	Confounding bias	Detection of bias	No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
175	Yip, 2020[176]	Cohort study	EHR (Clinical Data Analysis and Reporting System (CDARS))	E: Use of tenofovir disoproxil fumarate (TDF) (vs. entecavir) O: Hepatocellular carcinoma (HCC) NCO: Acute myocardial infarction (AMI), lung cancer	Sub-distribution hazard ratio	Outcome	2	Confounding bias	Detection of bias	No	NA
176	You, 2020[177]	Cohort study	Healthcare administrative data (OptumInsight's Clinformatics™ Data Mart, Truven MarketScan Commercial Claims and Encounters, Truven MarketScan Medicare Supplemental Beneficiaries, Truven MarketScan Multi-State Medicaid, National Health Insurance Service-National Sample Cohort from Korea)	E: Angiotensin-converting enzyme (ACE)/angiotensin-receptor blocker (ARB) + calcium channel blocker (CCB) vs. ACEI/ARB + thiazide-type diuretics (TZD) vs. CCB+TZD O: Primary outcomes - all-cause mortality. Myocardial infarction, heart failure, stroke; Secondary outcomes - major adverse cardiac and cerebrovascular events as a composite outcome N: Thirty-nine outcomes identified through a data-rich algorithm (refer to study text for entire list)	HR	Outcome	39	Any residual bias	Detection of bias, p-value calibration	Yes	The study used Schuemie's empirical p-value calibration method.[39]
177	Ystrom, 2017[178]	Cohort study	Research data, Vital records (Prospective cohort data - Norwegian Mother and Child Cohort Study (MoBa), Medical Birth Registry of Norway)	E: Maternal use of acetaminophen during pregnancy O: Attention-deficit/hyperactivity disorder NCE: Use of acetaminophen pre-pregnancy	HR	Exposure	1	Confounding bias	Detection of bias	No	NA
178	Yuan, 2018[179]	Cohort study	Healthcare administrative data (Administrative claims database - Truven MarketScan)	E: Sodium glucose co-transporter 2 inhibitors (overall), and canagliflozin (specifically) (vs. non-sodium glucose co-transporter 2 inhibitor antihyperglycemic agents) O: Below-knee lower extremity amputation NCO: NR	Incidence rate, HR	Outcome	NR	Confounding bias	Detection of bias, p-value calibration	Yes	The study used Schuemie's empirical p-value calibration method.[39]
179	Yuan, 2020[180]	Cohort study	Research data (Prospective cohort study data - Nurses' Health Study, Nurses' Health Study II)	E: Regular use of proton pump inhibitor O: Incidence rheumatoid arthritis NCE: Regular use of H2 receptor antagonist NCO: Basal cell skin cancer, squamous cell skin cancer, cervical cancer	HR	Exposure and Outcome	1 exposure and 3 outcomes	NCE (H2 receptor blocker): Protopathic bias and imbalance in the underlying diseases for acid suppressant use NCOs: Confounding bias	Detection of bias	NCE (H2 receptor blocker): No NCOs: Squamous cell skin cancer: No Basal cell skin cancer: No Cervical cancer: No	NA

No	First Author, Year (Reference No.)	Study Design	Type of Data	Hypothesized Causal Association (E: Exposure; O: Outcome; NC: Negative control; PC: Positive control)	Primary Study Effect Measure	Type of negative control	Number of Negative Controls	Type of Bias as Reported by Study	Utility Domain of Negative Control Use	Presence of Bias as Concluded from Study Based on Negative Control Analysis	Methods Used to Correct for Effect of Bias (in point estimate, confidence interval, p-value) (NA: not applicable)
180	Zhang, 2017[181]	Cohort study	Healthcare administrative data (Administrative claims database - Medicare data)	E: Receipt of seasonal influenza vaccination O: All-cause mortality during the influenza season NCO: All-cause mortality prior to the influenza season	HR	Outcome	1	Residual bias; Confounding bias	Detection of bias	Yes	NA
181	Zhang, 2019[182]	Cohort study	Healthcare administrative data (Administrative claims database - Medicare data)	E: Receipt of seasonal influenza vaccination O: All-cause mortality during the influenza season NCO: All-cause mortality prior to the influenza season	HR	Outcome	1	Residual bias; Confounding bias	Detection of bias	Yes	NA
183	Zhou, M., 2020[183]	Self-controlled case series	Healthcare administrative data (Administrative claims database - Optum Clinformatics Data Mart)	E: Concomitant use of a precipitant of interest (vs. not receiving a precipitant) with anticoagulants O: Thromboembolism (a composite outcome of stroke and venous thromboembolism) NCE: Concomitant use of a precipitant of interest with pravastatin	Rate ratio	Exposure	1	Confounding bias (Confounding by inherent effect of the precipitant on the primary outcome)	Detection of bias, Point estimate and CI calibration	Yes	The ratio of the semi-Bayes-adjusted rate ratio associated with the exposure to the semi-Bayes-adjusted rate ratio associated with the corresponding NCE was estimated. The delta method was used for 95% CI calibration.
182	Zhou, Z., 2020[184]	Cohort study	Research data (Clinical trial data - ASPREE (Aspirin in Reducing Events in Elderly) trial)	E: Use of statin at baseline O: Primary outcome - disability-free survival; secondary outcomes - death, dementia, persistent physical disability, major adverse cardiovascular events (MACE), fatal cardiovascular disease (CVD), myocardial infarction (MI), and stroke NCO: Cancer	HR	Outcome	1	Confounding bias	Detection of bias	No	NA
184	Zullo, 2019[185]	Cohort study	Healthcare administrative data (Administrative claims database - Medicare data linked to Minimum Data Set (MDS) version 2.0 and Online Survey Certification and Reporting System (OSCAR) data)	E: Initiation of Bisphosphonate (vs. no use) O: Hospitalized hip fracture, non-vertebral fracture, and esophagitis NCO: Hospitalized heart failure	HR	Outcome	1	Confounding bias	Detection of bias	No	NA

Web Table 2. Details of the Reference Sets Proposed to Systematically Rule Out a Causal Effect for Negative Controls or Confirm the Presence of an Effect for Positive Controls

Reference set	Details
The EU-ADR reference set[28]	The EU-ADR reference set was developed as part of the EU-ADR project, which aimed to develop integrated system for early signal detection using large electronic health record data from European countries. Ten health outcomes that were considered as of importance for pharmacovigilance was selected (i.e., liver disorder, acute myocardial infarction, renal failure acute, anaphylactic shock, erythema multiform, mitral valve disease, neutropenia, aplastic anemia, rhabdomyolysis, and gastrointestinal hemorrhage). The set was constructed based on negative controls and positive controls selected and classified based on the following algorithm: 1) information from published literature and drug product labels were used to identify a drug-outcome association (a tool developed within the EU-ADR project that automatically searches MEDLINE-indexed publications concerning adverse drug reactions). If more than 3 sources of data previously reported on the association, it was categorized as a positive association, 2) pool of potential 'negative controls' was further evaluated by review of a spontaneous reporting system to exclude associations flagged as a potential signal (using the WHO spontaneous reporting database (VigiBase™)), and 3) manual verification of the positive associations and negative controls was conducted by expert physicians with proficiency in clinical medicine, epidemiology and pharmacovigilance. The proposed set included 94 drug-event associations including 44 positive control and 50 negative control associations for the 10 health outcomes.
The OMOP reference set[128,186]	The OMOP reference set was developed to be used for evaluating performance of methods for identifying drug safety signals as part of the initiative to evaluate the methods across different healthcare databases of the network. The set was constructed based on a classification algorithm determining causality of an drug-outcome pair, which uses following 3 criteria: 1) a negative control pair should not be listed in the FDA structured product labeling to have any relationship, 2) the candidate drug should not be mentioned as a causative agent for the outcome of interest in the systematic literature review by Tisdale et al. in the book 'Drug-Induced Diseases: Prevention, Detection, and Management'[187], and 3) manual search of the prior literature should not show any effects for the

	pair. The proposed set included 165 positive control and 234 negative control drug-outcome associations.
The OHDSI automatic approach with application of the LAERTES data[164]	The OHDSI automatic approach automatically combines existing sources of evidence (spontaneous reports, scientific literature, both American and European product labeling) and implements into a system named the LAERTES. The authors used evidence aggregated in LAERTES and developed prediction models for adverse event signals using information collected from the data sources as variables. Validation of the models was conducted using the existing reference sets (OMOP and EU-ADR).
The GRiP pediatric-specific reference set[11]	The GRiP pediatric-specific reference set consists of 37 positive control and 90 negative control drug-outcome pairs identified for detecting signals for potential ADRs and validating pharmacovigilance methods in the pediatric population. The candidate drugs and ADRs for the reference set were identified in the literature reporting drugs commonly used in the pediatric population around the world. The causal association of each drug-outcome combination was assessed against 1) information from drug labels (SPC) and Micromedex, and 2) published literature searched on Embase and Medline for classification into one of three categories: positive control, negative control, or unclassified.
The GRiP pediatric-specific vaccine reference set	Extending the work of the GRiP pediatric-specific reference set, the GRiP pediatric-specific vaccine reference set was created for vaccine safety surveillance in the pediatric population. The candidate vaccines that are routinely used and commonly reported ADRs in the population were identified from the literature, and each unique vaccine-outcome combination was assessed against 1) information from drug labels and Micromedex, 2) evidence from Medline literature search, and 3) expert committee reports. The candidate pairs were classified into one of three categories: positive control, negative control, or unclassified. The final proposed reference set consisted of 18 positive control and 113 negative control vaccine-outcome pairs.

EU-ADR indicates the Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical Knowledge project; WHO, World Health Organization; OMOP, Observational Medical Outcomes Partnership; FDA, Food and Drug Administration; LAERTES, Largescale Adverse Effect Related to Treatment Evidence Standardization; GRiP, Global Research in Pediatrics–Network of Excellence; ADR, adverse drug reaction; SPC, summary of product characteristics.

References

1. Shi X, Miao W, Tchetgen Tchetgen E. A Selective Review of Negative Control Methods in Epidemiology. *Curr Epidemiol Rep*. 2020;7(4):190-202. doi:10.1007/s40471-020-00243-4

2. Abrahami D, Douros A, Yin H, et al. Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: Population based cohort study. *BMJ Online*. 2018;363. doi:10.1136/bmj.k4880

3. Abrahami D, Douros A, Yin H, et al. Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: Population based cohort study. *BMJ Online*. 2018;360. doi:10.1136/bmj.k872

4. Ajrouche A, De Rycke Y, Dalichampt M, et al. Reduced risk of cancer among low-dose aspirin users: Data from French health care databases. *Pharmacoepidemiol Drug Saf*. 2019;28(9):1258-1266. doi:10.1002/pds.4870

5. Arfè A, Corrao G. Tutorial: Strategies addressing detection bias were reviewed and implemented for investigating the statins-diabetes association. *J Clin Epidemiol*. 2015;68(5):480-488. doi:10.1016/j.jclinepi.2014.12.001

6. Aronson JK, Ferner RE. Analysis of reports of unintended pregnancies associated with the combined use of non-enzyme-inducing antibiotics and hormonal contraceptives. *BMJ Evid-Based Med*. 2021;26(3):112-113. doi:10.1136/bmjebm-2020-111363

7. Backenroth D, Chase H, Friedman C, Wei Y. Using rich data on comorbidities in case-control study design with electronic health record data improves control of confounding in the detection of adverse drug reactions. *PLoS ONE*. 2016;11(10). doi:10.1371/journal.pone.0164304

8. Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain*. 2019;23(5):908-922. doi:10.1002/ejp.1357

9. Bijlsma MJ, Vansteelandt S, Janssen F, Hak E. The effect of adherence to statin therapy on cardiovascular mortality: Quantification of unmeasured bias using falsification end-points. *BMC Public Health*. 2016;16(1). doi:10.1186/s12889-016-2986-0

10. Brassard P, Wu JW, Ernst P, Dell'Aniello S, Smiechowski B, Suissa S. The effect of statins on influenza-like illness morbidity and mortality. *Pharmacoepidemiol Drug Saf*. 2017;26(1):63-70. doi:10.1002/pds.4112

11. Brauchli Pernus Y, Nan C, Verstraeten T, et al. Reference set for performance testing of pediatric vaccine safety signal detection methods and systems. *Vaccine*. 2016;34(51):6626-6633. doi:10.1016/j.vaccine.2015.10.013

12. Brookhart MA, Patrick AR, Dormuth C, 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):348-354. doi:10.1093/aje/kwm070

13. Brookhart MA, Walker AM, Yun L, et al. Characterizing vaccine-associated risks using cubic smoothing splines. *Am J Epidemiol*. 2012;176(10):949-957. doi:10.1093/aje/kws158

14. Brown JS, Kulldorff M, Chan KA, et al. Early detection of adverse drug events within population-based health networks: application of sequential testing methods. *Pharmacoepidemiol Drug Saf*. 2007;16(12):1275-1284. doi:10.1002/pds.1509

15. Brown JS, Kulldorff M, Petronis KR, et al. Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations. *Pharmacoepidemiol Drug Saf*. 2009;18(3):226-234. doi:10.1002/pds.1706

16. Burkard T, Hügle T, Layton JB, et al. Risk of Incident Osteoarthritis of the Hand in Statin Initiators: A Sequential Cohort Study. *Arthritis Care Res*. 2018;70(12):1795-1805. doi:10.1002/acr.23616

17. Busby J, McMenamin Ú, Spence A, Johnston BT, Hughes C, Cardwell CR. Angiotensin receptor blocker use and gastro-oesophageal cancer survival: a population-based cohort study. *Aliment Pharmacol Ther*. 2018;47(2):279-288. doi:10.1111/apt.14388

18. Busby J, Mills K, Zhang SD, Liberante FG, Cardwell CR. Selective serotonin reuptake inhibitor use and breast cancer survival: A population-based cohort study. *Breast Cancer Res*. 2018;20(1). doi:10.1186/s13058-017-0928-0

19. Butler AM, Layton JB, Krueger WS, Kshirsagar AV, McGrath LJ. Assessing Residual Bias in Estimating Influenza Vaccine Effectiveness. *Med Care*. 2019;57(1):73-78. doi:10.1097/MLR.0000000000001018

20. Casula M, Scotti L, Galimberti F, et al. Use of proton pump inhibitors and risk of ischemic events in the general population. *Atherosclerosis*. 2018;277:123-129. doi:10.1016/j.atherosclerosis.2018.08.035

21. Casula M, Olmastroni E, Galimberti F, et al. Association between the cumulative exposure to bisphosphonates and hospitalization for atherosclerotic cardiovascular events: A population-based study. *Atherosclerosis*. 2020;301:1-7. doi:10.1016/j.atherosclerosis.2020.03.021

22. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: A population-based study. *Gut*. 2018;67(1):28-35. doi:10.1136/gutjnl-2017-314605

23. Chien LN, Huang YJ, Shao YHJ, et al. Proton pump inhibitors and risk of periampullary cancers - A nested case-control study. *Int J Cancer*. 2016;138(6):1401-1409. doi:10.1002/ijc.29896

24. Chou YT, Farley JF, Stinchcombe TE, Proctor AE, Lafata JE, Dusetzina SB. The Association Between Medicare Low-Income Subsidy and Anticancer Treatment Uptake in Advanced Lung Cancer. *JNCI J Natl Cancer Inst*. 2020;112(6):637-646. doi:10.1093/jnci/djz183

25. Christiansen CF, Thomsen RW, Schmidt M, Pedersen L, Sørensen HT. Influenza vaccination and 1-year risk of myocardial infarction, stroke, heart failure, pneumonia, and mortality among intensive care unit survivors aged 65 years or older: a nationwide population-based cohort study. *Intensive Care Med*. 2019;45(7):957-967. doi:10.1007/s00134-019-05648-4

26. Cohen JM, Hernández-Díaz S, Bateman BT, et al. Placental Complications Associated With Psychostimulant Use in Pregnancy. *Obstet Gynecol*. 2017;130(6):1192-1201. doi:10.1097/AOG.0000000000002362

27. Cohen JM, Wood ME, Hernández-Díaz S, Ystrom E, Nordeng H. Paternal antidepressant use as a negative control for maternal use: assessing familial confounding on gestational length and anxiety traits in offspring. *Int J Epidemiol*. 2019;48(5):1665-1672. doi:10.1093/ije/dyz170

28. Coloma PM, Avillach P, Salvo F, et al. A Reference Standard for Evaluation of Methods for Drug Safety Signal Detection Using Electronic Healthcare Record Databases. *Drug Saf*. 2013;36(1):13-23. doi:10.1007/s40264-012-0002-x

29. Danaei G, García Rodríguez LA, Cantero OF, Hernán MA. Statins and risk of diabetes: An analysis of electronic medical records to evaluate possible bias due to differential survival. *Diabetes Care*. 2013;36(5):1236-1240. doi:10.2337/dc12-1756

30. Dave CV, Schneeweiss S, Patorno E. Association of Sodium-Glucose Cotransporter 2 Inhibitor Treatment with Risk of Hospitalization for Fournier Gangrene among Men. *JAMA Intern Med*. 2019;179(11):1587-1590. doi:10.1001/jamainternmed.2019.2813

31. Davies NM, Thomas KH, Taylor AE, et al. How to compare instrumental variable and conventional regression analyses using negative controls and bias plots. *Int J Epidemiol*. 2017;46(6):2067-2077. doi:10.1093/ije/dyx014

32. de Groot MCH, Klungel OH, Leufkens HGM, van Dijk L, Grobbee DE, van de Garde EMW. Sources of heterogeneity in case–control studies on associations between statins, ACE-inhibitors, and proton pump inhibitors and risk of pneumonia. *Eur J Epidemiol*. 2014;29(10):767-775. doi:10.1007/s10654-014-9941-0

33. Desai RJ, Sarpatwari A, Dejene S, et al. Comparative effectiveness of generic and brand-name medication use: A database study of US health insurance claims. *PLoS Med*. 2019;16(3):1-20. doi:10.1371/journal.pmed.1002763

34. Dillon P, Smith SM, Gallagher PJ, Cousins G. Association between gaps in antihypertensive medication adherence and injurious falls in older community-dwelling adults: A prospective cohort study. *BMJ Open*. 2019;9(3). doi:10.1136/bmjopen-2018-022927

35. Dormuth CR, Patrick AR, Shrank WH, et al. Statin Adherence and Risk of Accidents. *Circulation*. 2009;119(15):2051-2057. doi:10.1161/CIRCULATIONAHA.108.824151

36. Douros A, Dell'Aniello S, Yu OHY, Filion KB, Azoulay L, Suissa S. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: Population based cohort study. *BMJ Online*. 2018;362. doi:10.1136/bmj.k2693

37. Douros A, Filion KB, Yin H, et al. Glucagon-like peptide 1 receptor agonists and the risk of incident diabetic retinopathy. *Diabetes Care*. 2018;41(11):2330-2338. doi:10.2337/dc17-2280

38. Duke JD, Ryan PB, Suchard MA, et al. Risk of angioedema associated with levetiracetam compared with phenytoin: Findings of the observational health data sciences and informatics research network. *Epilepsia*. 2017;58(8):e101-e106. doi:10.1111/epi.13828

39. Schuemie MJ, Ryan PB, Dumouchel W, Suchard MA, Madigan D. Interpreting observational studies: why empirical calibration is needed to correct p-values. *Stat Med*. 2014;33(2):209-218. doi:10.1002/sim.5925

40. DuMouchel W, Ryan PB, Schuemie MJ, Madigan D. Evaluation of disproportionality safety signaling applied to healthcare databases. *Drug Saf*. 2013;36 Suppl 1:S123-32. doi:10.1007/s40264-013-0106-y

41. Etminan M, Westerberg BD, Kozak FK, Guo MY, Carleton BC. Risk of sensorineural hearing loss with macrolide antibiotics: A nested case-control study. *Laryngoscope*. 2017;127(1):229-232. doi:10.1002/lary.26190

42. Farhat N, Birkett N, Haddad N, et al. Risk of Adverse Cardiovascular Events Following a Myocardial Infarction in Patients Receiving Combined Clopidogrel and Proton Pump Inhibitor Treatment: A Nested Case–Control Study. *Drugs - Real World Outcomes*. 2020;7(3):191-203. doi:10.1007/s40801-020-00204-9

43. Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: A cohort study. *Ann Intern Med*. 2014;161(6):400-407. doi:10.7326/M13-2942

44. Gagne JJ, Wang SV, Rassen JA, Schneeweiss S. A modular, prospective, semi-automated drug safety monitoring system for use in a distributed data environment. *Pharmacoepidemiol Drug Saf*. 2014;23(6):619-627. doi:10.1002/pds.3616

45. Gandhi S, Shariff SZ, Al-Jaishi A, et al. Second-Generation Antidepressants and Hyponatremia Risk: A Population-Based Cohort Study of Older Adults. *Am J Kidney Dis*. 2017;69(1):87-96. doi:10.1053/j.ajkd.2016.08.020

46. Gerhard T, Devanand DP, Huang C, Crystal S, Olfson M. Lithium treatment and risk for dementia in adults with bipolar disorder: Population-based cohort study. *Br J Psychiatry*. 2015;207(1):46-51. doi:10.1192/bjp.bp.114.154047

47. Gidaya NB, Lee BK, Burstyn I, Yudell M, Mortensen EL, Newschaffer CJ. In utero exposure to selective serotonin reuptake inhibitors and risk for autism spectrum disorder. *J Autism Dev Disord*. 2014;44(10):2558-2567. doi:10.1007/s10803-014-2128-4

48. Gokhale M, Girman C, Chen Y, Pate V, Funk MJ, Stürmer T. Comparison of diagnostic evaluations for cough among initiators of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf*. 2016;25(5):512-520. doi:10.1002/pds.3977

49. Gottlieb A, Yanover C, Cahan A, Goldschmidt Y. Estimating the effects of second-line therapy for type 2 diabetes mellitus: Retrospective cohort study. *BMJ Open Diabetes Res Care*. 2017;5(1). doi:10.1136/bmjdrc-2017-000435

50. Greene SK, Li L, Shay DK, et al. Risk of adverse events following oseltamivir treatment in influenza outpatients, Vaccine Safety Datalink Project, 2007-2010. *Pharmacoepidemiol Drug Saf*. 2013;22(4):335-344. doi:10.1002/pds.3363

51. Gruber JF, Becker-Dreps S, Hudgens MG, Alan Brookhart M, Thomas JC, Funk MJ. Timing of Rotavirus Vaccine Doses and Severe Rotavirus Gastroenteritis Among Vaccinated Infants in Low- and Middle-income Countries. *Epidemiology*. 2018;29(6):867-875. doi:10.1097/EDE.0000000000000909

52. Hamad AF, Alessi-Severini S, Mahmud S, Brownell M, Kuo I fan. Prenatal antibiotic exposure and risk of attention-deficit/hyperactivity disorder: a population-based cohort study. *CMAJ Can Med Assoc J*. 2020;192(20):E527-E535. doi:10.1503/cmaj.190883

53. Han X, ChienWei Chiang, Leonard CE, et al. Biomedical Informatics Approaches to Identifying Drug-Drug Interactions: Application to Insulin Secretagogues. *Epidemiology*. 2017;28(3):459-468. doi:10.1097/EDE.0000000000000638

54. Bieler GS, Williams RL. Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics*. 1993;49(3):793-801.

55. Harpaz R, Leung J. When zoster hits close to home: Impact of personal zoster awareness on zoster vaccine uptake in the U.S. *Vaccine*. 2017;35(27):3457-3460. doi:10.1016/j.vaccine.2017.04.072

56. Harrison PJ, Luciano S, Colbourne L. Rates of delirium associated with calcium channel blockers compared to diuretics, renin-angiotensin system agents and beta-blockers: An electronic health records network study. *J Psychopharmacol*. 2020;34(8):848-855. doi:10.1177/0269881120936501

57. Hauben M, Hung E, Wood J, Soitkar A, Reshef D. The impact of database restriction on pharmacovigilance signal detection of selected cancer therapies. *Ther Adv Drug Saf*. 2017;8(5):145-156. doi:10.1177/2042098616685010

58. Hripcsak G, Suchard MA, Shea S, et al. Comparison of Cardiovascular and Safety Outcomes of Chlorthalidone vs Hydrochlorothiazide to Treat Hypertension. *JAMA Intern Med*. 2020;180(4):542-551. doi:10.1001/jamainternmed.2019.7454

59. Schuemie MJ, Hripcsak G, Ryan PB, Madigan D, Suchard MA. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proc Natl Acad Sci U A*. 2018;115(11):2571-2577. doi:10.1073/pnas.1708282114

60. Huang W, Sundquist J, Sundquist K, Ji J. Use of Phosphodiesterase 5 Inhibitors Is Associated With Lower Risk of Colorectal Cancer in Men With Benign Colorectal Neoplasms. *Gastroenterology*. 2019;157(3):672-681.e4. doi:10.1053/j.gastro.2019.05.012

61. Imfeld P, Bodmer M, Jick SS, Meier CR. Proton Pump Inhibitor Use and Risk of Developing Alzheimer's Disease or Vascular Dementia: A Case-Control Analysis. *Drug Saf*. 2018;41(12):1387-1396. doi:10.1007/s40264-018-0704-9

62. Ing C, Ma X, Sun M, et al. Exposure to Surgery and Anesthesia in Early Childhood and Subsequent Use of Attention Deficit Hyperactivity Disorder Medications. *Anesth Analg*. 2020;131(3):723-733. doi:10.1213/ANE.0000000000004619

63. Ivers LC, Hilaire IJ, Teng JE, et al. Effectiveness of reactive oral cholera vaccination in rural Haiti: A case-control study and bias-indicator analysis. *Lancet Glob Health*. 2015;3(3):e162-e168. doi:10.1016/S2214-109X(14)70368-7

64. Izurieta HS, Wernecke M, Kelman J, et al. Effectiveness and Duration of Protection Provided by the Live-attenuated Herpes Zoster Vaccine in the Medicare Population Ages 65 Years and Older. *Clin Infect Dis*. 2017;64(6):785-793. doi:10.1093/cid/ciw854

65. Izurieta HS, Chillarige Y, Kelman JA, et al. Statin use and risks of influenza-related outcomes among older adults receiving standard-dose or high-dose influenza vaccines through medicare during 2010-2015. *Clin Infect Dis*. 2018;67(3):378-387. doi:10.1093/cid/ciy100

66. Izurieta HS, Wu X, Lu Y, et al. Zostavax vaccine effectiveness among US elderly using real-world evidence: Addressing unmeasured confounders by using multiple imputation after linking beneficiary surveys with Medicare claims. *Pharmacoepidemiol Drug Saf*. 2019;28(7):993-1001. doi:10.1002/pds.4801

67. 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):337-344. doi:10.1093/ije/dyi274

68. Jensen A, Andersen PK, Stensballe LG. Early childhood vaccination and subsequent mortality or morbidity: Are observational studies hampered by residual confounding? A Danish register-based cohort study. *BMJ Open*. 2019;9(9). doi:10.1136/bmjopen-2019-029794

69. Johanson CE, Arfken CL, di Menza S, Schuster CR. Diversion and abuse of buprenorphine: Findings from national surveys of treatment patients and physicians. *Drug Alcohol Depend*. 2012;120(1-3):190-195.

70. Kaiser P, Arnold AM, Benkeser D, et al. Comparing methods to address bias in observational data: statin use and cardiovascular events in a US cohort. *Int J Epidemiol*. 2018;47(1):246-254. doi:10.1093/ije/dyx179

71. Kim Y, Tian Y, Yang J, et al. Comparative safety and effectiveness of alendronate versus raloxifene in women with osteoporosis. *Sci Rep*. 2020;10(1). doi:10.1038/s41598-020-68037-8

72. Kioumourtzoglou MA, Coull BA, O'Reilly EJ, Ascherio A, Weisskopf MG. Association of exposure to diethylstilbestrol during pregnancy with multigenerational neurodevelopmental deficits. *JAMA Pediatr*. 2018;172(7):670-677. doi:10.1001/jamapediatrics.2018.0727

73. Kipp R, Askari M, Fan J, Field ME, Turakhia MP. Real-World Comparison of Classes IC and III Antiarrhythmic Drugs as an Initial Rhythm Control Strategy in Newly Diagnosed Atrial Fibrillation: From the TREAT-AF Study. *JACC Clin Electrophysiol*. 2019;5(2):231-241. doi:10.1016/j.jacep.2018.08.025

74. Kjerpeseth LJ, Selmer R, Ariansen I, Karlstad Ø, Ellekjær H, Skovlund E. Comparative effectiveness of warfarin, dabigatran, rivaroxaban and apixaban in nonvalvular atrial fibrillation: A nationwide pharmacoepidemiological study. *PLoS ONE*. 2019;14(8). doi:10.1371/journal.pone.0221500

75. Kürüm E, Warren JL, Schuck-Paim C, et al. Bayesian model averaging with change points to assess the impact of vaccination and public health interventions. *Epidemiology*. 2017;28(6):889-897. doi:10.1097/EDE.0000000000000719

76. Lane J, Weaver J, Kostka K, et al. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. *Lancet Rheumatol*. Published online 2020. doi:10.1016/S2665-9913(20)30276-9

77. Lavikainen P, Helin-Salmivaara A, Eerola M, et al. Statin adherence and risk of acute cardiovascular events among women: A cohort study accounting for time-dependent confounding affected by previous adherence. *BMJ Open*. 2016;6(6). doi:10.1136/bmjopen-2016-011306

78. Lazarus B, Yuan Chen, Wilson FP, et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Intern Med*. 2016;176(2):238-246. doi:10.1001/jamainternmed.2015.7193

79. Leonard CE, Brensinger CM, Bilker WB, Kimmel SE, Whitaker HJ, Hennessy S. Thromboembolic and neurologic sequelae of discontinuation of an antihyperlipidemic drug during ongoing warfarin therapy. *Sci Rep*. 2017;7(1):18037. doi:10.1038/s41598-017-18318-6

80. Leonard CE, Zhou M, Brensinger CM, et al. Clopidogrel Drug Interactions and Serious Bleeding: Generating Real-World Evidence via Automated High-Throughput Pharmacoepidemiologic Screening. *Clin Pharmacol Ther*. 2019;106(5):1067-1075. doi:10.1002/cpt.1507

81. Leung J, Harpaz R, Molinari NA, Jumaan A, Zhou F. Herpes zoster incidence among insured persons in the United States, 1993-2006: evaluation of impact of varicella vaccination. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2011;52(3):332-340. doi:10.1093/cid/ciq077

82. Levine SZ, Kodesh A, Viktorin A, et al. Association of maternal use of folic acid and multivitamin supplements in the periods before and during pregnancy with the risk of autism spectrum disorder in offspring. *JAMA Psychiatry*. 2018;75(2):176-184. doi:10.1001/jamapsychiatry.2017.4050

83. Liew Z, Kioumourtzoglou MA, Roberts AL, O'Reilly ÉJ, Ascherio A, Weisskopf MG. Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II. *Am J Epidemiol*. 2019;188(4):768-775. doi:10.1093/aje/kwy288

84. Lin HW, Ho YF, Lin FJ. Statin use associated with lower risk of epilepsy after intracranial haemorrhage: A population-based cohort study. *Br J Clin Pharmacol*. 2018;84(9):1970-1979. doi:10.1111/bcp.13626

85. Lip GYH, Skjoth F, Nielsen PB, Kjældgaard JN, Larsen TB. Effectiveness and safety of standard-dose nonvitamin k antagonist oral anticoagulants andwarfarin among patients with atrial fibrillation with a single stroke risk factor: A nationwide cohort study. *JAMA Cardiol*. 2017;2(8):872-881. doi:10.1001/jamacardio.2017.1883

86. Liu CH, Yeh YC, Huang WT, Chie WC, Chan KA. Assessment of pre-specified adverse events following varicella vaccine: A population-based self-controlled risk interval study. *Vaccine*. 2020;38(11):2495-2502. doi:10.1016/j.vaccine.2020.01.090

87. Madigan D, Ryan PB, Schuemie M, et al. Evaluating the Impact of Database Heterogeneity on Observational Study Results. *Am J Epidemiol*. 2013;178(4):645-651. doi:10.1093/aje/kwt010

88. Madigan D, Schuemie MJ, Ryan PB. Empirical performance of the case-control method: lessons for developing a risk identification and analysis system. *Drug Saf*. 2013;36:73-82. doi:10.1007/s40264-013-0105-z

89. Man KKC, Lau WCY, Coghill D, et al. Association between methylphenidate treatment and risk of seizure: a population-based, self-controlled case-series study. *Lancet Child Adolesc Health*. 2020;4(6):435-443. doi:10.1016/S2352-4642(20)30100-0

90. Marbac M, Tubert-Bitter P, Sedki M. Bayesian model selection in logistic regression for the detection of adverse drug reactions. *Biom J Biom Z*. 2016;58(6):1376-1389. doi:10.1002/bimj.201500098

91. Markovic M, Swanson SA, Stricker BH, et al. Prenatal exposure to non-steroidal anti-inflammatory drugs (NSAIDs) and neurodevelopmental outcomes in children. *Pharmacoepidemiol Drug Saf*. 2019;28(4):452-459. doi:10.1002/pds.4625

92. Matthews A, Langan SM, Douglas IJ, Smeeth L, Bhaskaran K. Phosphodiesterase Type 5 Inhibitors and Risk of Malignant Melanoma: Matched Cohort Study Using Primary Care Data from the UK Clinical Practice Research Datalink. *PLoS Med*. 2016;13(6):1-15. doi:10.1371/journal.pmed.1002037

93. McGrath LJ, Ellis AR, Brookhart MA. Controlling Time-Dependent Confounding by Health Status and Frailty: Restriction Versus Statistical Adjustment. *Am J Epidemiol*. 2015;182(1):17-25. doi:10.1093/aje/kwu485

94. McGrath LJ, Spangler L, Curtis JR, et al. Using negative control outcomes to assess the comparability of treatment groups among women with osteoporosis in the United States. *Pharmacoepidemiol Drug Saf*. 2020;29(8):854-863. doi:10.1002/pds.5037

95. Moon AM, Jiang Y, Rogal SS, Tapper EB, Lieber SR, Barritt AS IV. Opioid prescriptions are associated with hepatic encephalopathy in a national cohort of patients with compensated cirrhosis. *Aliment Pharmacol Ther*. 2020;51(6):652-660. doi:10.1111/apt.15639

96. Morales D, Pacurariu A, Slattery J, Pinheiro L, McGettigan P, Kurz X. Association Between Peripheral Neuropathy and Exposure to Oral Fluoroquinolone or Amoxicillin-Clavulanate Therapy. *JAMA Neurol*. 2019;76(7):827-833. doi:10.1001/jamaneurol.2019.0887

97. Morales DR, Slattery J, Pacurariu A, Pinheiro L, McGettigan P, Kurz X. Relative and Absolute Risk of Tendon Rupture with Fluoroquinolone and Concomitant Fluoroquinolone/Corticosteroid Therapy: Population-Based Nested Case–Control Study. *Clin Drug Investig*. 2019;39(2):205-213. doi:10.1007/s40261-018-0729-y

98. Morales DR, Pacurariu A, Slattery J, Kurz X. Association between hydrochlorothiazide exposure and different incident skin, lip and oral cavity cancers: A series of population-based nested case–control studies. *Br J Clin Pharmacol*. 2020;86(7):1336-1345. doi:10.1111/bcp.14245

99. Morales DR, Conover MM, You SC, et al. Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis. *Lancet Digit Health*. 2021;3(2):e98-e114. doi:10.1016/S2589-7500(20)30289-2

100. Moran LV, Ongur D, Hsu J, Castro VM, Perlis RH, Schneeweiss S. Psychosis with Methylphenidate or Amphetamine in Patients with ADHD. *N Engl J Med*. 2019;380(12):1128-1138. doi:10.1056/NEJMoa1813751

101. Moulis G, Sommet A, Lapeyre-Mestre M, Montastruc JL. Is the risk of tumour necrosis factor inhibitor-induced lupus or lupus-like syndrome the same with monoclonal antibodies and soluble receptor? A case/non-case study in a nationwide pharmacovigilance database. *Rheumatology*. 2014;53(10):1864-1871. doi:10.1093/rheumatology/keu214

102. Muanda FT, Weir MA, Bathini L, et al. Association of Baclofen with Encephalopathy in Patients with Chronic Kidney Disease. *JAMA*. 2019;322(20):1987-1995. doi:10.1001/jama.2019.17725

103. Nishtala PS, Chyou T -y. Exploring New Zealand prescription data using sequence symmetry analyses for predicting adverse drug reactions. *J Clin Pharm Ther*. 2017;42(2):189-194. doi:10.1111/jcpt.12491

104. Norén GN, Bergvall T, Ryan PB, Juhlin K, Schuemie MJ, Madigan D. Empirical Performance of the Calibrated Self-Controlled Cohort Analysis Within Temporal Pattern Discovery: Lessons for Developing a Risk Identification and Analysis System. *Drug Saf*. 2013;36(1):107-121. doi:10.1007/s40264-013-0095-x

105. O'Grady M, Clarke L, Turner G, et al. Statin use and risk of acute diverticulitis: A population-based case-control study. *Medicine (Baltimore)*. 2020;99(20):e20264. doi:10.1097/MD.0000000000020264

106. Osokogu OU, Dodd C, Pacurariu A, Kaguelidou F, Weibel D, Sturkenboom MCJM. Drug Safety Monitoring in Children: Performance of Signal Detection Algorithms and Impact of Age Stratification. *Drug Saf*. 2016;39(9):873-881. doi:10.1007/s40264-016-0433-x

107. Ospina-Romero M, Brenowitz WD, Glymour MM, et al. The Association Between Cancer and Spousal Rate of Memory Decline: A Negative Control Study to Evaluate (Unmeasured) Social Confounding of the Cancer-memory Relationship. *Alzheimer Dis Assoc Disord*. 2020;35(3):271-274. doi:10.1097/WAD.0000000000000398

108. Ou SM, Shih CJ, Chao PW, et al. Effects on clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. *Ann Intern Med*. 2015;163(9):663-672. doi:10.7326/M15-0308

109. Ou SM, Chen HT, Kuo SC, Chen TJ, Shih CJ, Chen YT. Dipeptidyl peptidase-4 inhibitors and cardiovascular risks in patients with pre-existing heart failure. *Heart*. 2017;103(6):414-420. doi:10.1136/heartjnl-2016-309687

110. Pan SW, Yen YF, Feng JY, et al. Opposite effects of statins on the risk of tuberculosis and herpes zoster in patients with diabetes: A population-based cohort study. *Br J Clin Pharmacol*. 2020;86(3):569-579. doi:10.1111/bcp.14142

111. Paul S, Zahurak M, Luznik L, et al. Non-Myeloablative Allogeneic Transplantation with Post-Transplant Cyclophosphamide after Immune Checkpoint Inhibition for Classic Hodgkin Lymphoma: A Retrospective Cohort Study: Checkpoint Inhibition before NMA alloBMT with PTCy in cHL. *Biol Blood Marrow Transpl*. Published online 2020. doi:10.1016/j.bbmt.2020.06.012

112. Pierce C, Bouri K, Pamer C, et al. Evaluation of Facebook and Twitter Monitoring to Detect Safety Signals for Medical Products: An Analysis of Recent FDA Safety Alerts. *Drug Saf*. 2017;40(4):317-331. doi:10.1007/s40264-016-0491-0

113. Pottegård A, Broe A, Stage TB, Brøsen K, Hallas J, Damkier P. Use of Dicloxacillin and Risk of Pregnancy among Users of Oral Contraceptives. *Basic Clin Pharmacol Toxicol*. 2018;123(3):288-293. doi:10.1111/bcpt.13000

114. Pratt N, Chan EW, Choi NK, et al. Prescription sequence symmetry analysis: assessing risk, temporality, and consistency for adverse drug reactions across datasets in five countries. *Pharmacoepidemiol Drug Saf*. 2015;24(8):858-864. doi:10.1002/pds.3780

115. Quinn PD, Chang Z, Hur K, et al. ADHD medication and substance-related problems. *Am J Psychiatry*. 2017;174(9):877-885. doi:10.1176/appi.ajp.2017.16060686

116. Rai D, Lee BK, Dalman C, Newschaffer C, Lewis G, Magnusson C. Antidepressants during pregnancy and autism in offspring: Population based cohort study. *BMJ Online*. 2017;358:j2811. doi:10.1136/bmj.j2811

117. Ray GT, Lewis N, Klein NP, et al. Intraseason waning of influenza vaccine effectiveness. *Clin Infect Dis*. 2019;68(10):1623-1630. doi:10.1093/cid/ciy770

118. Raymakers A, Sin DD, Sadatsafavi M, et al. Statin use and lung cancer risk in chronic obstructive pulmonary disease patients: a population-based cohort study. *Respir Res*. 2020;21(1):1-11. doi:10.1186/s12931-020-01344-w

119. Reich CG, Ryan PB, Schuemie MJ. Alternative outcome definitions and their effect on the performance of methods for observational outcome studies. *Drug Saf*. 2013;36 Suppl 1:S181-93. doi:10.1007/s40264-013-0111-1

120. Reich CG, Ryan PB, Suchard MA. The impact of drug and outcome prevalence on the feasibility and performance of analytical methods for a risk identification and analysis system. *Drug Saf*. 2013;36(SUPPL.1):S195-S204. doi:10.1007/s40264-013-0112-0

121. Ridenhour BJ, Campitelli MA, Kwong JC, et al. Effectiveness of Inactivated Influenza Vaccines in Preventing Influenza-Associated Deaths and Hospitalizations among Ontario Residents Aged ≥65 Years: Estimates with Generalized Linear Models Accounting for Healthy Vaccinee Effects. *PLoS ONE*. 2013;8(10). doi:10.1371/journal.pone.0076318

122. Rodgers LR, Dennis JM, Shields BM, Mounce L. Prior event rate ratio adjustment produced estimates consistent with randomized trial: a diabetes case study. 2020;122:78-86. doi:10.1016/j.jclinepi.2020.03.007

123. Rodríguez AJ, Ernst MT, Nybo M, et al. Oral Bisphosphonate use Reduces Cardiovascular Events in a Cohort of Danish Patients Referred for Bone Mineral Density. *J Clin Endocrinol Metab*. 2020;105(10). doi:10.1210/clinem/dgaa481

124. Roshanov PS, Rochwerg B, Patel A, et al. Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery. *Anesthesiology*. 2017;126(1):16-27. doi:10.1097/ALN.0000000000001404

125. Ryan PB, Madigan D, Stang PE, Overhage JM, Racoosin JA, Hartzema AG. Empirical assessment of methods for risk identification in healthcare data: results from the experiments of the Observational Medical Outcomes Partnership. *Stat Med*. 2012;31(30):4401-4415. doi:10.1002/sim.5620

126. Ryan PB, Schuemie MJ, Gruber S, Zorych I, Madigan D. Empirical performance of a new user cohort method: lessons for developing a risk identification and analysis system. *Drug Saf*. 2013;36:59-72. doi:10.1007/s40264-013-0099-6

127. Ryan PB, Schuemie MJ, Madigan D. Empirical performance of a self-controlled cohort method: lessons for developing a risk identification and analysis system. *Drug Saf*. 2013;36:95-106. doi:10.1007/s40264-013-0101-3

128. Ryan PB, Schuemie MJ, Welebob E, Duke J, Valentine S, Hartzema AG. Defining a reference set to support methodological research in drug safety. *Drug Saf*. 2013;36:33-47. doi:10.1007/s40264-013-0097-8

129. Ryan PB, Stang PE, Overhage JM, et al. A comparison of the empirical performance of methods for a risk identification system. *Drug Saf*. 2013;36:143-158. doi:10.1007/s40264-013-0108-9

130. Ryan PB, Schuemie MJ. Evaluating Performance of Risk Identification Methods Through a Large-Scale Simulation of Observational Data. *Drug Saf*. 2013;36(1):171-180. doi:10.1007/s40264-013-0110-2

131. Sarvet AL, Wall MM, Keyes KM, Olfson M, Cerdá M, Hasin DS. Self-medication of mood and anxiety disorders with marijuana: Higher in states with medical marijuana laws. *Drug Alcohol Depend*. Published online 2018:10-15. doi:10.1016/j.drugalcdep.2018.01.009

132. Schuemie MJ, Coloma PM, Straatman H, et al. Using electronic health care records for drug safety signal detection: a comparative evaluation of statistical methods. *Med Care*. 2012;50(10):890-897.

133. Schuemie MJ, Gini R, Coloma PM, et al. Replication of the OMOP experiment in Europe: evaluating methods for risk identification in electronic health record databases. *Drug Saf*. 2013;36:159-169. doi:10.1007/s40264-013-0109-8

134. Schuemie MJ, Madigan D, Ryan PB. Empirical performance of LGPS and LEOPARD: lessons for developing a risk identification and analysis system. *Drug Saf*. 2013;36:133-142. doi:10.1007/s40264-013-0107-x

135. Schuemie MJ, Ryan PB, Hripcsak G, Madigan D, Suchard MA. Improving reproducibility by using high-throughput observational studies with empirical calibration. *Philos Trans R Soc Math Phys Eng Sci*. 2018;376(2128). doi:10.1098/rsta.2017.0356

136. Schuemie MJ, Ryan PB, Man KKC, Wong ICK, Suchard MA, Hripcsak G. A plea to stop using the case-control design in retrospective database studies. *Stat Med*. 2019;38(22):4199-4208. doi:10.1002/sim.8215

137. Shao SC, Chang KC, Hung MJ, et al. Comparative risk evaluation for cardiovascular events associated with dapagliflozin vs. empagliflozin in real-world type 2 diabetes patients: A multi-institutional cohort study. *Cardiovasc Diabetol*. 2019;18(1). doi:10.1186/s12933-019-0919-9

138. Shi X, Miao W, Nelson JC, Tchetgen Tchetgen EJ. Multiply robust causal inference with double-negative control adjustment for categorical unmeasured confounding. *J R Stat Soc Ser B Stat Methodol*. 2020;82(2):521-540. doi:10.1111/rssb.12361

139. Shoag JE, Patel N, Posada L, et al. Kidney Stones and Risk of Narcotic Use. *J Urol*. 2019;202(1):114-117. doi:10.1097/JU.0000000000000197

140. Simonov M, Abel EA, Skanderson M, et al. Use of Proton Pump Inhibitors Increases Risk of Incident Kidney Stones. *Clin Gastroenterol Hepatol*. 2020;19(1):72-79.e21. doi:10.1016/j.cgh.2020.02.053

141. Simonsen L, Taylor RJ, Schuck-Paim C, Lustig R, Haber M, Klugman KP. Effect of 13-valent pneumococcal conjugate vaccine on admissions to hospital 2 years after its introduction in the USA: A time series analysis. *Lancet Respir Med*. 2014;2(5):387-394. doi:10.1016/S2213-2600(14)70032-3

142. Sinnott SJ, Smeeth L, Williamson E, et al. The comparative effectiveness of fourth-line drugs in resistant hypertension: An application in electronic health record data. *Pharmacoepidemiol Drug Saf*. 2019;28(9):1267-1277. doi:10.1002/pds.4808

143. Sköldberg F, Svensson T, Olén O, Hjern F, Schmidt PT, Ljung R. A population-based case-control study on statin exposure and risk of acute diverticular disease. *Scand J Gastroenterol*. 2016;51(2):203-210. doi:10.3109/00365521.2015.1081274

144. Sørup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Simultaneous vaccination with MMR and DTaP-IPV-Hib and rate of hospital admissions with any infections: A nationwide register based cohort study. *Vaccine*. 2016;34(50):6172-6180. doi:10.1016/j.vaccine.2016.11.005

145. Spoendlin J, Gagne JJ, Lewey JJ, Patorno E, Schneeweiss S, Desai RJ. Comparative effectiveness and safety of antiplatelet drugs in patients with diabetes mellitus and acute coronary syndrome. *Pharmacoepidemiol Drug Saf*. 2018;27(12):1361-1370. doi:10.1002/pds.4668

146. Stolfo D, Uijl A, Benson L, et al. Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction. A propensity score-matched analysis from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2020;22(1):103-112. doi:10.1002/ejhf.1615

147. Suchard MA, Zorych I, Simpson SE, Schuemie MJ, Ryan PB, Madigan D. Empirical performance of the self-controlled case series design: lessons for developing a risk identification and analysis system. *Drug Saf*. 2013;36:83-93. doi:10.1007/s40264-013-0100-4

148. Sundbakk LM, Wood M, Gran JM, Nordeng H. Impact of prenatal exposure to benzodiazepines and z-hypnotics on behavioral problems at 5 years of age: A study from the Norwegian Mother and Child Cohort Study. *PLoS ONE*. 2019;14(6). doi:10.1371/journal.pone.0217830

149. Symes RJ, Etminan M, Mikelberg FS. Risk of angle-closure glaucoma with bupropion and topiramate. *JAMA Ophthalmol*. 2015;133(10):1187-1189. doi:10.1001/jamaophthalmol.2015.2180

150. Tate JE, Curns AT, Cortese MM, et al. Burden of acute gastroenteritis hospitalizations and emergency department visits in US children that is potentially preventable by rotavirus vaccination: a probe study using the now-withdrawn rotashield vaccine. *Pediatrics*. 2009;123(3):744-749. doi:10.1542/peds.2008-1200

151. Thomsen RW, Öztürk B, Pedersen L, et al. Hospital Records of Pain, Fatigue, or Circulatory Symptoms in Girls Exposed to Human Papillomavirus Vaccination: Cohort, Self-Controlled Case Series, and Population Time Trend Studies. *Am J Epidemiol*. 2020;189(4):277-285. doi:10.1093/aje/kwz284

152. Thorrington D, Andrews N, Stowe J, Miller E, van Hoek AJ. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. *BMC Med*. 2018;16(1). doi:10.1186/s12916-018-1004-z

153. Thurin NH, Lassalle R, Schuemie M, et al. Empirical assessment of case-based methods for identification of drugs associated with upper gastrointestinal bleeding in the French National Healthcare System database (SNDS). *Pharmacoepidemiol Drug Saf*. 2020;29(8):890-903. doi:10.1002/pds.5038

154. Tielemans SMAJ, De Melker HE, Hahné SJM, et al. Non-specific effects of measles, mumps, and rubella (MMR) vaccination in high income setting: Population based cohort study in the Netherlands. *BMJ Online*. 2017;358. doi:10.1136/bmj.j3862

155. Tien KL, Sheng WH, Shieh SC, et al. Chlorhexidine Bathing to Prevent Central Line-Associated Bloodstream Infections in Hematology Units: A Prospective, Controlled Cohort Study. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2020;71(3):556-563. doi:10.1093/cid/ciz874

156. Totterdell J, Phillips A, Glover C, et al. Safety of live attenuated herpes zoster vaccine in adults 70–79 years: A self-controlled case series analysis using primary care data from Australia's MedicineInsight program. *Vaccine*. 2020;38(23):3968-3979. doi:10.1016/j.vaccine.2020.03.054

157. Toulis KA, Willis BH, Marshall T, et al. All-cause mortality in patients with diabetes under treatment with dapagliflozin: A population-based, open-cohort study in the health improvement network database. *J Clin Endocrinol Metab*. 2017;102(5):1719-1725. doi:10.1210/jc.2016-3446

158. Trinh NTH, Solé E, Benkebil M. Benefits of combining change-point analysis with disproportionality analysis in pharmacovigilance signal detection. *Pharmacoepidemiol Drug Saf*. 2019;28(3):370-376. doi:10.1002/pds.4613

159. Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. *Paediatr Perinat Epidemiol*. Published online 2019. doi:10.1111/ppe.12568

160. Tseng HF, Smith N, Harpaz R, Bialek SR, Sy LS, Jacobsen SJ. Herpes Zoster Vaccine in Older Adults and the Risk of Subsequent Herpes Zoster Disease. *JAMA*. 2011;305(2):160-166. doi:10.1001/jama.2010.1983

161. Tsujimoto T, Kajio H. Use of Nitrates and Risk of Cardiovascular Events in Patients With Heart Failure With Preserved Ejection Fraction. *Mayo Clin Proc*. 2019;94(7):1210-1220. doi:10.1016/j.mayocp.2018.11.032

162. van Rein N, Cannegieter SC, Rosendaal FR, Reitsma PH, Lijfering WM. Suspected survivor bias in case-control studies: stratify on survival time and use a negative control. *J Clin Epidemiol*. 2014;67(2):232-235. doi:10.1016/j.jclinepi.2013.05.011

163. Vonesh E, Gooch KL, Khangulov V, et al. Cardiovascular risk profile in individuals initiating treatment for overactive bladder – Challenges and learnings for comparative analysis using linked claims and electronic medical record databases. *PLoS ONE*. 2018;13(10). doi:10.1371/journal.pone.0205640

164. Voss EA, Boyce RD, Ryan PB, van der Lei J, Rijnbeek PR, Schuemie MJ. Accuracy of an automated knowledge base for identifying drug adverse reactions. *J Biomed Inform*. 2017;66:72-81. doi:10.1016/j.jbi.2016.12.005

165. Vouri SM, Jiang X, Manini TM, et al. Magnitude of and Characteristics Associated with the Treatment of Calcium Channel Blocker-Induced Lower-Extremity Edema with Loop Diuretics. *JAMA Netw Open*. 2019;2(12):e1918425. doi:10.1001/jamanetworkopen.2019.18425

166. Walsh LK, Donelle J, Dodds L, et al. Health outcomes of young children born to mothers who received 2009 pandemic H1N1 influenza vaccination during pregnancy: Retrospective cohort study. *BMJ*. 2019;366. doi:10.1136/bmj.l4151

167. Wei Y, Lin FJ, Lin SY, Wang CC. Risk of Hypoglycemia and Concomitant Use of Repaglinide and Clopidogrel: A Population-Based Nested Case-Control Study. *Clin Pharmacol Ther*. 2019;106(6):1346-1352. doi:10.1002/cpt.1556

168. Weinstein RB, Schuemie MJ, Ryan PB, Stang PE. Seasonality in acute liver injury? Findings in two health care claims databases. *Drug Healthc Patient Saf*. 2016;8:39-48. doi:10.2147/DHPS.S95399

169. Weinstein R, Ryan P, Berlin J, et al. Channeling in the Use of Nonprescription Paracetamol and Ibuprofen in an Electronic Medical Records Database: Evidence and Implications. *Drug Saf*. 2017;40(12):1279-1292. doi:10.1007/s40264-017-0581-7

170. Weinstein RB, Ryan PB, Berlin JA, Schuemie MJ, Swerdel J, Fife D. Channeling Bias in the Analysis of Risk of Myocardial Infarction, Stroke, Gastrointestinal Bleeding, and Acute Renal Failure with the Use of Paracetamol Compared with Ibuprofen. *Drug Saf*. 2020;43(9):927-942. doi:10.1007/s40264-020-00950-3

171. Welk B, McClure JA, Clarke C, Vogt K, Campbell J. An Opioid Prescription for Men Undergoing Minor Urologic Surgery Is Associated with an Increased Risk of New Persistent Opioid Use. *Eur Urol*. 2020;77(1):68-75. doi:10.1016/j.eururo.2019.08.031

172. Whitlock RH, Hougen I, Komenda P, Rigatto C, Clemens KK, Tangri N. A Safety Comparison of Metformin vs Sulfonylurea Initiation in Patients With Type 2 Diabetes and Chronic Kidney Disease: A Retrospective Cohort Study. *Mayo Clin Proc*. 2020;95(1):90-100. doi:10.1016/j.mayocp.2019.07.017

173. Xian Y, Xu H, O'Brien EC, et al. Clinical Effectiveness of Direct Oral Anticoagulants vs Warfarin in Older Patients with Atrial Fibrillation and Ischemic Stroke: Findings from the Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) Study. *JAMA Neurol*. 2019;76(10):1192-1202. doi:10.1001/jamaneurol.2019.2099

174. Xie Y, Bowe B, Yan Y, Xian H, Li T, Al-Aly Z. Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: Cohort study. *BMJ*. 2019;365. doi:10.1136/bmj.l1580

175. Yates TA, Tomlinson LA, Bhaskaran K, et al. Lansoprazole use and tuberculosis incidence in the United Kingdom Clinical Practice Research Datalink: A population based cohort. *PLoS Med*. 2017;14(11):1-15. doi:10.1371/journal.pmed.1002457

176. Yip TCF, Wong VWS, Chan HLY, Tse YK, Lui GCY, Wong GLH. Tenofovir Is Associated With Lower Risk of Hepatocellular Carcinoma Than Entecavir in Patients With Chronic HBV Infection in China. *Gastroenterology*. 2020;158(1):215-225.e6. doi:10.1053/j.gastro.2019.09.025

177. You SC, Jung S, Swerdel JN, et al. Comparison of first-line dual combination treatments in hypertension: Real-world evidence from multinational heterogeneous cohorts. *Korean Circ J*. 2020;50(1):52-68. doi:10.4070/kcj.2019.0173

178. Ystrom E, Gustavson K, Brandlistuen RE, et al. Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics*. 2017;140(5). doi:10.1542/peds.2016-3840

179. Yuan Z, DeFalco FJ, Ryan PB, et al. Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: A retrospective cohort study. *Diabetes Obes Metab*. 2018;20(3):582-589. doi:10.1111/dom.13115

180. Yuan J, Zhang C, Sparks JA, et al. Regular use of proton pump inhibitor and risk of rheumatoid arthritis in women: a prospective cohort study. *Aliment Pharmacol Ther*. 2020;52(3):449-458. doi:10.1111/apt.15834

181. Zhang HT, McGrath LJ, Wyss R, Ellis AR, Stürmer 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):1500-1506. doi:10.1002/pds.4298

182. Zhang HT, McGrath LJ, Ellis AR, Wyss R, Lund JL, Stürmer T. Restriction of Pharmacoepidemiologic Cohorts to Initiators of Medications in Unrelated Preventive Drug Classes to Reduce Confounding by Frailty in Older Adults. *Am J Epidemiol*. 2019;188(7):1371-1382. doi:10.1093/aje/kwz083

183. Zhou M, Leonard CE, Brensinger CM, et al. Pharmacoepidemiologic Screening of Potential Oral Anticoagulant Drug Interactions Leading to Thromboembolic Events. *Clin Pharmacol Ther*. 2020;108(2):377-386. doi:10.1002/cpt.1845

184. Zhou Z, Ofori-Asenso R, Curtis AJ, et al. Association of Statin Use With Disability-Free Survival and Cardiovascular Disease Among Healthy Older Adults. *J Am Coll Cardiol*. 2020;76(1):17-27. doi:10.1016/j.jacc.2020.05.016

185. Zullo AR, Zhang T, Lee Y, et al. Effect of Bisphosphonates on Fracture Outcomes Among Frail Older Adults. *J Am Geriatr Soc*. 2019;67(4):768-776. doi:10.1111/jgs.15725

186. Stang PE, Ryan PB, Racoosin JA, et al. Advancing the Science for Active Surveillance: Rationale and Design for the Observational Medical Outcomes Partnership. *Ann Intern Med*. 2010;153(9):600. doi:10.7326/0003-4819-153-9-201011020-00010

187. Tisdale JE, Miller DA. *Drug-Induced Diseases: Prevention, Detection, and Management*. 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2010.