Evaluation of methods for synthesizing interaction effect estimates

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# 1 Introduction

There are several challenges when estimating causal effects across a distributed (federated) research network:

1. Sharing of individual patient data (IPD) is not allowed.
2. The nature of the data gathering process leads to censored observation periods that require a time-to-event analysis rather than simpler incidence rate estimation.
3. Due to the observational nature of the data and the consequent potential for confounding, some correction for baseline differences between exposure groups always proves necessary, typically via stratifying, matching, or weighting by a propensity score or disease risk score.
4. Since different data sites represent different patient populations, inter-site heterogeneity often arises.
5. Even though many of these health care databases contain the records of large numbers of patients, co-occurrences of even moderately rare exposures and/or outcomes often prove to be sparse to non-existent.

In our prior work (Schuemie et al. 2022) we proposed to solve this problem by sharing likelihood profiles between sites; Instead of sharing the point estimates and standard errors (which imply the likelihood follows a normal distribution), sites would share the shape of the likelihood curve. Our result shows that, when counts are low (as often happens as mentioned under 5), our approach provides unbiased estimates. In contrast, using a normal approximation can lead to substantial bias.

Here we aim to extend our work to situations where there is more than one parameter of interest. Specifically, we are interested in the synthesis of evidence on interactions between two exposures. Our prior work applied to single parameters of interest (e.g. the main effect), but often we want to know both the main effect and some interaction effect (e.g. is the causal effect larger in some subgroup of interest?).

The research described here aims to completed extensive simulation studies by testing several approaches to likelihood profiling for effect interactions in a real worl setting.

# 2 Example interaction effect study

To evaluate the use of likelihood profiles when synthesizing evidence on interaction effects, we will use the following example: non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) are known to increase the risk of gastrointestinal (GI) bleeding, and this risk is known to increase when the patient is also on an oral anticoagulant such as warfarin. (Choi et al. 2010)

We therefore formulate an example comparative cohort study as follows:

* **Target**: New users of diclofenac (a non-selective NSAID)
* **Comparator**: New users of celecoxib (a selective COX-2 inhibitor NSAID)
* **Outcome**: GI bleed
* **Interaction term**: Warfarin exposure at the time of NSAID initiation
* **Time at risk**: On-treatment: starting on the day of treatment initiation, ending when treatment is stopped (for at least 30 days).
* **Model**: Either Cox or Poisson regression

Cohort definitions of the target, comparator, and outcome are provided in Appendix A. The outcome cohort definition was taken from the OHDSI Phenotype Library.

Warfarin exposure is defined as a drug era overlapping with the target or comparator index date, having ingredient concept ID 1310149 (Warfarin).

We will require at least 365 days of continuous observation prior to the index date.

Large-scale propensity scores (PS) will be fitted using the standard set of features, including all drugs, conditions, procedures, measurements, and observations in the year prior to index date, as well as demographics. We will use the PS to stratify the population in 10 equally-sized strata.

The cohort and comparator cohorts will be restricted to at most 100,000 subjects. If these cohorts are larger, a 100,000 random sample will be taken.

A set of 34 negative control outcomes, outcomes believed to be caused by neither the target nor the comparator, has been defined. (See Appendix B). We assume that these controls are negative both for the main effect and the interaction effect.

# 3 Evaluation of evidence synthesis methods

The example study will be executed across the databases described in the ‘Data sources’ section. Various approaches for likelihood profiling will be applied to produce summary estimates for the main effect and the interaction effect, both for the outcome of interest (GI bleed) as well as the negative control outcomes.

The summary estimates for GI bleed will be compared with the gold standard, produced by pooling the data (stratified by data source).

The negative control summary estimates will be used to estimate residual systematic error.

# 4 Data sources

The DatabaseDiagnostics package was used to select those databases that appear to have the elements needed for the example estimation questions:

# 5 References

Choi, K. H., A. J. Kim, I. J. Son, K. H. Kim, K. B. Kim, H. Ahn, and E. B. Lee. 2010. “Risk factors of drug interaction between warfarin and nonsteroidal anti-inflammatory drugs in practical setting.” *J Korean Med Sci* 25 (3): 337–41.

Schuemie, M. J., Y. Chen, D. Madigan, and M. A. Suchard. 2022. “Combining cox regressions across a heterogeneous distributed research network facing small and zero counts.” *Stat Methods Med Res* 31 (3): 438–50.

# 6 Appendix A: Cohort Definitions

## 6.1 Target

### 6.1.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug era of ‘DOAC’ for the first time in the person’s history.

### 6.1.2 Inclusion Criteria

#### 6.1.2.1 1. Prior afib

Entry events having at least 1 condition occurrence of ‘Atrial fibrillation’, starting anytime on or before cohort entry start date.

### 6.1.3 Cohort Exit

The cohort end date will be based on a continuous exposure to ‘DOAC’: allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

### 6.1.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 6.1.5 DOAC

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 43013020 | apixaban | 1364430 | RxNorm | NO | YES | NO |
| 45892850 | edoxaban | 1599538 | RxNorm | NO | YES | NO |
| 45775370 | dabigatran | 1546356 | RxNorm | NO | YES | NO |
| 40241330 | rivaroxaban | 1114195 | RxNorm | NO | YES | NO |
| 1592988 | betrixaban | 1927851 | RxNorm | NO | YES | NO |
| 40228150 | dabigatran etexilate | 1037042 | RxNorm | NO | YES | NO |

### 6.1.6 Atrial fibrillation

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | 49436004 | SNOMED | NO | YES | NO |

## 6.2 Comparator

### 6.2.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug era of ‘Warfarin’ for the first time in the person’s history.

### 6.2.2 Inclusion Criteria

#### 6.2.2.1 1. Prior afib

Entry events having at least 1 condition occurrence of ‘Atrial fibrillation’, starting anytime on or before cohort entry start date.

### 6.2.3 Cohort Exit

The cohort end date will be based on a continuous exposure to ‘Warfarin’: allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

### 6.2.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 6.2.5 Warfarin

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 1310149 | warfarin | 11289 | RxNorm | NO | YES | NO |

### 6.2.6 Atrial fibrillation

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 313217 | Atrial fibrillation | 49436004 | SNOMED | NO | YES | NO |

## 6.3 Mediator

### 6.3.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘[EPI\_1001] Bleeding’, a condition status that is: “primary diagnosis”.
2. condition occurrences of ‘[EPI\_1001] Bleeding related disorders’, a condition status that is: “primary diagnosis”; having at least 1 condition occurrence of ‘[EPI\_1001] Bleeding’, starting between 0 days before and 0 days after ‘[EPI\_1001] Bleeding related disorders’ start date.

### 6.3.2 Inclusion Criteria

#### 6.3.2.1 1. During inpatient or ER visit

Entry events having at least 1 visit occurrence of ‘Inpatient or ER’, starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

### 6.3.3 Cohort Exit

The cohort end date will be offset from index event’s start date plus 30 days.

### 6.3.4 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 6.3.5 [EPI\_1001] Bleeding

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 437312 | Bleeding | 131148009 | SNOMED | NO | YES | NO |

### 6.3.6 Inpatient or ER

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 9201 | Inpatient Visit | IP | Visit | NO | YES | NO |
| 262 | Emergency Room and Inpatient Visit | ERIP | Visit | NO | YES | NO |
| 8717 | Inpatient Hospital | 21 | CMS Place of Service | NO | YES | NO |
| 581379 | Inpatient Critical Care Facility | OMOP4822042 | CMS Place of Service | NO | YES | NO |
| 581383 | Inpatient Cardiac Care Facility | OMOP4822038 | CMS Place of Service | NO | YES | NO |
| 9203 | Emergency Room Visit | ER | Visit | NO | YES | NO |
| 262 | Emergency Room and Inpatient Visit | ERIP | Visit | NO | YES | NO |
| 8870 | Emergency Room - Hospital | 23 | CMS Place of Service | NO | YES | NO |
| 581381 | Emergency Room Critical Care Facility | OMOP4822040 | CMS Place of Service | NO | YES | NO |

### 6.3.7 [EPI\_1001] Bleeding related disorders

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 439777 | Anemia | 271737000 | SNOMED | NO | YES | NO |
| 195562 | Hemorrhoids | 70153002 | SNOMED | NO | YES | NO |
| 30753 | Esophagitis | 16761005 | SNOMED | NO | YES | NO |
| 4265600 | Gastric ulcer | 397825006 | SNOMED | NO | YES | NO |
| 4028242 | Chronic duodenal ulcer | 128286008 | SNOMED | NO | YES | NO |
| 4057053 | Acute duodenal ulcer | 196652006 | SNOMED | NO | YES | NO |
| 4027663 | Peptic ulcer | 13200003 | SNOMED | NO | YES | NO |
| 4059178 | Gastrojejunal ulcer | 16121001 | SNOMED | NO | YES | NO |
| 201340 | Gastritis | 4556007 | SNOMED | NO | YES | NO |
| 433516 | Duodenitis | 72007001 | SNOMED | NO | YES | NO |
| 193252 | Diverticulosis of small intestine | 8114009 | SNOMED | NO | YES | NO |
| 42535740 | Diverticulosis of colon | 733657002 | SNOMED | NO | YES | NO |
| 4306267 | Coag./bleeding tests abnormal | 165563002 | SNOMED | NO | YES | NO |

## 6.4 Outcome

### 6.4.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘Acute myocardial Infarction’.
2. condition occurrences of ‘Sudden cardiac death’.
3. condition occurrences of ‘Ischemic stroke’.
4. condition occurrences of ’ Intracranial bleed Hemorrhagic stroke’.

Restrict entry events to having at least 1 visit occurrence of ‘Inpatient or ER visit’, starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

### 6.4.2 Cohort Exit

The cohort end date will be offset from index event’s start date plus 14 days.

### 6.4.3 Cohort Eras

Remaining events will be combined into cohort eras if they are within 0 days of each other.

### 6.4.4 Inpatient or ER visit

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 262 | Emergency Room and Inpatient Visit | ERIP | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | ER | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | IP | Visit | NO | YES | NO |

### 6.4.5 Acute myocardial Infarction

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | 22298006 | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | 1755008 | SNOMED | YES | YES | NO |

### 6.4.6 Sudden cardiac death

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 4048809 | Brainstem death | 230802007 | SNOMED | NO | YES | NO |
| 321042 | Cardiac arrest | 410429000 | SNOMED | NO | YES | NO |
| 442289 | Death in less than 24 hours from onset of symptoms | 53559009 | SNOMED | NO | YES | NO |
| 4317150 | Sudden cardiac death | 95281009 | SNOMED | NO | YES | NO |
| 4132309 | Sudden death | 26636000 | SNOMED | NO | YES | NO |
| 437894 | Ventricular fibrillation | 71908006 | SNOMED | YES | YES | NO |

### 6.4.7 Ischemic stroke

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 372924 | Cerebral artery occlusion | 20059004 | SNOMED | NO | NO | NO |
| 375557 | Cerebral embolism | 75543006 | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | 432504007 | SNOMED | NO | YES | NO |
| 441874 | Cerebral thrombosis | 71444005 | SNOMED | NO | NO | NO |

### 6.4.8 Intracranial bleed Hemorrhagic stroke

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 376713 | Cerebral hemorrhage | 274100004 | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | 1386000 | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | 21454007 | SNOMED | NO | NO | NO |
| 43530730 | Spontaneous cerebral hemorrhage | 291571000119106 | SNOMED | NO | NO | NO |
| 4148906 | Spontaneous subarachnoid hemorrhage | 270907008 | SNOMED | NO | NO | NO |

### 6.4.9 Heart Failure

| Concept ID | Concept Name | Code | Vocabulary | Excluded | Descendants | Mapped |
| --- | --- | --- | --- | --- | --- | --- |
| 315295 | Congestive rheumatic heart failure | 82523003 | SNOMED | YES | YES | NO |
| 316139 | Heart failure | 84114007 | SNOMED | NO | YES | NO |

# 7 Appendix B: Negative controls

| Concept ID | Name |
| --- | --- |
| 437643 | Abnormal gait |
| 260139 | Acute bronchitis |
| 257007 | Allergic rhinitis |
| 442077 | Anxiety disorder |
| 4153359 | Arthritis of spine |
| 4324765 | Arthropathy of knee joint |
| 261880 | Atelectasis |
| 443344 | Barrett’s esophagus |
| 378425 | Blepharitis |
| 256449 | Bronchiectasis |
| 313791 | Bundle branch block |
| 435613 | Cellulitis |
| 257012 | Chronic sinusitis |
| 134441 | Chronic ulcer of skin |
| 4150614 | Communication disorder |
| 201606 | Crohn’s disease |
| 73302 | Curvature of spine |
| 4242416 | Cutis laxa |
| 74726 | Dislocation of joint |
| 192279 | Disorder of kidney due to diabetes mellitus |
| 443730 | Disorder of nervous system due to diabetes mellitus |
| 435657 | Dyssomnia |
| 197684 | Dysuria |
| 79903 | Effusion of joint |
| 4050747 | Fracture of upper limb |
| 196456 | Gallstone |
| 4007453 | Gammopathy |
| 441788 | Human papilloma virus infection |
| 197032 | Hyperplasia of prostate |
| 4208390 | Inflammation of sacroiliac joint |
| 139099 | Ingrowing nail |
| 4112853 | Malignant tumor of breast |
| 374919 | Multiple sclerosis |
| 24134 | Neck pain |
| 433736 | Obesity |
| 141663 | Osteomyelitis |
| 372328 | Otitis media |
| 78162 | Peripheral vertigo |
| 4002650 | Plantar fasciitis |
| 373478 | Presbyopia |
| 199876 | Prolapse of female genital organs |
| 436073 | Psychotic disorder |
| 4174977 | Retinopathy due to diabetes mellitus |
| 141932 | Senile hyperkeratosis |
| 141825 | Simple goiter |
| 313459 | Sleep apnea |
| 4077081 | Superficial mycosis |
| 193326 | Urge incontinence of urine |
| 81902 | Urinary tract infectious disease |
| 140641 | Verruca vulgaris |