|  |
| --- |
|  |
| **Janssen Research & Development\*** |
|  |
| **Study Protocol for Retrospective Observational Studies Using Secondary Data** |
|  |
| **Quantifying Bias in Epidemiological Studies on the Association Between Acetaminophen and Cancer** |
|  |
| **Protocol** |

\* Janssen Research & Development (Janssen R&D) is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for studies of Janssen R&D may vary. The term "sponsor" is used throughout the protocol to represent these various legal entities.

**Status:** Approved

**Date:** 19 October 2019

**Prepared by:** Janssen Research & Development, LLC; Janssen Research & Development,

**EDMS number:**

**Confidentiality Statement**

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you that is indicated as *privileged or confidential*.

# TABLE OF CONTENTS

1. TABLE OF CONTENTS 2

2. LIST OF ABBREVIATIONS 4

3. RESPONSIBLE PARTIES 4

3.1. Investigator(s) and Authors 4

3.2. Sponsor 4

4. ABSTRACT 4

5. AMENDMENTS AND UPDATES 4

6. RATIONALE AND BACKGROUND 5

7. STUDY Objectives 5

7.1. Primary Objective(s) 5

7.2. Secondary Objective(s) 6

8. Study Design and Setting 6

8.1. Describe Data Source(s) 6

8.2. Study Population(s) 6

8.3. Outcome(s) of Interest 6

8.3.1. Renal cell carcinoma 7

8.3.2. Primary liver cancer 7

8.3.3. Lymphoma 8

8.3.4. Multiple myeloma 10

8.4. Negative Control Outcomes 10

8.5. Exposure(s) of Interest 11

8.6. Other Variables of Interest 12

8.6.1. Case-control designs: Variables used for matching 12

8.6.2. Case-control designs: Variables used in multivariable outcome models 12

8.6.3. Cohort design: Variables used in the outcome model 12

8.6.4. Cohort design: Variables used for descriptive statistics 13

9. SAMPLE SIZE AND STUDY POWER 14

9.1. Case-control designs 14

9.2. Cohort design 14

10. DATA ANALYSIS PLAN 15

10.1. Case-control designs 15

10.1.1. Selection of controls 15

10.1.2. Matching 15

10.1.3. Exposure status 15

10.1.4. Model Specification 16

10.1.5. Patient Characteristics Summary 16

10.2. Cohort design 16

10.2.1. Exposure status 17

10.2.2. Outcome status 17

10.2.3. Model specification 17

10.2.4. Patient Characteristics Summary 17

10.3. Quantification of bias 17

11. STRENGTHS AND LIMITATIONS OF THE RESEARCH METHODS 18

12. PROTECTION OF HUMAN SUBJECTS 18

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE REACTIONS 18

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 18

15. references 18

# LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| **Abbreviation** | **Description of abbreviated term** |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| CDM | Common Data Model |
| CPRD | Clinical Practice Research Database |
| CPT4 | Current Procedural Terminology, 4th Edition |
| ER | Emergency Room |
| HCPCS | Healthcare Common Procedure Coding System |
| ICD9 | International Classification of Diseases, 9th Edition |
| ICD9P | International Classification of Diseases, 9th Edition, Procedures |
| ICD10 | International Classification of Diseases, 10th Edition |
| ICD10P | International Classification of Diseases, 10th Edition, Procedures |
| LASSO | Least Absolute Shrinkage and Selection Operator |
| LOINC | Logical Observation Identifiers Names and Codes |
| MDRR | Minimum Detectable Relative Risk |
| MeSH | Medical Subject Headings |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| NHS | National Health Services |
| NIHR | National Institute for Health Research |
| OMOP | Observational Medical Outcomes Partnership |
| UK | United Kingdom |
| US | United States |

# RESPONSIBLE PARTIES

## Investigator(s) and Authors

Martijn Schuemie, Patrick Ryan

## Sponsor

Janssen Research & Development, LLC

# ABSTRACT

**Purpose**: To quantify bias in observational study designs used to study the relationship between acetaminophen and cancer.

**Methods**: To mimic these study designs including several variants of the case-control design and a cohort design, while including negative control outcomes (outcomes known not to be caused by acetaminophen) in addition to several cancer outcomes.

**Analysis**: We will assess to what extent these study designs produce estimates in line with the known effect true sizes of the negative controls, and to what extent the estimates for the cancer outcomes are distinguishable from those for the negative controls.

# AMENDMENTS AND UPDATES

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number | Date | Section of study protocol | Amendment or update | Reason |
| 1.0 | October 12, 2019 |  | Initial draft |  |
| 1.1 | October 13, 2019 | Various sections | Minor textual modifications. | For clarity and correction of typing errors. |
| 1.2 | October 19, 2019 | Various sections + Outcome(s) of Interest | Minor textual modification + changing lymphoma outcome to restrict to b-cell + removing polymyalgia rheumatica and erythema nodusum from list of negative controls + changing characterization to contrast exposed vs. unexposed instead of cases and controls | For clarity and correction of typing errors. + to make outcome definition more similar to the one used in the Walter paper + because these outcomes may be related to the indication for acetaminophen + because the comparability of exposed to unexposed is most relevant for study validity. |

# RATIONALE AND BACKGROUND

A large number of epidemiologic studies have been conducted to examine whether use of acetaminophen predisposes to the occurrence of one or more forms of cancer. There are many limitations to many of these studies as noted earlier1, including vulnerability to channeling, protopathic bias, and uncontrolled confounding. However, the magnitude of the bias resulting from these limitation remains unknown, hampering the interpretability of the results of these studies.

Recent methodological developments have focused on using large sets of negative controls – exposure-outcome pairs where no causal effect is believed to exist – to measure the operating characteristics of study designs by observing to what extent these designs produce effect size estimates in line with the truth (that there is no effect for the negative controls). Previously, this approach has been used to show substantial bias in a comparative cohort study comparing acetaminophen to ibuprofen, even after adjustment using propensity scores.2

Because the vast majority of studies on the association between acetaminophen and cancer are case-control studies, we aim to extend this research to the case-control design. Recent work already previously explored the operating characteristics of case-control designs in general.3 In this study we will perform a similar analysis, but focusing specifically on the case-control design variants used to study the association between acetaminophen and cancer, and using negative controls outcomes for acetaminophen.

Although most studies used a case-control design, some studies applied a cohort design. Here we will use the study by Walter et al.4 as an example of such studies. This particular study linking a regional survey to a cancer registry to compare prevalent users of acetaminophen to non-users. We aim to replicate this study as closely as possible to examine its risk of residual bias.

In all these replications, we will include negative control outcomes as well as four cancer outcomes that some have suggested may be associated to acetaminophen exposure. The negative controls will allow quantification of the error due to the limitations of these study designs. This quantification in turn can be used to help interpret study results by determining whether an observed effect size falls outside of what can be expected based solely on error (both systematic and random error).

# STUDY Objectives

## Primary Objective(s)

To emulate typical case-control studies performed in the past as well as the Walter et al. cohort study, while including negative controls to quantify residual bias in these study designs.

The definition of ‘typical case-control studies’ is based on a review of a set of published studies. Throughout this protocol we highlight the design choices in this set of studies, and the design choices we implement in our study.

## Secondary Objective(s)

Estimate the effect of acetaminophen on the risk of several types of cancer using the same study designs as used for the primary objective.

# Study Design and Setting

This study includes a set of retrospective case-control study design variants as well as a retrospective cohort study design. By ‘retrospective’ we mean using data that has already been collected.

## Describe Data Source(s)

We will use the Clinical Practice Research Datalink (CPRD), which was used in one of the prior studies, as well as in the most recent channeling bias paper. The CPRD is a governmental, not-for-profit research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare Products Regulatory Agency (MHRA), a part of the Department of Health, United Kingdom (UK). CPRD consists of data collected from a sample of UK primary care physicians for patients of all ages. This includes conditions, observations, measurements, and procedures that the general practitioner is made aware of in additional to any prescriptions by the general practitioner.

CPRD has been transformed into the OMOP Common Data Model (CDM) version 5. The complete specification for OMOP Common Data Model, version 5 is available at:

<https://github.com/OHDSI/CommonDataModel>

The ETL specification for transforming CPRD into the OMOP CDM is available at:

<https://github.com/OHDSI/ETL-CDMBuilder/tree/master/man/CPRD>

## Study Population(s)

Case-control studies are sometimes nested in some subpopulation of interest, for example subjects having a particular disease. However, none of the reviewed studies use nesting (as defined here). Some studies do restrict to specific genders depending on the outcome (females for breast cancer5 or ovarian cancer6, males for prostate cancer7), and/or to specific age groups. In our case-control analyses we will therefore not nest within a clinical subpopulation, but we will restrict age to 30 years and older.

Similar to the study by Walter et al.4, our cohort study will restrict to ages 50-76 at baseline, excluding people with prior history of cancer other than nonmelanoma skin cancer reported at baseline.

## Outcome(s) of Interest

We include four types of cancer which have been associated with acetaminophen use in prior studies:

* Renal cell carcinoma
* Primary liver cancer
* Lymphoma
* Multiple myeloma

Outcome definitions will be evaluated using the PheValuator framework.8

Although hepatocellular carcinoma specifically might be of more clinical interest than the broader ‘Primary Liver Cancer’ selected here, the data does not support a finer distinction. Most primary liver cancers are coded as ‘Primary malignant neoplasm of liver’ (READ code B150.00). For this reason we define our outcome of interest as ‘Primary liver cancer’, similar to other studies performed in CPRD.9-11

The events described below as the ‘initial event cohort’ determine the date of the outcome, which will be used as the index date for cases in the case-control studies. Note that these formal definitions do not yet require a minimum prior observation time. These criteria are applied at a later stage in the analysis, as described in Sections 10.1 and 10.2.

### Renal cell carcinoma

Within Johnson & Johnson’s intranet, a computer-readable version of this definition can be found at: <https://epi.jnj.com/atlas/#/cohortdefinition/11666>

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of Primary renal cell carcinoma1

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.**

Limit qualifying cohort to: **earliest event per person.**

#### End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

#### Cohort Collapse Strategy

Collapse cohort by era with a gap size of 0 days.

#### Appendix 1: Concept Set Definitions

1. Primary renal cell carcinoma

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 4181357 | Malignant tumor of renal pelvis | Condition | SNOMED | NO | YES | NO |
| 198985 | Primary malignant neoplasm of kidney | Condition | SNOMED | NO | YES | NO |
| 196653 | Malignant tumor of kidney | Condition | SNOMED | NO | YES | NO |
| 196053 | Secondary malignant neoplasm of kidney | Condition | SNOMED | YES | YES | NO |

### Primary liver cancer

Within Johnson & Johnson’s intranet, a computer-readable version of this definition can be found at: <https://epi.jnj.com/atlas/#/cohortdefinition/11667>

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of Malignant neoplasms of liver1

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.**

Limit qualifying cohort to: **earliest event per person.**

#### End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

#### Cohort Collapse Strategy

Collapse cohort by era with a gap size of 0 days.

#### Appendix 1: Concept Set Definitions

1. Malignant neoplasms of liver

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4246127 | Malignant neoplasm of liver | Condition | SNOMED | NO | YES | NO |

### Lymphoma

Within Johnson & Johnson’s intranet, a computer-readable version of this definition can be found at: <https://epi.jnj.com/atlas/#/cohortdefinition/12021>

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of Malignant neoplasms of lymphoma1

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**.

Limit qualifying cohort to: **earliest event per person.**

#### End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

#### Cohort Collapse Strategy

Collapse cohort by era with a gap size of 0 days.

#### Appendix 1: Concept Set Definitions

1. Malignant neoplasms of lymphoma

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 432571 | Malignant lymphoma | Condition | SNOMED | NO | YES | NO |
| 432851 | Secondary malignant neoplastic disease | Condition | SNOMED | YES | YES | NO |
| 441235 | Large cell anaplastic lymphoma | Condition | SNOMED | YES | YES | NO |
| 4003183 | T-cell lymphoma | Condition | SNOMED | YES | YES | NO |
| 4038835 | Hodgkin's disease | Condition | SNOMED | YES | YES | NO |
| 4040380 | Mycosis fungoides | Condition | SNOMED | YES | YES | NO |
| 4082311 | B-cell chronic lymphocytic leukemia | Condition | SNOMED | YES | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4216139 | Plasmacytoma | Condition | SNOMED | YES | YES | NO |

### Multiple myeloma

Within Johnson & Johnson’s intranet, a computer-readable version of this definition can be found at: <https://epi.jnj.com/atlas/#/cohortdefinition/12022>

#### Initial Event Cohort

People having any of the following:

* a condition occurrence of Multiple myeloma1

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**.

Limit qualifying cohort to: **earliest event per person**.

#### End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

#### Cohort Collapse Strategy

Collapse cohort by era with a gap size of 0 days.

#### Appendix 1: Concept Set Definitions

1. Multiple myeloma

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 437233 | Multiple myeloma | Condition | SNOMED | NO | YES | NO |
| 42538151 | Osteoporosis co-occurrent and due to multiple myeloma | Condition | SNOMED | YES | YES | NO |

## Negative Control Outcomes

Negative control outcomes are those determined a priori to have no association with the exposure of interest. We will use the same set of negative control outcomes as an earlier study.2 Briefly, in this study we identified outcomes as follows: Person counts of all potential drug-condition pairs are reviewed in observational data; this person count data helps determine which pairs are even feasible for use in calibration. Given the list of potential drug-condition pairs, the concepts in the pairs must meet the following requirements to be considered as negative controls: (1) that there is no Medline abstract where the MeSH terms suggest a negative association between the drug and the condition12, (2) that there is no mention of the drug-condition pair on a US Product Label in the “Adverse Drug Reactions” or “Postmarketing” section13, (3) there are no US spontaneous reports suggesting that the pair is in an adverse event relationship14 15, (4) that the OMOP Vocabulary does not suggest that the drug is indicated for the condition, (5) that the concepts are usable (i.e. not too broad, not suggestive of an adverse event relationship, not pregnancy related), and (6) the exact concept itself is utilized in patient level data (i.e. concepts that are not usually used within the data are usually indicative of a broad concept that has a child that is more specific).  The remaining concepts are “optimized”, meaning parent concepts remove children as defined by the OMOP Vocabulary (e.g. if both “Non-Hodgkin’s Lymphoma” and “B-Cell Lymphoma” were selected, the child concept “B-Cell Lymphoma would be removed for its parent “Non-Hodgkin’s Lymphoma”).  Once potential negative control candidates are selected, manual clinical review to exclude any pairs that may still be in a causal relationship or similar to the study outcome should be performed to select the top 50 or so concepts by patient exposure.

The 37 negative control outcomes we will be using from the prior study are as follows:

1. Achilles tendinitis
2. Atrophic vaginitis
3. Breath smells unpleasant
4. Bronchiectasis
5. Disorders of initiating and maintaining sleep
6. Ear problem
7. Falls
8. Foot-drop
9. Ganglion and cyst of synovium, tendon and bursa
10. Hemangioma
11. Hydrocele
12. Hyperthyroidism
13. Impaired glucose tolerance
14. Impingement syndrome of shoulder region
15. Impotence
16. Incontinence of feces
17. Interpersonal relationship finding
18. Irregular periods
19. Irritability and anger
20. Joint stiffness
21. Loss of sense of smell
22. Mixed hyperlipidemia
23. Osteitis deformans
24. Panic attack
25. Perforation of tympanic membrane
26. Pes planus
27. Premature menopause
28. Prolapse of female genital organs
29. Pure hypercholesterolemia
30. Respiratory symptom
31. Restless legs
32. Restlessness and agitation
33. Rosacea
34. Simple goiter
35. Skin sensation disturbance
36. Snapping thumb syndrome
37. Urinary symptoms

We will identify a negative control outcome occurrence as the first occurrence of the negative control concept or any of its descendants in any position in the patient’s record.

## Exposure(s) of Interest

Our exposure of interest is any drug containing the ingredient acetaminophen (concept ID 1125315). See Appendix A for a full list of the drug codes in CPRD that fall under this definition.

## Other Variables of Interest

Other variables are captured at the index date to address potential confounding. The definition of the index date varies, as explained in Section 10.

### Case-control designs: Variables used for matching

As will be discussed later, several studies match cases to controls. This matching is almost always done on these variables:

* Age at index date16-20
* Sex16-20
* Index date16-20
* Time observed prior to the index date16-19
* Practice, hospital or geographical area16-18 20

These variables will also be used for matching in our study.

### Case-control designs: Variables used in multivariable outcome models

Most studies include the following variables in the outcome model (the logistic regression):

* Age at index date5-7 20-27

We will categorize age in five-year intervals.

* Sex6 20-26
* Index year5-7 21 24 27
* BMI (Body Mass Index)5 16-18 21 24-26

BMI will be computed from body height (measurement concept ID 3036277) and weight (measurement concept ID 3013762) recorded within one year from each other, or directly from BMI measurements (measurement concept ID 3038553). We will discretize BMI into three categories: BMI < 25, 25 <= BMI < 30, BMI >=30

* Alcohol intake5 21 26 or alcohol-related disorders18

We will identify regular drinkers as patients who self-report as regular drinkers (an observation with concept ID 40770351 and value “yes”), and patients reporting they drink more than two alcoholic beverages per week (observations with concept ID 3043872 and value > 2).

* Smoking5 16-18 20 21 24-27

We will identify smokers as those reporting smoking at least one cigarette per day (an observation with concept ID 40766929 and value >= 1), or those classified as smoker (observations with concept ID 4144271, 4052030, 4052029, 4052947, 4217594, 37395605, 4058137, 4295004, 4199818, 44802474, 4085459, 4144273, 4193014, 44806696, 44802794, 4086132, 4058136, 4190573, 4215409, 4052948, 44810930, or 4204653)

* Diabetes (medication use)18 21 26

We will identify diabetes as any exposure to a drug in ATC class A10 (drugs used in diabetes).

We will also adjust for these in our study. Note that only those variables need to be included that are not used to match cases to controls.

### Cohort design: Variables used in the outcome model

Walter et al.4 adjusted for these variables:

* Sex
* Race/ethnicity (white, Hispanic, other)

This information is not available in CRPD and will therefore not be used.

* Education

This information is not available in CRPD and will therefore not be used.

* Smoking

We will identify smokers as described in Section 8.6.2.

* Self-rated health

This information is not available in CRPD. Instead, we will include the Charlson Index (Romano adaptation)28 as indicator of overall health.

* History of rheumatoid arthritis

Defined as any occurrence of concept 80809 (Rheumatoid arthritis) or any of its descendants on or before the index date.

* History of non-rheumatoid arthritis or chronic neck/back/joint pain.

Defined as any occurrence of concept 4291025 (Arthritis) or any of its descendants, excluding concept 80809 (Rheumatoid arthritis) and any of its descendants, as well as concept 43530622 (chronic neck pain) or 4046660 (chronic back pain), or any of their descendants on or before the index date.

* History of fatigue or lack of energy

Defined as any occurrence of 439926 (Malaise and fatigue) on or before the index date.

* History of migraines or frequent headaches

Defined as any occurrence of 318736 (Migraine) or 375527 (headache disorder) on or before the index date.

* Number of first-degree relatives with a history of leukemia or lymphoma

This information is not available in CRPD and will therefore not be used.

### Cohort design: Variables used for descriptive statistics

Descriptive analysis of the baseline covariates will be generated to provide a characterization of the exposed and unexposed cohort. The following baseline variables will be included.

* Demographics
  + Gender
  + Age group (5-year bands)
  + Initial drug exposure month
* Condition occurrence record for the concept or any of its descendants observed during 365d on or prior to cohort index
* Drug exposure record for the concept or any its descendants observed during 365d on or prior to cohort index
* Procedure occurrence record for the concept or any its descendants observed during 365d on or prior to cohort index
* Measurement record for the verbatim concept observed during 365d on or prior to cohort index
* Charlson Index - Romano adaptation, using conditions all time on or prior to cohort index
* Number of distinct conditions observed in 365d on or prior to cohort index (defined as unique SNOMED condition concepts)
* Number of distinct drugs observed in 365d on or prior to cohort index (defined as unique RxNorm ingredient concepts)
* Number of distinct procedures observed in 365d on or prior to cohort index (defined as unique CPT4/HCPCS/ICD9P/ICD10P concepts)
* Number of distinct observations observed in 365d on or prior to cohort index
* Number of distinct measurements observed in 365d on or prior to cohort index (defined as unique LOINC concepts)
* Number of visits observed in 365d on or prior to cohort index
* Number of inpatient visits observed in 365d on or prior to cohort index
* Number of ER visits observed in 365d on or prior to cohort index

An explicit head-to-head comparison between two cohorts of baseline covariates, using standardized difference as a metric to compare individual factors, will be conducted. Covariates with standardized difference > 10% will be highlighted as potential imbalanced confounding factors.

When computing a propensity score, we will exclude acetaminophen from the set of covariates, because this is the exposure the propensity model aims to predict. In addition, we will also exclude these ingredients that are contained in products containing acetaminophen: aspirin, caffeine, chlormezanone, codeine, dextromethorphan, dihydrocodeine, diphenhydramine, domperidone, isometheptene, methionine, metoclopramide, orphenadrine, oxycodone, pentazocine, phenylephrine, phenylpropanolamine, promethazine, propoxyphene, pseudoephedrine, salicylic acid, and tramadol.

# SAMPLE SIZE AND STUDY POWER

## Case-control designs

Appendix B lists the number of cases and controls for each of the outcomes described in Sections 8.3 and 8.4 and the analysis variants described in Section 10.1.4. Also listed is the fraction of controls considered to be exposed to acetaminophen according to the various exposure status definitions described in Section 10.1.3, ranging from 31% to 63%, as well as the Minimum Detectable Relative Risk (MDRR), assuming alpha = 0.05, and a power of 80%.29

## Cohort design

Following the description of ‘high use’ and ‘no use’ of acetaminophen described in Section 10.2.1, and accounting for the inclusion and exclusion criteria defined in Section 8.2, the following numbers of subjects were identified in the CPRD database, for the two analysis variants described in Section 10.2.3:

|  |  |  |  |
| --- | --- | --- | --- |
| Analysis ID | Exclude subjects with the outcome in the 2 years following the index date | Number of subjects | |
| High use | No use |
| 9 | No | 5,284 | 84,551 |
| 10 | Yes | 3,935 | 69,526 |

**Table 1.** Number of subjects in the exposure cohorts for the two analyses variants.

Note that the main reason for the different counts between the two analysis variants is not because those subjects experienced the outcome during the two years, but because those subjects were observed for less than two years after the index date.

For comparison, Walter et al. reported 3,258 high-use subjects and 48,928 non-use subjects in their primary analysis (equivalent to our analysis 9).4

The final number of subjects in the two exposure cohorts depends on the outcome that is studied, since subjects who experienced the outcome of interest were excluded for that outcome. Appendix C lists, for each analysis variant and outcome, the number of subjects in the exposure cohorts, as the number of subjects experiencing the outcome across both cohorts, and the MDRR (assuming alpha = 0.05 and power = 0.80).30

# DATA ANALYSIS PLAN

Each design variant described below will be used to estimate effect sizes for the negative controls as well as the outcomes of interest.

## Case-control designs

We will perform several variants of the case-control design, reflecting the analytic design choices made in prior published studies. For all case-control designs we will require at least 2 years of observation prior to index date.

### Selection of controls

Most studies5-7 21-27 define controls simply as all non-cases or a random sample of non-cases, and randomly assign index dates to these controls. The index dates are often drawn from the distribution of dates observed for the cases.

Several studies16-20 select controls specifically for each case, giving controls the same index date as the case for which they were selected. Subsequently the outcome model (logistic regression) is conditioned on the matched set.

Since these two designs could have very different implications for the residual bias, we will evaluate both:

1. Sampling index dates from the distribution observed for cases, and randomly applying these to viable controls (i.e. non-cases that were observed at the index date). The size of the control group will be limited to four times the number of cases.
2. Randomly selecting up to four matched controls per case.

### Matching

Like most studies that match cases to controls, when performing matching we will match on:

* Age using a two-year caliper (i.e., ± 2 years)
* Sex
* Index date
* Time observed prior to the index date, using a one-year caliper
* Practice

### Exposure status

Some studies6 16 18 19 22 set the index date to one year before the outcome, and evaluate exposure on or prior to that date, since it is not believed biologically plausible for any effect to occur within a shorter time frame. Other studies also included a ‘current use’ category, or do not distinguish between current and past use (e.g. when exposure status is ascertained using questionnaires). 5 7 17 20 21 23-26

In our study, we will evaluate using the following algorithms to define exposure status:

1. All time prior: exposed on or any time prior to the index date, where the index date is the date of the outcome (for cases).
2. One-year delay: exposed on or any time prior to the index date, where the index date is one year before the date of the outcome (for cases).

### Model Specification

After controls have been selected, exposure status has been ascertained, and covariates have been constructed, we will fit a logistic regression to estimate the effect size (odds ratio) and 95% confidence interval. For those analyses where controls are matched to cases this regression will be conditioned on the matched sets. The following case-control variants will be performed:

**Table 2**. Case-control design analysis variants.

|  |  |  |  |
| --- | --- | --- | --- |
| Analysis ID | Control selection | Exposure status | Covariate adjustment |
| 1 | Sampling | All time prior | Age, sex, index year |
| 2 | Sampling | All time prior | Age, sex, index year, BMI, alcohol, smoking, diabetes |
| 3 | Sampling | One-year delay | Age, sex, index year |
| 4 | Sampling | One-year delay | Age, sex, index year, BMI, alcohol, smoking, diabetes |
| 5 | Matching | All time prior | None |
| 6 | Matching | All time prior | BMI, alcohol, smoking, diabetes |
| 7 | Matching | One-year delay | None |
| 8 | Matching | One-year delay | BMI, alcohol, smoking, diabetes |

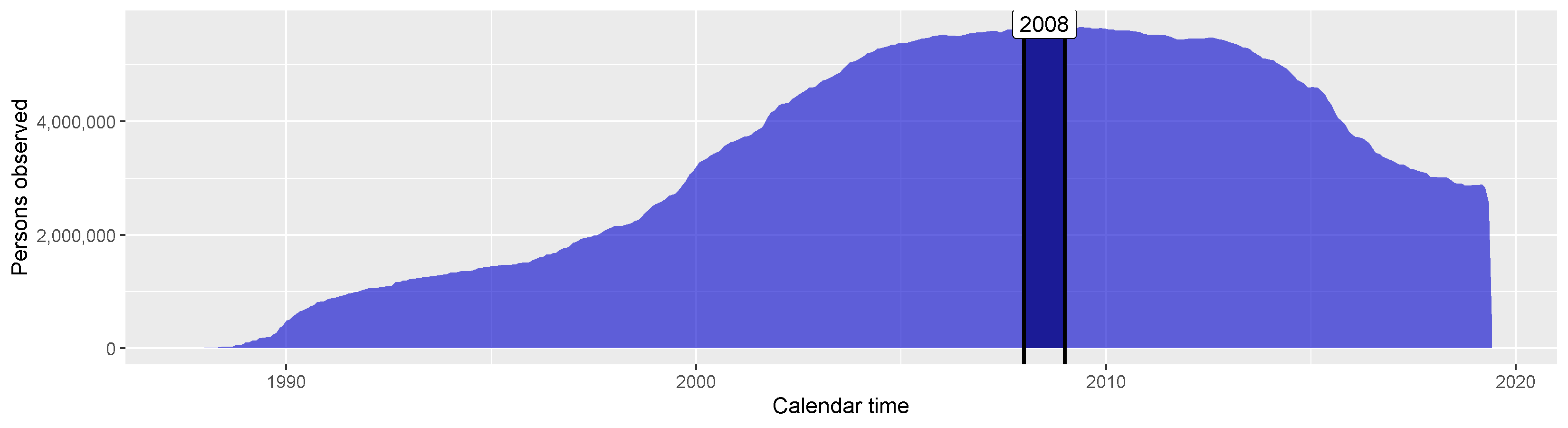
These eight analyses will be used to estimate odds ratios for all 37 negative controls and four outcomes of interest, resulting in 8 x (37 + 4) = 328 odds ratios and confidence intervals.

### Patient Characteristics Summary

Descriptive analyses will be comprised of covariate balance of age group, gender, and selected variables in exposed and unexposed.

## Cohort design

The original study4 determined exposure status and baseline characteristics using a mailed questionnaire, with responses returned between October 2000 and December 2002. The outcome status was ascertained by linking the survey to a cancer registry, using data up to December 31, 2008, thus allowing a maximum follow-up time of approximately six to eight years. To emulate this design, while selecting the period in time with the largest number of subjects captured in CRPD, we will select a random date (the index date) for each person in the year 2008. We include every person aged 50-76 at the index date, requiring that they are observed at that date as well as the four years before. We will ascertain outcome status in the period from the index date until the end of observation.



**Figure 1.** Persons observed per month in the CPRD database. Index dates will be sampled throughout the year 2008.

### Exposure status

Similar to Walter et al,4 our focus will be on ‘high use’, defined in the original study as >= 4 days/week for >= 4 years.4 In our analysis, we will classify subjects as ‘exposed’ if they are continuously exposed in the 4 years prior to the index date, allowing for gaps representing use of acetaminophen only 4 out of 7 days, with a minimum allowed gap of 30 days. For example, if someone received a 25-day prescription of acetaminophen, we will consider them continuously exposed if they receive the next prescription in *n* days of the first prescription start, were *n = max(25 \* 7 / 4, 25+30)* = 55 days.

Subjects will be classified as ‘unexposed’ if they were not prescribed any acetaminophen in the 4 years prior to the index date.

### Outcome status

Outcome status will be classified based on the occurrence of the outcome during the time after the index date until the end of observation. Subjects who had the outcome prior to the index date will be excluded in the analysis for that outcome.

Similar to Walter et al.4 a separate analysis will be performed excluding those who experienced the outcome in the 2 years following the index date.

### Model specification

The following cohort design analyses will be performed:

**Table 3**. Cohort design analysis variants.

|  |  |
| --- | --- |
| Analysis ID | Exclude subjects with the outcome in the 2 years following the index date |
| 9 | No |
| 10 | Yes |

These two analyses will be used to estimate hazard ratios for all 37 negative controls and four outcomes of interest, resulting in 2 x (37 + 4) = 82 hazard ratios and confidence intervals.

### Patient Characteristics Summary

Descriptive analyses will be comprised of covariate balance of the variables described in Section 8.6.4.

Additionally, the propensity score will be estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e-7. We will plot the propensity score distribution for exposed and unexposed to assess comparability.

## Quantification of bias

We will plot the estimated odds ratios/hazard ratios and standard errors (linearly related to the width of the confidence interval). Study designs that adequately control for confounding factors should produce odds ratio estimates in line with the known true effect size (i.e., a odds ratio/hazard ratio of 1.0) for the negative control outcomes. We will compute the percentage of negative controls having a p-value below 0.05, with the expectation that for an unbiased study design this percentage should be 5%. We will fit an empirical null distribution31 to the distribution of negative control estimates and report the estimated distribution parameters.

# STRENGTHS AND LIMITATIONS OF THE RESEARCH METHODS

This is an observational study and as such is subject to the inherent bias because we were not able to randomize treatment. For example, in this data source, the drug data is based on prescriptions written, not dispensed, so we do not know if the drugs were taken and how. For those prescriptions that were repeated, the likelihood that the medication was ingested increases. Exposure attribution based on a single prescription may be seen as a limitation, however we would argue that any other measures such as dose or drug era would be similarly confounded with underlying health.

# PROTECTION OF HUMAN SUBJECTS

Approval for CPRD use will be obtained from the Independent Scientific Advisory Committee (ISAC).

# MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE REACTIONS

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the *minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available* and adverse events are not reportable as individual AE reports. The study results will be assessed for medically important results.

# PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be presented to the California Office of Environmental Health Hazard Assessment as part of the Proposition 65 Implementation Program. An article will be written and submitted to a peer review journal for publication.

# references

1. Weiss NS. Use of acetaminophen in relation to the occurrence of cancer: a review of epidemiologic studies. *Cancer causes & control : CCC* 2016;27(12):1411-18. doi: 10.1007/s10552-016-0818-2 [published Online First: 2016/11/11]

2. Weinstein RB, Ryan P, Berlin JA, et al. Channeling in the Use of Nonprescription Paracetamol and Ibuprofen in an Electronic Medical Records Database: Evidence and Implications. *Drug safety* 2017;40(12):1279-92. doi: 10.1007/s40264-017-0581-7 [published Online First: 2017/08/07]

3. Schuemie MJ, Ryan PB, Man KKC, et al. A plea to stop using the case-control design in retrospective database studies. *Statistics in medicine* 2019;38(22):4199-208. doi: 10.1002/sim.8215 [published Online First: 2019/08/23]

4. Walter RB, Milano F, Brasky TM, et al. Long-term use of acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs and risk of hematologic malignancies: results from the prospective Vitamins and Lifestyle (VITAL) study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011;29(17):2424-31. doi: 10.1200/jco.2011.34.6346 [published Online First: 2011/05/11]

5. Garcia Rodriguez LA, Gonzalez-Perez A. Risk of breast cancer among users of aspirin and other anti-inflammatory drugs. *British journal of cancer* 2004;91(3):525-9. doi: 10.1038/sj.bjc.6602003 [published Online First: 2004/07/01]

6. Hannibal CG, Rossing MA, Wicklund KG, et al. Analgesic drug use and risk of epithelial ovarian cancer. *American journal of epidemiology* 2008;167(12):1430-7. doi: 10.1093/aje/kwn082 [published Online First: 2008/04/09]

7. Garcia Rodriguez LA, Gonzalez-Perez A. Inverse association between nonsteroidal anti-inflammatory drugs and prostate cancer. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2004;13(4):649-53. [published Online First: 2004/04/07]

8. Swerdel JN, Hripcsak G, Ryan PB. PheValuator: Development and evaluation of a phenotype algorithm evaluator. *Journal of biomedical informatics* 2019;97:103258. doi: 10.1016/j.jbi.2019.103258 [published Online First: 2019/08/02]

9. Hagberg KW, Sahasrabuddhe VV, McGlynn KA, et al. Does Angiotensin-Converting Enzyme Inhibitor and beta-Blocker Use Reduce the Risk of Primary Liver Cancer? A Case-Control Study Using the U.K. Clinical Practice Research Datalink. *Pharmacotherapy* 2016;36(2):187-95. doi: 10.1002/phar.1704 [published Online First: 2016/02/06]

10. McGlynn KA, Hagberg K, Chen J, et al. Menopausal hormone therapy use and risk of primary liver cancer in the clinical practice research datalink. *International journal of cancer* 2016;138(9):2146-53. doi: 10.1002/ijc.29960 [published Online First: 2015/12/15]

11. Thistle JE, Petrick JL, Yang B, et al. Domperidone use and risk of primary liver cancer in the Clinical Practice Research Datalink. *Cancer epidemiology* 2018;55:170-75. doi: 10.1016/j.canep.2018.06.009 [published Online First: 2018/07/10]

12. Winnenburg R, Sorbello A, Ripple A, et al. Leveraging MEDLINE indexing for pharmacovigilance - Inherent limitations and mitigation strategies. *Journal of biomedical informatics* 2015;57:425-35. doi: 10.1016/j.jbi.2015.08.022 [published Online First: 2015/09/08]

13. Duke J, Friedlin J, Li X. Consistency in the safety labeling of bioequivalent medications. *Pharmacoepidemiology and drug safety* 2013;22(3):294-301. doi: 10.1002/pds.3351 [published Online First: 2012/10/09]

14. Banda JM, Evans L, Vanguri RS, et al. A curated and standardized adverse drug event resource to accelerate drug safety research. *Scientific data* 2016;3:160026. doi: 10.1038/sdata.2016.26 [published Online First: 2016/05/20]

15. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and drug safety* 2001;10(6):483-6. doi: 10.1002/pds.677 [published Online First: 2002/02/07]

16. Kaye JA, Myers MW, Jick H. Acetaminophen and the risk of renal and bladder cancer in the general practice research database. *Epidemiology (Cambridge, Mass)* 2001;12(6):690-4. [published Online First: 2001/10/27]

17. Meier CR, Schmitz S, Jick H. Association between acetaminophen or nonsteroidal antiinflammatory drugs and risk of developing ovarian, breast, or colon cancer. *Pharmacotherapy* 2002;22(3):303-9. [published Online First: 2002/03/20]

18. Yang B, Petrick JL, Chen J, et al. Associations of NSAID and paracetamol use with risk of primary liver cancer in the Clinical Practice Research Datalink. *Cancer epidemiology* 2016;43:105-11. doi: 10.1016/j.canep.2016.06.009 [published Online First: 2016/07/16]

19. Derby LE, Jick H. Acetaminophen and renal and bladder cancer. *Epidemiology (Cambridge, Mass)* 1996;7(4):358-62. [published Online First: 1996/07/01]

20. Fortuny J, Kogevinas M, Garcia-Closas M, et al. Use of analgesics and nonsteroidal anti-inflammatory drugs, genetic predisposition, and bladder cancer risk in Spain. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2006;15(9):1696-702. doi: 10.1158/1055-9965.epi-06-0038 [published Online First: 2006/09/21]

21. Garcia-Rodriguez LA, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. *Epidemiology (Cambridge, Mass)* 2001;12(1):88-93. [published Online First: 2001/01/04]

22. Becker N, Fortuny J, Alvaro T, et al. Medical history and risk of lymphoma: results of a European case-control study (EPILYMPH). *Journal of cancer research and clinical oncology* 2009;135(8):1099-107. doi: 10.1007/s00432-009-0551-2 [published Online First: 2009/02/12]

23. Chang ET, Zheng T, Weir EG, et al. Aspirin and the risk of Hodgkin's lymphoma in a population-based case-control study. *Journal of the National Cancer Institute* 2004;96(4):305-15. doi: 10.1093/jnci/djh038 [published Online First: 2004/02/19]

24. Erickson P, Gardner LD, Loffredo CA, et al. Racial and Ethnic Differences in the Relationship between Aspirin Use and Non-Small Cell Lung Cancer Risk and Survival. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2018;27(12):1518-26. doi: 10.1158/1055-9965.epi-18-0366 [published Online First: 2018/09/02]

25. Karami S, Daughtery SE, Schwartz K, et al. Analgesic use and risk of renal cell carcinoma: A case-control, cohort and meta-analytic assessment. *International journal of cancer* 2016;139(3):584-92. doi: 10.1002/ijc.30108 [published Online First: 2016/03/25]

26. Kho PF, Fawcett J, Fritschi L, et al. Nonsteroidal anti-inflammatory drugs, statins, and pancreatic cancer risk: a population-based case-control study. *Cancer causes & control : CCC* 2016;27(12):1457-64. doi: 10.1007/s10552-016-0824-4 [published Online First: 2016/11/07]

27. Moysich KB, Bonner MR, Beehler GP, et al. Regular analgesic use and risk of multiple myeloma. *Leukemia research* 2007;31(4):547-51. doi: 10.1016/j.leukres.2006.07.027 [published Online First: 2006/09/12]

28. Schneeweiss S, Wang PS, Avorn J, et al. Improved comorbidity adjustment for predicting mortality in Medicare populations. *Health Serv Res* 2003;38(4):1103-20. doi: 10.1111/1475-6773.00165

29. Miettinen OS. Individual matching with multiple controls in the case of all-or-none responses. *Biometrics* 1969;25(2):339-55. [published Online First: 1969/06/01]

30. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983;39(2):499-503. [published Online First: 1983/06/01]

31. Schuemie MJ, Ryan PB, DuMouchel W, et al. Interpreting observational studies: why empirical calibration is needed to correct p-values. *Statistics in medicine* 2014;33(2):209-18. doi: 10.1002/sim.5925 [published Online First: 2013/08/01]