Supplementary Material for:

Evaluating Large-Scale Propensity Score Performance Through Real-World and Synthetic Data Experiments

Supplementary Material 1: Treatments - Anticoagulants Study

Dabigatran New Users with Prior Atrial Fibrillation

Initial Event Cohort

People having any of the following:

- a drug era of dabigatran[4]
  - for the first time in the person's history
  - era start is on or after 2010-10-19
  - with age at era start ≥ 65

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Inclusion Criteria 1: Has prior atrial fibrillation of atrial flutter diagnosis

Having any of the following criteria:

- at least 1 occurrences of a condition occurrence of Atrial fibrillation[2] starting between all days Before and 0 days After event index date
- or at least 1 occurrences of a condition occurrence of Atrial flutter[3] starting between all days Before and 0 days After event index date

Inclusion Criteria 2: Has no prior treatment with comparator drug (warfarin)

Having any of the following criteria:

- exactly 0 occurrences of a drug exposure of warfarin[13] starting between all days Before and 0 days Before event index date

Inclusion Criteria 3: Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)

Having any of the following criteria:

- exactly 0 occurrences of a drug exposure of rivaroxaban[12]

  starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of apixaban[1]

  starting between all days Before and 0 days After event index date

Inclusion Criteria 4: Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date

Having any of the following criteria:

- exactly 0 occurrences of a visit occurrence of long term care visit[10]

  starting between 0 days Before and 0 days After event index date

- and exactly 0 occurrences of a procedure of Hospice observations[9]

  starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of an observation of Hospice observations[9]

  starting between all days Before and 0 days After event index date

Inclusion Criteria 5: Not undergoing dialysis or kidney transplant recipient

Having any of the following criteria:

- exactly 0 occurrences of a condition occurrence of Hemodialysis, peritoneal dialysis, or kidney transplant[7]

  starting between 183 days Before and 0 days After event index date

- and exactly 0 occurrences of a procedure of Hemodialysis, peritoneal dialysis, or kidney transplant[7]

  starting between 183 days Before and 0 days After event index date

- and exactly 0 occurrences of an observation of Hemodialysis, peritoneal dialysis, or kidney transplant[7]

  starting between 183 days Before and 0 days After event index date

Inclusion Criteria 6: No mitral valve disease, heart valve repair, or replacement in the prior 6 months

Having any of the following criteria:

- exactly 0 occurrences of a condition occurrence of Heart valve disease, repair or replacement[6] starting between 183 days Before and 0 days After event index date
- and exactly 0 occurrences of a procedure of Heart valve disease, repair or replacement[6] starting between 183 days Before and 0 days After event index date
- and exactly 0 occurrences of an observation of Heart valve disease, repair or replacement[6] starting between 183 days Before and 0 days After event index date

Inclusion Criteria 7: No deep vein thrombosis or pulmonary embolism in the prior 6 months

Having any of the following criteria:

- exactly 0 occurrences of a condition occurrence of Deep vein thrombosis[5] starting between 183 days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of Pulmonary embolism[11] starting between 183 days Before and 0 days After event index date

Inclusion Criteria 8: No joint replacement surgery in the prior 6 months

Having any of the following criteria:

- exactly 0 occurrences of a procedure of Hip/knee joint replacement or revision[8] starting between 183 days Before and 0 days After event index date

Cohort Exit Criteria

Cohort end date is the end of the observation period that contains the index event.

Warfarin New Users with Prior Atrial Fibrillation

Initial Event Cohort

People having any of the following:

- a drug era of warfarin[13]
  - for the first time in the person's history
  - era start is on or after 2010-10-19
  - with age at era start ≥ 65

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Inclusion Criteria 1, 3-8: Same as Dabigatran Cohort

Inclusion Criteria 2: Has no prior treatment with comparator drug (dabigatran)

Having any of the following criteria:

- exactly 0 occurrences of a drug exposure of dabigatran[4]
  starting between all days Before and 0 days Before event index date

Appendix: Concept Set Definitions

Codes given use the Observational Medical Outcomes Partnership Common Data Model Version 5 format (1). The "Vocabulary" column indicates the source vocabulary set for the concept. The "Excluded" column indicates whether the covariate is included (NO) or excluded (YES) from the cohort definition. The "Descendants" column incidates whether all descendent concepts in the vocabulary hierarchy are also incorporated.

1. apixaban

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
43013024	apixaban	Drug	RxNorm	NO	YES

2. Atrial fibrillation

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
313217	Atrial fibrillation	Condition	SNOMED	NO	YES

3. Atrial flutter

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
314665	Atrial flutter	Condition	SNOMED	NO	YES

4. dabigatran

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
40228152	dabigatran etexilate	Drug	RxNorm	NO	YES

5. Deep vein thrombosis

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
435887	Antepartum deep vein thrombosis	Condition	SNOMED	YES	YES
195562	Hemorrhoids	Condition	SNOMED	YES	YES
4179912	Intracranial venous thrombosis	Condition	SNOMED	YES	YES
318137	Phlebitis and thrombophlebitis of intracranial sinuses	Condition	SNOMED	YES	YES
199837	Portal vein thrombosis	Condition	SNOMED	YES	YES
438820	Postpartum deep phlebothrombosis	Condition	SNOMED	YES	YES
4235812	Septic thrombophlebitis	Condition	SNOMED	YES	YES
4187790	Thrombosis of retinal vein	Condition	SNOMED	YES	YES
318775	Venous embolism	Condition	SNOMED	NO	YES
444247	Venous thrombosis	Condition	SNOMED	NO	YES

6. Heart valve disease, repair or replacement

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
4060089	H/O: artificial heart valve	Observation	SNOMED	NO	YES
4195003	Heart valve stenosis	Condition	SNOMED	NO	YES
44782431	History of mechanical heart valve replacement	Observation	SNOMED	NO	YES
4013355	Implantation of heart valve	Procedure	SNOMED	NO	YES
4165384	Implantation of heart valve prosthesis or synthetic device	Procedure	SNOMED	NO	YES
2617335	Md inr test revie inter mgmt	Observation	HCPCS	NO	YES
43020459	Mechanical breakdown of prosthetic heart valve	Condition	SNOMED	NO	YES
312773	Mechanical complication due to heart valve prosthesis	Condition	SNOMED	NO	YES
4020159	Mechanical complication of heart valve prosthesis	Condition	SNOMED	NO	YES
44783274	Mechanical heart valve replacement	Procedure	SNOMED	NO	YES
315273	Mitral valve stenosis	Condition	SNOMED	NO	YES
4110937	Non-rheumatic mitral valve stenosis	Condition	SNOMED	NO	YES
2001447	Open and other replacement of heart valve	Procedure	ICD9Proc	NO	YES
2001448	Open and other replacement of unspecified heart valve	Procedure	ICD9Proc	NO	YES
4119522	Prosthetic heart valve sample	Specimen	SNOMED	NO	YES

4145884	Prosthetic replacement of heart valve	Procedure	SNOMED	NO	YES
2617334	Provide inr test mater/equip	Observation	HCPCS	NO	YES
4339971	Reinsertion of heart valve, prosthetic	Procedure	SNOMED	NO	YES
4121484	Replacement of heart valve poppet, prosthetic	Procedure	SNOMED	NO	YES
4013356	Resuture of heart valve prosthesis, poppet	Procedure	SNOMED	NO	YES
4181749	Revision of prosthesis of heart valve	Procedure	SNOMED	NO	YES
4304541	Rheumatic mitral valve insufficiency AND aortic valve stenosis	Condition	SNOMED	NO	YES

7. Hemodialysis, peritoneal dialysis, or kidney transplant

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
4126124	Acute disorder of hemodialysis	Condition	SNOMED	NO	YES
4092504	Adequacy of hemodialysis	Observation	SNOMED	NO	YES
435649	Complication of hemodialysis	Condition	SNOMED	NO	YES
40480136	Dependence on hemodialysis	Observation	SNOMED	NO	YES
4181476	Dependence on hemodialysis due to end stage renal disease	Observation	SNOMED	NO	YES
44786469	Docrsn for cath maint dia	Observation	HCPCS	NO	YES
4120120	Hemodialysis	Procedure	SNOMED	NO	YES
2101833	Hemodialysis plan of care documented (esrd, p-esrd)	Observation	CPT4	NO	YES
4137616	Hemodialysis-associated amyloidosis	Condition	SNOMED	NO	YES
313232	Hemodialysis-associated hypotension	Condition	SNOMED	NO	YES
4300099	Hemodialysis-associated pruritus	Condition	SNOMED	NO	YES
4297919	Hemodialysis-associated pseudoporphyria	Condition	SNOMED	NO	YES
4297658	Hemodialysis-associated secondary amyloidosis of skin	Condition	SNOMED	NO	YES
4099603	Megaloblastic anemia due to hemodialysis	Measurement	SNOMED	NO	YES
44782924	Misplacement of hemodialysis catheter	Condition	SNOMED	NO	YES
44786470	Patient receiving maintenance hemodialysis for greater than or equal to 90 days with a catheter as the mode of vascular access	Observation	HCPCS	NO	YES
44786471	Patient receiving maintenance hemodialysis for greater than or equal to 90 days without a catheter as the mode of vascular access	Observation	HCPCS	NO	YES
43533281	Patient receiving maintenance hemodialysis in an outpatient dialysis facility	Observation	HCPCS	NO	YES
4324124	Peritoneal dialysis	Procedure	SNOMED	NO	YES
2003564	Peritoneal dialysis	Procedure	ICD9Proc	NO	YES
4300106	Skin lesion associated with hemodialysis	Condition	SNOMED	NO	YES
4046829	Anesthesia for renal transplant, recipient	Procedure	SNOMED	NO	YES

2109584	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each	Procedure	CPT4	NO	YES
4021107	Cadaveric renal transplant	Procedure	SNOMED	NO	YES
4197300	Donor renal transplantation	Procedure	SNOMED	NO	YES
4324754	Examination of recipient after kidney transplant	Procedure	SNOMED	NO	YES
4002215	Kidney implantation	Procedure	SNOMED	NO	YES
4022805	Live donor renal transplant	Procedure	SNOMED	NO	YES
2003626	Other kidney transplantation	Procedure	ICD9Proc	NO	YES
40664909	Patient receiving hemodialysis, peritoneal dialysis or kidney transplantation	Observation	HCPCS	NO	YES
2109586	Renal allotransplantation, implantation of graft; without recipient nephrectomy	Procedure	CPT4	NO	YES
2109589	Renal autotransplantation, reimplantation of kidney	Procedure	CPT4	NO	YES
4163566	Renal replacement	Procedure	SNOMED	NO	YES
4346636	Renal transplant arteriogram	Procedure	SNOMED	NO	YES
4346505	Renal transplant venogram	Procedure	SNOMED	NO	YES
4347789	Renal transplant venous sampling	Procedure	SNOMED	NO	YES
2721092	Simultaneous pancreas kidney transplantation	Procedure	HCPCS	NO	YES
4322471	Transplant of kidney	Procedure	SNOMED	NO	YES
4343000	Xenograft renal transplant	Procedure	SNOMED	NO	YES

8. Hip/knee joint replacement or revision

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
2101660	Anesthesia for open or surgical arthroscopic procedures on knee joint; total knee arthroplasty	Procedure	CPT4	NO	YES
2101635	Anesthesia for open procedures involving hip joint; revision of total hip arthroplasty	Procedure	CPT4	NO	YES
2101634	Anesthesia for open procedures involving hip joint; total hip arthroplasty	Procedure	CPT4	NO	YES
2104836	Arthroplasty, acetabular and proximal femoral prosthetic replacement (total hip arthroplasty), with or without autograft or allograft	Procedure	CPT4	NO	YES
2103931	Arthroplasty, elbow; with distal humerus and proximal ulnar prosthetic replacement (eg, total elbow)	Procedure	CPT4	NO	YES

2105103	Arthroplasty, knee, condyle and plateau; medial AND lateral compartments with or without patella resurfacing (total knee arthroplasty)	Procedure	CPT4	NO	YES
2104837	Conversion of previous hip surgery to total hip arthroplasty, with or without autograft or allograft	Procedure	CPT4	NO	YES
2104835	Hemiarthroplasty, hip, partial (eg, femoral stem prosthesis, bipolar arthroplasty)	Procedure	CPT4	NO	YES
2000075	Hip bearing surface, ceramic-on-ceramic	Procedure	ICD9Proc	NO	YES
2000076	Hip bearing surface, ceramic-on-polyethylene	Procedure	ICD9Proc	NO	YES
2000074	Hip bearing surface, metal-on-metal	Procedure	ICD9Proc	NO	YES
2000073	Hip bearing surface, metal-on-polyethylene	Procedure	ICD9Proc	NO	YES
4001859	Hip joint implantation	Procedure	SNOMED	NO	YES
4134857	Insertion of hip prosthesis	Procedure	SNOMED	NO	YES
4207955	Insertion of hip prosthesis, total	Procedure	SNOMED	NO	YES
2005902	Partial hip replacement	Procedure	ICD9Proc	NO	YES
4162099	Prosthetic arthroplasty of the hip	Procedure	SNOMED	NO	YES
2000085	Resurfacing hip, partial, acetabulum	Procedure	ICD9Proc	NO	YES
2000084	Resurfacing hip, partial, femoral head	Procedure	ICD9Proc	NO	YES
2000083	Resurfacing hip, total, acetabulum and femoral head	Procedure	ICD9Proc	NO	YES
4010119	Revision of hip replacement	Procedure	SNOMED	NO	YES
2000070	Revision of hip replacement, acetabular component	Procedure	ICD9Proc	NO	YES
2000072	Revision of hip replacement, acetabular liner and/or femoral head only	Procedure	ICD9Proc	NO	YES
2000069	Revision of hip replacement, both acetabular and femoral components	Procedure	ICD9Proc	NO	YES
2000071	Revision of hip replacement, femoral component	Procedure	ICD9Proc	NO	YES
2000080	Revision of knee replacement, femoral component	Procedure	ICD9Proc	NO	YES
2000081	Revision of knee replacement, patellar component	Procedure	ICD9Proc	NO	YES
2000079	Revision of knee replacement, tibial component	Procedure	ICD9Proc	NO	YES
2000078	Revision of knee replacement, total (all components)	Procedure	ICD9Proc	NO	YES
45887894	Revision of total hip arthroplasty	Procedure	CPT4	NO	YES

2104839	Revision of total hip arthroplasty; acetabular component only, with or without autograft or allograft	Procedure	CPT4	NO	YES
2104838	Revision of total hip arthroplasty; both components, with or without autograft or allograft	Procedure	CPT4	NO	YES
2104840	Revision of total hip arthroplasty; femoral component only, with or without allograft	Procedure	CPT4	NO	YES
4266062	Revision of total hip replacement	Procedure	SNOMED	NO	YES
2105128	Revision of femoral component of total arthroplasty of knee without allograft	Procedure	CPT4	NO	YES
2105129	Revision of total knee arthroplasty, with or without allograft; femoral and entire tibial component	Procedure	CPT4	NO	YES
2000082	Revision of total knee replacement, tibial insert (liner)	Procedure	ICD9Proc	NO	YES
2005891	Total hip replacement	Procedure	ICD9Proc	NO	YES
2005904	Total knee replacement	Procedure	ICD9Proc	NO	YES
4203771	Total replacement of hip	Procedure	SNOMED	NO	YES
2005903	Revision of hip replacement, not otherwise specified	Procedure	ICD9Proc	NO	YES
2104914	Open treatment of femoral fracture, proximal end, neck, internal fixation or prosthetic replacement	Procedure	CPT4	YES	YES

9. Hospice Observations

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
40483762	Acute care hospice service	Observation	SNOMED	NO	YES
4123927	Admission to hospice	Observation	SNOMED	NO	YES
4086294	Admission to hospice for respite	Observation	SNOMED	NO	YES
4137269	Discharge from hospice	Observation	SNOMED	NO	YES
4137272	Discharge from hospice day hospital	Observation	SNOMED	NO	YES
4062333	Full care by hospice	Observation	SNOMED	NO	YES
40481548	Home hospice service	Observation	SNOMED	NO	YES
4109386	Hospice	Observation	SNOMED	NO	YES
4301458	Hospice care	Observation	SNOMED	NO	YES
4301459	Hospice care management	Procedure	SNOMED	NO	YES
2720815	Hospice care provided in inpatient hospice facility	Observation	HCPCS	NO	YES
2720814	Hospice care provided in inpatient hospital	Observation	HCPCS	NO	YES
2720817	Hospice care provided in inpatient psychiatric facility	Observation	HCPCS	NO	YES
2720816	Hospice care provided in long term care facility	Observation	HCPCS	NO	YES

2720812	Hospice care provided in nursing long term care facility (ltc) or non-skilled nursing facility (nf)	Observation	HCPCS	NO	YES
2720813	Hospice care provided in skilled nursing facility (snf)	Observation	HCPCS	NO	YES
2617270	Hospice care supervision	Observation	HCPCS	NO	YES
2721445	Hospice care, in the home, per diem	Observation	HCPCS	NO	YES
2721700	Hospice continuous home care; per hour	Observation	HCPCS	NO	YES
2721702	Hospice general inpatient care; per diem	Observation	HCPCS	NO	YES
40664432	Hospice home care provided in a hospice facility	Observation	HCPCS	NO	YES
2721701	Hospice inpatient respite care; per diem	Observation	HCPCS	NO	YES
2721703	Hospice long term care, room and board only; per diem	Observation	HCPCS	NO	YES
2720811	Hospice or home health care provided in assisted living facility	Observation	HCPCS	NO	YES
38003372	Hospice Room Board-Nursing facility	Revenue Code	Revenue Code	NO	YES
2721699	Hospice routine home care; per diem	Observation	HCPCS	NO	YES
38003368	Hospice Service - Continuous Home Care	Revenue Code	Revenue Code	NO	YES
38003366	Hospice Service - General Classification	Revenue Code	Revenue Code	NO	YES
38003370	Hospice Service - General Inpatient Care (Non-respite)	Revenue Code	Revenue Code	NO	YES
38003369	Hospice Service - Impatient Respite Care	Revenue Code	Revenue Code	NO	YES
38003373	Hospice Service - Other	Revenue Code	Revenue Code	NO	YES
38003371	Hospice Service - Physician Services	Revenue Code	Revenue Code	NO	YES
38003367	Hospice Service - Routine Home Care	Revenue Code	Revenue Code	NO	YES
38003131	Incremental Nursing Charge Rate - Hospice	Revenue Code	Revenue Code	NO	YES
38003066	Private (Deluxe) - Hospice	Revenue Code	Revenue Code	NO	YES
38003036	Room Board - Private (Medical or General) - Hospice	Revenue Code	Revenue Code	NO	YES
38003046	Room Board - Semi-private Two Bed (Medical or General) - Hospice	Revenue Code	Revenue Code	NO	YES

38003076	Room Board Ward (Medical or General) - Hospice	Revenue Code	Revenue Code	NO	YES
4082084	Routine admission to hospice	Observation	SNOMED	NO	YES
4140947	Seen in hospice	Observation	SNOMED	NO	YES
38003056	Semi-Private - Three and Four Beds - Hospice	Revenue Code	Revenue Code	NO	YES
915618	Services performed by care coordinator in the hospice setting, each 15 minutes	Observation	HCPCS	NO	YES
915614	Services performed by chaplain in the hospice setting, each 15 minutes	Observation	HCPCS	NO	YES
915615	Services performed by dietary counselor in the hospice setting, each 15 minutes	Observation	HCPCS	NO	YES
915616	Services performed by other counselor in the hospice setting, each 15 minutes	Observation	HCPCS	NO	YES
915619	Services performed by other qualified therapist in the hospice setting, each 15 minutes	Observation	HCPCS	NO	YES
915620	Services performed by qualified pharmacist in the hospice setting, each 15 minutes	Observation	HCPCS	NO	YES
915617	Services performed by volunteer in the hospice setting, each 15 minutes	Observation	HCPCS	NO	YES
4062044	Shared care - hospice and GP	Observation	SNOMED	NO	YES
2514512	Supervision of care of hospice patient, without patient present - 15-29 minutes	Procedure	CPT4	NO	YES
4086777	Urgent admission to hospice	Observation	SNOMED	NO	YES

10. long term care visit

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
42898160	Long Term Care Visit	Visit	Visit	NO	YES

11. Pulmonary embolism

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
40480461	Infarction of lung due to iatrogenic pulmonary embolism	Condition	SNOMED	NO	YES
435026	Obstetric pulmonary embolism	Condition	SNOMED	YES	YES
440417	Pulmonary embolism	Condition	SNOMED	NO	YES
40479606	Septic pulmonary embolism	Condition	SNOMED	NO	YES

12. rivaroxaban

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
40241331	rivaroxaban	Drug	RxNorm	NO	YES

13. warfarin

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
1310149	Warfarin	Drug	RxNorm	NO	YES

Supplementary Material 2: Outcome - Anticoagulants Study

Incident Intracranial Hemorrhage, Observed in Inpatient Setting

Initial Event Cohort

People having any of the following:

- a condition occurrence of Intracranial hemorrhage[1]
  - condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Inpatient detail - 1st position, Inpatient header - 1st position
  - visit occurrence is any of: Emergency Room Visit, Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

1. Intracranial hemorrhage

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
376713	Cerebral hemorrhage	Condition	SNOMED	NO	YES
4014781	Closed traumatic subdural hemorrhage	Condition	SNOMED	NO	YES
252477	Extradural hemorrhage following injury without open intracranial wound	Condition	SNOMED	NO	YES
439847	Intracranial hemorrhage	Condition	SNOMED	NO	NO
42873157	Intracranial hemorrhage following injury	Condition	SNOMED	NO	NO
436430	Nontraumatic extradural hemorrhage	Condition	SNOMED	NO	YES
432923	Subarachnoid hemorrhage	Condition	SNOMED	NO	YES
435959	Subarachnoid hemorrhage following injury without open intracranial wound	Condition	SNOMED	NO	YES
439040	Subdural hemorrhage	Condition	SNOMED	NO	YES
260841	Perinatal subarachnoid hemorrhage	Condition	SNOMED	YES	YES
436519	Perinatal intraventricular hemorrhage	Condition	SNOMED	YES	YES
4071732	Intracranial nontraumatic hemorrhage of fetus and newborn	Condition	SNOMED	YES	YES
4345688	Intracerebral hemorrhage in fetus or newborn	Condition	SNOMED	YES	YES

443752	Ventricular hemorrhage	Condition	SNOMED	YES	YES
4174299	Perinatal intracranial hemorrhage	Condition	SNOMED	YES	YES
380113	Hemorrhage in optic nerve sheaths	Condition	SNOMED	YES	YES
42872434	Intracranial hematoma	Condition	SNOMED	NO	YES

Supplementary Material 3: Treatments - NSAIDs Study

Celecoxib New Users

Initial Event Cohort

People having any of the following:

- a drug era of celecoxib[2]
  - for the first time in the person's history
  - era start is between 2004-01-01 and 2007-12-31 (inclusive)
  - with age at era start ≥ 16

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events and qualifying cohort to: earliest event per person.

Inclusion Criteria:

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of Broad malignancies excluding skin cancer (including primary, secondary)[1]
  starting between 365 days Before and 0 days Before event index date
- and exactly 0 occurrences of a drug exposure of NSAIDs[4]
  starting between 365 days Before and 1 days Befor event index date

Cohort Exit Criteria

Cohort definition end date is index event's end date plus 0 days

Diclofenac New Users

Initial Event Cohort

People having any of the following:

- a drug era of diclofenac[3]
  - ○ for the first time in the person's history
  - ○ era start is between 2004-01-01 and 2007-12-31 (inclusive)
  - ○ with age at era start ≥ 16

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

Inclusion Criteria: Same as celecoxib cohort

Cohort Exit Criteria: Same as celecoxib cohort

Appendix: Concept Set Definitions

1. Broad malignancies excluding skin cancer (including primary, secondary)

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
4179980	Malignant basal cell neoplasm of skin	Condition	SNOMED	YES	YES
443392	Malignant neoplastic disease	Condition	SNOMED	NO	YES
4300118	Squamous cell carcinoma	Condition	SNOMED	YES	YES

2. celecoxib

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
1118084	celecoxib	Drug	RxNorm	NO	YES

3. diclofenac

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
1124300	Diclofenac	Drug	RxNorm	NO	YES

4. NSAIDs

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants

21603933	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	Drug	ATC	NO	YES

Supplementary Material 4: Outcome - NSAIDs Study

Upper gastrointestinal complication (UGIC) events

Initial Event Cohort

People having any of the following:

- a condition era of Upper gastrointestinal complication (UGIC)[1]

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events and qualifying cohort to: earliest event per person.

Inclusion Criteria:

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of Upper gastrointestinal complication (UGIC)[1] starting between 30 days Before and 1 day Before event index date

Appendix: Concept Set Definitions

1. Broad malignancies excluding skin cancer (including primary, secondary)

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
192671	Gastrointestinal hemorrhage	Condition	SNOMED	NO	YES
194158	Perinatal gastrointestinal hemorrhage	Condition	SNOMED	YES	YES
26441	Bleeding ulcer of esophagus	Condition	SNOMED	YES	YES
316457	Mallory-Weiss syndrome	Condition	SNOMED	YES	YES
46273478	Rectal hemorrhage due to ulcerative colitis	Condition	SNOMED	YES	YES
4071070	Neonatal hematemesis	Condition	SNOMED	YES	YES
4048286	Neonatal rectal hemorrhage	Condition	SNOMED	YES	YES
4103703	Melena	Condition	SNOMED	NO	YES
4048608	Neonatal melena	Condition	SNOMED	YES	YES
4265600	Gastric ulcer	Condition	SNOMED	NO	YES
4027663	Peptic ulcer	Condition	SNOMED	NO	YES
4059178	Gastrojejunal ulcer	Condition	SNOMED	NO	YES
4198381	Duodenal ulcer disease	Condition	SNOMED	NO	YES
4172869	Peptic ulcer of newborn	Condition	SNOMED	YES	YES

Supplementary Material 5: Synthetic Framework

Notation

There are N total study subjects indexed by i, and each subject has have treatment indicator w_i and p-length baseline covariate vector $\boldsymbol{x}_i$. The event time is t_i, and δ_i is the censoring indicator, with $\delta_i = 0$ indicating censoring and $\delta_i = 1$ indicating the outcome of interest. Under the proportional hazards model, η and $\boldsymbol{\beta}$ are the log hazard ratios for the treatment and the baseline covariates, respectively; the subject-specific hazard is then $\theta_i = w_i\eta + \boldsymbol{x}_i\boldsymbol{\beta}$. The baseline survival function $S(t)$ traces the probability of surviving to time t after treatment initiation and The analagous baseline censoring function is $C(t)$.

Estimate simulation components

Outcome simulation requires estimates for $S(t)$, $C(t)$, and $\boldsymbol{\beta}$. We estimate $S(t)$ by fitting a distribution to the observed outcome of interest, and $C(t)$ by fitting a distribution to the censoring times. Critically, the censoring function must be covariate-free to maintain non-informative censoring for the proportional hazards model, meaning that a subject's censoring time and survival time are independent. This point is overlooked in the "plasmode" framework, leading to inaccurate true hazard ratios that are not proportional hazards. Possible forms for $S(t)$ and $C(t)$ include parametric distributions such as exponential, Weibull, Gompertz, gamma, and lognormal; discrete nonparametric estimators such as the Breslow and Kalbfleisch-Prentice estimators (2) (which without covariates are respectively the Nelson-Aalen and Kaplan-Meier estimators); and nonparametric spline functions (3). The $S(t)$ distribution determines how the covariate coefficients $\boldsymbol{\beta}$ are estimated. For parametric and spline estimators, the parameters that characterize $S(t)$ are jointly estimated with the covariate coefficients often using maximum likelihood estimation on the full survival likelihood function. For the discrete nonparametric estimators, covariate coefficients are first estimated via the partial likelihood function, and then used to produce $S(t)$ (4, 5). The subject-specific hazard is then $\theta_i = w_i\hat{\eta} + \boldsymbol{x_i}\hat{\boldsymbol{\beta}}$ and the subject-specific survival function $S(t)^{\exp\{\theta_i\}}$, where $\hat{\eta}$ and $\hat{\boldsymbol{\beta}}$ are maximum likelihood estimates.

The nonparametric Breslow and Kalbfleisch-Prentice baseline survival function estimators are discrete functions that assign outcome probability only to empirically observed outcome times. In scenarios with relatively extreme hazard ratios or outcome prevalences, these discrete estimators can affect estimation bias by simulating excessive outcome time ties. To avoid this, we smooth these estimators to produce a non-disjoint function by linearly connecting each point in the estimators. Let the M increasingly ordered observed outcome times be $t_{(k)}, 1 \leq k \leq M$. Assume $S(t_{(0)}) = 1$ and $S(t_{(M+1)}) = 0$. We assign to $S(t : t_{(k)} < t < t_{(k+1)})$ the value at t on the straight line between $(t_{(k)}, S(t_{(k)}))$ and $(t_{(k+1)}, S(t_{(k+1)}))$. Because only the ordering of survival times affects the proportional hazards likelihood, our simple smoothing approach suffices to prevent excessively tied times.

For our simulations, we obtain $\hat{\boldsymbol{\beta}}$ through partial likelihood maximum likelihood estimation, and include L_1-regularization on all covariates except treatment to promote model fitting (6). We manually select the regularization penalty to yield an approximate model size of 500, coinciding with the number of covariates selected by the hdPS. We use the Breslow estimator for $S(t)$ (5), and the Nelson-Aalen estimator for $C(t)$.

Simulate outcome and censoring times

Under the proportional hazards framework, each subject's survival process is $S(t)^{\exp\{\theta_i\}}$ and censoring process $C(t)$. We use inverse transform sampling and draw for each subject two Unif$(0, 1)$ random variables $R_{i,s}$ and $R_{i,c}$. The respective outcome and censoring times are $t_{i,s} = \min\{t : S_i(t) \leq R_{i,s}\}$ and $t_{i,c} = \min\{t : C(t) \leq R_{i,c}\}$. The final simulated event is the miminum time:

$$\begin{aligned} t_i &= \min\{t_{i,s}, t_{i,c}\} \\ \delta_i &= \begin{cases} 1 & t_{i,s} < t_{i,c} \\ 0 & t_{i,s} \geq t_{i,c} \end{cases}. \end{aligned} \tag{1}$$

Adjust simulation for hazard ratio and outcome prevalence

To simulate under a desired treatment hazard ratio η^*, we replace the empirically estimated $\hat{\eta}$ by η^*: $\theta_i = w_i\eta^* + x_i\hat{\beta}$. The expected resultant simulated outcome prevalence (OP) is

$$p = \frac{1}{N}\sum_i \int_0^\infty \Pr\left(t_{i,s} = t < t_{i,c}\right) \mathrm{d}t = \frac{1}{N}\sum_i \int_0^\infty \left(\frac{\partial}{\partial t} S(t)^{\exp\{\theta_i\}}\right) C(t) \,\mathrm{d}t. \tag{2}$$

Let $t_{(k)}$ be the observed outcome times; the corresponding equation for discrete estimators is

$$p = \frac{1}{N} \sum_{i} \sum_{t_{(k)}} \left[S\left(t_{(k-1)}\right)^{\exp\{\theta_i\}} - S\left(t_{(k)}\right)^{\exp\{\theta_i\}} \right] C(t_{(k)}). \tag{3}$$

To adjust the simulated outcome prevalence, several different approaches are available that can suit the investigator. Each requires solving outcome prevalence Equation (2) for an adjustment factor γ:

- Adjust outcome hazard – multiply the outcome baseline hazard by a fixed constant $\gamma \in (0, \infty)$ so the baseline survival function becomes $S(t) \to S(t)^{\gamma}$. This aligns with a proportional hazards interpretation of adjusting the baseline function.

- Adjust censoring hazard – multiply the censoring hazard by a fixed constant $\gamma \in (0, \infty)$, so the censoring function becomes $C(t) \to C(t)^{\gamma}$. Note that the maximum achievable outcome prevalence is $1 - S(T)$ when $C(t) = 1$, where T is the maximum observed outcome time.

- Accelerate survival process – scale time by a factor $\gamma \in (0, \infty)$ in the survival function, to obtain a new survival function $S(t) \to S(\gamma t)$. This aligns with an accelerated life interpretation of adjusting the baseline function

For our simulations, we use the first approach, similar to the "plasmode" framework.

Supplementary Material 6: Anticoagulants Study Negative Controls

Negative controls were selected using the following criteria from (7):

- No evidence found in literature on clinical trials using the method proposed by Avillach (8)

- No evidence found in literature using the method used in SemMedDB (9)

- No evidence found in the structured product label (US and EU).

- FAERS Proportional Reporting Ratio (PRR) needed to be less than 2.

Negative controls were rank-ordered by prevalence in study cohort, and manually reviewed until 50 controls were selected. Negative controls with fewer than 0.02% prevalence were discarded.

Acute bronchitis	Allergic rhinitis
Anxiety disorder	Arthritis of spine
Arthropathy of knee joint	Atelectasis
Barrett's esophagus	Blepharitis
Bronchiectasis	Bundle branch block
Cellulitis	Chronic sinusitis
Chronic ulcer of skin	Communication disorder
Crohn's disease	Curvature of spine
Cutis laxa	Diabetic renal disease
Diabetic retinopathy	Dislocation of joint
Dyssomnia	Dysuria
Effusion of joint	Fracture of upper limb
Gallstone	Gammopathy
Human papilloma virus infection	Hyperplasia of prostate
Inflammation of sacroiliac joint	Ingrowing nail
Malignant tumor of breast	Multiple sclerosis
Neck pain	Neurologic disorder associated with diabetes mellitus
Obesity	Osteomyelitis
Otitis media	Peripheral vertigo
Plantar fasciitis	Presbyopia
Prolapse of female genital organs	Psychotic disorder
Seborrheic keratosis	Simple goiter
Sleep apnea	Superficial mycosis
Urge incontinence of urine	Urinary tract infectious disease
Verruca vulgaris	

Supplementary Material 7: NSAIDs Study Negative controls

Negative controls selected similarly to Anticoagulants study (Supplementary Material 6).

Adjustment disorder	Alcohol abuse
Aphasia	Astigmatism
Atelectasis	Bell's palsy
Candida infection of genital region	Carcinoma in situ of breast
Chalazion	Curvature of spine
Cutis laxa	Deficiency of macronutrients
Diabetic oculopathy	Drug withdrawal
Exostosis	Fibrocystic disease of breast
Human papilloma virus infection	Hydrocele
Ingrowing nail	Intracranial injury
Meniere's disease	Non-toxic nodular goiter
Non-toxic uninodular goiter	Presbyopia
Scoliosis deformity of spine	Secondary malignant neoplastic disease
Tinea pedis	Verruca vulgaris
Vitamin D deficiency	

Supplementary Material 8: Covariate Sets

OHDSI Covariates

- Demographics (age in 5-year increments, gender, year of index date)
- Condition Occurrence (condition occurrence in lookback window)
  - in 365 days prior to index date
  - in 180 days prior to index date
  - in 30 days prior to index date
- Condition Era (span of time when person assumed to have condition)

  - ever
  - overlapping with index date
- Drug Exposure (drug occurrence in lookback window)
  - in 365 days prior to index date
  - in 30 days prior to index date
- Drug Era (span of time when person assumed to have drug)
  - in 365 days prior to index date
  - in 30 days prior to index date
  - ever
  - overlapping with index date
- Procedure Occurrence
  - in 365 days prior to index date
  - in 30 days prior to index date
- Observation
  - in 365 days prior to index date
  - in 30 days prior to index date
  - observations count in 365 days prior to index date
- Measurement
  - in 365 days prior to index date
  - in 30 days prior to index date
  - high measurement in 180 days prior to index date
  - low measurement in 180 days prior to index date
  - measurements count in 365 days prior to index date
- Concepts Count in 365 days prior to index date
- Risk Scores (Charlson, DCSI, CHADS2)

hdPS Covariates

- Demographics (age in 5-year increments, gender, year of index date)
- Inpatient 3-Digit ICD9 Condition Codes
    - in 180 days prior to index date
    - $> 50^{\text{th}}$ percentile in 180 days prior to index date
    - $> 75^{\text{th}}$ percentile in 180 days prior to index date
- Outpatient 3-Digit ICD9 Condition Codes
    - in 180 days prior to index date
    - $> 50^{\text{th}}$ percentile in 180 days prior to index date
    - $> 75^{\text{th}}$ percentile in 180 days prior to index date
- Drug Ingredient Exposure
    - in 180 days prior to index date
    - $> 50^{\text{th}}$ percentile in 180 days prior to index date
    - $> 75^{\text{th}}$ percentile in 180 days prior to index date
- Inpatient CPT-4 Procedure Codes
    - in 180 days prior to index date
    - $> 50^{\text{th}}$ percentile in 180 days prior to index date
    - $> 75^{\text{th}}$ percentile in 180 days prior to index date
- Outpatient CPT-4 Proceudre Codes
    - in 180 days prior to index date
    - $> 50^{\text{th}}$ percentile in 180 days prior to index date
    - $> 75^{\text{th}}$ percentile in 180 days prior to index date

Covariates Excluded in Anticoagulants Study

RxNorm drugs Dabigatran (concept id 40228152), Warfarin (concept id 1310149); and all decescendent drugs / formulations.

Covariates Excluded in NSAIDs Study

RxNorm drugs Diclofenac (concept id 1124300), Celecoxib (concept id 1118084), Ingredients NSAIDs (concept id 21603933), Coxibs (concept id 21603991); and all decescendent drugs / formulations.

Supplementary Material 9: Propensity Score Methods

We use the default hdPS settings including considering only the 200 most prevalent covariates in each "data dimension" and selecting the top 500 overall ranked covariates.

After estimating the PS, we perform PS matching and then estimate the treatment hazard ratio using a stratified Cox survival outcome model with treatment as the only covariate. We avoid one-to-one matching due to inferior covariate balance (10) and bias reduction (11), and instead use variable length matching (12) with a maximum ratio of 10:1 and a propensity score caliper of 0.05, and use a greedy matching algorithm (13). We use the less prevalent treatment as the "one" in the many-to-one matching to maximize the number of subjects that are matched.

Supplementary Material 10: Propensity Score Estimate Existence

Supplementary Table 1 shows the convergence frequency of the hdPS across a spectrum of simulated sample sizes and outcome prevalences. The NSAIDs study demonstrates poorer hdPS estimate existence compared to the Anticoagulants study, including a complete failure of the exposure-based hdPS at any cohort size. In both studies, simulations with smaller cohorts and lower outcome prevalences have less likely PS estimate existence. Overall, the feasible use of the hdPS without regularization is data dependent and better suited for larger cohorts and more common outcomes. The inclusion of statistical regularization in the PS model readily solves this convergence problem.

	Sample	exp-	bias-hdPS			
Study	size	hdPS	0.5%	1%	5%	10%
Anticoagulants	72,489	100%*	100%	100%	100%	100%
	30,000	100%	99%	100%	100%	100%
	10,000	76%	63%	83%	100%	99%
	5,000	26%	46%	24%	80%	81%
NSAIDs	121,317	0%*	99%	99%	100%	100%
	30,000	0%	0%	9%	43%	63%
	10,000	0%	1%	0%	0%	0%
	5,000	0%	1%	0%	0%	0%

Supplementary Table 1: Frequency of propensity score estimate existence “convergence” in simulations using hdPS without regularization, over 100 simulations. Smaller cohort sizes are drawn repeatedly without replacement from the full cohort size. *exp-hdPS on full cohorts is tested only once.

Supplementary Material 11: Bias Towards Null in Simulation Experiment

In the simulation experiments, the data are simulated under a proportional hazards survival model, matched on estimated propensity scores, and then fit under a Cox proportional hazards outcome model with treatment as the only covariate. The partial likelihood of the outcome model is

$$\log L = \sum_{k} \sum_{i:\delta_{i,k}=1} \left(w_{i,k}\eta - \log \sum_{j \in R_{i,k}} e^{w_{j,k}\eta} \right), \tag{4}$$

where k indexes the strata/matched sets, i indexes the subjects in each strata, $w_{i,k}$ is the exposure indicator, $\delta_{i,k}$ is the censoring indicator, and $R_{i,k}$ is the risk set for a subject in the strata.

We consider the case of one-to-one matching, in which the maximum likelihood estimate can be derived analytically. In matched set k, let $t_{0,k}$ and $t_{1,k}$ be the outcome times of the untreated and treated subjects, respectively. Because there is contribution to the log-likelihood only from non-censored subjects, the only configurations for matched sets that contribute to the log-likelihood are as follows:

Case	$\delta_{0,k}$	$\delta_{1,k}$	$t_{0,k}$? $t_{1,k}$	log-L contribution
A	1	0	$\leq$	$0 - \log(1+e^{\eta})$
B	0	1	$\geq$	$\eta - \log(1+e^{\eta})$
C	1	1	$<$	$0 - \log(1+e^{\eta})$
D	1	1	$>$	$\eta - \log(1+e^{\eta})$
E	1	1	$=$	$\eta - 2\log(1+e^{\eta})$

Supplementary Table 2: Contribution of matched sets to likelihood

Let N_A denote the number of sets with case A, and likewise for the other cases. The log-likelihood can be written:

$$\log L = (N_A + N_C + N_E)[-\log(1 + e^{\eta})] + (N_B + N_D + N_E)[\eta - \log(1 + e^{\eta})]. \tag{5}$$

The sum $N_A + N_C + N_E$ is equal to the number of sets with $\delta_{0,k} = 1$ and $t_{0,k} \leq t_{1,k}$. Similarly, the sum $N_B + N_D + N_E$ is equal to the number of sets with $\delta_{1,k} = 1$ and $t_{0,k} \geq t_{1,k}$. Define $N_0 = N_A + N_C + N_E$ and $N_1 = N_B + N_D + N_E$. A second-derivative test with respect to η shows this is concave in η; we solve by setting the first-derivative to zero:

$$\begin{aligned} \left.\frac{\partial \log L}{\partial \eta}\right|_{\eta=\hat{\eta}} = N_0(-\frac{e^{\hat{\eta}}}{1+e^{\hat{\eta}}}) + N_1(1 - \frac{e^{\hat{\eta}}}{1+e^{\hat{\eta}}}) &= 0 \\ N_0(-e^{\hat{\eta}}) + N_1(1) &= 0 \\ e^{\hat{\eta}} &= \frac{N_1}{N_0} \\ \hat{\eta} &= \log N_1 - \log N_0. \end{aligned} \tag{6}$$

The observed bias to the null arises from the nonlinear effect that differences in hazard under the generative outcome model between matched subjects has on the estimated hazard ratio. In our simulation process, each subject has a simulated outcome and censoring time, and the minimum is the observed time. Let $t_{i,k,s}$ and $t_{i,k,c}$ be the simulated outcome and censoring time for subject i in set k. Then N_0 is a sum of indicators $N_0 = \sum_k \mathbb{1}_{\{t_{0,k,s} \leq \min\{t_{0,k,c}, t_{1,k,s}, t_{1,k,c}\}\}}$ and N_1 is a sum of indicators $N_1 = \sum_k \mathbb{1}_{\{t_{1,k,s} \leq \min\{t_{1,k,c}, t_{0,k,s}, t_{0,k,c}\}\}}$. These indicators have the probabilities:

$$\begin{aligned} \Pr\left(t_{0,k,s} \leq \min\{t_{0,k,c}, t_{1,k,s}, t_{1,k,c}\}\right) &= \int_0^{\infty} \left(\frac{\partial}{\partial t} S(t)^{\exp\{\theta_{0,k}\}}\right) S(t)^{\exp\{\theta_{1,k}\}} C(t) C(t) \mathrm{d}t \text{ and} \\ \Pr\left(t_{1,k,s} \leq \min\{t_{1,k,c}, t_{0,k,s}, t_{0,k,c}\}\right) &= \int_0^{\infty} \left(\frac{\partial}{\partial t} S(t)^{\exp\{\theta_{1,k}\}}\right) S(t)^{\exp\{\theta_{0,k}\}} C(t) C(t) \mathrm{d}t. \end{aligned} \tag{7}$$

The subject-specific hazards are $\theta_{0,k} = \boldsymbol{x_{0,k}\beta}$ and $\theta_{1,k} = \eta^* + \boldsymbol{x_{1,k}\beta}$. There is a complicated relationship between η^* and $\hat{\eta}$ that contributes to the observed bias.

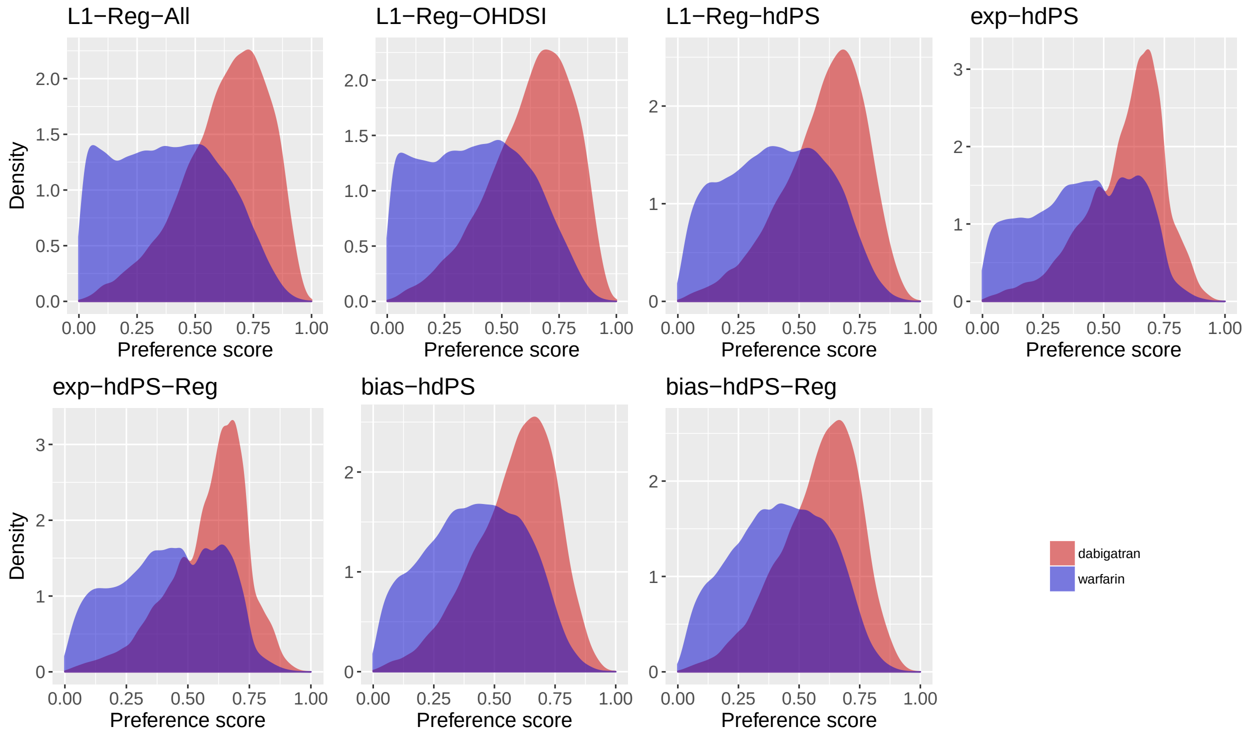
We use simple simulations to empirically reproduce the bias towards the null observed in our simulation experiment results. We assign hazards to subjects in 1-1 matched sets, simulate event times, and then fit a stratified Cox model. We draw $\theta_{0,k}$ and $\theta_{1,k}$ from independent normal distributions and introduce different true effect sizes η^*. We use a decaying exponential function for both $S(t)$ and $C(t)$. We use a dataset of 50,000 assigned to 25,000 matched sets. For each effect size, we run 100 simulations.

θ dist	η^*	bias	sd
$\theta_{0,k}, \theta_{1,k} \sim N(0, 0.1)$	-1.0	0.0026	0.0023
$\theta_{0,k}, \theta_{1,k} \sim N(0, 0.1)$	-0.5	0.0009	0.0019
$\theta_{0,k}, \theta_{1,k} \sim N(0, 0.1)$	0.0	-0.0002	0.0018
$\theta_{0,k}, \theta_{1,k} \sim N(0, 0.1)$	0.5	-0.0006	0.0018
$\theta_{0,k}, \theta_{1,k} \sim N(0, 0.1)$	1.0	-0.0045	0.0017
$\theta_{0,k}, \theta_{1,k} \sim N(0, 1.0)$	-1.0	0.1677	0.0022
$\theta_{0,k}, \theta_{1,k} \sim N(0, 1.0)$	-0.5	0.0910	0.0017
$\theta_{0,k}, \theta_{1,k} \sim N(0, 1.0)$	0.0	0.000027	0.0017
$\theta_{0,k}, \theta_{1,k} \sim N(0, 1.0)$	0.5	-0.1007	0.0018
$\theta_{0,k}, \theta_{1,k} \sim N(0, 1.0)$	1.0	-0.2097	0.0015
$\theta_{0,k}, \theta_{1,k} \sim N(1, 1.0)$	-1.0	0.2085	0.0019
$\theta_{0,k}, \theta_{1,k} \sim N(1, 1.0)$	0.0	0.0011	0.0017
$\theta_{0,k}, \theta_{1,k} \sim N(1, 1.0)$	1.0	-0.2380	0.0016
$\theta_{0,k} \sim N(0, 1), \theta_{1,k} = \theta_{0,k}$	-1.0	0.0035	0.0023
$\theta_{0,k} \sim N(0, 1), \theta_{1,k} = \theta_{0,k}$	0.0	-0.0006	0.0017
$\theta_{0,k} \sim N(0, 1), \theta_{1,k} = \theta_{0,k}$	1.0	0.0023	0.0018

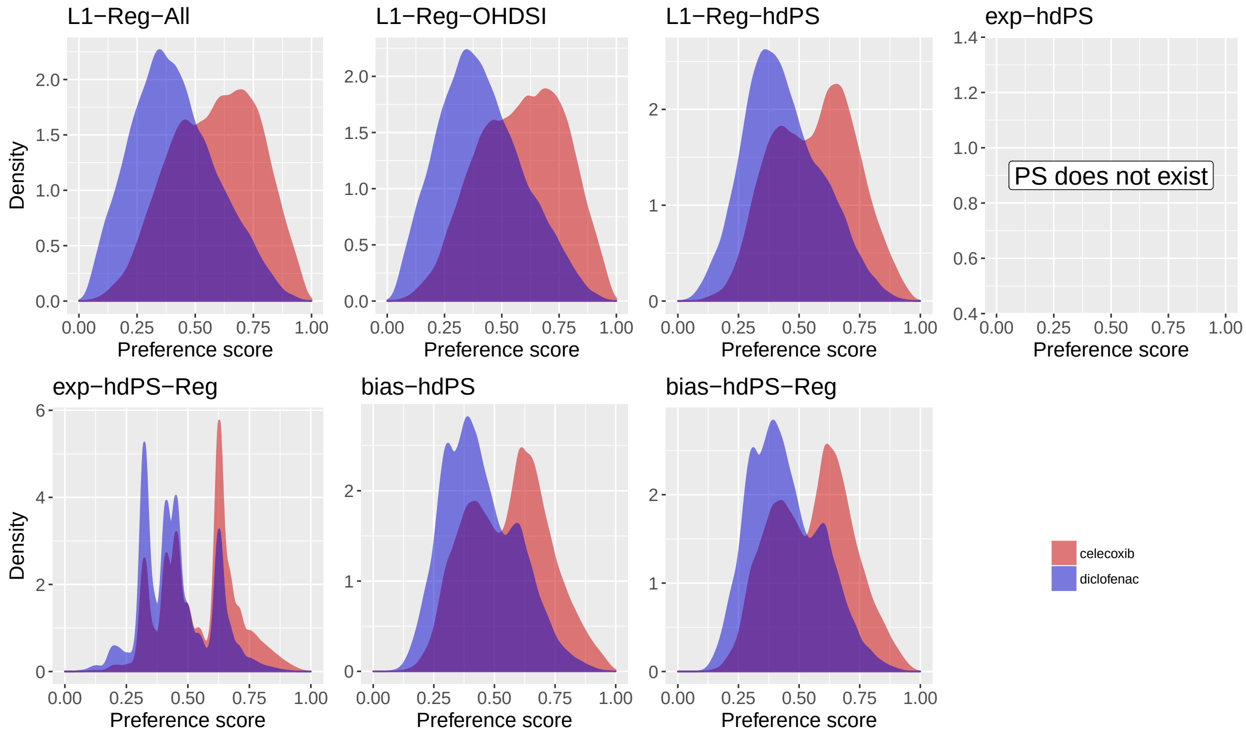
Supplementary Table 3: Estimation bias from true hazard ratio for different distributions of matched hazards

The simulations show that the observed bias arises from the distribution of hazard differences $\theta_{1,k} - \theta_{0,k}$ across matched sets. Even if the average hazard difference is exactly η^*, the variance in the hazard differences causes a bias towards the null. The larger the variance, the greater the bias.

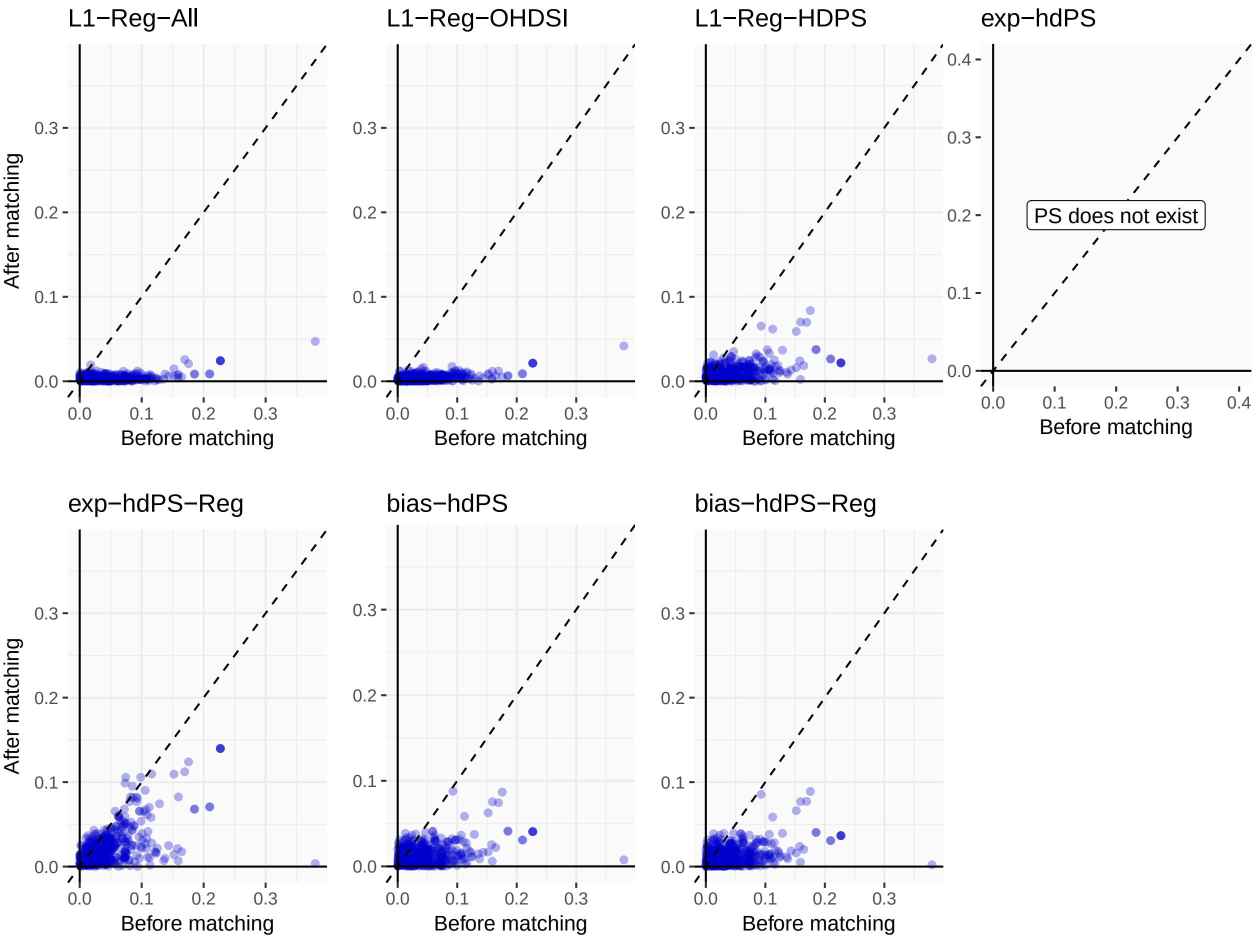
Supplementary Material 12: Additional Results



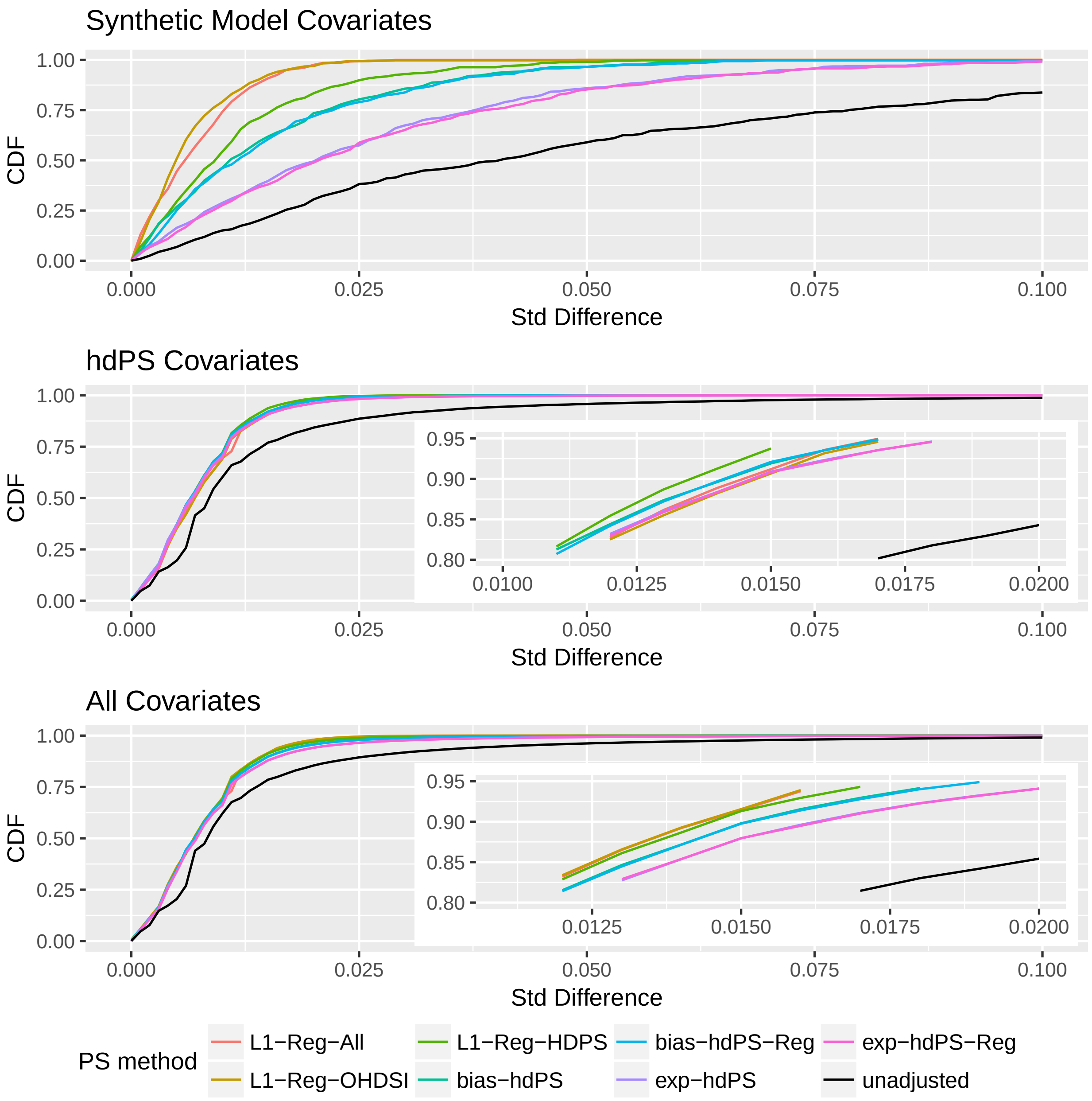
Supplementary Figure 1: Anticoagulants study: preference score distributions. Bias-based hdPS used on the empirical outcome of interest.



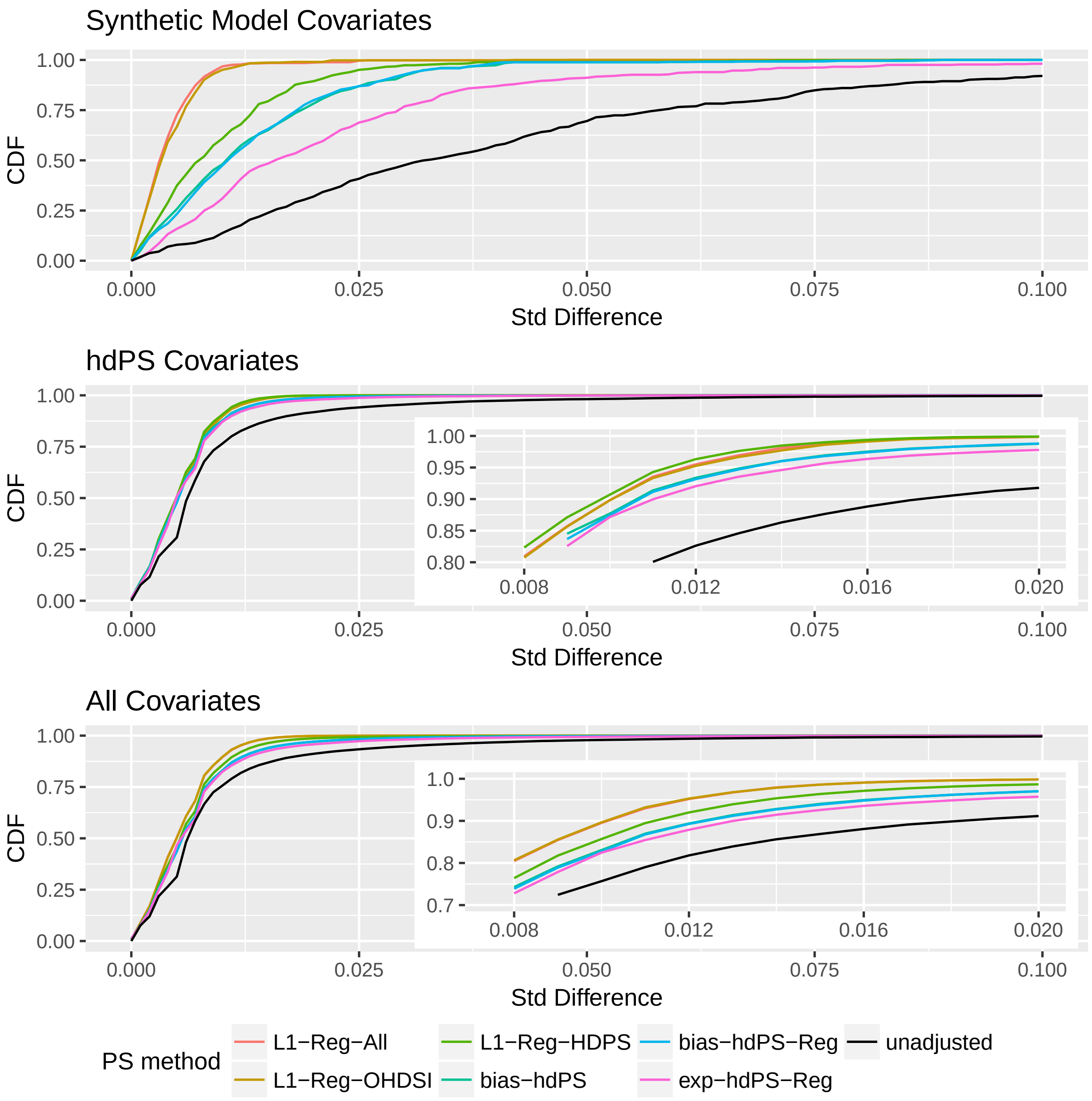
Supplementary Figure 2: NSAIDs study: preference score distributions. Bias-based hdPS used on the empirical outcome of interest.



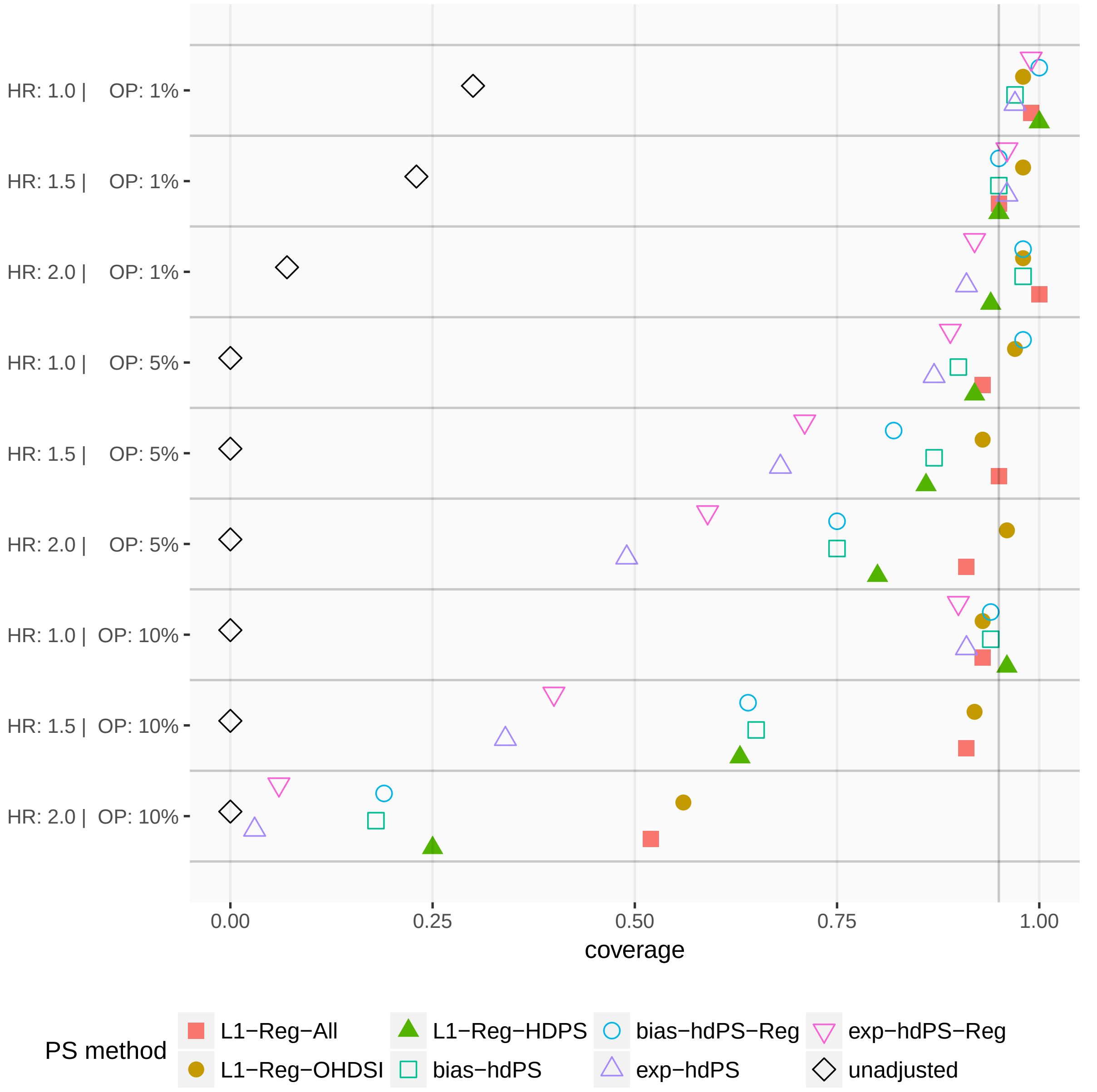
Supplementary Figure 3: NSAIDs study: before and after PS matching scatterplot of absolute standardized differences for synthetic model covariates. Before matching outlier is “Index Year: 2005,” and corresponds to a documented decrease in celecoxib marketing and sales.



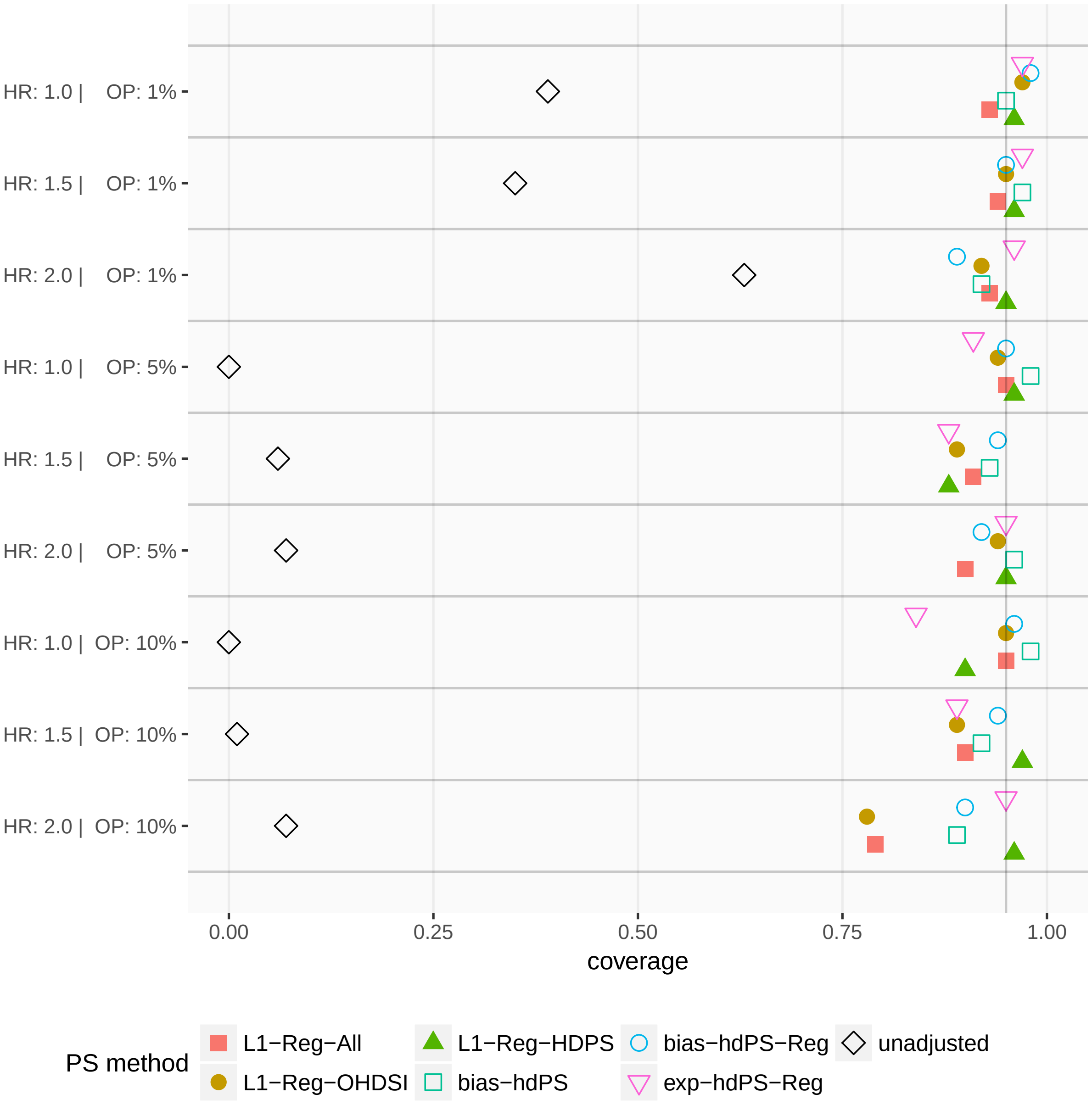
Supplementary Figure 4: Anticoagulants study: empirical cumulative distribution function of post-PS matching standardized differences for synthetic model covariates (top), hdPS Covariates (middle), and all covariates (bottom). Inlets provide closer view of differences between methods



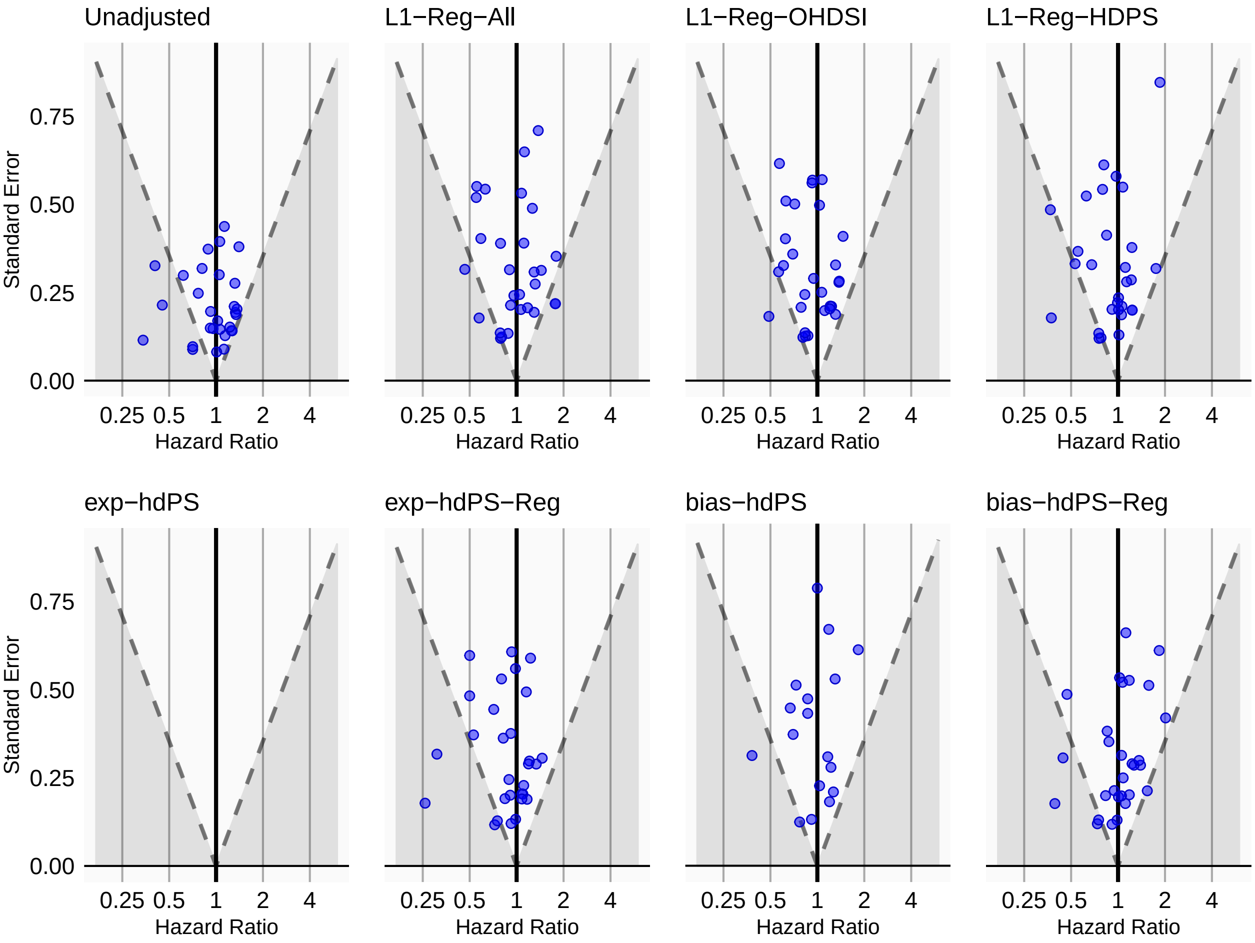
Supplementary Figure 5: NSAIDs study: empirical cumulative distribution function of post-PS matching standardized differences for synthetic model covariates (top), hdPS Covariates (middle), and all covariates (bottom). Inlets provide closer view of differences between methods



Supplementary Figure 6: Anticoagulants study: coverage of true hazard ratio (HR) across 100 simulations under different simulation parameters of true HR and outcome prevalence (OP)



Supplementary Figure 7: NSAIDs study: coverage of true hazard ratio (HR) across 100 simulations under different simulation parameters of true HR and outcome prevalence (OP)



Supplementary Figure 8: NSAIDs study: hazard ratio estimates (horizontal axis) and width of 95% confidence interval [via standard error] (vertical axis) for 29 negative control outcomes. Dashed line represents the straight line boundary at where the 95% confidence interval does (above) or does not (below) contain the assumed true hazard ratio of 1. Coverage indicates proportion of intervals that contains 1. bias-hdPS fails to construct 12 of the 29 PS models, and exp-hdPS fails to construct all 29.

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