Study Report

P3-C3-003

DARWIN EU® - Suicidality following exposure to doxycycline

29/11/2024

Version 5.0

Contents

Study Title	DARWIN EU® - Suicidality following exposure to doxycycline
Study Report Version	5.0
Date	29/11/2024
EU PAS number	EUPAS1000000294
Active substance	Exposure: doxycycline Comparators: erythromycin, isotretinoin, azithromycin, or amoxicillin
Medicinal product	Doxycycline for systemic use
Research question and objectives	Research questions: 1. Is there a causal association between the use of doxycycline and suicide-related events? 2. Does the association between doxycycline use and completed suicide and suicide-related events vary by indication of use, compared to active comparators? Objectives: 1. To use a new-user cohort study to assess the association between doxycycline and completed suicide, composite suicide and suicide-related events (completed suicide, suicide ideation and suicide attempt, self-harm), composite suicide-related events (suicide ideation, suicide attempt, self-harm), depression and anxiety, compared to active comparators, stratified by indication of acne vulgaris, rosacea, chlamydia and lower respiratory tract infection (CAP or bronchitis) 2. To use a self-controlled case series study to assess the association between use of doxycycline and composite suicide-related events (including suicide ideation, suicide attempt, self-harm), depression and anxiety.
Countries of study	Netherlands, Spain, United Kingdom
Author	Nicholas Hunt, n.hunt@darwin-eu.org Katia Verhamme, k.verhamme@darwin-eu.org Guido van Leeuwen, g.vanleeuwen@darwin-eu.org Daniel Prieto Alhambra, d.prietoalhambra@darwin-eu.org Talita Duarte Salles, t.duarte@darwin-eu.org

TITLE

DARWIN EU® - Suicidality following exposure to doxycycline

1. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Nicholas Hunt Katia Verhamme Daniel Prieto-Alhambra Talita Duarte-Salles	Erasmus MC Erasmus MC University of Oxford/Erasmus MC Erasmus MC
Data Scientist	Maarten van Kessel Ross Williams	Erasmus MC
Clinical Epidemiologist	Guido van Leeuwen	Erasmus MC
Data Partner*	**Names**	**Organisation**
IPCI	Katia Verhamme	Erasmus MC
SIDIAP	Agustina Giuliodori Anna Palomar	IDIAPJGol
CPRD GOLD	Antonella Delmestri Mandickel Kamtengeni	University of Oxford

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

2. DATA SOURCES

Country	Name of Database	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Calendar period covered by each data source.
United Kingdom	CPRD GOLD	PC	EHR	17m	01/01/2010 to 01/05/2024
The Netherlands	IPCI	PC	EHR	1.4m	01/01/2010 to 01/12/2023
Spain	SIDIAP	PC	EHR	5.8m	01/01/2010 to 01/06/2023

m=million

3. ABSTRACT

Title

DARWIN EU® - Suicidality following exposure to doxycycline

Rationale and background

There have been reports of a potential association between use of doxycycline and suicide. By means of a self-controlled case series and an active comparator cohort study, the study aimed to assess the association between use of doxycycline and suicide-related events .

Research questions

1. Is there an association between the use of doxycycline and suicide-related events?
2. Does the association between doxycycline use and completed suicide and suicide-related events vary by indication of use, compared to active comparators?

Objectives

1. To use a new-user cohort study to assess the association between doxycycline and completed suicide, composite suicide and suicide-related events (completed suicide, suicide ideation and suicide attempt, self-harm), composite non-fatal suicide-related events (suicide ideation, suicide attempt, self-harm), depression and anxiety, compared to active comparators, stratified by indication of acne vulgaris, rosacea, chlamydia and lower respiratory tract infection (CAP or bronchitis)
2. To use a self-controlled case series study to assess the association between use of doxycycline and composite suicide-related events (including suicide ideation, suicide attempt, self-harm), depression and anxiety.

Research methods

Study design

New-user cohort study with active comparator (objective 1) and self-controlled case series (objective 2)

Population

The study population consisted of new users cohorts of doxycycline (SCCS and cohort study) or the active comparators (cohort) used for the following indications: acne, rosacea, chlamydia and lower respiratory tract infection.

Variables

Exposures of interest in the new-user cohorts were evaluated per the following indications: *acne vulgaris*: doxycycline, erythromycin or isotretinoin; *rosacea*: doxycycline, erythromycin or isotretinoin; *chlamydia*: doxycycline, azithromycin, erythromycin or amoxicillin; and *lower respiratory tract infection* (CAP and bronchitis): doxycycline, azithromycin, or amoxicillin. In the SCCS study, doxycycline was the only exposure of interest.

Outcomes of interest for the new-user cohort study were completed suicide, composite completed suicide and non-fatal suicide-related events (suicide ideation, suicide attempt and self-harm), suicide-related events (suicide ideation, suicide attempting and self-harm), depression, and anxiety. Outcomes of interest for the SCCS study were non-fatal suicide-related events (suicide ideation, suicide attempting and self-harm), depression, and anxiety.

Data sources

1. Integrated Primary Care Information (IPCI), Netherlands
2. The Information System for Research in Primary Care (SIDIAP), Spain
3. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom

Sample size

In the cohort study, with the assumption follow-up duration of 90-days and incidence rate ratio (IRR) = 2.0 for the exposure-outcome association (composite completed suicide, suicide attempt, ideation or self-harm) the sample size should be at least 191,000 per group. To detect an IRR = 2.0 for the exposure-outcome association of depression with the assumed follow-up duration of 90-days, the sample size should be at least 38,000 per exposure group. In the SCCS to detect an IRR = 2.0 for the exposure-outcome association, the study size should be at least 245 persons. For an IRR = 1.5, the study size should include at least 828 persons.

Analytical methods

In the new-user cohort study the *CohortMethods* R package was used to perform propensity-score matching of patients prescribed doxycycline to the respective active comparator cohorts. This analysis was conducted separately within cohorts with different indications for doxycycline (acne, rosacea, chlamydia and LRTI). Cox-proportional hazards regression was used to estimate hazards ratios for the association between doxycycline and each outcome of interest. In the SCCS, the *SelfControlledCaseSeries* R package was used to perform conditional Poisson regression to estimate adjusted IRRs for each outcome of interest in the SCCS study. The IRR was calculated for each assessment window that consisted of the baseline window (>90 days prior to the index date when non-exposed), a pre-treatment assessment window [-90,0], and the risk windows [1,90], [1,30], [31,60], [61,90], [91,inf], where day 0 is the index date.

Results

Objective 1 cohort study

Indication acne vulgaris: In SIDIAP an increased risk of suicide-related events without death was found in patients using doxycycline in comparison with patients using erythromycin (HR of 3.77 (95% CI [1.03-17.80]). An increased but non-statistically significant association was seen in CRPD GOLD (HR 1.71, 95% CI [0.74-4.07]). The increased association was observed when estimates from CPRD GOLD and SIDIAP were meta-analysed (HR 2.11 (95% CI [1.01-4.39]). No increased association for suicide-related events without death was found in patients using doxycycline for acne compared to patients using isotretinoin.

In IPCI an increased association with anxiety in doxycycline users for acne was observed compared to isotretinoin users (HR 1.94, 95%CI [1.28-2.94]). No associations were found between doxycycline use and anxiety compared to erythromycin in CPRD GOLD and SIDIAP (HR 1.06, 95% CI [0.84-1.32] and HR 0.96, 95% CI [0.73-1.26] respectively). No association was observed in the meta-analysis based on the estimates from CPRD GOLD and SIDIAP (HR 1.02, 95% CI [0.85-1.21]). Lastly, there were no associations found between doxycycline and the outcome of depression with using any active comparator.

Indication rosacea: In CPRD GOLD there were no statistically significant associations for any of the outcomes in the comparison of doxycycline with erythromycin and no estimates were produced in the comparison with isotretinoin. In IPCI and SIDIAP no estimates were produced for any of the outcomes of interest or active comparators.

Indication chlamydia: In SIDIAP no statistically significant associations were observed between doxycycline and the outcomes anxiety and depression compared to azithromycin; no estimates were produced in comparison with the other active comparators. In IPCI and CPRD GOLD no estimates were produced for any of the outcomes of interest or active comparators.

Indication LRTI: In CPRD GOLD, compared to amoxicillin, a statistically significant decreased association was observed for exposure to doxycycline and suicide-related events (HR 0.40, 95% CI [0.15-0.87]), no estimates were produced in the comparison with azithromycin. In IPCI and SIDIAP no estimates were produced for the outcome of suicide-related events without death with both active comparators. In both CPRD GOLD and IPCI no associations were observed between doxycycline and the outcomes anxiety or depression in comparison with both active comparators.

Objective 2 SCCS study

Overall doxycycline users with any indication: In the overall group with any indication in CPRD GOLD there were statistically significant decreased associations between doxycycline and suicide-related events without death in the 31-60 day risk period (IRR 0.83, 95% CI [0.75-0.92]; the 61-90 day risk period (IRR 0.90, 95% CI [0.81-0.99]) and the 1-90 day risk period (IRR 0.83, 95% CI [0.78-0.88]). The associations between doxycycline and suicide-related events were not statistically significant when estimates were meta-analysed.

For the outcome anxiety in CPRD, an increased association of anxiety was observed with doxycycline in the 31-60 day risk period (IRR 1.09, 95% CI [1.05-1.12]; the 61-90 day risk period (IRR 1.06, 95% CI [1.02-1.09]), the >90 day risk period (IRR 1.13, 95% CI [1.00-1.27]) and the 1-90 day risk period (IRR 1.07, 95% CI [1.05-1.09]). Similar significant associations were observed in IPCI in the -90-0 (pre-exposure) and 1-90 day risk periods (IRRs 1.30, 95% CI [1.27-1.34] and 1.05, 95% CI [1.02-1.08] respectively) and in SIDIAP in the >90 day risk period (IRR 1.18, 95% CI [1.03-1.35]). In the meta-analysis the decreased association in both the 1-30and 1-90 day risk period were statistically significant (IRRs 0.87, 95% CI [0.79-0.96] and 0.93, 95% CI [0.88-0.99] respectively).

For the outcome depression in IPCI increased associations were observed between doxycycline and depression in the -90-0 day risk period (IRR 1.10, 95% CI [1.05-1.15]) and the 1-90 day risk period (IRR 1.07 [1.02-1.13]). In both CPRD and SIDIAP there was a statistically significant increased associations between doxycycline and depression in the 61-90 day risk period (IRRs 1.07, 95% CI [1.03-1.11] and 1.16, 95% CI [1.01-1.32] respectively). In the meta-analysis these statistically significant associations between doxycycline and depression were not present anymore.

Indications acne vulgaris: In the group with acne there were no statistically significant associations between doxycycline and suicide-related events without death. In CPRD GOLD the 1-30 day risk period there was a statistically significant decreased association between doxycycline and anxiety (IRR 0.89, 95% CI [0.79-0.99]) and no association in the 1-90 day risk period (IRR 0.94, 95% CI [0.88-1.00]).

In IPCI there were no statistically significant associations between doxycycline and anxiety in the 1-30 day risk period (IRR 0.82, 95% CI [0.66-1.00]) and the 1-90 day risk period (IRR 0.91, 95% CI [0.80-1.02]. In the meta-analysis the decreased associations in both the 1-30 and 1-90 day risk period were statistically significant (IRRs 0.87, 95% CI [0.79-0.96] and 0.93, 95% CI [0.88-0.99] respectively). In CPRD GOLD there were statistically significant decreased associations between doxycycline and depression in the 1-30 day risk period (IRR 0.80, 95% CI [0.71-0.90]) and the 1-90 day risk period (IRR 0.90, 95% CI [0.84-0.97]). In IPCI there were no statistically significant associations in the 1-30 day risk period (IRR 1.11, 95% CI [0.83-1.45]) and in the 1-90 day risk period (IRR 0.98, 95% CI [0.81-1.16]). In SIDIAP there were no estimates produced for the 1-30 and 1-90 day risk periods. In the meta-analysis of in the indication with outcome depression there was a statistically significant decreased association in the 1-90 day risk period (IRR 0.91, 95% CI [0.86-0.97]).

Indication rosacea: In the group with rosacea there were no statistically significant associations between doxycycline and outcome suicide-related events without death or outcome depression. In IPCI there was a statistically significant decreased association of anxiety in the 1-90 day and >90 day risk periods in the

group with rosacea (IRRs 0.40, 95% CI [0.16-0.87] and 0.78, 95% CI [0.63-0.96] respectively). In CPRD GOLD and SIDIAP there were no statistically significant associations identified between doxycycline and anxiety in any of the risk periods. In the meta-analysis of patients with rosacea and outcome anxiety there was only a statistically significant increased association between doxycycline and anxiety in the -90-0 day risk period (IRR 1.18, 95% CI [1.03-1.37]).

Indication chlamydia: In the group with chlamydia there were no statistically significant associations between doxycycline and outcome suicide-related events without death or outcome anxiety. For the outcome depression chlamydia there was a statistically significant increased association in CPRD GOLD for depression in the >90 day risk period (IRR 7.48, 95% CI [1.32-31.30]). In IPCI and SIDIAP and the meta-analysis there were no statistically significant associations present in the group with indication chlamydia.

Indication LRTI: In the group with LRTI there were statistically significant decreased associations in CPRD GOLD between doxycycline and suicide-related events without death in the -30-0 day risk period (IRR 0.83, 95% CI [0.71-0.96]), the 1-30 day risk period (IRR 0.72, 95% CI [0.61-0.84]), the 31-60 days risk period (IRR 0.81, 95% CI [0.70-0.94]), the -90-0 day risk period (IRR 0.85, 95% CI [0.77-0.93]) and the 1-90 day risk period (IRR 0.83, 95% CI [0.76-0.91]). In IPCI and SIDIAP no estimates were produced for the outcome of suicide-related events without death. In patients with LRTI there were statistically significant increased associations of anxiety in the -90-0 risk day period in IPCI and SIDIAP (IRRs 1.14, 95% CI [1.06-1.23] and 1.25, 95% CI [1.13-1.37] respectively) and the 1-90 day risk period in SIDIAP (IRR 1.12, 95% CI [1.02-1.14]). In IPCI there were no statistically significant associations in the 31-60 and the 1-90 day risk period (IRRs 1.07, 95% CI [0.96-1.18]) and 1.03, 95% CI [0.97-1.10]) respectively). In SIDIAP there was also no statistically significant association in the 31-60 day risk period (IRR 1.14, 95% CI [0.97-1.34]). In the meta-analysis of the group with LRTI with outcome anxiety there were there were statistically significant increased associations in the 31-60 day risk period (IRR 1.06, 95% CI [1.02-1.11]) and the 1-90 day risk period (IRR 1.05, 95% CI [1.02-1.08]). For the outcome depression there was a statistically significant increased association with depression in the -90-0 day risk period (IRR 1.15, 95% CI [1.12-1.19]) for CPRD GOLD and the 1-90 day risk period (IRR 1.18, 95% CI [1.02-1.35]) in SIDIAP. In the meta-analysis these statistically significant associations between doxycycline and depression were not present anymore.

Conclusions

In this study for both the cohort study as the SCCS many estimates could not be produced because cohort comparisons failed quality diagnostics. From the estimates passing diagnostics a two-fold increased association of suicide-related events in users of doxycycline was observed compared to users of erythromycin in patients with acne in the cohort study was found. However, these findings were not consistent and conversely, we also observed a decreased association of doxycycline (compared to amoxicillin and combinations) on suicide-related events in LRTI patients in the cohort study. Differences in study population characteristics, baseline risk and treatment duration by indication could explain these differential observations.

4. LIST OF ABBREVIATIONS

Acronyms/term	Description
CAP	Community Acquired Pneumonia
CDM	Common Data Model
CC	Coordinating Centre
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DRE	Digital Research Environment
DQD	Data Quality Dashboard
EEA	European Economic Area
EHR	Electronic Health Records
EMA	European Medicines Agency
ED	Emergency department
EU	European Union
GDPR	General Data Protection Regulation
ICD	International Classification of Diseases
ID	Index date
IP	Inpatient
LPD	Longitudinal Patient Database
LRTI	Lower Respiratory Tract Infection
MA	Marketing Authorisation
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
SCCS	Self-Controlled Case Series
SD	Standard deviation
SNOMED	Systematized Nomenclature of Medicine
STD	Sexually Transmittable Disease
WHO	World Health Organisation

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	19th June 2024	18th June 2024
Final Study Protocol	5th July 2024	19th July 2024
Creation of Analytical code	July 2024	
Execution of Analytical Code on the data	July 2024	
Draft Study Report	15th August 2024	21st October 2024
Final Study Report	26th November 2024	21st November 2024

7. RATIONALE AND BACKGROUND

Doxycycline, a tetracycline antibiotic, is widely used for treating bacterial infections including respiratory and sexually transmittable diseases, acne, and (papulopustular) rosacea.[1] Despite long-term and widespread use of Doxycycline, recent concerns have been raised about potential neuropsychiatric side effects of doxycycline, particularly regarding suicidality, including suicidal ideation, attempts, and completed suicide.[2-5] Some case study reports and epidemiological studies have suggested a possible link between doxycycline and enhanced risks of psychiatric symptoms, including depression and anxiety, which are known risk factors for suicidality.[3-5] However, data specifically examining the relationship between doxycycline and suicidality are limited. The aim of this study was to generate further information to assess these potential safety concerns.

8. RESEARCH QUESTION AND OBJECTIVES

Table 1. Primary and secondary research questions and objectives.

A. Primary research question 1 and objective 1.

Objective:	To use a new-user cohort study to assess the association between doxycycline and i) completed suicide, ii) composite suicide and suicide-related events (completed suicide, suicide ideation and suicide attempt, self-harm), iii) composite non-fatal suicide-related events (suicide ideation, suicide attempt, self-harm), iv) depression, and v) anxiety, compared to active comparators, stratified by indication of acne vulgaris, rosacea, lower respiratory tract infection, and chlamydia.
Hypothesis:	Doxycycline increases the risk of suicide, suicide-related events (including self-harm, suicide attempt and ideation), depression, and anxiety.

Population *(mention key inclusion-exclusion criteria):*	Inclusion • New users of doxycycline, erythromycin, isotretinoin, azithromycin or amoxicillin in the study period depending on indication. • Diagnosis of the indication (acne vulgaris, rosacea, chlamydia, or LRTI) based on presence of a disease code ±30 days of the index date (i.e. first use of exposure of interest during study period) for LRTI and chlamydia, and in the period [-180,30] around the index date for acne and rosacea. Exclusion • Use of doxycycline, erythromycin, isotretinoin, azithromycin or amoxicillin <365 days prior to the index date • Start date in database is <365 days prior to the index date • Occurrence of the outcome in the 365 days prior to index date
Exposure:	Doxycycline
Comparator exposures (by indication):	Acne vulgaris: Erythromycin, Isotretinoin Rosacea: Erythromycin, Isotretinoin Chlamydia: Azithromycin, Erythromycin, Amoxicillin LRTI (CAP and bronchitis): Azithromycin, Amoxicillin
Outcome:	Composite suicide and suicide-related events (condition or observation of a completed suicide, suicide attempt, suicide ideation, and self-harm); composite suicide-related events (condition or observation of a suicide attempt, suicide ideation, and self-harm with or without death date ±30 days); and completed suicide (condition record of suicide plus death date in ±30 days)
Time *(when follow up begins and ends):*	1st January 2010 to data lock which was the date of the most recent data release (01/05/2024 CPRD GOLD, 01/12/2023 IPCI, and 01/06/2023 SIDIAP)
Setting:	Primary care
Main measure of effect:	Hazard ratio (RR) and corresponding 95% confidence intervals (CI)

B. Primary research question 2 and objective.

Objective:	To use a self-controlled case series study to assess the association between use of doxycycline and composite suicide events (including suicide ideation, suicide attempt, self-harm), depression, and anxiety.
Hypothesis:	Is there an association between the use of doxycycline and suicide-related events?
Population *(mention key inclusion-exclusion criteria):*	**Inclusion** • Prescription of doxycycline in the study period • Individuals with the outcome of interest

	Exclusion • Use of doxycycline ever before the index date • Start date in database is <365 days prior to the index date • Occurrence of the outcome prior to the observation period (prior to 1st January 2010)
Exposure:	Doxycycline
Comparator:	None, self-controlled
Outcome:	There were three different outcomes namely one composite outcome of non-fatal suicide-related events (suicide attempt, ideation and self-harm), depression, and anxiety.
Time *(when follow up begins and ends):*	1st January 2010 to data lock (date of most recent data release) (01/05/2024 CPRD GOLD, 01/12/2023 IPCI, and 01/06/2023 SIDIAP)
Setting:	Primary care
Main measure of effect:	Incidence rate ratios (IRR) and corresponding 95% confidence intervals (CI)

9. RESEARCH METHODS

9.1 Study type and study design

We performed a new-user active comparator cohort study and a self-controlled case series (SCCS) study to assess the association between doxycycline and the composite outcome of non-fatal suicide-related events (suicide attempt, suicide ideation and/or self-harm), depression, and anxiety events. The new-user cohort study additionally analysed the outcomes completed suicide (with death) and composite suicide and suicide-related events (completed suicide, suicide attempted, suicide ideation or self-harm events). The repository of the study programme can be found at: https://github.com/darwin-eu-studies/P3-C3-003-Doxycycline

Table 2. Description of potential study types and related study designs.

Study type	Study design	Study classification
Drug/Vaccine Safety Studies	Self-controlled case series (SCCS).	Complex
Drug/Vaccine Safety Studies	New User Active Comparator Cohorts	Complex

9.2 Study setting and data sources

The selection of databases for this study was performed based on data reliability and relevance for the proposed research question among those databases onboarded and available within DARWIN EU®. The selected databases fulfilled the criteria required for the availability of key information on exposures, outcomes, and covariates, while covering different settings and regions of Europe. All data were apriori mapped to the OMOP CDM. This study was conducted using routinely collected data from 3 primary care data sources in 3 European countries:

- Clinical Practice Research Datalink (CPRD GOLD), United Kingdom
- Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
- The Integrated Primary Care Information (IPCI), the Netherlands

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management.[6] The source population encompasses 98% of the UK, registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. Covering 4.6% of the current UK population, GOLD includes 4.9% of contributing GP practices, providing comprehensive information within its defined source population. GOLD contains data from all four UK constituent countries and the current regional distribution of its GP practices is 5.7% in England, 55.6% in Scotland, 28.4% in Wales, and 10.2% in Northern Ireland (May 2022).

GOLD data include patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity.[6] GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical database so far.[7-9].

In terms of quality checks, the integrity, structure and format of the data is reviewed. Collection-level validation ensures integrity by checking that data received from practices contain only expected data files and ensures that all data elements are of the correct type, length and format. Duplicate records are identified and removed.[6] Transformation-level validation checks for referential integrity between records ensure that there are no orphan records included in the database (for example, that all event records link to a patient), while research-quality-level validation covers the actual content of the data. CPRD provides a patient-level data quality metric in the form of a binary 'acceptability' flag.[6] This is based on recording and internal consistency of key variables including date of birth, practice registration date and transfer out date.

The Integrated Primary Care Information (IPCI), the Netherlands

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data extracted from computer-based patient records of a selected group of general practitioners (GPs) across the Netherlands.[10] IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex. Although the geographical spread is limited, GP practices are located in urban and non-urban areas.

Patient-level data includes demographic information, patient's complaints and symptoms, diagnoses, laboratory test results, lifestyle factors and correspondence with secondary care, such as referral and discharge letters. For complaints, symptoms and diagnoses, Dutch GPs use International Classification of Primary Care (ICPC-1) coding, an international standard developed and updated by the World Organization of Family Doctors' (WONCA) International Classification Committee.

IPCI data quality has been previously documented and IPCI has proved valuable for epidemiological studies.[11-15] In terms of quality control, extensive quality control steps are performed prior to each data release. These include comparison of patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g. reliability of birth and mortality rates) and medical data (e.g. availability of durations of prescriptions, completeness of laboratory results, availability of hospital letters and prescriptions, proportion of patients with blood pressure measurement, etc).[10] Based on this information, two quality scores have been created. Practices with low scores have been excluded.

Information System for Research in Primary Care (SIDIAP), Spain

The Information System for Research in Primary Care (SIDIAP) is a dynamic database of pseudo-anonymized electronic health records of the primary care patient population in Catalonia, Spain.[16] It contains data of approximately 80% of the Catalan population registered in over 280 primary care practices throughout Catalonia since 2005.

The database contains data recorded in primary care centres on a daily basis. Additionally, it integrates data from external sources including biomarkers data from laboratories and records of drug prescription and dispensation. The dataset covers demographics, all-cause mortality, disease diagnoses classified under the International Classification of Diseases 10th revision (ICD-10), prescription and dispensation records of drugs, results of laboratory tests, socio-economic indicators, vaccination records, lifestyle information, parent–child linkage and various clinical parameters. Additional data from other data sources such as hospital discharges, mental health centres or specific disease registries can be obtained through diverse linkages. The demographic composition within SIDIAP closely mirrors that of the broader Catalan population, encompassing a representative spectrum of geographic distribution, age, and sex proportions. The database is updated every 6 months.

SIDIAP data quality has been previously documented and SIDIAP has proved valuable for epidemiological studies.[17-26] In terms of data integrity and reliability, SIDIAP has been subject to rigorous evaluation. Quality checks have been implemented including central identification of duplicate patient ID and visual inspection for temporal patterns in the registry of a certain variable. Furthermore, the data undergoes assessment for availability (longitudinally and reliability), plausibility (range checks and unusual values) and consistency using visualisation tools. Specifically, for biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

9.3 Study period

The observation period began on the 1st of January 2010 and continued to the last available date of data collection for each contributing data source (01/01/2024 CPRD GOLD, 30/04/2024 IPCI, and 30/06/2023 SIDIAP).

9.4 Follow-up

For the new-user cohort analysis, the index date was the first date of prescription of doxycycline or active comparator in the study period. At index date the patients were followed until the end of the drug treatment episode plus 7 days, death, occurrence of the outcome, end of patient observation or end date

of data source availability. A treatment episode is a succession of repeated prescriptions which are determined to be continuous treatment. A sensitivity analysis was carried out using cohorts for the indications acne and rosacea where we followed patients for 30 days after the drug treatment episode ended instead of only 7 days as with the indications LRTI and chlamydia. This was to account for potentially longer periods of exposure associated with these indications and to account for potential variations in adherence over the longer period of usage.

For the SCCS analysis the index date was the date of first doxycycline prescription with no prior use in the study period. This was the first drug era, from which several assessment windows are examined including a pre-treatment window [-90,0 days] and risk windows [1,90], [1,30], [31,60], [61,90], [91,inf], as well as baseline assessment window outside of these 6 windows. Patients were followed until the end of data availability for the person (death, move out of the data source capture) or end of data collection for the data source. The SCCS study design is illustrated in **Figure 1**.

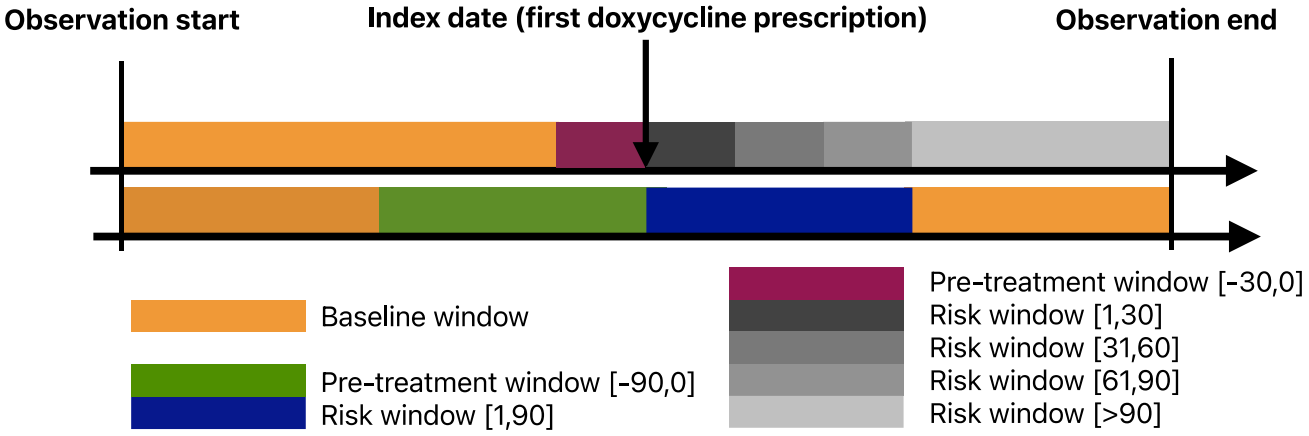


Figure 1. An illustration of the self-controlled case series study design.

9.5 Study population with inclusion and exclusion criteria

New-user cohort study

In the new-user cohort study, the index date was the date of first prescription of doxycycline or active comparator in the study period, after the diagnosis of the respective indication. Each cohort was constructed per indication and therefore doxycycline had different active comparators per indication. Patients were excluded from the study if there was a prescription record of the same drug in the study period prior to the index date. Patients were also excluded if the start date in the database or occurrence of the outcome fell within 365 days prior to the index date as this does not guarantee sufficient database history to track information on covariates (comorbidity and/or use of concomitant medication). It also makes the index date likely to represent the first use of exposure and a new outcome event.

The indications, target exposure and active comparators were as follows:

1. Acne vulgaris: Doxycycline versus either erythromycin or isotretinoin
2. Rosacea: Doxycycline versus either erythromycin or isotretinoin
3. Chlamydia: Doxycycline versus either azithromycin, erythromycin or amoxicillin
4. LRTI (CAP or bronchitis): Doxycycline versus either azithromycin or amoxicillin

We performed the cohort study for each cohort indication but also restricted to individuals with a history of depression. This stratification in individuals with a history of depression was not conducted for the outcome of depression.

SCCS study

In the SCCS study, patients were included if they have a prescription of doxycycline and a record of the outcome during the observation period. The index date was the date of the first prescription of doxycycline with no prior prescription in the study period.

The incidence of the outcomes of interest was compared in the risk windows [1,90 days], [1,30 days], [31,60 days], [61,90 days], [91,inf] and the pre-treatment risk window [-90,0 days], to the baseline window (the remaining time in the study period when not exposed, nor in the 90-day pre-treatment window).

Persons who had their database start date within 365 days prior to index date were excluded, as sufficient data availability is required. Persons with an occurrence of the outcome prior to the observation period (1st January 2010) were excluded from the study.

9.6 Variables

Preliminary concept/code lists used for the identification of exposures and outcomes are included as Supplementary Documents in Appendix I. These codes were identified during the study execution following the DARWIN EU® Phenotyping standard operating practice which involve the review of code lists by clinical experts, and the review of phenotypes after their execution in the participating databases through cohort diagnostics.[27]

9.6.1. Exposures

Doxycycline exposure consisted of a prescription record of doxycycline (for systemic use thus oral or parenteral use), accounting for the first prescription in the study period with no prior prescription of doxycycline or comparator drugs. In the new-user cohort study, treatment episodes of sequential prescriptions were generated (i.e. drug era), with a maximum of 30 days between the end date of one prescription and the start date of the next prescription. The risk window therefore accounted for all periods when the patient is likely to be using the drug.

For the new-user cohort study, doxycycline we had several active comparators, based on indication of doxycycline.

- Comparator for acne vulgaris: either erythromycin or isotretinoin
- Comparator for rosacea: either erythromycin or isotretinoin
- Comparator for chlamydia: either azithromycin, erythromycin, or amoxicillin
- Comparator for lower respiratory tract infection (CAP and bronchitis): either azithromycin, or amoxicillin.

We measured only from the first prescription of each of the comparator i.e., no prior prescription in the study period. We only assessed systemic use of these drugs and thus not topical use.

9.6.2 Outcomes

The primary outcomes for the SCCS and the new-user cohort of the study were different. In the SCCS study, completed suicide was not included because this type of outcome affects subsequent follow-up time such as death breaches the assumptions of the SCCS study design.[28]

The new-user cohort design outcomes were as follows: Completed suicide (condition record of suicide plus death date in ±30 days); composite suicide-related events (includes completed suicide, suicide attempt, suicide ideation and self-harm); composite non-fatal suicide-related events (suicide attempt, suicide ideation and self-harm); depression (for general study population, not the subgroup with history of depression); and anxiety.

The outcomes for the SCCS study were as follows: composite non-fatal suicide-related events (suicide attempt, suicide ideation and self-harm); depression; and anxiety. Due to the risk of duplicate recording events, we only assessed the first outcome occurring after entry into the study.

9.6.3 Other covariates, including confounders, effect modifiers and other variables (where relevant)

For the new-user cohort study, we calculated propensity scores based on large-scale characterisation for diagnoses recorded within 183 days prior to the index date. In addition, we measured and included the following pre-specified conditions:[29, 30] depression (not for the outcome depression), anxiety (not for the outcome anxiety), personality disorder, bipolar disorder, schizophrenia, cancer, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, and cardiovascular disease

As associations might further be confounded by a medical history of depression, we separately conducted the new-user cohort analysis in patients with a prior diagnosis of depression in the study period prior to index date (in addition to the general study population). This cohort was not used to study the outcome of depression.

We did not adjust for additional covariates in the SCCS study, other than controlling for age group, year and seasonality (the latter two only in the standard SCCS method used to study depression or anxiety as an outcome). To control for potential effect modification by indication of use, the SCCS was conducted in all users of doxycycline, but also conducted stratified by the following indications of use: acne vulgaris, rosacea, chlamydia, or LRTI (CAP and bronchitis).

9.7 Study size

In the *new-user cohort study*, we assumed a baseline incidence rate of completed suicide of 10 per 100,000 person-years.[31] Assuming a follow-up duration to be 90-days and an IRR = 5.0 for the exposure-outcome association, a study sample of size should have at least 240,000 per group. For the composite outcome of completed suicide, attempted suicide, suicide ideation and self-harm events, we assumed a baseline incidence rate of 100 per 100,000 person-years.[32] Assuming a follow-up duration of 90-days and a lower detectable IRR = 2.0 for the exposure-outcome association, the sample size should have at least 191,000 per group. For the outcome of depression, we assumed a baseline incidence rate of 500 per 100,000 person-years.[33] To detect an IRR = 2.0 for the exposure-outcome association with the assumed follow-up duration of 90-days, the sample size should have been at least 38,000 per exposure group (see **Table 3** for values when exposure duration is set to different lengths).

For the *SCCS study* we assumed an approximate follow-up time of 5-years, a 90-day risk window (e.g. risk window [1,90]) and all cases are exposed.[6, 10, 16] Where alpha = 0.05 and power of 0.8, to detect an IRR = 2.0 for the exposure-outcome association, the study size should have been at least 245 persons. For an IRR = 1.5, the study size should have included at least 828 persons.

Table 3. Minimum sample size to detect an incidence rate ratio (IRR) of 2.0 or greater for each outcome.

	Baseline IR per 100,000 person-years*	Minimum no. of persons per exposure group		
		30-days follow-up	90-days follow-up	180-days follow-up
Completed suicide	10	>1,000,000	>1,000,000	956,000
Composite suicide related events (suicide attempt, ideation, self-harm)	100	573,000	191,200	96,000
Depression	500	115,000	38,000	19,150
Anxiety	1,500	38,000	12,800	6,400

**Conservative estimates of the baseline incidence rates.*

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on the data sources and quality control checks were performed. After all tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics in R studio and reviewed and approved the – by default – aggregated results.

The study results of all data sources were checked after they were made available to the team and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical methods

9.9.1 Main summary measures

Incidence rates, incidence rate ratios (IRR) and corresponding 95% confidence intervals were calculated for the matched cohorts and outcomes. Cox proportional hazard models were used to calculate hazard ratios (HR) and corresponding 95% confidence intervals for the outcomes of completed suicide, composite suicide and suicide-related events (completed suicide, suicide attempt, suicide ideation and self-harm), composite non-fatal suicide-related events (suicide attempt, suicide ideation, self-harm) and anxiety. In the general study population (not stratified to those with a history of depression) were investigated the outcome depression.

9.9.2 New-user cohort with active comparator analyses

To perform the new-user cohort analysis we used the *CohortMethods* R package.[34] We performed large-scale characterisation of participants in the target and comparator cohorts, including all diagnoses and prescriptions available in the data within 183 days before the index date [-183,0]. Using a propensity-score (PS) matched cohort design, target (doxycycline) and comparator cohorts, participants were matched up to 1:5 based on propensity scores, and exact-matched on age and calendar year of index date. Large-scale propensity scores (LSPS) were estimated as the probability of exposure (target cohort) conditional on all available covariates available in the data with a prevalence >1%. LSPS were estimated using Lasso regression. The LSPS were used to estimate the probability of being in the target cohorts, potentially

including any of the covariates. The resulting equations were manually inspected by two clinical epidemiologists to identify any strong instrumental variables.

Up to 5 matches were found for each participant in the target cohort using PS matching with nearest neighbour matching with a calliper width of 0.2. Matches were sampled from the pool of comparator cohort participants identified as potential matches in the first step. Then, the index date of the target cohort participant was applied to all the identified comparator cohort matches, and large-scale PS were re-calculated on this index date. Anyone in the comparator cohort with a PS greater than 0.2 of the proposed calliper width compared to their matched active cohort participant, as well as those censored or changing exposure status before the newly imposed index date were excluded.

A full list of the subgroup analyses of doxycycline versus active comparator, per indication to be compared can be seen in table 5. In summary:

- Acne vulgaris: Doxycycline versus erythromycin or isotretinoin
- Rosacea: Doxycycline versus erythromycin or isotretinoin
- Chlamydia: Doxycycline versus erythromycin, azithromycin or amoxicillin
- LRTI (CAP and bronchitis): Doxycycline versus amoxicillin or azithromycin

Negative control outcomes and exposures were used to identify residual (unobserved) confounding in the cohort and SCCS analyses respectively (**Appendix Table 5**). A validated list of negative control outcomes was utilised and refined to identify potential outcomes not associated with outcome risk but sharing similar confounders as the association between doxycycline and outcomes. These negative controls were used in the diagnostic stage of the analysis to calculate expected absolute systematic error (EASE) score.

Kaplan-Meier plots were used to illustrate time-to-event analyses. Log-log plots were visually inspected to identify scenarios with a violation of the proportional hazards' assumption. If these plots showed evidence of violation, we did not unblind the results from the Cox regression and instead, we only reported incidence rates in the shiny app.

In all new user cohorts, people were followed up from their index date until the earliest of:

- End of their observation (i.e. date of data extraction, death)
- Occurrence of the outcome
- End of the drug era plus 7 days (or 30 days in sensitivity analysis for the indications acne and rosacea)
- Participants in the comparator cohort were censored when and if they fulfil the entry criteria for the matched target cohort i.e., if they are prescribed doxycycline after the index date.

9.9.3 Self-controlled case series analysis

We performed an SCCS study for all new doxycycline users irrespective of indication. The SCCS design ensures that confounding by indication is largely controlled, but to account for effect modification for indications of use, we also performed the analysis per indication of use (diagnosis record in any period [-inf, 0] before the first prescription date). We assessed consistency across the different indications:

- No restriction to any indication (thus including individuals using doxycycline *not limited* to acne vulgaris, rosacea, chlamydia or LRTI only)
- Acne vulgaris
- Rosacea
- Chlamydia

- Lower respiratory tract infection (CAP and bronchitis)

Using the *SelfControlledCaseSeries* R package Incidence rate ratios and 95% confidence intervals were estimated using conditional Poisson regression models, comparing the exposed vs the baseline period.[35] The IR was calculated for each assessment window including the baseline window (>90 days prior to the index date and when non-exposed), the pre-treatment assessment window [-90,0], and the risk windows [1,90], [1,30], [31,60], [61,90], [91,inf], where day 0 is the index date.

In the [91,inf] period, patients were assessed in the 90 days beyond index date. The IRR therefore estimated from comparing these risk windows to the baseline window. Adjusted incidence rate ratios and 95% confidence intervals were calculated after adjustment for age group (<18, 18-39, 40-59, 60-79 and >=80 years at index date) and seasonality. Seasonality was accounted for in the *SelfControlledCaseSeries* R package where splines were used and weighted mean ratios were subsequently calculated using the time stability options. The IR and IRR were calculated for the for each exposure and per indication to the outcomes: composite suicide related events (suicide attempt, suicide ideation, self-harm), depression, and anxiety.

For the outcome composite non-fatal suicide-related events (attempted suicide, ideation and self-harm), we used the SCCS extension proposed by Farrington et al. to handle outcomes which may have influence on the length of subsequent follow-up time, an optional setting in the *SelfControlledCaseSeries* R package.[35, 36] This assessed whether there is an association between the occurrence of the outcome and the end of observation (to check for the potential breaking of assumptions of the SCCS design), we plotted the dependency of event-observation end. This allowed us to compare between censored (i.e. cases) and uncensored persons. For the outcomes depression and anxiety, we used the standard SCCS approach.

Diagnostics included assessments of the event-exposure independence: a histogram of the time between the event date and the end of observation for individuals censored and uncensored were plotted to assess potential for event-dependent observation time. The results of analyses were unblinded when only the power (MDRR) diagnostic failed. Which allowed for the results to be included in the meta-analysis.

Table 4. Primary, secondary, and subgroup analysis specification.

A. Primary analysis 1 (new-user cohort with active comparator study)

Hypothesis:	Doxycycline increases the risk of suicide, suicide-related events (including self-harm, suicide attempt and ideation), depression, and anxiety
Exposure contrast:	Doxycycline versus erythromycin, isotretinoin, azithromycin or amoxicillin
Outcome:	Composite suicide and suicide-related events (condition or observation of a completed suicide, suicide attempt, suicide ideation, and self-harm); composite suicide-related events (condition or observation of a suicide attempt, suicide ideation, and self-harm with or without death date ±30 days); and completed suicide (condition record of suicide plus death date in ±30 days)
Analytic software:	R
Model(s): *(provide details or code)*	Incidence rates, incidence rate ratios, Cox proportional Hazards models, Kaplan-Meier Time-to-event.

Confounding adjustment method	
	All subjects in the target cohort were exact matched by age and calendar year to all potential matches not belonging in the target cohort at any time in that calendar year. A propensity score (PS) were estimated as follows for doxycycline versus active comparator groups: a PS was calculated at the beginning of the calendar year for both the target and comparator cohorts. Up to 5 matches were found for each participant in the target cohort using PS matching with nearest neighbour matching with a calliper width of 0.2. Matches were sampled from the pool of comparator cohort participants identified as potential matches in the first step. Then, the index date of the target cohort participant was applied to all the identified comparator cohort matches, and large-scale PS was then re-calculated on this index date. Anyone in the comparator cohort with a new PS out of the proposed calliper width compared to their matched active cohort participant, as well as those censored or changing exposure status before the newly imposed index date were excluded. We analysed per indication of the doxycycline or active comparator (see subgroup analyses). Furthermore, we performed negative control outcome calibration to reduce the risk of unobserved or unmeasured confounding, by allowing us to understand if these biases are present. If the effect estimates differ then it is possible unobserved or unmeasured confounding is present.
Missing data methods	
	None
Subgroup Analyses	
	<u>Cohorts:</u> Doxycycline + acne vulgaris diagnosis Doxycycline + acne vulgaris diagnosis and history of depression Erythromycin + acne vulgaris diagnosis Erythromycin + acne vulgaris diagnosis and history of depression Isotretinoin + acne vulgaris diagnosis Isotretinoin + acne vulgaris diagnosis and history of depression Doxycycline + rosacea diagnosis Doxycycline + rosacea diagnosis and history of depression Erythromycin + rosacea diagnosis Erythromycin + rosacea diagnosis and history of depression

Isotretinoin + rosacea diagnosis

Isotretinoin + rosacea diagnosis and history of depression

Doxycycline + chlamydia diagnosis

Doxycycline + chlamydia diagnosis and history of depression

Azithromycin + chlamydia diagnosis

Azithromycin + chlamydia diagnosis and history of depression

Erythromycin + chlamydia diagnosis

Erythromycin + chlamydia diagnosis and history of depression

Amoxicillin + chlamydia diagnosis

Amoxicillin + chlamydia diagnosis and history of depression

Doxycycline + LRTI diagnosis

Doxycycline + LRTI diagnosis and history of depression

Amoxicillin + LRTI diagnosis

Amoxicillin + LRTI diagnosis and history of depression

Azithromycin + LRTI diagnosis

Azithromycin + LRTI diagnosis and history of depression

Analyses per indication :

Acne vulgaris

Doxycycline versus erythromycin

Doxycycline versus isotretinoin

Rosacea

Doxycycline versus erythromycin

Doxycycline versus isotretinoin

Chlamydia

Doxycycline versus azithromycin

Doxycycline versus erythromycin

Doxycycline versus amoxicillin

Lower respiratory tract infection

Doxycycline versus amoxicillin

Doxycycline versus azithromycin

Sub-analysis: history of depression

Acne vulgaris

Doxycycline versus erythromycin

Doxycycline versus isotretinoin

Rosacea

Doxycycline versus erythromycin

Doxycycline versus isotretinoin

Chlamydia

Doxycycline versus azithromycin

Doxycycline versus erythromycin

Doxycycline versus amoxicillin

Lower respiratory tract infection

Doxycycline versus amoxicillin

Doxycycline versus azithromycin

Sensitivity analyses: cohort end date is 30 days after the end date of the drug era instead of 7 days

Acne vulgaris

Doxycycline versus erythromycin

Doxycycline versus isotretinoin

Acne vulgaris (with history of depression)

Doxycycline versus erythromycin

Doxycycline versus isotretinoin

Rosacea

Doxycycline versus erythromycin

Doxycycline versus isotretinoin

Rosacea (with history of depression)

Doxycycline versus erythromycin

Doxycycline versus isotretinoin

	Sensitivity analyses: negative control outcomes *Acne vulgaris* Doxycycline versus erythromycin Doxycycline versus isotretinoin

B. Primary analysis 2 (self-controlled case series study)

Hypothesis:	Doxycycline increases the risk of suicide-related events, self-harm, depression, and anxiety
Exposure contrast:	Self-controlled
Outcome:	Composite non-fatal suicide-related events (suicide ideation, suicide attempt or self-harm), depression, and anxiety.
Analytic software:	R
Model(s): *(provide details or code)*	Incidence rates and (adjusted) incidence rate ratios
Confounding adjustment method	
	Study design is self-controlled case series which accounts for confounding by indication and selection bias. Effect modification that remains was accounted for by stratifying by indication (see subgroup analyses section). Incidence rate ratios were adjusted by age and seasonality.
Missing data methods	
	None
Subgroup Analyses	
	All indications, no restriction Acne vulgaris (in any period before index date) Rosacea (in any period before index date) Chlamydia (in any period before index date) Lower respiratory tract infection (CAP or bronchitis, in any period before index date)

9.10 Evidence synthesis

Estimated incidence of the outcomes, incidence rate ratios and median survival were reported separately for each of the three databases included. No pooling of data took place in this federated analysis. We meta-analysed the effect estimates of the new-user cohort study across the databases with random effects, where results were available. Forest plots were used to show results from the meta-analyses.

9.10.1 Missing values

We carried out a complete case analysis where we assumed that if there were any missing data (for example a diagnosis not recorded in the EHR), it may be missing completely at random.

9.10.2 Sensitivity analysis

For the new-user cohort study, a sensitivity analysis was carried out for the indications acne vulgaris and rosacea where patients were followed up to 30 days after the drug era instead of 7 days. This was to account for potentially longer periods of exposure associated with those indications.

In the SCCS study, for the cohort of patients unrestricted to indication (largest cohort), we carried out an additional sensitivity analysis where we used a pre-treatment window of [-30,0]. This in-part accounted for a potential overlap between the pre-treatment window and a prior exposure period. Patients were followed until the end of data availability for the person (death, move out of the data source capture) or end of data collection for the data source.

10. DATA MANAGEMENT

All databases have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org. The analytic code for this study will be written in R and will use standardised analytics. Each data partner will execute the study code against their database containing patient-level data, and then return the results (csv files) which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

11. QUALITY CONTROL

General database quality control

Several open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). Data partners ran the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories were evaluated in two

contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

Phenotyping of outcomes and indication of use was done, and quality of the phenotype was assessed by running CohortDiagnostics. The study code was based on several R packages including the *CohortDiagnostics*, *SelfControlledCaseSeries*, and *CohortMethods*. These packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R-programme was made publicly available via the DARWIN EU® GitHub repository.

Protocol deviations

In **Table 5** we outline several deviations from the protocol which were undertaken in response to cohort diagnostics output.

Table 5. Protocol deviations.

Number	Date	Deviation from protocol	Reason
1	16/09/2024	We aimed to classify indication by diagnoses in the period surrounding index date (e.g. ±30 days for LRTI). However, in the SCCS analysis we classified indication by a recorded diagnosis any time before, within the study period.	The power of the SCCS was often very low and as a result analyses failed diagnostics. Increasing the time of the indication window increased the number of persons included in the indication sub-analyses.
2	14/10/2024	Results were unblinded when the only reason to fail diagnostics was that they did not have sufficient power (i.e., MDRR too high). These would have been blinded as they failed diagnostics.	To allow the results with lower power to be included in the meta-analysis.
3	16/09/2024	Using only the first outcome in the SCCS analysis	In IPCI some of the data vendors have repeated events for the same diagnosis recorded at subsequent visits automatically. Using only the first diagnosis avoids undue bias of these repeated events.
4	14/10/2024	Meta analysis was conducted with random effects instead of fixed effects	The R packages used (*CohortMethod* and *SelfControlledCaseSeries*) provide meta-analysis estimates with random (mixed) effects
5	31/10/2024	In the SCCS, the different windows around the index date relate to “risk-windows” and not “exposure-windows” The SCCS used risk windows after the first prescription of doxycycline, rather than considering treatment episodes as the protocol set out to do. We initially referred to these windows as “exposure windows”, however, we have rephrased these to risk windows.	The current version of the *SelfControlledCaseSeries* does not allow to specify ‘conditional’ exposure windows The R package *SelfControlledCaseSeries* did not allow for associating the risk window with treatment regimen.

12. RESULTS

In this report, we describe the main findings of our analyses. The full results of the new-user cohort and self-controlled case series analysis can be found in the Shiny app: https://data-dev.darwin-eu.org/P3-C3-003/Analyis/Run-2/.

12.1 Participants

Table 6 describes the number of individuals (with sex distribution) exposed to doxycycline and the active comparator of interest, as well as the number of individuals with outcomes of interest (results generated via the CohortDiagnostics package). Following the first run of the cohort diagnostics, the phenotype of exposure, indication and outcome were updated. **Table 6** describes the counts of the different phenotypes per database. As can be observed, the largest number of users of doxycycline was observed in CPRD, followed by IPCI and SIDIAP. In all databases, use was higher in females compared to males.

Anxiety and depression were prevalent conditions within all databases with more women affected than males. This female dominance could also be observed for suicide related events (without death) especially for IPCI and SIDIAP. In contrast, male dominance was observed for completed suicide or for suicide related events with mortality in the 30 days following the attempt.

Table 6. Number of persons exposed and number of individuals with an outcome of interest during study period.

Cohort		CPRD (UK) Person count	IPCI (NL) Person count	SIDIAP (Spain) Person count
Doxycycline	Overall (n)	1,775,083	332,611	249,326
	Female (%)	59.1	57.9	52.6
Anxiety	Overall (n)	1,672,592	530,604	1,575,815
	Female (%)	64.3	61.0	63.8
Depression	Overall (n)	1,556,578	117,196	730,939
	Female (%)	64.6	63.8	68.4
Composite suicide and suicide-related events	Overall (n)	146,276	7,934	29,838
	Female (%)	51.7	56.8	61.4
Composite suicide-related events (non-fatal)	Overall (n)	137,651	7,426	29,716
	Female (%)	51.9	58.2	61.5
Composite suicide-related events (fatal)	Overall (n)	1669	610	133
	Female (%)	23.8	37.2	33.0
Suicide (fatal)	Overall (n)	500	483	0
	Female (%)	24.4	35.0	-

Composite suicide and suicide-related events (condition or observation of a completed suicide, suicide attempt, suicide ideation, and self-harm); composite suicide-related events (condition or observation of a suicide attempt, suicide ideation, and self-harm with or without death date ±30 days); and completed suicide (condition record of suicide plus death date in ±30 days)

12.2Descriptive data

12.2.1 Descriptive data of new user comparator cohort

Descriptives of the new-user cohort with active comparator study in terms of number of individuals being exposed, number of individuals with the outcome of interest during exposure, and number of follow-up days can be consulted from the shiny app. Within this report, we focus the descriptives on suicide and suicide related events as the main outcome, but all results are available within the shiny app.

The attrition plots for the following cohorts of interest: Acne, Rosacea, LRTI and chlamydia with suicide related events as outcome, doxycycline as exposure as interest and with the different comparator drugs (by indication of use) can be found in **Appendix Figures 1-9**.

Country specific differences regarding use of comparator of drugs for the indications of interest could be observed with for instance low use of isotretinoin for treatment of acne in CPRD (UK), and low use of erythromycin for treatment of acne in IPCI (NL). Rosacea appeared to be mainly treated with doxycycline in all 3 databases whereas use of comparator drugs (erythromycin and isotretinoin) was much lower. In Spain, LRTI was mainly treated with azithromycin and less frequently with doxycycline whereas in the UK, the opposite was observed. In all databases, the use of amoxicillin as comparator drug for doxycycline within the cohort of individuals with LRTI was the highest.

Population characteristics before and after propensity score adjustment are provided in **Appendix Table 6-32**. For almost all cohorts, the SMD values of the covariates were less than 0.1, which implies that the difference in covariates between the two groups after PS matching was low. Regarding cohort characteristics, individuals within the acne cohort were younger than those from the rosacea and LRTI cohorts. Most individuals within the acne cohort were in the age-group 15-19 years while most individuals in the rosacea and LRTI cohort were 45-49 years and 65-69 years respectively. The individuals in the acne cohort were only slightly younger than the chlamydia cohort, where most individuals were aged 20-24.

The final size of the cohorts (doxycycline and comparator drugs) following PS matching is provided in **Table 7.** The largest cohorts were observed for LRTI (with amoxicillin as comparator drug) and for Acne with erythromycin or isotretinoin as comparator drug. As can be observed from **Table 7** the number of outcomes within the different cohorts of interest was low.

Table 7. Cohort size of doxycycline and comparator drugs and number of events of suicide-related events (non-fatal) by indication of use.

Indication of use	Database	Target subjects (n)	Comparator subjects (n)	Target events (n)	Comparator events (n)
Acne		Doxycycline	Erythromycin	Doxycycline suicide events	Erythromycin suicide events
	CPRD	18,054	30,682	12	10
	IPCI	778	793	0	0
	SIDIAP	6,090	9,350	7	<5
Acne		Doxycycline	Isotretinoin	Doxycycline suicide events	Isotretinoin suicide events
	CPRD	655	1,064	0	<5
	IPCI	2,757	3,534	<5	<5
	SIDIAP	12,265	16,998	<5	6

Indication of use	Database	Target subjects (n)	Comparator subjects (n)	Target events (n)	Comparator events (n)
Rosacea		Doxycycline	Erythromycin	Doxycycline suicide events	Erythromycin suicide events
	CPRD	5,086	5,393	<5	<5
	IPCI	90	90	0	0
	SIDIAP	831	846	0	0
Rosacea		Doxycycline	Isotretinoin	Doxycycline suicide events	Isotretinoin suicide events
	CPRD	47	70	0	0
	IPCI	146	146	0	0
	SIDIAP	599	608	0	0
LRTI		Doxycycline	Azithromycin	Doxycycline suicide events	Azithromycin suicide events
	CPRD	6,957	7,329	0	<5
	IPCI	9,889	10,392	<5	0
	SIDIAP	2,289	11,023	<5	<5
LRTI		Doxycycline	Amoxicillin	Doxycycline suicide events	Amoxicillin suicide events
	CPRD	113,147	282,984	6	38
	IPCI	20,969	24,267	<5	0
	SIDIAP	2,046	8,732	<5	<5
Chlamydia		Doxycycline	Erythromycin	Doxycycline suicide events	Erythromycin suicide events
	CPRD	110	133	0	0
	IPCI	17	17	0	0
	SIDIAP	92	100	0	0
Chlamydia		Doxycycline	Azithromycin	Doxycycline suicide events	Azithromycin suicide events
	CPRD	1,310	3,616	<5	<5
	IPCI	1,614	6,032	0	0
	SIDIAP	5,726	9,335	0	0
Chlamydia		Doxycycline	Amoxicillin	Doxycycline suicide events	Amoxicillin suicide events
	CPRD	112	137	0	0
	IPCI	164	199	0	0
	SIDIAP	311	329	0	0

12.2.2 Descriptive data SCCS

Descriptives of the SCCS can be consulted from the shiny app. Within this report, we focus on suicide attempts as the main outcome but descriptive data of anxiety and depression as outcome can be consulted in the shiny app.

The number of individuals within the SCCS with suicide attempts as outcome is described in **Table 8**. The SCCS cohorts had the largest size in the LRTI cohorts followed by the acne cohorts, rosacea cohorts and lastly the chlamydia cohorts. In general, the cohort size was the largest in CPRD and smallest in IPCI.

Table 8. SCCS cohort size for individuals with doxycycline and a non-fatal suicide-related events per indication of use.

	CPRD (UK)	IPCI (NL)	SIDIAP (Spain)
Overall	17,769	1,261	1,855
Doxycycline for acne	2,011	82	379
Doxycycline for rosacea	485	20	49
Doxycycline for LRTI	6,368	226	513
Doxycycline for chlamydia	205	17	91

N.B. Indication is determined from a prior diagnosis record in the EHR because indication is not consistently linked to prescription. Doxycycline may be prescribed for other conditions and there may be missing diagnosis records for the indications under study.

12.3 Outcome Data

12.3.1 Results for cohort method

Full results of the uncalibrated new-user cohort analysis can be found in the **Appendix Tables 33-44** and calibrated hazard ratios and corresponding 95% confidence intervals for patients with the indication acne, are presented in **Figures 2,5 and 9**. Many analyses did not pass diagnostics and the majority of which fail with the MDRR diagnostic, which means the analysis has too low power to ascertain an effect estimate. To study the association in individuals treated with doxycycline for reasons of acne, in line with the protocol, we also explored the effect of negative control outcomes. If negative control diagnostic failed, this suggests that unmeasured confounding may be present and as such the effect estimate may be biased and we therefore kept the output blinded.

Unblinding was only provided for those analyses that passed diagnostics. (which are described in the main section of the report). The complete table also describing analyses that failed diagnostics is available in the appendix.

Outcome of suicide-related events without death

Use of doxycycline for acne

In SIDIAP there was a statistically significant increased association between doxycycline use and suicide-related events without death (uncalibrated HR 3.77, 95% CI [1.03-17.80]) compared to erythromycin in individuals with acne. In CPRD GOLD no statistically significant association with suicide related events was observed in individuals treated with doxycycline compared to erythromycin (uncalibrated HR 1.71, 95% CI [0.74-4.07]) (**Table 9**). In both SIDIAP and CPRD GOLD no estimates were produced for suicide-related events in individuals treated with doxycycline compared to isotretinoin. For IPCI, no estimates were produced as all analyses failed diagnostics for both active comparators and there were no events in either group. The meta-analysis resulted based on estimates from CPRD GOLD and SIDIAP in a significant increased association between doxycycline use and suicide-related events without death (uncalibrated HR 2.11, 95% CI [1.01-4.39]) compared to erythromycin (**Figure 2**). No meta-analysis could be performed for suicide-related events in individuals with acne treated with doxycycline compared to isotretinoin.

Sensitivity analyses

In a sensitivity analysis, where the treatment episode was extended to 30 days after the end of the last prescription date instead of 7 days, in SIDIAP the statistically significant increased association between doxycycline use and suicide-related events without death compared to erythromycin remained (uncalibrated HR 3.35, 95% CI [1.02-12.99]), but no statistically significant association was observed compared to isotretinoin (uncalibrated HR 1.90, 95% CI [0.45-7.16]). In CPRD GOLD no statistically significant association found between doxycycline use and suicide-related events without death compared to erythromycin (uncalibrated HR 1.76, 95% CI [0.93-3.41]). In CPRD GOLD no estimates were produced for suicide-related events without death in individuals with acne treated with doxycycline compared to isotretinoin. For IPCI, no estimates were produced as all analyses also failed diagnostics for both active comparators in the sensitivity analysis, and there were no events in either the target or comparator cohorts (**Appendix Table 35**).

Residual confounding

Calibrating for residual confounding made the association between doxycycline use and suicide-related events without death compared to erythromycin in SIDIAP stronger (calibrated HR 4.53 95% CI [1.08-19.96]). In CRPD GOLD calibrating for residual confounding did not significantly change the increased association between doxycycline use and suicide-related events without death (calibrated HR 1.61, 95% CI [0.68-3.83]) compared to erythromycin (**Figure**).

Use of doxycycline for acne with a history of depression

In CPRD GOLD, no statistically significant association was found between doxycycline use and suicide-related events without death compared to erythromycin in individuals with acne and a history of depression (uncalibrated HR 1.52, 95% CI [0.40-6.16]). In CPRD GOLD no estimates were produced for suicide-related events in individuals with acne and a history of depression treated with doxycycline compared to isotretinoin. In individuals with acne and a history of depression and the outcome of suicide-related events without death all analyses in both IPCI and SIDIAP failed diagnostics (**Table 10**).

Sensitivity analyses

The sensitivity analysis did not provide any different associations. For CRPD a no statistically significant increased association was observed between doxycycline and suicide-related events without death compared to erythromycin (uncalibrated HR 1.47, 95% CI [0.51-4.46]), while no estimates were available for suicide-related events in individuals treated with doxycycline compared to isotretinoin (**Appendix Table 36**). All analyses in IPCI and SIDIAP still failed diagnostics.

Use of doxycycline for rosacea

In CPRD GOLD, no statistically significant association with suicide related events was observed in individuals with rosacea treated with doxycycline compared to erythromycin was found (uncalibrated HR 1.73, 95% CI [0.34-12.48]) (**Table 11, Figure**). In CPRD GOLD there were also no estimates produced for suicide-related events without death in individuals with rosacea treated with doxycycline compared to isotretinoin. In both IPCI and SIDIAP there were no estimates produced for doxycycline users with the indication rosacea since all analyses failed diagnostics.

Sensitivity analyses

The sensitivity analysis did not provide any different associations. For CRPD once again a non-statistically significant association was observed between doxycycline and suicide-related events without death compared to erythromycin (uncalibrated HR 1.32, 95% CI [0.92-6.73]), while no estimates were produced for suicide-related events in individuals treated with doxycycline compared to isotretinoin (**Appendix Table 39**). All analyses in IPCI and SIDIAP still failed diagnostics.

Use of doxycycline for rosacea with a history of depression

There were no estimates produced for doxycycline users with the indication rosacea and a history of depression the outcome of suicide-related events without death in either CPRD GOLD, IPCI or SIDIAP since all analyses failed diagnostics (**Table 12** and **Appendix Table 38**).

Sensitivity analyses
Sensitivity analysis also did not provide any associations. In either CPRD GOLD, IPCI or SIDIAP all analyses still failed diagnostics (**Appendix Table 40**).

Use of doxycycline for chlamydia

There were no estimates produced for doxycycline users with the indication of chlamydia and the outcome of suicide-related events without death in either CPRD, IPCI or SIDIAP since all analyses failed diagnostics (**Table 15**). Due to the absence of results no figure was produced.

Use of doxycycline for chlamydia with a history of depression

There were no estimates produced for doxycycline users with the indication of chlamydia and a history of depression and the outcome of suicide-related events without death in either CPRD, IPCI or SIDIAP since all analyses failed diagnostics (**Appendix Table 44**).

Use of doxycycline for LRTI

In CPRD GOLD there was a statistically significant decreased association of suicide-related events without death with doxycycline use (HR 0.40, 95% CI [0.15-0.87]) compared to amoxicillin in individuals with LRTI. In CPRD GOLD there were no estimates produced for suicide-related events in individuals with LRTI treated with doxycycline compared to azithromycin (**Figure 4**). There were no estimates produced for doxycycline users with the indication of LRTI and the outcome of suicide-related events without death in IPCI or SIDIAP since all analyses failed diagnostics (**Table 13**).

Use of doxycycline for LRTI with a history of depression

In CPRD GOLD there was a statistically significant decreased association between doxycycline use and suicide-related events without death (HR 0.29, 95% CI [0.07-0.85]) compared to amoxicillin in individuals with LRTI and a history of depression. In CPRD GOLD there were no estimates produced for suicide-related events in individuals with LRTI treated with doxycycline compared to azithromycin. There were no estimates produced for doxycycline users with the indication of LRTI and the outcome of suicide-related events without death in IPCI or SIDIAP since all analyses failed diagnostics (**Table 14**).

Outcome of suicide
There were no estimates produced for doxycycline users and the outcome of suicide in either CPRD, IPCI or SIDIAP since all analyses failed diagnostics. This was the case for all indications with and without the sensitivity analyses (**Appendix Tables 33-44**).

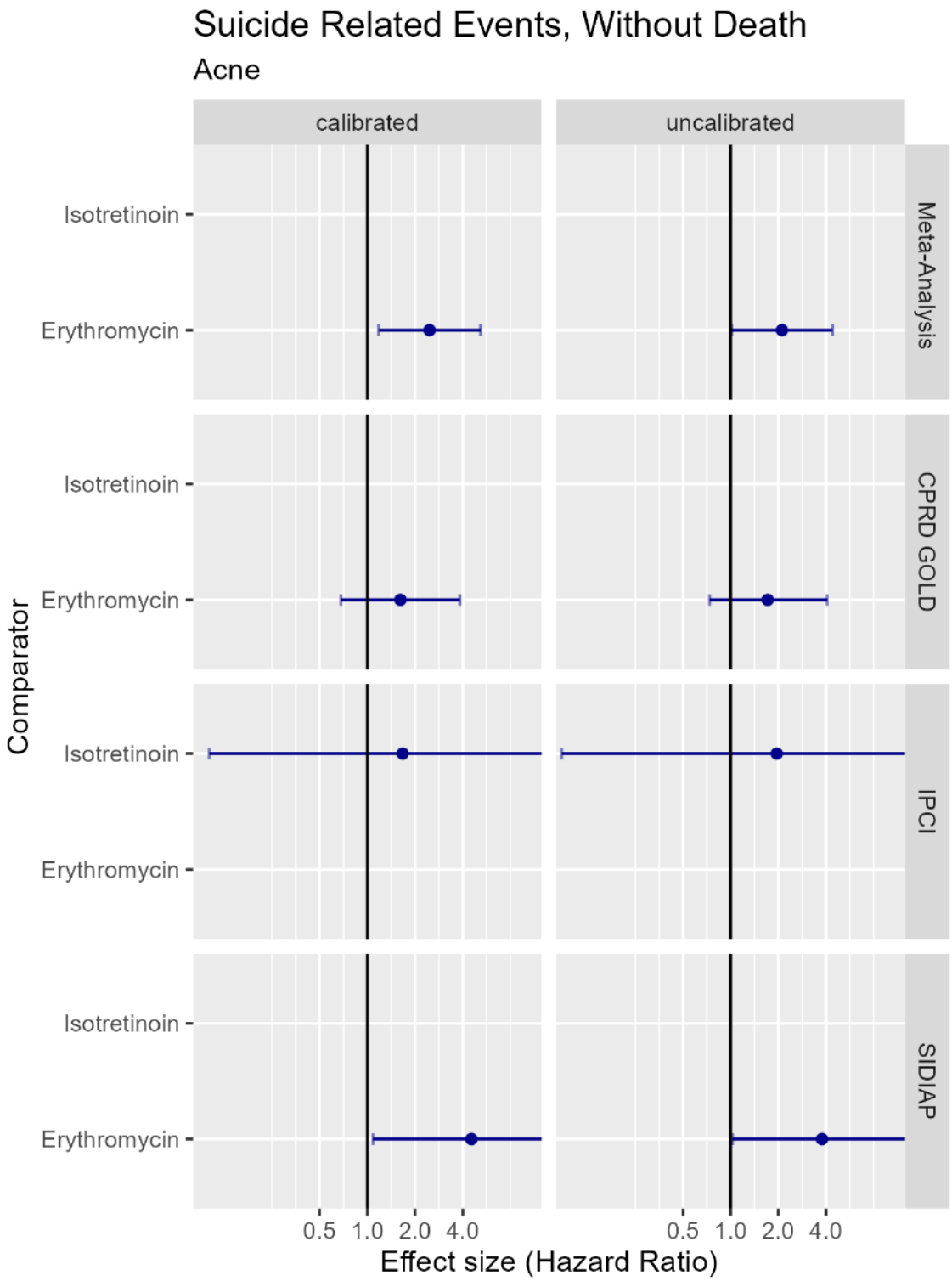


Figure 2. Forest plot of Cox-proportional hazards ratios (calibrated and uncalibrated) assessing the association between doxycycline for persons with acne and the outcome suicide-related events versus active comparator in CPRD GOLD, IPCI, SIDIAP, and meta-analysed. Output from data sources are blinded in the case they do not pass diagnostic tests.

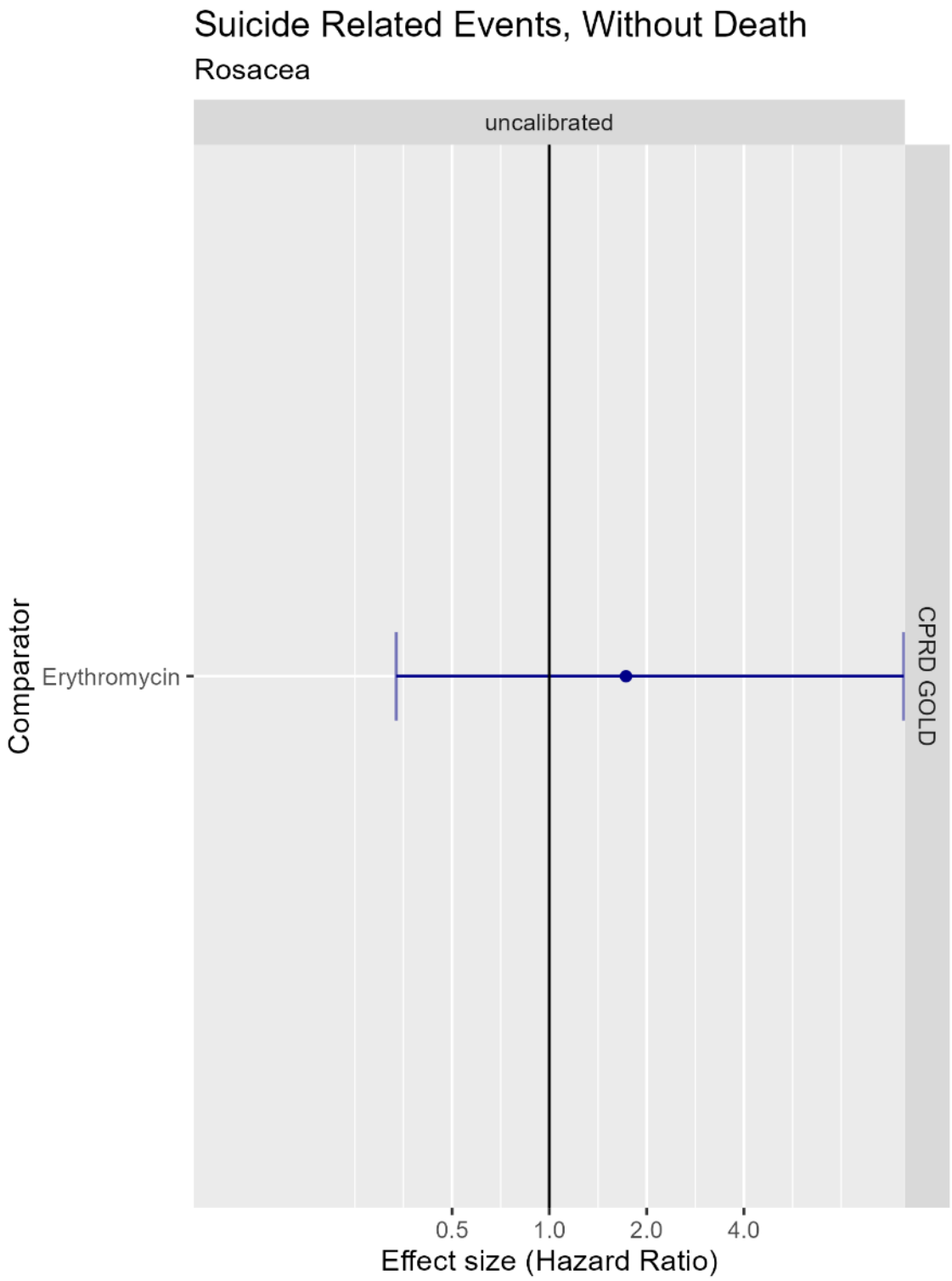


Figure 3. Forest plot of Cox-proportional hazards ratios assessing the association between doxycycline for persons with rosacea and the outcome suicide-related events versus active comparator in CPRD GOLD, IPCI, and SIDIAP. Output from data sources are blinded in the case they do not pass diagnostic tests.

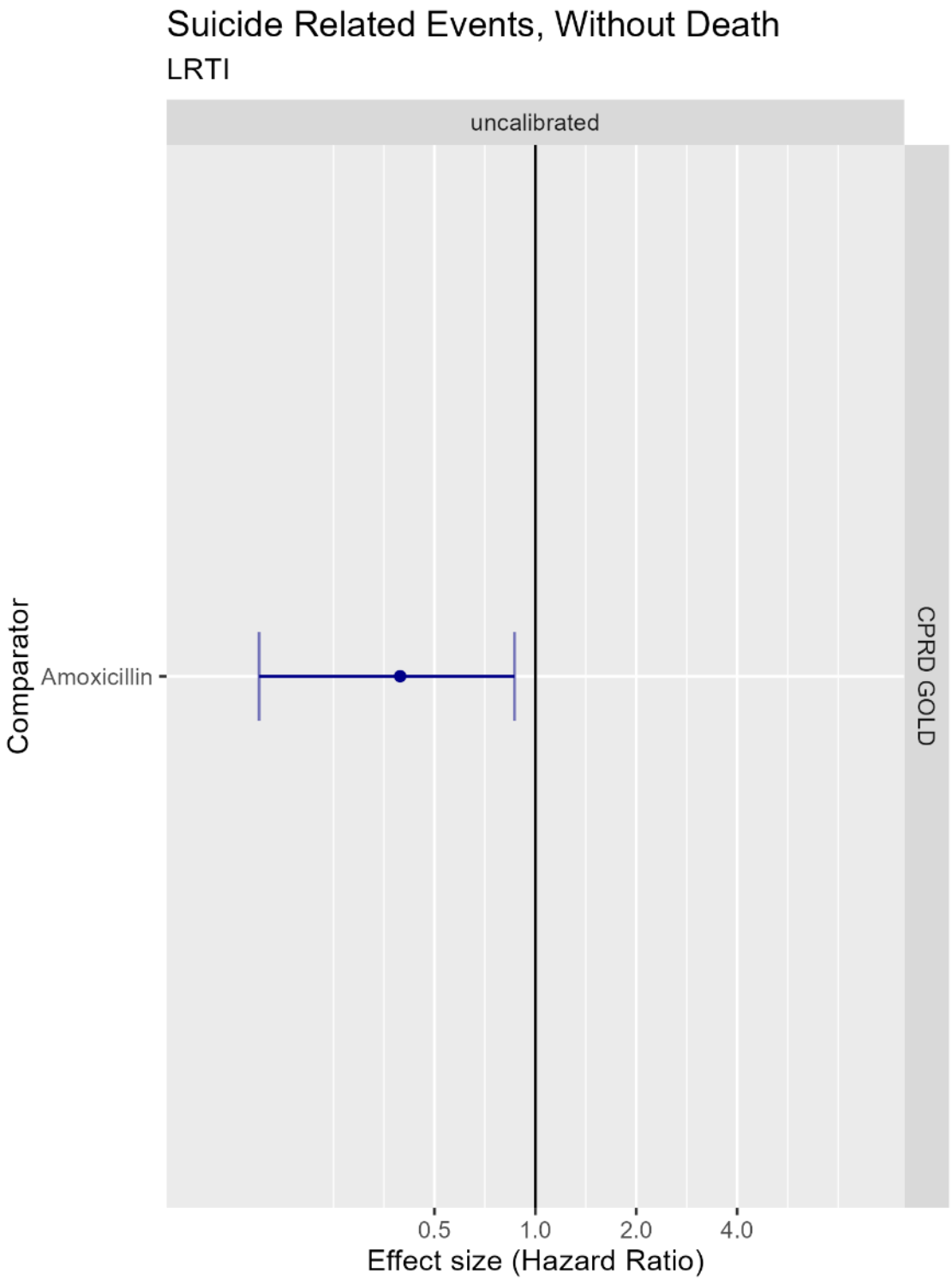


Figure 4. Forest plot of Cox-proportional hazards ratios assessing the association between doxycycline for persons with lower-respiratory tract infections (LRTI) and the outcome suicide-related events versus active comparator in CPRD GOLD, IPCI, and SIDIAP. Output from data sources are blinded in the case they do not pass diagnostic tests.

Outcome of anxiety

Use of doxycycline for acne

In IPCI there was a statistically significant increased association between doxycycline use and anxiety (uncalibrated HR 1.94, 95% CI [1.28-2.94], calibrated HR 1.65, 95% CI 1.03-2.68]) compared to isotretinoin in individuals with acne. In CPRD GOLD and SIDIAP no statistically significant associations were found between doxycycline use and anxiety compared to erythromycin (uncalibrated HR 1.06, 95% CI [0.84-1.32] and uncalibrated HR 0.96, 95% CI [0.73-1.26] respectively). In CPRD GOLD and SIDIAP there were no estimates produced for anxiety in individuals with acne treated with doxycycline compared to isotretinoin (**Appendix Table 33**). The meta-analysis based on the estimates from CPRD GOLD and SIDIAP resulted in no statistically significant association between doxycycline and anxiety (uncalibrated HR 1.02, 95% CI [0.85-1.21]) compared to erythromycin (**Figure 5**).

Sensitivity analyses
In the sensitivity analysis the statistically significant increased association that was found in IPCI between doxycycline use and anxiety compared to isotretinoin no longer was statistically significant (uncalibrated HR 1.45, 95% CI [0.96-2.15]) In IPCI there were still no estimates produced for anxiety in individuals with acne treated with doxycycline compared to erythromycin. The sensitivity analysis found a new non-statistically significant decreased association in SIDIAP between doxycycline and anxiety (uncalibrated HR 0.86, 95% CI [0.61-1.19]) compared to isotretinoin in individuals with acne. In CPRD GOLD and SIDIAP the non-statistically significant associations that were found between doxycycline use and anxiety compared to erythromycin remained in the sensitivity analysis. In CPRD GOLD the direction of this association remained the same (uncalibrated HR 1.03, 95% CI [0.85-1.24]) while in SIDIAP the direction changed slightly (uncalibrated HR 1.04, 95% CI [0.81-1.32]) (**Appendix Table 35**).

Residual confounding
Calibrating for residual confounding made the increased association between doxycycline use and anxiety compared to isotretinoin in IPCI slightly less strong (calibrated HR 1.65 95% CI [1.03-2.68]). In CRPD GOLD calibrating for residual confounding did not significantly change the association between doxycycline use and anxiety compared to erythromycin (calibrated HR 1.00, 95% CI [0.76-1.30]). In SIDIAP calibrating for residual confounding changed the direction of the non-statistically significant association between doxycycline use and anxiety (calibrated HR 1.17, 95% CI [0.85-1.56]) compared to erythromycin (**Figure 5**).

Use of doxycycline for acne with a history of depression

There were no estimates produced for doxycycline users with the indication of acne with a history of depression and the outcome of anxiety in either CPRD, IPCI or SIDIAP since all analyses failed diagnostics (**Appendix Table 34**).

Sensitivity analyses
Sensitivity analyses also did not produce any estimates in either CPRD GOLD, IPCI or SIDIAP all analyses still failed diagnostics (**Appendix Table 36**).

Use of doxycycline for rosacea

In CPRD GOLD no statistically significant association between doxycycline use and anxiety (uncalibrated HR 1.41, 95% CI [0.83-2.45]) was observed compared to erythromycin in individuals with rosacea (**Figure 6**). In CPRD GOLD there were no estimates produced in individuals with rosacea treated with doxycycline compared to azithromycin for the outcome anxiety. There were no estimates produced for doxycycline users with the indication of rosacea with and the outcome of anxiety in either IPCI or SIDIAP since all analyses failed diagnostics (**Appendix Table 37**).

Sensitivity analyses
The sensitivity analysis did not provide any different associations. For CRPD once again a non-statistically significant association was observed between doxycycline and anxiety compared to erythromycin (uncalibrated HR 1.32, 95% CI [0.92-6.73]), while no estimates were produced for suicide-related events in individuals treated with doxycycline compared to isotretinoin (**Appendix Table 39**). All analyses in IPCI and SIDIAP still failed diagnostics.

Use of doxycycline for rosacea with a history of depression

There were no estimates produced for doxycycline users with the indication of rosacea with a history of depression and the outcome of anxiety in either CPRD, IPCI or SIDIAP since all analyses failed diagnostics (**Appendix Table 38**).

Sensitivity analyses
Sensitivity analyses also did not produce estimates for anxiety in individuals with rosacea and a history of depression. In either CPRD GOLD, IPCI or SIDIAP all analyses still failed diagnostics (**Appendix Table 40**).

Use of doxycycline for chlamydia

In SIDIAP no association was found between doxycycline use and anxiety (uncalibrated HR 0.83, 95% CI [0.50-1.37]) compared to azithromycin in individuals with chlamydia (**Figure 7**) In SIDIAP there were no estimates produced for anxiety in individuals with chlamydia treated with doxycycline compared to erythromycin or amoxicillin. In IPCI and CPRD GOLD there were no estimates produced for anxiety in individuals with chlamydia since all analyses failed diagnostics (**Appendix Table 43**).

Use of doxycycline for chlamydia with a history of depression

No estimates could be produced for doxycycline users with the indication of chlamydia with a history of depression and the outcome of anxiety in either CPRD, IPCI or SIDIAP since all analyses failed diagnostics (**Appendix Table 44**).

Use of doxycycline for LRTI

In CPRD GOLD no associations were found in individuals with LRTI between doxycycline use and anxiety compared to both azithromycin and amoxicillin (uncalibrated HR 1.08, 95% CI [0.48-2.30] and uncalibrated HR 0.94, 95% CI [0.78-1.12] respectively). Similarly, in IPCI there were also no associations found in individuals with LRTI between doxycycline use and anxiety compared to both azithromycin and amoxicillin (uncalibrated HR 0.89, 95% CI [0.53-1.49] and uncalibrated HR 0.84, 95% CI [0.60-1.16] respectively). In SIDIAP no estimates could be produced for anxiety in individuals with LRTI since all analyses failed diagnostics. In the meta-analysis there were no associations between doxycycline use and anxiety compared to both azithromycin and amoxicillin (uncalibrated HR 0.94, 95% CI [0.61-1.44] and uncalibrated HR 0.91, 95% CI [0.78-1.07] respectively) (**Appendix Tables 41** & **Figure 8**).

Use of doxycycline for LRTI with a history of depression

In CPRD GOLD no association was found in individuals with LRTI and a history of depression between doxycycline use and anxiety (uncalibrated HR 1.08, 95% CI [0.48-2.30]) compared to amoxicillin. In CPRD there were no estimates produced for anxiety in individuals with chlamydia treated with doxycycline compared to azithromycin. In IPCI also a non-statistically significant association was found in individuals with LRTI and a history of depression between doxycycline use and anxiety (uncalibrated HR 0.62, 95% CI [0.30-1.23]) compared to amoxicillin. In IPCI also no estimates produced for anxiety in individuals with chlamydia treated with doxycycline compared to azithromycin. In SIDIAP no estimates could be produced for anxiety in individuals with LRTI and a history of depression since all analyses failed diagnostics (**Appendix Tables 42**).

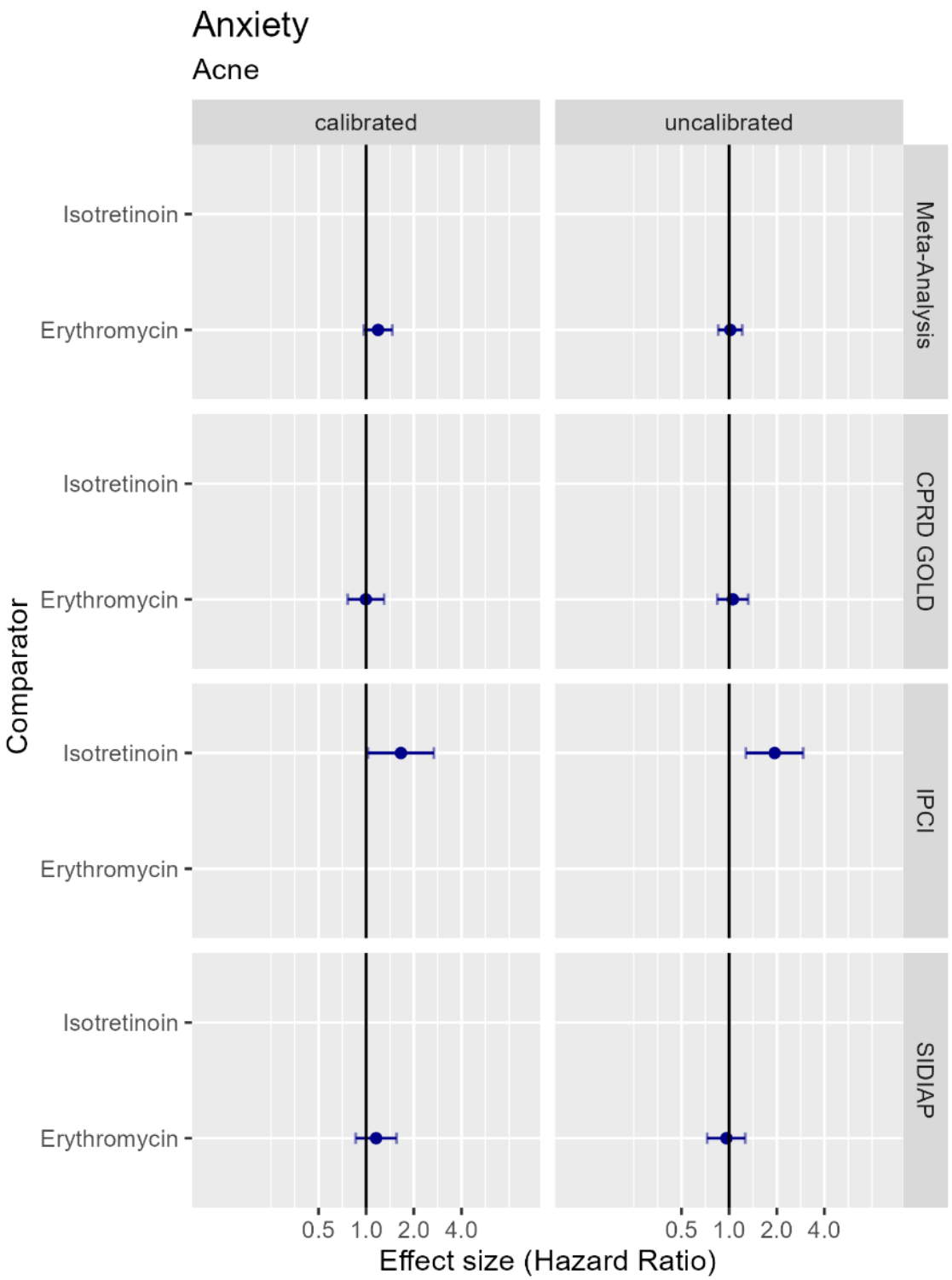


Figure 5. Forest plot of Cox-proportional hazards ratios (calibrated and uncalibrated) assessing the association between doxycycline for persons with acne and the outcome anxiety versus active comparator in CPRD GOLD, IPCI, SIDIAP, and meta-analysed. Output from data sources are blinded in the case they do not pass diagnostic tests.

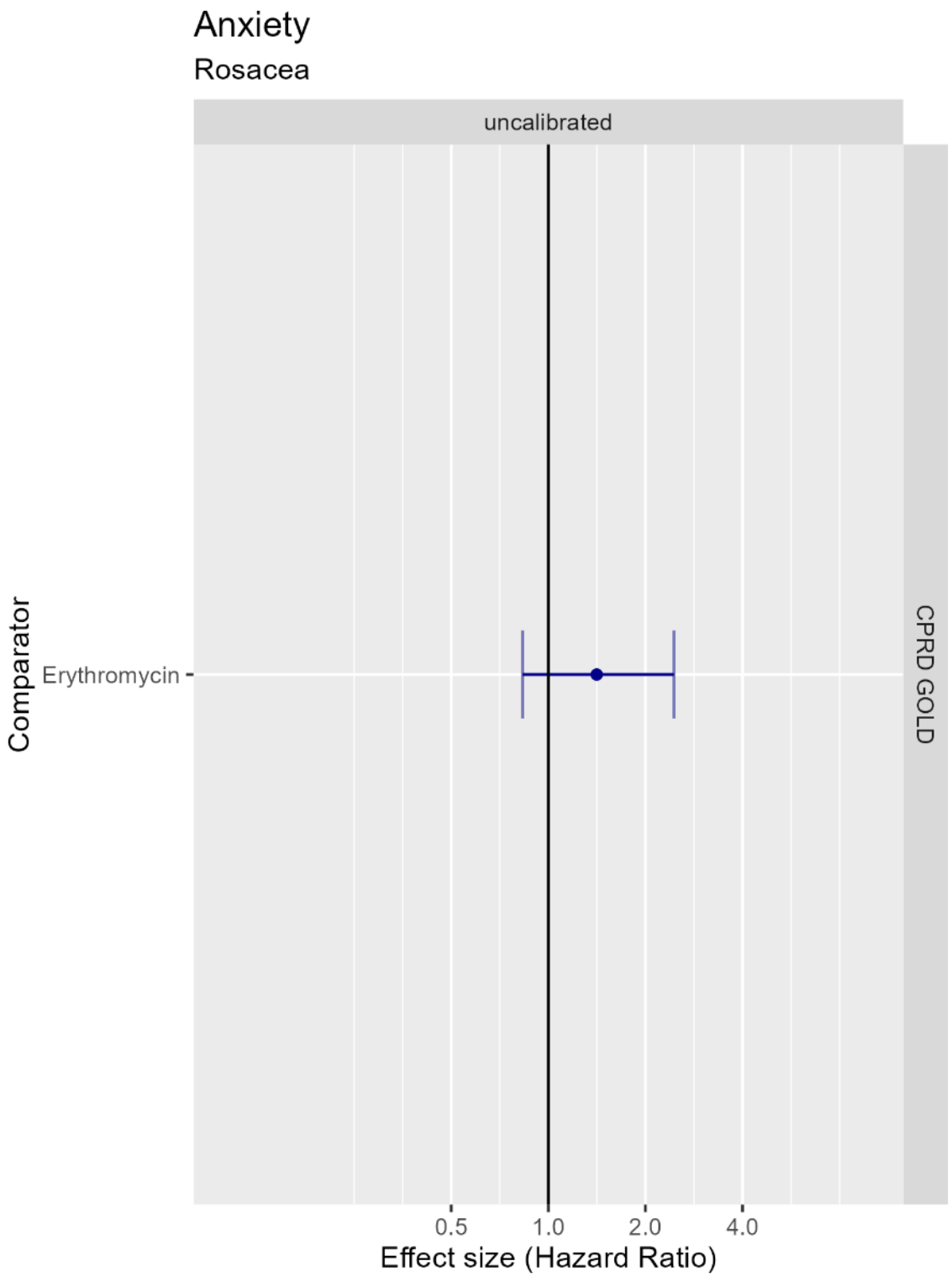


Figure 6. Forest plot of Cox-proportional hazards ratios assessing the association between doxycycline for persons with rosacea and the outcome anxiety versus active comparator in CPRD GOLD, IPCI, and SIDIAP. Output from data sources are blinded in the case they do not pass diagnostic tests.

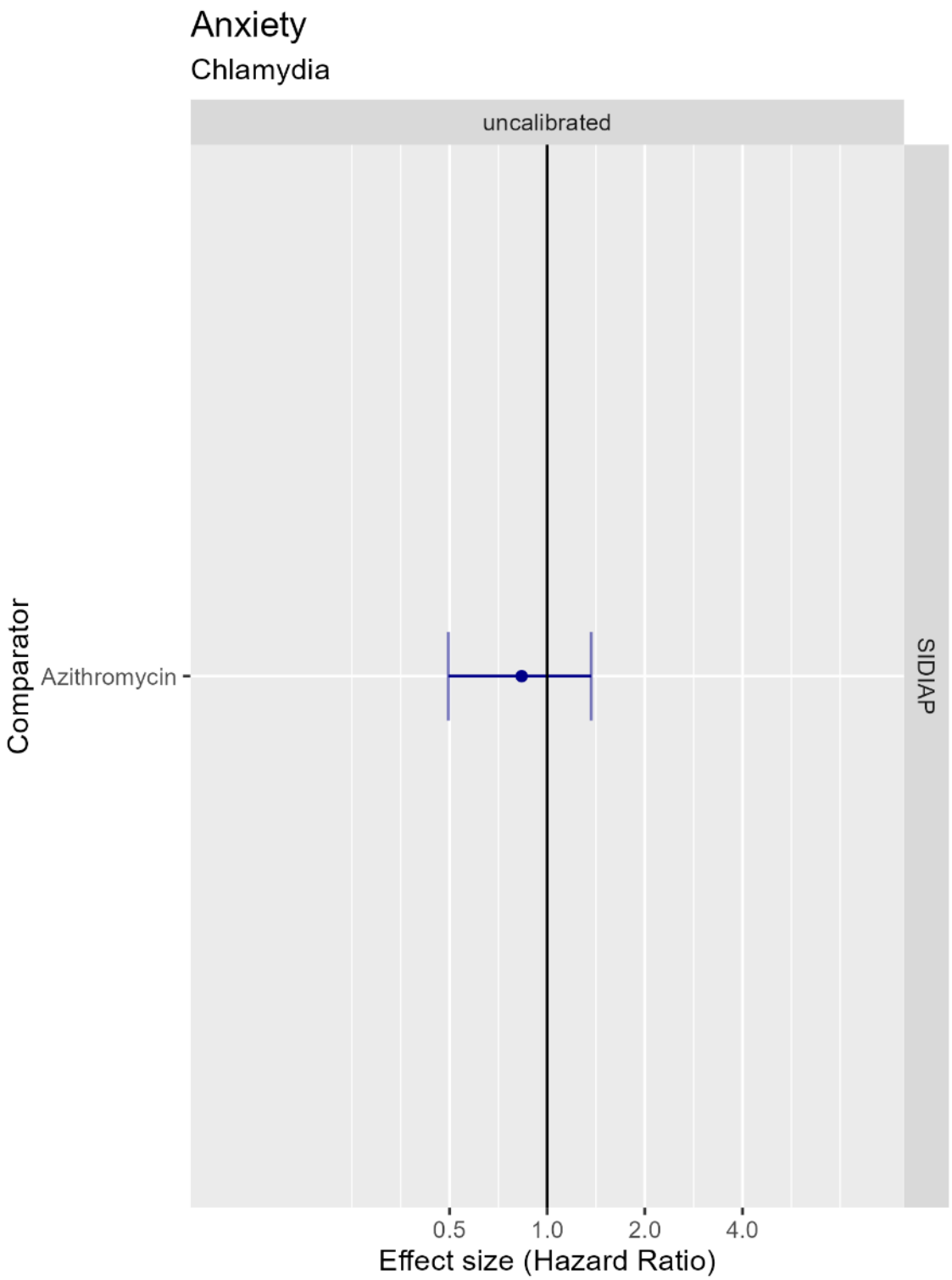


Figure 7. Forest plot of Cox-proportional hazards ratios assessing the association between doxycycline for persons with chlamydia and the outcome anxiety versus active comparator in CPRD GOLD, IPCI, and SIDIAP. Output from data sources are blinded in the case they do not pass diagnostic tests.

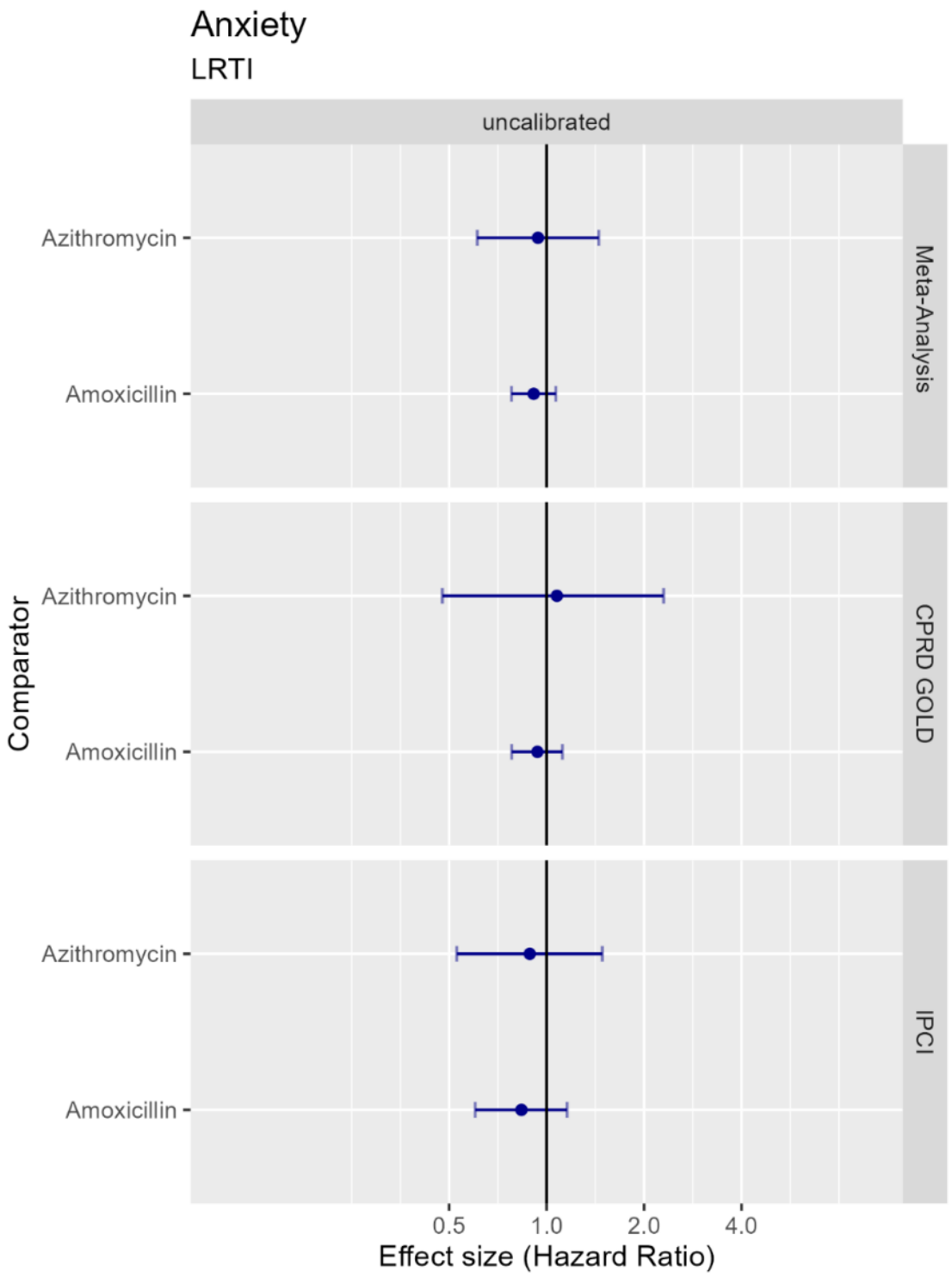


Figure 8. Forest plot of Cox-proportional hazards ratios assessing the association between doxycycline for persons with lower-respiratory tract infections (LRTI) and the outcome anxiety versus active comparator in CPRD GOLD, IPCI, SIDIAP, and meta-analysed. Output from data sources are blinded in the case they do not pass diagnostic tests.

Outcome of depression

Use of doxycycline for acne

In IPCI a non-statistically significant association was found in individuals with acne between doxycycline and depression (uncalibrated HR 1.13, 95% CI [0.52-2.46]) compared to isotretinoin, while no estimates were produced compared to erythromycin. In both CPRD GOLD and SIDIAP no statistically significant associations in individuals with acne were found between doxycycline and depression compared to erythromycin (uncalibrated HR 1.17, 95%CI [0.93-1.47] and uncalibrated HR 1.51, 95%CI [0.88-2.57] respectively). In both CPRD GOLD and SIDIAP no estimates were produced for depression in individuals with acne treated with doxycycline compared to isotretinoin (**Appendix Tables 33**). The meta-analysis based on estimates from CPRD GOLD and SIDIAP resulted in no statistically significant association between doxycycline use and depression (uncalibrated HR 1.22, 95% CI [0.99-1.51]) compared to erythromycin (**Figure 9**).

Sensitivity analyses

In the sensitivity analysis in IPCI in individuals with acne there was still no association between doxycycline and depression (uncalibrated HR 1.33, 95% CI [0.71-2.46]) compared to isotretinoin, while no estimates were produced compared to erythromycin. In the sensitivity analysis performed in SIDIAP no associations were found in individuals with acne between doxycycline and depression compared to erythromycin and isotretinoin (uncalibrated HR 1.28, 95%CI [0.79-2.06] and uncalibrated HR 1.39, 95%CI [0.75-2.49] respectively). In CPRD GOLD there also still was no association in individuals with acne between doxycycline and depression (uncalibrated HR 1.02, 95% CI [0.84-1.23]) compared to erythromycin remained, while no estimates produced compared to isotretinoin (**Appendix Tables 35**).

Residual confounding

Calibrating for residual confounding made the increased association between doxycycline use and depression compared to erythromycin in SIDIAP statistically significant (calibrated HR 1.81 95% CI [1.04-3.13]). In CRPD GOLD calibrating for residual confounding did not significantly change the association between doxycycline use and depression compared to erythromycin (calibrated HR 1.11, 95% CI [0.85-1.45]). In IPCI calibrating for residual confounding also did not significantly change the association between doxycycline use and depression (calibrated HR 1.12, 95% CI [0.52-2.46]) compared to isotretinoin (**Figure 9**).

Use of doxycycline for rosacea

In CPRD GOLD a no association was found in individuals with rosacea between doxycycline and depression (uncalibrated HR 1.01, 95% CI [0.58-1.76]) compared to erythromycin, while no estimates were produced compared to isotretinoin (**Figure 10**). No estimates could be produced for doxycycline users with the indication of rosacea and the outcome of depression in either IPCI or SIDIAP since all analyses failed diagnostics (**Appendix Tables 37**).

Sensitivity analyses

The sensitivity analysis in CPRD GOLD in individuals with rosacea also resulted in no association between doxycycline and depression (uncalibrated HR 1.33, 95% CI [0.71-2.46]) compared to erythromycin, while no estimates were produced compared to isotretinoin. In either IPCI or SIDIAP still no estimates could be produced for doxycycline users with the indication of rosacea and the outcome of depression since all analyses failed diagnostics (**Appendix Tables 39**).

Use of doxycycline for chlamydia

In SIDIAP no association was found in individuals with chlamydia between doxycycline and depression (uncalibrated HR 1.94, 95% CI [0.81-4.70] compared to azithromycin, while no estimates were produced compared to erythromycin or amoxicillin (**Figure 11**). No estimates could be produced for doxycycline users with the indication of rosacea and the outcome of depression in either CPRD GOLD or IPCI since all analyses failed diagnostics (**Appendix Tables 43**).

Use of doxycycline for LRTI

In CPRD GOLD no associations were found in individuals with LRTI between doxycycline use and depression compared to both azithromycin and amoxicillin (uncalibrated HR 1.15, 95% CI [0.61-2.14] and uncalibrated HR 0.92, 95% CI [0.78-1.08] respectively). In IPCI also no associations were found in individuals with LRTI between doxycycline use and depression compared to both azithromycin and amoxicillin (uncalibrated HR 0.57, 95% CI [0.23-1.34] and uncalibrated HR 1.18, 95% CI [0.67-2.08] respectively (**Figure 12**). In SIDIAP no estimates could be produced for doxycycline users with the indication of rosacea and the outcome of depression since all analyses failed diagnostics. In the meta-analysis there were no statistically significant associations between doxycycline use and depression compared to both azithromycin and amoxicillin (uncalibrated HR 0.87, 95% CI [0.44-1.72] and uncalibrated HR 0.94, 95% CI [0.80-1.09] respectively) (**Appendix Tables 41**).

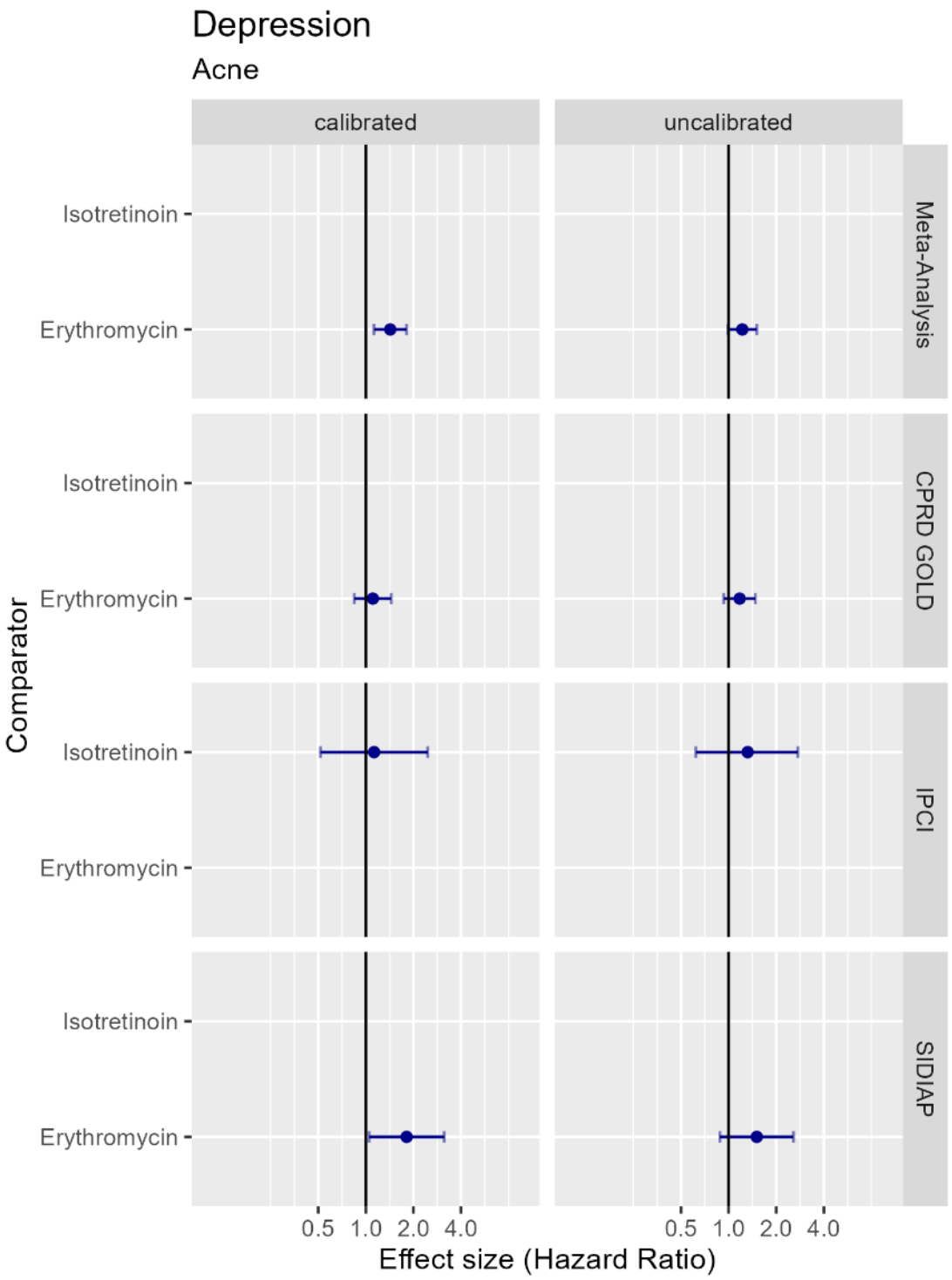


Figure 9. Forest plot of Cox-proportional hazards ratios (calibrated and uncalibrated) assessing the association between doxycycline for persons with acne and the outcome depression versus active comparator in CPRD GOLD, IPCI, SIDIAP, and meta-analysed. Output from data sources are blinded in the case they do not pass diagnostic tests.

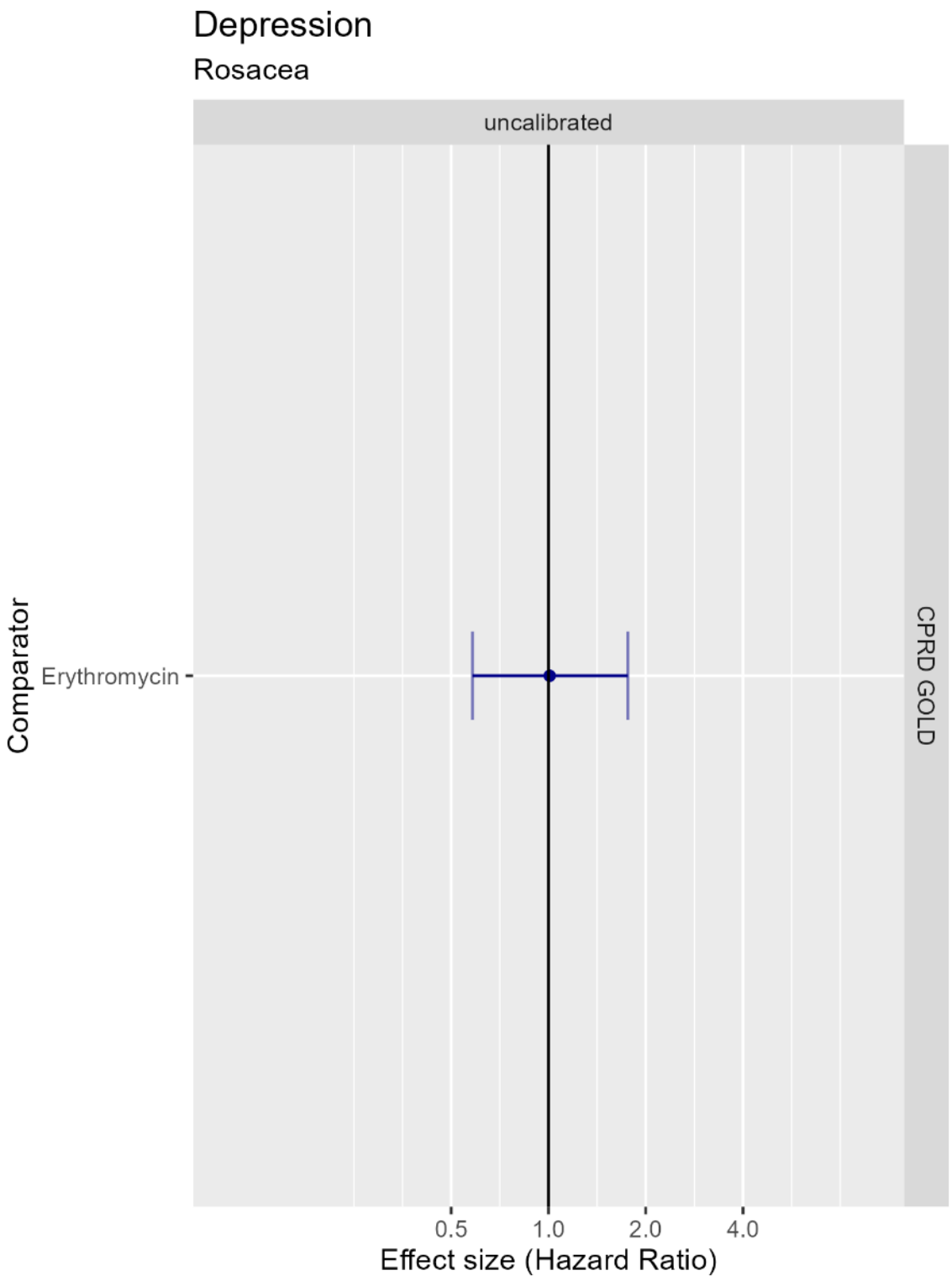


Figure 10. Forest plot of Cox-proportional hazards ratios assessing the association between doxycycline for persons with rosacea and the outcome depression versus active comparator in CPRD GOLD, IPCI, SIDIAP, and meta-analysed. Output from data sources are blinded in the case they do not pass diagnostic tests.

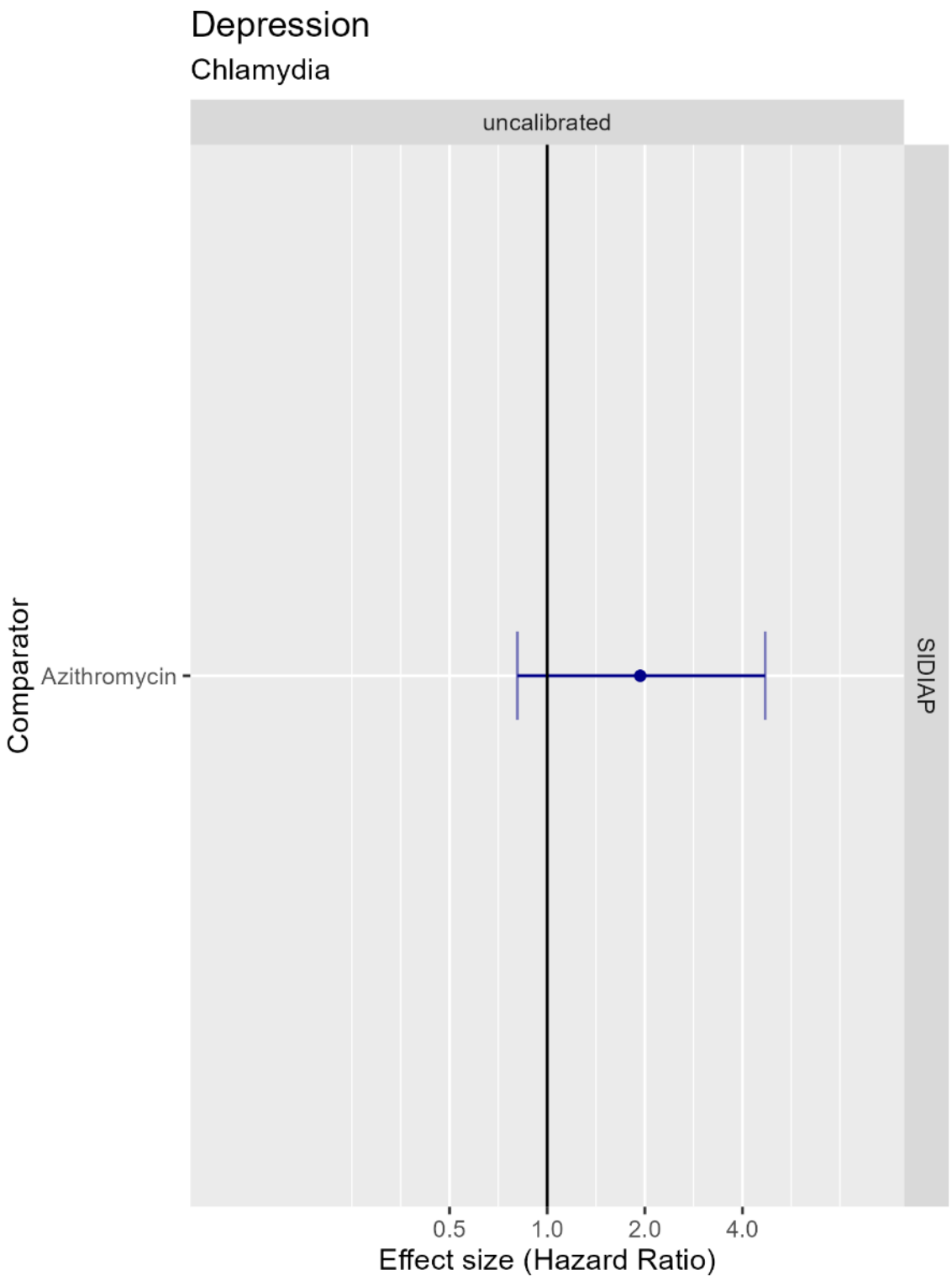


Figure 11. Forest plot of Cox-proportional hazards ratios assessing the association between doxycycline for persons with chlamydia and the outcome depression versus active comparator in CPRD GOLD, IPCI, SIDIAP, and meta-analysed. Output from data sources are blinded in the case they do not pass diagnostic tests.

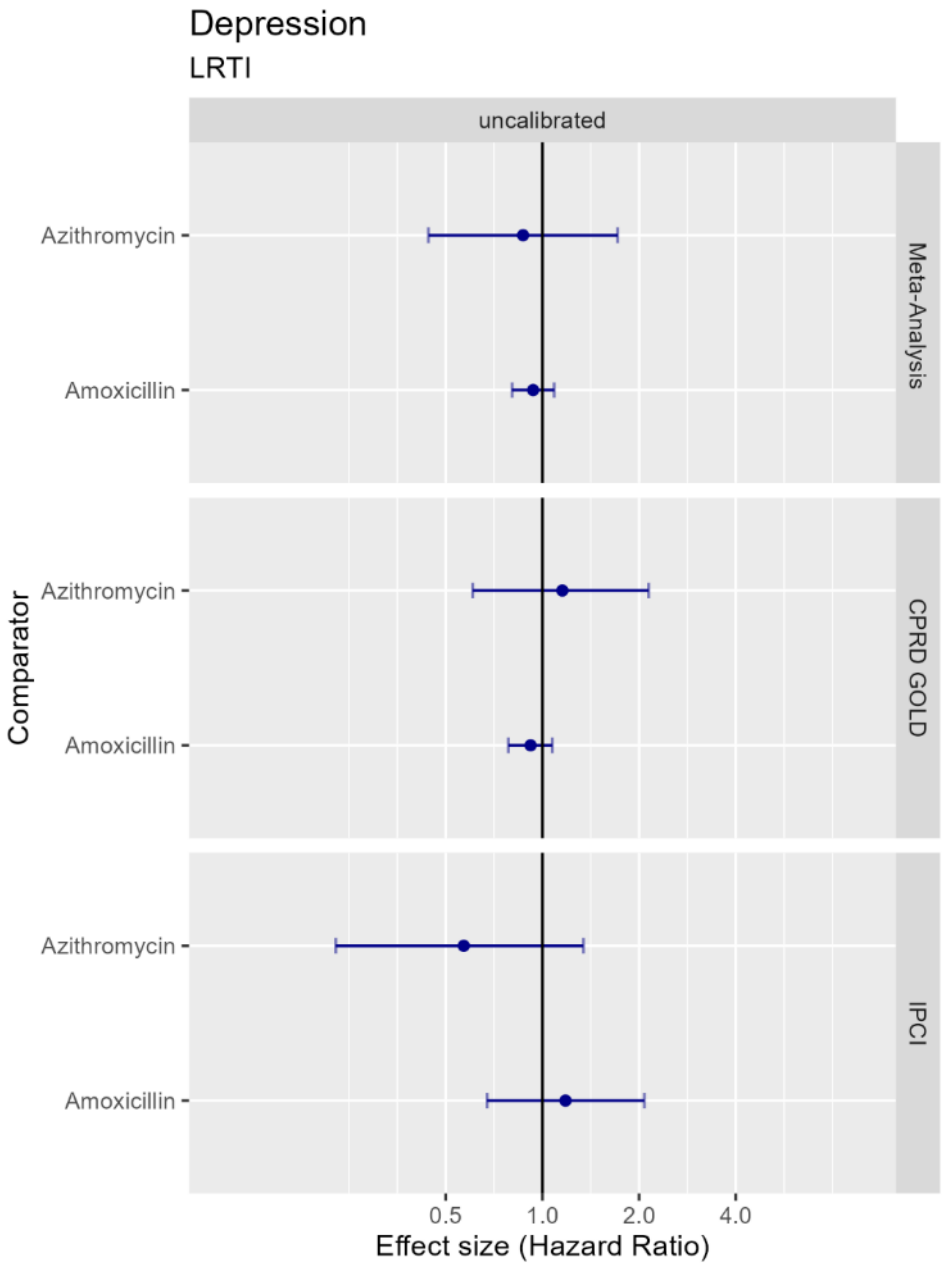


Figure 12. Forest plot of Cox-proportional hazards ratios assessing the association between doxycycline for persons with lower-respiratory tract infections (LRTI) and the outcome depression versus active comparator in CPRD GOLD, IPCI, SIDIAP, and meta-analysed. Output from data sources are blinded in the case they do not pass diagnostic tests.

Table 9. Uncalibrated hazard ratios (HRs) of the cohort study in persons with the indication acne for the outcome suicide-related events.

Database	Target subjects (n)	Target events (n)	Mean target treatment duration (days)	Comparator	Comparator subjects (n)	Comparator events (n)	Mean comparator treatment duration (days)	Diagnostics	Uncalibrated HR	95% CI
IPCI	778	0	64	Erythromycin	793	0	58	FAIL	-	-
IPCI	2757	≤5	68	Isotretinoin	3534	≤5	145	FAIL	-	-
SIDIAP	12265	7	88	Erythromycin	16998	≤5	114	PASS	3.77	1.03-17.80
SIDIAP	6090	≤5	90	Isotretinoin	9350	6	204	FAIL	-	-
CPRD GOLD	18054	12	79	Erythromycin	30682	10	65	PASS	1.71	0.74-4.07
CPRD GOLD	655	0	74	Isotretinoin	1064	≤5	52	FAIL	-	-

N.B., the cohort counts may differ within the same data source and drug due to propensity-score matching

Table 10. Uncalibrated hazard ratios (HRs) of the cohort study in persons with the indication acne and a history of depression, for the outcome suicide-related events.

Database	Target subjects (n)	Target events (n)	Mean target treatment duration (days)	Comparator	Comparator subjects (n)	Comparator events (n)	Mean comparator treatment duration (days)	Diagnostics	Uncalibrated HR	95% CI
IPCI	89	0	53	Erythromycin	89	0	53	FAIL	-	-
IPCI	64	0	48	Isotretinoin	104	0	120	FAIL	-	-
SIDIAP	365	≤5	78	Erythromycin	405	0	111	FAIL	-	-
SIDIAP	222	≤5	88	Isotretinoin	396	0	230	FAIL	-	-
CPRD GOLD	2733	5	67	Erythromycin	3767	≤5	57	PASS	1.52	0.40-6.16
CPRD GOLD	7	0	160	Isotretinoin	17	0	68	FAIL	-	-

N.B., the cohort counts may differ within the same data source and drug due to propensity-score matching

Table 11. Uncalibrated hazard ratios (HRs) of the cohort study in persons with the indication rosacea, for the outcome suicide-related events.

Database	Target subjects (n)	Target events (n)	Mean target treatment duration (days)	Comparator	Comparator subjects (n)	Comparator events (n)	Mean comparator treatment duration (days)	Diagnostics	Uncalibrated HR	95% CI
IPCI	90	0	50	Erythromycin	90	0	43	FAIL	-	-
IPCI	146	0	58	Isotretinoin	146	0	131	FAIL	-	-
SIDIAP	831	0	75	Erythromycin	846	0	89	FAIL	-	-
SIDIAP	599	0	94	Isotretinoin	608	0	235	FAIL	-	-
CPRD GOLD	5086	≤5	87	Erythromycin	5939	≤5	59	PASS	1.73	0.34-12.48
CPRD GOLD	47	0	86	Isotretinoin	70	0	61	FAIL	-	-

N.B., the cohort counts may differ within the same data source and drug due to propensity-score matching.

Table 12. Uncalibrated hazard ratios (HRs) of the cohort study in persons with the indication rosacea and a history of depression, for the outcome suicide-related events.

Database	Target subjects (n)	Target events (n)	Mean target treatment duration (days)	Comparator	Comparator subjects (n)	Comparator events (n)	Mean comparator treatment duration (days)	Diagnostics	Uncalibrated HR	95% CI
IPCI	14	0	52	Erythromycin	14	0	38	FAIL	-	-
IPCI	107	0	60	Isotretinoin	134	0	132	FAIL	-	-
SIDIAP	75	0	69	Erythromycin	75	0	78	FAIL	-	-
SIDIAP	264	0	90	Isotretinoin	512	0	233	FAIL	-	-
CPRD GOLD	1073	≤5	84	Erythromycin	1222	≤5	55	FAIL	-	-
CPRD GOLD	12	0	57	Isotretinoin	17	0	64	FAIL	-	-

N.B., the cohort counts may differ within the same data source and drug due to propensity-score matching

Table 13. Uncalibrated hazard ratios (HRs) of the cohort study in persons with the indication LRTI, for the outcome suicide-related events.

Database	Target subjects (n)	Target events (n)	Mean target treatment duration (days)	Comparator	Comparator subjects (n)	Comparator events (n)	Mean comparator treatment duration (days)	Diagnostics	Uncalibrated HR	95% CI
IPCI	9889	≤5	16	Azithromycin	10392	0	15	FAIL	-	-
IPCI	20969	≤5	15	Amoxicillin	24267	0	14	FAIL	-	-
SIDIAP	2289	≤5	60	Azithromycin	11023	≤5	47	FAIL	-	-
SIDIAP	2046	≤5	59	Amoxicillin	8732	≤5	40	FAIL	-	-
CPRD GOLD	6957	0	19	Azithromycin	7329	≤5	107	FAIL	-	-
CPRD GOLD	113147	6	16	Amoxicillin	282984	38	15	PASS	0.40	0.15-0.87

N.B., the cohort counts may differ within the same data source and drug due to propensity-score matching

Table 14. Uncalibrated hazard ratios (HRs) of the cohort study in persons with the indication LRTI and a history of depression, for the outcome suicide-related events.

Database	Target subjects (n)	Target events (n)	Mean target treatment duration (days)	Comparator	Comparator subjects (n)	Comparator events (n)	Mean comparator treatment duration (days)	Diagnostics	Uncalibrated HR	95% CI
IPCI	1754	≤5	16	Azithromycin	1767	0	16	FAIL	-	-
IPCI	3576	0	16	Amoxicillin depress	4041	0	14	FAIL	-	-
SIDIAP	412	≤5	68	Azithromycin	1975	≤5	49	FAIL	-	-
SIDIAP	325	≤5	62	Amoxicillin depress	1293	0	42	FAIL	-	-
CPRD GOLD	2156	0	20	Azithromycin	2260	≤5	114	FAIL	-	-
CPRD GOLD	27471	≤5	16	Amoxicillin depress	62651	23	16	PASS	0.29	0.07-0.85

N.B., the cohort counts may differ within the same data source and drug due to propensity-score matching

Table 15. Uncalibrated hazard ratios (HRs) of the cohort study in persons with the indication chlamydia, for the outcome suicide-related events.

Database	Target subjects (n)	Target events (n)	Mean target treatment duration (days)	Comparator	Comparator subjects (n)	Comparator events (n)	Mean comparator treatment duration (days)	Diagnostics	Uncalibrated HR	95% CI
IPCI	17	0	18	Erythromycin	17	0	28	FAIL	-	-
IPCI	1614	0	16	Azithromycin	6032	0	10	FAIL	-	-
IPCI	164	0	16	Amoxicillin	199	0	15	FAIL	-	-
SIDIAP	92	0	37	Erythromycin	100	0	45	FAIL	-	-
SIDIAP	5726	0	39	Azithromycin	9335	≤5	38	FAIL	-	-
SIDIAP	311	0	39	Amoxicillin	329	0	37	FAIL	-	-
CPRD GOLD	110	0	16	Erythromycin	133	0	17	FAIL	-	-
CPRD GOLD	1310	≤5	15	Azithromycin	3616	≤5	9	FAIL	-	-
CPRD GOLD	112	0	16	Amoxicillin	137	0	14	FAIL	-	-

N.B., the cohort counts may differ within the same data source and drug due to propensity-score matching

Table 16. Uncalibrated hazard ratios (HRs) of the cohort study in persons with the indication chlamydia and a history of depression, for the outcome suicide-related events.

Database	Target subjects (n)	Target events (n)	Mean target treatment duration (days)	Comparator	Comparator subjects (n)	Comparator events (n)	Mean comparator treatment duration (days)	Diagnostics	Uncalibrated HR	95% CI
IPCI	≤5	0	-	Erythromycin	≤5	0	-	FAIL	-	-
IPCI	351	0	16	Azithromycin	1137	0	11	FAIL	-	-
IPCI	19	0	18	Amoxicillin	28	0	16	FAIL	-	-
SIDIAP	7	0	38	Erythromycin	7	0	38	FAIL	-	-
SIDIAP	329	0	39	Azithromycin	457	0	38	FAIL	-	-
SIDIAP	11	0	39	Amoxicillin	11	0	32	FAIL	-	-
CPRD GOLD	18	0	17	Erythromycin	31	0	14	FAIL	-	-
CPRD GOLD	389	≤5	16	Azithromycin	991	≤5	10	FAIL	-	-
CPRD GOLD	≤5	0	-	Amoxicillin	≤5	0	-	FAIL	-	-

N.B., the cohort counts may differ within the same data source and drug due to propensity-score matching

12.3.2 Results for self-controlled case series study

SCCS analyses were conducted overall, and by indication of use (i.e. prior diagnosis of acne, rosacea, LRTI or chlamydia).

Suicide-related events without death

Table 17 shows the uncalibrated IRRs and corresponding 95% confidence intervals of the association between doxycycline and non-fatal suicide-related events overall and per indication per database.

Overall (any indication)

In CPRD GOLD in the overall group, there were statistically significant decreased associations between doxycycline and suicide-related events without death in the 31–60-day risk period (uncalibrated IRR 0.83, 95% CI [0.75-0.92]; the 61-90 day risk period (uncalibrated IRR 0.90, 95% CI [0.81-0.99]) and the 1-90 day risk period (uncalibrated IRR 0.83, 95% CI [0.78-0.88]).

In IPCI there were no associations between doxycycline and suicide-related events without death in the 31-60 day risk period (uncalibrated IRR 1.12, 95% CI [0.75-1.60]), the 61-90 day risk period (uncalibrated IRR 1.03, 95% CI [0.68-1.49]), the >90 day risk period (uncalibrated IRR 1.41, 95% CI [0.18-5.95]) and the 1-90 day risk period (uncalibrated IRR 1.07, 95% CI [0.84-1.34]).
In SIDIAP in the overall group, no estimates could be produced for any of the risk periods because all analyses failed diagnostics (**Table 18**, **Figure**).

Meta analyses
In the meta-analysis in the overall group, there were no associations between doxycycline and suicide-related events without death in the 61–90-day risk period (uncalibrated IRR 0.91, 95% CI [0.82-1.00]). There were no results in the meta-analysis for the other risk periods.

Residual confounding
In CPRD GOLD after calibrating for residual confounding, the statistically significant decreased associations between doxycycline and suicide-related events without death in the 31–60-day risk period (calibrated IRR 0.85, 95% CI [0.49-1.48], the 61-90 day risk period (calibrated IRR 0.95, 95% CI [0.60-1.52]) and the 1-90 day risk period (calibrated IRR 0.85, 95% CI [0.50-1.41]) were no longer statistically significant since calibration increases the 95% CIs. Calibrating for residual confounding in IPCI did not significantly change the non-statistically significant associations between doxycycline and suicide-related events without death in in the 31-60 day risk period (calibrated IRR 0.93, 95% CI [0.58-1.49]), the 61-90 day risk period (calibrated IRR 0.89, 95% CI [0.58-1.35]), the >90 day risk period (calibrated IRR 1.32, 95% CI [0.23-7.69]) and the 1-90 day risk period (calibrated IRR 0.86, 95% CI [0.57-1.28]).

Indication acne

In CPRD GOLD , there were no statistically significant associations between doxycycline and suicide-related events without death in all risk periods, namely in the -30-0 day risk period (uncalibrated IRR 0.97, 95% CI [0.71-1.29]), the 1-30 day risk period (uncalibrated IRR 1.19, 95% CI [0.89-1.54]), the 31-60 days risk period (uncalibrated IRR 1.21, 95% CI [0.91-1.57]), the 61-90 day risk period (uncalibrated IRR 0.88, 95% CI [0.63-1.21]), the >90 day risk period (uncalibrated IRR 1.21, 95% CI [0.69-2.00]), the -90-0 day risk period (uncalibrated IRR 0.92, 95% CI [0.76-1.11]) and the 1-90 day risk period (uncalibrated IRR 1.09, 95% CI [0.91-1.30]) (**Figure 14**).

In IPCI, there were no associations identified between doxycycline and suicide-related events without death in the 31-60 day risk period (uncalibrated IRR 0.95, 95% CI [0.15-3.31]), the 61-90 day risk period

(uncalibrated IRR 0.70, 95% CI [0.09-2.84]) and the 1-90 day risk period (uncalibrated IRR 0.56, 95% CI [0.13-1.60]) (**Figure**).

In SIDIAP, there were a non-statistically significant increased association of suicide-related events without death with doxycycline use in the -30-0 day risk period (uncalibrated IRR 1.91, 95% CI [0.94-3.42]), the 1-30 day risk period (uncalibrated IRR 1.13, 95% CI [0.48-2.22]), the 31-60 days risk period (uncalibrated IRR 1.03, 95% CI [0.44-2.03]), the 61-90 day risk period (uncalibrated IRR 1.02, 95% CI [0.43-2.01]), the >90 day risk period (uncalibrated IRR 1.73, 95% CI [0.72-3.65]), the -90-0 day risk period (uncalibrated IRR 1.21, 95% CI [0.72-1.91]) and the 1-90 day risk period (uncalibrated IRR 1.03, 95% CI [0.63-1.58]) (**Table 17**, **Figure 14**).

Meta analyses

In the meta-analysis, no associations were observed between doxycycline and suicide-related events without death in the 1-30 day risk period (uncalibrated HR 1.18, 95% CI [0.91-1.53]), the 31-60 day risk period (uncalibrated HR 1.18, 95% CI [0.92-1.52]), the 61-90 day risk period (uncalibrated IRR 0.90, 95% CI [0.67-1.21]), the >90 day risk period (uncalibrated IRR 1.34, 95% CI [0.86-2.0]), the -90-0 day risk period (uncalibrated IRR 0.92, 95% CI [0.76-1.11]) and the 1-90 day risk period (calibrated IRR 1.07, 95% CI [0.91-1.26]). There were no results in the meta-analysis for the other risk periods.

Residual confounding

Calibrating for residual confounding in IPCI did not significantly change the non-significant association identified between doxycycline and suicide-related events without death in the 31–60-day risk period (uncalibrated IRR 0.79, 95% CI [0.17-3.78]), the 61-90 day risk period (uncalibrated IRR 0.62, 95% CI [0.11-3.54]) and the 1-90 day risk period (uncalibrated IRR 0.48, 95% CI [0.14-1.70]). For SIDIAP and CPRD GOLD, there were no calibrated IRRs available and thus cannot be reported.

Indication rosacea

In CPRD GOLD in the group with the indication rosacea there were no statistically significant associations between doxycycline and suicide-related events without death in all risk periods, namely the -30-0 day risk period (uncalibrated IRR 1.53, 95% CI [0.93-2.36]), the 1-30 day risk period (uncalibrated IRR 1.55, 95% CI [0.94-2.39]), the 31-60 days risk period (uncalibrated IRR 1.08, 95% CI [0.60-1.79]), the 61-90 day risk period (uncalibrated IRR 1.25, 95% CI [0.71-2.04]), the >90 day risk period (uncalibrated IRR 0.85, 95% CI [0.35-1.87]) the -90-0 day risk period (uncalibrated IRR 1.14, 95% CI [0.81-1.58]) and the 1-90 day risk period (uncalibrated IRR 1.30, 95% CI [0.94-1.76]).
In IPCI and SIDIAP in the group with the indication rosacea no estimates could be produced for any of the risk periods because all analyses failed diagnostics (**Table 17**, **Figure 15**).

Meta analyses

There were no results in the meta-analysis in the group with indication rosacea and outcome suicide-related events without death since CPRD GOLD was the only database that produced estimates.

Residual confounding

There were no calibrated results available for the indication rosacea and the outcome suicide-related events without death.

Indication Chlamydia

In CPRD GOLD in the group with the indication chlamydia we identified no statistically significant associations between doxycycline and suicide-related events without death in the -30-0 day risk period (uncalibrated IRR 2.01, 95% CI [0.89-3.90]), the 1-30 day risk period (uncalibrated IRR 1.45, 95% CI [0.61-2.93]), the 31-60 days risk period (uncalibrated IRR 0.80, 95% CI [0.24-1.93]), the 61-90 day risk period

(uncalibrated IRR 0.83, 95% CI [0.25-1.99]), the -90-0 day risk period (uncalibrated IRR 1.54, 95% CI [0.88-2.53]) and the 1-90 day risk period (uncalibrated IRR 1.02, 95% CI [0.56-1.72]).

In IPCI, no estimates could be produced for any of the risk periods because all analyses failed diagnostics.

In SIDIAP, there were non-significant associations identified between doxycycline and suicide-related events without death in the -30-0 day risk period (uncalibrated IRR 0.57, 95% CI [0.03-2.69]), the 1-30 day risk period (uncalibrated IRR 0.39, 95% CI [0.02-1.78]), the 31-60 days risk period (uncalibrated IRR 0.83, 95% CI [0.20-2.29]), the 61-90 day risk period (uncalibrated IRR 0.54, 95% CI [0.09-1.77]), the -90-0 day risk period (uncalibrated IRR 0.86, 95% CI [0.25-2.20]) and the 1-90 day risk period (uncalibrated IRR 0.61, 95% CI [0.23-1.34]) (**Table 17, Figure 16**).

Meta analyses
In the meta-analysis in the group with chlamydia there were no statistically significant associations between doxycycline and suicide-related events without death in the 30-0 day risk period (uncalibrated IRR 1.69, 95% CI [0.72-3.95]), the 1-30 day risk period (uncalibrated IRR 1,14, 95% CI [0.42-3.11]), the 31-60 days risk period (uncalibrated IRR 0.81, 95% CI [0.37-1.79]), the 61-90 day risk period (uncalibrated IRR 0.72, 95% CI [0.31-1.69]), the -90-0 day risk period (uncalibrated IRR 1.37, 95% CI [0.85-2.21]) and the 1-90 day risk period (uncalibrated IRR 0.88, 95% CI [0.55-1.41]).

Residual confounding
There were no calibrated results available for the indication chlamydia and the outcome suicide-related events without death.

Indication LRTI

In CPRD GOLD in the group with the indication LRTI there were statistically significant decreased association between doxycycline and suicide-related events without death in the -30-0 day risk period (uncalibrated IRR 0.83, 95% CI [0.71-0.96]), the 1-30 day risk period (uncalibrated IRR 0.72, 95% CI [0.61-0.84]), the 31-60 days risk period (uncalibrated IRR 0.81, 95% CI [0.70-0.94]), the -90-0 day risk period (uncalibrated IRR 0.85, 95% CI [0.77-0.93]) and the 1-90 day risk period (uncalibrated IRR 0.83, 95% CI [0.76-0.91]) and no association in the 61-90 day risk period (uncalibrated IRR 0.98, 95% CI [0.85-1.12]) and the >90 day risk period (uncalibrated IRR 0.81, 95% CI [0.45-1.38]).
In IPCI and SIDIAP in the group with the indication LRTI and outcome suicide-related events without death no estimates could be produced for any of the risk periods because all analyses failed diagnostics (**Table 17, Figure 17**).

Meta analyses
In the meta-analysis in group with the indication acne we identified no statistically significant association between doxycycline and suicide-related events without death in the >90 day risk period (uncalibrated IRR 0.81, 95% CI [0.45-1.38]). There were no results in the meta-analysis for the other risk periods.

Residual confounding
There were no calibrated results available for the indication LRTI and the outcome suicide-related events without death.

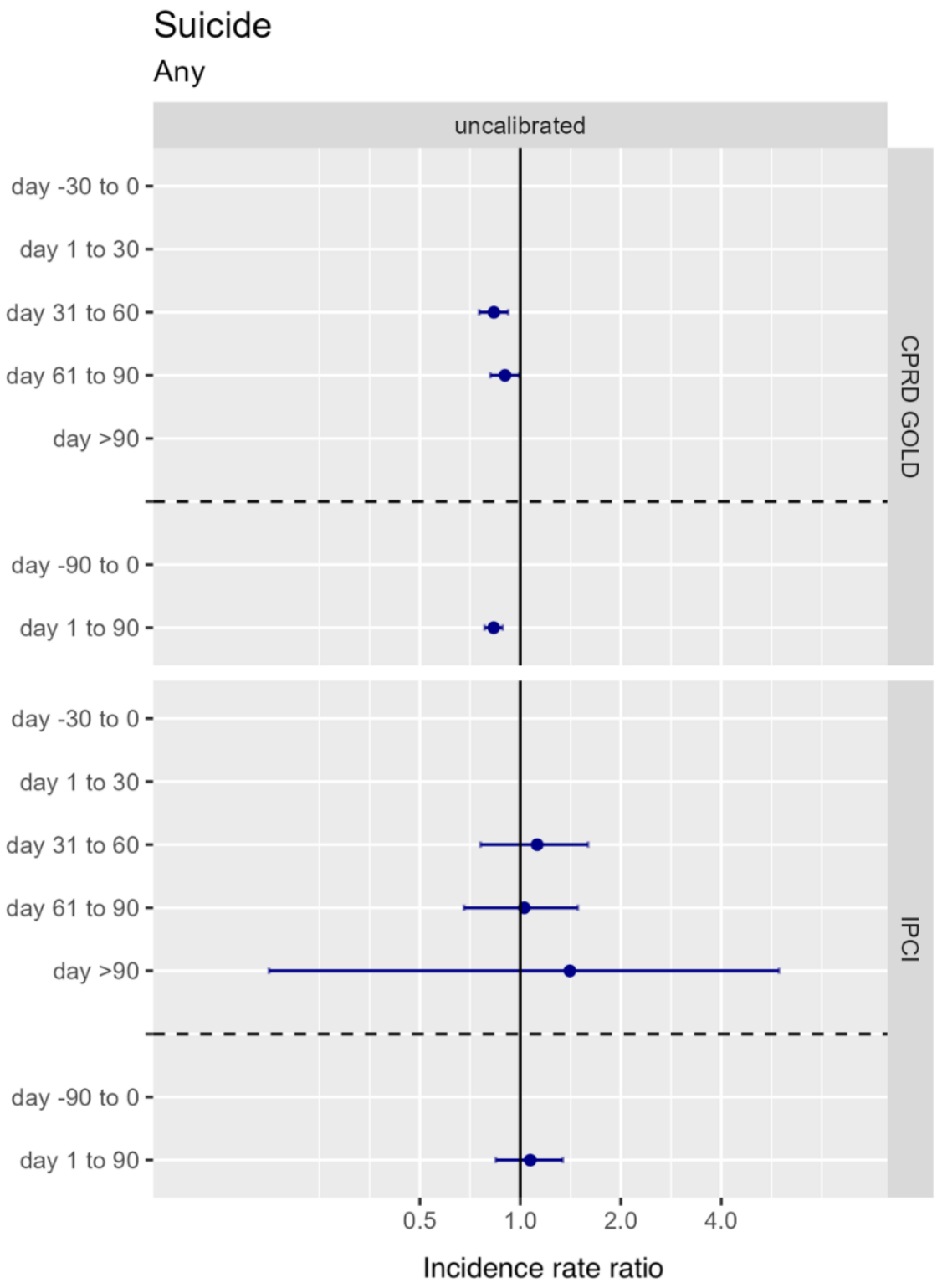


Figure 13. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome suicide-related events (without death), in all indications in CPRD GOLD, IPCI, and SIDIAP.

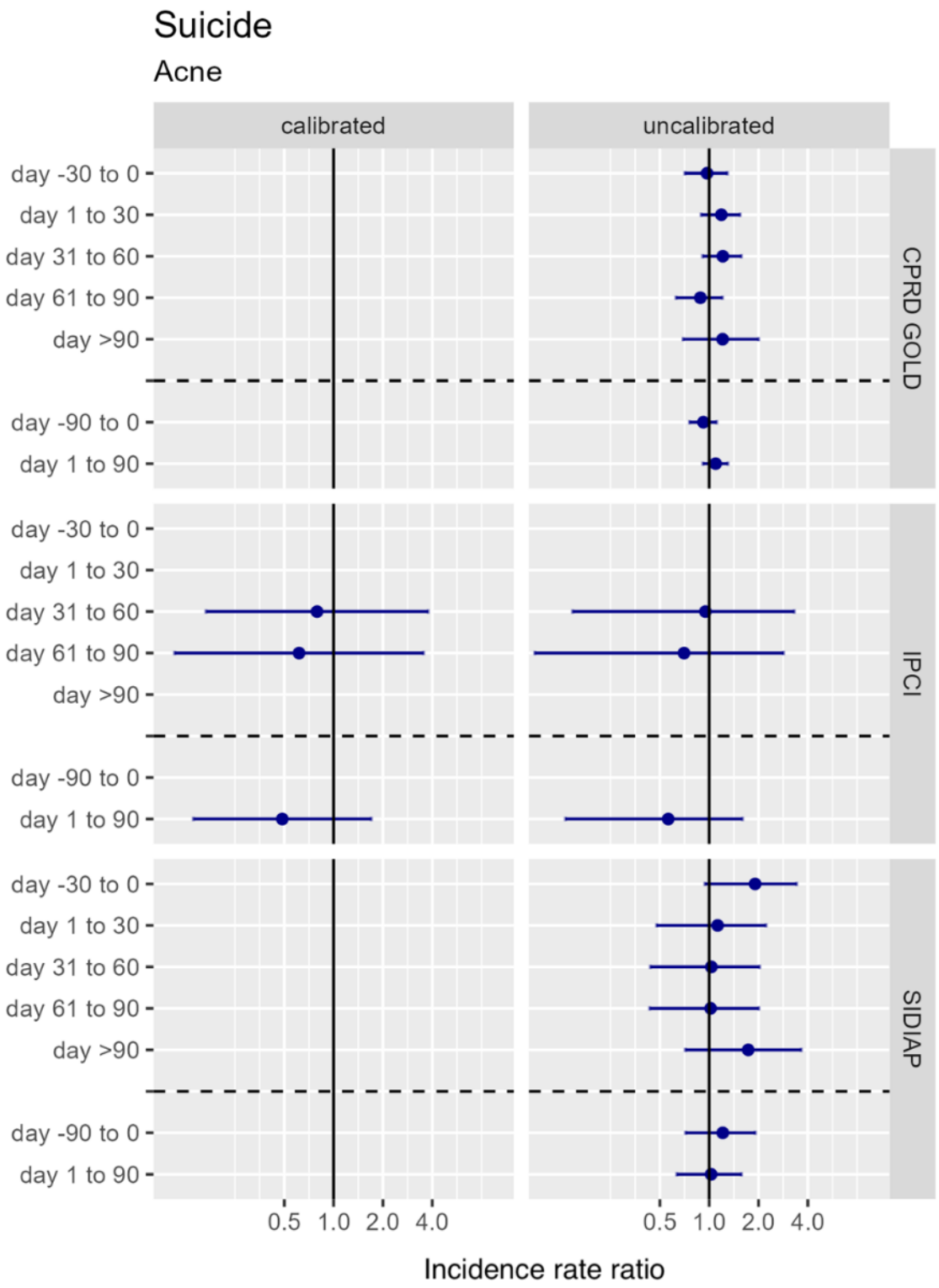


Figure 14. Incidence rate ratios and 95% confidence intervals (calibrated and uncalibrated) of the self-controlled case series study examining the association between doxycycline use and the outcome suicide-related events (without death), in patients with acne in CPRD GOLD, IPCI, and SIDIAP.

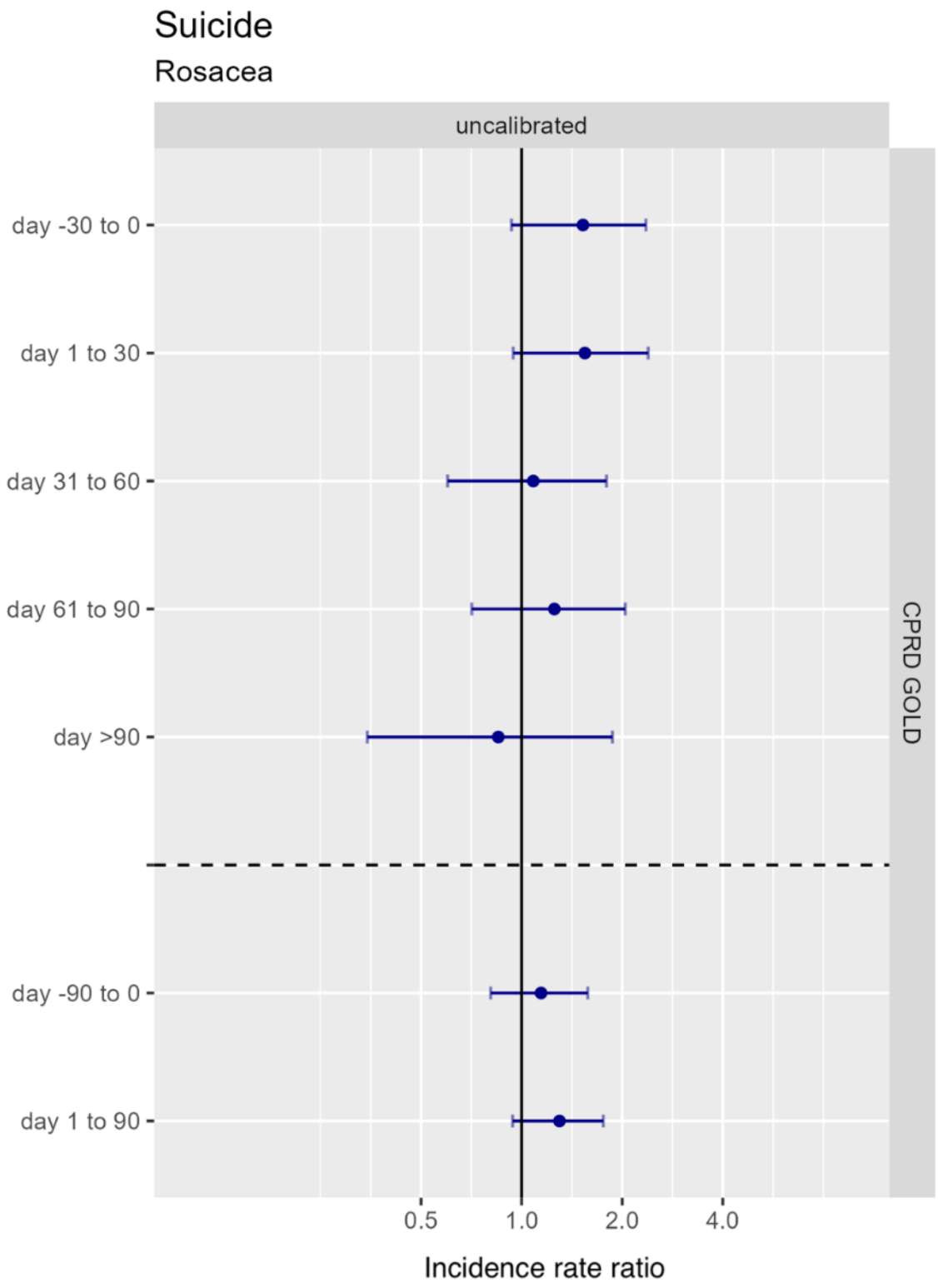


Figure 15. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome suicide-related events (without death), in patients with rosacea in CPRD GOLD, IPCI, and SIDIAP.

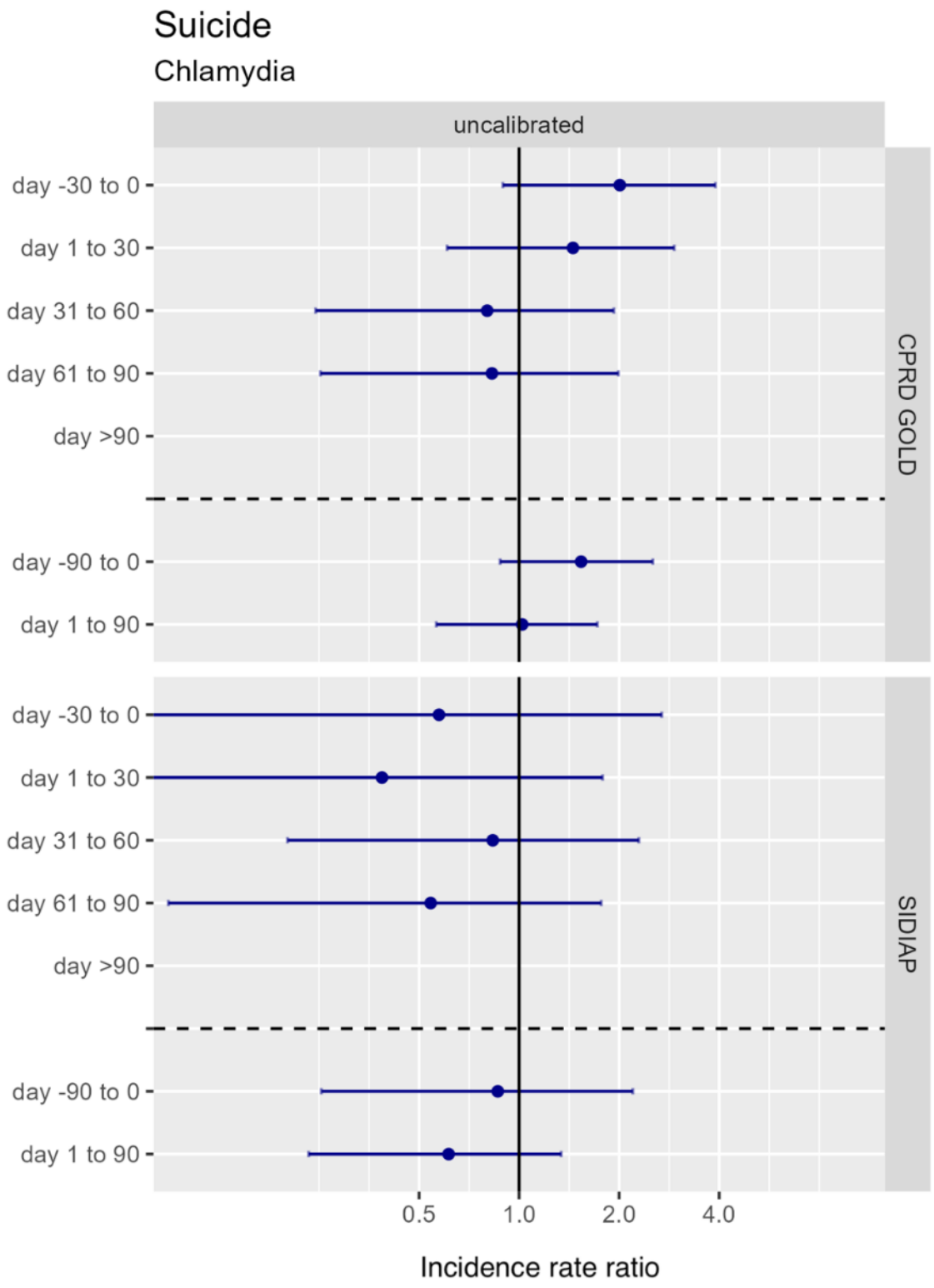


Figure 16. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome suicide-related events (without death), in patients with chlamydia in CPRD GOLD, IPCI, and SIDIAP.

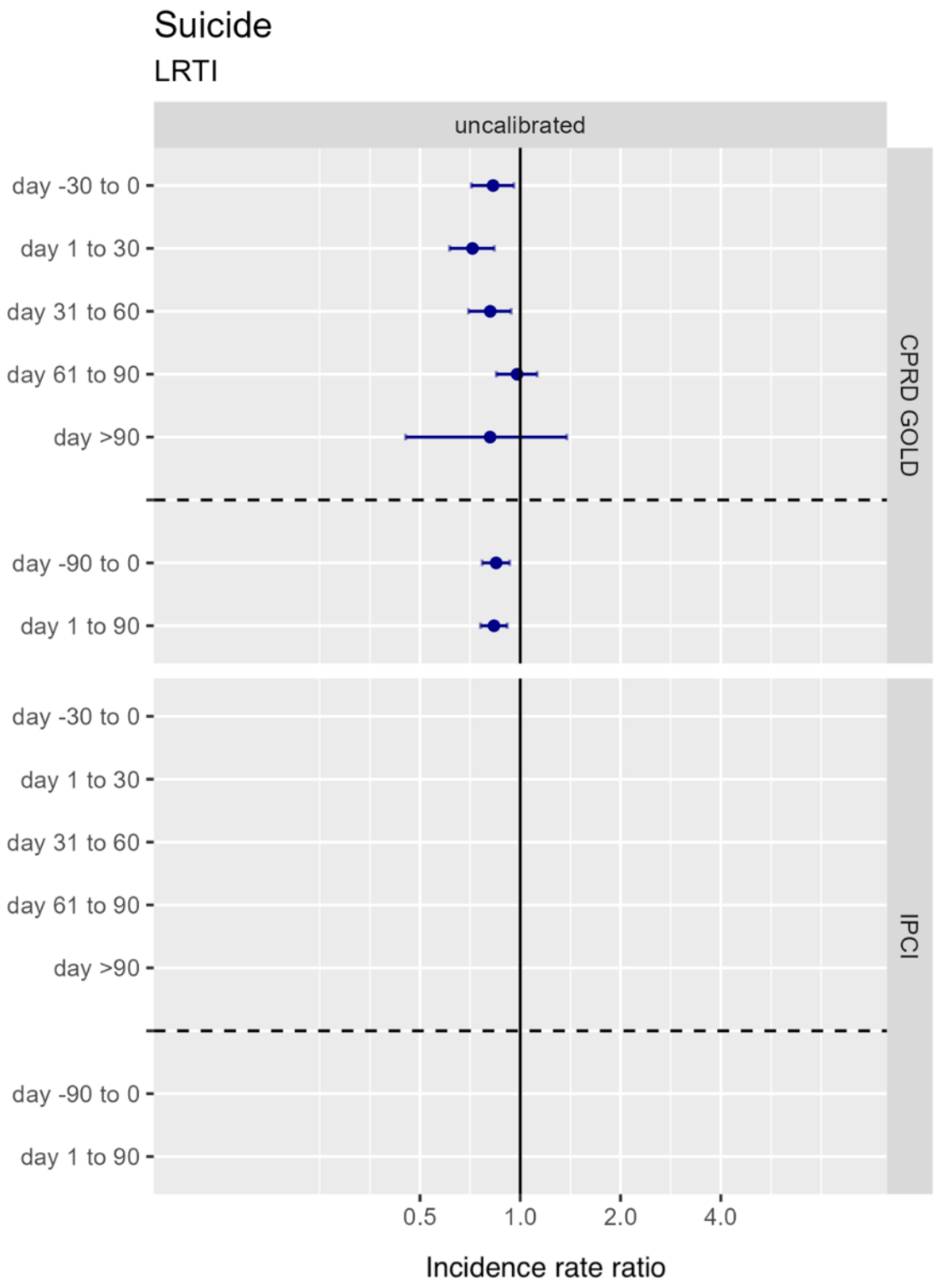


Figure 17. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome suicide-related events (without death), in patients with lower respiratory tract infection (LRTI) in CPRD GOLD, IPCI, and SIDIAP.

Table 17. Uncalibrated incidence rate ratios and corresponding 95% confidence intervals of the association of doxycycline on suicide-related events (without death).

		Day [-30,-0]		Day [1,30]		Day [31,60]		Day [61,90]		Day [>90]		Day [-90,0]		Day [1,90]	
		IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
CPRD	All	-	-	-	-	0.83	0.75 - 0.92	0.90	0.81 - 0.99	-	-	-	-	0.83	0.78 - 0.88
	LRTI	0.83	0.71 - 0.96	0.72	0.61 - 0.84	0.81	0.70 - 0.94	0.98	0.85 - 1.12	0.81	0.45 - 1.38	0.85	0.77 - 0.93	0.83	0.76 - 0.91
	Acne	0.97	0.71 - 1.29	1.19	0.89 - 1.54	1.21	0.91 - 1.57	0.88	0.63 - 1.21	1.21	0.69 - 2.00	0.92	0.76 - 1.11	1.09	0.91 - 1.30
	Rosacea	1.53	0.93 - 2.36	1.55	0.94 - 2.39	1.08	0.60 - 1.79	1.25	0.71 - 2.04	0.85	0.35 - 1.87	1.14	0.81 - 1.58	1.30	0.94 - 1.76
	Chlamydia	2.01	0.89 - 3.90	1.45	0.61 - 2.93	0.80	0.24 - 1.93	0.83	0.25 - 1.99	-	-	1.54	0.88 - 2.53	1.02	0.56 - 1.72
IPCI	All	-	-	-	-	1.12	0.75-1.60	1.03	0.68 - 1.49	1.41	0.18 - 5.95	-	-	1.07	0.84 - 1.34
	LRTI	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Acne	-	-	-	-	0.95	0.15 - 3.31	0.70	0.09-2.84	-	-	-	-	0.56	0.13-1.60
	Rosacea	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Chlamydia	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SIDIAP	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	LRTI	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Acne	1.91	0.94 - 3.42	1.13	0.48 - 2.22	1.03	0.44 - 2.03	1.02	0.43 - 2.01	1.73	0.72 - 3.65	1.21	0.72 - 1.91	1.03	0.63 - 1.58
	Rosacea	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Chlamydia	0.57	0.03 - 2.69	0.39	0.02 - 1.78	0.83	0.20 - 2.29	0.54	0.09 - 1.77	-	-	0.86	0.25 - 2.20	0.61	0.23 - 1.34

IRR incidence rate ratio, CI confidence interval, LRTI lower respiratory tract infection

Anxiety

Table 18 shows the uncalibrated IRRs and corresponding 95% confidence intervals of the association between doxycycline and suicide-related events without death overall and per indication per DP.

Overall (any indication)

In CPRD GOLD in the overall group there were statistically significant increased associations between doxycycline and anxiety in the 31-60 day risk period (uncalibrated IRR 1.09, 95% CI [1.05-1.12]; the 61-90 day risk period (uncalibrated IRR 1.06, 95% CI [1.02-1.09]), the >90 day risk period (uncalibrated IRR 1.13, 95% CI [1.00-1.27]) and the 1-90 day risk period (uncalibrated IRR 1.07, 95% CI [1.05-1.09]).
In IPCI there were statistically significant increased associations between doxycycline and anxiety in the -90-0 day risk period (uncalibrated IRR 1.30, 95% CI [1.27-1.34]) and the 1-90 day risk period (uncalibrated IRR 1.05, 95% CI [1.02-1.08]) and no associations in the 31-60 day risk period (uncalibrated IRR 1.02, 95% CI [0.97-1.08]) and the 61-90 day risk period (uncalibrated IRR 1.01, 95% CI [0.96-1.06]).

In SIDIAP in the overall group there was a statistically significant increased association between doxycycline and anxiety in the >90 day risk period (uncalibrated IRR 1.18, 95% CI [1.03-1.35]) and no association in the 61-90 day risk period (uncalibrated IRR 1.05, 95% CI [0.96-1.14]) (**Table 18**, **Figure 18**).

Meta analyses

In the meta-analysis in the overall group there were statistically significant but small associations between doxycycline and anxiety in the 61-90 day risk period (uncalibrated IRR 1.04, 95% CI [1.01-1.08]), the >90 day risk period (uncalibrated IRR 1.15, 95% CI [1.06-1.25]) and the 1-90 day risk period (uncalibrated IRR 1.06, 95% CI[1.04-1.08]). There were no results in the meta-analysis for the other risk periods.

Residual confounding

In CPRD GOLD after calibrating for residual confounding, the associations between doxycycline and anxiety in the 31-60 day risk period (calibrated IRR 0.93, 95% CI [0.57-1.53], the 61-90 day risk period (calibrated IRR 0.94, 95% CI [0.62-1.44]), the >90 day risk period (calibrated IRR 1.05, 95% CI [0.63-1.75]) and the 1-90 day risk period (calibrated IRR 0.91, 95% CI [0.56-1.47]) were no longer statistically significant. Moreover, the associations in the 31-60, 61-90 and the 1-90 day risk periods changed direction.

Calibrating for residual confounding in IPCI changed the associations between doxycycline and anxiety in the -90-0 day risk period (calibrated IRR 1.09, 95% CI [0.71-1.66]) and the 1-90 day risk period (calibrated IRR 0.91, 95% CI [0.65-1.29]) to non-statistically significant associations. The non-statistically significant associations in the 31-60 day risk period (calibrated IRR 0.93, 95% CI [0.69-1.25]), the 61-90 day risk period (calibrated IRR 0.96, 95% CI [0.83-1.10]), the >90 day risk period (calibrated IRR 0.97, 95% CI [0.77-1.24]) did not change significantly. In the 31-60, 61-90, >90, and -90-0 day risk periods the direction of the associations also changed slightly.
In SIDIAP after calibrating for residual confounding the association between doxycycline and anxiety in the >90 day risk period remained slightly increased (calibrated IRR 1.15, 95% CI [0.99-1.33]). To a lesser extent, also the 61-90 day risk period (calibrated IRR 1.05, 95% CI [0.94-1.18]).

Indication acne

In CPRD GOLD in the group with indication acne there was a statistically significant decreased association between doxycycline and anxiety in the 1-30 day risk period (uncalibrated IRR 0.89, 95% CI [0.79-0.99]) and no associations in the 31-60 day risk period (uncalibrated IRR 0.99, 95% CI [0.89-1.10]), the 61-90 day risk period (uncalibrated IRR 0.95, 95% CI [0.84-1.06]), the >90 day risk period (uncalibrated IRR 0.92, 95% CI [0.76-1.12]) and 1-90 day risk period (uncalibrated IRR 0.94, 95% CI [0.88-1.00]).
In IPCI there was a small decreased risk between doxycycline and anxiety in the 1-30 day risk period (uncalibrated IRR 0.82, 95% CI [0.66-1.00]), but not in the 31-60 day risk period (uncalibrated IRR 1.00, 95%

CI [0.83-1.20]), the 61-90 day risk period (uncalibrated IRR 0.94, 95% CI [0.77-1.13]), the >90 day risk period (uncalibrated IRR 1.20, 95% CI [0.83-1.69]) and the 1-90 day risk period (uncalibrated IRR 0.91, 95% CI [0.80-1.02]).

In SIDIAP there were no associations identified between doxycycline and anxiety in the 61-90 day risk period (uncalibrated IRR 0.90, 95% CI [0.76-1.07]) and the >90 day risk period (uncalibrated IRR 1.06, 95% CI [0.85-1.30]) (**Table 19**).

Meta analyses

In the meta-analysis in the group with the indication acne there were decreased associations identified between doxycycline and anxiety in the 1-30 day risk period (uncalibrated IRR 0.87, 95% CI [0.79-0.96]) and the 1-90 day risk period (uncalibrated IRR 0.93, 95% CI[0.88-0.99]) and no associations in the 31-60 day risk period (uncalibrated IRR 0.99, 95% CI [0.91-1.09]), the 61-90 day risk period (uncalibrated HR 0.93, 95% CI [0.88-1.02]) and the >90 day risk period (uncalibrated HR 1.01, 95% CI [0.88-1.15]) and the. There were no results in the meta-analysis for the other risk period.

Residual confounding

In CPRD GOLD after calibrating for residual confounding the statistically significant association between doxycycline and anxiety in the 1-30 day risk period (calibrated IRR 0.82, 95% CI [0.48-1.38] was no longer statistically significant. The association in the 31-60 day risk period (calibrated IRR 0.93, 95% CI [0.69-1.25]), the 61-90 day risk period (calibrated IRR 0.96, 95% CI [0.83-1.10]), the >90 day risk period (calibrated IRR 0.97, 95% CI [0.77-1.24]) did not change.

Calibrating for residual confounding in IPCI did not change the associations between doxycycline and anxiety in the 1-30 day risk period (calibrated IRR 0.75, 95% CI [0.43-1.32]), the 31-60 day risk period (calibrated IRR 0.98, 95% CI [0.78-1.23]), the 61-90 day risk period (calibrated IRR 0.96, 95% CI [0.78-1.18]), the >90 day risk period (calibrated IRR 1.00, 95% CI [0.69-1.46]) and the 1-90 day risk period (calibrated IRR 0.91, 95% CI [0.78-1.05]) (**Figure 19**).

Indication rosacea

In CPRD GOLD in the group with indication rosacea there were no associations identified between doxycycline and anxiety in the 61-90 day risk period (uncalibrated IRR 0.98, 95% CI [0.81-1.16]), the >90 day risk period (uncalibrated IRR 1.10, 95% CI [0.84-1.43]) and the 1-90 day risk period (uncalibrated IRR 1.04, 95% CI [0.93-1.15]).

In IPCI there was a statistically significant decreased association between doxycycline and anxiety in the >90 day risk period (uncalibrated IRR 0.40, 95% CI [0.16-0.87]) and the 1-90 day risk period (uncalibrated IRR 0.78, 95% CI [0.63-0.96]), but not in the 1-30 day risk period (uncalibrated IRR 0.85, 95% CI [0.60-1.17]), the 31-60 day risk period (uncalibrated IRR 0.74, 95% CI [0.51-1.03]), the 61-90 day risk period (uncalibrated IRR 0.74, 95% CI [0.51-1.03]). In the -90-0 day risk period the risk increased slightly (uncalibrated IRR 1.19, 95% CI [0.99-1.44]).

In SIDIAP there were no associations identified between doxycycline and anxiety in the 31-60 day risk period (uncalibrated IRR 0.98, 95% CI [0.69-1.35]), the 61-90 day risk period (uncalibrated IRR 0.89, 95% CI [0.61-1.24]), the >90 day risk period (uncalibrated IRR 0.96, 95% CI [0.65-1.40]), the -90-0 day risk period (uncalibrated IRR 1.17, 95% CI [0.93-1.46]) and the 1-90 day risk period (uncalibrated IRR 1.06, 95% CI [0.87-1.28]) (**Table 18**, **Figure 20**).

Meta analyses

In the meta-analysis in the group with the indication rosacea there was a statistically significant increased association between doxycycline and anxiety in the -90-0 day risk period (uncalibrated IRR 1.18, 95% CI [1.03-1.37]) and no associations in the 31-60 day risk period (uncalibrated IRR 0.86, 95% CI [0.65-1.13]) and

the 61-90 day risk period (uncalibrated HR 0.91, 95% CI [0.78-1.07]).There were no results in the meta-analysis for the other risk periods.

Residual confounding
Calibrating for residual confounding in CPRD GOLD did not significantly change the effect estimates in the group with indication rosacea between doxycycline and anxiety in the 61-90 day risk period (calibrated IRR 0.98, 95% CI [0.81-1.18]), the >90 day risk period (calibrated IRR 1.03, 95% CI [0.77-1.39]) and the 1-90 day risk period (calibrated IRR 0.97, 95% CI [0.69-1.36]).

In IPCI in the group with indication rosacea, calibrating for residual confounding changed the associations between doxycycline and anxiety in the 1-30 day risk period (calibrated IRR 0.68, 95% CI [0.49-0.96]) and the 61-90 day risk period (calibrated IRR 0.60, 95% CI [0.41-0.86]) to statistically significant associations. The statistically significant associations in the in the >90 day risk period (calibrated IRR 0.34, 95% CI [0.14-0.85]) and the 1-90 day risk period (uncalibrated IRR 0.69, 95% CI [0.56-0.86]) remained. The effect estimates in IPCI in the 31-60 day risk period (calibrated IRR 0.72, 95% CI [0.50-1.02]) and the -90-0 day risk period (calibrated IRR 1.05, 95% CI [0.65-1.68]) did not change significantly.

In SIDIAP the effect estimates the 31-60 day risk period (calibrated IRR 0.87, 95% CI [0.61-1.24]), the 61-90 day risk period (calibrated IRR 1.00, 95% CI [0.69-1.43]), the >90 day risk period (calibrated IRR 0.95, 95% CI [0.63-1.42]), the -90-0 day risk period (calibrated IRR 1.10, 95% CI [0.86-1.42]) and the 1-90 day risk period (calibrated IRR 0.91, 95% CI [0.74-1.11]) did not change significantly.

Indication Chlamydia

In CPRD GOLD in the group with indication chlamydia there was no association between doxycycline and anxiety in the 1-90 day risk period (uncalibrated IRR 1.08, 95% CI [0.83-1.37]).
In IPCI in the group with indication chlamydia and chlamydia no estimates could be produced for any of the risk periods because all analyses failed diagnostics.
In SIDIAP in the group with indication chlamydia there was no association between doxycycline and anxiety in the 61-90 day risk period (uncalibrated IRR 1.03, 95% CI [0.75-1.36]) (**Table 18**, **Figure 21**).

Meta analyses
There were no results in the meta-analysis in the group with indication chlamydia and outcome anxiety.

Residual confounding
Calibrating for residual confounding in CPRD GOLD did not significantly change the effect estimate in the group with indication chlamydia between doxycycline and anxiety in the 1-90 day risk period (calibrated IRR 0.93, 95% CI [0.71-1.23]), nevertheless the direction of the association did change.
In SIDIAP the effect estimates in the 61-90 day risk period (calibrated IRR 0.98, 95% CI [0.73-1.33]) also did not change significantly, aside from the association also changing direction slightly.

Indication LRTI

In CPRD GOLD in the group with indication LRTI there were small but increased association between doxycycline and anxiety in the 31-60 day risk period (uncalibrated IRR 1.05, 95% CI [1.00-1.11]), the -90-0 day risk period (uncalibrated IRR 1.13, 95% CI [1.10-1.17]) and the 1-90 day risk period (uncalibrated IRR 1.05, 95% CI [1.01-1.08]). There were no associations identified in the 61-90 day risk period (uncalibrated IRR 1.00, 95% CI [0.95-1.06]), the > 90 day risk period (uncalibrated IRR 1.11, 95% CI [0.91-1.34]).
In IPCI in the group with indication LRTI there was a statistically significant increased association between doxycycline and anxiety in the -90-0 day risk period (uncalibrated IRR 1.14, 95% CI [1.06-1.23]) and no associations in the 31-60 day risk period (uncalibrated IRR 1.07, 95% CI [0.96-1.18]), the 61-90 day risk

period (uncalibrated IRR 0.94, 95% CI [0.84-1.04]), the > 90 day risk period (uncalibrated IRR 0.92, 95% CI [0.42-1.81]), and the 1-90 day risk period (uncalibrated IRR 1.03, 95% CI [0.97-1.10]).

In SIDIAP in the group with indication LRTI there were statistically significant increased association between doxycycline and anxiety in the -90-0 day risk period (uncalibrated IRR 1.25, 95% CI [1.13-1.37]) and the 1-90 day risk period (uncalibrated IRR 1.12, 95% CI [1.02-1.14]) and non-significant associations in the 31-60 day risk period (uncalibrated IRR 1.14, 95% CI [0.97-1.34]), the 61-90 day risk period (uncalibrated IRR 0.84, 95% CI [0.69-1.01]), the > 90 day risk period (uncalibrated IRR 1.07, 95% CI [0.81-1.38]) (**Table 18, Figure 22**)

Meta analyses

In the meta-analysis in the group with the indication LRTI there were significant increased associations in the 31-60 day risk period (uncalibrated IRR 1.06, 95% CI [1.02-1.11]) and the 1-90 day risk period (uncalibrated IRR 1.05, 95% CI [1.02-1.08]) and no association in the >90 day risk period (uncalibrated IRR 1.08, 95% CI [0.93-1.26]). There were no results in the meta-analysis for the other risk periods.

Residual confounding

After calibrating for residual confounding In CPRD GOLD in the group with indication LRTI, there were no associations identified between doxycycline and anxiety in the 31-60 day risk period (calibrated IRR 0.96, 95% CI [0.66-1.41]), the 61-90 day risk period (calibrated IRR 0.92, 95% CI [0.64-1.33]), the > 90 day risk period (calibrated IRR 0.99, 95% CI [0.79-1.25]), the -90-0 day risk period (calibrated IRR 0.97, 95% CI [0.61-1.54]) and the 1-90 day risk period (calibrated IRR 0.95, 95% CI [1.01-1.08]).

In IPCI after calibrating for residual confounding in the group with indication LRTI, no associations were identified doxycycline and anxiety in the 31-60 day risk period (calibrated IRR 0.94, 95% CI [0.77-1.16]), the 61-90 day risk period (calibrated IRR 0.88, 95% CI [0.80-1.01]), the > 90 day risk period (calibrated IRR 0.78, 95% CI [0.38-1.64]), the -90-0 day risk period (calibrated IRR 1.00, 95% CI [0.72-1.37]) and the 1-90 day risk period (calibrated IRR 0.92, 95% CI [0.66-1.29]).

Also for SIDIAP after calibrating for residual confounding in the group with indication LRTI, no associations were identified between doxycycline and anxiety in the 31-60 day risk period (calibrated IRR 1.03, 95% CI [0.60-1.75]), the 61-90 day risk period (calibrated IRR 0.82, 95% CI [0.67-1.01]), the > 90 day risk period (calibrated IRR 1.06, 95% CI [0.80-1.40]), the -90-0 day risk period (calibrated IRR 1.02, 95% CI [0.82-1.27]) and the 1-90 day risk period (calibrated IRR 0.91, 95% CI [0.66-1.24]).

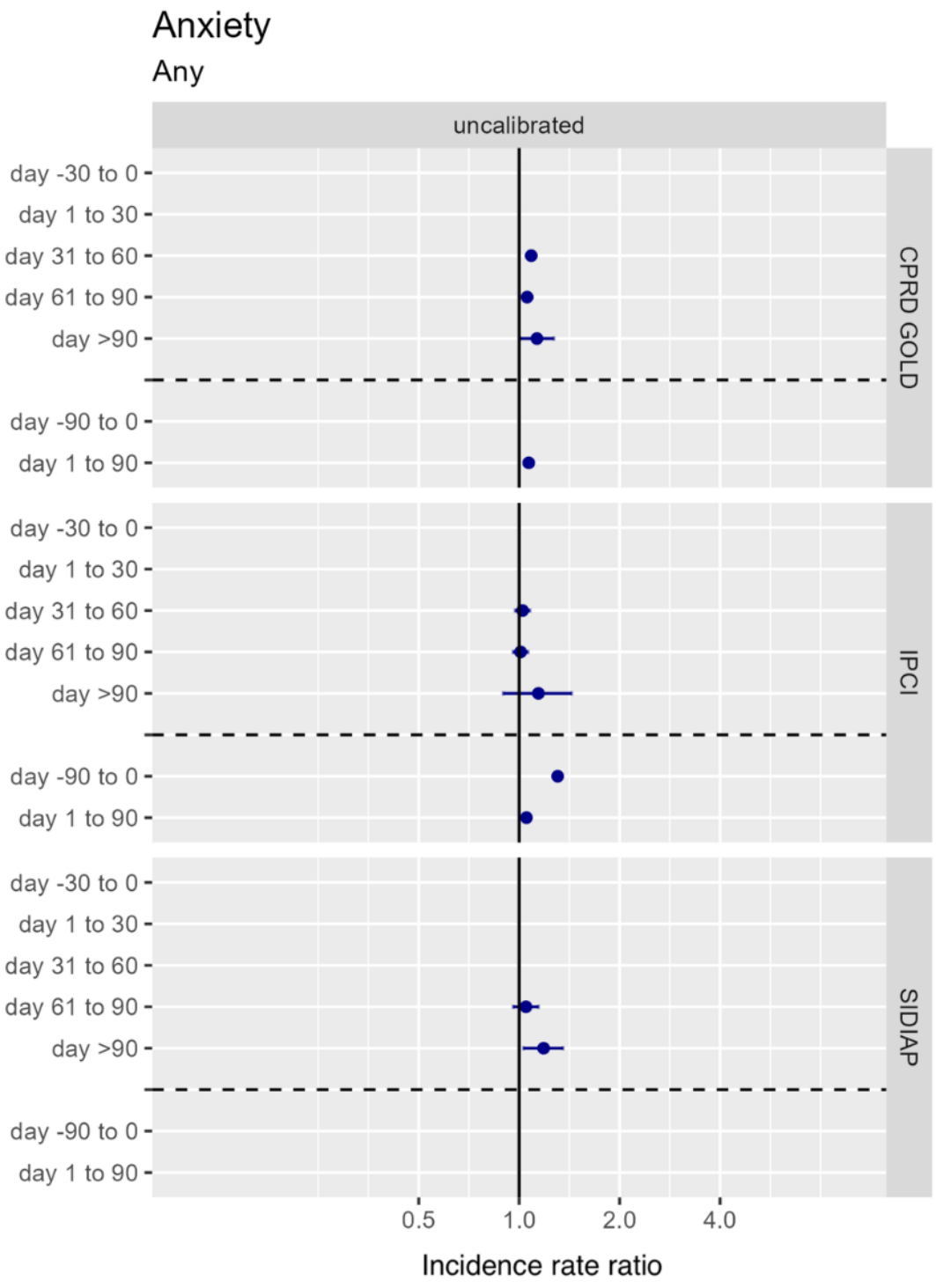


Figure 18. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome anxiety, in all indications in CPRD GOLD, IPCI, and SIDIAP.

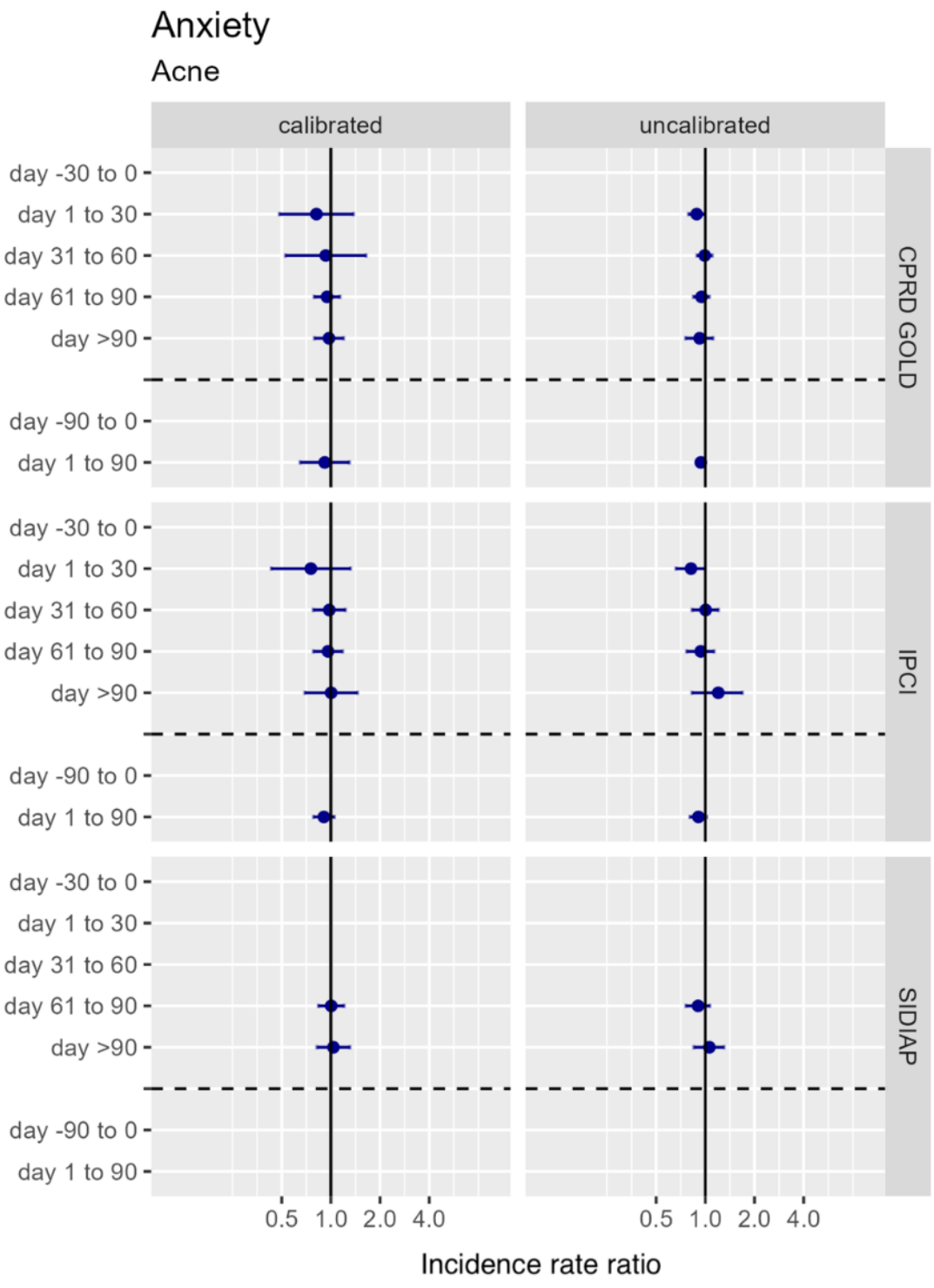


Figure 19. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining (calibrated and uncalibrated) the association between doxycycline use and the outcome anxiety, in patients with acne in CPRD GOLD, IPCI, and SIDIAP.

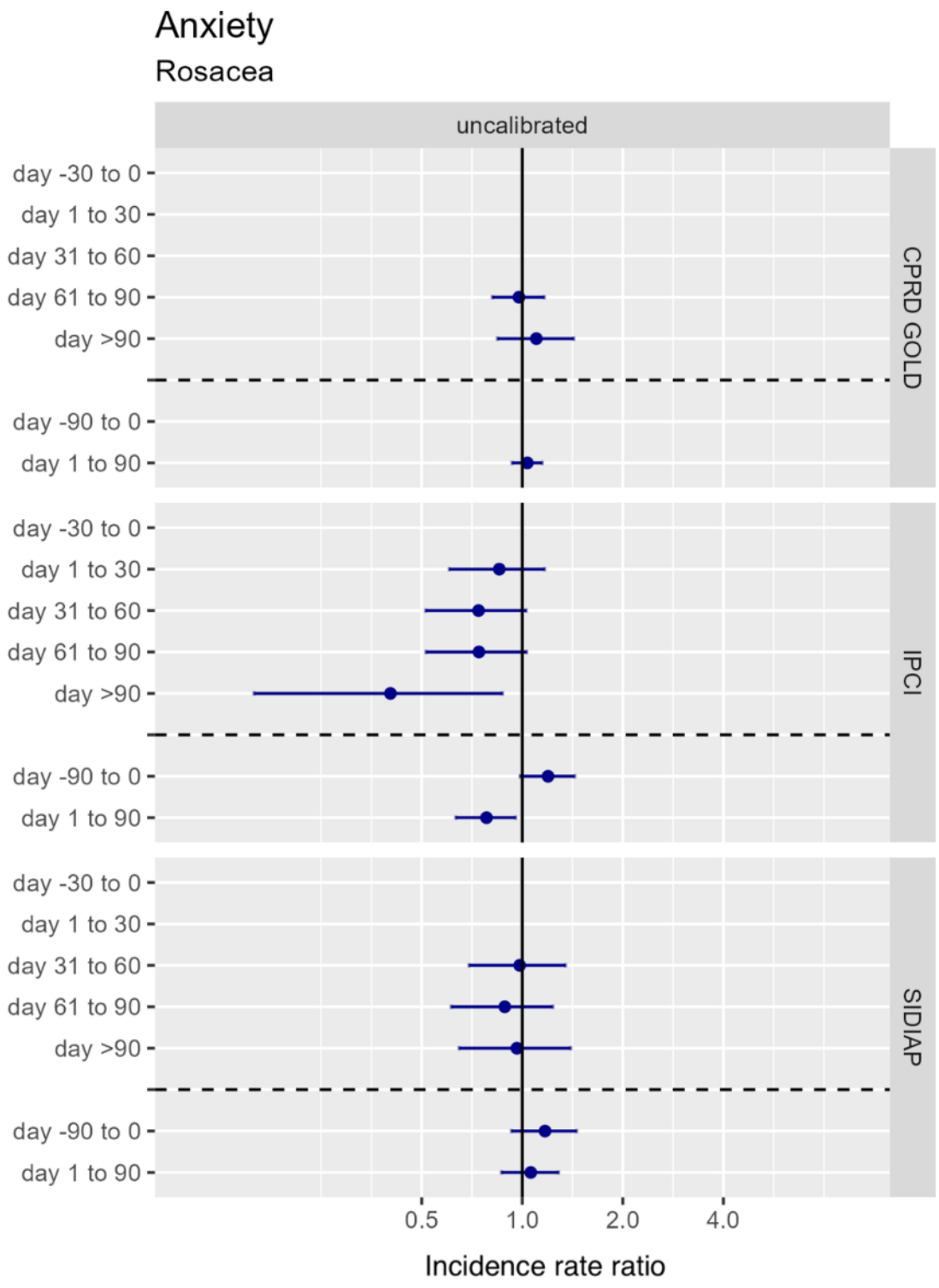


Figure 20. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining (calibrated and uncalibrated) the association between doxycycline use and the outcome anxiety, in patients with rosacea in CPRD GOLD, IPCI, and SIDIAP.

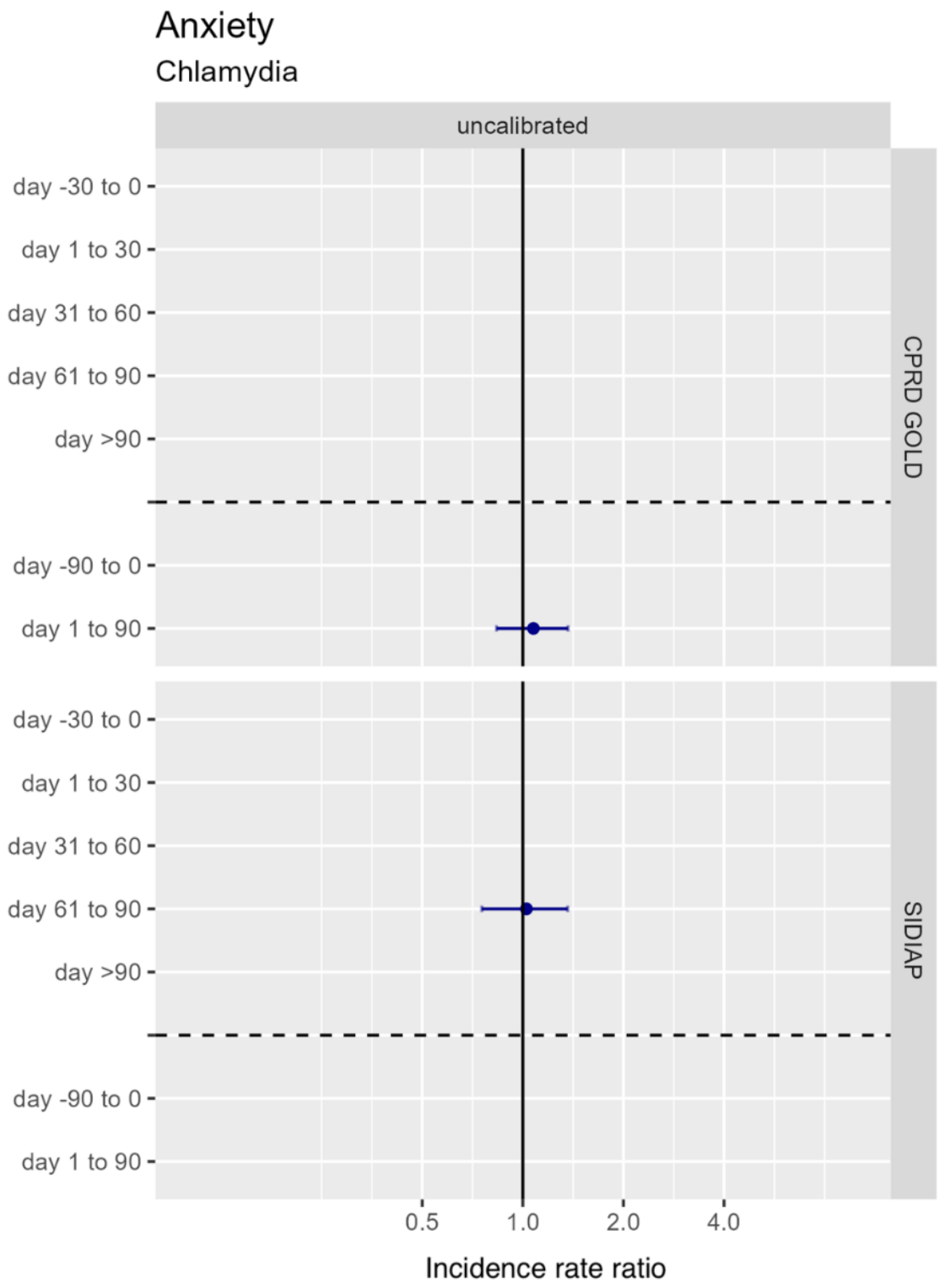


Figure 21. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome anxiety, in patients with chlamydia in CPRD GOLD, IPCI, and SIDIAP.

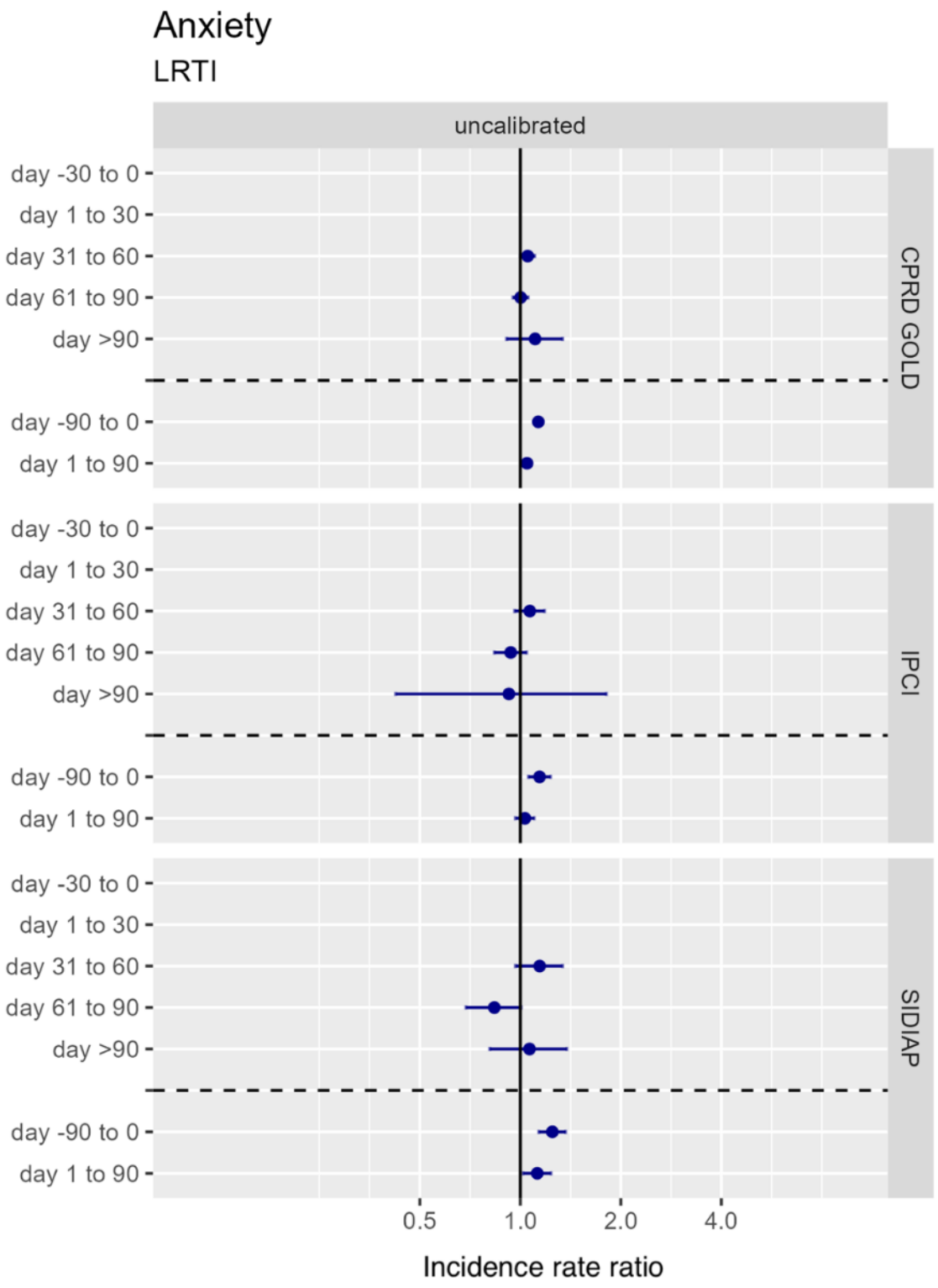


Figure 22. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome anxiety, in patients with lower-respiratory tract infection (LRTI) in CPRD GOLD, IPCI, and SIDIAP.

Table 18. Uncalibrated incidence rate ratios and corresponding 95% confidence intervals of the association of doxycycline on anxiety outcomes.

		Day [-30,-0]		Day [1,30]		Day [31,60]		Day [61,90]		Day [>90]		Day [-90,0]		Day [1,90]	
		IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
CPRD	All	-	-	-	-	1.09	1.05 - 1.12	1.06	1.02 - 1.09	1.13	1.00 - 1.27	-	-	1.07	1.05 - 1.09
	LRTI	-	-	-	-	1.05	1.00 - 1.11	1.00	0.95 - 1.06	1.11	0.91 - 1.34	1.13	1.10 - 1.17	1.05	1.01 - 1.08
	Acne	-	-	0.89	0.79 - 0.99	0.99	0.89 - 1.10	0.95	0.84 - 1.06	0.92	0.76 - 1.12	-	-	0.94	0.88 - 1.00
	Rosacea	-	-	-	-	-	-	0.98	0.81 - 1.16	1.10	0.84 - 1.43	-	-	1.04	0.93 - 1.15
	Chlamydia	-	-	-	-	-	-	-	-	-	-	-	-	1.08	0.83 - 1.37
IPCI	All	-	-	-	-	1.02	0.97 - 1.08	1.01	0.96 - 1.06	1.14	0.90 - 1.44	1.30	1.27 - 1.34	1.05	1.02 - 1.08
	LRTI	-	-	-	-	1.07	0.96 - 1.18	0.94	0.84 - 1.04	0.92	0.42 - 1.81	1.14	1.06 - 1.23	1.03	0.97 - 1.10
	Acne	-	-	0.82	0.66 - 1.00	1.00	0.83 - 1.20	0.94	0.77 - 1.13	1.20	0.83 - 1.69	-	-	0.91	0.80 - 1.02
	Rosacea	-	-	0.85	0.60 - 1.17	0.74	0.51 - 1.03	0.74	0.51 - 1.03	0.40	0.16 - 0.87	1.19	0.99 - 1.44	0.78	0.63 - 0.96
	Chlamydia	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SIDIAP	All	-	-	-	-	-	-	1.05	0.96 - 1.14	1.18	1.03 - 1.35	-	-	-	-
	LRTI	-	-	-	-	1.14	0.97 - 1.34	0.84	0.69 - 1.01	1.07	0.81 - 1.38	1.25	1.13 - 1.37	1.12	1.02 - 1.24
	Acne	-	-	-	-	-	-	0.90	0.76 - 1.07	1.06	0.85 - 1.30	-	-	-	-
	Rosacea	-	-	-	-	0.98	0.69 - 1.35	0.89	0.61 - 1.24	0.96	0.65 - 1.40	1.17	0.93 - 1.46	1.06	0.87 - 1.28
	Chlamydia	-	-	-	-	-	-	1.03	0.75 - 1.36	-	-	-	-	-	-

IRR incidence rate ratio, CI confidence interval, LRTI lower respiratory tract infection

Depression

Table 19 shows the uncalibrated IRRs and corresponding 95% confidence intervals of the association between doxycycline and suicide-related events without death overall and per indication per DP.

Overall (any indication)

In CPRD GOLD in the overall group there was a small, statistically significant increased association between doxycycline and depression in the 61-90 day risk period (uncalibrated IRR 1.07, 95% CI [1.03-1.11]) and no associations in the 31-60 day risk period (uncalibrated IRR 0.99, 95% CI [0.96-1.03]), the >90 day risk period (uncalibrated IRR 0.98, 95% CI [0.87-1.10]) and the 1-90 day risk period (uncalibrated IRR 1.02, 95% CI [0.99-1.04]).
In IPCI in the overall group there was statistically significant increased association between doxycycline and depression in the -90-0 day risk period (uncalibrated IRR 1.10, 95% CI [1.05-1.15]) and the 1-90 day risk period (uncalibrated IRR 1.07 [1.02-1.13]) and no associations in the 31-60 day risk period (uncalibrated IRR 1.05, 95% CI [0.97-1.14]), the 61-90 day risk period (uncalibrated IRR 1.00, 95% CI [0.92-1.08] and the >90 day risk period (uncalibrated IRR 0.77 [0.50-1.14]).
In SIDIAP in the overall group there was a statistically significant increased association between doxycycline and depression in the 61-90 day risk period (uncalibrated IRR 1.16, 95% CI [1.01-1.32]) and no association in the >90 day risk period (uncalibrated IRR 1.02, 95% CI [0.81-1.26]) (**Table 19, Figure 23**).

Meta analyses

In the meta-analysis there was no association in the >90 day risk period (uncalibrated IRR 0.97, 95% CI [0.88-1.07]). There were no results in the meta-analysis for the other risk periods (**Figure 23**).

Residual confounding

After calibrating for residual confounding In CPRD GOLD in the overall group there were no associations in between doxycycline and depression in the 31-60 day risk period (calibrated IRR 0.85, 95% CI [0.52-1.40]), the 61-90 day risk period (calibrated IRR 0.96, 95% CI [0.63-1.46]), the > 90 day risk period (calibrated IRR 0.90, 95% CI [0.54-1.51]) and the 1-90 day risk period (calibrated IRR 0.86, 95% CI [0.53-1.40]).

In IPCI after calibrating for residual confounding in the overall group the statistically significant associations between doxycycline and depression in the -90-0 day risk period (calibrated IRR 0.92, 95% CI [0.60-1.40]) and the 1-90 day risk period (calibrated IRR 0.94 [0.66-1.32]) were not statistically significant anymore and also the direction of the effect estimate changed direction. The calibration did result in a new statistically significant decreased risk in the >90 day risk period (calibrated IRR 0.65, 95% CI [0.43-0.99], suggesting confounding in the underlying uncalibrated estimate. There were no significant changes in the 31-60 and 61-90 day risk periods (uncalibrated IRR 0.95, 95% CI [0.70-1.29] and uncalibrated IRR 0.94, 95% CI [0.80-1.10] respectively.

In SIDIAP after calibrating for residual confounding in the overall group the statistically significant increased association between doxycycline and depression in the 61-90 day risk period (calibrated IRR 1.16, 95% CI [0.99-1.36]) was not statistically significant anymore. Moreover, the non-association in the >90 day risk period (calibrated IRR 0.99 [0.79-1.24]) did not change significantly.

Indication acne

In CPRD GOLD in the group with indication acne there were statistically significant decreased associations between doxycycline and depression in the 1-30 day risk period (uncalibrated IRR 0.80, 95% CI [0.71-0.90]) and the 1-90 day risk period (uncalibrated IRR 0.90, 95% CI [0.84-0.97]) and no associations in the 31-60 day risk period (uncalibrated IRR 0.95, 95% CI [0.85-1.06]), the 61-90 day risk period (uncalibrated IRR 0.98, 95% CI [0.87-1.09]) and the >90 day risk period (uncalibrated IRR 0.90, 95% CI [0.73-1.09]).

In IPCI in the group with indication acne there were no associations identified in the 1-30 day risk period (uncalibrated IRR 1.11, 95% CI [0.83-1.45]), the 31-60 day risk period (uncalibrated IRR 1.08, 95% CI [0.81-1.42]), the 61-90 day risk period (uncalibrated IRR 0.72, 95% CI [0.50-1.00]) and the >90 day risk period (uncalibrated IRR 0.77, 95% CI [0.35-1.45]) and the 1-90 day risk period (uncalibrated IRR 0.98, 95% CI [0.81-1.16]).

In SIDIAP in the group with indication acne there were no associations in the 61-90 day risk period (uncalibrated IRR 0.99, 95% CI [0.70-1.34], and a non-statistically significant decreased risk in the >90 day risk period (uncalibrated IRR 0.67, 95% CI [0.39-1.08]) (**Table 19, Figure 24**).

Meta analyses

In the meta-analysis there was a statistically significant decreased association between doxycycline and depression in the 1-90 day risk period (uncalibrated IRR 0.91, 95% CI [0.86-0.97]) and no statistically significant decreased associations in the 31-60 day risk period (uncalibrated IRR 0.96, 95% CI [0.87-1.07]), the 61-90 day risk period (uncalibrated IRR 0.94, 95% CI [0.81-1.07]) and the >90 day risk period (uncalibrated IRR 0.86, 95% CI [0.72-1.02]) and. There were no results in the meta-analysis for the other risk periods.

Residual confounding

After calibrating for residual confounding In CPRD GOLD in the group with acne there remained no associations between doxycycline and depression in the 1-30 day risk period (calibrated IRR 0.74, 95% CI [0.44-1.26]), the 31-60 day risk period (calibrated IRR 0.89, 95% CI [0.50-1.57]), the 61-90 day risk period (calibrated IRR 0.97, 95% CI [0.80-1.19]) and the >90 day risk period (calibrated IRR 0.95, 95% CI [0.77-1.17]) and the 1-90 day risk period (calibrated IRR 0.88, 95% CI [0.62-1.25]).

In IPCI in the group with indication acne after calibrating all of the effect estimates in the 1-30 day risk period (calibrated IRR 1.02, 95% CI [0.57-1.82]), the 31-60 day risk period (calibrated IRR 1.05, 95% CI [0.78-1.43]), the 61-90 day risk period (calibrated IRR 0.74, 95% CI [0.52-1.05]) and the >90 day risk period (calibrated IRR 0.64, 95% CI [0.31-1.30]) and the 1-90 day risk period (uncalibrated IRR 0.98, 95% CI [0.80-1.19]) remained non-statistically significant.

After calibrating for residual confounding in SIDIAP no associations were identified in the 61-90 day risk period (calibrated IRR 1.09, 95% CI [0.79-1.53] and the >90 day risk period (calibrated IRR 0.66, 95% CI [0.39-1.10]) remained non-statistically significant. However, the direction of the association in the 61-90 day risk period changed direction (**Figure 24**).

Indication rosacea

In CPRD GOLD in the group with indication rosacea there were no associations identified between doxycycline and depression in the 61-90 day risk period (uncalibrated IRR 0.95, 95% CI [0.79-1.14]), the >90 day risk period (uncalibrated IRR 1.03, 95% CI [0.79-1.34]) and the 1-90 day risk period (uncalibrated IRR 1.00, 95% CI [0.90-1.11]).

In IPCI in the group with indication rosacea there were no associations identified between doxycycline and depression in the 1-30 day risk period (uncalibrated IRR 1.17, 95% CI [0.71-1.82]), the 31-60 day risk period (uncalibrated IRR 0.81, 95% CI [0.44-1.35]), the 61-90 day risk period (uncalibrated IRR 0.88, 95% CI [0.49-1.44]) and the >90 day risk period (uncalibrated IRR 0.53, 95% CI [0.07-2.27]), the -90-0 day risk period (uncalibrated IRR 1.16, 95% CI [0.84-1.57]) and the 1-90 day risk period (uncalibrated IRR 0.97, 95% CI [0.70-1.31]).

In SIDIAP in the group with indication rosacea there no associations identified between doxycycline and depression in the 31-60 day risk period (uncalibrated IRR 1.22, 95% CI [0.77-1.83]), the 61-90 day risk period (uncalibrated IRR 1.02, 95% CI [0.61-1.58]) and the >90 day risk period (uncalibrated IRR 0.60, 95% CI

[0.30-1.09]), the -90-0 day risk period (uncalibrated IRR 1.08, 95% CI [0.76-1.49]) and the 1-90 day risk period (uncalibrated IRR 1.23, 95% CI [0.93-1.59]) (**Table 19, Figure 25**).

Meta analyses
In the meta-analysis in the group with indication rosacea there were no associations identified between doxycycline and depression in the 31-60 day risk period (uncalibrated IRR 1.03, 95% CI [0.70-1.53]), the 61-90 day risk period (uncalibrated IRR 0.95, 95% CI [0.81-1.12]), the >90 day risk period (uncalibrated IRR 0.83, 95% CI [0.52-1.33]), the -90-0 day risk period (uncalibrated IRR 1.12, 95% CI [0.90-1.41]) and the 1-90 day risk period (uncalibrated IRR 1.02, 95% CI [0.93-1.12]). There were no results in the meta-analysis for the other risk periods.

Residual confounding
In CPRD GOLD in the group with indication rosacea after calibrating the effect estimates associations 61-90 day risk period (calibrated IRR 0.95, 95% CI [0.77-1.15]) and the >90 day risk period (calibrated IRR 0.97, 95% CI [0.73-1.29]) and the 1-90 day risk period (uncalibrated IRR 0.94, 95% CI [0.67-1.31]) did not substantially change.

Also in IPCI in the group with indication rosacea after calibrating for residual confounding there were no associations identified in the 1-30 day risk period (calibrated IRR 0.94, 95% CI [0.58-1.52]), the 31-60 day risk period (calibrated IRR 0.79, 95% CI [0.45-1.38]), the 61-90 day risk period calibrated IRR 0.71, 95% CI [0.41-1.23]) and the >90 day risk period (calibrated IRR 0.45, 95% CI [0.08-2.67]), the -90-0 day risk period (calibrated IRR 1.02, 95% CI [0.59-1.75]) and the 1-90 day risk period (calibrated IRR 0.86, 95% CI [0.63-1.18]) remained non-statistically significant. Nevertheless, the association in the 1-30 day risk period did change direction.

After adjustment for residual confounding in SIDIAP, there were no associations identified in the 31-60 day risk period (calibrated IRR 1.07, 95% CI [0.68-1.69]), the 61-90 day risk period (calibrated IRR 1.14, 95% CI [0.70-1.85]) and the >90 day risk period (calibrated IRR 0.59, 95% CI [0.31-1.13]), the -90-0 day risk period (calibrated IRR 1.02, 95% CI [0.72-1.45]) and the 1-90 day risk period (calibrated IRR 1.05, 95% CI [0.80-1.38]) also remained non-statistically significant.

Indication Chlamydia

In CPRD in the group with indication chlamydia there was a statistically significant increased associations in the >90 day risk period (uncalibrated IRR 7.48, 95% CI [1.32-31.30], but not in 1-90 day risk period (uncalibrated IRR 0.79, 95% CI [0.58-1.04]).

In IPCI in the group with indication chlamydia there were no associations identified in the 1-30 day risk period (uncalibrated IRR 1.29, 95% CI [0.70-2.19] and the 1-90 day risk period (uncalibrated IRR 1.23, 95% CI [0.84-1.74]).

In SIDIAP in the group with indication chlamydia there was no association between doxycycline and depression in the 61-90 day risk period (uncalibrated IRR 0.90, 95% CI [0.44-1.62]) (**Table 19, Figure 26**).

Meta analyses
There were no results in the meta-analysis in the group with indication chlamydia and outcome depression.

Residual confounding
After calibrating for residual confounding in CPRD GOLD in the group with indication chlamydia there was a statistically significant decreased association in the 1-90 risk day period (calibrated IRR 0.68, 95% CI [0.49-0.94]).

In IPCI calibrating for residual confounding in the group with indication chlamydia there still were no associations in the 1-30 day risk period (calibrated IRR 1.17, 95% CI [0.63-2.18]) and the 1-90 day risk period (calibrated IRR 1.03, 95% CI [0.62-1.72]).

After calibrating for residual confounding in SIDIAP in the group with indication chlamydia there also still was no association in the 61-90 day risk period (calibrated IRR 0.86, 95% CI [0.45-1.66]).

Indication LRTI

In CPRD GOLD in the group with indication LRTI there was a statistically significant increased association between doxycycline and depression in the -90-0 day risk period (uncalibrated IRR 1.15, 95% CI [1.12-1.19]). There were no associations in the 31-60 day risk period (uncalibrated IRR 0.98, 95% CI [0.93-1.03), the 61-90 day risk period (uncalibrated IRR 1.04, 95% CI [0.99-1.09]), the > 90 day risk period (uncalibrated IRR 0.99, 95% CI [0.81-1.20]) and the 1-90 day risk period (uncalibrated IRR 1.01, 95% CI [0.98-1.04]).

In IPCI in the group with indication LRTI there were no associations between doxycycline and depression in the 31-60 day risk period (uncalibrated IRR 0.97, 95% CI [0.82-1.14), the 61-90 day risk period (uncalibrated IRR 1.08, 95% CI [0.92-1.27]), the > 90 day risk period (uncalibrated IRR 1.23, 95% CI [0.46-2.79]), the -90-0 day risk period (uncalibrated IRR 1.01, 95% CI [0.89-1.13]) and the 1-90 day risk period (uncalibrated IRR 1.06, 95% CI [0.96-1.17]).

In SIDIAP in the group with indication LRTI there was a statistically significant increased association between doxycycline and depression in the 1-90 day risk period (uncalibrated IRR 1.18, 95% CI [1.02-1.35]). There were no associations in the 31-60 day risk period (uncalibrated IRR 1.13, 95% CI [0.88-1.44), the 61-90 day risk period (uncalibrated IRR 0.88, 95% CI [0.66-1.15]), the > 90 day risk period (uncalibrated IRR 1.11, 95% CI [0.77-1.56]) and the -90-0 day risk period (uncalibrated IRR 1.14, 95% CI [0.99-1.32]) (**Table 19, Figure 27**).

Meta analyses

In the meta-analysis of the group with indication LRTI there were no associations between doxycycline and depression in the 31-60 day risk period (uncalibrated IRR 0.99, 95% CI [0.94-1.03], the 61-90 day risk period (uncalibrated IRR 1.03, 95% CI [0.99-1.09]) and the >90 day risk period (uncalibrated IRR 1.03, 95% CI [0.87-1.21]). There were no results in the meta-analysis for the other risk periods.

Residual confounding

After calibrating for residual confounding in CPRD GOLD in the group with LRTI there was no association in the -90-0 day risk period (calibrated IRR 0.98, 95% CI [0.62-1.57]). There also still were no associations identified in the 31-60 day risk period (calibrated IRR 0.89, 95% CI [0.61-1.31), the 61-90 day risk period (calibrated IRR 0.96, 95% CI [0.67-1.38]), the > 90 day risk period (calibrated IRR 0.89, 95% CI [0.70-1.13]) and the 1-90 day risk period (uncalibrated IRR 0.91, 95% CI [0.60-1.38]).

In IPCI in the group with indication LRTI after calibrating for residual confounding there were still no associations identified between doxycycline and depression in the 31-60 day risk period (calibrated IRR 0.86, 95% CI [0.66-1.11), the 61-90 day risk period (calibrated IRR 1.04, 95% CI [0.88-1.23]), the > 90 day risk period (calibrated IRR 1.05, 95% CI [0.42-2.61]), the -90-0 day risk period (calibrated IRR 0.88, 95% CI [0.63-1.23]) and the 1-90 day risk period (calibrated IRR 0.95, 95% CI [0.68-1.33]).

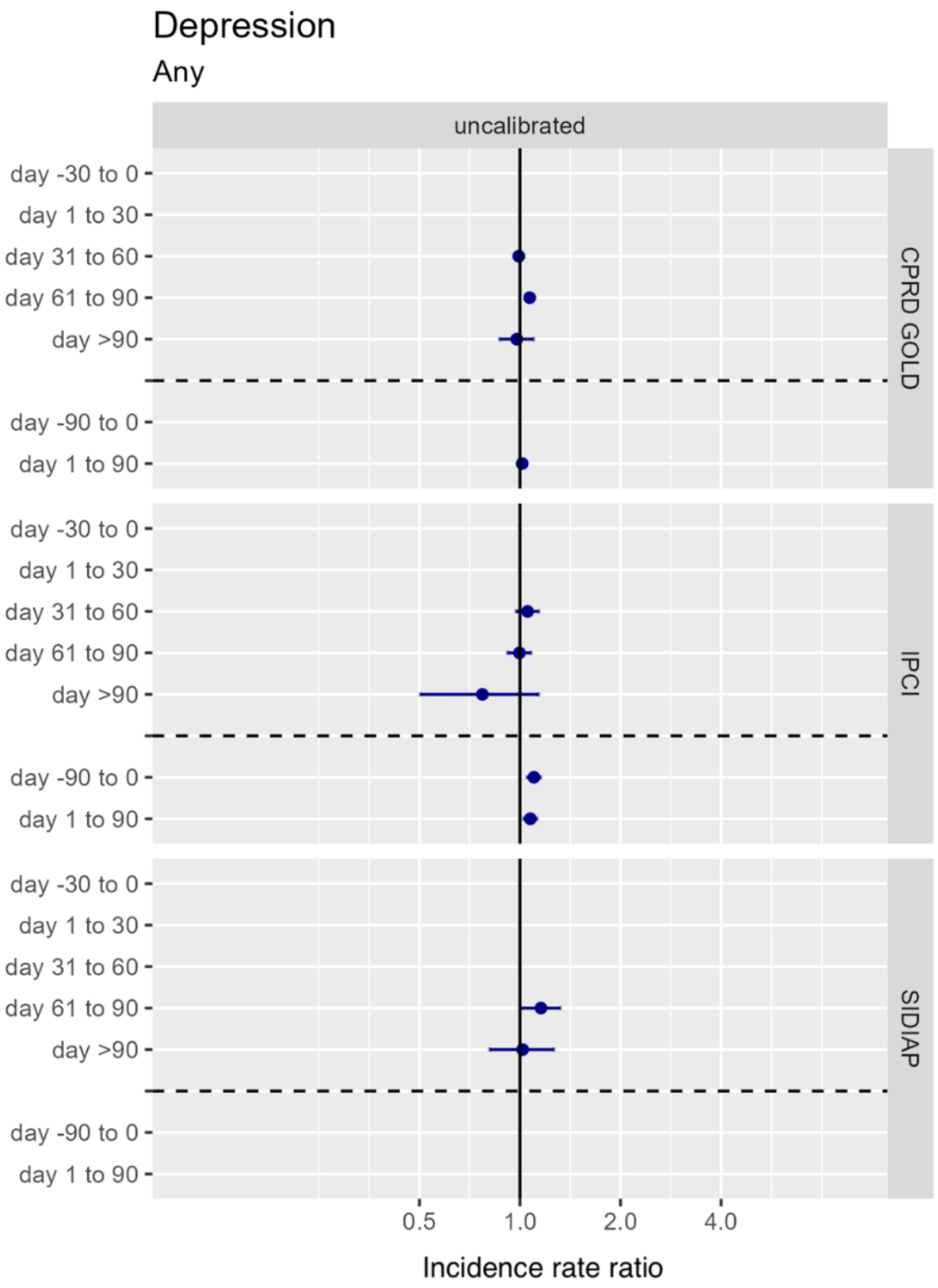


Figure 23. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome depression, in all indications in CPRD GOLD, IPCI, and SIDIAP.

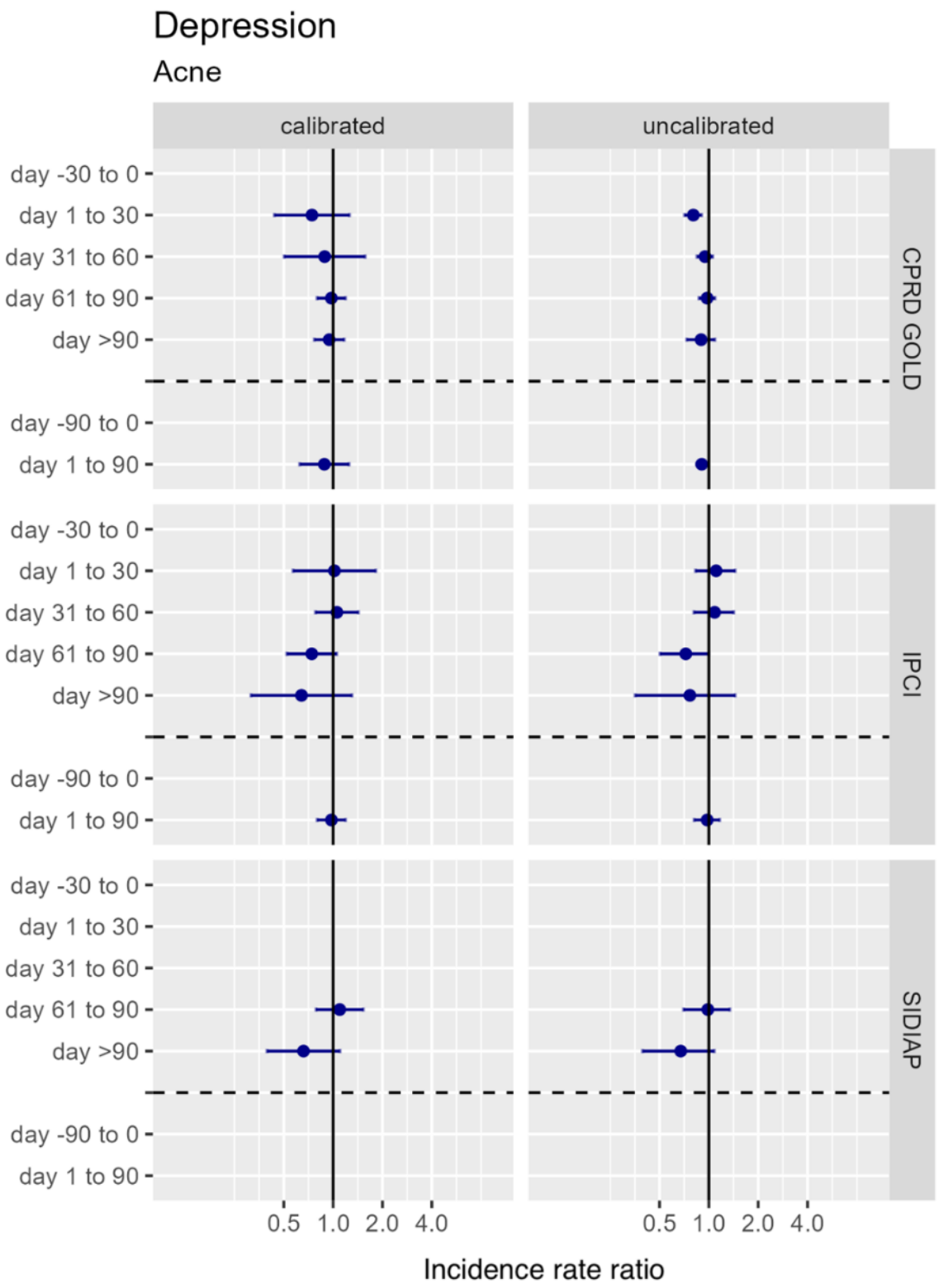


Figure 24. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study (calibrated and uncalibrated) examining the association between doxycycline use and the outcome depression, in patients with acne in CPRD GOLD, IPCI, and SIDIAP.

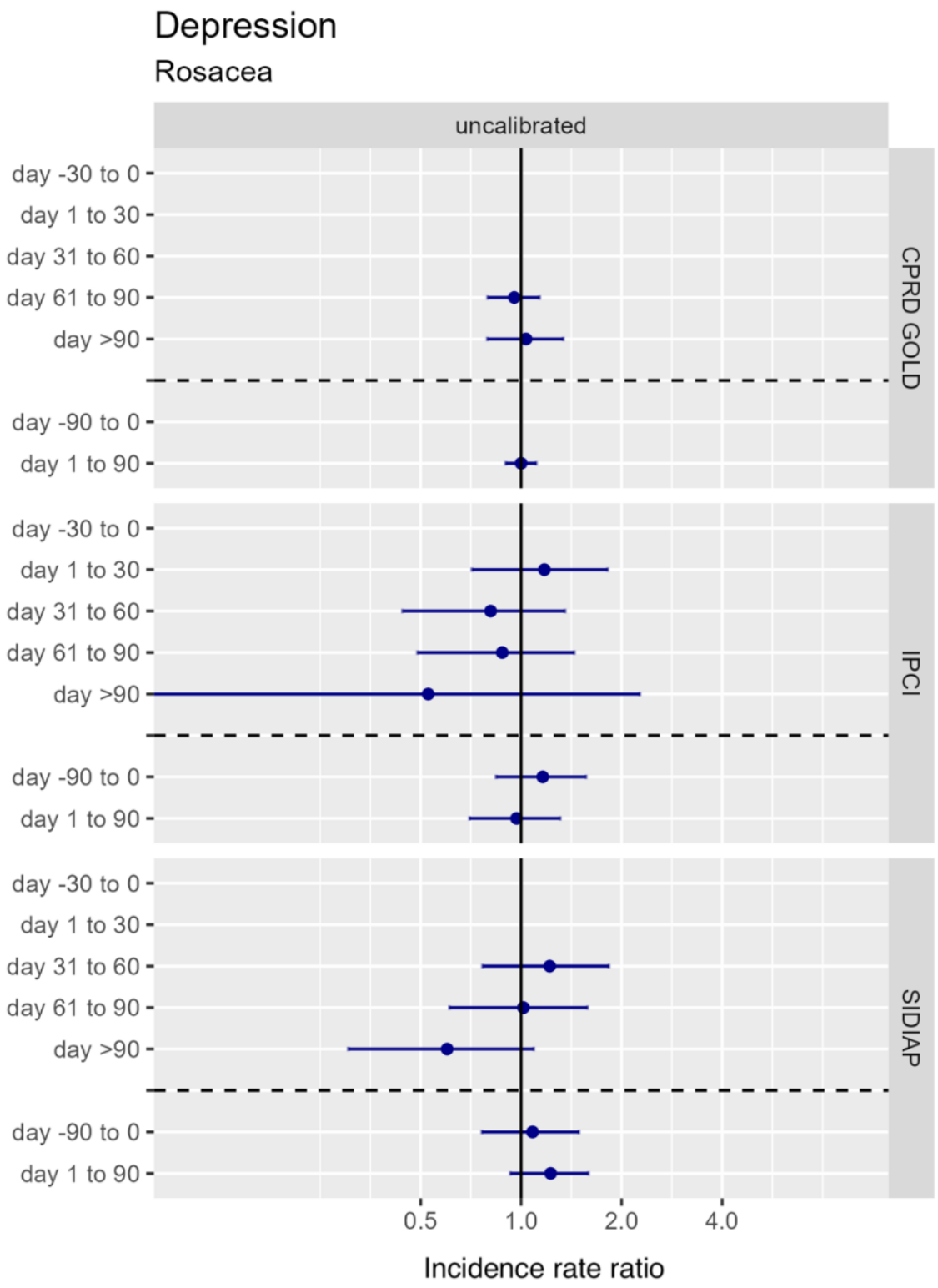


Figure 25. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome depression, in patients with rosacea in CPRD GOLD, IPCI, and SIDIAP.

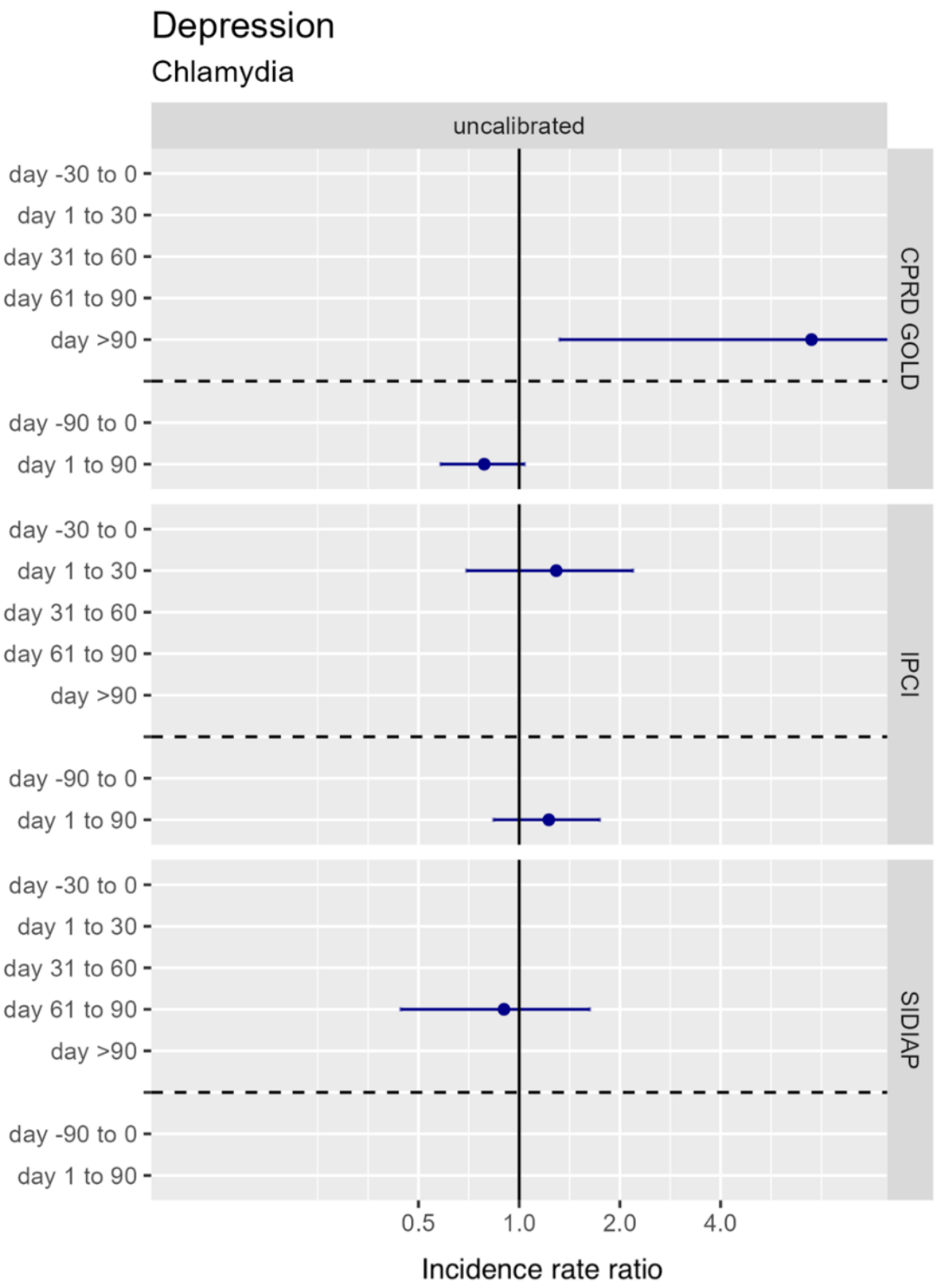


Figure 26. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome depression, in patients with chlamydia in CPRD GOLD, IPCI, and SIDIAP.

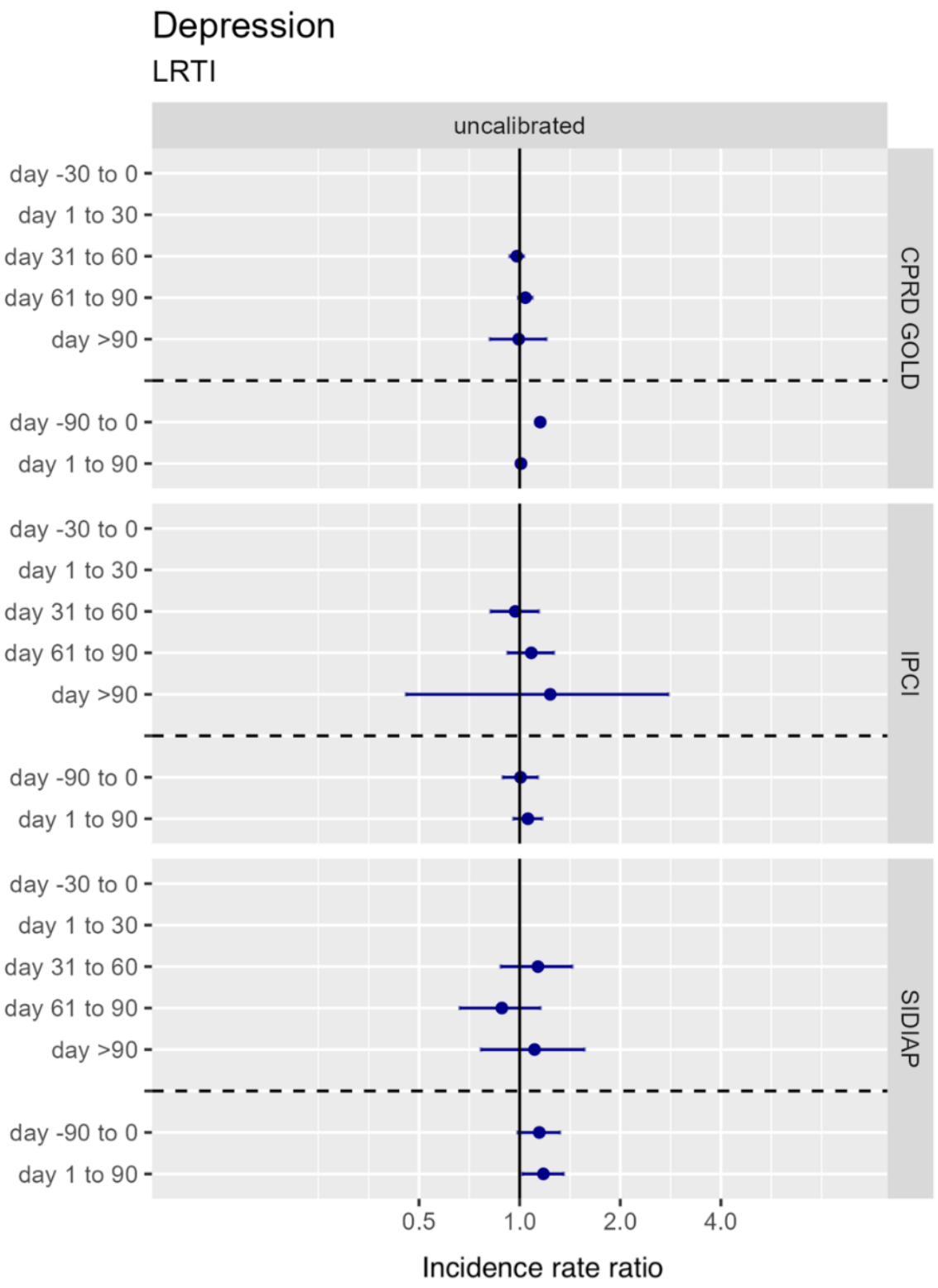


Figure 27. Incidence rate ratios and 95% confidence intervals of the self-controlled case series study examining the association between doxycycline use and the outcome depression, in patients with lower respiratory tract infections (LRTI) in CPRD GOLD, IPCI, and SIDIAP.

Table 19. Uncalibrated incidence rate ratios and corresponding 95% confidence intervals of the association of doxycycline on depression outcomes.

		Day [-30,-0]		Day [1,30]		Day [31,60]		Day [61,90]		Day [>90]		Day [-90,0]		Day [1,90]	
		IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
CPRD	All	-	-	-	-	0.99	0.96 - 1.03	1.07	1.03 - 1.11	0.98	0.87 - 1.10	-	-	1.02	0.99 - 1.04
	LRTI	-	-	-	-	0.98	0.93 - 1.03	1.04	0.99 - 1.09	0.99	0.81 - 1.20	1.15	1.12 - 1.19	1.01	0.98 - 1.04
	Acne	-	-	0.80	0.71 - 0.90	0.95	0.85 - 1.06	0.98	0.87 - 1.09	0.90	0.73 - 1.09	-	-	0.90	0.84 - 0.97
	Rosacea	-	-	-	-	-	-	0.95	0.79 - 1.14	1.03	0.79 - 1.34	-	-	1.00	0.90 - 1.11
	Chlamydia	-	-	-	-	-	-	-	-	7.48	1.32 - 31.30	-	-	0.79	0.58 - 1.04
IPCI	All	-	-	-	-	1.05	0.97 - 1.14	1.00	0.92 - 1.08	0.77	0.50 - 1.14	1.10	1.05 - 1.15	1.07	1.02 - 1.13
	LRTI	-	-	-	-	0.97	0.82 - 1.14	1.08	0.92 - 1.27	1.23	0.46 - 2.79	1.01	0.89 - 1.13	1.06	0.96 - 1.17
	Acne	-	-	1.11	0.83 - 1.45	1.08	0.81 - 1.42	0.72	0.50 - 1.00	0.77	0.35 - 1.45	-	-	0.98	0.81 - 1.16
	Rosacea	-	-	1.17	0.71 - 1.82	0.81	0.44 - 1.35	0.88	0.49 - 1.44	0.53	0.07 - 2.27	1.16	0.84 - 1.57	0.97	0.70 - 1.31
	Chlamydia	-	-	1.29	0.70 - 2.19	-	-	-	-	-	-	-	-	1.23	0.84 - 1.74
SIDIAP	All	-	-	-	-	-	-	1.16	1.01 - 1.32	1.02	0.81 - 1.26	-	-	-	-
	LRTI	-	-	-	-	1.13	0.88 - 1.44	0.88	0.66 - 1.15	1.11	0.77 - 1.56	1.14	0.99 - 1.32	1.18	1.02 - 1.35
	Acne	-	-	-	-	-	-	0.99	0.70 - 1.34	0.67	0.39 - 1.08	-	-	-	-
	Rosacea	-	-	-	-	1.22	0.77 - 1.83	1.02	0.61 - 1.58	0.60	0.30 - 1.09	1.08	0.76 - 1.49	1.23	0.93 - 1.59
	Chlamydia	-	-	-	-	-	-	0.90	0.44 - 1.62	-	-	-	-	-	-

IRR incidence rate ratio, CI confidence interval, LRTI lower respiratory tract infection

12.4 Other analysis

Sensitivity analyses include the extending the treatment episode by 30 days after the end of prescription date instead of 7 days for patients diagnosed with acne or rosacea. The full results can be seen in **Appendix Tables 35, 36, 39,** and **40**.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

14. DISCUSSION

14.1 Key results

In the cohort study, the largest cohorts were observed for patients diagnosed with LRTI and acne. The age of individuals in the acne cohort was younger than the other cohorts, especially compared to the rosacea and LRTI cohorts. Indeed, in the acne cohort most individuals were in the age-group 15-19 years while most individuals in the rosacea and LRTI cohort were 45-49 years and 65-69 years respectively. Also, for the SCCS the LRTI cohorts were the largest, followed by acne, rosacea and chlamydia.

The number of suicide-related events within the different cohorts of interest was low, the maximum number of target events was 12 and maximum number of comparator events, 38. For anxiety the maximum number of events were higher namely a maximum number of target events of 163 and 438 comparator events. Lastly, for depression the maximum number of target events was 131 while the maximum number of comparator events was 168.

In the cohort study in SIDIAP an increased association between suicide-related events without death was found in patients using doxycycline for acne in comparison with patients using erythromycin, with an uncalibrated HR of 3.77 (95% CI [1.03-17.80]). A non-significant association was seen in CRPD GOLD (uncalibrated HR 1.71, 95% CI [0.74-4.07]). The increased association of suicide-related events without death in patients using doxycycline for acne in comparison with patients using erythromycin was also observed in the meta-analysis (uncalibrated HR (from CPRD GOLD and SIDIAP) of 2.11 (95% CI [1.01-4.39]). No association for suicide-related events without death was found in patients using doxycycline for acne compared to isotretinoin. In CPRD GOLD there was a statistically significant decreased association of suicide-related events without death in patients using doxycycline with LRTI compared to amoxicillin (uncalibrated HR 0.40, 95% CI [0.15-0.87]). In patients with rosacea no associations between doxycycline use and suicide-related events without death were found in comparison with both erythromycin and isotretinoin use. Similarly, no associations were found in patients with chlamydia using doxycycline versus patients using erythromycin, azithromycin or amoxicillin. In IPCI a statistically significant increased association on anxiety in doxycycline users for acne compared to isotretinoin users (uncalibrated HR 1.94, 95%CI [1.28-2.94]) was found. No associations were found between doxycycline use and anxiety compared to erythromycin in CPRD GOLD and SIDIAP (uncalibrated HR 1.06, 95% CI [0.84-1.32] and uncalibrated HR

0.96, 95% CI [0.73-1.26] respectively). This was also observed in the meta-analysis based on the estimates from CPRD GOLD and SIDIAP (uncalibrated HR 1.02, 95% CI [0.85-1.21]). There were no associations identified between doxycycline and anxiety for the other indications. Similarly, there were no statistically associations between doxycycline and the outcome depression for any of the indications.

In the SCCS in the overall group with any indication in CPRD GOLD there were statistically significant decreased associations between doxycycline and suicide-related events without death in the 31-60 day risk period (uncalibrated IRR 0.83, 95% CI [0.75-0.92]; the 61-90 day risk period (uncalibrated IRR 0.90, 95% CI [0.81-0.99]) and the 1-90 day risk period (uncalibrated IRR 0.83, 95% CI [0.78-0.88]). In IPCI there were no associations in the 31-60 day risk period (uncalibrated IRR 1.12, 95% CI [0.75-1.60]), the 61-90 day risk period (uncalibrated IRR 1.03, 95% CI [0.68-1.49]), and the 1-90 day risk period (uncalibrated IRR 1.07, 95% CI [0.84-1.34]). The decreased associations in the risk periods were not present in the meta-analysis. In the group with indication LRTI in CPRD GOLD there were significant decreased associations between doxycycline and suicide-related events without death in the -30-0 day risk period (uncalibrated IRR 0.83, 95% CI [0.71-0.96]), the 1-30 day risk period (uncalibrated IRR 0.72, 95% CI [0.61-0.84]), the 31-60 days risk period (uncalibrated IRR 0.81, 95% CI [0.70-0.94]), the -90-0 day risk period (uncalibrated IRR 0.85, 95% CI [0.77-0.93]) and the 1-90 day risk period (uncalibrated IRR 0.83, 95% CI [0.76-0.91]). In IPCI and SIDIAP no estimates could be produced for the outcome of suicide-related events without death in individuals with LRTI. There were no associations in patients with acne, rosacea or chlamydia between doxycycline and suicide-related events without death.

In the overall group with any indication for the outcome anxiety in CPRD there were significant increased associations between doxycycline and anxiety in the 31-60 day risk period (uncalibrated IRR 1.09, 95% CI [1.05-1.12]; the 61-90 day risk period (uncalibrated IRR 1.06, 95% CI [1.02-1.09]), the >90 day risk period (uncalibrated IRR 1.13, 95% CI [1.00-1.27]) and the 1-90 day risk period (uncalibrated IRR 1.07, 95% CI [1.05-1.09]). Similar increased associations were seen In IPCI in the -90-0 and 1-90 day risk periods (uncalibrated IRRs 1.30, 95% CI [1.27-1.34] and 1.05, 95% CI [1.02-1.08] respectively) and in SIDIAP in the >90 day risk period (uncalibrated IRR 1.18, 95% CI [1.03-1.35]). In the meta-analysis in the overall group there were significant associations between doxycycline and anxiety in the 61-90 day risk period (uncalibrated IRR 1.04, 95% CI [1.01-1.08]), the >90 day risk period (uncalibrated IRR 1.15, 95% CI [1.06-1.25]), the -90-0 day risk period (uncalibrated IRR 1.30, 95% CI [1.27-1.34]) and the 1-90 day risk period (uncalibrated IRR 1.06, 95% CI[1.04-1.08]). In the group with acne in CPRD GOLD the 1-30 day risk period there was a significant decreased association between doxycycline and anxiety (uncalibrated IRR 0.89, 95% CI [0.79-0.99]) and non-significant association in the 1-90 day risk period (uncalibrated IRR 0.94, 95% CI [0.88-1.00]). In IPCI there were non-significant associations between doxycycline and anxiety in the 1-30 day risk period (uncalibrated IRR 0.82, 95% CI [0.66-1.00]) and the 1-90 day risk period (uncalibrated IRR 0.91, 95% CI [0.80-1.02]. In the meta-analysis the decreased associations in both the 1-30 and 1-90 day risk period were statistically significant (uncalibrated IRRs 0.87, 95% CI [0.79-0.96] and 0.93, 95% CI [0.88-0.99] respectively).

In IPCI there was a statistically significant decreased association between doxycycline and anxiety in the >90 and 1-90 day risk periods in the group with rosacea (uncalibrated IRRs 0.40, 95% CI [0.16-0.87] and 0.78, 95% CI [0.63-0.96] respectively) and non-statistically significant increased association in the -90-0 day risk period (uncalibrated IRR 1.19, 95% CI [0.99-1.44]). In CPRD there were no associations identified between doxycycline and anxiety in the >90 day risk period (uncalibrated IRR 1.10, 95% CI [0.84-1.43]) and the 1-90 day risk period (uncalibrated IRR 1.04, 95% CI [0.93-1.15]). Similarly, there were no associations in SIDIAP in the >90 day risk period (uncalibrated IRR 0.96, 95% CI [0.65-1.40]), the -90-0 day risk period (uncalibrated IRR 1.17, 95% CI [0.93-1.46]) and the 1-90 day risk period (uncalibrated IRR 1.06, 95% CI [0.87-1.28]) identified. In the meta-analysis of patients with rosacea and outcome anxiety there was only a

statistically significant increased association between doxycycline and anxiety in the -90-0 day risk period (uncalibrated IRR 1.18, 95% CI [1.03-1.37]). In patients with LRTI there were statistically significant increased associations between doxycycline and anxiety in the -90-0 risk day period in IPCI and SIDIAP (uncalibrated IRRs 1.14, 95% CI [1.06-1.23] and 1.25, 95% CI [1.13-1.37] respectively) and the 1-90 day risk period in SIDIAP (uncalibrated IRR 1.12, 95% CI [1.02-1.14]). In IPCI there were no associations in the 31-60 and the 1-90 day risk period (uncalibrated IRRs 1.07, 95% CI [0.96-1.18]) and 1.03, 95% CI [0.97-1.10]) respectively). In SIDIAP there was also no association in the 31-60 day risk period (uncalibrated IRR 1.14, 95% CI [0.97-1.34]). In the meta-analysis of the group with LRTI with outcome anxiety there were there were statistically significant increased associations in the 31-60 day risk period (uncalibrated HR 1.06, 95% CI [1.02-1.11]) and the 1-90 day risk period (uncalibrated IRR 1.05, 95% CI [1.02-1.08]). There were no associations in patients with chlamydia between doxycycline and outcome anxiety.

In the overall group for the outcome depression in IPCI there were statistically significant increased associations between doxycycline and depression in the -90-0 day risk period (uncalibrated IRR 1.10, 95% CI [1.05-1.15]) and the 1-90 day risk period (uncalibrated IRR 1.07 [1.02-1.13]) and no associations in the 61-90 day risk period (uncalibrated IRR 1.00, 95% CI [0.92-1.08]) and in the >90 day risk period (uncalibrated IRR 0.77 [0.50-1.14]). In SIDIAP there was a statistically significant increased association in the 61-90 day risk period (uncalibrated 1.16, 95% CI [1.01-1.32]) and no association in the >90 day risk period (uncalibrated IRR 1.02, 95% CI [0.81-1.26]). In CPRD there was a statistically significant increased association between doxycycline and depression in the 61-90 day risk period (uncalibrated IRR 1.07, 95% CI [1.03-1.11]) and no statistically significant associations in the >90 day risk period (uncalibrated IRR 0.98, 95% CI [0.87-1.10]) and the 1-90 day risk period (uncalibrated IRR 1.02, 95% CI [0.99-1.04]). In the meta-analysis of the overall group with any indication there was only no significant association between doxycycline and depression in the >90 day risk period (uncalibrated IRR 0.97, 95% CI [0.88-1.07]), while there were no results for the other risk periods.

In CPRD in the group with indication acne there were statistically significant decreased associations between doxycycline and depression in the 1-30 day risk period (uncalibrated IRR 0.80, 95% CI [0.71-0.90]) and the 1-90 day risk period (uncalibrated IRR 0.90, 95% CI [0.84-0.97]). In IPCI there were no associations in the 1-30 day risk period (uncalibrated IRR 1.11, 95% CI [0.83-1.45]) and in the 1-90 day risk period (uncalibrated IRR 0.98, 95% CI [0.81-1.16]). In SIDIAP there were no estimates produced for the 1-30 and 1-90 day risk periods. In the meta-analysis of in the indication with outcome depression there was a statistically significant decreased association in the 1-90 day risk period (uncalibrated IRR 0.91, 95% CI [0.86-0.97]). In the group with indication chlamydia in CPRD GOLD there was a statistically significant increased association between doxycycline and depression in the >90 day risk period (uncalibrated IRR 7.48, 95% CI [1.32-31.30]). In IPCI and SIDIAP and the meta-analysis there were no associations present in the group with indication chlamydia. In the group with indication LRTI there was a statistically significant increased association in the -90-0 day risk period (uncalibrated IRR 1.15, 95% CI [1.12-1.19]) for CPRD GOLD. In CPRD GOLD there were no associations in the 1-90 day risk period (uncalibrated IRR 1.01, 95% CI [0.98-1.04]). In SIDIAP there was a statistically significant increased association in the 1-90 day risk period (uncalibrated IRR 1.18, 95% CI [1.02-1.35]) and no statistically significant association in the -90-0 day risk period (uncalibrated IRR 1.14, 95% CI [0.99-1.32]). Lastly, in IPCI there were no associations in the -90-0 day risk period (uncalibrated IRR 1.01, 95% CI [0.89-1.13]) and the 1-90 day risk period (uncalibrated IRR 1.06, 95% CI [0.96-1.17]). In the meta-analysis there were no associations in the group with indication LRTI. In the group with indication rosacea and outcome depression there were no associations in any of the risk periods in CPRD GOLD, IPCI, SIDIAP and the meta-analysis.

14.2 Limitations of the research methods

There are some limitations in the study design and data sources. *First*, the standard SCCS method cannot account for outcomes which have influence on the potentiality of future events. In case of concerns of a potential violation, the extended SCCS as recommended by Farrington et al. can be used but this method cannot be applied for death as an outcome. For this reason, we could not study suicide as an outcome in the SCCS but used the extended SCCS method on the outcome suicide-related events (attempt, ideation and self-harm) as recommended by Farrington et al.[36] This often meant that deviations in an otherwise consistent time-trend cannot be adjusted for via splines. The analyses were there more likely to fail time-trend diagnostic tests. *Second*, the recording of suicide and suicide related events might be under-reported in EHR. Severe events are more likely to be known to the clinician and are therefore more likely to be recorded. Linkages of the primary care to the secondary care data could enrich the data by potentially capturing more events, but using these data sources was not feasible for the data partners other than SIDIAP within the timeframe of the study. *Third*, the exposure to the drugs of interest might be overestimated as prescription and no dispensing records were used. *Forth*, misclassification of the indication is likely, especially in the SCCS study as we used a recorded diagnosis ever before to classify indication of use to increase power. *Fifth*, it was not possible to include certain factors in the large-scale propensity score calculation including family history, lifestyle factors, educational level and socioeconomic status because these are not routinely available in the data sources. To minimise the resulting residual confounding, we used empirical calibration by use of negative control outcomes to assess whether there were any differences after calibration which suggest unmeasured confounding. *Sixth*, we only took the first outcome into account in the SCCS analysis due to the risk of repeating the occurrence of the outcome in subsequent visits (which would violate one of the assumptions namely that occurrences of events should be independent of each other). This can result in bias in if the observation time becomes relatively long.[37] However, this may not apply to the SCCS we performed, as the total observation time per subject is low so bias would be minimised. *Seventh*, the active comparators were chosen to minimise confounding by indication in the new-user cohort study. However, the drugs chosen were likely not used in the same way in the different countries studied which relates to local guidelines. *Finally*, sample size was often too low to study the association between doxycycline and suicide or the composite endpoint of suicide-related events (suicide ideation, self-harm or suicide attempts) in the cohort study. Section 8.7 describes the sample size calculation for the outcomes of interest and for all the outcomes, a high sample size is needed (for a RR of 2) when assuming a 30-day follow-up time following treatment initiation. Power was less of a concern for the SCCS, but this analysis cannot assess association of doxycycline with completed suicide as outcome.

14.3 Interpretation

In individuals with acne, we observed an association between doxycycline on the risk of suicide-related events compared to erythromycin which culminates in a meta-analytic estimate HR of 2.47 (95% CI [1.18-5.17]), largely driven by findings from SIDIAP (uncalibrated HR 3.77, 95% CI [1.03-17.80]), and CPRD GOLD to a lesser extent (uncalibrated HR 1.71, 95% CI [0.74-4.07]). We did not have results that passed diagnostics in IPCI due to low counts leading to underpowered results. Low counts in IPCI was likely because the comparator erythromycin is more often used topically than orally in the Netherlands for the treatment of acne, and we excluded topical treatment in our phenotype.[38] This association was not observed by the SCCS, in fact, for SIDIAP, we observed an increased risk of suicide-related events in the pre-exposure period days -30 to 0 in persons with acne with an uncalibrated IRR of 1.91 (95% CI [0.94-3.42]), although this association was not seen in CPRD GOLD data (uncalibrated IRR 0.97, 95% CI [0.71-1.29]). This increased risk prior to treatment initiation suggests that the condition itself negatively affects psychological well-being which might lead to suicide-related events in the period prior to receiving treatment. This would certainly hold for more severe acne requiring systemic treatment. Furthermore, there are some small differences between the calibrated a non-calibrated results of the association between doxycycline and

suicide-related events in acne patients in the cohort study suggesting the potential for the presence of unmeasured confounding. Also, there was an increased risk of anxiety identified in the SCCS in the pre-exposed window -30 to 0 days, with an uncalibrated IRR in IPCI of 1.30 (95% CI [1.27-1.34]). When restricted to the indication of acne, there was a small decreased risk of anxiety observed in the first risk window 1-30 days in CPRD GOLD (uncalibrated IRR, 95% CI [0.79-0.99]) and IPCI (uncalibrated IRR 0.82, 95% CI 0.66-1.00]). This is perhaps confounded by the effect of treatment successfully treating symptoms, thereby reducing the risk of anxiety which may in turn have some impact suicide-related events. The later exposure windows identified no associations.

In contrast to the increased risk of suicide-related events in acne patients, we found a reduced risk of doxycycline versus amoxicillin in patients with LRTI in the cohort study (uncalibrated HR 0.40, 95% CI [0.15-0.87]). This cohort of patients had different characteristics to the cohort of acne patients, as the patients within the LRTI cohorts, were older and use of doxycycline was much shorter compared to when used to treat acne, which often spans into months rather than one week as with LRTI treatment. In addition, the active comparator within the LRTI cohort was amoxicillin which may be prescribed along with clavulanic acid for the treatment of severe LRTI, thereby presenting as potential confounding by indication from severity with those with increased morbidity having a reduced risk of the outcome.[39]

Doxycycline slightly increased the risk of anxiety outcomes compared to erythromycin in acne patients (meta-analytic HR 1.19, 95% CI [0.97-1.46]). This increased risk of anxiety outcomes was more pronounced when compared to isotretinoin use (meta-analytic HR 1.65, 95% CI [1.05-2.60]). We found an increased risk of depression in the cohort study meta-analysis for patients with acne, particularly high in SIDIAP with a calibrated IRR of 1.81 (95% CI [1.05-3.12]). This association was confirmed (but with a smaller increased risk estimate) in the SCCS study in SIDIAP, when unrestricted to indication in longer use (days 61-90, calibrated IRR 1.16, 95% CI [0.99-1.36]). We found a reduced risk of doxycycline for the outcomes anxiety and depression in rosacea patients in the self-controlled case series study. For example, for the outcome anxiety in the window of days 1-90 following doxycycline initiation in IPCI, the calibrated IRR was 0.69 (95% CI [0.56-0.85]). A possible explanation could be due to time-varying confounding with the improvement of symptoms of rosacea, as the effect strengthens with longer use, as we do not see these improvements against the active comparator (erythromycin) in the cohort study in CPRD GOLD.

Despite widespread use of doxycycline, recent concerns have been raised about the potential neuropsychiatric side effects of doxycycline, particularly regarding suicidality, including suicidal ideation, attempts, and completed suicide.[2-4, 40] Some case study reports and epidemiological studies have suggested a possible link between doxycycline and enhanced risks of psychiatric symptoms, including depression and anxiety, which are known risk factors for suicidality, which we see reflected in our results particularly in acne patients.[3, 4, 40] Against other tetracyclines including minocycline and tigecycline, safety signals from doxycycline from depression and suicide seem to be noticeably greater in the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database.[41] Older case reports on the association between doxycycline and suicide ideation suggest genetic polymorphism (CYP2C19*2 heterozygote genotype) as one of the contributing factors. However, in observational studies, association between doxycycline and outcomes of suicide and depression are less well studied until now.[5]

Literature on use of doxycycline and potential association with depression is conflicting. Recent pre-clinical studies demonstrated a potentially anti-depressant effect of doxycycline by in mice mediated by inhibition of nitric oxide which is associated with stress exposure, or by protecting against inflammation associated with depression.[42, 43] However these observations may differ in humans, in the situation of skin conditions where biological effects are not the only in the association pathway of doxycycline and psychiatric symptoms.[44-49]

This potential protective effect on mental illness has been investigated in observational research. In a recent study using data from the Swedish registry, Upmark et al. found no association between doxycycline use and non-affective psychosis, but an increased risk of bipolar disorder but similar associations were seen with other antibiotics.[50] De Witte et al. found a sex-related association of doxycycline with schizophrenia risk, with doxycycline use increased the risk of schizophrenia onset in women, and decreased the risk in men, which was not observed for other tetracycline antibiotics.[51] Another cohort study which analysed minocycline use for acne, a different tetracycline antibiotic, appeared to have no protective effect on the incidence of severe mental illness, perhaps indicating it may not be a class effect.[45]

Confounding by indication and confounding by severity is a potential issue when analysing the association between doxycycline and outcomes like suicidality, depression and anxiety. Confounding by indication was a contributing reason to our use of the SCCS study design and new-user cohort per indication. However potential confounding by severity remains a concern. Severe acne is often alternatively treated with isotretinoin and recent evidence based on a meta-analysis from 25 observational studies suggests no increased risk of suicide or psychiatric conditions for the use of isotretinoin.[52] Unfortunately, because of limited data, there are yet no meta-analysis data exploring the association between use of doxycycline and suicide (attempts), anxiety or depression.

14.4 Generalisability

We used electronic healthcare data from three data sources across three European countries which increased the generalisability of our results to the wider European region. These data sources included primary healthcare data and so represent the broadest part of the healthcare pathway and each of the data sources have a wide coverage in the area they represent. There are differing prescribing and healthcare practices within the countries studied here, which may also differ to countries outside of those included. Generalisability to regions outside of Europe depends on the healthcare system, demographics, and prescribing practices of doxycycline of the region in question.

14.5 Other information

None.

15. CONCLUSION

In this drug safety study using two study designs across three European electronic healthcare databases, we identified a two-fold increased association of suicide-related events with doxycycline use compared to erythromycin use in acne patients in the cohort study. However, these findings were not consistent and we also found an increased risk of non-fatal suicide-related events in the pre-exposure period in the SCCS study, showing there is uncertainty around the causality of the association with non-fatal suicide-related events we find in doxycycline use. We found a smaller but increased association of anxiety with doxycycline use compared to erythromycin and isotretinoin, as well as an increased risk of depression with doxycycline use compared to erythromycin in patients with acne. We did not observe these increased associations for other indications in the cohort study, and in addition, many of the analyses remained blinded due to non-passing of diagnostic tests. In contrast to the increased risk of psychiatric outcomes we found in acne patients, we observed a reduced risk of suicide-related events in doxycycline versus amoxicillin in LRTI patients in the cohort study.

Although we observed an association between use of doxycycline and suicide related events in individuals with acne, this could not be confirmed in the SCCS, where an increased risk in the pre-exposure period was observed. Studying the association between use of doxycycline and suicide related events in a population of individuals with acne might have been hindered by confounding. It is possible that conditions such as (severe) acne that impact self-esteem, especially in adolescents, might ultimately result in suicidal ideation and attempts.

16. REFERENCES

1. Holmes, N.E. and P.G.P. Charles, *Safety and Efficacy Review of Doxycycline.* Clinical Medicine. Therapeutics, 2009. **1**: p. CMT.S2035.
2. Essali, N. and B.J. Miller, *Psychosis as an adverse effect of antibiotics.* Brain Behav Immun Health, 2020. **9**: p. 100148.
3. Lee, J.-W., H. Lee, and H.-Y. Kang, *Association between depression and antibiotic use: analysis of population-based National Health Insurance claims data.* BMC Psychiatry, 2021. **21**(1): p. 536.
4. Lurie, I., et al., *Antibiotic exposure and the risk for depression, anxiety, or psychosis: a nested case-control study.* J Clin Psychiatry, 2015. **76**(11): p. 1522-8.
5. Atigari, O.V., C. Hogan, and D. Healy, *Doxycycline and suicidality.* BMJ Case Rep, 2013. **2013**.
6. Herrett, E., et al., *Data Resource Profile: Clinical Practice Research Datalink (CPRD).* International Journal of Epidemiology, 2015: p. 827-836.
7. Carey, I.M., et al., *Prevalence of co-morbidity and history of recent infection in patients with neuromuscular disease: A cross-sectional analysis of United Kingdom primary care data.* PLoS One, 2023. **18**(3): p. e0282513.
8. Wigglesworth S, N.A., Dickson JM, Pullen A, Yelland E, Anjuman T, Reuber M., *The incidence and prevalence of epilepsy in the United Kingdom 2013-2018: A retrospective cohort study of UK primary care data.* Seizure, 2023. **105**: p. 37-42.
9. Fahmi, A., et al., *Combinations of medicines in patients with polypharmacy aged 65–100 in primary care: Large variability in risks of adverse drug related and emergency hospital admissions.* PLOS ONE, 2023. **18**(2): p. e0281466.
10. de Ridder, M.A.J., et al., *Data Resource Profile: The Integrated Primary Care Information (IPCI) database, The Netherlands.* Int J Epidemiol, 2022. **51**(6): p. e314-e323.
11. James, G., et al., *Treatment pathway analysis of newly diagnosed dementia patients in four electronic health record databases in Europe.* Soc Psychiatry Psychiatr Epidemiol, 2021. **56**(3): p. 409-416.
12. Engelkes, M., et al., *Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study.* Pediatr Allergy Immunol, 2020. **31**(5): p. 496-505.
13. Baan, E.J., et al., *Hair cortisol and inhaled corticosteroid use in asthmatic children.* Pediatr Pulmonol, 2020. **55**(2): p. 316-321.
14. Ali, M.S., et al., *Comparative cardiovascular safety of strontium ranelate and bisphosphonates: a multi-database study in 5 EU countries by the EU-ADR Alliance.* Osteoporos Int, 2020. **31**(12): p. 2425-2438.
15. Berencsi, K., et al., *Impact of risk minimisation measures on the use of strontium ranelate in Europe: a multi-national cohort study in 5 EU countries by the EU-ADR Alliance.* Osteoporos Int, 2020. **31**(4): p. 721-755.

16. Recalde, M., et al., *Data Resource Profile: The Information System for Research in Primary Care (SIDIAP).* Int J Epidemiol, 2022. **51**(6): p. e324-e336.
17. Ly, N.F., et al., *Impact of European Union Label Changes for Fluoroquinolone-Containing Medicinal Products for Systemic and Inhalation Use: Post-Referral Prescribing Trends.* Drug Saf, 2023. **46**(4): p. 405-416.
18. Recalde, M., et al., *Body mass index and waist circumference in relation to the risk of 26 types of cancer: a prospective cohort study of 3.5 million adults in Spain.* BMC Med, 2021. **19**(1): p. 10.
19. Ramos, R., et al., *Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study.* Bmj, 2018. **362**: p. k3359.
20. Burn, E., et al., *The natural history of symptomatic COVID-19 during the first wave in Catalonia.* Nat Commun, 2021. **12**(1): p. 777.
21. Mata-Cases, M., et al., *Therapeutic inertia in patients treated with two or more antidiabetics in primary care: Factors predicting intensification of treatment.* Diabetes Obes Metab, 2018. **20**(1): p. 103-112.
22. Lane, J.C., et al., *Preschool Obesity Is Associated With an Increased Risk of Childhood Fracture: A Longitudinal Cohort Study of 466,997 Children and Up to 11 Years of Follow-up in Catalonia, Spain.* J Bone Miner Res, 2020. **35**(6): p. 1022-1030.
23. Monteagudo, M., et al., *Treatment Pathways Before and After Triple Therapy in COPD: A Population-based Study in Primary Care in Spain.* Arch Bronconeumol (Engl Ed), 2021. **57**(3): p. 205-213.
24. Ortega, Y., et al., *Impact of depression and/or anxiety on the presentation of cardiovascular events in a cohort with metabolic syndrome. StreX project: Five years of follow-up.* Prim Care Diabetes, 2018. **12**(2): p. 163-171.
25. Troncoso-Mariño, A., et al., *Medication-related problems in older people in Catalonia: A real-world data study.* Pharmacoepidemiol Drug Saf, 2021. **30**(2): p. 220-228.
26. Braeye, T., et al., *Age-specific vaccination coverage estimates for influenza, human papillomavirus and measles containing vaccines from seven population-based healthcare databases from four EU countries - The ADVANCE project.* Vaccine, 2020. **38**(16): p. 3243-3254.
27. Daniel Prieto Alhambra, F.D., George Corby, Abigail Robinson, James Bezer, Rowan Parry, Annika M. Jo¨dicke, Talita Duarte-Salles, Peter Rijnbeek, Katia Verhamme, Alexandra Pacurariu, Daniel Morales, Lu´ıs Pinheiro, and Albert Prats-Uribe, *Standardised and reproducible phenotyping using distributed analytics and tools in the Data Analysis and Real World Interrogation Network (DARWIN EU®).* Pharmacoepidemiology and Drug Safety (preprint), 2024.
28. Petersen, I., I. Douglas, and H. Whitaker, *Self controlled case series methods: an alternative to standard epidemiological study designs.* BMJ, 2016. **354**: p. i4515-i4515.
29. Song, A., et al., *Suicide risk of chronic diseases and comorbidities: A Korean case-control study.* J Affect Disord, 2024. **349**: p. 431-437.
30. Rockett, I.R., et al., *Suicide-associated comorbidity among US males and females: a multiple cause-of-death analysis.* Inj Prev, 2007. **13**(5): p. 311-5.
31. Eurostat. *Deaths by suicide down by almost 14% in a decade*. 2023; Available from: https://ec.europa.eu/eurostat/web/products-eurostat-news/w/edn-20230908-3#:~:text=In%202020%2C%20there%20were%2047,deaths%20per%20100%20000%20people.
32. Jakobsen, S.G., et al., *Definitions and incidence rates of self-harm and suicide attempts in Europe: A scoping review.* J Psychiatr Res, 2023. **164**: p. 28-36.

33. Mar, J., et al., *Incidence of mental disorders in the general population aged 1-30 years disaggregated by gender and socioeconomic status.* Soc Psychiatry Psychiatr Epidemiol, 2023. **58**(6): p. 961-971.
34. Schuemie M, S.M., Ryan P, *CohortMethod: New-User Cohort Method with Large Scale Propensity and Outcome Models*. 2024.
35. Schuemie M, R.P., Shaddox T, Suchard M *SelfControlledCaseSeries: Self-Controlled Case Series. R package version 5.2.2*. 2024.
36. Farrington, C.P., et al., *Self-Controlled Case Series Analysis With Event-Dependent Observation Periods.* Journal of the American Statistical Association, 2011. **106**(494): p. 417-426.
37. Whitaker, H.J., C.D. Steer, and C.P. Farrington, *Self-controlled case series studies: Just how rare does a rare non-recurrent outcome need to be?* Biom J, 2018. **60**(6): p. 1110-1120.
38. Bruinsma M, D.R.W., Jaspar AHJ, Van der Zee HH,Van Vugt SF, Verhoeven ICL, Verstappen V en Wiersma TJ. *NHG-Richtlijnen Acne*. 2024; Available from: https://richtlijnen.nhg.org/standaarden/acne#volledige-tekst.
39. Woodhead, M., et al., *Guidelines for the management of adult lower respiratory tract infections--full version.* Clin Microbiol Infect, 2011. **17 Suppl 6**(Suppl 6): p. E1-59.
40. Atigari, O.V., C. Hogan, and D. Healy, *Doxycycline and suicidality.* BMJ Case Reports, 2013. **2013**: p. bcr2013200723.
41. Qiao, Y., et al., *Safety profiles of doxycycline, minocycline, and tigecycline in pediatric patients: a real-world pharmacovigilance analysis based on the FAERS database.* Front Pharmacol, 2024. **15**: p. 1413944.
42. Sales, A.J., et al., *The antidepressant-like effect of doxycycline is associated with decreased nitric oxide metabolite levels in the prefrontal cortex.* Behav Brain Res, 2024. **458**: p. 114764.
43. Wilbert, J.K.W., et al., *A 24-Week, Worldwide, Multicenter, Double-Blind, Randomized, Parallel, Placebo-Controlled Study to Assess the Efficacy and Tol- erability of Anacetrapib When Added to Ongoing Statin Therapy With or Without Other Lipid Modifying Medication(s) in Patients w.* 2016. **2**(2): p. 1-18.
44. Christensen, R.E. and M. Jafferany, *Psychiatric and psychologic aspects of chronic skin diseases.* Clin Dermatol, 2023. **41**(1): p. 75-81.
45. Herrero-Zazo, M., et al., *Examining the potential preventative effects of minocycline prescribed for acne on the incidence of severe mental illnesses: A historical cohort study.* J Psychopharmacol, 2018. **32**(5): p. 559-568.
46. Halvorsen, J.A., et al., *Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study.* J Invest Dermatol, 2011. **131**(2): p. 363-70.
47. Dalgard, F., et al., *Self-esteem and body satisfaction among late adolescents with acne: results from a population survey.* J Am Acad Dermatol, 2008. **59**(5): p. 746-51.
48. Picardi, A., I. Lega, and E. Tarolla, *Suicide risk in skin disorders.* Clin Dermatol, 2013. **31**(1): p. 47-56.
49. Barlow, R., et al., *Suicide and Suicidality in Children and Adolescents with Chronic Skin Disorders: A Systematic Review.* Acta Derm Venereol, 2023. **103**: p. adv00851.
50. Upmark, F., et al., *Doxycycline exposure during adolescence and future risk of non-affective psychosis and bipolar disorder: a total population cohort study.* Transl Psychiatry, 2021. **11**(1): p. 468.
51. de Witte, L.D., et al., *A Sex-Dependent Association Between Doxycycline Use and Development of Schizophrenia.* Schizophr Bull, 2023. **49**(4): p. 953-961.
52. Tan, N.K.W., et al., *Risk of Suicide and Psychiatric Disorders Among Isotretinoin Users: A Meta-Analysis.* JAMA Dermatol, 2024. **160**(1): p. 54-62.

17. ANNEXES

Appendix I: List of outcome definitions.

Appendix Table 1. List of outcome definitions.

Concept	Concept IDs (including descendants)	Exclude
Observation of completed suicide	440925	none
Observation of suicide and suicide-related (completed suicide, attempted suicide, suicide ideation, and self-harm)	440925,600767,4219484,4303690	none
Condition occurrence of suicide and suicide-related (completed suicide, attempted suicide, suicide ideation, and self-harm)	608248,4021336,4021339,4037303,4190443, 4214582,4216115,4257906,44814145	none
Depression	440383,40546087	44782943,44813499,35 622958
Anxiety	441542	none

Appendix Table 2. List of indication definitions.

Concept	Concept IDs (including descendants)	Exclude
Acne vulgaris	4227594	none
Rosacea	136773	none
Chlamydia	438066,4133775,4212724	none
Lower respiratory tract infection (Community-acquired pneumonia and bronchitis)	256451,4175297,4293463	none

Appendix Table 3. List of exposure definitions.

Concept	Concept IDs (including descendants)	Excluded
Doxycycline	1738521	1525128,35806103,35861018
Isotretinoin	984232	19002679,19009781,19017195,19104685,19104847,21022612,21034307,21039265,21049051,21049069,21061866,21068752,21081480,21081481,21083459,21093225,21098112,21098113,21103114,21103117,21107967,21112974,21120630,21127445,21127461,21132403,21142335,21147174,21157177,21169939,21171846,21176705,35806907,35848129,36220240,36221888,36224731,36923028,36923543,36930243,36934660,36936678,36942618,36951381,36954582,36955288,36957094,36957330,36959746,36968439,40040110,40052514,40052515,40052516,40705798,40705799,40705800,40705801,40705802,40705803,40705804,40705805,40705806,40705807,40754296,40754297,40754302,40754303,40754304,40754305,40754306,40754308,40754309,40844462,40866689,40875667,40875672,40897836,40928924,40960223,40968943,40991454,40991455,41031357,41062480,41062487,41085248,41125275,41125279,41159001,41179005,41219104,41221310,41241397,41250151,41269331,41280945,41303382,41303383,41487925,41488827,41489228,41489311,41489445,41489699,41489845,41489908,41490671,41491728,41492997,41493614,41493750,41493775,41493986,41494035,41494120,41494183,41494246,41494465,41494786,41494905,41494906,41494907,41495035,41496426,41496569,41497633,41497891,41498219,41499683,41499813,41500585,41501056,41501291,41501292,41501486,41501973,41502058,41502171,41502409,41502433,41502445,41502539,41502616,41502679,42483149,43044896,43134187,43134188,43134189,43142390,43153527,43161320,43164547,43164613,43164614,43167250,43183226,43183227,43197484,43205176,43208371,43208407,43219414,43219415,43586898,43592853,43593453,43607628,43610936,43610937,43611415,43613183,43628373,43629251,43645368,43646504,43646505,43647031,43649442,43661951,43664642,43665150,43665151,43665274,43677227,43681739,43683038,43683157,43685426,43695042,43701057,43701058,43701059,43701346,43701626,43703324,43717126,43718907,43719327,43735673,43736390,43736884,43736885,43737160,43737161,43748800,43748801,43753521,43754278,43754944,43769630,43769631,43773098,43773414,43775150,43790648,43790762,43790950,43791225,43791226,43808915,43809394,43823608,43823609,43826362,43827116,43827411,43838999,43845053,43845528,43845529,43861494,43862627,43862628,43863438,43863439,43865580,44034410,44076015,44110074
Erythromycin	1746940	783828,783829,784838,784839,784840,918363,1235628,1593644,1593645,1593646,1746940,1747050,1747078,1747104,1747107,1747292,1747330,1747331,1747353,2022575,2022576,2022577,2023792,2023793,2023794,2050016,2050017,19002458,19002459,19008692,19017195,19031037,19031651,190316

Concept	Concept IDs (including descendants)	Excluded
		52,19031653,19031654,19031655,19031656,19031659,19031660,19031741,19031742,19031743,19031744,19031745,19031746,19031747,19031748,19031749,19047522,19060707,19060911,19061197,19063408,19063438,19076953,19076954,19076956,19082703,19096594,19101783,19105446,19105889,19118051,19118052,19124901,19128233,19131817,21022591,21022612,21022613,21022614,21022615,21029420,21029490,21032339,21032340,21032353,21037669,21039252,21039491,21042287,21049015,21049051,21052056,21052057,21058713,21058810,21059064,21061850,21061866,21061867,21061868,21068175,21068708,21068783,21068991,21071756,21071761,21071762,21071777,21071779,21078499,21078500,21078619,21081472,21081480,21081481,21081482,21081483,21088169,21088240,21088383,21088493,21091204,21091217,21096565,21098100,21098146,21101112,21101121,21107967,21108199,21110957,21117710,21120630,21127445,21127493,21130412,21137359,21137360,21137404,21147174,21147276,21150201,21157056,21157122,21157199,21157200,21157284,21160125,21160132,21160133,21160134,21160143,21166335,21167018,21169939,21169940,21176760,21176761,35132759,35141083,35141610,35144461,35151763,35155212,35162057,35790648,35790824,35794110,35794113,35794195,35794262,35794278,35794328,36055766,36061832,36119168,36119169,36121444,36121445,36121789,36218160,36220240,36220243,36220244,36220246,36220247,36220252,36221502,36227990,36228388,36228940,36229123,36229155,36232428,36233342,36233351,36233352,36233353,36233358,36233361,36234211,36234256,36236451,36237067,36237354,36243235,36243940,36246047,36259244,36259469,36260485,36260486,36263055,36264572,36267093,36268424,36272462,36272463,36277303,36280520,36280523,36280526,36280663,36280678,36280786,36281586,36281593,36283231,36283232,36283233,36777681,36777682,36777683,36778644,36778645,36779085,36779087,36779088,36779089,36779379,36779380,36779381,36783605,36783606,36783607,36783608,36783609,36783610,36783616,36787175,36787176,36880317,36882917,36886642,36925356,36925806,36926074,36932318,36940776,36943337,36944050,36956123,36964194,40015668,40015671,40040110,40040112,40040113,40040114,40040115,40041238,40041239,40041269,40041270,40041271,40041272,40041273,40041274,40041275,40041276,40041277,40041278,40041279,40041280,40041281,40041282,40041283,40041284,40041285,40041286,40041287,40041288,40041289,40041292,40112579,40112646,40126022,40153421,40169033,40169060,40169061,40705016,40705017,40705019,40705020,40705021,40705022,40705023,40705024,40705025,40705798,40705799,40705800,40705975,40705976,40705977,40706037,40706038,40706039,40706040,40706041,40706587,40706588,40706820,40708561,40712747,40713863,40713974,40713975,40726396,40726425,40726441,40726442,40726443,40741904,40741905,40754296,40754297,40821079,40822051,40831103,40832478,40832479,40836488,40836490,40836495

Concept	Concept IDs (including descendants)	Excluded
		,40846671,40846672,40846684,40846685,40846686,40846688,40846689,40846690,40846709,40863672,40863673,40867570,40867571,40867574,40877802,40877803,40877810,40877811,40877812,40877815,40877832,40894890,40898674,40898687,40908841,40908857,40908858,40908861,40908863,40908864,40908865,40909987,40925868,40926123,40929773,40929787,40940096,40940097,40940098,40940120,40940122,40940123,40940125,40940126,40940127,40940128,40940129,40940146,40957134,40957135,40961104,40961105,40961107,40971130,40971131,40971132,40972317,40992356,41002462,41002475,41002477,41002498,41002499,41019340,41023279,41025679,41033568,41033572,41033573,41033574,41033578,41033596,41033597,41033604,41033605,41037898,41050623,41054532,41054541,41055123,41055124,41064707,41064710,41064712,41064713,41064733,41064734,41080198,41080200,41082116,41082117,41083219,41086107,41086114,41086123,41096275,41096276,41096283,41096287,41096288,41096289,41096293,41096294,41096306,41096307,41096308,41111587,41113347,41113348,41117334,41117338,41117342,41127529,41127530,41127549,41127550,41127553,41127575,41141617,41143036,41144945,41144946,41148821,41158999,41159000,41159001,41159028,41159047,41159048,41159049,41159050,41159056,41175899,41175900,41175902,41179904,41179905,41179912,41179915,41179922,41182210,41190149,41190150,41190154,41190158,41190160,41190162,41190179,41190180,41194566,41204231,41221310,41221311,41221322,41221323,41221324,41221345,41238380,41238381,41242248,41242249,41242250,41242253,41242257,41242804,41252308,41252314,41252315,41252317,41252318,41252319,41252321,41252323,41252342,41267438,41269331,41269332,41269333,41283205,41283206,41283210,41283211,41283213,41283214,41283215,41283240,41283241,41284422,41300327,41304207,41304211,41304214,41304217,41314485,41314486,41314507,41314515,41314516,41314517,41314518,41314519,41314536,41314537,41314538,41314539,41383713,41383716,41383854,41383978,41384004,41384115,41384116,41384150,41384151,41384185,41384342,41384343,41384376,41384405,41384473,41384517,41384593,41384622,41384623,41384649,41384694,41384751,41384752,41385212,41386439,41386944,41386945,41388258,41388259,41388260,41388634,41388690,41388968,41389095,41389096,41389183,41391953,41392162,41393515,41393680,41393872,41394260,41395875,41396222,41397009,41397162,41398063,41398543,41398544,41398548,41398768,41400101,41400637,41400639,41401696,41401797,41401813,41402162,41402211,41402248,41402386,41402559,41402577,41402605,41469524,41469528,41469535,41469568,41469577,41469582,41469586,41469610,41472484,41472602,41472681,41472756,41473234,41487848,41487937,41487938,41487972,41488048,41488072,41488073,41488096,41488097,41488098,41488099,41488100,41488123,41488124,41488170,41488171,41488208,41488209,41488243,41488244,41488245,41488252,41488294,4

Concept	Concept IDs (including descendants)	Excluded
		1488295,41488338,41488380,41488393,41488394,41488465,41488466,41488467,41488468,41488469,41488499,41488534,41488581,41488607,41488608,41488620,41488621,41488655,41488656,41488678,41488679,41488736,41488737,41488762,41488844,41488873,41488894,41488895,41488944,41488964,41488965,41488966,41488967,41488968,41489088,41489089,41489127,41489228,41489229,41489230,41489264,41489287,41489310,41489311,41489399,41489422,41489445,41489446,41489447,41489513,41489514,41489535,41489536,41489537,41489538,41489557,41489558,41489559,41489627,41489628,41489630,41489631,41489676,41489683,41489684,41489730,41489765,41489766,41489767,41489796,41489797,41489798,41489829,41489830,41489855,41489856,41489857,41489858,41489859,41489884,41489908,41489909,41489910,41489911,41489912,41490051,41490190,41490206,41490207,41490232,41490376,41490377,41490407,41490408,41490464,41490506,41490507,41490509,41490510,41490511,41490512,41490513,41490551,41490552,41490571,41490682,41490683,41490732,41490798,41490921,41490922,41490974,41490975,41491071,41491107,41491162,41491295,41491354,41491485,41491486,41491487,41491529,41491549,41491550,41491632,41491673,41491849,41491850,41491851,41491885,41491886,41492032,41492033,41492102,41492124,41492147,41492223,41492224,41492274,41492300,41492301,41492446,41492447,41492448,41492449,41492450,41492451,41492452,41492453,41492541,41492542,41492637,41492638,41492639,41492640,41492700,41492821,41492822,41492823,41492824,41492900,41492925,41492964,41493014,41493015,41493016,41493017,41493054,41493077,41493099,41493100,41495318,41495377,41495550,41495551,41495709,41495840,41495926,41496020,41496063,41496338,41496508,41496569,41496570,41496798,41496962,41497136,41497366,41498032,41498163,41498313,41498973,41499053,41499226,41499446,41499447,41499683,41500168,41500389,41500962,41501056,41501145,41501146,41501243,41501318,41501486,42948109,43042493,43043251,43043252,43043253,43044928,43044975,43134181,43134182,43134187,43134188,43134189,43142389,43142390,43142465,43142466,43142985,43142986,43145122,43145123,43145129,43145130,43153526,43153527,43154151,43154152,43154153,43154154,43154155,43156299,43156301,43156302,43156307,43164547,43165145,43167244,43167245,43167250,43175587,43175588,43178312,43178319,43186460,43187065,43187066,43189223,43189225,43197483,43197484,43197557,43197558,43197559,43198096,43198097,43198098,43200262,43200266,43208368,43208369,43208370,43208371,43208941,43208942,43208943,43211052,43211053,43211056,43211058,43211059,43211063,43219371,43219952,43219953,43286120,43296889,43521580,43583929,43591245,43591821,43592828,43592829,43592830,43592870,43607628,43610813,43611552,43611768,43619980,43619981,43627798,43628931,43628970,43629051,43638077,43647012,43647126,43649307,43656187,43664095,436

Concept	Concept IDs (including descendants)	Excluded
		65118,43665231,43665232,43674319,43674320,43683012,43683053,43683054,43683310,43683726,43683928,43692071,43692072,43692073,43692074,43699351,43699352,43700512,43701029,43701030,43701073,43701760,43709973,43709974,43717692,43718211,43718790,43718791,43727988,43727989,43735669,43736378,43736865,43736866,43736900,43736989,43736990,43737583,43739116,43745888,43745889,43745890,43745894,43754787,43754788,43754789,43754834,43755534,43755535,43757030,43757031,43771520,43771728,43773562,43775425,43781946,43781947,43789383,43790626,43790720,43790930,43791162,43799826,43808766,43808880,43809331,43811065,43823326,43823608,43823609,43825835,43826835,43827104,43827787,43829050,43829051,43836116,43843879,43843880,43844914,43844954,43845467,43847160,43847161,43847548,43862050,43863105,43863106,43863107,43863108,43863139,43863140,43863141,43863864,43865818,44030339,44031217,44031219,44031917,44032763,44037628,44038583,44043415,44043416,44044273,44044275,44045731,44047739,44056388,44057232,44058751,44059485,44063799,44063801,44065059,44070786,44070787,44072308,44072311,44073566,44073567,44073569,44074420,44074422,44076493,44077783,44081628,44085183,44086464,44089370,44089373,44089374,44095927,44096597,44097373,44100316,44102385,44102388,44102389,44103721,44112241,44112243,44112244,44113149,44121899,44121900,44129707,44194650,44196459,44196481,44196494,44196510,44196546,44208093,44208117
Amoxicillin	1713332	912002,912003,35805035
Azithromycin	1734104	36212960

Appendix Table 4. List of comorbidity definitions.

Concept	Concept IDs (including descendants)	Exclude
Cardiovascular disease	134057	none
Heart failure	316139	none
Personality disorder	441838	432300,433734,433742,435235,439274,440077,4100362,4100681,4168389,4333686,4335173

Schizophrenia	435783	434318
Cancer	443392	none
Chronic obstructive pulmonary disease	255573	none
Depression	440383,40546087	44782943,44813499,35622958
Anxiety	441542	none
Diabetes mellitus	201820	none

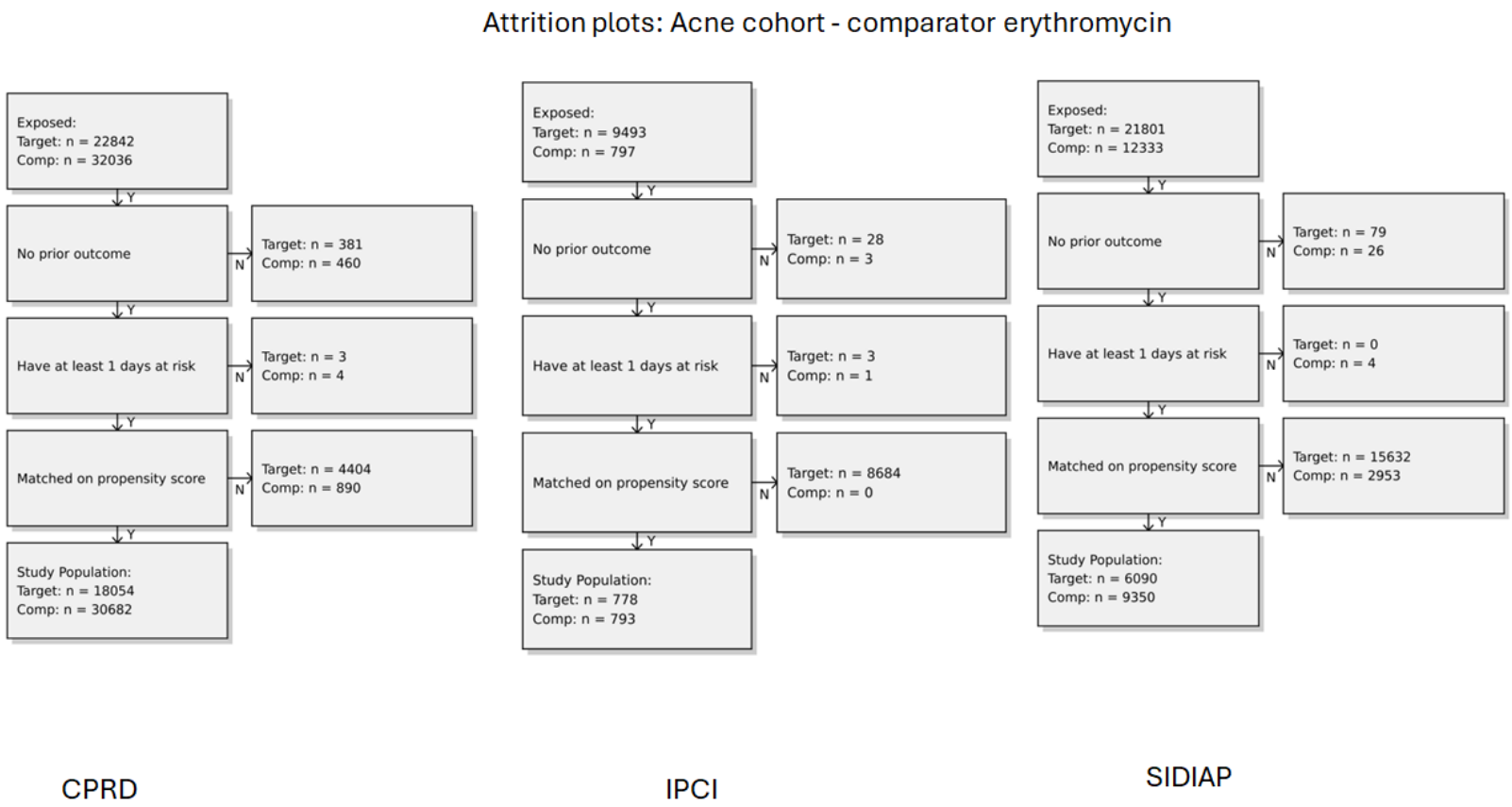
Appendix Table 5. List of negative control outcomes and exposures.

Concept	Concept IDs (including descendants)	Exclude
Vitamin Deficiency	436658	437246
Hypercholesterolemia	437827,4029305	None
Constipation	75860,4008552	None
Palpitations	315078	None
Cerumen	374375,4131101	None
Dehydration	435796	None
Iron deficiency anemia	436659	None
Allergic rhinitis	257007	None
Deviated nasal septum	377910	None
Syncope	135360	None
Nasal congestion	4195085	None
Bradycardia and abnormal heart beat	4169095,4262562	None
Snoring	4248728	None
Anemia	439777	None
Pain in eye	379031	None
Urethral stricture	195590	None

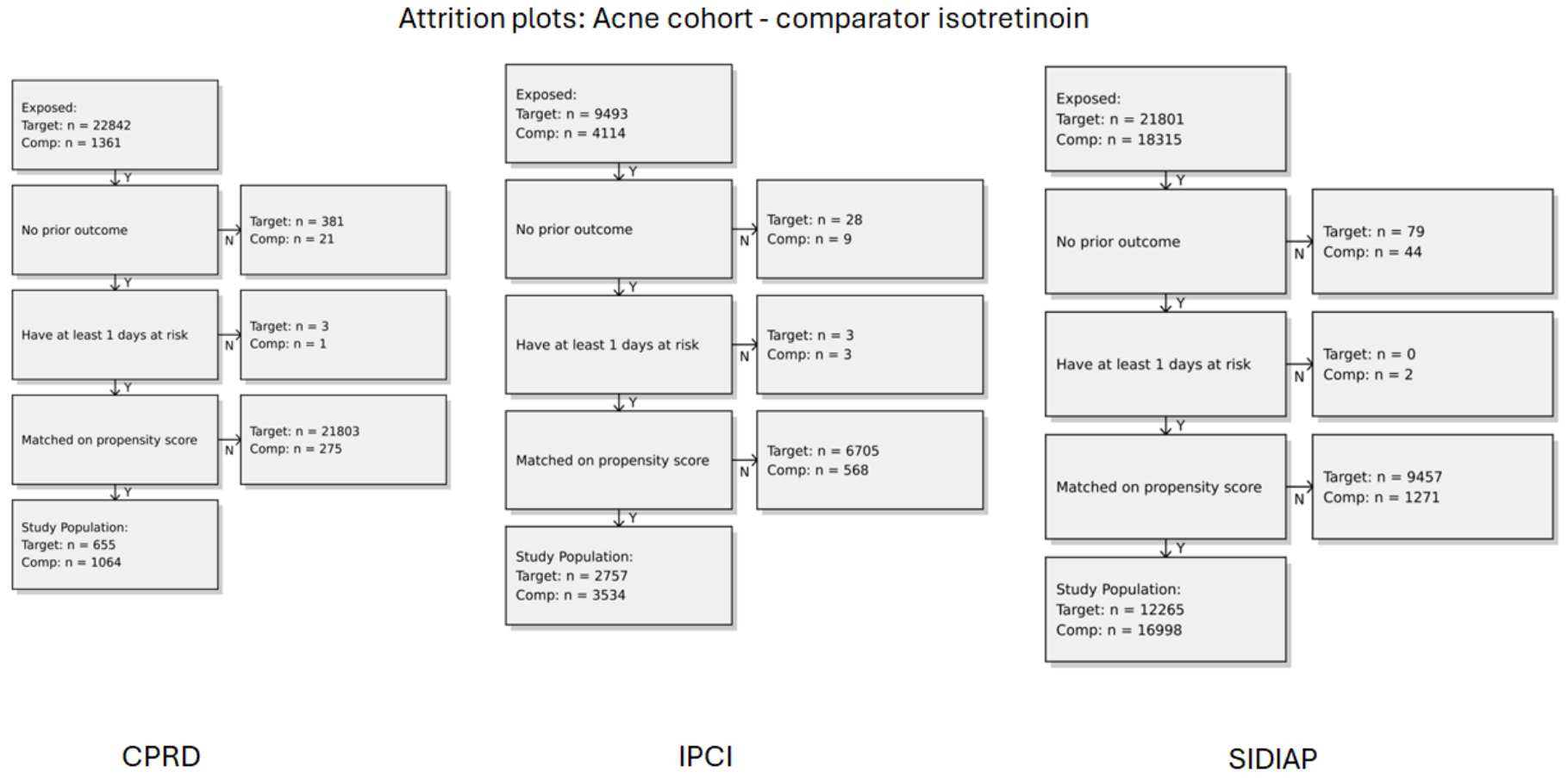
Lack or loss of sexual desire	443262	None
Pneumothorax	253796	None
Perforation of tympanic membrane	375292	260730,760161,760204,45769847
Glycosuria	434164	None
Conjunctival hyperemia	377283,45766466	None
Speech and language disorders	440424,4125590,4338039	None
Ganglion Cyst	40481632	None
Pyogenic granuloma	4308074	None
Otosclerosis	439035	None
Non-Hodgkin's Lymphoma	4038838	None
Carpal tunnel syndrome	380094	None
Porphyria	4305376	None
Hodgkin's disease	4038835	None
Simvastatin	1539403	40737400
Glipizide	1560171	None
Tadalafil	1336926	None
Lovastatin	1592085	None
Mebendazole	1794280	35858615
Vardenafil	1311276	None
Risedronate	1516800	None
Rivaroxaban	40241331	None
Nadolol	1313200	None
Alfuzosin	930021	None
Fosinopril	1363749	None
Fluvastatin	1549686	None
Apixaban	43013024	None
Prasugrel	40163718	None
Silodosin	19012925	None
Albendazole	1753745	None
Ticagrelor	40241186	None
Avanafil	42800040	None
Meloxicam	1150345	35871066,36217206,36217211
Naproxen	1115008	36215490,36216152,36217206,40064742
Metoprolol	1307046	1235129

Ranitidine	961047	None
Atenolol	1314002	None
Tamsulosin	924566	None
Clopidogrel	1322184	None
Pravastatin	1551860	None
Sildenafil	1316262	None
Diltiazem	1328165	21076185,36409560,36812377
Alendronate	1557272	None
Tolterodine	913782	None
Allopurinol	1167322	None
Labetalol	1386957	None
Amiodorone	1309944	None
Ivermectin	1784444	36217206,42479018
Itraconazole	1703653	None
Sotalol	1370109	None
Captopril	1340128	None
Ticlopidine	1302398	None
Nimodipine	1319133	None
Disopyramide	1335606	None

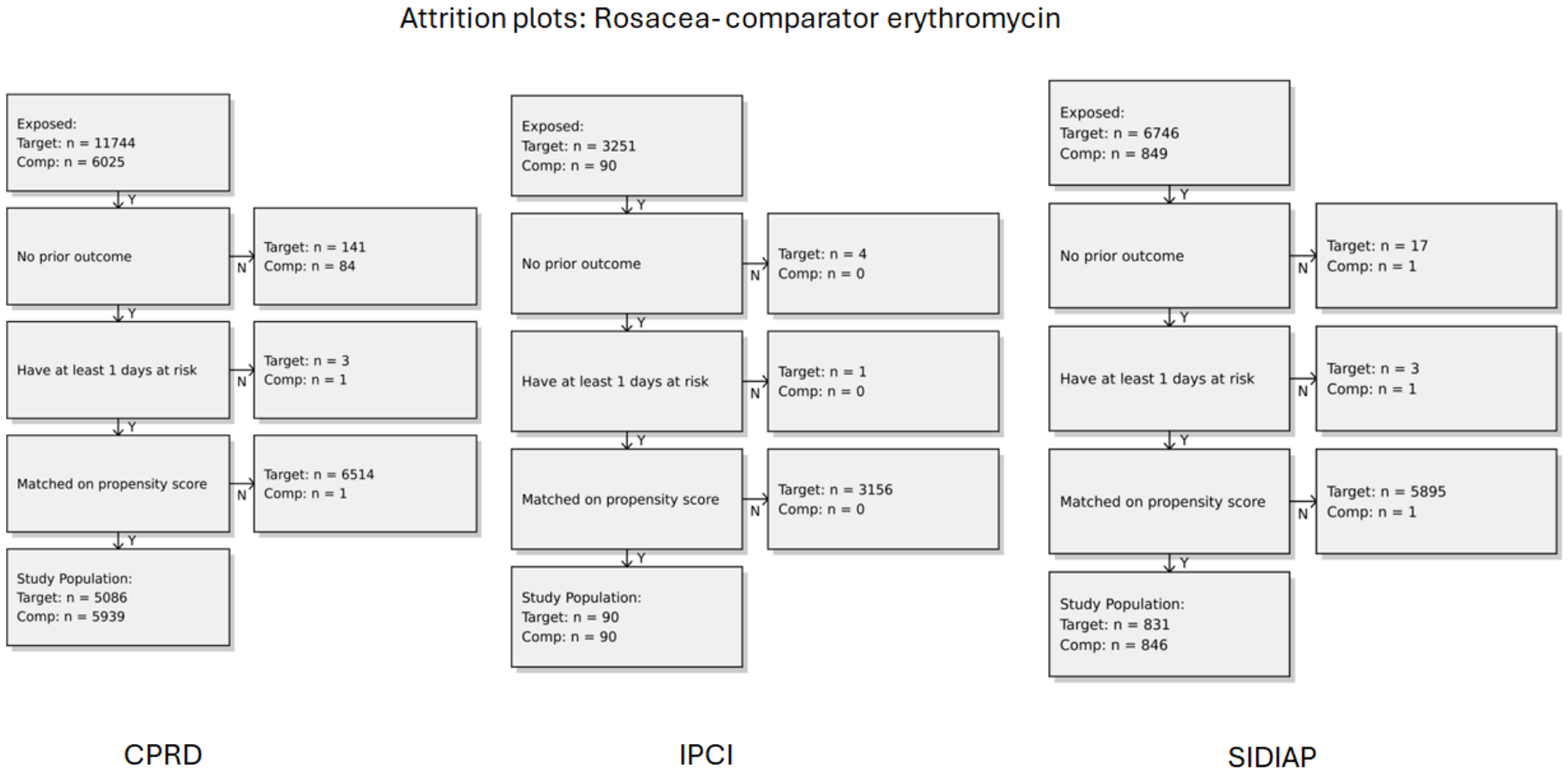
Appendix II: Attrition flow charts



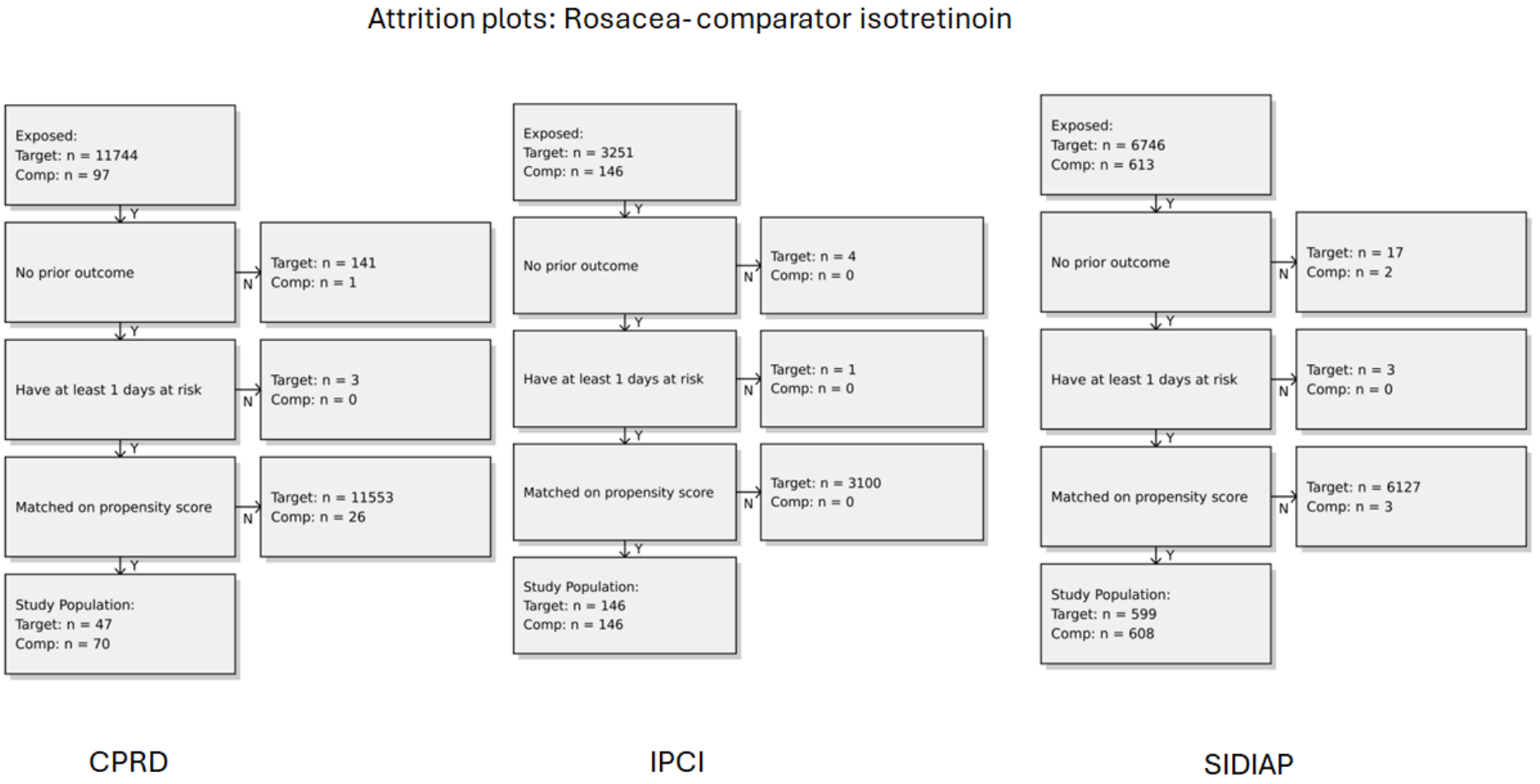
Appendix Figure 1. Acne cohort with erythromycin as comparator for the different databases – suicide and suicide related events as outcome.



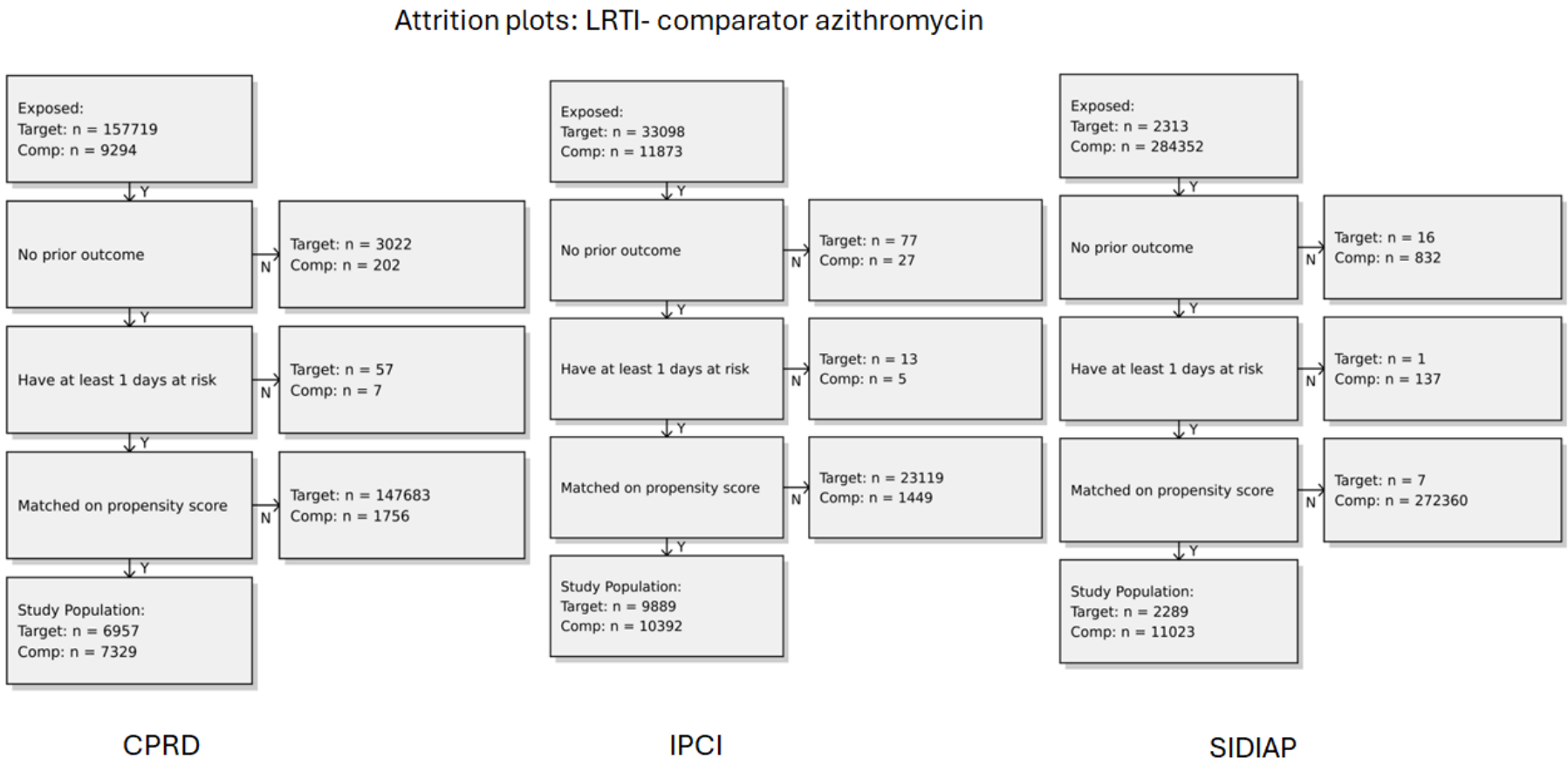
Appendix Figure 2. Acne cohort with isotretinoin as comparator for the different databases.



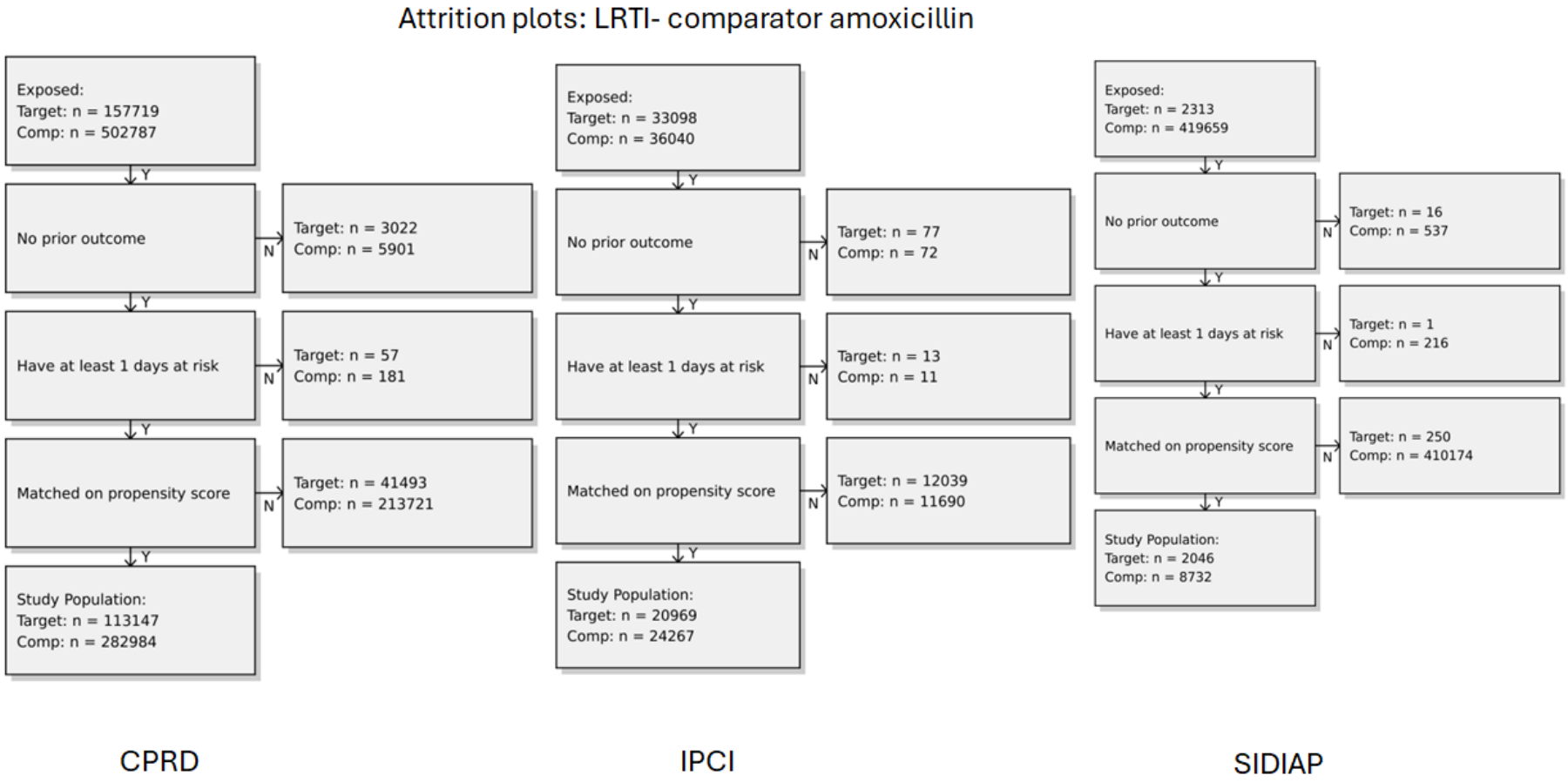
Appendix Figure 3. Rosacea cohort with erythromycin as comparator for the different databases



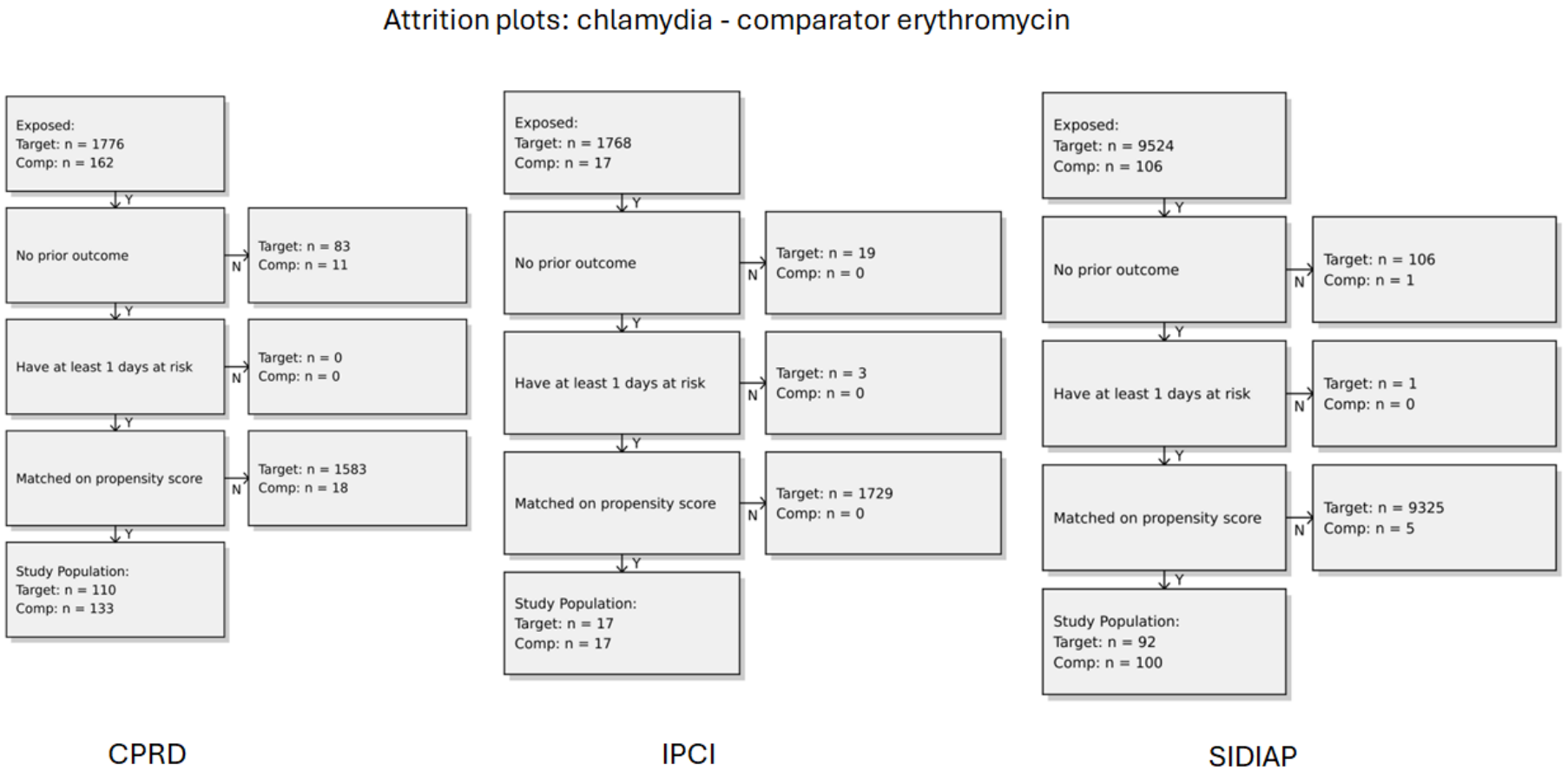
Appendix Figure 4. Rosacea cohort with isotretinoin as comparator for the different databases.



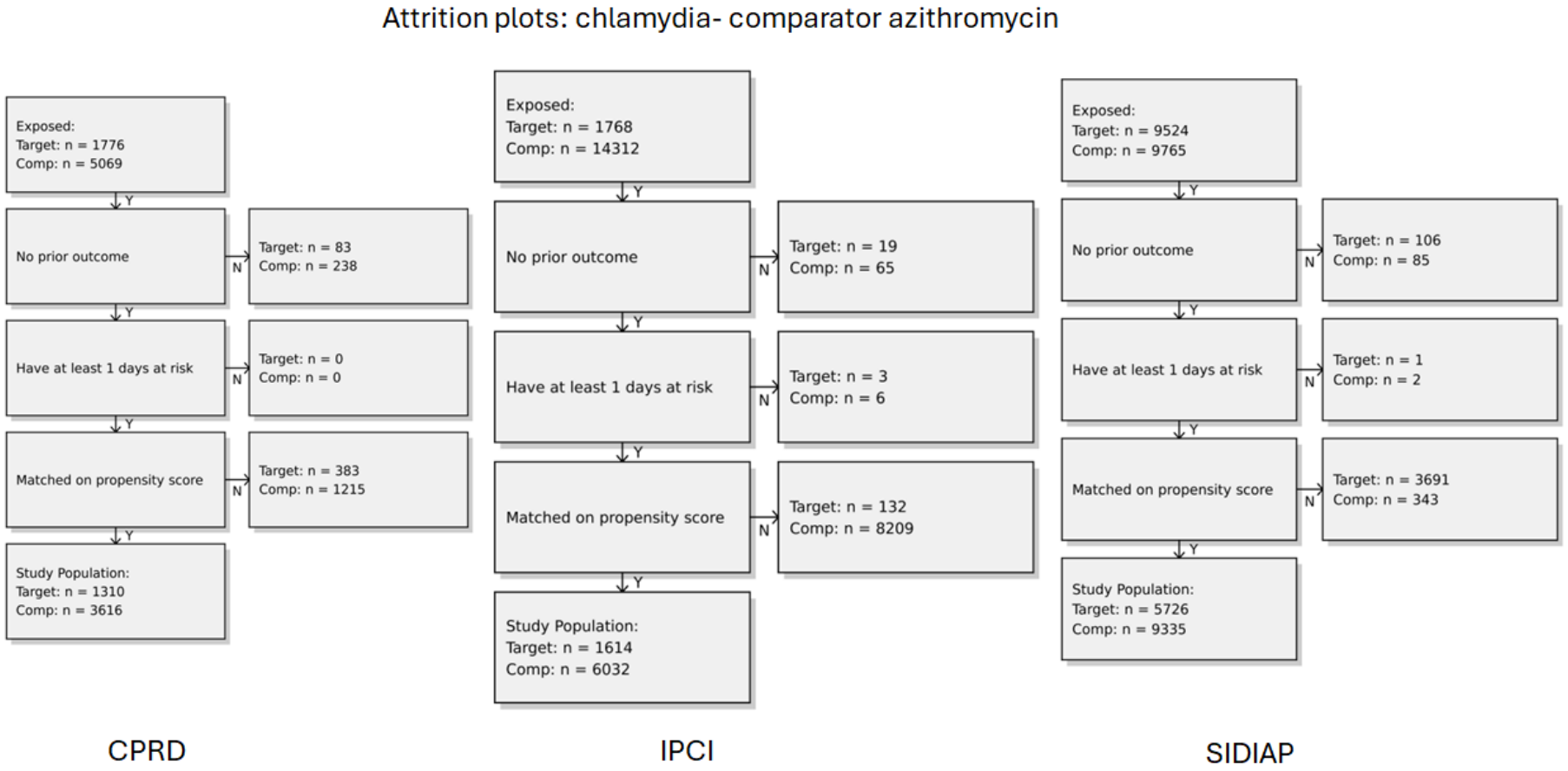
Appendix Figure 5. LRTI cohort with azithromycin as comparator for the different databases.



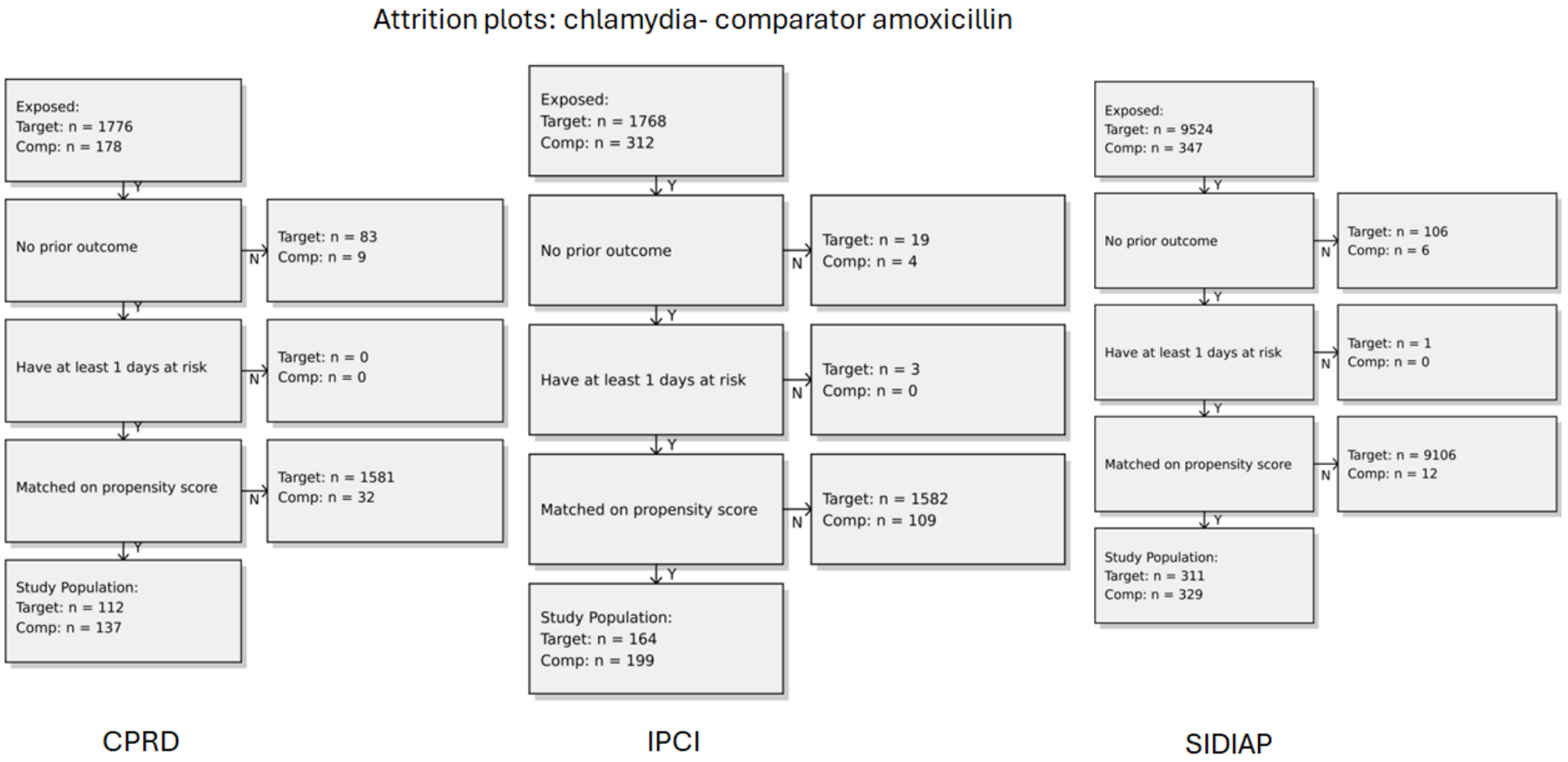
Appendix Figure 6. LRTI cohort with amoxicillin as comparator for the different databases.



Appendix Figure 7. chlamydia cohort with erythromycin as comparator for the different databases.



Appendix Figure 8. Chlamydia cohort with azithromycin as comparator for the different databases.



Appendix Figure 9. Chlamydia cohort with amoxicillin as comparator for the different databases.

Appendix III: Patient characteristics and propensity scores

Appendix Table 6. Characteristics before and after propensity score adjustment, showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Acne*) and comparator (*Erythromycin Acne*) group, as well as the standardized difference of the means – CPRD.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age category						
0 - 4	0	0.002	0	0	0	0
5 - 9	0	0.001	0.046	0	0.001	0.023
10 - 14	0.097	0.134	0.116	0.111	0.106	0.014
15 - 19	0.427	0.417	0.02	0.428	0.434	0.013
20 - 24	0.181	0.161	0.053	0.174	0.175	0.001
25 - 29	0.114	0.114	0.001	0.112	0.112	0.001
30 - 34	0.072	0.074	0.009	0.071	0.071	0.002
35 - 39	0.044	0.045	0.007	0.044	0.043	0.002
40 - 44	0.03	0.025	0.032	0.028	0.028	0
45 - 49	0.018	0.014	0.031	0.017	0.016	0.006
50 - 54	0.007	0.006	0.017	0.007	0.006	0.007
55 - 59	0.004	0.002	0.031	0.003	0.003	0.011
60 - 64	0.002	0.001	0.036	0.002	0.001	0.01
65 - 69	0.002	0.001	0.022	0.001	0.001	0.011
70 - 74	0.001	0.001	0.009	0.001	0.001	0.003
75 - 79	0.001	0.001	0	0.001	0.001	0.001
80 - 84	0	0	0.006	0	0	0.013
85 - 89	0	0	0.007	0	0	0.001
90 - 94	0	0	0	0	0	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
110 - 114	0	0	0	0	0	0
gender = FEMALE	0.57	0.61	0.081	0.575	0.574	0.001
Conditions assessed in the year prior to the index date						
Atrial fibrillation	0	0	0.004	0	0	0.008
Cerebrovascular disease	0	0	0.003	0	0	0.006
Heart disease	0.001	0.002	0.009	0.001	0.002	0.019
Ischemic heart disease	0	0	0.006	0	0	0.003
Peripheral vascular disease	0	0	0.001	0	0	0
Pulmonary embolism	0	0	0.014	0	0	0.013
Venous thrombosis	0.001	0.001	0.003	0.001	0.001	0.01
Acute respiratory disease	0.064	0.074	0.037	0.062	0.061	0.004
Attention deficit hyperactivity disorder	0.002	0.001	0.026	0.002	0.001	0.013
Chronic liver disease	0	0	0.006	0	0	0.003
Chronic obstructive lung disease	0.001	0	0.014	0	0	0
Crohn's disease	0.001	0.001	0.003	0.001	0.001	0
Dementia	0	0	0.002	0	0	0.003
Diabetes mellitus	0.001	0.001	0.002	0.001	0.002	0.008
Gastroesophageal reflux disease	0.001	0.002	0.012	0.001	0.002	0.014
Gastrointestinal hemorrhage	0.005	0.006	0.01	0.005	0.005	0
Hyperlipidemia	0.001	0.001	0.014	0.001	0.001	0.008
Hypertensive disorder	0.001	0.001	0.009	0.001	0.001	0.002

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Lesion of liver	0	0	0.004	0	0	0.007
Obesity	0.002	0.002	0.009	0.002	0.002	0.001
Osteoarthritis	0.002	0.002	0.001	0.002	0.002	0.01
Pneumonia	0	0	0.008	0	0	0.007
Psoriasis	0.004	0.005	0.011	0.004	0.005	0.012
Renal impairment	0.001	0.001	0.008	0.001	0.001	0.005
Rheumatoid arthritis	0	0	0.013	0	0	0.016
Schizophrenia	0	0	0.004	0	0	0.006
Ulcerative colitis	0.001	0.001	0.003	0.001	0.001	0
Urinary tract infectious disease	0.013	0.014	0.011	0.012	0.013	0.004
Viral hepatitis C	0	0	0.015	0	0	0.02
Malignant lymphoma	0	0	0.002	0	0	0
Malignant neoplasm of anorectum	0	0	0.002	0	0	0
Malignant neoplastic disease	0.001	0.001	0.006	0.001	0.001	0.003
Malignant tumor of breast	0	0	0.002	0	0	0.004
Malignant tumor of colon	0	0	0.008	0	0	0
Malignant tumor of lung	0	0	0	0	0	0

Appendix Table 7. Characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Acne*) and comparator (*Erythromycin Acne*) group. as well as the standardized difference of the means – IPCI.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age category						
10 - 14	0.068	0.092	0.093	0.091	0.091	0.002
15 - 19	0.427	0.368	0.12	0.364	0.37	0.013
20 - 24	0.239	0.216	0.054	0.221	0.217	0.009
25 - 29	0.113	0.132	0.059	0.114	0.13	0.047
30 - 34	0.066	0.083	0.068	0.08	0.083	0.012
35 - 39	0.037	0.043	0.03	0.059	0.042	0.076
40 - 44	0.021	0.033	0.079	0.03	0.032	0.015
45 - 49	0.014	0.02	0.053	0.022	0.02	0.013
50 - 54	0.007	-0.006	0.039	0.009	-0.006	0.064
55 - 59	0.004	-0.006	0	-0.006	-0.006	0
60 - 64	0.002	-0.006	0.02	0	-0.006	0
65 - 69	0.001	-0.006	0.053	-0.006	-0.006	0.029
70 - 74	0.001	-0.006	0.014	-0.006	-0.006	0
75 - 79	0.001	-0.006	0.024	-0.006	-0.006	0.029
85 - 89	-0.001	0	0	-0.006	0	0
gender = FEMALE	0.573	0.617	0.09	0.627	0.614	0.028
Conditions assessed in the year prior to the index date						
Atrial fibrillation	0.001	0	0	-0.006	0	0
Cerebrovascular disease	-0.001	-0.006	0.086	0	-0.006	0
Heart disease	0.004	0.008	0.048	-0.006	0.007	0.008

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Ischemic heart disease	0.001	-0.006	0.067	-0.006	-0.006	0.029
Pulmonary embolism	0.001	0	0	-0.006	0	0
Venous thrombosis	0.002	-0.006	0.004	-0.006	-0.006	0.024
Acute respiratory disease	0.104	0.134	0.097	0.143	0.132	0.03
Attention deficit hyperactivity disorder	0.022	0.013	0.064	0.023	0.012	0.083
Chronic obstructive lung disease	0.001	-0.006	0.014	0	-0.006	0
Crohn's disease	0.001	-0.006	0.03	-0.006	-0.006	0.029
Diabetes mellitus	0.005	-0.006	0.006	0.012	-0.006	0.079
Gastroesophageal reflux disease	0.002	-0.006	0.02	-0.006	-0.006	0.024
Gastrointestinal hemorrhage	0.004	-0.006	0.024	-0.006	-0.006	0.017
Hyperlipidemia	0.002	-0.006	0.038	-0.006	-0.006	0.023
Hypertensive disorder	0.005	-0.006	0.002	0.008	-0.006	0.032
Obesity	0.005	0.006	0.017	0.013	-0.006	0.073
Osteoarthritis	0.001	-0.006	0.003	-0.006	-0.006	0.068
Pneumonia	0.005	0.008	0.027	0.008	0.008	0
Psoriasis	0.003	-0.006	0.037	0.008	-0.006	0.032
Rheumatoid arthritis	0.001	-0.006	0.131	0	-0.006	0
Schizophrenia	0.001	-0.006	0.048	0	-0.006	0
Ulcerative colitis	0.002	-0.006	0.008	0	-0.006	0
Urinary tract infectious disease	0.041	0.048	0.034	0.078	0.047	0.13
Malignant lymphoma	0	-0.006	0	0	-0.006	0
Malignant neoplastic disease	0.003	-0.006	0.027	-0.006	-0.006	0.051
Malignant tumor of breast	0.001	0	0	-0.006	0	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Drugs assessed within 365 days prior to the index date						
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.006	0.006	0.001	0.018	0.006	0.107
ANTIBACTERIALS FOR SYSTEMIC USE	0.416	0.503	0.177	0.505	0.496	0.018
ANTIDEPRESSANTS	0.035	0.041	0.037	0.045	0.04	0.022
ANTIEPILEPTICS	0.006	0.01	0.054	0.01	0.01	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.118	0.188	0.213	0.189	0.184	0.013
ANTINEOPLASTIC AGENTS	0.174	0.203	0.077	0.186	0.201	0.037
ANTIPSORIATICS	0.019	0.036	0.124	0.024	0.036	0.068
ANTITHROMBOTIC AGENTS	0.01	0.018	0.078	0.019	0.018	0.01
BETA BLOCKING AGENTS	0.018	0.018	0.002	0.024	0.017	0.05
CALCIUM CHANNEL BLOCKERS	0.006	0.009	0.037	0.012	0.009	0.026
DIURETICS	0.005	0.01	0.064	0.01	0.01	0.007
DRUGS FOR ACID RELATED DISORDERS	0.066	0.112	0.18	0.123	0.111	0.04
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.22	0.232	0.03	0.261	0.231	0.069
DRUGS USED IN DIABETES	0.005	-0.006	0.033	0.01	-0.006	0.098
IMMUNOSUPPRESSANTS	0.004	-0.006	0	-0.006	-0.006	0.036
LIPID MODIFYING AGENTS	0.006	0.009	0.04	0.009	0.009	0
OPIOIDS	0.05	0.079	0.131	0.076	0.078	0.007
PSYCHOLEPTICS	0.059	0.073	0.057	0.078	0.072	0.024

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.033	0.02	0.072	0.028	0.02	0.054

Appendix Table 8. Characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Acne*) and comparator (*Erythromycin Acne*) group. as well as the standardized difference of the means – SIDIAP.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age						
0 - 4	0	0	0	0	0	0
5 - 9	0	0.008	0.127	0	0.001	0.02
10 - 14	0.084	0.357	0.67	0.147	0.133	0.042
15 - 19	0.424	0.352	0.15	0.455	0.469	0.028
20 - 24	0.18	0.108	0.204	0.151	0.151	0.002
25 - 29	0.109	0.067	0.15	0.092	0.092	0.001
30 - 34	0.078	0.046	0.133	0.063	0.065	0.008
35 - 39	0.047	0.026	0.11	0.034	0.037	0.011
40 - 44	0.034	0.019	0.091	0.028	0.028	0.001
45 - 49	0.017	0.009	0.077	0.013	0.012	0.004
50 - 54	0.01	0.003	0.074	0.006	0.005	0.012
55 - 59	0.005	0.002	0.05	0.004	0.003	0.017
60 - 64	0.003	0.001	0.043	0.002	0.002	0.016
65 - 69	0.003	0.001	0.042	0.002	0.001	0.027
70 - 74	0.002	0.001	0.043	0.001	0.001	0.017

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
75 - 79	0.001	0.001	0.008	0.001	0.001	0.009
80 - 84	0.001	0	0.018	0	0	0.013
85 - 89	0	0	0.016	0	0	0.021
gender = FEMALE	0.528	0.593	0.13	0.569	0.563	0.013
Conditions assessed in the year prior to the index date						
Atrial fibrillation	0	0	0.02	0	0	0.01
Cerebrovascular disease	0.001	0	0.018	0	0	0.015
Coronary arteriosclerosis	0	0	0.002	0	0	0
Heart disease	0.006	0.004	0.027	0.005	0.005	0.008
Heart failure	0	0	0.016	0	0	0.006
Ischemic heart disease	0.001	0	0.016	0	0	0.008
Peripheral vascular disease	0	0	0.012	0	0	0
Pulmonary embolism	0	0	0.014	0	0	0.006
Venous thrombosis	0.002	0.001	0.02	0.001	0.001	0.012
Acute respiratory disease	0.138	0.17	0.089	0.148	0.15	0.007
Attention deficit hyperactivity disorder	0.004	0.006	0.025	0.004	0.004	0
Chronic liver disease	0.001	0	0.02	0.001	0	0.018
Chronic obstructive lung disease	0.001	0	0.026	0.001	0	0.015
Crohn's disease	0.001	0	0.01	0	0.001	0.012
Dementia	0	0	0.012	0	0	0
Diabetes mellitus	0.003	0.002	0.008	0.002	0.003	0.009
Gastroesophageal reflux disease	0.003	0.002	0.009	0.002	0.003	0.005
Gastrointestinal hemorrhage	0.004	0.003	0.011	0.004	0.004	0.007

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Human immunodeficiency virus infection	0	0	0.014	0	0	0.005
Hyperlipidemia	0.006	0.007	0.006	0.006	0.006	0.004
Hypertensive disorder	0.005	0.003	0.02	0.004	0.004	0.005
Lesion of liver	0.001	0	0.026	0	0	0.019
Obesity	0.019	0.029	0.065	0.022	0.022	0
Osteoarthritis	0.003	0.002	0.023	0.003	0.003	0.001
Pneumonia	0.004	0.005	0.016	0.004	0.004	0.006
Psoriasis	0.002	0.002	0.012	0.002	0.002	0.007
Renal impairment	0.001	0.001	0.001	0.001	0.001	0.011
Rheumatoid arthritis	0	0	0.007	0	0	0.009
Schizophrenia	0	0	0.007	0	0	0.008
Ulcerative colitis	0.001	0	0.015	0.001	0.001	0
Urinary tract infectious disease	0.045	0.036	0.042	0.041	0.043	0.012
Viral hepatitis C	0.001	0	0.022	0.001	0	0.022
Malignant lymphoma	0	0	0.006	0	0	0.008
Malignant neoplasm of anorectum	0	0	0	0	0	0
Malignant neoplastic disease	0.004	0.002	0.042	0.003	0.002	0.006
Malignant tumor of breast	0	0	0.016	0	0	0.005
Malignant tumor of colon	0.001	0	0.026	0	0	0.027
Malignant tumor of lung	0.001	0	0.026	0	0	0.021
Malignant tumor of urinary bladder	0	0	0.002	0	0	0.017

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Primary malignant neoplasm of prostate	0	0	0	0	0	0
Drugs assessed within 365 days prior to the index date						
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.013	0.006	0.07	0.009	0.009	0.005
ANTIBACTERIALS FOR SYSTEMIC USE	0.294	0.261	0.073	0.272	0.27	0.006
ANTIDEPRESSANTS	0.06	0.038	0.101	0.049	0.049	0.002
ANTIEPILEPTICS	0.026	0.018	0.052	0.02	0.022	0.013
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.383	0.426	0.088	0.394	0.394	0.002
ANTINEOPLASTIC AGENTS	0.01	0.005	0.055	0.006	0.006	0
ANTIPSORIATICS	0.005	0.003	0.037	0.004	0.004	0.005
ANTITHROMBOTIC AGENTS	0.017	0.009	0.071	0.014	0.012	0.017
BETA BLOCKING AGENTS	0.009	0.005	0.053	0.008	0.006	0.018
CALCIUM CHANNEL BLOCKERS	0.004	0.002	0.038	0.004	0.003	0.015
DIURETICS	0.008	0.004	0.056	0.006	0.005	0.011
DRUGS FOR ACID RELATED DISORDERS	0.088	0.068	0.075	0.08	0.081	0.004
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.158	0.157	0.004	0.149	0.152	0.007
DRUGS USED IN DIABETES	0.008	0.005	0.037	0.006	0.006	0.002
IMMUNOSUPPRESSANTS	0.006	0.004	0.032	0.005	0.004	0.01
LIPID MODIFYING AGENTS	0.012	0.005	0.083	0.008	0.007	0.012

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
OPIOIDS	0.045	0.034	0.057	0.041	0.041	0.001
PSYCHOLEPTICS	0.11	0.076	0.114	0.093	0.093	0
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.021	0.022	0.009	0.02	0.021	0.003

Appendix Table 9. Characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Acne*) and comparator (*Isotretinoin Acne*) group. as well as the standardized difference of the means – CPRD.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
10 - 14	0.097	0.043	0.186	0.04	0.044	0.022
15 - 19	0.427	0.486	0.12	0.423	0.467	0.088
20 - 24	0.181	0.226	0.116	0.214	0.218	0.011
25 - 29	0.114	0.114	0	0.119	0.116	0.01
30 - 34	0.072	0.054	0.07	0.061	0.062	0.002
35 - 39	0.044	0.032	0.059	0.049	0.037	0.061
40 - 44	0.03	0.026	0.021	0.04	0.035	0.026
45 - 49	0.018	0.01	0.06	0.02	0.013	0.052
50 - 54	0.007	0.005	0.027	0.015	0.006	0.088
55 - 59	0.004	0	0	0.012	0	0
60 - 64	0.002	-0.004	0.02	-0.008	-0.004	0
65 - 69	0.002	-0.004	0.004	-0.008	-0.004	0.085
70 - 74	0.001	-0.004	0.01	0	0	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
75 - 79	0.001	0	0	-0.008	0	0
gender = FEMALE	0.57	0.497	0.147	0.528	0.502	0.053
Conditions assessed in the year prior to the index date						
Venous thrombosis	0.001	-0.004	0.011	-0.008	-0.004	0.021
Acute respiratory disease	0.064	0.044	0.083	0.064	0.057	0.032
Attention deficit hyperactivity disorder	0.002	-0.004	0.009	-0.008	-0.004	0.032
Chronic obstructive lung disease	0.001	-0.004	0.009	0	-0.004	0
Diabetes mellitus	0.001	-0.004	0.002	-0.008	-0.004	0.058
Gastroesophageal reflux disease	0.001	-0.004	0.001	0	-0.004	0
Gastrointestinal hemorrhage	0.005	0.005	0.003	-0.008	0.005	0.062
Hyperlipidemia	0.001	0	0	-0.008	0	0
Hypertensive disorder	0.001	-0.004	0.003	-0.008	-0.004	0.038
Obesity	0.002	-0.004	0.011	-0.008	-0.004	0.065
Osteoarthritis	0.002	-0.004	0.014	0	-0.004	0
Psoriasis	0.004	0.004	0.005	-0.008	0.004	0.047
Renal impairment	0.001	-0.004	0.009	-0.008	-0.004	0
Rheumatoid arthritis	0	-0.004	0.093	0	-0.004	0
Ulcerative colitis	0.001	0	0	-0.008	0	0
Urinary tract infectious disease	0.013	0.006	0.061	0.014	0.006	0.072
Malignant neoplastic disease	0.001	-0.004	0.01	0	-0.004	0

Appendix Table 10. Characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Acne*) and comparator (*Isotretinoin Acne*) group. as well as the standardised difference of the means – IPCI.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
10 - 14	0.068	0.041	0.114	0.041	0.046	0.027
15 - 19	0.427	0.443	0.032	0.431	0.433	0.005
20 - 24	0.239	0.264	0.058	0.254	0.259	0.014
25 - 29	0.113	0.119	0.019	0.116	0.118	0.005
30 - 34	0.066	0.063	0.009	0.072	0.067	0.022
35 - 39	0.037	0.034	0.018	0.034	0.036	0.009
40 - 44	0.021	0.018	0.018	0.026	0.021	0.035
45 - 49	0.014	0.009	0.044	0.009	0.01	0.009
50 - 54	0.007	0.004	0.033	0.008	0.005	0.039
55 - 59	0.004	0.001	0.042	0.003	0.002	0.035
60 - 64	0.002	0.002	0	0.002	-0.001	0.028
65 - 69	0.001	-0.001	0.023	-0.002	-0.001	0.027
70 - 74	0.001	-0.001	0.013	-0.002	-0.001	0.016
75 - 79	0.001	-0.001	0.017	-0.002	-0.001	0
80 - 84	-0.001	0	0	-0.002	0	0
85 - 89	-0.001	-0.001	0.004	-0.002	-0.001	0
gender = FEMALE	0.573	0.52	0.106	0.538	0.532	0.01
Conditions assessed in the year prior to the index date						
Atrial fibrillation	0.001	-0.001	0.017	-0.002	-0.001	0.034
Cerebrovascular disease	-0.001	-0.001	0.003	-0.002	-0.001	0.016

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Heart disease	0.004	0.003	0.027	0.004	0.003	0.023
Ischemic heart disease	0.001	-0.001	0.017	-0.002	-0.001	0.035
Peripheral vascular disease	0.001	-0.001	0.02	0	-0.001	0
Pulmonary embolism	0.001	-0.001	0.016	-0.002	-0.001	0.012
Venous thrombosis	0.002	-0.001	0.037	0.003	-0.001	0.042
Acute respiratory disease	0.104	0.104	0.002	0.1	0.107	0.02
Attention deficit hyperactivity disorder	0.022	0.021	0.006	0.025	0.02	0.034
Chronic liver disease	-0.001	-0.001	0.004	0	-0.001	0
Chronic obstructive lung disease	0.001	-0.001	0.013	-0.002	-0.001	0.013
Crohn's disease	0.001	-0.001	0.019	0.002	-0.001	0.031
Diabetes mellitus	0.005	0.002	0.045	0.007	0.003	0.065
Gastroesophageal reflux disease	0.002	0.002	0.012	0.002	0.002	0.003
Gastrointestinal hemorrhage	0.004	0.004	0.005	0.004	0.004	0.004
Hyperlipidemia	0.002	0.003	0.014	0.003	0.003	0.002
Hypertensive disorder	0.005	0.003	0.026	0.004	0.004	0.014
Obesity	0.005	0.005	0.001	0.005	0.004	0.022
Osteoarthritis	0.001	-0.001	0.022	0.002	-0.001	0.04
Pneumonia	0.005	0.005	0.012	0.007	0.005	0.019
Psoriasis	0.003	0.002	0.015	0.004	0.002	0.034
Renal impairment	0.001	-0.001	0.004	0	-0.001	0
Rheumatoid arthritis	0.001	-0.001	0.02	-0.002	-0.001	0
Schizophrenia	0.001	-0.001	0.026	-0.002	-0.001	0.028
Ulcerative colitis	0.002	0.002	0.003	0.002	0.002	0.002

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Urinary tract infectious disease	0.041	0.044	0.014	0.038	0.043	0.022
Viral hepatitis C	-0.001	0	0	-0.002	0	0
Malignant neoplastic disease	0.003	0.001	0.025	0.002	0.002	0.014
Malignant tumor of lung	-0.001	0	0	-0.002	0	0
Drugs assessed within 365 days prior to the index date						
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.006	0.005	0.011	0.007	0.005	0.029
ANTIBACTERIALS FOR SYSTEMIC USE	0.416	0.487	0.144	0.429	0.404	0.051
ANTIDEPRESSANTS	0.035	0.037	0.012	0.032	0.032	0
ANTIEPILEPTICS	0.006	0.005	0.009	0.006	0.005	0.012
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.118	0.13	0.035	0.127	0.126	0.001
ANTINEOPLASTIC AGENTS	0.174	0.166	0.022	0.143	0.142	0.004
ANTIPSORIATICS	0.019	0.02	0.007	0.018	0.021	0.015
ANTITHROMBOTIC AGENTS	0.01	0.008	0.015	0.011	0.008	0.026
BETA BLOCKING AGENTS	0.018	0.018	0.001	0.021	0.017	0.027
CALCIUM CHANNEL BLOCKERS	0.006	0.006	0.002	0.006	0.006	0.001
DIURETICS	0.005	0.004	0.02	0.003	0.003	0.007
DRUGS FOR ACID RELATED DISORDERS	0.066	0.066	0	0.065	0.065	0
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.22	0.214	0.012	0.213	0.217	0.01
DRUGS USED IN DIABETES	0.005	0.004	0.009	0.007	0.004	0.036

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
IMMUNOSUPPRESSANTS	0.004	0.007	0.05	0.005	0.007	0.027
LIPID MODIFYING AGENTS	0.006	0.005	0.005	0.008	0.005	0.041
OPIOIDS	0.05	0.044	0.027	0.048	0.046	0.007
PSYCHOLEPTICS	0.059	0.054	0.024	0.054	0.055	0.006
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.033	0.039	0.035	0.036	0.037	0.008

Appendix Table 11. Characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Acne*) and comparator (*Isotretinoin Acne*) group. as well as the standardised difference of the means – SIDIAP.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	0	0	0	0	0	0
5 - 9	0	0	0	-0.001	0	0
10 - 14	0.084	0.062	0.086	0.06	0.065	0.018
15 - 19	0.424	0.472	0.096	0.429	0.444	0.031
20 - 24	0.18	0.178	0.004	0.182	0.178	0.011
25 - 29	0.109	0.109	0.001	0.115	0.113	0.007
30 - 34	0.078	0.068	0.037	0.076	0.075	0.002
35 - 39	0.047	0.044	0.014	0.053	0.05	0.011
40 - 44	0.034	0.029	0.029	0.035	0.031	0.026
45 - 49	0.017	0.016	0.014	0.019	0.017	0.014
50 - 54	0.01	0.008	0.012	0.011	0.01	0.005

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
55 - 59	0.005	0.005	0.001	0.006	0.006	0.002
60 - 64	0.003	0.003	0.011	0.004	0.003	0.03
65 - 69	0.003	0.002	0.007	0.004	0.003	0.009
70 - 74	0.002	0.002	0.006	0.003	0.002	0.011
75 - 79	0.001	0.001	0.009	0.002	0.001	0.024
80 - 84	0.001	0	0.005	-0.001	0.001	0.009
85 - 89	0	0	0.012	-0.001	0	0.01
90 - 94	0	0	0	-0.001	0	0
95 - 99	0	0	0	-0.001	0	0
gender = FEMALE	0.528	0.488	0.08	0.514	0.514	0.002
Conditions assessed in the year prior to the index date						
Atrial fibrillation	0	0	0.007	-0.001	0	0.002
Cerebrovascular disease	0.001	0.001	0.003	-0.001	0.001	0.012
Coronary arteriosclerosis	0	0	0.001	0	0	0
Heart disease	0.006	0.006	0.007	0.007	0.006	0.009
Heart failure	0	0	0.012	-0.001	0	0.012
Ischemic heart disease	0.001	0	0.024	0.001	0	0.038
Peripheral vascular disease	0	0	0.007	-0.001	0	0.015
Pulmonary embolism	0	0	0.005	-0.001	0	0.004
Venous thrombosis	0.002	0.001	0.005	0.001	0.001	0.002
Acute respiratory disease	0.138	0.123	0.045	0.125	0.123	0.007
Attention deficit hyperactivity disorder	0.004	0.004	0.008	0.003	0.005	0.041
Chronic liver disease	0.001	0	0.027	0.001	0	0.057

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Chronic obstructive lung disease	0.001	0	0.016	0.001	0	0.024
Crohn's disease	0.001	0	0.005	-0.001	0.001	0.002
Dementia	0	0	0	-0.001	0	0
Diabetes mellitus	0.003	0.003	0.003	0.003	0.003	0.005
Gastroesophageal reflux disease	0.003	0.002	0.017	0.002	0.002	0.002
Gastrointestinal hemorrhage	0.004	0.004	0.003	0.005	0.004	0.017
Human immunodeficiency virus infection	0	0	0.005	0.001	0	0.02
Hyperlipidemia	0.006	0.006	0.003	0.007	0.006	0.009
Hypertensive disorder	0.005	0.004	0.016	0.005	0.004	0.015
Lesion of liver	0.001	0	0.029	0.001	0	0.032
Obesity	0.019	0.015	0.032	0.017	0.015	0.02
Osteoarthritis	0.003	0.003	0.002	0.004	0.003	0.013
Pneumonia	0.004	0.004	0.008	0.002	0.003	0.019
Psoriasis	0.002	0.003	0.006	0.003	0.003	0.008
Renal impairment	0.001	0.001	0.004	0.001	0.001	0.004
Rheumatoid arthritis	0	0	0.009	-0.001	0	0.005
Schizophrenia	0	0	0.001	-0.001	0	0.001
Ulcerative colitis	0.001	0	0.02	0.001	0	0.035
Urinary tract infectious disease	0.045	0.034	0.055	0.034	0.035	0.004
Viral hepatitis C	0.001	0	0.026	0.001	0	0.053
Malignant lymphoma	0	0	0.008	-0.001	0	0.013
Malignant neoplasm of anorectum	0	0	0.014	-0.001	0	0.011
Malignant neoplastic disease	0.004	0.002	0.032	0.006	0.004	0.031

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Malignant tumor of breast	0	0	0.018	-0.001	0	0.02
Malignant tumor of colon	0.001	0	0.018	0.001	0	0.023
Malignant tumor of lung	0.001	0	0.018	0.001	0	0.032
Primary malignant neoplasm of prostate	0	0	0	-0.001	0	0
Drugs assessed within 365 days prior to the index date						
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.013	0.012	0.013	0.015	0.014	0.005
ANTIBACTERIALS FOR SYSTEMIC USE	0.294	0.363	0.148	0.321	0.313	0.017
ANTIDEPRESSANTS	0.06	0.055	0.022	0.061	0.058	0.011
ANTIEPILEPTICS	0.026	0.024	0.013	0.028	0.026	0.013
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.383	0.348	0.072	0.349	0.344	0.01
ANTINEOPLASTIC AGENTS	0.01	0.017	0.064	0.014	0.015	0.011
ANTIPSORIATICS	0.005	0.007	0.027	0.008	0.008	0.008
ANTITHROMBOTIC AGENTS	0.017	0.016	0.006	0.02	0.017	0.02
BETA BLOCKING AGENTS	0.009	0.008	0.012	0.009	0.009	0.007
CALCIUM CHANNEL BLOCKERS	0.004	0.005	0.001	0.004	0.005	0.017
DIURETICS	0.008	0.006	0.02	0.008	0.007	0.012
DRUGS FOR ACID RELATED DISORDERS	0.088	0.091	0.01	0.095	0.093	0.007
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.158	0.157	0.001	0.162	0.156	0.015

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
DRUGS USED IN DIABETES	0.008	0.008	0	0.01	0.008	0.018
IMMUNOSUPPRESSANTS	0.006	0.009	0.036	0.01	0.012	0.016
LIPID MODIFYING AGENTS	0.012	0.012	0.005	0.017	0.014	0.031
OPIOIDS	0.045	0.04	0.023	0.042	0.041	0.004
PSYCHOLEPTICS	0.11	0.097	0.04	0.108	0.102	0.018
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.021	0.028	0.047	0.023	0.025	0.008

Appendix Table 12. Select characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Rosacea*) and comparator (*Erythromycin Rosacea*) group. as well as the standardised difference of the means – CPRD.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	0	-0.001	0	0	-0.001	0
5 - 9	0	-0.001	0	0	-0.001	0
10 - 14	0.008	0.025	0.142	0.016	0.017	0.01
15 - 19	0.035	0.082	0.212	0.067	0.059	0.033
20 - 24	0.028	0.041	0.077	0.04	0.038	0.009
25 - 29	0.036	0.057	0.103	0.05	0.051	0.002
30 - 34	0.056	0.073	0.07	0.073	0.07	0.009
35 - 39	0.078	0.085	0.026	0.087	0.086	0.003
40 - 44	0.103	0.107	0.014	0.115	0.109	0.019

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
45 - 49	0.12	0.129	0.026	0.128	0.132	0.012
50 - 54	0.11	0.098	0.038	0.103	0.103	0.001
55 - 59	0.097	0.071	0.092	0.075	0.079	0.014
60 - 64	0.09	0.066	0.086	0.072	0.073	0.001
65 - 69	0.087	0.064	0.088	0.066	0.07	0.015
70 - 74	0.065	0.042	0.097	0.046	0.047	0.002
75 - 79	0.044	0.032	0.06	0.034	0.035	0.01
80 - 84	0.028	0.016	0.075	0.018	0.018	0.003
85 - 89	0.011	0.008	0.035	0.008	0.009	0.006
90 - 94	0.003	0.002	0.011	0.002	0.002	0.013
95 - 99	0	-0.001	0.008	-0.001	-0.001	0.009
gender = FEMALE	0.584	0.65	0.136	0.652	0.635	0.035
Atrial fibrillation	0.003	0.003	0.013	0.002	0.003	0.015
Cerebrovascular disease	0.003	0.001	0.039	0.002	0.001	0.027
Coronary arteriosclerosis	0	-0.001	0.013	-0.001	-0.001	0.02
Heart disease	0.013	0.007	0.052	0.01	0.008	0.026
Heart failure	0.001	-0.001	0.017	-0.001	-0.001	0.011
Ischemic heart disease	0.003	0.002	0.027	0.003	0.002	0.028
Peripheral vascular disease	0.001	-0.001	0.022	-0.001	-0.001	0.005
Pulmonary embolism	0.001	-0.001	0.02	-0.001	-0.001	0.004
Venous thrombosis	0.005	0.003	0.023	0.006	0.003	0.036

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Acute respiratory disease	0.062	0.068	0.023	0.062	0.061	0.003
Attention deficit hyperactivity disorder	0	-0.001	0.014	-0.001	-0.001	0.027
Chronic liver disease	0.001	-0.001	0.012	-0.001	-0.001	0
Chronic obstructive lung disease	0.009	0.007	0.028	0.006	0.008	0.03
Crohn's disease	0.002	-0.001	0.025	0.002	-0.001	0.041
Dementia	0.001	0.001	0.001	-0.001	0.001	0.022
Diabetes mellitus	0.011	0.006	0.053	0.005	0.007	0.027
Gastroesophageal reflux disease	0.004	0.005	0.026	0.004	0.006	0.031
Gastrointestinal hemorrhage	0.008	0.011	0.026	0.011	0.01	0.004
Hyperlipidemia	0.008	0.005	0.033	0.007	0.005	0.02
Hypertensive disorder	0.016	0.012	0.033	0.011	0.013	0.019
Lesion of liver	0.001	-0.001	0.017	-0.001	-0.001	0
Obesity	0.005	0.004	0.004	0.005	0.003	0.019
Osteoarthritis	0.022	0.018	0.032	0.018	0.019	0.004
Pneumonia	0	-0.001	0	-0.001	-0.001	0.002
Psoriasis	0.012	0.01	0.019	0.011	0.01	0.007
Renal impairment	0.009	0.009	0.002	0.008	0.01	0.02
Rheumatoid arthritis	0.001	0.001	0.001	0.001	0.001	0.005
Schizophrenia	0	0	0	-0.001	0	0
Ulcerative colitis	0.001	0.001	0.004	0.001	0.001	0.009

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Urinary tract infectious disease	0.017	0.019	0.011	0.016	0.017	0.007
Malignant lymphoma	0	-0.001	0.003	0	-0.001	0
Malignant neoplasm of anorectum	0	-0.001	0	0	-0.001	0
Malignant neoplastic disease	0.01	0.008	0.019	0.008	0.009	0.005
Malignant tumor of breast	0.001	0.001	0.002	-0.001	0.001	0.017
Malignant tumor of colon	0	-0.001	0.008	-0.001	-0.001	0
Malignant tumor of lung	0	0	0	-0.001	0	0
Malignant tumor of urinary bladder	0	-0.001	0	-0.001	-0.001	0.008

Appendix Table 13. Select characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Rosacea*) and comparator (*Erythromycin Rosacea*) group as well as the standardised difference of the means – IPCI.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
0 - 4	0	-0.056	0	0	-0.056	0
10 - 14	-0.002	-0.056	0.551	0	-0.056	0
15 - 19	0.016	-0.056	0.037	-0.056	-0.056	0
20 - 24	0.039	-0.056	0.086	-0.056	-0.056	0.124
25 - 29	0.056	0.067	0.045	-0.056	0.067	0.097
30 - 34	0.074	0.122	0.182	0.067	0.122	0.19
35 - 39	0.097	0.111	0.047	0.133	0.111	0.068
40 - 44	0.107	0.111	0.014	-0.056	0.111	0.249
45 - 49	0.13	0.067	0.19	0.167	0.067	0.311
50 - 54	0.114	0.111	0.008	0.067	0.111	0.156
55 - 59	0.083	0.056	0.099	0.089	0.056	0.129
60 - 64	0.074	0.111	0.139	0.078	0.111	0.114
65 - 69	0.067	-0.056	0.092	0.056	-0.056	0.051
70 - 74	0.06	0.067	0.028	0.078	0.067	0.043
75 - 79	0.038	-0.056	0.081	-0.056	-0.056	0.124
80 - 84	0.029	0	0	-0.056	0	0
85 - 89	0.013	-0.056	0.182	-0.056	-0.056	0.057
90 - 94	0.002	-0.056	0.183	0	-0.056	0
gender = FEMALE	0.716	0.811	0.211	0.722	0.811	0.21
Cerebrovascular disease	0.011	-0.056	0.105	-0.056	-0.056	0
Heart disease	0.037	-0.056	0.078	-0.056	-0.056	0
Ischemic heart disease	0.014	-0.056	0.028	-0.056	-0.056	0.087
Pulmonary embolism	-0.002	0	0	-0.056	0	0
Venous thrombosis	0.006	-0.056	0.058	0	-0.056	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Acute respiratory disease	0.128	0.144	0.048	0.211	0.144	0.174
Chronic obstructive lung disease	0.016	-0.056	0.14	-0.056	-0.056	0.068
Crohn's disease	0.004	-0.056	0.119	-0.056	-0.056	0
Dementia	0.002	0	0	-0.056	0	0
Diabetes mellitus	0.039	-0.056	0.089	-0.056	-0.056	0
Gastroesophageal reflux disease	0.005	-0.056	0.094	-0.056	-0.056	0
Gastrointestinal hemorrhage	0.012	0	0	-0.056	0	0
Hyperlipidemia	0.022	0	0	0.056	0	0
Hypertensive disorder	0.102	0.067	0.116	0.133	0.067	0.222
Osteoarthritis	0.031	-0.056	0.115	-0.056	-0.056	0.151
Pneumonia	0.022	-0.056	0.073	0	-0.056	0
Renal impairment	0.006	-0.056	0.058	-0.056	-0.056	0
Rheumatoid arthritis	0.006	0	0	-0.056	0	0
Ulcerative colitis	0.006	0	0	-0.056	0	0
Urinary tract infectious disease	0.077	0.067	0.04	0.078	0.067	0.043
Malignant neoplastic disease	0.036	-0.056	0.013	0.078	-0.056	0.194
Malignant tumor of breast	0.005	-0.056	0.094	-0.056	-0.056	0.203
Malignant tumor of lung	0.002	-0.056	0.226	0	-0.056	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.143	0.111	0.091	0.167	0.111	0.161
ANTIBACTERIALS FOR SYSTEMIC USE	0.798	0.756	0.105	0.822	0.756	0.163
ANTIDEPRESSANTS	0.077	0.1	0.086	0.067	0.1	0.121
ANTIEPILEPTICS	0.023	-0.056	0.07	-0.056	-0.056	0.151
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.233	0.3	0.157	0.311	0.3	0.024
ANTINEOPLASTIC AGENTS	0.028	-0.056	0.03	0	-0.056	0
ANTIPSORIATICS	0.026	-0.056	0.116	-0.056	-0.056	0.203
ANTITHROMBOTIC AGENTS	0.083	0.078	0.018	0.067	0.078	0.043
BETA BLOCKING AGENTS	0.106	0.1	0.02	0.111	0.1	0.036
CALCIUM CHANNEL BLOCKERS	0.061	-0.056	0.116	0.056	-0.056	0.108
DIURETICS	0.114	0.1	0.044	0.122	0.1	0.071
DRUGS FOR ACID RELATED DISORDERS	0.241	0.256	0.034	0.189	0.256	0.16
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.385	0.433	0.1	0.411	0.433	0.045

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
DRUGS USED IN DIABETES	0.047	-0.056	0.119	-0.056	-0.056	0.087
IMMUNOSUPPRESSANTS	0.029	-0.056	0.042	-0.056	-0.056	0.087
LIPID MODIFYING AGENTS	0.123	0.056	0.206	0.1	0.056	0.166
OPIOIDS	0.128	0.189	0.182	0.1	0.189	0.253
PSYCHOLEPTICS	0.137	0.167	0.085	0.222	0.167	0.14
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.008	-0.056	0.156	0	-0.056	0

Appendix Table 14. Select characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Rosacea*) and comparator (*Erythromycin Rosacea*) group as well as the standardised difference of the means – SIDIAP.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
0 - 4	0	-0.006	0	0	-0.006	0
5 - 9	-0.001	-0.006	0.063	0	-0.006	0
10 - 14	0.005	0.033	0.298	0.031	0.027	0.025
15 - 19	0.027	0.046	0.113	0.043	0.046	0.012
20 - 24	0.035	0.042	0.037	0.039	0.042	0.018
25 - 29	0.053	0.075	0.098	0.073	0.075	0.007

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
30 - 34	0.065	0.085	0.079	0.085	0.084	0.004
35 - 39	0.089	0.1	0.039	0.123	0.1	0.073
40 - 44	0.114	0.107	0.02	0.143	0.108	0.105
45 - 49	0.115	0.075	0.127	0.064	0.077	0.052
50 - 54	0.092	0.09	0.009	0.09	0.091	0.004
55 - 59	0.088	0.064	0.088	0.073	0.065	0.033
60 - 64	0.078	0.059	0.073	0.049	0.058	0.04
65 - 69	0.076	0.058	0.071	0.057	0.057	0.003
70 - 74	0.064	0.062	0.006	0.055	0.064	0.036
75 - 79	0.045	0.049	0.02	0.034	0.049	0.078
80 - 84	0.031	0.026	0.03	0.019	0.026	0.049
85 - 89	0.017	0.019	0.017	0.019	0.019	0
90 - 94	0.004	0.006	0.038	-0.006	0.006	0.08
100 - 104	-0.001	-0.006	0.063	0	-0.006	0
gender = FEMALE	0.678	0.724	0.1	0.703	0.725	0.049
Atrial fibrillation	0.008	0.007	0.015	0.008	0.007	0.014
Cerebrovascular disease	0.003	-0.006	0.006	-0.006	-0.006	0
Coronary arteriosclerosis	0.002	-0.006	0.023	0	-0.006	0
Heart disease	0.034	0.027	0.036	0.031	0.026	0.029
Heart failure	0.006	-0.006	0.051	-0.006	-0.006	0.022
Ischemic heart disease	0.005	0.006	0.01	-0.006	-0.006	0.039
Peripheral vascular disease	0.003	0.006	0.044	-0.006	-0.006	0.072
Pulmonary embolism	0.001	-0.006	0.008	-0.006	-0.006	0.028

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Venous thrombosis	0.005	0.006	0.01	-0.006	0.006	0.016
Acute respiratory disease	0.103	0.12	0.056	0.136	0.116	0.06
Attention deficit hyperactivity disorder	-0.001	0	0	-0.006	0	0
Chronic liver disease	0.003	-0.006	0.02	-0.006	-0.006	0
Chronic obstructive lung disease	0.01	0.006	0.042	0.007	0.006	0.015
Crohn's disease	-0.001	-0.006	0.111	0	-0.006	0
Dementia	0.001	-0.006	0.055	-0.006	-0.006	0
Diabetes mellitus	0.018	0.014	0.027	0.023	0.014	0.067
Gastroesophageal reflux disease	0.01	0.008	0.021	0.006	0.008	0.029
Gastrointestinal hemorrhage	0.011	0.013	0.014	0.012	0.013	0.011
Human immunodeficiency virus infection	-0.001	-0.006	0.023	0	-0.006	0
Hyperlipidemia	0.032	0.028	0.02	0.026	0.028	0.011
Hypertensive disorder	0.042	0.032	0.051	0.036	0.032	0.02
Lesion of liver	0.003	-0.006	0.013	-0.006	-0.006	0.022
Obesity	0.033	0.046	0.07	0.043	0.046	0.015
Osteoarthritis	0.031	0.032	0.002	0.034	0.032	0.01
Pneumonia	0.009	0.006	0.03	-0.006	0.006	0.016
Psoriasis	0.01	-0.006	0.053	0.006	-0.006	0.016

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Renal impairment	0.009	0.007	0.023	-0.006	0.007	0.031
Rheumatoid arthritis	0.001	-0.006	0	-0.006	-0.006	0.028
Schizophrenia	0.001	0	0	-0.006	0	0
Ulcerative colitis	0.001	-0.006	0.004	-0.006	-0.006	0.028
Urinary tract infectious disease	0.076	0.09	0.052	0.091	0.09	0.004
Viral hepatitis C	0.001	-0.006	0.004	-0.006	-0.006	0
Malignant neoplastic disease	0.024	0.014	0.064	0.017	0.014	0.019
Malignant tumor of breast	0.003	-0.006	0.032	-0.006	-0.006	0.028
Malignant tumor of colon	0.001	0	0	-0.006	0	0
Malignant tumor of urinary bladder	0.002	0	0	-0.006	0	0
Primary malignant neoplasm of prostate	0.001	-0.006	0.008	-0.006	-0.006	0.049
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.191	0.161	0.075	0.135	0.164	0.081
ANTIBACTERIALS FOR SYSTEMIC USE	0.573	0.538	0.071	0.517	0.538	0.041
ANTIDEPRESSANTS	0.148	0.13	0.053	0.119	0.131	0.035
ANTIEPILEPTICS	0.073	0.08	0.027	0.07	0.079	0.037

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.453	0.482	0.058	0.475	0.476	0.001
ANTINEOPLASTIC AGENTS	0.019	0.016	0.019	0.019	0.016	0.023
ANTIPSORIATICS	0.023	0.013	0.07	0.013	0.013	0.005
ANTITHROMBOTIC AGENTS	0.103	0.102	0.002	0.094	0.103	0.032
BETA BLOCKING AGENTS	0.074	0.058	0.062	0.064	0.059	0.02
CALCIUM CHANNEL BLOCKERS	0.059	0.062	0.015	0.051	0.064	0.057
DIURETICS	0.129	0.113	0.048	0.079	0.115	0.12
DRUGS FOR ACID RELATED DISORDERS	0.315	0.302	0.028	0.277	0.304	0.06
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.284	0.263	0.047	0.253	0.262	0.022
DRUGS USED IN DIABETES	0.067	0.053	0.056	0.047	0.054	0.03
IMMUNOSUPPRESSANTS	0.031	0.021	0.058	0.017	0.022	0.035
LIPID MODIFYING AGENTS	0.151	0.134	0.047	0.126	0.134	0.023
OPIOIDS	0.121	0.102	0.057	0.103	0.103	0.002
PSYCHOLEPTICS	0.27	0.24	0.067	0.227	0.242	0.034

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.014	0.016	0.023	0.007	0.017	0.088

Appendix Table 15. Select characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Rosacea*) and comparator (*Isotretinoin Rosacea*) group as well as the standardised difference of the means– CPRD.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
10 - 14	0.008	-0.052	0.137	0	-0.047	0
15 - 19	0.035	0.32	1.499	0.362	0.207	0.343
20 - 24	0.028	0.072	0.268	0.149	0.111	0.12
25 - 29	0.036	0.072	0.193	-0.106	0.047	0.132
30 - 34	0.056	0.093	0.158	-0.106	0.129	0.307
35 - 39	0.078	-0.052	0.138	-0.106	0.068	0.068
40 - 44	0.103	0.103	0.002	-0.106	0.094	0.104
45 - 49	0.12	0.052	0.212	-0.106	0.079	0.148
50 - 54	0.11	0.072	0.12	-0.106	0.079	0.256
55 - 59	0.097	-0.052	0.189	-0.106	-0.047	0
60 - 64	0.09	0.062	0.098	-0.106	0.082	0.157
65 - 69	0.087	-0.052	0.237	-0.106	-0.047	0.058
70 - 74	0.065	-0.052	0.222	-0.106	0	0
75 - 79	0.044	-0.052	0.165	-0.106	0	0

80 - 84	0.028	-0.052	0.106	0	-0.047	0
gender = FEMALE	0.584	0.443	0.285	0.34	0.407	0.137
Cerebrovascular disease	0.003	-0.052	0.14	0	-0.047	0
Acute respiratory disease	0.062	0.062	0.002	0.106	0.084	0.074
Dementia	0.001	0	0	-0.106	0	0
Gastroesophageal reflux disease	0.004	-0.052	0.107	0	-0.047	0
Hypertensive disorder	0.016	-0.052	0.044	0	-0.047	0
Psoriasis	0.012	-0.052	0.079	-0.106	-0.047	0.068
Renal impairment	0.009	0	0	-0.106	0	0
Urinary tract infectious disease	0.017	-0.052	0.055	-0.106	0	0

Appendix Table 16. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Rosacea*) and comparator (*Isotretinoin Rosacea*) group as well as the standardised difference of the means– IPCI.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
10 - 14	-0.002	-0.034	0.173	0	-0.034	0
15 - 19	0.016	0.034	0.146	0.034	0.034	0
20 - 24	0.039	0.048	0.047	0.062	0.048	0.06
25 - 29	0.056	0.096	0.169	0.041	0.096	0.217
30 - 34	0.074	0.089	0.057	0.075	0.089	0.05
35 - 39	0.097	0.123	0.088	0.11	0.123	0.043

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
40 - 44	0.107	0.144	0.119	0.151	0.144	0.019
45 - 49	0.13	0.13	0	0.158	0.13	0.078
50 - 54	0.114	0.11	0.012	0.11	0.11	0
55 - 59	0.083	0.082	0.002	0.068	0.082	0.052
60 - 64	0.074	0.034	0.155	0.055	0.034	0.1
65 - 69	0.067	0.055	0.05	0.048	0.055	0.031
70 - 74	0.06	-0.034	0.139	0.041	-0.034	0.075
75 - 79	0.038	-0.034	0.127	0.041	-0.034	0.168
85 - 89	0.013	-0.034	0.052	-0.034	-0.034	0
gender = FEMALE	0.716	0.692	0.054	0.76	0.692	0.153
Atrial fibrillation	0.01	-0.034	0.032	-0.034	-0.034	0.068
Cerebrovascular disease	0.011	-0.034	0.041	0	-0.034	0
Heart disease	0.037	-0.034	0.088	-0.034	-0.034	0.045
Heart failure	0.005	0	0	-0.034	0	0
Ischemic heart disease	0.014	-0.034	0.064	-0.034	-0.034	0.068
Venous thrombosis	0.006	0	0	-0.034	0	0
Acute respiratory disease	0.128	0.089	0.118	0.103	0.089	0.047
Attention deficit hyperactivity disorder	0.005	-0.034	0.022	0	-0.034	0
Chronic obstructive lung disease	0.016	-0.034	0.072	-0.034	-0.034	0
Crohn's disease	0.004	-0.034	0.156	0	-0.034	0
Diabetes mellitus	0.039	-0.034	0.098	0.041	-0.034	0.119

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Gastrointestinal hemorrhage	0.012	0	0	-0.034	0	0
Hyperlipidemia	0.022	0	0	-0.034	0	0
Hypertensive disorder	0.102	0.062	0.133	0.055	0.062	0.029
Obesity	0.011	-0.034	0.043	-0.034	-0.034	0.068
Osteoarthritis	0.031	-0.034	0.141	-0.034	-0.034	0.068
Pneumonia	0.022	-0.034	0.013	-0.034	-0.034	0.118
Psoriasis	0.011	0	0	-0.034	0	0
Renal impairment	0.006	0	0	-0.034	0	0
Rheumatoid arthritis	0.006	-0.034	0.009	-0.034	-0.034	0
Ulcerative colitis	0.006	-0.034	0.018	0	-0.034	0
Urinary tract infectious disease	0.077	0.082	0.019	0.096	0.082	0.048
Malignant neoplastic disease	0.036	-0.034	0.158	-0.034	-0.034	0.068
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.143	0.103	0.116	0.103	0.103	0
ANTIBACTERIALS FOR SYSTEMIC USE	0.798	0.795	0.008	0.822	0.795	0.069
ANTIDEPRESSANTS	0.077	0.075	0.006	0.096	0.075	0.073
ANTIEPILEPTICS	0.023	-0.034	0.015	-0.034	-0.034	0.053
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.233	0.219	0.034	0.233	0.219	0.033

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ANTINEOPLASTIC AGENTS	0.028	0.103	0.426	0.089	0.103	0.047
ANTIPSORIATICS	0.026	-0.034	0.033	0.034	-0.034	0.084
ANTITHROMBOTIC AGENTS	0.083	0.048	0.127	0.041	0.048	0.033
BETA BLOCKING AGENTS	0.106	0.048	0.191	0.055	0.048	0.031
CALCIUM CHANNEL BLOCKERS	0.061	0.048	0.054	-0.034	0.048	0.108
DIURETICS	0.114	0.048	0.21	0.075	0.048	0.114
DRUGS FOR ACID RELATED DISORDERS	0.241	0.192	0.115	0.247	0.192	0.132
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.385	0.377	0.017	0.301	0.377	0.159
DRUGS USED IN DIABETES	0.047	-0.034	0.095	0.041	-0.034	0.075
IMMUNOSUPPRESSANTS	0.029	0.055	0.149	0.048	0.055	0.031
LIPID MODIFYING AGENTS	0.123	0.068	0.167	0.096	0.068	0.1
OPIOIDS	0.128	0.137	0.028	0.11	0.137	0.083
PSYCHOLEPTICS	0.137	0.116	0.061	0.116	0.116	0
PSYCHOSTIMULANTS. AGENTS USED FOR	0.008	-0.034	0.063	-0.034	-0.034	0.068

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ADHD AND NOOTROPICS						

Appendix Table 17. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Rosacea*) and comparator (*Isotretinoin Rosacea*) group as well as the standardised difference of the means– SIDIAP.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	0	-0.008	0	0	-0.008	0
10 - 14	0.005	0.008	0.035	-0.008	0.008	0.019
15 - 19	0.027	0.057	0.178	0.032	0.055	0.114
20 - 24	0.035	0.055	0.106	0.04	0.052	0.056
25 - 29	0.053	0.09	0.16	0.073	0.085	0.043
30 - 34	0.065	0.08	0.06	0.072	0.082	0.038
35 - 39	0.089	0.116	0.093	0.117	0.119	0.005
40 - 44	0.114	0.113	0.003	0.11	0.115	0.016
45 - 49	0.115	0.122	0.022	0.152	0.122	0.086
50 - 54	0.092	0.07	0.077	0.09	0.071	0.072
55 - 59	0.088	0.052	0.129	0.058	0.052	0.029
60 - 64	0.078	0.052	0.098	0.065	0.051	0.062
65 - 69	0.076	0.073	0.011	0.07	0.075	0.019
70 - 74	0.064	0.036	0.116	0.04	0.037	0.017
75 - 79	0.045	0.041	0.022	0.033	0.042	0.044
80 - 84	0.031	0.02	0.068	0.02	0.02	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
85 - 89	0.017	0.01	0.054	0.017	0.01	0.058
90 - 94	0.004	-0.008	0.005	-0.008	-0.008	0
gender = FEMALE	0.678	0.604	0.158	0.614	0.603	0.023
Atrial fibrillation	0.008	0.01	0.015	-0.008	0.01	0.082
Cerebrovascular disease	0.003	-0.008	0.02	-0.008	-0.008	0
Coronary arteriosclerosis	0.002	-0.008	0.013	-0.008	-0.008	0
Heart disease	0.034	0.029	0.023	0.025	0.03	0.031
Heart failure	0.006	-0.008	0.017	-0.008	-0.008	0.058
Ischemic heart disease	0.005	0.008	0.04	-0.008	0.008	0.066
Peripheral vascular disease	0.003	-0.008	0	0	-0.008	0
Venous thrombosis	0.005	-0.008	0.027	-0.008	-0.008	0
Acute respiratory disease	0.103	0.086	0.055	0.088	0.087	0.004
Attention deficit hyperactivity disorder	-0.001	-0.008	0.156	0	-0.008	0
Chronic liver disease	0.003	0	0	-0.008	0	0
Chronic obstructive lung disease	0.01	-0.008	0.087	-0.008	-0.008	0.033
Dementia	0.001	-0.008	0.008	-0.008	-0.008	0
Diabetes mellitus	0.018	0.013	0.035	0.008	0.013	0.049
Gastroesophageal reflux disease	0.01	0.008	0.022	0.013	0.008	0.048

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Gastrointestinal hemorrhage	0.011	0.013	0.015	0.013	0.012	0.015
Human immunodeficiency virus infection	-0.001	0	0	-0.008	0	0
Hyperlipidemia	0.032	0.036	0.024	0.037	0.036	0.006
Hypertensive disorder	0.042	0.047	0.027	0.035	0.048	0.067
Lesion of liver	0.003	0	0	-0.008	0	0
Obesity	0.033	0.024	0.049	0.023	0.024	0.004
Osteoarthritis	0.031	0.026	0.031	0.015	0.025	0.071
Pneumonia	0.009	-0.008	0.041	-0.008	-0.008	0.026
Psoriasis	0.01	0.013	0.033	0.017	0.013	0.027
Renal impairment	0.009	0.011	0.023	-0.008	0.012	0.053
Schizophrenia	0.001	-0.008	0.082	-0.008	-0.008	0.033
Ulcerative colitis	0.001	-0.008	0.008	-0.008	-0.008	0
Urinary tract infectious disease	0.076	0.062	0.052	0.047	0.063	0.07
Viral hepatitis C	0.001	0	0	-0.008	0	0
Malignant neoplasm of anorectum	-0.001	-0.008	0.09	0	-0.008	0
Malignant neoplastic disease	0.024	0.02	0.027	-0.008	0.02	0.116
Malignant tumor of breast	0.003	0	0	-0.008	0	0
Malignant tumor of lung	0.001	-0.008	0.031	0	-0.008	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Malignant tumor of urinary bladder	0.002	-0.008	0.01	0	-0.008	0
Primary malignant neoplasm of prostate	0.001	-0.008	0.004	0	-0.008	0
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.191	0.135	0.142	0.149	0.139	0.029
ANTIBACTERIALS FOR SYSTEMIC USE	0.573	0.566	0.015	0.583	0.56	0.046
ANTIDEPRESSANTS	0.148	0.137	0.032	0.125	0.135	0.028
ANTIEPILEPTICS	0.073	0.078	0.021	0.082	0.077	0.016
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.453	0.401	0.103	0.381	0.399	0.038
ANTINEOPLASTIC AGENTS	0.019	0.026	0.05	0.027	0.025	0.011
ANTIPSORIATICS	0.023	0.021	0.014	0.032	0.022	0.062
ANTITHROMBOTIC AGENTS	0.103	0.106	0.009	0.088	0.108	0.065
BETA BLOCKING AGENTS	0.074	0.052	0.084	0.053	0.053	0
CALCIUM CHANNEL BLOCKERS	0.059	0.049	0.043	0.047	0.05	0.016
DIURETICS	0.129	0.082	0.144	0.07	0.083	0.05
DRUGS FOR ACID RELATED DISORDERS	0.315	0.287	0.06	0.267	0.287	0.044

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.284	0.248	0.08	0.234	0.252	0.042
DRUGS USED IN DIABETES	0.067	0.034	0.133	0.033	0.035	0.009
IMMUNOSUPPRESSANTS	0.031	0.054	0.127	0.05	0.054	0.018
LIPID MODIFYING AGENTS	0.151	0.121	0.086	0.119	0.122	0.012
OPIOIDS	0.121	0.085	0.112	0.105	0.087	0.062
PSYCHOLEPTICS	0.27	0.214	0.128	0.18	0.212	0.08
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.014	0.02	0.049	0.012	0.019	0.059

Appendix Table 18. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline LRTI*) and comparator (*Azithromycin LRTI*) group as well as the standardised difference of the means – CPRD.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	0	0.143	1.606	-0.001	-0.001	0.011
5 - 9	0	0.053	0.975	-0.001	0.002	0.033
10 - 14	0.002	0.023	0.41	0.023	0.025	0.01
15 - 19	0.013	0.017	0.029	0.02	0.021	0.008

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
20 - 24	0.022	0.015	0.045	0.017	0.019	0.014
25 - 29	0.028	0.013	0.091	0.019	0.017	0.021
30 - 34	0.038	0.019	0.101	0.024	0.024	0.003
35 - 39	0.048	0.028	0.093	0.031	0.035	0.024
40 - 44	0.059	0.037	0.093	0.044	0.047	0.015
45 - 49	0.072	0.043	0.111	0.052	0.054	0.007
50 - 54	0.083	0.056	0.1	0.062	0.067	0.02
55 - 59	0.093	0.068	0.085	0.084	0.083	0.001
60 - 64	0.102	0.086	0.053	0.107	0.107	0.001
65 - 69	0.107	0.092	0.046	0.123	0.115	0.028
70 - 74	0.1	0.095	0.017	0.116	0.118	0.007
75 - 79	0.086	0.079	0.026	0.105	0.099	0.019
80 - 84	0.07	0.063	0.028	0.082	0.08	0.006
85 - 89	0.046	0.043	0.017	0.056	0.055	0.008
90 - 94	0.023	0.018	0.031	0.024	0.023	0.004
95 - 99	0.007	0.007	0.008	0.008	0.009	0.008
100 - 104	0.001	0.001	0.003	0.002	0.002	0.01
gender = FEMALE	0.583	0.573	0.02	0.607	0.601	0.013
Atrial fibrillation	0.013	0.014	0.004	0.018	0.017	0.009
Cerebrovascular disease	0.009	0.008	0.007	0.013	0.01	0.03
Coronary arteriosclerosis	0.001	0.001	0.011	0.001	0.001	0.004
Heart disease	0.038	0.046	0.042	0.052	0.053	0.007
Heart failure	0.007	0.01	0.038	0.012	0.012	0.001

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Ischemic heart disease	0.012	0.013	0.009	0.016	0.016	0.005
Peripheral vascular disease	0.003	0.003	0.007	0.005	0.003	0.027
Pulmonary embolism	0.003	0.003	0.003	0.005	0.003	0.027
Venous thrombosis	0.008	0.009	0.022	0.01	0.012	0.019
Acute respiratory disease	0.101	0.204	0.333	0.19	0.183	0.017
Attention deficit hyperactivity disorder	0	-0.001	0	-0.001	-0.001	0
Chronic liver disease	0.001	0.001	0.007	-0.001	0.001	0.014
Chronic obstructive lung disease	0.049	0.119	0.31	0.151	0.137	0.039
Crohn's disease	0.001	0.002	0.025	0.002	0.002	0.003
Dementia	0.007	0.005	0.021	0.009	0.006	0.028
Diabetes mellitus	0.017	0.016	0.005	0.02	0.02	0.002
Gastroesophageal reflux disease	0.006	0.007	0.017	0.007	0.007	0.004
Gastrointestinal hemorrhage	0.012	0.013	0.005	0.018	0.015	0.028
Human immunodeficiency virus infection	0	-0.001	0.046	0	-0.001	0
Hyperlipidemia	0.008	0.007	0.006	0.009	0.009	0.008
Hypertensive disorder	0.018	0.013	0.036	0.017	0.016	0.007
Lesion of liver	0.001	0.001	0.008	0.002	0.001	0.02
Obesity	0.005	0.007	0.036	0.007	0.008	0.013

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Osteoarthritis	0.033	0.027	0.034	0.035	0.032	0.017
Pneumonia	0.003	0.011	0.136	0.012	0.011	0.013
Psoriasis	0.008	0.009	0.01	0.009	0.01	0.009
Renal impairment	0.023	0.022	0.002	0.03	0.028	0.014
Rheumatoid arthritis	0.004	0.004	0.004	0.006	0.005	0.012
Schizophrenia	0	0.001	0.012	0	0.001	0
Ulcerative colitis	0.001	0.001	0.003	0.002	0.001	0.01
Urinary tract infectious disease	0.035	0.045	0.053	0.058	0.05	0.038
Viral hepatitis C	0	-0.001	0.005	0	-0.001	0
Malignant lymphoma	0.001	0.001	0.021	0.002	0.002	0.002
Malignant neoplasm of anorectum	0	-0.001	0.005	-0.001	-0.001	0.004
Malignant neoplastic disease	0.021	0.027	0.036	0.033	0.033	0.004
Malignant tumor of breast	0.002	0.002	0.006	0.002	0.003	0.018
Malignant tumor of colon	0.001	0.001	0.006	-0.001	0.001	0.023
Malignant tumor of lung	0.002	0.004	0.032	0.006	0.005	0.025
Malignant tumor of urinary bladder	0.001	0.001	0.01	0.001	0.001	0.002

Appendix Table 19. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline LRTI*) and comparator (*Azithromycin LRTI*) group as well as the standardized difference of the means – IPCI.

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	0	0.075	0.539	-0.001	0	0.001
5 - 9	0	0.048	0.425	-0.001	0	0.004
10 - 14	0.004	0.032	0.265	0.013	0.012	0.005
15 - 19	0.021	0.034	0.078	0.039	0.038	0.008
20 - 24	0.02	0.024	0.025	0.027	0.027	0.001
25 - 29	0.022	0.023	0.005	0.026	0.027	0.001
30 - 34	0.032	0.029	0.019	0.035	0.035	0.005
35 - 39	0.046	0.044	0.013	0.052	0.051	0.008
40 - 44	0.062	0.06	0.008	0.07	0.069	0.003
45 - 49	0.074	0.067	0.027	0.073	0.078	0.019
50 - 54	0.084	0.073	0.043	0.085	0.085	0.001
55 - 59	0.103	0.079	0.081	0.09	0.093	0.01
60 - 64	0.107	0.083	0.08	0.1	0.097	0.009
65 - 69	0.103	0.083	0.068	0.094	0.097	0.01
70 - 74	0.093	0.072	0.075	0.087	0.084	0.009
75 - 79	0.081	0.06	0.082	0.068	0.07	0.009
80 - 84	0.068	0.055	0.053	0.066	0.065	0.007
85 - 89	0.048	0.039	0.042	0.045	0.046	0.002
90 - 94	0.025	0.018	0.045	0.022	0.022	0
95 - 99	0.005	0.005	0.008	0.006	0.005	0.013
100 - 104	0.001	0.001	0	0.001	0.001	0.007

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
105 - 109	0	0	0	-0.001	0	0
gender = FEMALE	0.576	0.604	0.058	0.632	0.623	0.017
Atrial fibrillation	0.028	0.019	0.058	0.022	0.022	0.001
Cerebrovascular disease	0.022	0.02	0.016	0.022	0.023	0.005
Coronary arteriosclerosis	0.002	0.003	0.012	0.002	0.004	0.033
Heart disease	0.103	0.084	0.065	0.096	0.098	0.006
Heart failure	0.023	0.023	0.004	0.025	0.026	0.007
Ischemic heart disease	0.045	0.037	0.041	0.043	0.043	0.002
Peripheral vascular disease	0.01	0.009	0.014	0.01	0.011	0.005
Pulmonary embolism	0.003	0.004	0.012	0.004	0.005	0.006
Venous thrombosis	0.009	0.008	0.004	0.01	0.009	0.004
Acute respiratory disease	0.142	0.223	0.22	0.204	0.19	0.035
Attention deficit hyperactivity disorder	0.004	0.006	0.024	0.006	0.005	0.014
Chronic liver disease	0.001	0.001	0.005	0.001	0.001	0.012
Chronic obstructive lung disease	0.045	0.046	0.007	0.055	0.053	0.006
Crohn's disease	0.003	0.004	0.023	0.004	0.005	0.004
Dementia	0.009	0.007	0.011	0.008	0.009	0.009
Diabetes mellitus	0.089	0.074	0.056	0.085	0.085	0.003
Gastroesophageal reflux disease	0.008	0.01	0.025	0.008	0.01	0.015
Gastrointestinal hemorrhage	0.013	0.012	0.004	0.016	0.014	0.017
Human immunodeficiency virus infection	0.001	0	0.008	-0.001	0	0.012
Hyperlipidemia	0.037	0.029	0.045	0.033	0.033	0.002

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Hypertensive disorder	0.158	0.127	0.086	0.14	0.147	0.022
Lesion of liver	0.001	0.001	0.009	0.001	0.001	0.008
Obesity	0.01	0.011	0.012	0.013	0.012	0.002
Osteoarthritis	0.053	0.05	0.011	0.056	0.058	0.005
Pneumonia	0.049	0.076	0.115	0.076	0.071	0.016
Psoriasis	0.01	0.01	0.005	0.011	0.011	0.006
Renal impairment	0.02	0.021	0.009	0.023	0.024	0.009
Rheumatoid arthritis	0.009	0.011	0.011	0.011	0.012	0.001
Schizophrenia	0.001	0.001	0.006	0.001	0.001	0.006
Ulcerative colitis	0.003	0.004	0.028	0.005	0.005	0.002
Urinary tract infectious disease	0.077	0.082	0.022	0.093	0.091	0.005
Viral hepatitis C	0	0	0.013	-0.001	0	0.006
Malignant lymphoma	0.002	0.002	0.009	0.002	0.002	0.005
Malignant neoplasm of anorectum	0.001	0.001	0.009	0.001	0.001	0
Malignant neoplastic disease	0.053	0.049	0.016	0.057	0.057	0.001
Malignant tumor of breast	0.009	0.008	0.01	0.01	0.009	0.008
Malignant tumor of colon	0.002	0.004	0.028	0.003	0.004	0.009
Malignant tumor of lung	0.004	0.006	0.023	0.005	0.006	0.023
Malignant tumor of urinary bladder	0.003	0.002	0.006	0.002	0.003	0.01
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.265	0.203	0.145	0.231	0.237	0.014

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ANTIBACTERIALS FOR SYSTEMIC USE	0.308	0.364	0.12	0.378	0.366	0.024
ANTIDEPRESSANTS	0.118	0.1	0.054	0.114	0.115	0.001
ANTIEPILEPTICS	0.038	0.043	0.024	0.049	0.048	0.003
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.333	0.284	0.105	0.324	0.327	0.005
ANTINEOPLASTIC AGENTS	0.026	0.025	0.005	0.03	0.029	0.003
ANTIPSORIATICS	0.028	0.031	0.019	0.034	0.035	0
ANTITHROMBOTIC AGENTS	0.203	0.158	0.115	0.18	0.185	0.014
BETA BLOCKING AGENTS	0.235	0.174	0.147	0.196	0.205	0.022
CALCIUM CHANNEL BLOCKERS	0.122	0.095	0.086	0.109	0.11	0.005
DIURETICS	0.232	0.187	0.108	0.213	0.218	0.012
DRUGS FOR ACID RELATED DISORDERS	0.38	0.342	0.079	0.398	0.393	0.01
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.49	0.537	0.094	0.564	0.549	0.03
DRUGS USED IN DIABETES	0.112	0.089	0.074	0.101	0.104	0.011
IMMUNOSUPPRESSANTS	0.018	0.019	0.012	0.022	0.022	0
LIPID MODIFYING AGENTS	0.258	0.2	0.136	0.229	0.234	0.012
OPIOIDS	0.269	0.275	0.014	0.318	0.313	0.011
PSYCHOLEPTICS	0.205	0.188	0.043	0.215	0.215	0.001
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.01	0.013	0.031	0.013	0.013	0.005

Appendix Table 20. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline LRTI*) and comparator (*Azithromycin LRTI*) group as well as the standardised difference of the means – SIDIAP.

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	-0.002	0.133	0.39	-0.002	0.017	0.132
5 - 9	-0.002	0.067	0.263	-0.002	0.002	0.002
10 - 14	0.015	0.041	0.129	0.015	0.014	0.008
15 - 19	0.054	0.023	0.205	0.054	0.054	0.002
20 - 24	0.056	0.023	0.214	0.055	0.057	0.007
25 - 29	0.056	0.029	0.162	0.056	0.055	0.004
30 - 34	0.07	0.038	0.168	0.069	0.067	0.01
35 - 39	0.073	0.053	0.087	0.072	0.074	0.01
40 - 44	0.074	0.061	0.054	0.075	0.066	0.033
45 - 49	0.071	0.059	0.052	0.071	0.066	0.02
50 - 54	0.057	0.059	0.008	0.057	0.051	0.026
55 - 59	0.063	0.061	0.008	0.063	0.057	0.026
60 - 64	0.074	0.064	0.039	0.074	0.073	0.003
65 - 69	0.064	0.062	0.008	0.064	0.065	0.003
70 - 74	0.068	0.059	0.041	0.069	0.064	0.018
75 - 79	0.059	0.052	0.034	0.06	0.067	0.028
80 - 84	0.054	0.047	0.033	0.054	0.058	0.017
85 - 89	0.057	0.038	0.099	0.058	0.056	0.009
90 - 94	0.022	0.022	0.005	0.023	0.026	0.022
95 - 99	0.007	0.007	0.007	0.007	0.009	0.016
100 - 104	-0.002	0.001	0.017	-0.002	0.001	0.015

105 - 109	0	0	0	0	0	0
gender = FEMALE	0.573	0.572	0.002	0.573	0.568	0.01
Atrial fibrillation	0.045	0.019	0.19	0.045	0.052	0.031
Cerebrovascular disease	0.013	0.008	0.054	0.013	0.014	0.01
Coronary arteriosclerosis	0.012	0.005	0.106	0.012	0.011	0.007
Heart disease	0.117	0.061	0.23	0.116	0.13	0.044
Heart failure	0.055	0.019	0.265	0.055	0.06	0.021
Ischemic heart disease	0.025	0.014	0.095	0.025	0.028	0.021
Peripheral vascular disease	0.014	0.006	0.114	0.014	0.016	0.016
Pulmonary embolism	0.006	0.002	0.112	0.006	0.006	0.001
Venous thrombosis	0.019	0.008	0.121	0.019	0.018	0.006
Acute respiratory disease	0.22	0.2	0.049	0.217	0.231	0.034
Attention deficit hyperactivity disorder	-0.002	0.001	0.007	-0.002	0.001	0.006
Chronic liver disease	0.011	0.003	0.146	0.011	0.009	0.03
Chronic obstructive lung disease	0.066	0.018	0.354	0.065	0.069	0.014
Crohn's disease	0.002	0.001	0.061	0.002	0.002	0
Dementia	0.014	0.009	0.055	0.014	0.017	0.021
Diabetes mellitus	0.058	0.027	0.196	0.056	0.064	0.03
Gastroesophageal reflux disease	0.02	0.013	0.064	0.02	0.022	0.015
Gastrointestinal hemorrhage	0.019	0.012	0.064	0.019	0.02	0.007
Human immunodeficiency virus infection	0.005	0.001	0.174	0.005	0.004	0.023
Hyperlipidemia	0.081	0.043	0.186	0.08	0.09	0.034
Hypertensive disorder	0.096	0.054	0.184	0.096	0.108	0.04

Lesion of liver	0.007	0.002	0.11	0.007	0.008	0.004
Obesity	0.068	0.039	0.154	0.068	0.07	0.007
Osteoarthritis	0.056	0.038	0.093	0.057	0.063	0.025
Pneumonia	0.061	0.032	0.169	0.061	0.064	0.014
Psoriasis	0.011	0.004	0.127	0.011	0.011	0.008
Renal impairment	0.054	0.024	0.194	0.054	0.062	0.034
Rheumatoid arthritis	0.006	0.002	0.087	0.005	0.005	0.002
Schizophrenia	0.003	0.001	0.054	0.003	0.004	0.023
Ulcerative colitis	0.003	0.001	0.061	0.003	0.002	0.022
Urinary tract infectious disease	0.13	0.074	0.211	0.128	0.139	0.033
Viral hepatitis C	0.006	0.002	0.1	0.007	0.005	0.025
Malignant lymphoma	0.007	0.002	0.145	0.007	0.008	0.016
Malignant neoplasm of anorectum	-0.002	0.001	0.029	-0.002	0.002	0.011
Malignant neoplastic disease	0.061	0.023	0.251	0.06	0.071	0.044
Malignant tumor of breast	0.009	0.003	0.114	0.009	0.005	0.045
Malignant tumor of colon	0.005	0.002	0.081	0.005	0.004	0.017
Malignant tumor of lung	0.007	0.001	0.174	0.007	0.009	0.022
Malignant tumor of urinary bladder	0.002	0.002	0.011	-0.002	0.005	0.045
Primary malignant neoplasm of prostate	0.003	0.002	0.039	0.003	0.005	0.019
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.249	0.211	0.095	0.249	0.249	0.001
ANTIBACTERIALS FOR SYSTEMIC USE	0.611	0.378	0.481	0.609	0.648	0.08

ANTIDEPRESSANTS	0.25	0.159	0.247	0.244	0.257	0.028
ANTIEPILEPTICS	0.138	0.077	0.231	0.134	0.148	0.042
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.569	0.511	0.116	0.567	0.579	0.024
ANTINEOPLASTIC AGENTS	0.027	0.015	0.102	0.027	0.026	0.004
ANTIPSORIATICS	0.023	0.012	0.102	0.023	0.025	0.01
ANTITHROMBOTIC AGENTS	0.229	0.149	0.225	0.229	0.237	0.019
BETA BLOCKING AGENTS	0.137	0.103	0.113	0.137	0.143	0.017
CALCIUM CHANNEL BLOCKERS	0.101	0.078	0.087	0.101	0.102	0.003
DIURETICS	0.224	0.169	0.146	0.224	0.231	0.017
DRUGS FOR ACID RELATED DISORDERS	0.483	0.328	0.33	0.483	0.502	0.039
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.587	0.412	0.355	0.586	0.612	0.053
DRUGS USED IN DIABETES	0.123	0.084	0.141	0.122	0.125	0.011
IMMUNOSUPPRESSANTS	0.029	0.014	0.128	0.028	0.031	0.017
LIPID MODIFYING AGENTS	0.214	0.177	0.096	0.214	0.219	0.012
OPIOIDS	0.248	0.15	0.273	0.245	0.254	0.02
PSYCHOLEPTICS	0.403	0.273	0.29	0.398	0.41	0.025
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.03	0.019	0.078	0.03	0.028	0.011

Appendix Table 21. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline LRTI*) and comparator (*Amoxicillin LRTI*) group as well as the standardized difference of the means – CPRD.

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	0	0.103	0.423	0	0	0.007
5 - 9	0	0.033	0.235	0	0	0.006
10 - 14	0.002	0.025	0.188	0.002	0.002	0
15 - 19	0.013	0.033	0.127	0.016	0.015	0.006
20 - 24	0.022	0.036	0.084	0.025	0.025	0.001
25 - 29	0.028	0.042	0.071	0.032	0.033	0.006
30 - 34	0.038	0.049	0.051	0.042	0.043	0.002
35 - 39	0.048	0.054	0.029	0.051	0.052	0
40 - 44	0.059	0.062	0.012	0.062	0.064	0.007
45 - 49	0.072	0.067	0.018	0.074	0.074	0.001
50 - 54	0.083	0.069	0.053	0.085	0.083	0.004
55 - 59	0.093	0.069	0.09	0.092	0.09	0.006
60 - 64	0.102	0.075	0.098	0.102	0.099	0.01
65 - 69	0.107	0.072	0.124	0.102	0.103	0.001
70 - 74	0.1	0.062	0.141	0.093	0.094	0.002
75 - 79	0.086	0.054	0.13	0.081	0.082	0.002
80 - 84	0.07	0.043	0.121	0.066	0.066	0.001
85 - 89	0.046	0.03	0.087	0.044	0.045	0.004
90 - 94	0.023	0.016	0.052	0.023	0.023	0.001
95 - 99	0.007	0.005	0.032	0.007	0.007	0.006
100 - 104	0.001	0.001	0.014	0.001	0.001	0.01

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentMe anComparator	absBeforePsAdjust mentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMe anComparator	absAfterPsAdjust mentStdDiff
105 - 109	0	0	0.002	0	0	0.008
gender = FEMALE	0.583	0.523	0.12	0.565	0.566	0.001
Atrial fibrillation	0.013	0.007	0.065	0.012	0.012	0.001
Cerebrovascular disease	0.009	0.005	0.042	0.008	0.008	0.003
Coronary arteriosclerosis	0.001	0.001	0.019	0.001	0.001	0.005
Heart disease	0.038	0.021	0.102	0.034	0.034	0.001
Heart failure	0.007	0.003	0.051	0.006	0.006	0.001
Ischemic heart disease	0.012	0.007	0.051	0.011	0.011	0.001
Peripheral vascular disease	0.003	0.002	0.034	0.003	0.003	0.005
Pulmonary embolism	0.003	0.001	0.03	0.002	0.002	0.002
Venous thrombosis	0.008	0.005	0.04	0.006	0.007	0.003
Acute respiratory disease	0.101	0.063	0.142	0.074	0.075	0.003
Attention deficit hyperactivity disorder	0	0	0.004	0	0	0.003
Chronic liver disease	0.001	0.001	0.013	0.001	0.001	0.002
Chronic obstructive lung disease	0.049	0.015	0.207	0.033	0.034	0.002
Crohn's disease	0.001	0.001	0.013	0.001	0.001	0.003
Dementia	0.007	0.004	0.032	0.007	0.007	0.002
Diabetes mellitus	0.017	0.011	0.049	0.015	0.016	0.006
Gastroesophageal reflux disease	0.006	0.005	0.018	0.005	0.006	0.001
Gastrointestinal hemorrhage	0.012	0.009	0.039	0.011	0.012	0.001
Human immunodeficiency virus infection	0	0	0.001	0	0	0.001

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentMe anComparator	absBeforePsAdjust mentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMe anComparator	absAfterPsAdjust mentStdDiff
Hyperlipidemia	0.008	0.007	0.015	0.008	0.008	0.003
Hypertensive disorder	0.018	0.014	0.032	0.017	0.018	0.008
Lesion of liver	0.001	0.001	0.013	0.001	0.001	0.002
Obesity	0.005	0.004	0.006	0.004	0.005	0.003
Osteoarthritis	0.033	0.021	0.075	0.03	0.031	0.001
Pneumonia	0.003	0.001	0.039	0.002	0.002	0.002
Psoriasis	0.008	0.006	0.02	0.008	0.008	0
Renal impairment	0.023	0.015	0.056	0.021	0.022	0.002
Rheumatoid arthritis	0.004	0.002	0.038	0.003	0.003	0.001
Schizophrenia	0	0	0.002	0	0.001	0.009
Ulcerative colitis	0.001	0.001	0.014	0.001	0.001	0.004
Urinary tract infectious disease	0.035	0.021	0.089	0.029	0.03	0.009
Viral hepatitis C	0	0	0.002	0	0	0.003
Malignant lymphoma	0.001	0	0.01	0.001	0.001	0
Malignant neoplasm of anorectum	0	0	0.009	0	0	0.003
Malignant neoplastic disease	0.021	0.014	0.06	0.02	0.02	0.002
Malignant tumor of breast	0.002	0.002	0.016	0.002	0.002	0.004
Malignant tumor of colon	0.001	0	0.011	0.001	0.001	0.002
Malignant tumor of lung	0.002	0.001	0.03	0.002	0.002	0.004
Malignant tumor of urinary bladder	0.001	0	0.011	0.001	0.001	0.004

Appendix Table 22. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline LRTI*) and comparator (*Amoxicillin LRTI*) group as well as the standardised difference of the means – IPCI.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	0	0.111	0.476	0	0	0.018
5 - 9	0	0.051	0.316	0	0.001	0.023
10 - 14	0.004	0.029	0.197	0.006	0.006	0
15 - 19	0.021	0.026	0.03	0.028	0.028	0.004
20 - 24	0.02	0.019	0.01	0.022	0.023	0.006
25 - 29	0.022	0.021	0.006	0.025	0.026	0.008
30 - 34	0.032	0.032	0.003	0.038	0.038	0.001
35 - 39	0.046	0.042	0.02	0.054	0.053	0.002
40 - 44	0.062	0.049	0.056	0.062	0.063	0.002
45 - 49	0.074	0.056	0.071	0.073	0.071	0.004
50 - 54	0.084	0.065	0.075	0.083	0.081	0.004
55 - 59	0.103	0.076	0.093	0.095	0.097	0.009
60 - 64	0.107	0.087	0.067	0.107	0.105	0.005
65 - 69	0.103	0.082	0.073	0.101	0.1	0.003
70 - 74	0.093	0.075	0.067	0.092	0.091	0.001
75 - 79	0.081	0.065	0.063	0.077	0.079	0.006
80 - 84	0.068	0.052	0.068	0.063	0.063	0.004
85 - 89	0.048	0.037	0.052	0.045	0.044	0.003
90 - 94	0.025	0.018	0.046	0.023	0.022	0.007
95 - 99	0.005	0.005	0	0.006	0.007	0.013
100 - 104	0.001	0.001	0.004	0.001	0.001	0.001
105 - 109	0	0	0	0	0	0
gender = FEMALE	0.576	0.55	0.052	0.58	0.578	0.005

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Atrial fibrillation	0.028	0.022	0.036	0.026	0.026	0
Cerebrovascular disease	0.022	0.02	0.018	0.021	0.023	0.011
Coronary arteriosclerosis	0.002	0.002	0.007	0.002	0.002	0.007
Heart disease	0.103	0.08	0.079	0.092	0.093	0.002
Heart failure	0.023	0.018	0.039	0.02	0.019	0.009
Ischemic heart disease	0.045	0.034	0.058	0.039	0.038	0.001
Peripheral vascular disease	0.01	0.008	0.026	0.009	0.009	0.006
Pulmonary embolism	0.003	0.003	0.007	0.003	0.003	0.011
Venous thrombosis	0.009	0.006	0.026	0.008	0.008	0.002
Acute respiratory disease	0.142	0.185	0.115	0.145	0.144	0.004
Attention deficit hyperactivity disorder	0.004	0.006	0.026	0.004	0.004	0
Chronic liver disease	0.001	0.001	0.004	0.001	0.001	0.008
Chronic obstructive lung disease	0.045	0.035	0.049	0.034	0.037	0.016
Crohn's disease	0.003	0.002	0.005	0.003	0.003	0.002
Dementia	0.009	0.007	0.02	0.008	0.007	0.008

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Diabetes mellitus	0.089	0.072	0.062	0.082	0.085	0.009
Gastroesophageal reflux disease	0.008	0.008	0.005	0.007	0.007	0.004
Gastrointestinal hemorrhage	0.013	0.011	0.014	0.012	0.013	0.01
Human immunodeficiency virus infection	0.001	0.001	0.004	0.001	0.001	0.004
Hyperlipidemia	0.037	0.026	0.062	0.033	0.032	0.006
Hypertensive disorder	0.158	0.12	0.107	0.145	0.146	0.004
Lesion of liver	0.001	0.001	0.008	0.001	0.001	0.012
Obesity	0.01	0.008	0.016	0.01	0.01	0.002
Osteoarthritis	0.053	0.044	0.043	0.051	0.053	0.008
Pneumonia	0.049	0.063	0.058	0.051	0.048	0.014
Psoriasis	0.01	0.009	0.016	0.009	0.011	0.015
Renal impairment	0.02	0.018	0.013	0.02	0.022	0.01
Rheumatoid arthritis	0.009	0.008	0.011	0.01	0.01	0.001
Schizophrenia	0.001	0.001	0.006	0.001	0.002	0.007
Ulcerative colitis	0.003	0.002	0.001	0.003	0.003	0.004
Urinary tract infectious disease	0.077	0.065	0.046	0.073	0.072	0.003

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Viral hepatitis C	0	0	0.004	0	0	0.002
Malignant lymphoma	0.002	0.001	0.002	0.002	0.001	0.002
Malignant neoplasm of anorectum	0.001	0.001	0.003	0.001	0.001	0.006
Malignant neoplastic disease	0.053	0.046	0.029	0.051	0.053	0.009
Malignant tumor of breast	0.009	0.007	0.023	0.009	0.008	0.008
Malignant tumor of colon	0.002	0.002	0.003	0.002	0.002	0.012
Malignant tumor of lung	0.004	0.004	0.001	0.004	0.004	0.002
Malignant tumor of urinary bladder	0.003	0.002	0.006	0.003	0.003	0.001
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.265	0.205	0.144	0.244	0.25	0.016
ANTIBACTERIALS FOR SYSTEMIC USE	0.308	0.377	0.145	0.254	0.255	0.003
ANTIDEPRESSANTS	0.118	0.091	0.087	0.109	0.11	0.003
ANTIEPILEPTICS	0.038	0.033	0.029	0.035	0.037	0.009

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.333	0.254	0.174	0.306	0.31	0.009
ANTINEOPLASTIC AGENTS	0.026	0.021	0.029	0.026	0.026	0.002
ANTIPSORIATICS	0.028	0.026	0.012	0.027	0.028	0.004
ANTITHROMBOTIC AGENTS	0.203	0.162	0.108	0.19	0.193	0.008
BETA BLOCKING AGENTS	0.235	0.179	0.139	0.217	0.219	0.003
CALCIUM CHANNEL BLOCKERS	0.122	0.096	0.082	0.118	0.117	0.003
DIURETICS	0.232	0.177	0.135	0.211	0.217	0.015
DRUGS FOR ACID RELATED DISORDERS	0.38	0.3	0.169	0.352	0.356	0.007
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.49	0.482	0.016	0.481	0.481	0.001
DRUGS USED IN DIABETES	0.112	0.087	0.081	0.101	0.104	0.01
IMMUNOSUPPRESSANTS	0.018	0.016	0.017	0.019	0.018	0.004
LIPID MODIFYING AGENTS	0.258	0.206	0.125	0.247	0.248	0.004

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
OPIOIDS	0.269	0.207	0.147	0.248	0.251	0.007
PSYCHOLEPTICS	0.205	0.162	0.112	0.186	0.188	0.006
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.01	0.01	0.005	0.01	0.01	0.002

Table 23. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline LRTI*) and comparator (*Amoxicillin LRTI*) group as well as the standardised difference of the means – SIDIAP.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	-0.002	0.235	0.553	-0.002	0.027	0.17
5 - 9	-0.002	0.039	0.194	-0.002	0.003	0.023
10 - 14	0.015	0.017	0.018	0.016	0.014	0.017
15 - 19	0.054	0.019	0.258	0.054	0.052	0.011
20 - 24	0.056	0.02	0.256	0.052	0.053	0.001
25 - 29	0.056	0.027	0.172	0.053	0.053	0.001
30 - 34	0.07	0.041	0.146	0.069	0.073	0.015
35 - 39	0.073	0.054	0.084	0.073	0.077	0.012
40 - 44	0.074	0.056	0.078	0.07	0.064	0.024
45 - 49	0.071	0.055	0.071	0.072	0.067	0.018
50 - 54	0.057	0.056	0.004	0.056	0.051	0.023

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentM eanComparator	absBeforePsAdjust mentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMe anComparator	absAfterPsAdjust mentStdDiff
55 - 59	0.063	0.058	0.021	0.065	0.063	0.006
60 - 64	0.074	0.06	0.06	0.075	0.069	0.024
65 - 69	0.064	0.057	0.032	0.066	0.061	0.022
70 - 74	0.068	0.05	0.086	0.07	0.059	0.044
75 - 79	0.059	0.047	0.057	0.061	0.059	0.007
80 - 84	0.054	0.045	0.044	0.054	0.054	0.001
85 - 89	0.057	0.036	0.113	0.059	0.059	0.003
90 - 94	0.022	0.02	0.015	0.023	0.03	0.044
95 - 99	0.007	0.005	0.025	0.008	0.011	0.036
100 - 104	-0.002	0.001	0.016	-0.002	-0.001	0.004
105 - 109	0	0	0	0	-0.001	0
gender = FEMALE	0.573	0.51	0.127	0.567	0.559	0.017
Atrial fibrillation	0.045	0.017	0.221	0.039	0.048	0.042
Cerebrovascular disease	0.013	0.007	0.066	0.013	0.017	0.038
Coronary arteriosclerosis	0.012	0.004	0.127	0.008	0.011	0.031
Heart disease	0.117	0.055	0.269	0.106	0.117	0.036
Heart failure	0.055	0.016	0.31	0.051	0.057	0.025
Ischemic heart disease	0.025	0.012	0.115	0.022	0.029	0.039
Peripheral vascular disease	0.014	0.005	0.141	0.013	0.017	0.035
Pulmonary embolism	0.006	0.001	0.126	0.006	0.005	0.007
Venous thrombosis	0.019	0.006	0.158	0.016	0.013	0.025
Acute respiratory disease	0.22	0.173	0.124	0.198	0.218	0.048
Attention deficit hyperactivity disorder	-0.002	0.001	0.03	-0.002	0.002	0.015
Chronic liver disease	0.011	0.003	0.134	0.009	0.011	0.018

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Chronic obstructive lung disease	0.066	0.014	0.436	0.057	0.068	0.044
Crohn's disease	0.002	0	0.101	-0.002	0.001	0.009
Dementia	0.014	0.01	0.042	0.013	0.019	0.047
Diabetes mellitus	0.058	0.023	0.234	0.052	0.066	0.057
Gastroesophageal reflux disease	0.02	0.01	0.102	0.019	0.017	0.01
Gastrointestinal hemorrhage	0.019	0.011	0.08	0.018	0.021	0.021
Human immunodeficiency virus infection	0.005	0.001	0.151	0.004	0.008	0.047
Hyperlipidemia	0.081	0.036	0.24	0.074	0.084	0.039
Hypertensive disorder	0.096	0.049	0.215	0.093	0.103	0.035
Lesion of liver	0.007	0.003	0.095	0.006	0.009	0.026
Obesity	0.068	0.03	0.227	0.064	0.067	0.012
Osteoarthritis	0.056	0.032	0.14	0.051	0.06	0.04
Pneumonia	0.061	0.022	0.261	0.052	0.062	0.041
Psoriasis	0.011	0.003	0.159	0.009	0.01	0.006
Renal impairment	0.054	0.021	0.23	0.051	0.06	0.041
Rheumatoid arthritis	0.006	0.001	0.114	0.003	0.005	0.02
Schizophrenia	0.003	0.001	0.054	0.002	0.003	0.014
Ulcerative colitis	0.003	0	0.092	0.003	0.003	0
Urinary tract infectious disease	0.13	0.043	0.419	0.117	0.121	0.01
Viral hepatitis C	0.006	0.002	0.089	0.005	0.007	0.022
Malignant lymphoma	0.007	0.001	0.173	0.007	0.006	0.023

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Malignant neoplasm of anorectum	-0.002	0.001	0.032	-0.002	0.001	0.002
Malignant neoplastic disease	0.061	0.021	0.283	0.056	0.067	0.048
Malignant tumor of breast	0.009	0.002	0.142	0.007	0.006	0.022
Malignant tumor of colon	0.005	0.002	0.081	0.003	0.002	0.018
Malignant tumor of lung	0.007	0.002	0.148	0.007	0.011	0.042
Malignant tumor of urinary bladder	0.002	0.002	0.015	-0.002	0.004	0.043
Primary malignant neoplasm of prostate	0.003	0.002	0.036	0.003	0.004	0.008
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.249	0.183	0.172	0.251	0.248	0.006
ANTIBACTERIALS FOR SYSTEMIC USE	0.611	0.291	0.702	0.565	0.616	0.105
ANTIDEPRESSANTS	0.25	0.119	0.403	0.234	0.242	0.02
ANTIEPILEPTICS	0.138	0.051	0.397	0.128	0.14	0.035
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.569	0.436	0.267	0.545	0.572	0.053
ANTINEOPLASTIC AGENTS	0.027	0.01	0.168	0.026	0.025	0.009
ANTIPSORIATICS	0.023	0.008	0.171	0.021	0.025	0.028
ANTITHROMBOTIC AGENTS	0.229	0.121	0.327	0.225	0.231	0.013
BETA BLOCKING AGENTS	0.137	0.085	0.187	0.14	0.136	0.012
CALCIUM CHANNEL BLOCKERS	0.101	0.066	0.139	0.103	0.113	0.034
DIURETICS	0.224	0.147	0.215	0.224	0.227	0.006

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
DRUGS FOR ACID RELATED DISORDERS	0.483	0.265	0.495	0.469	0.492	0.045
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.587	0.339	0.523	0.552	0.599	0.095
DRUGS USED IN DIABETES	0.123	0.07	0.209	0.119	0.12	0.002
IMMUNOSUPPRESSANTS	0.029	0.009	0.208	0.026	0.029	0.016
LIPID MODIFYING AGENTS	0.214	0.155	0.163	0.217	0.211	0.016
OPIOIDS	0.248	0.099	0.497	0.225	0.241	0.037
PSYCHOLEPTICS	0.403	0.215	0.456	0.386	0.409	0.048
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.03	0.016	0.109	0.031	0.026	0.031

Appendix Table 24. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Erythromycin Chlamydia*) group as well as the standardised difference of the means– CPRD.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
10 - 14	-0.003	-0.031	0.128	0	-0.029	0
15 - 19	0.203	0.29	0.213	0.264	0.287	0.052
20 - 24	0.4	0.389	0.022	0.364	0.399	0.073
25 - 29	0.184	0.222	0.098	0.191	0.227	0.087
30 - 34	0.097	0.062	0.122	0.091	0.052	0.149
35 - 39	0.05	-0.031	0.149	0.045	-0.029	0.134

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
40 - 44	0.025	0	0	-0.045	0	0
45 - 49	0.018	-0.031	0.092	-0.045	-0.029	0.143
50 - 54	0.01	-0.031	0.04	0	-0.029	0
gender = FEMALE	0.721	0.944	0.51	0.945	0.918	0.108
Acute respiratory disease	0.07	0.074	0.014	0.109	0.069	0.142
Gastroesophageal reflux disease	0.003	0	0	-0.045	0	0
Gastrointestinal hemorrhage	0.009	-0.031	0.035	-0.045	0	0
Obesity	-0.003	-0.031	0.099	0	-0.029	0
Psoriasis	0.01	-0.031	0.089	0	-0.029	0
Urinary tract infectious disease	0.043	0.062	0.089	0.091	0.044	0.186

Appendix Table 25. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Erythromycin Chlamydia*) group as well as the standardised difference of the means–IPCI.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
15 - 19	0.124	0	0	-0.294	0	0
20 - 24	0.313	0.353	0.087	-0.294	0.353	0.257
25 - 29	0.201	0.294	0.231	-0.294	0.294	0.276

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
30 - 34	0.122	0	0	-0.294	0	0
35 - 39	0.072	-0.294	0.177	-0.294	-0.294	0.207
40 - 44	0.062	-0.294	0.012	-0.294	-0.294	0.365
45 - 49	0.035	-0.294	0.133	-0.294	-0.294	0
50 - 54	0.033	-0.294	0.146	0	-0.294	0
60 - 64	0.011	-0.294	0.457	0	-0.294	0
gender = FEMALE	0.639	0.588	0.105	0.412	0.588	0.35
Cerebrovascular disease	0	-0.294	0	0	-0.294	0
Heart disease	0.01	-0.294	0.493	0	-0.294	0
Acute respiratory disease	0.115	-0.294	0.376	-0.294	-0.294	0.145
Attention deficit hyperactivity disorder	0.031	0	0	-0.294	0	0
Diabetes mellitus	0.007	0	0	-0.294	0	0
Gastrointestinal hemorrhage	0.018	0	0	-0.294	0	0
Hypertensive disorder	0.006	-0.294	0.644	0	-0.294	0
Psoriasis	0.005	0	0	-0.294	0	0
Urinary tract infectious disease	0.111	-0.294	0.208	-0.294	-0.294	0.166
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.012	0	0	-0.294	0	0
ANTIBACTERIALS FOR SYSTEMIC USE	0.387	0.588	0.412	0.412	0.588	0.35
ANTIDEPRESSANTS	0.083	-0.294	0.127	-0.294	-0.294	0.207
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.17	-0.294	0.018	-0.294	-0.294	0
ANTINEOPLASTIC AGENTS	0.01	-0.294	0.493	-0.294	-0.294	0
ANTIPSORIATICS	0.018	-0.294	0.728	0	-0.294	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
BETA BLOCKING AGENTS	0.022	-0.294	0.248	0	-0.294	0
DRUGS FOR ACID RELATED DISORDERS	0.106	-0.294	0.037	-0.294	-0.294	0
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.232	0.294	0.146	-0.294	0.294	0.133
DRUGS USED IN DIABETES	0.008	0	0	-0.294	0	0
OPIOIDS	0.07	0	0	-0.294	0	0
PSYCHOLEPTICS	0.101	0	0	-0.294	0	0
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.037	0	0	-0.294	0	0

Appendix Table 26. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Erythromycin Chlamydia*) group as well as the standardised difference of the means– SIDIAP.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
10 - 14	0.001	0	0	-0.054	0	0
15 - 19	0.13	0.113	0.049	0.12	0.109	0.035
20 - 24	0.309	0.302	0.015	0.283	0.321	0.083
25 - 29	0.206	0.189	0.043	0.217	0.167	0.128
30 - 34	0.136	0.198	0.182	0.174	0.205	0.079
35 - 39	0.083	0.057	0.095	0.065	-0.049	0.103
40 - 44	0.06	0.085	0.104	0.065	0.092	0.1
45 - 49	0.039	-0.047	0.152	-0.054	-0.049	0.149

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentM eanComparator	absBeforePsAdjust mentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMe anComparator	absAfterPsAdjust mentStdDiff
50 - 54	0.02	-0.047	0.077	-0.054	-0.049	0
55 - 59	0.009	-0.047	0.098	-0.054	-0.049	0.086
65 - 69	0.002	-0.047	0.157	-0.054	-0.049	0
90 - 94	0	-0.047	0	0	-0.049	0
gender = FEMALE	0.644	0.858	0.449	0.793	0.837	0.112
Atrial fibrillation	0.001	0	0	-0.054	0	0
Heart disease	0.005	-0.047	0.068	-0.054	-0.049	0
Heart failure	-0.001	0	0	-0.054	0	0
Ischemic heart disease	-0.001	0	0	-0.054	0	0
Acute respiratory disease	0.155	0.104	0.141	0.13	0.103	0.085
Attention deficit hyperactivity disorder	0.003	0	0	-0.054	0	0
Chronic liver disease	0.001	-0.047	0.248	-0.054	-0.049	0.091
Chronic obstructive lung disease	-0.001	-0.047	0.523	-0.054	-0.049	0.091
Dementia	-0.001	0	0	-0.054	0	0
Diabetes mellitus	0.004	-0.047	0.246	0.054	-0.049	0.184
Gastroesophageal reflux disease	0.004	-0.047	0.086	0	-0.049	0
Gastrointestinal hemorrhage	0.009	-0.047	0	0	-0.049	0
Hyperlipidemia	0.006	0	0	-0.054	0	0
Hypertensive disorder	0.003	-0.047	0.422	-0.054	-0.049	0.036
Lesion of liver	-0.001	-0.047	0.448	-0.054	-0.049	0.091
Obesity	0.013	-0.047	0.212	-0.054	-0.049	0
Osteoarthritis	0.004	0	0	-0.054	0	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Psoriasis	0.003	0	0	-0.054	0	0
Urinary tract infectious disease	0.162	0.123	0.107	0.228	0.125	0.273
Malignant neoplastic disease	0.003	0	0	-0.054	0	0
Malignant tumor of breast	0.001	0	0	-0.054	0	0
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.014	-0.047	0.206	-0.054	-0.049	0.06
ANTIBACTERIALS FOR SYSTEMIC USE	0.367	0.396	0.061	0.5	0.391	0.218
ANTIDEPRESSANTS	0.1	0.132	0.106	0.12	0.13	0.033
ANTIEPILEPTICS	0.034	-0.047	0.085	0.054	-0.049	0.204
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.444	0.5	0.113	0.554	0.475	0.159
ANTINEOPLASTIC AGENTS	0.004	-0.047	0.089	-0.054	-0.049	0
ANTIPSORIATICS	0.007	0	0	-0.054	0	0
ANTITHROMBOTIC AGENTS	0.02	-0.047	0.074	-0.054	-0.049	0.215
BETA BLOCKING AGENTS	0.009	-0.047	0.193	-0.054	-0.049	0
CALCIUM CHANNEL BLOCKERS	0.004	-0.047	0.393	-0.054	-0.049	0.149
DIURETICS	0.007	-0.047	0.247	-0.054	-0.049	0.149
DRUGS FOR ACID RELATED DISORDERS	0.12	0.179	0.183	0.196	0.172	0.061
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.151	0.17	0.052	0.196	0.158	0.1
DRUGS USED IN DIABETES	0.008	-0.047	0.223	-0.054	-0.049	0.069
LIPID MODIFYING AGENTS	0.011	-0.047	0.011	0	-0.049	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
OPIOIDS	0.056	0.085	0.128	0.076	0.082	0.02
PSYCHOLEPTICS	0.174	0.255	0.214	0.272	0.232	0.092
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.008	0	0	-0.054	0	0

Appendix Table 27. Select characteristics before and after propensity score adjustment. showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Azithromycin Chlamydia*) group as well as the standardised difference of the means– CPRD.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
10 - 14	-0.003	0.001	0.004	-0.004	-0.001	0.012
15 - 19	0.203	0.232	0.07	0.202	0.197	0.013
20 - 24	0.4	0.403	0.007	0.398	0.416	0.037
25 - 29	0.184	0.201	0.042	0.186	0.196	0.024
30 - 34	0.097	0.088	0.034	0.095	0.099	0.014
35 - 39	0.05	0.035	0.081	0.051	0.042	0.042
40 - 44	0.025	0.02	0.034	0.026	0.025	0.004
45 - 49	0.018	0.011	0.062	0.016	0.013	0.029
50 - 54	0.01	0.006	0.051	0.011	0.005	0.07
55 - 59	0.007	0.003	0.069	0.007	0.005	0.031
60 - 64	-0.003	-0.001	0.028	-0.004	-0.001	0.044
65 - 69	-0.003	-0.001	0.044	-0.004	-0.001	0.044

70 - 74	-0.003	-0.001	0.044	-0.004	-0.001	0.05
80 - 84	-0.003	0	0	-0.004	0	0
gender = FEMALE	0.721	0.739	0.04	0.734	0.738	0.009
Atrial fibrillation	-0.003	0	0	-0.004	0	0
Heart disease	-0.003	0.001	0.008	-0.004	0.002	0.007
Ischemic heart disease	0	-0.001	0	0	-0.001	0
Peripheral vascular disease	0	-0.001	0	0	-0.001	0
Pulmonary embolism	0	-0.001	0	0	-0.001	0
Venous thrombosis	-0.003	0.001	0.007	-0.004	0.003	0.043
Acute respiratory disease	0.07	0.078	0.028	0.08	0.084	0.013
Attention deficit hyperactivity disorder	-0.003	0.001	0.002	-0.004	-0.001	0.002
Crohn's disease	0	-0.001	0	0	-0.001	0
Diabetes mellitus	-0.003	0.002	0.003	-0.004	0.002	0.01
Gastroesophageal reflux disease	0.003	0.002	0.009	-0.004	0.002	0.024
Gastrointestinal hemorrhage	0.009	0.009	0.004	0.009	0.01	0.006
Hyperlipidemia	0	0.001	0	0	-0.001	0
Hypertensive disorder	0.003	0.001	0.046	0.004	0.002	0.027
Lesion of liver	0	-0.001	0	0	-0.001	0
Obesity	-0.003	0.003	0.025	-0.004	0.004	0.056
Osteoarthritis	0.003	-0.001	0.088	-0.004	-0.001	0.075
Pneumonia	0	-0.001	0	0	-0.001	0
Psoriasis	0.01	0.008	0.014	0.011	0.008	0.033
Renal impairment	0	-0.001	0	0	-0.001	0

Rheumatoid arthritis	0	-0.001	0	0	-0.001	0
Schizophrenia	-0.003	-0.001	0.021	-0.004	-0.001	0.038
Urinary tract infectious disease	0.043	0.04	0.016	0.047	0.048	0.002
Viral hepatitis C	0	-0.001	0	0	-0.001	0
Malignant lymphoma	-0.003	0	0	-0.004	0	0
Malignant neoplastic disease	-0.003	-0.001	0.008	-0.004	-0.001	0.025

Appendix Table 28. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Azithromycin Chlamydia*) group as well as the standardized difference of the means–IPCI.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
10 - 14	-0.003	0.001	0.004	-0.003	0.001	0.021
15 - 19	0.124	0.129	0.013	0.126	0.129	0.011
20 - 24	0.313	0.349	0.075	0.309	0.325	0.033
25 - 29	0.201	0.225	0.056	0.203	0.207	0.011
30 - 34	0.122	0.113	0.026	0.124	0.115	0.028
35 - 39	0.072	0.064	0.031	0.069	0.07	0.005
40 - 44	0.062	0.043	0.09	0.062	0.06	0.01
45 - 49	0.035	0.032	0.013	0.037	0.034	0.015
50 - 54	0.033	0.022	0.073	0.031	0.028	0.017
55 - 59	0.018	0.013	0.048	0.019	0.018	0.007
60 - 64	0.011	0.006	0.062	0.012	0.008	0.034

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
65 - 69	0.004	0.002	0.033	0.003	0.003	0.007
70 - 74	0.004	0.001	0.091	0.004	0.001	0.081
75 - 79	-0.003	0	0.078	-0.003	0	0
80 - 84	0	0	0	0	-0.001	0
gender = FEMALE	0.639	0.502	0.273	0.621	0.599	0.045
Atrial fibrillation	0.003	0.001	0.085	0.003	-0.001	0.085
Cerebrovascular disease	0	0.001	0	0	-0.001	0
Coronary arteriosclerosis	-0.003	0	0.063	-0.003	-0.001	0.022
Heart disease	0.01	0.005	0.054	0.01	0.004	0.07
Ischemic heart disease	-0.003	0.001	0.007	-0.003	0.001	0.004
Peripheral vascular disease	0	0	0	0	-0.001	0
Pulmonary embolism	-0.003	0	0.007	0	-0.001	0
Venous thrombosis	0.005	0.002	0.069	0.004	0.002	0.035
Acute respiratory disease	0.115	0.1	0.048	0.116	0.118	0.006
Attention deficit hyperactivity disorder	0.031	0.024	0.043	0.03	0.027	0.02
Chronic liver disease	-0.003	0.001	0.053	-0.003	-0.001	0.043

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Chronic obstructive lung disease	-0.003	0.002	0.014	-0.003	0.002	0.02
Crohn's disease	0.003	0.002	0.027	0.004	0.004	0.004
Diabetes mellitus	0.007	0.005	0.032	0.007	0.006	0.008
Gastroesophageal reflux disease	0.003	0.002	0.029	0.004	0.004	0.001
Gastrointestinal hemorrhage	0.018	0.007	0.11	0.017	0.012	0.046
Human immunodeficiency virus infection	0.013	0.002	0.213	0.013	0.008	0.051
Hyperlipidemia	0.006	0.003	0.038	0.006	0.005	0.022
Hypertensive disorder	0.006	0.007	0.013	0.006	0.008	0.028
Lesion of liver	0	0	0	0	-0.001	0
Obesity	0.007	0.005	0.038	0.007	0.005	0.033
Osteoarthritis	0.003	0.002	0.017	-0.003	0.002	0.011
Pneumonia	0.006	0.005	0.011	0.007	0.007	0.005
Psoriasis	0.005	0.005	0.004	0.005	0.005	0.002
Renal impairment	0	0.001	0	0	0.001	0
Rheumatoid arthritis	-0.003	0.001	0.053	-0.003	0.001	0.035
Schizophrenia	-0.003	0	0.007	-0.003	-0.001	0.002
Ulcerative colitis	0.003	0.001	0.039	-0.003	0.002	0.002
Urinary tract infectious disease	0.111	0.079	0.115	0.107	0.102	0.014

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Viral hepatitis C	-0.003	0	0.063	-0.003	-0.001	0.049
Malignant neoplastic disease	0.006	0.003	0.057	0.005	0.003	0.033
Malignant tumor of breast	-0.003	0.001	0	-0.003	-0.001	0.003
Malignant tumor of colon	-0.003	0	0	-0.003	0	0
Malignant tumor of urinary bladder	0	0	0	0	-0.001	0
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.012	0.011	0.015	0.011	0.015	0.037
ANTIBACTERIALS FOR SYSTEMIC USE	0.387	0.293	0.205	0.374	0.39	0.033
ANTIDEPRESSANTS	0.083	0.043	0.186	0.079	0.085	0.02
ANTIEPILEPTICS	0.012	0.007	0.058	0.012	0.009	0.029
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.17	0.142	0.077	0.168	0.164	0.011
ANTINEOPLASTIC AGENTS	0.01	0.009	0.004	0.009	0.01	0.01
ANTIPSORIATICS	0.018	0.014	0.035	0.014	0.02	0.048

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ANTITHROMBOTIC AGENTS	0.015	0.009	0.06	0.014	0.009	0.05
BETA BLOCKING AGENTS	0.022	0.017	0.039	0.024	0.021	0.015
CALCIUM CHANNEL BLOCKERS	0.017	0.009	0.078	0.017	0.015	0.016
DIURETICS	0.007	0.005	0.02	0.006	0.008	0.023
DRUGS FOR ACID RELATED DISORDERS	0.106	0.078	0.102	0.102	0.11	0.025
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.232	0.196	0.091	0.227	0.23	0.006
DRUGS USED IN DIABETES	0.008	0.006	0.021	0.007	0.01	0.033
IMMUNOSUPPRESSANTS	0.004	0.004	0.008	-0.003	0.006	0.048
LIPID MODIFYING AGENTS	0.012	0.01	0.017	0.012	0.016	0.029
OPIOIDS	0.07	0.054	0.073	0.064	0.068	0.014
PSYCHOLEPTICS	0.101	0.069	0.12	0.095	0.101	0.021
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.037	0.027	0.059	0.035	0.032	0.013

Appendix Table 29. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Azithromycin Chlamydia*) group as well as the standardized difference of the means–SIDIAP.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
0 - 4	0	-0.001	0	0	0	0
5 - 9	0	-0.001	0	0	0	0
10 - 14	0.001	0.002	0.023	0.001	0.002	0.02
15 - 19	0.13	0.154	0.07	0.138	0.136	0.005
20 - 24	0.309	0.337	0.06	0.311	0.321	0.023
25 - 29	0.206	0.198	0.02	0.206	0.204	0.007
30 - 34	0.136	0.118	0.052	0.128	0.129	0.004
35 - 39	0.083	0.081	0.007	0.085	0.083	0.008
40 - 44	0.06	0.054	0.028	0.062	0.058	0.017
45 - 49	0.039	0.03	0.05	0.035	0.035	0.003
50 - 54	0.02	0.014	0.046	0.018	0.017	0.012
55 - 59	0.009	0.007	0.025	0.009	0.009	0.003
60 - 64	0.004	0.003	0.012	0.003	0.003	0.004
65 - 69	0.002	0.001	0.016	0.002	0.001	0.019
70 - 74	0.001	-0.001	0.025	-0.001	0	0.015
75 - 79	0.001	-0.001	0.019	-0.001	0.001	0
80 - 84	-0.001	0	0	-0.001	0	0
gender = FEMALE	0.644	0.712	0.147	0.652	0.649	0.007
Atrial fibrillation	0.001	-0.001	0.031	-0.001	0	0.035
Cerebrovascular disease	-0.001	-0.001	0	0	0	0

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentM eanComparator	absBeforePsAdjust mentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMe anComparator	absAfterPsAdjust mentStdDiff
Heart disease	0.005	0.004	0.016	0.005	0.004	0.012
Heart failure	-0.001	-0.001	0.012	-0.001	0	0.009
Ischemic heart disease	-0.001	-0.001	0	-0.001	0.001	0.009
Venous thrombosis	0.002	0.002	0.001	0.003	0.002	0.013
Acute respiratory disease	0.155	0.146	0.024	0.15	0.146	0.011
Attention deficit hyperactivity disorder	0.003	0.002	0.01	0.002	0.002	0.006
Chronic liver disease	0.001	0.001	0.008	-0.001	0.001	0.008
Chronic obstructive lung disease	-0.001	-0.001	0.011	-0.001	0.001	0.023
Crohn's disease	0.001	-0.001	0.015	-0.001	0	0.006
Dementia	-0.001	0	0	-0.001	0	0
Diabetes mellitus	0.004	0.002	0.026	0.003	0.002	0.022
Gastroesophageal reflux disease	0.004	0.003	0.017	0.003	0.003	0.002
Gastrointestinal hemorrhage	0.009	0.008	0.02	0.009	0.009	0.009
Human immunodeficiency virus infection	0.004	0.001	0.056	0.003	0.002	0.013
Hyperlipidemia	0.006	0.006	0.007	0.005	0.007	0.015
Hypertensive disorder	0.003	0.002	0.017	0.003	0.003	0.001
Lesion of liver	-0.001	-0.001	0.015	-0.001	0	0.012
Obesity	0.013	0.013	0.001	0.014	0.012	0.017
Osteoarthritis	0.004	0.003	0.021	0.002	0.003	0.008
Pneumonia	0.002	0.002	0.017	0.002	0.002	0.016
Psoriasis	0.003	0.003	0.011	0.003	0.003	0.007
Renal impairment	0.001	0.001	0.011	-0.001	0.001	0.013

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentM eanComparator	absBeforePsAdjust mentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMe anComparator	absAfterPsAdjust mentStdDiff
Rheumatoid arthritis	-0.001	-0.001	0.011	-0.001	0.001	0.022
Schizophrenia	-0.001	0.001	0.021	-0.001	0.001	0.019
Ulcerative colitis	0.001	-0.001	0.014	-0.001	0	0.017
Urinary tract infectious disease	0.162	0.144	0.052	0.153	0.154	0.003
Viral hepatitis C	0.001	0.001	0.013	-0.001	0.001	0.005
Malignant lymphoma	0	-0.001	0	0	0	0
Malignant neoplasm of anorectum	-0.001	0	0	-0.001	0	0
Malignant neoplastic disease	0.003	0.002	0.014	0.003	0.003	0.007
Malignant tumor of breast	0.001	-0.001	0.017	-0.001	0	0.01
Malignant tumor of colon	-0.001	-0.001	0	0	0	0
Malignant tumor of urinary bladder	-0.001	-0.001	0	-0.001	0	0
Primary malignant neoplasm of prostate	0	-0.001	0	0	0	0
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.014	0.008	0.053	0.011	0.011	0.004
ANTIBACTERIALS FOR SYSTEMIC USE	0.367	0.357	0.021	0.357	0.358	0.003
ANTIDEPRESSANTS	0.1	0.079	0.074	0.09	0.086	0.015
ANTIEPILEPTICS	0.034	0.028	0.035	0.032	0.031	0.007
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.444	0.403	0.082	0.414	0.416	0.002
ANTINEOPLASTIC AGENTS	0.004	0.003	0.018	0.003	0.003	0.001
ANTIPSORIATICS	0.007	0.006	0.02	0.007	0.006	0.011

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ANTITHROMBOTIC AGENTS	0.02	0.015	0.038	0.017	0.015	0.01
BETA BLOCKING AGENTS	0.009	0.008	0.018	0.009	0.009	0.006
CALCIUM CHANNEL BLOCKERS	0.004	0.003	0.014	0.003	0.003	0.002
DIURETICS	0.007	0.005	0.035	0.007	0.006	0.019
DRUGS FOR ACID RELATED DISORDERS	0.12	0.115	0.016	0.115	0.115	0
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.151	0.126	0.072	0.134	0.132	0.005
DRUGS USED IN DIABETES	0.008	0.006	0.024	0.007	0.007	0.006
IMMUNOSUPPRESSANTS	0.007	0.005	0.031	0.007	0.005	0.019
LIPID MODIFYING AGENTS	0.011	0.009	0.012	0.01	0.011	0.012
OPIOIDS	0.056	0.048	0.033	0.05	0.05	0
PSYCHOLEPTICS	0.174	0.152	0.06	0.16	0.158	0.006
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.008	0.011	0.03	0.007	0.01	0.028

Appendix Table 30. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Amoxicillin Chlamydia*) group as well as the standardized difference of the means–CPRD.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
15 - 19	0.203	0.264	0.15	0.268	0.278	0.022

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
20 - 24	0.4	0.337	0.128	0.411	0.346	0.134
25 - 29	0.184	0.191	0.018	0.134	0.194	0.16
30 - 34	0.097	0.107	0.031	0.062	0.071	0.033
35 - 39	0.05	0.039	0.05	-0.045	0.049	0.116
40 - 44	0.025	0.034	0.057	-0.045	-0.031	0.051
45 - 49	0.018	-0.028	0.052	-0.045	-0.031	0.094
50 - 54	0.01	-0.028	0.046	-0.045	-0.031	0.085
55 - 59	0.007	-0.028	0.014	-0.045	-0.031	0.123
65 - 69	-0.003	-0.028	0.115	0	-0.031	0
gender = FEMALE	0.721	0.803	0.186	0.804	0.775	0.069
Acute respiratory disease	0.07	0.124	0.202	0.196	0.122	0.203
Gastroesophageal reflux disease	0.003	-0.028	0.051	0	-0.031	0
Gastrointestinal hemorrhage	0.009	-0.028	0.037	-0.045	-0.031	0.052
Psoriasis	0.01	-0.028	0.072	-0.045	-0.031	0.099
Urinary tract infectious disease	0.043	0.084	0.193	-0.045	0.076	0.272

Appendix Table 31. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Amoxicillin Chlamydia*) group as well as the standardised difference of the means–IPCI.

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentM eanComparator	absBeforePsAdjust mentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMe anComparator	absAfterPsAdjust mentStdDiff
0 - 4	0	-0.016	0	0	-0.019	0
5 - 9	0	-0.016	0	0	-0.019	0
10 - 14	-0.003	-0.016	0.055	0	-0.019	0
15 - 19	0.124	0.119	0.018	0.134	0.115	0.057
20 - 24	0.313	0.24	0.158	0.274	0.238	0.083
25 - 29	0.201	0.224	0.057	0.195	0.241	0.11
30 - 34	0.122	0.141	0.059	0.098	0.104	0.022
35 - 39	0.072	0.058	0.056	0.079	0.073	0.026
40 - 44	0.062	0.09	0.113	0.122	0.108	0.044
45 - 49	0.035	0.029	0.031	0.03	0.023	0.049
50 - 54	0.033	0.032	0.004	-0.03	0.031	0.041
55 - 59	0.018	-0.016	0.04	-0.03	-0.019	0.117
60 - 64	0.011	0.019	0.078	-0.03	-0.019	0.075
65 - 69	0.004	-0.016	0.037	0	-0.019	0
70 - 74	0.004	-0.016	0.037	-0.03	-0.019	0.064
75 - 79	-0.003	-0.016	0.12	0	-0.019	0
85 - 89	0	-0.016	0	0	0	0
gender = FEMALE	0.639	0.692	0.112	0.75	0.723	0.061
Cerebrovascular disease	0	-0.016	0	0	-0.019	0
Heart disease	0.01	-0.016	0.034	-0.03	-0.019	0.154
Pulmonary embolism	-0.003	-0.016	0.085	0	-0.019	0
Venous thrombosis	0.005	-0.016	0.02	-0.03	0	0
Acute respiratory disease	0.115	0.228	0.333	0.293	0.202	0.211
Attention deficit hyperactivity disorder	0.031	0.029	0.013	-0.03	-0.019	0

covariateName	beforePsAdjustment MeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustment MeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Chronic obstructive lung disease	-0.003	0	0	-0.03	0	0
Crohn's disease	0.003	0	0	-0.03	0	0
Diabetes mellitus	0.007	0.019	0.125	-0.03	-0.019	0.089
Gastroesophageal reflux disease	0.003	-0.016	0.049	-0.03	-0.019	0
Gastrointestinal hemorrhage	0.018	0.022	0.037	-0.03	-0.019	0.023
Human immunodeficiency virus infection	0.013	-0.016	0.031	-0.03	-0.019	0.029
Hyperlipidemia	0.006	-0.016	0.01	-0.03	-0.019	0.034
Hypertensive disorder	0.006	0.032	0.258	-0.03	0.032	0.084
Obesity	0.007	-0.016	0.061	-0.03	-0.019	0.096
Pneumonia	0.006	0.016	0.112	0	0.021	0
Renal impairment	0	-0.016	0	0	-0.019	0
Rheumatoid arthritis	-0.003	-0.016	0.019	0	-0.019	0
Urinary tract infectious disease	0.111	0.173	0.191	0.238	0.125	0.295
Viral hepatitis C	-0.003	-0.016	0.055	0	0	0
Malignant lymphoma	0	-0.016	0	0	0	0
Malignant neoplastic disease	0.006	-0.016	0.05	0	-0.019	0
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.012	0.045	0.249	0.03	0.052	0.108
ANTIBACTERIALS FOR SYSTEMIC USE	0.387	0.654	0.538	0.512	0.439	0.146
ANTIDEPRESSANTS	0.083	0.099	0.06	0.14	0.109	0.096
ANTIEPILEPTICS	0.012	0.016	0.037	-0.03	0.02	0.058

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.17	0.272	0.265	0.293	0.241	0.117
ANTINEOPLASTIC AGENTS	0.01	0.019	0.092	-0.03	-0.019	0.149
ANTIPSORIATICS	0.018	0.032	0.099	-0.03	0.034	0.097
ANTITHROMBOTIC AGENTS	0.015	0.026	0.081	-0.03	0.027	0.108
BETA BLOCKING AGENTS	0.022	0.067	0.27	0.037	0.065	0.13
CALCIUM CHANNEL BLOCKERS	0.017	-0.016	0.033	-0.03	-0.019	0
DIURETICS	0.007	0.032	0.247	-0.03	0.03	0.078
DRUGS FOR ACID RELATED DISORDERS	0.106	0.17	0.199	0.165	0.152	0.033
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.232	0.298	0.153	0.329	0.273	0.122
DRUGS USED IN DIABETES	0.008	-0.016	0.053	-0.03	-0.019	0.117
IMMUNOSUPPRESSANTS	0.004	0.016	0.159	0	-0.019	0
LIPID MODIFYING AGENTS	0.012	0.032	0.166	-0.03	0.03	0.124
OPIOIDS	0.07	0.141	0.26	0.159	0.106	0.154
PSYCHOLEPTICS	0.101	0.112	0.038	0.152	0.122	0.089
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.037	0.035	0.011	-0.03	0.033	0.139

Appendix Table 32. Select characteristics before and after propensity score adjustment showing the (weighted) percentage of subjects with the characteristics in the target (*Doxycycline Chlamydia*) and comparator (*Amoxicillin Chlamydia*) group as well as the standardized difference of the means–SIDIAP.

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Age Category						
15 - 19	0.13	0.127	0.008	0.119	0.124	0.015
20 - 24	0.309	0.305	0.007	0.28	0.29	0.024
25 - 29	0.206	0.202	0.011	0.167	0.204	0.095
30 - 34	0.136	0.144	0.024	0.164	0.147	0.046
35 - 39	0.083	0.086	0.013	0.119	0.091	0.091
40 - 44	0.06	0.058	0.011	0.064	0.059	0.02
45 - 49	0.039	0.04	0.008	0.045	0.045	0
50 - 54	0.02	0.023	0.021	0.029	0.024	0.03
60 - 64	0.004	-0.014	0.015	0	-0.015	0
65 - 69	0.002	0	0	-0.016	0	0
70 - 74	0.001	-0.014	0.167	-0.016	-0.015	0.021
75 - 79	0.001	-0.014	0.075	0	-0.015	0
80 - 84	-0.001	0	0	-0.016	0	0
85 - 89	0	-0.014	0	0	-0.015	0
gender = FEMALE	0.644	0.695	0.106	0.675	0.677	0.005
Heart disease	0.005	-0.014	0.056	-0.016	-0.015	0.036
Heart failure	-0.001	-0.014	0.109	-0.016	-0.015	0.046
Acute respiratory disease	0.155	0.138	0.046	0.145	0.128	0.049
Attention deficit hyperactivity disorder	0.003	0	0	-0.016	0	0

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
Chronic liver disease	0.001	0	0	-0.016	0	0
Chronic obstructive lung disease	-0.001	0	0	-0.016	0	0
Diabetes mellitus	0.004	-0.014	0.08	-0.016	-0.015	0
Gastrointestinal hemorrhage	0.009	-0.014	0.069	-0.016	-0.015	0.108
Human immunodeficiency virus infection	0.004	0	0	-0.016	0	0
Hyperlipidemia	0.006	-0.014	0.063	-0.016	-0.015	0.031
Hypertensive disorder	0.003	-0.014	0.139	-0.016	-0.015	0.108
Lesion of liver	-0.001	0	0	-0.016	0	0
Obesity	0.013	0.02	0.06	0.032	0.023	0.059
Osteoarthritis	0.004	-0.014	0.016	-0.016	-0.015	0
Pneumonia	0.002	0	0	-0.016	0	0
Psoriasis	0.003	0	0	-0.016	0	0
Schizophrenia	-0.001	-0.014	0.128	0	-0.015	0
Urinary tract infectious disease	0.162	0.176	0.037	0.186	0.166	0.055
Malignant neoplastic disease	0.003	-0.014	0.003	-0.016	-0.015	0
Malignant tumor of breast	0.001	0	0	-0.016	0	0
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.014	0.017	0.031	0.026	0.018	0.056
ANTIBACTERIALS FOR SYSTEMIC USE	0.367	0.45	0.172	0.412	0.412	0.001
ANTIDEPRESSANTS	0.1	0.086	0.046	0.109	0.079	0.105
ANTIEPILEPTICS	0.034	0.023	0.062	0.026	0.023	0.021

covariateName	beforePsAdjustmentMeanTreated	beforePsAdjustmentMeanComparator	absBeforePsAdjustmentStdDiff	afterPsAdjustmentMeanTreated	afterPsAdjustmentMeanComparator	absAfterPsAdjustmentStdDiff
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.444	0.441	0.006	0.434	0.42	0.029
ANTINEOPLASTIC AGENTS	0.004	-0.014	0.075	-0.016	-0.015	0
ANTIPSORIATICS	0.007	0	0	-0.016	0	0
ANTITHROMBOTIC AGENTS	0.02	0.017	0.017	0.026	0.018	0.055
BETA BLOCKING AGENTS	0.009	-0.014	0.021	-0.016	-0.015	0.03
CALCIUM CHANNEL BLOCKERS	0.004	-0.014	0.013	0.016	-0.015	0.135
DIURETICS	0.007	-0.014	0.018	0.019	-0.015	0.098
DRUGS FOR ACID RELATED DISORDERS	0.12	0.164	0.137	0.158	0.161	0.009
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.151	0.13	0.06	0.129	0.13	0.005
DRUGS USED IN DIABETES	0.008	-0.014	0.026	-0.016	-0.015	0.066
IMMUNOSUPPRESSANTS	0.007	-0.014	0.047	-0.016	-0.015	0.066
LIPID MODIFYING AGENTS	0.011	-0.014	0.048	-0.016	-0.015	0.066
OPIOIDS	0.056	0.058	0.009	0.087	0.064	0.085
PSYCHOLEPTICS	0.174	0.156	0.048	0.193	0.154	0.102
PSYCHOSTIMULANTS. AGENTS USED FOR ADHD AND NOOTROPICS	0.008	0	0	-0.016	0	0

Appendix IV: Supplementary results

Appendix Table 33. Results of the cohort study in persons with the indication acne.

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	607	14	Erythromycin	620	9	FAIL	-	-
IPCI	Anxiety	2235	47	Isotretinoin	2872	59	PASS	1.94	1.28-2.94
SIDIAP	Anxiety	10589	82	Erythromycin	14988	146	PASS	0.96	0.73-1.26
SIDIAP	Anxiety	5251	39	Isotretinoin	8092	116	FAIL	-	-
CPRD GOLD	Anxiety	16165	129	Erythromycin	27788	185	PASS	1.06	0.84-1.32
CPRD GOLD	Anxiety	584	≤5	Isotretinoin	977	0	FAIL	-	-
IPCI	Suicide (with death)	781	0	Erythromycin	796	0	FAIL	-	-
IPCI	Suicide (with death)	2764	0	Isotretinoin	3542	≤5	FAIL	-	-
SIDIAP	Suicide (with death)	12300	0	Erythromycin	17037	0	FAIL	-	-
SIDIAP	Suicide (with death)	6101	0	Isotretinoin	9370	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	18339	0	Erythromycin	31126	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	675	0	Isotretinoin	1103	0	FAIL	-	-
IPCI	Depression	717	7	Erythromycin	730	0	FAIL	-	-
IPCI	Depression	2565	13	Isotretinoin	3300	19	PASS	1.32	0.62-2.74
SIDIAP	Depression	11905	27	Erythromycin	16600	31	PASS	1.51	0.88-2.57

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
SIDIAP	Depression	5844	13	Isotretinoin	8998	29	FAIL	-	-
CPRD GOLD	Depression	15862	131	Erythromycin	27205	168	PASS	1.17	0.93-1.47
CPRD GOLD	Depression	587	5	Isotretinoin	980	≤5	FAIL	-	-
IPCI	Suicide-related events (without death)	778	0	Erythromycin	793	0	FAIL	-	-
IPCI	Suicide-related events (without death)	2757	≤5	Isotretinoin	3534	≤5	FAIL	-	-
SIDIAP	**Suicide-related events (without death)**	**12265**	**7**	**Erythromycin**	**16998**	**≤5**	**PASS**	**3.77**	**1.03-17.80**
SIDIAP	Suicide-related events (without death)	6090	≤5	Isotretinoin	9350	6	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	18054	12	Erythromycin	30682	10	PASS	1.71	0.74-4.07
CPRD GOLD	Suicide-related events (without death)	655	0	Isotretinoin	1064	≤5	FAIL	-	-
IPCI	Suicide-related events (with death)	781	0	Erythromycin	796	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Suicide-related events (with death)	2764	0	Isotretinoin	3542	≤5	FAIL	-	-
SIDIAP	Suicide-related events (with death)	12300	0	Erythromycin	17037	≤5	FAIL	-	-
SIDIAP	Suicide-related events (with death)	6101	0	Isotretinoin	9370	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	18339	0	Erythromycin	31126	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	675	0	Isotretinoin	1103	0	FAIL	-	-
IPCI	Suicide-related events	778	0	Erythromycin	793	0	FAIL	-	-
IPCI	Suicide-related events	2757	≤5	Isotretinoin	3534	≤5	FAIL	-	-
SIDIAP	**Suicide-related events**	**12265**	**7**	**Erythromycin**	**16998**	**≤5**	**PASS**	**3.77**	**1.03-17.80**
SIDIAP	Suicide-related events	6090	≤5	Isotretinoin	9350	6	FAIL	-	-
CPRD GOLD	Suicide-related events	18054	12	Erythromycin	30682	10	PASS	1.71	0.74-4.07
CPRD GOLD	Suicide-related events	655	0	Isotretinoin	1064	≤5	FAIL	-	-

Appendix Table 34. Results of the cohort study in persons with the indication acne and a history of depression.

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	49	≤5	Erythromycin	49	0	FAIL	-	-
IPCI	Anxiety	39	0	Isotretinoin	73	≤5	FAIL	-	-
SIDIAP	Anxiety	185	5	Erythromycin	210	7	FAIL	-	-
SIDIAP	Anxiety	140	≤5	Isotretinoin	265	6	FAIL	-	-
CPRD GOLD	Anxiety	1679	37	Erythromycin	2317	40	FAIL	-	-
CPRD GOLD	Anxiety	7	0	Isotretinoin	14	0	FAIL	-	-
IPCI	Suicide (with death)	91	0	Erythromycin	91	0	FAIL	-	-
IPCI	Suicide (with death)	64	0	Isotretinoin	104	0	FAIL	-	-
SIDIAP	Suicide (with death)	383	0	Erythromycin	424	0	FAIL	-	-
SIDIAP	Suicide (with death)	224	0	Isotretinoin	401	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	2943	0	Erythromycin	4052	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	7	0	Isotretinoin	17	0	FAIL	-	-
IPCI	Suicide-related events (without death)	89	0	Erythromycin	89	0	FAIL	-	-
IPCI	Suicide-related events	64	0	Isotretinoin	104	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
	(without death)								
SIDIAP	Suicide-related events (without death)	365	≤5	Erythromycin	405	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	222	≤5	Isotretinoin	396	0	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	2733	5	Erythromycin	3767	≤5	PASS	1.52	0.40-6.16
CPRD GOLD	Suicide-related events (without death)	7	0	Isotretinoin	17	0	FAIL	-	-
IPCI	Suicide-related events (with death)	91	0	Erythromycin	91	0	FAIL	-	-
IPCI	Suicide-related events (with death)	64	0	Isotretinoin	104	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	383	0	Erythromycin	424	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	224	0	Isotretinoin	401	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide-related events (with death)	2943	0	Erythromycin	4052	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	7	0	Isotretinoin	17	0	FAIL	-	-
IPCI	Suicide-related events	89	0	Erythromycin	89	0	FAIL	-	-
IPCI	Suicide-related events	64	0	Isotretinoin	104	0	FAIL	-	-
SIDIAP	Suicide-related events	365	≤5	Erythromycin	405	0	FAIL	-	-
SIDIAP	Suicide-related events	222	≤5	Isotretinoin	396	0	FAIL	-	-
CPRD GOLD	Suicide-related events	2733	5	Erythromycin	3767	≤5	PASS	1.52	0.40-6.16
CPRD GOLD	Suicide-related events	7	0	Isotretinoin	17	0	FAIL	-	-

Appendix Table 35. Acne cohort, with sensitivity analysis (cohort end date 30 days after end date of drug era instead of 7 days).

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	612	11	Erythromycin	620	11	FAIL		
IPCI	Anxiety	2380	45	Isotretinoin	2914	68	PASS	1.45	0.96-2.15
SIDIAP	Anxiety	11376	111	Erythromycin	15278	176	PASS	1.04	0.81-1.32

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
SIDIAP	Anxiety	7647	51	Isotretinoin	10022	158	PASS	0.86	0.61-1.19
CPRD GOLD	Anxiety	19004	194	Erythromycin	28192	254	PASS	1.03	0.85-1.24
CPRD GOLD	Anxiety	750	5	Isotretinoin	1086	≤5	FAIL		
IPCI	Suicide (with death)	785	0	Erythromycin	796	0	FAIL		
IPCI	Suicide (with death)	2937	0	Isotretinoin	3602	≤5	FAIL		
SIDIAP	Suicide (with death)	13158	0	Erythromycin	17344	0	FAIL		
SIDIAP	Suicide (with death)	8865	0	Isotretinoin	11584	0	FAIL		
CPRD GOLD	Suicide (with death)	21552	0	Erythromycin	31635	0	FAIL		
CPRD GOLD	Suicide (with death)	864	0	Isotretinoin	1228	0	FAIL		
IPCI	Depression	719	7	Erythromycin	730	≤5	FAIL		
IPCI	Depression	2724	19	Isotretinoin	3339	27	PASS	1.33	0.71-2.46
SIDIAP	Depression	12744	32	Erythromycin	16907	41	PASS	1.28	0.79-2.06
SIDIAP	Depression	8522	18	Isotretinoin	11150	43	PASS	1.39	0.75-2.49
CPRD GOLD	Depression	18625	187	Erythromycin	27616	247	PASS	1.02	0.84-1.23
CPRD GOLD	Depression	763	8	Isotretinoin	1083	≤5	FAIL		
IPCI	Suicide-related events (without death)	782	0	Erythromycin	793	0	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Suicide-related events (without death)	2931	≤5	Isotretinoin	3594	≤5	FAIL		
SIDIAP	**Suicide-related events (without death)**	**13118**	**8**	**Erythromycin**	**17305**	**≤5**	**PASS**	**3.35**	**1.02-12.99**
SIDIAP	Suicide-related events (without death)	8843	≤5	Isotretinoin	11563	8	PASS	1.90	0.45-7.16
CPRD GOLD	Suicide-related events (without death)	21218	22	Erythromycin	31186	16	PASS	1.76	0.93-3.41
CPRD GOLD	Suicide-related events (without death)	846	≤5	Isotretinoin	1197	≤5	FAIL		
IPCI	Suicide-related events (with death)	785	0	Erythromycin	796	0	FAIL		
IPCI	Suicide-related events (with death)	2937	0	Isotretinoin	3602	≤5	FAIL		
SIDIAP	Suicide-related events (with death)	13158	0	Erythromycin	17344	≤5	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
SIDIAP	Suicide-related events (with death)	8865	0	Isotretinoin	11583	0	FAIL		
CPRD GOLD	Suicide-related events (with death)	21552	0	Erythromycin	31635	0	FAIL		
CPRD GOLD	Suicide-related events (with death)	864	0	Isotretinoin	1228	0	FAIL		
IPCI	Suicide-related events	782	0	Erythromycin	793	0	FAIL		
IPCI	Suicide-related events	2931	≤5	Isotretinoin	3594	≤5	FAIL		
SIDIAP	**Suicide-related events**	**13118**	**8**	**Erythromycin**	**17305**	**≤5**	**PASS**	**3.35**	**1.02-12.99**
SIDIAP	Suicide-related events	8843	≤5	Isotretinoin	11563	8	PASS	1.90	0.45-7.16
CPRD GOLD	Suicide-related events	21218	22	Erythromycin	31186	16	PASS	1.76	0.93-3.41
CPRD GOLD	Suicide-related events	846	≤5	Isotretinoin	1197	≤5	FAIL		

Appendix Table 36. Acne with history of depression cohort, with sensitivity analysis (cohort end date 30 days after end date of drug era instead of 7 days).

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	50	≤5	Erythromycin	50	≤5	FAIL		
IPCI	Anxiety	402	23	Isotretinoin	480	20	FAIL		
SIDIAP	Anxiety	214	9	Erythromycin	219	7	FAIL		
SIDIAP	Anxiety	187	10	Isotretinoin	223	20	FAIL		
CPRD GOLD	Anxiety	1760	72	Erythromycin	2319	49	FAIL		
CPRD GOLD	Anxiety	69	≤5	Isotretinoin	85	≤5	FAIL		
IPCI	Suicide (with death)	94	0	Erythromycin	95	0	FAIL		
IPCI	Suicide (with death)	969	0	Isotretinoin	1186	≤5	FAIL		
SIDIAP	Suicide (with death)	427	0	Erythromycin	430	0	FAIL		
SIDIAP	Suicide (with death)	1395	0	Isotretinoin	1782	0	FAIL		
CPRD GOLD	Suicide (with death)	3355	0	Erythromycin	4064	0	FAIL		
CPRD GOLD	Suicide (with death)	194	0	Isotretinoin	226	0	FAIL		
IPCI	Suicide-related events (without death)	91	0	Erythromycin	92	0	FAIL		
IPCI	Suicide-related events	964	0	Isotretinoin	1179	≤5	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
	(without death)								
SIDIAP	Suicide-related events (without death)	407	0	Erythromycin	410	0	FAIL		
SIDIAP	Suicide-related events (without death)	1378	≤5	Isotretinoin	1764	≤5	FAIL		
CPRD GOLD	Suicide-related events (without death)	3122	8	Erythromycin	3778	6	PASS	1.47	0.51-4.46
CPRD GOLD	Suicide-related events (without death)	181	0	Isotretinoin	210	≤5	FAIL		
IPCI	Suicide-related events (with death)	94	0	Erythromycin	95	0	FAIL		
IPCI	Suicide-related events (with death)	969	0	Isotretinoin	1186	≤5	FAIL		
SIDIAP	Suicide-related events (with death)	427	0	Erythromycin	430	0	FAIL		
SIDIAP	Suicide-related events (with death)	1395	0	Isotretinoin	1782	0	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide-related events (with death)	3355	0	Erythromycin	4064	0	FAIL		
CPRD GOLD	Suicide-related events (with death)	194	0	Isotretinoin	226	0	FAIL		
IPCI	Suicide-related events	91	0	Erythromycin	92	0	FAIL		
IPCI	Suicide-related events	964	0	Isotretinoin	1179	≤5	FAIL		
SIDIAP	Suicide-related events	407	0	Erythromycin	410	0	FAIL		
SIDIAP	Suicide-related events	1378	≤5	Isotretinoin	1764	≤5	FAIL		
CPRD GOLD	Suicide-related events	3122	8	Erythromycin	3778	6	PASS	1.47	0.51-4.46
CPRD GOLD	Suicide-related events	181	0	Isotretinoin	210	≤5	FAIL		

Appendix Table 37. Results of the cohort study in persons with the indication rosacea.

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	73	0	Erythromycin	73	0	FAIL	-	-
IPCI	Anxiety	100	0	Isotretinoin	100	5	FAIL	-	-
SIDIAP	Anxiety	633	5	Erythromycin	643	10	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
SIDIAP	Anxiety	464	9	Isotretinoin	471	12	FAIL	-	-
CPRD GOLD	Anxiety	4238	35	Erythromycin	4976	22	PASS	1.41	0.83-2.45
CPRD GOLD	Anxiety	42	0	Isotretinoin	58	0	FAIL	-	-
IPCI	Suicide (with death)	90	0	Erythromycin	90	0	FAIL	-	-
IPCI	Suicide (with death)	146	0	Isotretinoin	146	0	FAIL	-	-
SIDIAP	Suicide (with death)	832	0	Erythromycin	847	0	FAIL	-	-
SIDIAP	Suicide (with death)	601	0	Isotretinoin	610	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	5163	0	Erythromycin	6023	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	47	0	Isotretinoin	70	0	FAIL	-	-
IPCI	Depression	82	0	Erythromycin	82	0	FAIL	-	-
IPCI	Depression	127	0	Isotretinoin	128	0	FAIL	-	-
SIDIAP	Depression	758	≤5	Erythromycin	772	≤5	FAIL	-	-
SIDIAP	Depression	545	≤5	Isotretinoin	553	≤5	FAIL	-	-
CPRD GOLD	Depression	4049	28	Erythromycin	4737	24	PASS	1.01	0.58-1.76
CPRD GOLD	Depression	41	≤5	Isotretinoin	58	≤5	FAIL	-	-
IPCI	Suicide-related events (without death)	90	0	Erythromycin	90	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Suicide-related events (without death)	146	0	Isotretinoin	146	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	831	0	Erythromycin	846	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	599	0	Isotretinoin	608	0	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	5086	≤5	Erythromycin	5939	≤5	PASS	1.73	0.34-12.48
CPRD GOLD	Suicide-related events (without death)	47	0	Isotretinoin	70	0	FAIL	-	-
IPCI	Suicide-related events (with death)	90	0	Erythromycin	90	0	FAIL	-	-
IPCI	Suicide-related events (with death)	146	0	Isotretinoin	146	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	832	0	Erythromycin	847	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
SIDIAP	Suicide-related events (with death)	601	0	Isotretinoin	610	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	5161	0	Erythromycin	6021	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	47	0	Isotretinoin	70	0	FAIL	-	-
IPCI	Suicide-related events	90	0	Erythromycin	90	0	FAIL	-	-
IPCI	Suicide-related events	146	0	Isotretinoin	146	0	FAIL	-	-
SIDIAP	Suicide-related events	831	0	Erythromycin	846	0	FAIL	-	-
SIDIAP	Suicide-related events	599	0	Isotretinoin	608	0	FAIL	-	-
CPRD GOLD	Suicide-related events	5086	≤5	Erythromycin	5939	≤5	PASS	1.73	0.34-12.48
CPRD GOLD	Suicide-related events	47	0	Isotretinoin	70	0	FAIL	-	-

Appendix Table 38. Results of the cohort study in persons with the indication rosacea and a history of depression.

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	7	0	Erythromycin	7	0	FAIL	-	-
IPCI	Anxiety	75	≤5	Isotretinoin	89	≤5	FAIL	-	-
SIDIAP	Anxiety	35	0	Erythromycin	35	≤5	FAIL	-	-
SIDIAP	Anxiety	159	≤5	Isotretinoin	362	7	FAIL	-	-
CPRD GOLD	Anxiety	618	8	Erythromycin	691	6	FAIL	-	-
CPRD GOLD	Anxiety	10	0	Isotretinoin	16	0	FAIL	-	-
IPCI	Suicide (with death)	14	0	Erythromycin	14	0	FAIL	-	-
IPCI	Suicide (with death)	107	0	Isotretinoin	134	0	FAIL	-	-
SIDIAP	Suicide (with death)	75	0	Erythromycin	75	0	FAIL	-	-
SIDIAP	Suicide (with death)	266	0	Isotretinoin	515	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	1130	0	Erythromycin	1286	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	12	0	Isotretinoin	17	0	FAIL	-	-
IPCI	Suicide-related events (without death)	14	0	Erythromycin	14	0	FAIL	-	-
IPCI	Suicide-related events	107	0	Isotretinoin	134	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
	(without death)								
SIDIAP	Suicide-related events (without death)	75	0	Erythromycin	75	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	264	0	Isotretinoin	512	0	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	1073	≤5	Erythromycin	1222	≤5	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	12	0	Isotretinoin	17	0	FAIL	-	-
IPCI	Suicide-related events (with death)	14	0	Erythromycin	14	0	FAIL	-	-
IPCI	Suicide-related events (with death)	107	0	Isotretinoin	134	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	75	0	Erythromycin	75	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	266	0	Isotretinoin	515	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide-related events (with death)	1128	0	Erythromycin	1284	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	12	0	Isotretinoin	17	0	FAIL	-	-
IPCI	Suicide-related events	14	0	Erythromycin	14	0	FAIL	-	-
IPCI	Suicide-related events	107	0	Isotretinoin	134	0	FAIL	-	-
SIDIAP	Suicide-related events	75	0	Erythromycin	75	0	FAIL	-	-
SIDIAP	Suicide-related events	264	0	Isotretinoin	512	0	FAIL	-	-
CPRD GOLD	Suicide-related events	1073	≤5	Erythromycin	1222	≤5	FAIL	-	-
CPRD GOLD	Suicide-related events	12	0	Isotretinoin	17	0	FAIL	-	-

Appendix Table 39. Rosacea cohort, with sensitivity analysis (cohort end date 30 days after end date of drug era instead of 7 days).

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	73	≤5	Erythromycin	73	0	FAIL		
IPCI	Anxiety	100	0	Isotretinoin	100	5	FAIL		
SIDIAP	Anxiety	632	8	Erythromycin	643	12	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
SIDIAP	Anxiety	464	9	Isotretinoin	471	16	FAIL		
CPRD GOLD	Anxiety	4238	49	Erythromycin	4976	39	PASS	1.21	0.80-1.86
CPRD GOLD	Anxiety	42	0	Isotretinoin	58	0	FAIL		
IPCI	Suicide (with death)	90	0	Erythromycin	90	0	FAIL		
IPCI	Suicide (with death)	146	0	Isotretinoin	146	0	FAIL		
SIDIAP	Suicide (with death)	831	0	Erythromycin	847	0	FAIL		
SIDIAP	Suicide (with death)	601	0	Isotretinoin	610	0	FAIL		
CPRD GOLD	Suicide (with death)	5163	0	Erythromycin	6023	0	FAIL		
CPRD GOLD	Suicide (with death)	47	0	Isotretinoin	70	0	FAIL		
IPCI	Depression	82	0	Erythromycin	82	0	FAIL		
IPCI	Depression	127	0	Isotretinoin	128	0	FAIL		
SIDIAP	Depression	757	≤5	Erythromycin	772	≤5	FAIL		
SIDIAP	Depression	545	≤5	Isotretinoin	553	≤5	FAIL		
CPRD GOLD	Depression	4049	45	Erythromycin	4737	35	PASS	1.19	0.77-1.87
CPRD GOLD	Depression	41	≤5	Isotretinoin	58	≤5	FAIL		
IPCI	Suicide-related events (without death)	90	0	Erythromycin	90	0	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Suicide-related events (without death)	146	0	Isotretinoin	146	0	FAIL		
SIDIAP	Suicide-related events (without death)	830	0	Erythromycin	846	0	FAIL		
SIDIAP	Suicide-related events (without death)	599	0	Isotretinoin	608	0	FAIL		
CPRD GOLD	Suicide-related events (without death)	5086	≤5	Erythromycin	5939	≤5	PASS	1.32	0.29-6.73
CPRD GOLD	Suicide-related events (without death)	47	0	Isotretinoin	70	0	FAIL		
IPCI	Suicide-related events (with death)	90	0	Erythromycin	90	0	FAIL		
IPCI	Suicide-related events (with death)	146	0	Isotretinoin	146	0	FAIL		
SIDIAP	Suicide-related events (with death)	831	0	Erythromycin	847	0	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
SIDIAP	Suicide-related events (with death)	601	0	Isotretinoin	610	0	FAIL		
CPRD GOLD	Suicide-related events (with death)	5161	0	Erythromycin	6021	0	FAIL		
CPRD GOLD	Suicide-related events (with death)	47	0	Isotretinoin	70	0	FAIL		
IPCI	Suicide-related events	90	0	Erythromycin	90	0	FAIL		
IPCI	Suicide-related events	146	0	Isotretinoin	146	0	FAIL		
SIDIAP	Suicide-related events	830	0	Erythromycin	846	0	FAIL		
SIDIAP	Suicide-related events	599	0	Isotretinoin	608	0	FAIL		
CPRD GOLD	Suicide-related events	5086	≤5	Erythromycin	5939	≤5	PASS	1.32	0.29-6.73
CPRD GOLD	Suicide-related events	47	0	Isotretinoin	70	0	FAIL		

Appendix Table 40. Rosacea with history of depression cohort, with sensitivity analysis (cohort end date 30 days after end date of drug era instead of 7 days)

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	7	0	Erythromycin	7	0	FAIL		
IPCI	Anxiety	13	0	Isotretinoin	13	≤5	FAIL		
SIDIAP	Anxiety	35	0	Erythromycin	35	≤5	FAIL		
SIDIAP	Anxiety	18	0	Isotretinoin	24	≤5	FAIL		
CPRD GOLD	Anxiety	592	14	Erythromycin	688	10	FAIL		
CPRD GOLD	Anxiety	8	0	Isotretinoin	8	0	FAIL		
IPCI	Suicide (with death)	14	0	Erythromycin	14	0	FAIL		
IPCI	Suicide (with death)	28	0	Isotretinoin	28	0	FAIL		
SIDIAP	Suicide (with death)	75	0	Erythromycin	75	0	FAIL		
SIDIAP	Suicide (with death)	49	0	Isotretinoin	54	0	FAIL		
CPRD GOLD	Suicide (with death)	1182	0	Erythromycin	1290	0	FAIL		
CPRD GOLD	Suicide (with death)	15	0	Isotretinoin	15	0	FAIL		
IPCI	Suicide-related events (without death)	14	0	Erythromycin	14	0	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Suicide-related events (without death)	28	0	Isotretinoin	28	0	FAIL		
SIDIAP	Suicide-related events (without death)	75	0	Erythromycin	75	0	FAIL		
SIDIAP	Suicide-related events (without death)	47	0	Isotretinoin	52	0	FAIL		
CPRD GOLD	Suicide-related events (without death)	1120	0	Erythromycin	1225	≤5	FAIL		
CPRD GOLD	Suicide-related events (without death)	14	0	Isotretinoin	14	0	FAIL		
IPCI	Suicide-related events (with death)	14	0	Erythromycin	14	0	FAIL		
IPCI	Suicide-related events (with death)	28	0	Isotretinoin	28	0	FAIL		
SIDIAP	Suicide-related events (with death)	75	0	Erythromycin	75	0	FAIL		
SIDIAP	Suicide-related events (with death)	49	0	Isotretinoin	54	0	FAIL		
CPRD GOLD	Suicide-related events (with death)	1180	0	Erythromycin	1288	0	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide-related events (with death)	15	0	Isotretinoin	15	0	FAIL		
IPCI	Suicide-related events	14	0	Erythromycin	14	0	FAIL		
IPCI	Suicide-related events	28	0	Isotretinoin	28	0	FAIL		
SIDIAP	Suicide-related events	75	0	Erythromycin	75	0	FAIL		
SIDIAP	Suicide-related events	47	0	Isotretinoin	52	0	FAIL		
CPRD GOLD	Suicide-related events	1120	0	Erythromycin	1225	≤5	FAIL		
CPRD GOLD	Suicide-related events	14	0	Isotretinoin	14	0	FAIL		

Appendix Table 41. Results of the cohort study in persons with the indication LRTI.

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	8001	34	Azithromycin	8429	39	PASS	0.89	0.53-1.49
IPCI	Anxiety	17225	65	Amoxicillin	19967	85	PASS	0.84	0.60-1.16
SIDIAP	Anxiety	1613	17	Azithromycin	7862	78	FAIL	-	-
SIDIAP	Anxiety	1491	14	Amoxicillin	6492	43	FAIL	-	-
CPRD GOLD	Anxiety	5402	11	Azithromycin	5691	41	PASS	1.08	0.48-2.30

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Anxiety	92649	163	Amoxicillin	237358	438	PASS	0.94	0.78-1.12
IPCI	Suicide (with death)	9908	0	Azithromycin	10419	0	FAIL	-	-
IPCI	Suicide (with death)	21014	0	Amoxicillin	24323	0	FAIL	-	-
SIDIAP	Suicide (with death)	2305	0	Azithromycin	11099	0	FAIL	-	-
SIDIAP	Suicide (with death)	2055	0	Amoxicillin	8776	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	7142	0	Azithromycin	7532	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	115077	0	Amoxicillin	287066	0	FAIL	-	-
~~IPCI~~	~~Suicide (with death)~~	~~9908~~	~~0~~	~~Azithromycin~~	~~10419~~	~~0~~	~~FAIL~~	-	-
~~IPCI~~	~~Suicide (with death)~~	~~21014~~	~~0~~	~~Amoxicillin~~	~~24323~~	~~0~~	~~FAIL~~	-	-
~~SIDIAP~~	~~Suicide (with death)~~	~~2305~~	~~0~~	~~Azithromycin~~	~~11099~~	~~0~~	~~FAIL~~	-	-
~~SIDIAP~~	~~Suicide (with death)~~	~~2055~~	~~0~~	~~Amoxicillin~~	~~8776~~	~~0~~	~~FAIL~~	-	-
~~CPRD GOLD~~	~~Suicide (with death)~~	~~7142~~	~~0~~	~~Azithromycin~~	~~7532~~	~~0~~	~~FAIL~~	-	-
~~CPRD GOLD~~	~~Suicide (with death)~~	~~115077~~	~~0~~	~~Amoxicillin~~	~~287066~~	~~0~~	~~FAIL~~	-	-
IPCI	Suicide-related events (without death)	9889	≤5	Azithromycin	10392	0	FAIL	-	-
IPCI	Suicide-related events (without death)	20969	≤5	Amoxicillin	24267	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	2289	≤5	Azithromycin	11023	≤5	FAIL	-	-
SIDIAP	Suicide-related events (without death)	2046	≤5	Amoxicillin	8732	≤5	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide-related events (without death)	6957	0	Azithromycin	7329	≤5	FAIL	-	-
CPRD GOLD	**Suicide-related events (without death)**	**113147**	**6**	**Amoxicillin**	**282984**	**38**	**PASS**	**0.40**	**0.15-0.87**
IPCI	Suicide-related events (with death)	9906	0	Azithromycin	10415	0	FAIL	-	-
IPCI	Suicide-related events (with death)	21009	0	Amoxicillin	24319	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	2304	0	Azithromycin	11093	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	2055	0	Amoxicillin	8776	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	7132	0	Azithromycin	7522	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	115036	0	Amoxicillin	286982	≤5	FAIL	-	-
IPCI	Suicide-related events	9889	≤5	Azithromycin	10392	0	FAIL	-	-
IPCI	Suicide-related events	20969	≤5	Amoxicillin	24267	0	FAIL	-	-
SIDIAP	Suicide-related events	2289	≤5	Azithromycin	11023	≤5	FAIL	-	-
SIDIAP	Suicide-related events	2046	≤5	Amoxicillin	8732	≤5	FAIL	-	-
CPRD GOLD	Suicide-related events	6957	0	Azithromycin	7329	≤5	FAIL	-	-
CPRD GOLD	**Suicide-related events**	**113147**	**6**	**Amoxicillin**	**282984**	**38**	**PASS**	**0.40**	**0.15-0.87**

Appendix Table 42. Results of the cohort study in persons with the indication LRTI and a history of depression.

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	1171	10	Azithromycin	1183	8	FAIL	-	-
IPCI	Anxiety	2446	12	Amoxicillin depress	2780	22	PASS	0.62	0.30-1.23
SIDIAP	Anxiety	202	≤5	Azithromycin	995	18	FAIL	-	-
SIDIAP	Anxiety	168	≤5	Amoxicillin depress	715	11	FAIL	-	-
CPRD GOLD	Anxiety	1164	≤5	Azithromycin	1224	14	FAIL	-	-
CPRD GOLD	Anxiety	15619	55	Amoxicillin depress	36525	158	PASS	0.81	0.59-1.09
IPCI	Suicide (with death)	1775	0	Azithromycin	1790	0	FAIL	-	-
IPCI	Suicide (with death)	3611	0	Amoxicillin depress	4078	0	FAIL	-	-
SIDIAP	Suicide (with death)	419	0	Azithromycin	2012	0	FAIL	-	-
SIDIAP	Suicide (with death)	329	0	Amoxicillin depress	1307	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	2317	0	Azithromycin	2433	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	28997	0	Amoxicillin depress	65815	0	FAIL	-	-
IPCI	Suicide-related events	1754	≤5	Azithromycin	1767	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
	(without death)								
IPCI	Suicide-related events (without death)	3576	0	Amoxicillin depress	4041	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	412	≤5	Azithromycin	1975	≤5	FAIL	-	-
SIDIAP	Suicide-related events (without death)	325	≤5	Amoxicillin depress	1293	0	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	2156	0	Azithromycin	2260	≤5	FAIL	-	-
CPRD GOLD	**Suicide-related events (without death)**	**27471**	**≤5**	**Amoxicillin depress**	**62651**	**23**	**PASS**	**0.29**	**0.07-0.85**
IPCI	Suicide-related events (with death)	1772	0	Azithromycin	1787	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Suicide-related events (with death)	3608	0	Amoxicillin depress	4075	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	418	0	Azithromycin	2005	≤5	FAIL	-	-
SIDIAP	Suicide-related events (with death)	329	0	Amoxicillin depress	1307	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	2309	0	Azithromycin	2423	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	28968	0	Amoxicillin depress	65755	≤5	FAIL	-	-
IPCI	Suicide-related events	1754	≤5	Azithromycin	1767	0	FAIL	-	-
IPCI	Suicide-related events	3576	0	Amoxicillin depress	4041	0	FAIL	-	-
SIDIAP	Suicide-related events	412	≤5	Azithromycin	1975	≤5	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
SIDIAP	Suicide-related events	325	≤5	Amoxicillin depress	1293	0	FAIL	-	-
CPRD GOLD	Suicide-related events	2156	0	Azithromycin	2260	≤5	FAIL	-	-
CPRD GOLD	**Suicide-related events**	**27471**	**≤5**	**Amoxicillin depress**	**62651**	**23**	**PASS**	**0.29**	**0.07-0.85**

Appendix Table 43. Results of the cohort study in persons with the indication chlamydia.

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	10	≤5	Erythromycin	10	≤5	FAIL	-	-
IPCI	Anxiety	611	24	Azithromycin	2467	135	FAIL	-	-
IPCI	Anxiety	83	0	Amoxicillin	95	5	FAIL	-	-
SIDIAP	Anxiety	64	0	Erythromycin	71	0	FAIL	-	-
SIDIAP	Anxiety	4308	23	Azithromycin	7244	45	PASS	0.83	0.50-1.37
SIDIAP	Anxiety	233	≤5	Amoxicillin	260	≤5	FAIL	-	-
CPRD GOLD	Anxiety	99	0	Erythromycin	116	0	FAIL	-	-
CPRD GOLD	Anxiety	1100	≤5	Azithromycin	3056	6	FAIL	-	-
CPRD GOLD	Anxiety	100	≤5	Amoxicillin	122	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Suicide (with death)	17	0	Erythromycin	17	0	FAIL	-	-
IPCI	Suicide (with death)	1627	0	Azithromycin	6067	0	FAIL	-	-
IPCI	Suicide (with death)	165	0	Amoxicillin	201	0	FAIL	-	-
SIDIAP	Suicide (with death)	93	0	Erythromycin	101	0	FAIL	-	-
SIDIAP	Suicide (with death)	5772	0	Azithromycin	9411	0	FAIL	-	-
SIDIAP	Suicide (with death)	316	0	Amoxicillin	335	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	114	0	Erythromycin	138	0	FAIL		
CPRD GOLD	Suicide (with death)	1371	0	Azithromycin	3789	0	FAIL		
CPRD GOLD	Suicide (with death)	115	0	Amoxicillin	143	0	FAIL		
IPCI	Depression	15	0	Erythromycin	15	0	FAIL		
IPCI	Depression	1389	≤5	Azithromycin	5314	6	FAIL		
IPCI	Depression	140	≤5	Amoxicillin	172	≤5	FAIL		
SIDIAP	Depression	85	0	Erythromycin	94	0	FAIL		
SIDIAP	Depression	5446	11	Azithromycin	8936	10	PASS	1.94	0.81-4.70
SIDIAP	Depression	306	≤5	Amoxicillin	321	≤5	FAIL		

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Depression	81	0	Erythromycin	92	0	FAIL		
CPRD GOLD	Depression	939	≤5	Azithromycin	2699	8	FAIL		
CPRD GOLD	Depression	87	0	Amoxicillin	111	0	FAIL		
IPCI	Suicide-related events (without death)	17	0	Erythromycin	17	0	FAIL		
IPCI	Suicide-related events (without death)	1614	0	Azithromycin	6032	0	FAIL		
IPCI	Suicide-related events (without death)	164	0	Amoxicillin	199	0	FAIL		
SIDIAP	Suicide-related events (without death)	92	0	Erythromycin	100	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	5726	0	Azithromycin	9335	≤5	FAIL	-	-
SIDIAP	Suicide-related events (without death)	311	0	Amoxicillin	329	0	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	110	0	Erythromycin	133	0	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	1310	≤5	Azithromycin	3616	≤5	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide-related events (without death)	112	0	Amoxicillin	137	0	FAIL	-	-
IPCI	Suicide-related events (with death)	17	0	Erythromycin	17	0	FAIL	-	-
IPCI	Suicide-related events (with death)	1627	0	Azithromycin	6067	0	FAIL	-	-
IPCI	Suicide-related events (with death)	165	0	Amoxicillin	201	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	93	0	Erythromycin	101	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	5771	0	Azithromycin	9410	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	316	0	Amoxicillin	335	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	114	0	Erythromycin	138	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	1371	0	Azithromycin	3789	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide-related events (with death)	115	0	Amoxicillin	143	0	FAIL	-	-
IPCI	Suicide-related events	17	0	Erythromycin	17	0	FAIL	-	-
IPCI	Suicide-related events	1614	0	Azithromycin	6032	0	FAIL	-	-
IPCI	Suicide-related events	164	0	Amoxicillin	199	0	FAIL	-	-
SIDIAP	Suicide-related events	92	0	Erythromycin	100	0	FAIL	-	-
SIDIAP	Suicide-related events	5726	0	Azithromycin	9335	≤5	FAIL	-	-
SIDIAP	Suicide-related events	311	0	Amoxicillin	329	0	FAIL		
CPRD GOLD	Suicide-related events	110	0	Erythromycin	133	0	FAIL		
CPRD GOLD	Suicide-related events	1310	≤5	Azithromycin	3616	≤5	FAIL		
CPRD GOLD	Suicide-related events	112	0	Amoxicillin	137	0	FAIL		

Appendix Table 44. Results of the cohort study in persons with the indication chlamydia and a history of depression.

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
IPCI	Anxiety	0	0	Erythromycin	0	0	FAIL	-	-
IPCI	Anxiety	103	≤5	Azithromycin	352	19	FAIL	-	-
IPCI	Anxiety	6	0	Amoxicillin	11	0	FAIL	-	-
SIDIAP	Anxiety	≤5	0	Erythromycin	≤5	0	FAIL	-	-
SIDIAP	Anxiety	166	≤5	Azithromycin	224	≤5	FAIL	-	-
SIDIAP	Anxiety	8	0	Amoxicillin	8	0	FAIL	-	-
CPRD GOLD	Anxiety	14	0	Erythromycin	21	0	FAIL	-	-
CPRD GOLD	Anxiety	259	≤5	Azithromycin	699	6	FAIL	-	-
CPRD GOLD	Anxiety	≤5	0	Amoxicillin	≤5	0	FAIL	-	-
IPCI	Suicide (with death)	≤5	0	Erythromycin	≤5	0	FAIL	-	-
IPCI	Suicide (with death)	359	0	Azithromycin	1159	0	FAIL	-	-
IPCI	Suicide (with death)	20	0	Amoxicillin	33	0	FAIL	-	-
SIDIAP	Suicide (with death)	7	0	Erythromycin	7	0	FAIL	-	-
SIDIAP	Suicide (with death)	347	0	Azithromycin	478	0	FAIL	-	-
SIDIAP	Suicide (with death)	14	0	Amoxicillin	14	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	20	0	Erythromycin	33	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide (with death)	429	0	Azithromycin	1127	0	FAIL	-	-
CPRD GOLD	Suicide (with death)	≤5	0	Amoxicillin	≤5	0	FAIL	-	-
IPCI	Suicide-related events (without death)	≤5	0	Erythromycin	≤5	0	FAIL	-	-
IPCI	Suicide-related events (without death)	351	0	Azithromycin	1137	0	FAIL	-	-
IPCI	Suicide-related events (without death)	19	0	Amoxicillin	28	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	7	0	Erythromycin	7	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	329	0	Azithromycin	457	0	FAIL	-	-
SIDIAP	Suicide-related events (without death)	11	0	Amoxicillin	11	0	FAIL	-	-
CPRD GOLD	Suicide-related events	18	0	Erythromycin	31	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
	(without death)								
CPRD GOLD	Suicide-related events (without death)	389	≤5	Azithromycin	991	≤5	FAIL	-	-
CPRD GOLD	Suicide-related events (without death)	≤5	0	Amoxicillin	≤5	0	FAIL	-	-
IPCI	Suicide-related events (with death)	≤5	0	Erythromycin	≤5	0	FAIL	-	-
IPCI	Suicide-related events (with death)	359	0	Azithromycin	1159	0	FAIL	-	-
IPCI	Suicide-related events (with death)	20	0	Amoxicillin	33	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	7	0	Erythromycin	7	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	346	0	Azithromycin	477	0	FAIL	-	-
SIDIAP	Suicide-related events (with death)	14	0	Amoxicillin	14	0	FAIL	-	-

Database name	Outcome of interest	Target subjects (n)	Target events (n)	Comparator	Comparator subjects (n)	Comparator events (n)	Diagnostics	Uncalibrated HR	95% CI
CPRD GOLD	Suicide-related events (with death)	20	0	Erythromycin	33	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	429	0	Azithromycin	1127	0	FAIL	-	-
CPRD GOLD	Suicide-related events (with death)	≤5	0	Amoxicillin	≤5	0	FAIL	-	-
IPCI	Suicide-related events	≤5	0	Erythromycin	≤5	0	FAIL	-	-
IPCI	Suicide-related events	351	0	Azithromycin	1137	0	FAIL	-	-
IPCI	Suicide-related events	19	0	Amoxicillin	28	0	FAIL	-	-
SIDIAP	Suicide-related events	7	0	Erythromycin	7	0	FAIL	-	-
SIDIAP	Suicide-related events	329	0	Azithromycin	457	0	FAIL	-	-
SIDIAP	Suicide-related events	11	0	Amoxicillin	11	0	FAIL	-	-
CPRD GOLD	Suicide-related events	18	0	Erythromycin	31	0	FAIL	-	-
CPRD GOLD	Suicide-related events	389	≤5	Azithromycin	991	≤5	FAIL	-	-
CPRD GOLD	Suicide-related events	≤5	0	Amoxicillin	≤5	0	FAIL	-	-

Appendix V: ENCePP checklist for study protocols

Study title:

DARWIN EU® - Suicidality following exposure to doxycycline

EU PAS Register® number: N

Study reference number (if applicable): P3-C3-003

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.8
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2, 8.5
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.3
	4.2.2 Age and sex	☒	☐	☐	8.6
	4.2.3 Country of origin	☒	☐	☐	8.2
	4.2.4 Disease/indication	☒	☐	☐	8.6
	4.2.5 Duration of follow-up	☒	☐	☐	8.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	
5.3	Is exposure categorized according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☒	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.6.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	8.8

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.5, 8.8
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.5, 8.8

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.8

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.2, 8.6
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.6
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.2, 8.6
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.6
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6
	9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	8.7
10.3	Are descriptive analyses included?	☒	☐	☐	8.8
10.4	Are stratified analyses included?	☒	☐	☐	8.8
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.8
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	8.8
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	8.8
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	8.8

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2	Are methods of quality assurance described?	☒	☐	☐	10.0
11.3	Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias? 12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒ ☒ ☒	☐ ☐ ☐	☐ ☐ ☐	11
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	13
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

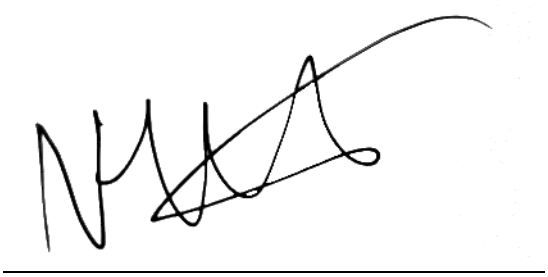
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: Nicholas Hunt

Date: 20th June 2024

Signature: 

Appendix III: Other Additional Information