Study Report

P3-C3-008

DARWIN EU® - Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives

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10/06/2025

Version 3.0

Contents

Study title	DARWIN EU® - Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives
Study report version	V3.0
Date	10/06/2025
EUPAS number	EUPAS1000000443
Active substance	Anti-inflammatory and antirheumatic products, non-steroids (NSAIDS) Defined by all M01A group except M01AX05, M01AX12, M01AX25 and M01AX26
Medicinal product	NA
Research question and objectives	The study aims to answer the question: Is there an association with VTE during concomitant use of NSAIDs prescribed to women hormonal contraceptive users aged 15-49 years old? Specific objectives: 1. To characterise the use of oral NSAIDs among women aged 15-49 using hormonal contraceptives. 2. To measure the association of any oral NSAID use with the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives. 3. To measure the association of ibuprofen, diclofenac and naproxen use with the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.
Countries of study	UK, Spain, Norway, Denmark
Authors	Xintong Li, Daniel Prieto-Alhambra

TITLE

DARWIN EU® - Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives

1. DESCRIPTION OF STUDY TEAM

Study team role(s)	Name(s)	Organisation(s)
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Epidemiologist	Xintong Li Annika Jödicke	University of Oxford
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Epidemiologist	Xintong Li Annika Jödicke	University of Oxford
Clinical Domain Expert	Albert Prats-Uribe Daniel Prieto-Alhambra	University of Oxford University of Oxford, Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data partner name*	**Data Partner member name(s)**	**Organisation(s)**
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DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	Danish Medicines Agency
SIDIAP	Talita Duarte Salles Anna Palomar Agustina Giuliodori Irene López	IDIAP JGOL
NLHR	Nhung Trinh Saeed Hayati Hedvig Nordeng	University of Oslo

*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

Table 1. Description of participated database.

Country	Name of Database	Health Care setting	Type of Data	Number of active subjects*	Calendar period covered by each data source
United Kingdom	Clinical Practice Research Datalink (CPRD) GOLD	primary care	EHR	2.89m	1987-09-09 to 2024-06-15
Spain	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP)	primary care + hospital	EHR	5.95m	2006-01-01 to 2023-06-30
Denmark	Danish Data Health Registries (DK-DHR)	community pharmacists, secondary care.	EHR	5.96m	1995-01-01 to 2024-11-07
Norway	Norwegian Linked Health Registry data (NLHR)	primary care, specialists, and hospital data	Registries	5.67m	2008-01-01 to 2023-12-31

* Based on number of people under observation in at the latest available data.

3. ABSTRACT

Title

DARWIN EU® – Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives

Rationale and background

Multiple studies have showed that oral combined hormonal contraception is associated with an increased risk of venous thromboembolism (VTE), especially for high dose combined oral contraception. Recently, a nationwide study from Denmark reported that NSAIDs use was associated with increased VTE risk in women 15-49 years old, especially among those with concomitant use of high/medium risk hormonal contraception. More data on the association of venous thromboembolism with NSAIDs in women of reproductive age has been requested by medicines regulators to see if such associations are seen in other databases.

Research question and objectives

The study aims to answer the question of: Is there an association with VTE during concomitant use of NSAIDs prescribed to women taking hormonal contraceptives (HC) aged 15-49 years old?

Specific objectives:

1. To characterise the use of oral NSAIDs among women aged 15-49 using hormonal contraceptives.
2. To measure the association between any oral NSAID use and the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.
3. To measure the association between ibuprofen, diclofenac and naproxen use, and the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.

Methods

Study design

A drug utilisation study was performed for objective 1 where new users of oral NSAIDs during HC use were characterised. A self-controlled case series (SCCS) design, nested within a cohort of HC users was performed for objectives 2 and 3.

Data source

This study was conducted using routinely collected health data from 4 databases in 4 European countries. All databases were previously mapped to the OMOP CDM.

1. Clinical Practice Research Datalink (CPRD GOLD), United Kingdom
2. Danish Data Health Registries (DK-DHR), Denmark
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
4. Norwegian Linked Health Registry data (NLHR), Norway

Population

In Objective 1, the study population was women aged 15-49 who initiated oral NSAIDs (ibuprofen, diclofenac, and naproxen) while using HC. In Objectives 2 and 3, the study population included women who had a VTE event during the concomitant use of HC and NSAIDs.

Variables

HC were classified into three groups based on the risk of VTE: low-, medium-, and high-risk HC. The exposures were any NSAIDs (Objective 2), and ibuprofen, diclofenac, and naproxen separately (Objective 3). We used paracetamol as a negative control exposure. The primary outcomes of interest were deep vein thrombosis (DVT), pulmonary embolism(PE), and VTE (composite of the two former). Other variables included potential time-varying confounders: recent surgery, trauma/ fracture, cancer, or hospitalisation.

Statistical analysis

Objective 1: Drug utilisation of oral NSAIDs among women using HC.

Among women using HC who initiated concomitant oral NSAIDs, we first identified treatment episodes using a 30-day grace period. We summarised the number of prescriptions, and time under prescription. We also assessed the potential indication of NSAIDs during the 7- and 30- days before initiation. Analysis was conducted for ibuprofen, diclofenac, and naproxen separately in each HC group.

Objectives 2 and 3: Association between oral NSAID use and the incidence of VTE

We described the patient characteristics among women who initiated HC, among women who initiated NSAIDs during HC, and among women who had a VTE event during HC and had contaminant NSAIDs use.

We allocated person-time exposed to HC into four intervals: Baseline period (only exposed to HC); Pre-exposure to NSAIDs period (2-week period before starting NSAIDs during exposure to HC); NSAIDs exposure risk period (concomitant use of HC and NSAIDs, further divided into three windows: day of initiation, the first 7 days use, and the remaining days use); and post-exposure of NSAIDs period (30-day period after stopping using NSAIDs while still using HC). We performed diagnostics to test the assumptions of SCCS analysis, including event-dependent exposures, and event-dependent observation periods.

The SCCS model was fitted using conditional Poisson regression with an offset of the length of risk periods. Incidence rate ratios (IRR) and 95% confidence intervals of events were estimated. We included age, season, and other risk factor of VTE as time-varying confounders. In objective 2, we defined NSAID exposure as any NSAIDs. In objective 3, ibuprofen, diclofenac and naproxen were analysed separately. All analyses were conducted for each HC group.

We conducted two sensitivity analyses: First, we excluded cases who died within 90 days of VTE outcome. Second, we excluded VTE recorded in the 6 months after cancer, trauma, or hospitalisation records.

For simplicity, we refer to "use" of NSAIDs throughout the report; however, this term specifically reflects dispensation/ prescriptions as captured in the available data sources. It is important to note that this does not capture actual consumption, nor does it include NSAIDs obtained over the counter (OTC).

Results

In CPRD GOLD data, we identified a total of 460,703, 391,679 and 150,053 women using low-, medium, and high-risk HC during the study period respectively. In DK-DHR data, we included a total of 636,348, 593,357, and 212,226 women respectively. In NLHR data, we studied a total of 448,284, 259,588, and 169,060 women respectively. Finally, in SIDIAP we identified a total of 132,381, 204,658, and 47,374 eligible women on low, medium and high-risk HC respectively.

In **objective 1**, we observed that use of ibuprofen, diclofenac, and naproxen during HC was typically short term, with range median 16-28, 15-25, 11-16 and 8-11 days in CPRD GOLD, DK-DHR, NLHR (except for naproxen, which had range median of 101-121 days) and SIDIAP respectively). Analysis of potential indications which were also risk factors for VTE showed a scarcity of these indication records during the 30 days prior to NSAID initiation.

In **objective 2**, In CPRD GOLD, SCCS analyses included 172, 92, 35 and women who had a VTE event during use of low-, medium, and high-risk HC. In DK-DHR data, SCCS included 414, 244, and 142 women with VTE. In NLHR data, equivalent numbers were 188, 212, and 243. Finally, SCCS in SIDIAP included 38, 130, and 23 participants.

Among women on low-risk HC, we observed that IRR was increased in the 14-day pre-exposure period, peaked on the day of NSAIDs exposure, remained high in the first 7 days of NSAIDs use (risk period 1), and the remaining NSAID use time (risk period 2), and then attenuated in the 30-day post-exposure period in all four databases. Adjusted IRRs for the 14 days pre-exposure were 2.18 [95%CI 1.00 - 4.77], 3.38 [2.19 - 5.22], 2.74 [1.46 - 5.12], and 6.71 [2.42 - 18.60] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 4.95 [95%CI 2.37 - 10.36], 3.33 [1.81 - 6.13], 6.03 [3.29 - 11.05], and 3.06 [0.40 - 23.38] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. As for risk period 2, the adjusted IRRs were 3.78 [2.19 - 6.53], 2.63 [1.78 - 3.87], 1.87 [1.14 - 3.08], and 6.80 [1.99 - 23.18] respectively. Post-exposure adjusted IRRs were 3.21 [1.93 - 5.35], 1.16 [0.71 - 1.91], 1.52 [0.83 - 2.78], and 4.03 [1.57 - 10.31] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Similar patterns were observed for women on medium- or high-risk HC, and in the analysis of DVT and PE as individual events. In the analysis of negative control exposure, paracetamol use also showed increased IRRs of similar magnitude, pattern and statistical significance during the pre-exposure period, day of NSAIDs initiation, risk periods 1 and 2, and the post-exposure period among women on low, medium, or high HC.

In **objective 3**, the association between diclofenac, ibuprofen, or naproxen use and VTE (composite and individual PE and DVT events) followed a similar pattern as the observed in Objective 2. For example, the IRRs of VTE for ibuprofen use among users of low-risk HC were 1.77 [0.24 - 12.97], 3.69 [2.37 - 5.75], 5.52 [2.31 - 13.18], 7.66 [2.45 - 23.91] during the pre-exposure period in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 7.49 [1.79 - 31.30], 3.78 [2.05 - 6.97], 13.30 [5.84 - 30.29], 4.45 [0.58 - 34.34] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 4.39 [1.29 - 14.93], 2.84 [1.89 - 4.28], 2.90 [1.00 - 8.44], 2.28 [0.24 - 21.54] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the post-exposure period, adjusted IRRs were 4.70 [1.81 - 12.22], 1.17 [0.69 - 1.99], 1.30 [0.40 - 4.23], 3.28 [0.94 - 11.44] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Discussion

We observed a positive association with VTE during NSAIDs exposure risk period. However, we also observed a counterintuitive positive association in the 2 weeks prior to NSAID initiation, and in most scenarios a remaining association in the post-exposure period. Additionally, we observed a similar association in VTE risk before and during use of paracetamol, pre-defined by protocol as a negative control exposure. All these findings were consistent across four large databases from different parts of Europe.

Our results suggest that residual unmeasured confounding may explain the observed association between NSAID use and VTE risk in women taking HC in this study. We observed the lack of recording of indication (for NSAIDs) in any of the contributing datasets, which limited our ability to adjust for it during our analyses. However, we cannot rule out the possibility that part of the observed excess risk may be directly linked to NSAID use.

4. LIST OF ABBREVIATIONS

Abbreviation	Name
VTE	Venous thromboembolism
NSAIDs	non-steroidal anti-inflammatory drugs
CPRD	Clinical Practice Research Datalink
NLHR	Norwegian Linked Health Registry data
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SCCS	self-controlled case series
DK-DHR	Danish Data Health Registries
HC	Hormonal contraceptives
ATC	Anatomical Therapeutic Chemical
DVT	deep vein thrombosis
PE	pulmonary embolism
IRR	Incidence rate ratio
OMOP CDM	The Observational Medical Outcomes Partnership Common Data Model
RWE	Real world evidence
RWD	Real world data

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	January 2024	8th of January
Creation of Analytical code	January - March 2025	March 2025
Execution of Analytical Code on the data	March - April 2025	20th March 2025
Draft Study Report	End of April 2025	1st April 2025
Final Study Report	End of May 2025	2nd of June

7. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE) refers to the formation of a blood clot in a deep vein and is a rare but potentially preventable cause of death in women of reproductive age. Multiple studies have showed that oral combined hormonal contraception is associated with an increased risk of VTE, especially high-dose combined oral contraception (>=50 µg ethinyl estradiol and progestins).(1) Compared to non-users, users of combined oral contraceptives have a 2- to 6-fold increased risk of VTE, with the highest risk observed among those using high-dose or third- and fourth-generation progestins. Although the absolute risk remains low in healthy young women, it represents a clinically important concern due to the widespread use of these contraceptives.

Additionally, the use of non-steroidal anti-inflammatory drugs (NSAIDs) has also been linked to increased VTE risk. Meta-analyses and observational studies have reported a 1.5- to 2-fold increased risk of VTE among NSAID users compared to non-users, with some studies indicating higher risks associated with specific agents such as diclofenac.(2,3)

Recently, a nationwide study from Denmark found that NSAIDs use is associated with increased VTE risk in women 15-49 years old, especially among those with concomitant use of high/medium risk hormonal contraception.(4) The study reported that NSAID use was associated with a 7-fold increased risk of VTE among users of high-risk hormonal contraception, and a 4-fold increased risk among users of medium-risk contraception, compared to women not using NSAIDs. This study had several limitations, particularly as the study design did not satisfactorily account for confounding by indication or attempt to measure residual confounding bias.

More data on the association of venous thromboembolism with NSAIDs in women of reproductive age has been requested by the European Medicines Agency PRAC committee with the aim of assessing whether similar associations are observed across other databases and through alternative study designs.

8. RESEARCH QUESTION AND OBJECTIVES

Study question: Is there an association with VTE during concomitant use of NSAIDs prescribed to women hormonal contraceptive (HC) users aged 15-49 years old?

Specific objectives:

1. To characterise the use of NSAIDs among women aged 15-49.
2. To measure the association of any NSAID use and the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.
3. To measure the association of ibuprofen, diclofenac and naproxen use on the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.

9. RESEARCH METHODS

9.1 Study type and study design

- Patient-level DUS - Drug utilisation study
- Drug Safety Studies - Self-controlled case series (SCCS)

9.2 Study setting and data sources

This study was conducted using routinely collected data from 4 databases in 4 European countries. All databases were previously mapped to the OMOP CDM.

- Clinical Practice Research Datalink (CPRD GOLD), United Kingdom
- Danish Data Health Registries (DK-DHR), Denmark
- Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
- Norwegian Linked Health Registry data (NLHR), Norway.

9.3 Study period

From 2014 or the earliest data available to end of 2023 or the latest data availability of the participating database. The study period was suggested by EMA based on a possible change in prescribing of diclofenac after a referral in 2013. In the NLHR (Norway) data, study period started on 2018 as secondary care data were available from 2018 onwards in that data source.

9.4 Follow-up

In objectives 2 and 3, we conducted SCCS analyses nested in a cohort of HC users.

Firstly, we constructed HC use episode within each HC category defined by VTE risk (detailed in section 9.6.1 Exposures). For oral HC, a 30-day gap (grace period) was used to define episodes of use. Treatment was assumed to be continuous if the time between stopping of the previous and starting of the next oral contraceptive prescription is 30 days or less. For implants and intrauterine devices, follow-up ended when either there was a record of removal, or based on the suggested period as per usual practice. For example, for the Mirena (levonorgestrel-releasing intrauterine system) a 5-year period was used to define end of HC use unless a code of removal was identified. For Nexplanon (Etonogestrel implant), a 3-year period was used.

For each HC episode, if the episode started after 2014, the follow-up started from the initiation of the HC episode (Scenario A, **Figure 1**). If the episode started before 2014, the follow-up time started from 1st January 2014 (Scenario B, **Figure 1**).

If individuals switch (start a new HC before the previous episode ends or start within 30 days after the previous ends) to a different contraceptive within the same VTE risk group (including change of route, e.g. oral to IUD), we kept following them up. If individuals switch to contraceptive in a different group, the follow-up stopped at time of switching, and the participant then contributed to the newly initiated HC cohort (Scenario C, **Figure 1**).

For each HC use episode, the follow-up time ended when the individual stopped the use of HC, defined as having a more than 30 days gap in prescription records. That is, at the end date of a prescription record (usually calculated by days of supply), if we do not identify the next prescription within 30 days, we defined that the current HC use episode discontinued.

Therefore, the times that an individual was not using a HC (e.g. period between discontinuation and re-start) was not included in the SCCS analysis. Individuals were censored from follow-up at the age 50, or at time of pregnancy.

Within the follow-up of each episode of HC use, we allocated the person-time into four intervals based on the concomitant exposure of NSAIDs: (**Figure 1**):

(i) Baseline period, defined as not exposed to a NSAIDs.
(ii) NSAIDs exposure risk period. The risk period was further divided into the day of initiation, first 7 days on NSAIDs, and >7 days after.
(iii) Pre-exposure period: 2-week period before starting NSAIDs.
(iv) Post-exposure period: 30-day period immediately after discontinuation of NSAIDs. The post-exposure period was introduced to allow the risk to return to baseline.(5)

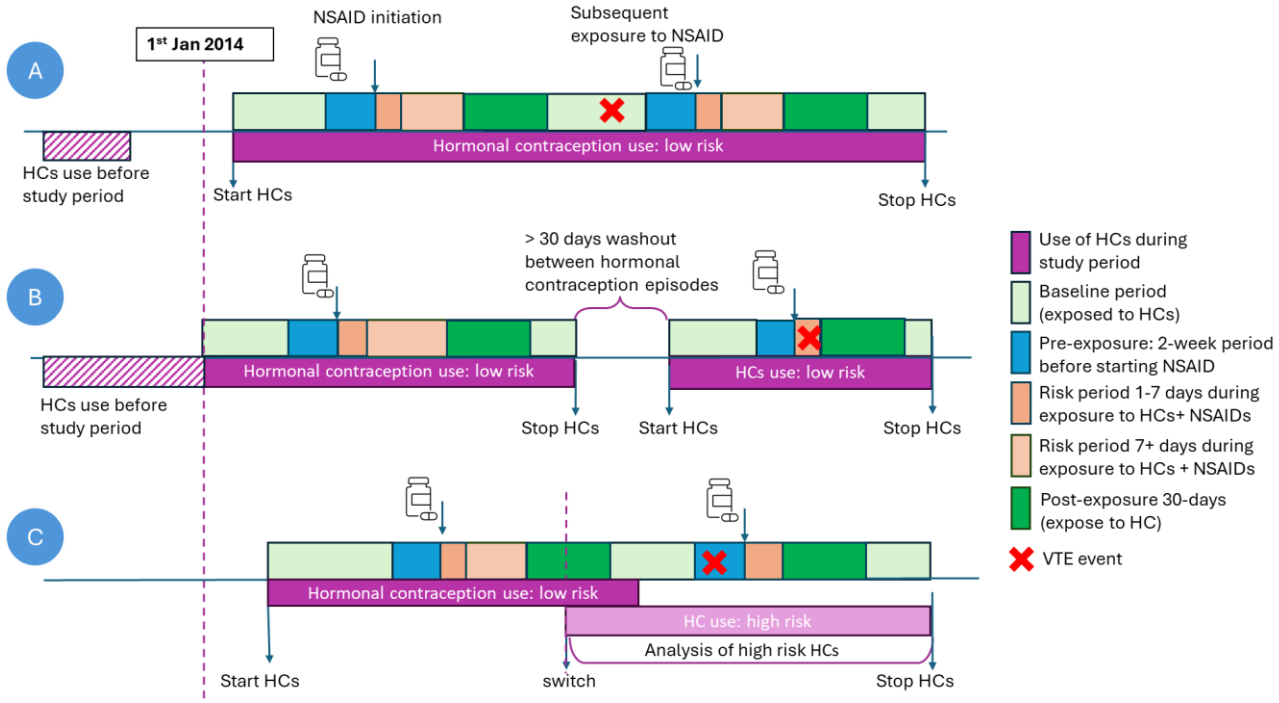

Figure 1. Pictorial representation of the study design. (A. Multiple NSAIDs exposure within one HCs episode; B. HCs use started before study period of 2014 and multiple HCs episodes; C. Switch between HCs categories.)

9.5 Study population with in and exclusion criteria

Objective 1: Drug utilisation of NSAIDs.

The study population included women aged 15-49 who had initiated oral NSAIDs of ibuprofen, diclofenac, and naproxen on or after January 1, 2014 while using HC, defined using a 90-day washout window. We required at least 365 days of data availability before NSAIDs use.

Objective 2 and 3: Incidence of VTE

The source population included women of reproductive age using HC or therapies. We did not limit to medication with contraceptive as indication, but also medications as a combination of estrogen and progestin for other indications. For example, the DIANE®-35, which contains ethinylestradiol and cyproterone acetate, is a treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age, was included in this study.

The study population included women aged 15-49, using HC, and with no history of venous or arterial thromboembolism, cancer (except non-melanoma skin cancer), thrombophilia, hysterectomy, bilateral oophorectomy, sterilisation, or infertility treatment.

We required at least 365 days of data availability before hormonal contraception use in the respective database. This enabled us to characterise the comorbidities of individuals and assess the inclusion/ exclusion criteria.

We excluded women who had any NSAIDs use during the 90-day time before starting the HC. Among those, people with a VTE during the HC usage was included in the SCCS analysis.

9.6 Variables

9.6.1 Exposures

HC were classified into three groups by VTE risk. The ATC codes to identify hormonal contraception are available in the appendix.

We used a grace period of 30 days to define the treatment episode of NSAIDs, that if the gap between two NSAID prescription/dispensation was smaller than 30 days, we joined those two records together to the same episode.

In objective 1, the exposures were oral ibuprofen, diclofenac, and naproxen. We used a grace period of 30 days to define the treatment episode of NSAIDs.

In objective 2, the exposures were any oral NSAIDs, including ibuprofen, diclofenac, and naproxen during the use of HC. Exposure to NSAIDs was then be classified into two periods: the first 7 days on NSAIDs, and days after. For example, if individual received one prescription of ibuprofen for 28 days, the 1-7 days contributed to risk period one, and 8-28 days contributed to risk period two. If individual received less than 7 days of NSAID, only risk period one was contributed.

In objective 3, ibuprofen, diclofenac, and naproxen use was identified separately. ATC codes for identifying the medication are available in the appendix.

We also included a negative control exposure to assess potential residual confounding. In this study, we used paracetamol with or without codeine as the negative control. Paracetamol has been previously used as active comparators for NSAIDs in other studies (6). Given the possibility that paracetamol is co-prescribed with NSAIDs, we only included individuals who initiate paracetamol without NSAIDs use during the 30 days prior to paracetamol.

For simplicity, we refer to "use" of NSAIDs throughout the report; however, this term specifically reflects dispensation/ prescriptions as captured in the available data sources. It is important to note that this does not capture actual consumption, nor does it include NSAIDs obtained over the counter (OTC).

9.6.2 Outcomes

The primary outcome of interest was incident VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE). Only the first-ever VTE event was included. We also included DVT and PE are individual outcomes.

The computational phenotypes for the study outcomes have been developed during another DARWIN EU study (P3-C3-001) and are available in the DARWIN EU library of phenotypes. Preliminary code lists for the study outcomes are available in the appendix.

9.6.3 Other covariates, including confounders, effect modifiers and other variables

Health conditions that are risk factors of VTE (for descriptive characteristics and time-varying cofounder)(7):

- Edema of lower leg
- Inflammatory bowel disease
- Behcet's syndrome
- Lupus erythematosus
- Rheumatoid arthritis
- Cancer (except non-melanoma skin cancer)
- Major trauma/ Fracture
- Surgery
- Hospitalisation
- Reduced mobility, wheelchair use
- Smoking
- BMI

Condition/ treatment for exclusion criteria (before start contributing to follow-up of HCs):

- Venous thromboembolism
- Arterial thromboembolism: ischemic stroke or myocardial infraction
- Cancer (except non-melanoma skin cancer)
- Inherited blood clotting disorders: Haemophilia, acquired or familial thrombophilia, hereditary antithrombin III deficiency, Factor V Leiden.
- Hysterectomy
- Bilateral oophorectomy
- Sterilisation
- Infertility treatment.

Conditions/procedure for end of follow up:

- Pregnancy

Conditions for exclusion of eligible VTE event (Risk factors that temporarily raise the likelihood of VTE, also indication of NSAIDs, for sensitivity analysis):

- Cancer (except non-melanoma skin cancer)
- Major trauma/ Fracture
- Surgery

- Hospitalisation

For conditions/procedures/medications where phenotypes from previous studies are available, the phenotypes were used. This applies to venous and arterial thromboembolism, and cancer. For other conditions/procedures/medications, we used the major concept with descendants.

The study covariates are described conceptually, and the context or rationale for the choices are provided in this section. The operational definition of the covariates is described in the Error! Reference source not found..

9.7 Study size

The self-controlled case series analysis included individuals with both the exposure and the study outcomes. Based on an exposure time of 30 days NSAIDs within a year of HC use, and level of significance of 0.05, and 80% power, a sample size of 246 people is needed to detect a relative risk ratio of 1.8 (based on a previous meta-analysis on NSAIDs and VTE risk) (2,8).

In the Meaidi et.al's study, a much larger effect size was reported, with an adjusted incidence rate ratio of VTE of 7.2. The sample size needed is 19 people under this scenario.

Sample size calculation/s or statistical power was estimated according to study objectives, and provided in this section, with a focus on primary study objective. In descriptive studies (Disease Epidemiology or Drug Utilisation Study/ies), this was based on the desired/available precision for the metric/s of interest. In hypothesis testing ones (e.g. Comparative Safety or Self-Controlled designs), size/power was estimated based on assumed values for the expected/available outcome rate/s and effect size.

9.8 Data transformation

Not applicable.

9.9 Statistical methods

9.9.1 Main summary measures

In objective 1, the main summary measures were median and inter quartal range of number of prescription and length of treatment episodes.

In objectives 2 and 3, the main summary measures were incidence rate ratios.

9.9.2 Main statistical methods

Objective 1: Drug utilisation of NSAIDs among women aged 15-49 using HC.

Among individuals who initiate oral ibuprofen, diclofenac, and naproxen during use of HC in 2014-2023, duration of the treatment episode was reported. A 90-days washout period was used to define NSAIDs initiation. That is, if the there was no NSAIDs use in the 90 days prior to a NSAID prescription, that prescription was considered as an incident use.

As explained in the previous section, a grace period of 30 days was used to define the treatment episode. Treatment duration was summarized providing the minimum, p25, median, p75, and maximum treatment duration. Number of prescriptions within the treatment episode was reported.

We also assessed the potential indication of NSAIDs which are factors that temporarily raise the likelihood of VTE during the 7- and 30- days before initiation.

Analysis was conducted for ibuprofen, diclofenac, and naproxen separately.

Objectives 2 and 3: Association with incidence of VTE.

Descriptive statistics:

For women with contraceptive use, we conducted large-scale characterisation as well as pre-specified patient-level characteristics of the study population at the following time point:

- Using index date of the cohort entry for each contraceptive group (start of HC or 1st Jan 2014, 2018, for NLHR data).
- Using index date of the start of NSAIDs exposure (First episode) during HC use (regardless of whether have VTE during the HC use).
- People with VTE during HC use at time of diagnosis (regardless of whether have NSAIDs use during the HC use).

For objective 2 and 3, variables included age, obesity status, smoking status, comorbidities (diabetes mellitus, arterial thrombosis, lupus erythematosus and antiphospholipid syndrome), medication use(vitamin K antagonists or other oral anticoagulants, low molecular weight heparin, antifibrinolytic agents, 2nd generation antipsychotics), and other important risk factors for VTE, and length and current episode of contraceptive use.

We reported the number and percentage of people who developed conditions that might increase the risk of VTE during each follow-up period, as listed in section 3.6.

Incidence:

We reported the number, proportion, and incidence rates of VTE after the initiation of hormonal contraceptive, e.g. rates within 1 year of contraceptive or over 1 year use of HC. We plotted the incident VTE since the start of hormonal contraceptive.

SCCS:

We conducted a self-controlled case series analysis(9), which compares the rate of events during exposed periods of time with the rate during all other observed time periods within individual.

Firstly, we performed diagnostics to test the assumptions of SCCS analysis, these includes:

- Event-dependent exposures(10)
  - A key assumption is that subsequent exposures should not appreciably be affected by previous events. One way to correct for this bias is to include a “pre-exposure period” just before an exposure. This can be examined by plotting the distribution of the interval between exposure and event time. If a peak or trough in events prior to exposure is apparent, the presence of short-term event-dependent exposures is indicated.
  - In this study, we included a 2-week pre-exposure period before the starts of NSAIDs.
- Event-dependent observation periods
  - If the event increases the probability of death, then there is a chance that observation periods could be cut short as a direct result of the event.
  - This can be examined by histograms of the times from event to end of observation, for those whose observation times are censored, and those are not separately. If a spike is apparent close to zero in the censored data histogram, the presence of event-dependent observation periods is indicated.
  - In this study, we conducted the analysis for both all first VTE and exclude people who die within 90 days after VTE. Cause of death is not available in the proposed databases.

In the SCCS analysis, we included HC episodes with both exposure to NSAIDs and an VTE event. In Figure 1, individual A has two exposures to NSAIDs during the use of hormonal contraceptive, and experienced a VTE

event, was included. Individual B experienced the event during the second episode of hormonal contraceptive, which was included in the SCCS analysis. Individual C experienced the event after switching to the high HC, therefore contributed to the analysis of the high risk HC category, and not contributed to the SCCS for the low risk analysis.

The SCCS model was fitted using conditional Poisson regression model with an offset of the length of risk periods. Incidence rate ratios (IRR) and 95% confidence intervals of events were estimated for the pre-exposure period and the risk periods. If individuals have overlapped risk periods, e.g. the post-exposure period overlapping with the pre-exposure period, we estimated the IRR for this overlapped period separately from the rest of the time in those two periods. Age was adjusted for as they are time-varying confounders. Health conditions that are risk factors of VTE (Section 9.6.3) was included as time-varying variable as well.

Stratification/ subpopulation:

All analysis was conducted for in each HC VTE groups (high, medium, low). In objective 2, we defined the exposure as any NSAIDs. In objective 3, ibuprofen, diclofenac and naproxen were analysed separately.

9.9.3 Missing values

We only included people with complete age and sex information. In the analysis, all four databases had full age and sex information on all participants.

9.9.4 Sensitivity analysis

Sensitivity analysis:

Two sensitivity analyses were performed.

In SCCS analysis, if an event increases the probability of death, the assumption of “occurrence of the outcome event does not affect an individual’s time observed” might be violated. We conducted sensitivity analysis to assess the robustness of results to assumptions such as that the occurrence of an outcome event did not influence the subsequent observation period, excluding those who died from the outcome within 90 days.

To assess the impact of confounding by indication, that NSAIDs were prescribed to some events which are also risk factors of VTE, we excluded VTE cases happened within 6 months after cancer, trauma/fracture, surgery, or hospitalisation.

9.9.5 Deviation from original protocol

For the SCCS analyses, we developed two models for each exposure-outcome pair. In the first model, we only adjusted for age as time-varying variable. In the second model, in addition to age, we also adjusted for seasonality and potential time-varying confounders. We grouped the potential indication into two categories to reduce the degrees of freedom in the resulting model. The first variable was “Inflammatory disease” which included any of: inflammatory bowel disease, Behcet’s syndrome, systemic lupus erythematous, rheumatoid arthritis, or cancer. The second variable was “external reason” and included: oedema of lower leg, hospitalisation, surgery, trauma/fracture, wheelchair use or reduced mobility.

Due to limited sample size in the SCCS, we did not conduct the last proposed sensitivity analysis restricting to the first HC use episode of each risk category.

10. DATA MANAGEMENT

All databases have previously mapped their data to the OMOP common data model. This enables 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 was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their database containing patient-level data, and then return the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then be combined in tables and figures for the study report.

11. QUALITY CONTROL.

A number of 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). In particular, data partners had run 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 and are 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.

12. RESULTS

The full study results are available in an interactive shiny app: https://data-dev.darwin-eu.org/P3-C3-008/. The following tabs are included for full reporting of all conducted analyses:

- Snapshot: provides the basic information for each database, including the total number of people in the database and the period of which the database covered.
- Cohort Count: provides the number of individuals and number of records in each of the study cohorts.
- Cohort Attrition: provides the attrition (table and diagram) of study cohorts.
- Drug utilisation: provides results for objective 1 on drug utilisation.
- Indication: provides results for objective 1 on the indication of NSAIDs during HC.
- Large scale characteristics: provides data-driven large-scale characteristics of study cohorts, summarising all recorded conditions and treatments anytime before, one year to one month before, and the month before NSAID initiation.
- Cohort characteristics: This provides the characteristics of the included study cohorts.
- SCCS plot assumptions: provides diagnostics testing the SCCS assumptions.
- SCCS full model: provides results from the SCCS analysis (objs 2,3) adjusted for age, seasonality, and time-varying covariates.
- SCCS age model: provides results from the SCCS analysis (objs 2,3) adjusted only for age.

12.1 Participants

The CPRD GOLD, DK-DHR, NLHR, and SIDIAP database included a total of 17,521,504, 8,593,356, 6,114,138, and 8,553,325 individuals, respectively.

Figures 2-5 below showed the cohort attritions of women having VTE and used any NSAIDs in the low-, medium, and high-risk hormonal contraceptives groups in each database.

After applying the inclusion and exclusion criteria, in CPRD GOLD data, we identified a total of 460,703, 391,679, and 150,053 women (15-49 years old) on low-, medium, and high-risk HC during the study period. Among those, 77,001, 45,804, and 14,359 had records of any NSAIDs use while on hormonal contraception. From these populations, we identified 172, 92, and 35 VTE events during low-, medium or high-risk contraceptive/s use respectively. There women were then included in the SCCS analysis. (Table 2)

In DK-DHR data, we respectively identified a total of 636,348, 593,357, and 212,226 women aged 15-49 years old used low-, medium, and high-risk HC during the study period. Among those, 183,586, 141,293, and 42,542 women had records of any NSAIDs use during HC. And a total of 414, 244, and 142 had a VTE event while on HC, who were consequently included in the SCCS.

In NLHR data, we respectively identified 448,284, 259,588, and 169,060 women on low-, medium, and high-risk HC during the study period. Among these, 123,315, 67,002, and 48,960 had records of any NSAIDs use during HC. Out of them, we identified 188, 212, 243 and women who had a VTE event during HC use, who were therefore included in the SCCS.

In SIDIAP, we respectively identified a total of 132,381, 204,658, and 47,374 women who used low-, medium, and high-risk HC respectively. Among these, 51,869, 95,539, and 14,310 had records of any NSAIDs use during HC. Of them, we identified 38, 130, and 23 and women who had a VTE event during HC, who were then included in the SCCS analysis.

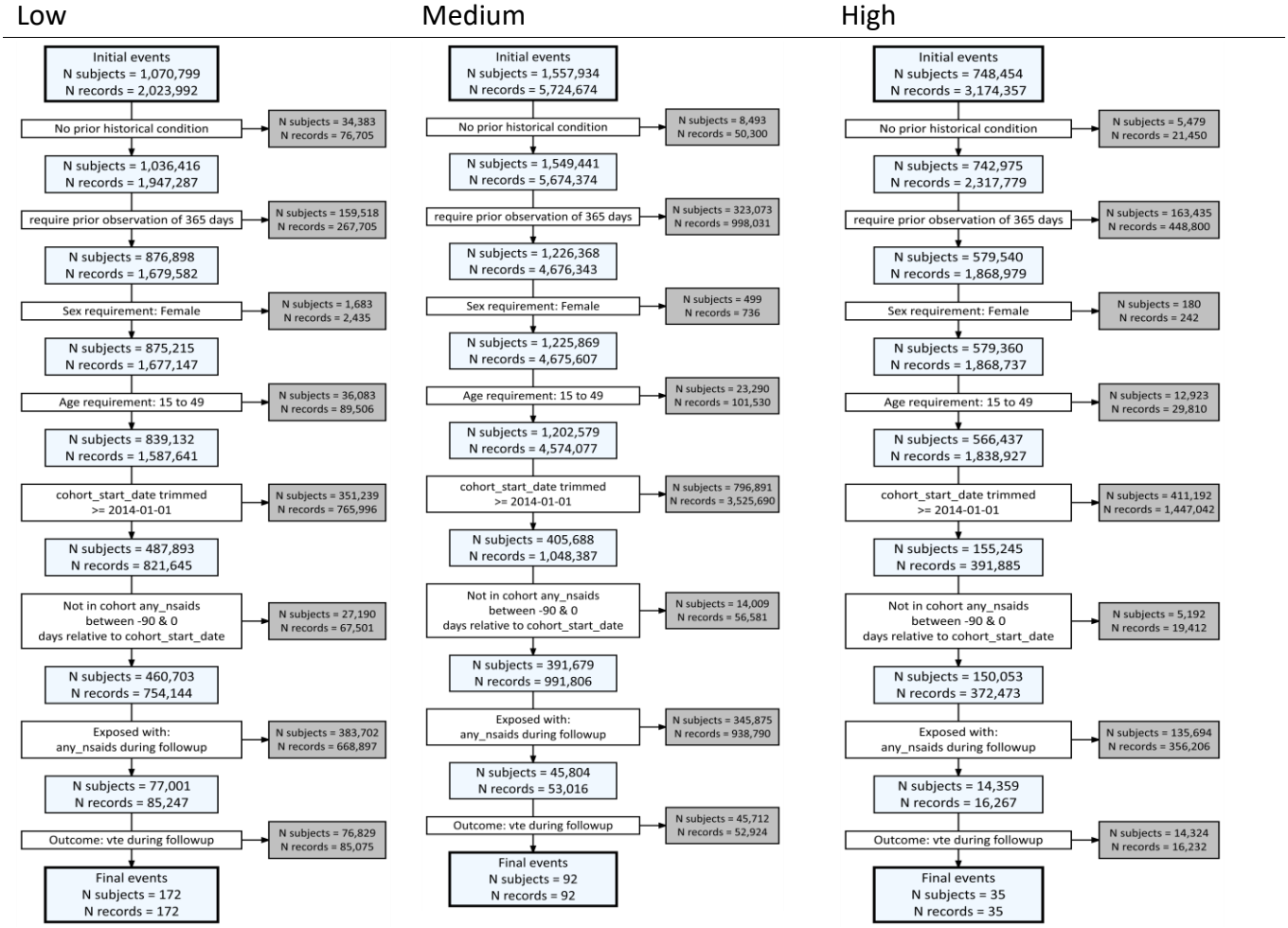

Figure 2. Cohort attrition of women having VTE and used any NSAIDs during high-,medium-,and low risk HC in CPRD GOLD.

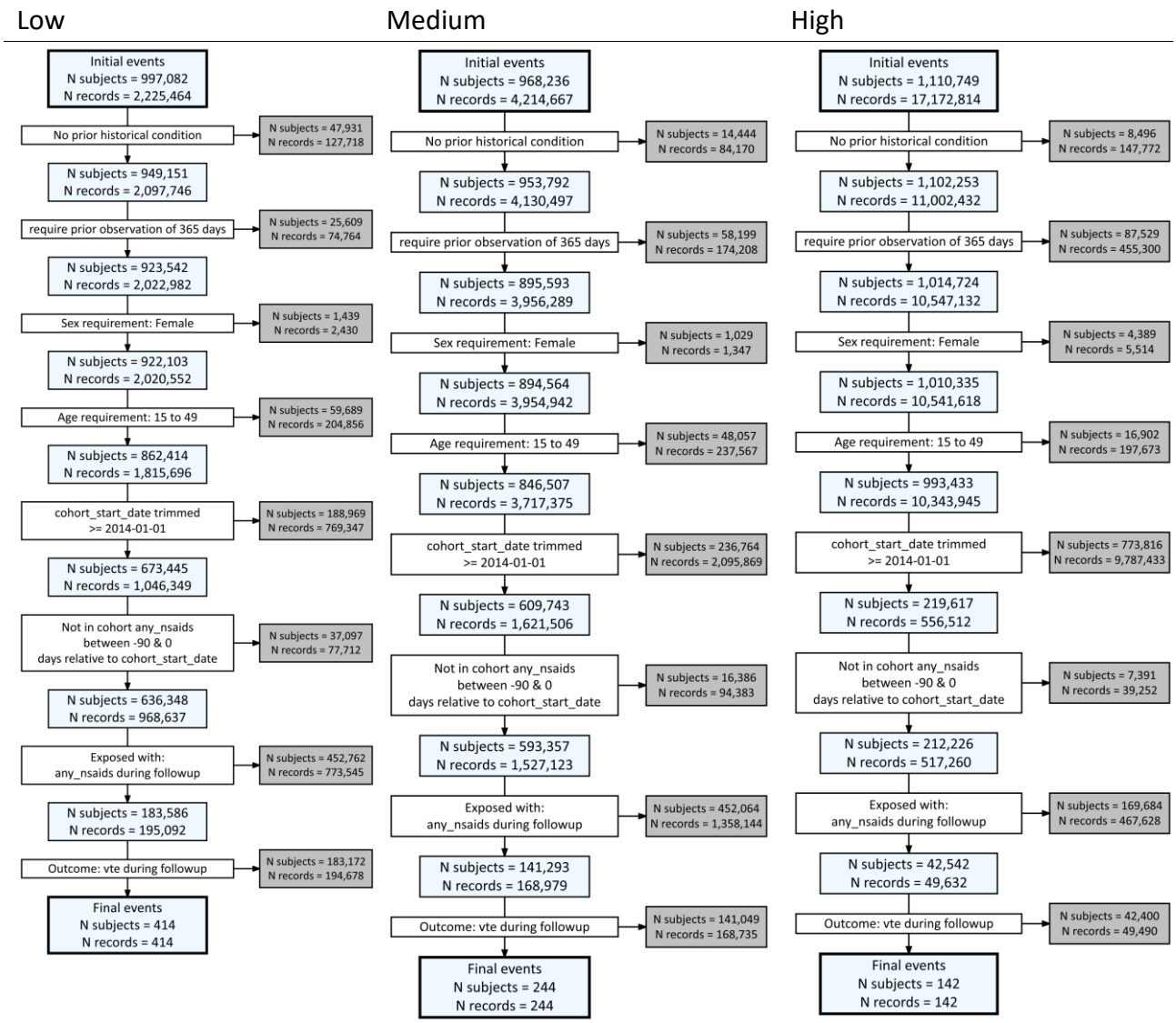

Figure 3. Cohort attrition of women having VTE and used any NSAIDs during high-,medium-,and low risk HC in DK-DHR.

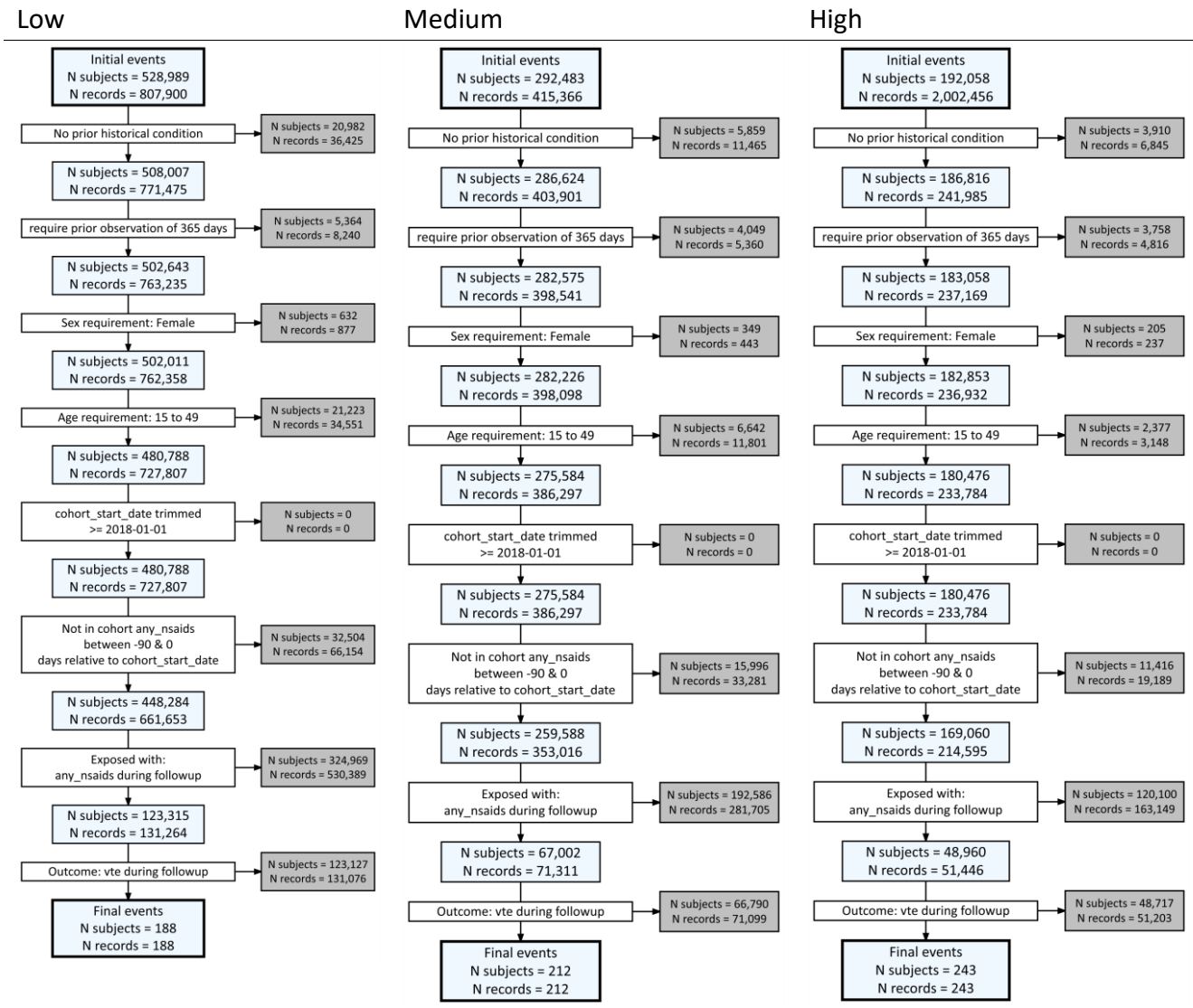

Figure 4. Cohort attrition of women having VTE and used any NSAIDs during high-,medium-,and low risk HC in NLHR.

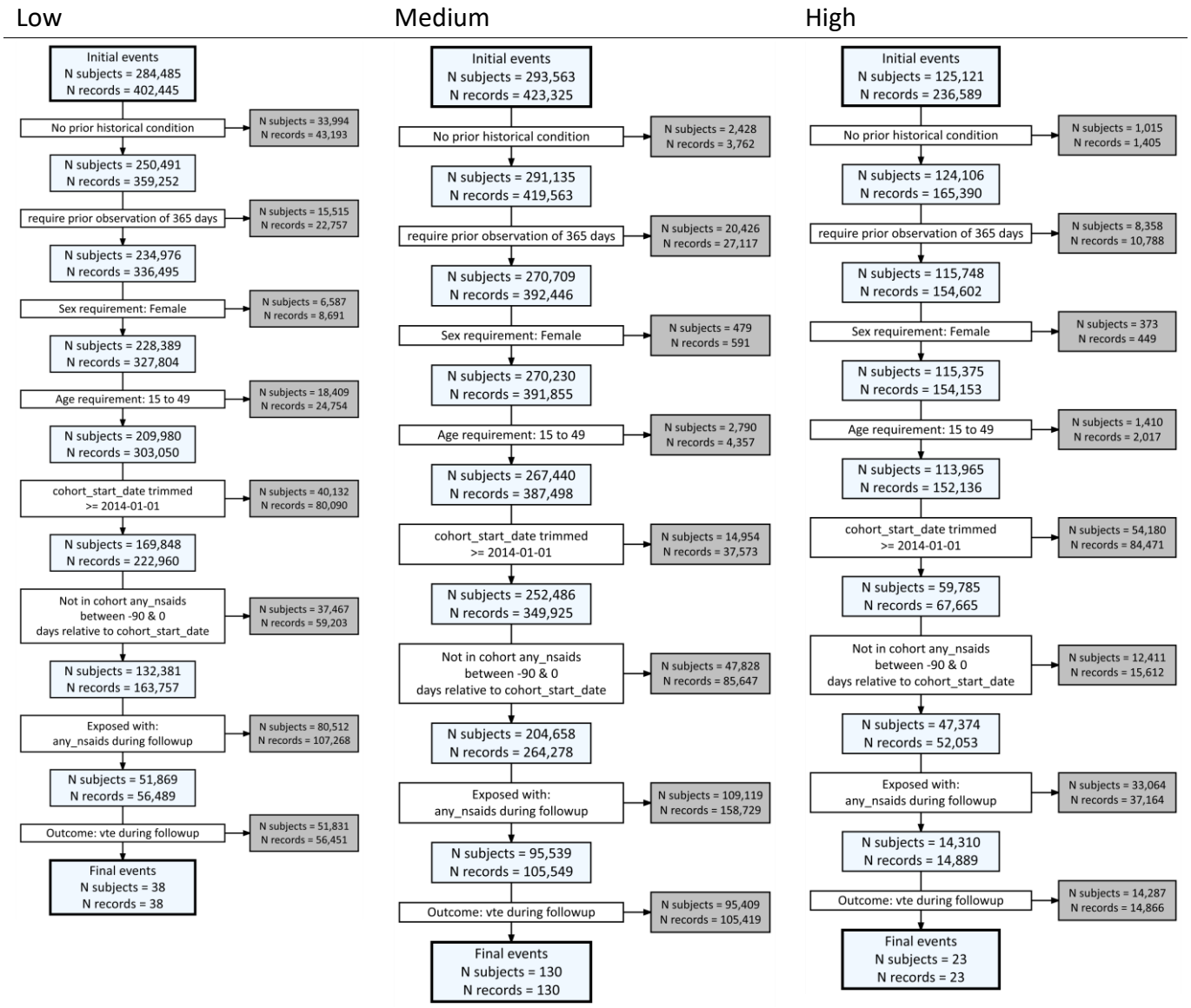

Figure 5. Cohort attrition of women having VTE and used any NSAIDs during high-,medium-,and low risk HC in SIDIAP.

Table 2. Number of individuals included according to HC, NSAID use and VTE status during study period.

Database		Hormonal contraceptives		
		Low	Medium	High
CPRD GOLD	Hormonal contraceptive use	460,703	391,679	150,053
	Used any NSAIDs during HC	77,001 (16.7%)	45,804 (11.7%)	14,359 (9.6%)
	Have VTE and NSAIDs during HC	172	92	35
	Have DVT and NSAIDs during HC	104	62	31
	Have PE and NSAIDs during HC	75	35	17
DK-DHR	Hormonal contraceptive use	636,348	593,357	212,226
	Used any NSAIDs during HC	183,586 (28.8%)	141,293 (23.8%)	42,542 (20.0%)
	Have VTE and NSAIDs during HC	414	244	142
	Have DVT and NSAIDs during HC	251	122	66
	Have PE and NSAIDs during HC	179	129	85
NLHR	Hormonal contraceptive use	448,284	259,588	169,060
	Used any NSAIDs during HC	123,315 (27.5%)	67,002 (25.8%)	48,960 (29.0%)
	Have VTE and NSAIDs during HC	188	212	243
	Have DVT and NSAIDs during HC	60	70	112
	Have PE and NSAIDs during HC	141	159	155
SIDIAP	Hormonal contraceptive use	132,381	204,658	47,374
	Used any NSAIDs during HC	51,869 (39.2%)	95,539 (46.7%)	14,310 (30.2%)
	Have VTE and NSAIDs during HC	38	130	23
	Have DVT and NSAIDs during HC	28	100	19
	Have PE and NSAIDs during HC	12	28	5

12.2 Patient-level cohort characterisation of women using HCs

Tables 3-6 below included the characteristics of women aged 15-49 years old using low-, medium, and high-risk HC.

In CPRD GOLD, a total of 460,703, 391,679, and 150,053 women used low-, medium, and high-risk HC during the study period, contributing a total of 754,144, 991,806, and 372,473 hormonal contraceptive use episodes respectively. The median (IQR) age at the start of hormonal contraception was 32 [24 - 39], 26 [21 - 33], and 26 [21 - 32] years old for the low-, medium, and high-risk HC users, respectively. The median (IQR) length of each hormonal contraception episode was 171 [84 - 504], 126 [84 - 252], and 126 [63 - 232] days respectively.

In DK-DHR, a total of 636,348, 593,357, and 212,226 women used low-, medium, and high-risk HC, who contributed 968,637, 1,527,123, and 517,260 HC episodes respectively. The median (IQR) age at the start of HC was 31 [24 - 39], 22 [18 - 28], and 26 [21 - 33] respectively. The median (IQR) length of each hormonal contraception episode was 402 [84 - 1,166], 206 [84 - 540], and 130 [34 - 364] days in the low-, medium, and high-risk group.

In NLHR, a total of 448,284, 259,588, and 169,060 women used low-, medium, and high-risk HC during the study period, and contributed to 661,653, 353,016, and 214,595 hormonal contraception episodes. The median (IQR) age at the start of HC use was 27 [20 - 35], 23 [18 - 29], and 25 [21 – 31] respectively for the low-, medium, and high-risk HC. The median (IQR) length of each HC use was 337 [87 - 908], 337 [169 - 803], and 417 [169 - 964] days in the low-, medium, and high-risk group.

In SIDIAP, a total of 132,381, 204,658, and 47,374 women used low-, medium, and high-risk HC during the study period, contributing 163,757, 264,278, and 52,053 HC use episodes. The median (IQR) age at the start of the HC was 33 [27 - 39], 26 [20 - 33], and 28 [22 - 35] for the low-, medium, and high-risk HC, respectively. The median (IQR) length of hormonal contraception was 321 [85 - 648], 366 [105 - 716], and 195 [78 - 432] days in the low-, medium, and high-risk group.

Most participants were healthy at the time of HC initiation, with low prevalence of most comorbidities. The most common comorbidities were anxiety (prevalence ranging from 17-23% in CPRD GOLD, 9-12% in DK-DHR, 26-31%in NLHR, 23-26% in SIDIAP), depression (prevalence 12-20% in CPRD GOLD, 11-17% in DK-DHR, 10-11% in NLHR, 5-7% in SIDIAP), urinary tract infection (prevalence 12-13% in CPRD GOLD, 25-32% in DK-DHR, 2-3% in NLHR, 22-30% in SIDIAP) and asthma (prevalence 9-10% in CPRD GOLD, 18-21% in DK-DHR, 15-16% in NLHR, 6% in SIDIAP).

Medicine/s use was also uncommon, with the most common medicines use in the year prior to HC initiation including antibacterials (prevalence 36-40% in CPRD GOLD, 36-38 % in DK-DHR, 21-25 % in NLHR, 36% in SIDIAP), antiinflammatory and antirheumatic products (prevalence 8-11% in CPRD GOLD, 9-11% in DK-DHR, 8-10% in NLHR, 30-33% in SIDIAP), psycholeptics (prevalence 7-10% in CPRD GOLD, 5-6% in DK-DHR, 8-9% in NLHR, 14-15% in SIDIAP), and antidepressants (prevalence 15-24% used in CPRD GOLD, 7-9% in DK-DHR, 6-7% in NLHR, 8-9% in SIDIAP).

Table 3. Baseline characteristics of women at the time entering the hormonal contraceptives cohorts (time of initiation of or 1st Jan 2014): CPRD GOLD.

			CPRD GOLD		
			Cohort name		
Variable name	Variable level	Estimate value	Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
Number records	-	N	754,144	991,806	372,473
Number subjects	-	N	460,703	391,679	150,053
Age	-	Median [Q25 - Q75]	32 [24 - 39]	26 [21 - 33]	26 [21 - 32]
Days in observation prior to index date	-	Median [Q25 - Q75]	4,245 [2,080 - 5,876]	4,440 [2,203 - 5,869]	4,484 [2,075 - 5,988]
Length of HC episode	-	Median [Q25 - Q75]	171 [84 - 504]	126 [84 - 252]	126 [63 - 232]
Comorbidity any time prior to index	Anxiety	N (%)	171,554 (22.75%)	164,796 (16.62%)	68,457 (18.38%)
	Depression	N (%)	149,018 (19.76%)	119,011 (12.00%)	44,292 (11.89%)
	Urinary tract infectious disease	N (%)	108,473 (14.38%)	120,621 (12.16%)	48,721 (13.08%)
	Asthma	N (%)	74,559 (9.89%)	91,575 (9.23%)	33,866 (9.09%)
	Gastrointestinal hemorrhage	N (%)	31,601 (4.19%)	31,144 (3.14%)	12,400 (3.33%)
	Psoriasis	N (%)	21,976 (2.91%)	23,905 (2.41%)	7,873 (2.11%)
	Obesity	N (%)	21,732 (2.88%)	9,103 (0.92%)	2,306 (0.62%)
	Hypertension	N (%)	21,205 (2.81%)	6,980 (0.70%)	1,794 (0.48%)
	Diabetes	N (%)	20,006 (2.65%)	10,773 (1.09%)	2,998 (0.80%)
	Gastroesophageal reflux disease	N (%)	12,724 (1.69%)	10,402 (1.05%)	3,896 (1.05%)
	Osteoarthritis	N (%)	10,752 (1.43%)	9,458 (0.95%)	3,602 (0.97%)
	Inflammatory bowel disease	N (%)	4,948 (0.66%)	5,512 (0.56%)	2,329 (0.63%)
	Pneumonia	N (%)	4,479 (0.59%)	4,810 (0.48%)	1,701 (0.46%)
	Renal impairment	N (%)	3,792 (0.50%)	2,720 (0.27%)	957 (0.26%)
	Hyperlipidaemia	N (%)	3,308 (0.44%)	1,553 (0.16%)	712 (0.19%)
	Crohn's disease	N (%)	2,395 (0.32%)	2,807 (0.28%)	1,107 (0.30%)
	Colitis	N (%)	2,282 (0.30%)	2,404 (0.24%)	1,142 (0.31%)

			CPRD GOLD		
			Cohort name		
Variable name	Variable level	Estimate value	Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Rheumatoid arthritis	N (%)	1,599 (0.21%)	1,234 (0.12%)	435 (0.12%)
	COPD	N (%)	934 (0.12%)	319 (0.03%)	55 (0.01%)
	Hepatitis	N (%)	661 (0.09%)	556 (0.06%)	165 (0.04%)
	Schizophrenia	N (%)	569 (0.08%)	394 (0.04%)	103 (0.03%)
	Chronic liver disease	N (%)	452 (0.06%)	215 (0.02%)	62 (0.02%)
	Malignancy	N (%)	444 (0.06%)	95 (0.01%)	30 (0.01%)
	HIV	N (%)	52 (0.01%)	72 (0.01%)	17 (0.00%)
	Parkinson	N (%)	23 (0.00%)	23 (0.00%)	-
Medication use during the year prior to index	Antibacterials	N (%)	303,762 (40.28%)	358,528 (36.15%)	149,945 (40.26%)
	Antidepressants	N (%)	181,908 (24.12%)	149,297 (15.05%)	57,593 (15.46%)
	Drugs for obstructive airway diseases	N (%)	133,736 (17.73%)	153,079 (15.43%)	58,218 (15.63%)
	Drugs for acid related disorders	N (%)	103,047 (13.66%)	84,757 (8.55%)	31,798 (8.54%)
	Opioids	N (%)	95,956 (12.72%)	77,425 (7.81%)	25,534 (6.86%)
	Antiinflammatory and antirheumatic products	N (%)	79,458 (10.54%)	79,310 (8.00%)	28,496 (7.65%)
	Psycholeptics	N (%)	78,956 (10.47%)	67,038 (6.76%)	25,451 (6.83%)
	Beta blocking agents	N (%)	50,541 (6.70%)	38,297 (3.86%)	15,738 (4.23%)
	Antiepileptics	N (%)	24,810 (3.29%)	17,682 (1.78%)	5,294 (1.42%)
	Antifibrinolytic agents	N (%)	22,571 (2.99%)	15,390 (1.55%)	5,747 (1.54%)
	Drugs used in diabetes	N (%)	17,112 (2.27%)	8,838 (0.89%)	3,957 (1.06%)
	Agents acting on the renin angiotensin system	N (%)	15,688 (2.08%)	3,865 (0.39%)	950 (0.26%)
	Second generation antipsychotics	N (%)	9,695 (1.29%)	7,108 (0.72%)	2,244 (0.60%)
	Calcium channel blockers	N (%)	8,219 (1.09%)	3,483 (0.35%)	1,003 (0.27%)
	Lipid modifying agents	N (%)	6,689 (0.89%)	2,653 (0.27%)	930 (0.25%)
	Drug diuretics	N (%)	5,021 (0.67%)	1,865 (0.19%)	1,035 (0.28%)
	Antithrombotic agents	N (%)	4,595 (0.61%)	1,815 (0.18%)	500 (0.13%)

Variable name	Variable level	Estimate value	CPRD GOLD Cohort name Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Immunosuppressants	N (%)	3,956 (0.52%)	3,898 (0.39%)	1,255 (0.34%)
	Low molecular weight heparin	N (%)	3,278 (0.43%)	1,417 (0.14%)	392 (0.11%)
	Antipsoriatics	N (%)	2,637 (0.35%)	3,020 (0.30%)	832 (0.22%)
	Antineoplastic agents	N (%)	2,313 (0.31%)	2,144 (0.22%)	736 (0.20%)
	Drug psychost	N (%)	1,602 (0.21%)	1,810 (0.18%)	768 (0.21%)

* "-" means there was less than 5 counts in the cell and the number was suppressed.

Table 4. Baseline characteristics of women at the time entering the hormonal contraceptives cohorts (time of initiation of or 1st Jan 2014): DK-DHR.

Variable name	Variable level	Estimate value	DK-DHR Cohort name Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
Number records	-	N	968,637	1,527,123	517,260
Number subjects	-	N	636,348	593,357	212,226
Age	-	Median [Q25 - Q75]	31 [24 - 39]	22 [18 - 28]	26 [21 - 33]
Days in observation prior to index date	-	Median [Q25 - Q75]	7,579 [6,940 - 8,926]	7,120 [6,357 - 7,978]	7,087 [6,940 - 7,558]
Length of HC episode	-	Median [Q25 - Q75]	402 [84 - 1,166]	206 [84 - 540]	130 [34 - 364]
Comorbidity any time prior to index	Urinary tract infectious disease	N (%)	307,719 (31.77%)	382,727 (25.06%)	128,814 (24.90%)
	Asthma	N (%)	190,619 (19.68%)	313,088 (20.50%)	92,342 (17.85%)
	Pneumonia	N (%)	174,595 (18.02%)	252,532 (16.54%)	79,251 (15.32%)
	Depression	N (%)	159,884 (16.51%)	175,249 (11.48%)	79,414 (15.35%)
	Obesity	N (%)	128,706 (13.29%)	94,063 (6.16%)	34,509 (6.67%)
	Anxiety	N (%)	117,553 (12.14%)	144,723 (9.48%)	51,943 (10.04%)
	Hypertension	N (%)	57,241 (5.91%)	29,789 (1.95%)	13,919 (2.69%)
	Psoriasis	N (%)	41,567 (4.29%)	51,099 (3.35%)	18,575 (3.59%)

			DK-DHR		
			Cohort name		
Variable name	Variable level	Estimate value	Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Diabetes	N (%)	39,352 (4.06%)	27,059 (1.77%)	10,940 (2.11%)
	Osteoarthritis	N (%)	36,457 (3.76%)	38,254 (2.50%)	17,040 (3.29%)
	Inflammatory bowel disease	N (%)	17,010 (1.76%)	18,281 (1.20%)	8,204 (1.59%)
	Hyperlipidaemia	N (%)	13,039 (1.35%)	8,131 (0.53%)	4,277 (0.83%)
	Gastrointestinal hemorrhage	N (%)	11,192 (1.16%)	11,514 (0.75%)	4,208 (0.81%)
	Colitis	N (%)	10,693 (1.10%)	10,681 (0.70%)	4,784 (0.92%)
	Gastroesophageal reflux disease	N (%)	9,582 (0.99%)	11,291 (0.74%)	3,260 (0.63%)
	Schizophrenia	N (%)	7,694 (0.79%)	10,083 (0.66%)	3,508 (0.68%)
	Crohn's disease	N (%)	7,586 (0.78%)	9,023 (0.59%)	4,156 (0.80%)
	Rheumatoid arthritis	N (%)	6,801 (0.70%)	6,589 (0.43%)	3,153 (0.61%)
	COPD	N (%)	6,019 (0.62%)	7,433 (0.49%)	3,067 (0.59%)
	Hepatitis	N (%)	3,199 (0.33%)	2,834 (0.19%)	1,072 (0.21%)
	Renal impairment	N (%)	2,006 (0.21%)	2,110 (0.14%)	850 (0.16%)
	Malignancy	N (%)	1,994 (0.21%)	542 (0.04%)	351 (0.07%)
	Chronic liver disease	N (%)	1,461 (0.15%)	1,142 (0.07%)	413 (0.08%)
	Parkinson	N (%)	667 (0.07%)	516 (0.03%)	264 (0.05%)
	HIV	N (%)	363 (0.04%)	263 (0.02%)	98 (0.02%)
Medication use during the year prior to index	Antibacterials	N (%)	347,259 (35.85%)	548,579 (35.92%)	197,306 (38.14%)
	Drugs for obstructive airway diseases	N (%)	114,297 (11.80%)	158,489 (10.38%)	52,091 (10.07%)
	Antiinflammatory and antirheumatic products	N (%)	105,424 (10.88%)	144,423 (9.46%)	56,303 (10.88%)
	Drugs for acid related disorders	N (%)	86,819 (8.96%)	97,492 (6.38%)	36,444 (7.05%)
	Antidepressants	N (%)	83,243 (8.59%)	99,909 (6.54%)	43,311 (8.37%)
	Psycholeptics	N (%)	57,005 (5.89%)	71,517 (4.68%)	26,566 (5.14%)
	Opioids	N (%)	41,225 (4.26%)	50,560 (3.31%)	25,830 (4.99%)

			DK-DHR		
			Cohort name		
Variable name	Variable level	Estimate value	Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Antiepileptics	N (%)	25,912 (2.68%)	26,045 (1.71%)	10,751 (2.08%)
	Drugs used in diabetes	N (%)	22,692 (2.34%)	17,173 (1.12%)	7,121 (1.38%)
	Agents acting on the renin angiotensin system	N (%)	20,903 (2.16%)	10,145 (0.66%)	6,189 (1.20%)
	Second generation antipsychotics	N (%)	19,446 (2.01%)	26,252 (1.72%)	8,826 (1.71%)
	Drug psychost	N (%)	19,410 (2.00%)	30,421 (1.99%)	8,504 (1.64%)
	Beta blocking agents	N (%)	16,329 (1.69%)	15,695 (1.03%)	7,048 (1.36%)
	Antifibrinolytic agents	N (%)	12,185 (1.26%)	5,645 (0.37%)	1,537 (0.30%)
	Drug diuretics	N (%)	11,609 (1.20%)	6,737 (0.44%)	4,965 (0.96%)
	Immunosuppressants	N (%)	10,908 (1.13%)	13,039 (0.85%)	5,161 (1.00%)
	Calcium channel blockers	N (%)	10,680 (1.10%)	5,009 (0.33%)	2,817 (0.54%)
	Lipid modifying agents	N (%)	9,662 (1.00%)	5,837 (0.38%)	3,238 (0.63%)
	Antithrombotic agents	N (%)	5,482 (0.57%)	3,113 (0.20%)	1,649 (0.32%)
	Antineoplastic agents	N (%)	3,942 (0.41%)	4,675 (0.31%)	1,919 (0.37%)
	Low molecular weight heparin	N (%)	1,271 (0.13%)	744 (0.05%)	208 (0.04%)
	Antipsoriatics	N (%)	942 (0.10%)	989 (0.06%)	327 (0.06%)

Table 5. Baseline characteristics of women at the time entering the hormonal contraceptives cohorts (time of initiation of or 1st Jan 2014): NLHR.

			NLHR		
			Cohort name		
Variable name	Variable level	Estimate value	Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
Number records	-	N	661,653	353,016	214,595
Number subjects	-	N	448,284	259,588	169,060
Age	-	Median [Q25 - Q75]	27 [20 - 35]	23 [18 - 29]	25 [21 - 31]

			NLHR		
			Cohort name		
Variable name	Variable level	Estimate value	Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
Days in observation prior to index date	-	Median [Q25 - Q75]	4,509 [3,919 - 5,120]	4,090 [3,711 - 4,755]	4,005 [3,696 - 4,822]
Length of HC episode	-	Median [Q25 - Q75]	337 [87 - 908]	337 [169 - 803]	417 [169 - 964]
Comorbidity any time prior to index	Anxiety	N (%)	204,758 (30.95%)	92,827 (26.30%)	65,816 (30.67%)
	Asthma	N (%)	104,577 (15.81%)	55,314 (15.67%)	33,132 (15.44%)
	Depression	N (%)	68,988 (10.43%)	33,561 (9.51%)	24,094 (11.23%)
	Pneumonia	N (%)	57,973 (8.76%)	30,126 (8.53%)	18,600 (8.67%)
	Obesity	N (%)	48,872 (7.39%)	20,565 (5.83%)	12,377 (5.77%)
	Hypertension	N (%)	44,368 (6.71%)	12,361 (3.50%)	8,773 (4.09%)
	Gastrointestinal hemorrhage	N (%)	27,560 (4.17%)	12,287 (3.48%)	8,335 (3.88%)
	Diabetes	N (%)	26,126 (3.95%)	7,905 (2.24%)	5,361 (2.50%)
	Psoriasis	N (%)	22,470 (3.40%)	10,533 (2.98%)	6,471 (3.02%)
	Gastroesophageal reflux disease	N (%)	17,179 (2.60%)	7,841 (2.22%)	4,897 (2.28%)
	Urinary tract infectious disease	N (%)	16,785 (2.54%)	7,500 (2.12%)	5,439 (2.53%)
	Osteoarthritis	N (%)	9,666 (1.46%)	4,324 (1.22%)	2,471 (1.15%)
	Rheumatoid arthritis	N (%)	8,906 (1.35%)	3,642 (1.03%)	2,332 (1.09%)
	Inflammatory bowel disease	N (%)	7,155 (1.08%)	3,194 (0.90%)	2,228 (1.04%)
	COPD	N (%)	4,451 (0.67%)	2,182 (0.62%)	1,204 (0.56%)
	Colitis	N (%)	4,362 (0.66%)	1,877 (0.53%)	1,309 (0.61%)
	Crohn's disease	N (%)	3,739 (0.57%)	1,831 (0.52%)	1,229 (0.57%)
	Renal impairment	N (%)	3,464 (0.52%)	1,252 (0.35%)	761 (0.35%)
	Hepatitis	N (%)	2,979 (0.45%)	1,595 (0.45%)	849 (0.40%)
	Malignancy	N (%)	2,930 (0.44%)	832 (0.24%)	592 (0.28%)
	Hyperlipidaemia	N (%)	2,592 (0.39%)	900 (0.25%)	568 (0.26%)
	Schizophrenia	N (%)	2,048 (0.31%)	1,444 (0.41%)	666 (0.31%)

			NLHR		
			Cohort name		
Variable name	Variable level	Estimate value	Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Chronic liver disease	N (%)	1,678 (0.25%)	909 (0.26%)	452 (0.21%)
	HIV	N (%)	288 (0.04%)	129 (0.04%)	89 (0.04%)
	Parkinson	N (%)	189 (0.03%)	142 (0.04%)	45 (0.02%)
Medication use during the year prior to index	Antibacterials	N (%)	162,728 (24.59%)	74,539 (21.11%)	48,727 (22.71%)
	Drugs for obstructive airway diseases	N (%)	96,384 (14.57%)	43,699 (12.38%)	25,615 (11.94%)
	Antiinflammatory and antirheumatic products	N (%)	66,632 (10.07%)	28,785 (8.15%)	16,759 (7.81%)
	Psycholeptics	N (%)	56,450 (8.53%)	28,882 (8.18%)	18,034 (8.40%)
	Opioids	N (%)	48,273 (7.30%)	23,828 (6.75%)	13,807 (6.43%)
	Antidepressants	N (%)	46,554 (7.04%)	21,553 (6.11%)	14,455 (6.74%)
	Drugs for acid related disorders	N (%)	40,522 (6.12%)	17,239 (4.88%)	10,225 (4.76%)
	Drugs used in diabetes	N (%)	15,226 (2.30%)	4,910 (1.39%)	3,576 (1.67%)
	Second generation antipsychotics	N (%)	13,081 (1.98%)	7,495 (2.12%)	4,407 (2.05%)
	Antiepileptics	N (%)	12,922 (1.95%)	6,162 (1.75%)	2,982 (1.39%)
	Beta blocking agents	N (%)	12,737 (1.93%)	3,731 (1.06%)	2,398 (1.12%)
	Drug psychost	N (%)	11,530 (1.74%)	6,310 (1.79%)	4,100 (1.91%)
	Agents acting on the renin angiotensin system	N (%)	11,032 (1.67%)	3,277 (0.93%)	1,628 (0.76%)
	Antifibrinolytic agents	N (%)	7,861 (1.19%)	2,841 (0.80%)	1,488 (0.69%)
	Antithrombotic agents	N (%)	7,077 (1.07%)	1,522 (0.43%)	998 (0.47%)
	Low molecular weight heparin	N (%)	6,436 (0.97%)	1,367 (0.39%)	922 (0.43%)
	Immunosuppressants	N (%)	6,276 (0.95%)	2,584 (0.73%)	1,515 (0.71%)
	Lipid modifying agents	N (%)	4,736 (0.72%)	1,633 (0.46%)	770 (0.36%)
	Calcium channel blockers	N (%)	3,879 (0.59%)	1,054 (0.30%)	532 (0.25%)
	Antineoplastic agents	N (%)	3,130 (0.47%)	1,467 (0.42%)	814 (0.38%)
	Drug diuretics	N (%)	2,357 (0.36%)	957 (0.27%)	749 (0.35%)

Variable name	Variable level	Estimate value	NLHR Cohort name: Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Antipsoriatics	N (%)	48 (0.01%)	21 (0.01%)	12 (0.01%)

Table 6 Baseline characteristics of women at the time entering the hormonal contraceptives cohorts (time of initiation of or 1st Jan 2014): SIDIAP.

Variable name	Variable level	Estimate value	SIDIAP Cohort name: Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
Number records	-	N	163,757	264,278	52,053
Number subjects	-	N	132,381	204,658	47,374
Age	-	Median [Q25 - Q75]	33 [27 - 39]	26 [20 - 33]	28 [22 - 35]
Days in observation prior to index date	-	Median [Q25 - Q75]	3,761 [2,922 - 4,940]	3,839 [2,922 - 4,988]	2,922 [2,922 - 4,140]
Length of HC episode	-	Median [Q25 - Q75]	321 [85 - 648]	366 [105 - 716]	195 [78 - 432]
Comorbidity any time prior to index	Urinary tract infectious disease	N (%)	49,144 (30.01%)	72,358 (27.38%)	11,515 (22.12%)
	Anxiety	N (%)	42,694 (26.07%)	60,533 (22.91%)	11,887 (22.84%)
	Obesity	N (%)	27,638 (16.88%)	30,475 (11.53%)	6,177 (11.87%)
	Diabetes	N (%)	11,654 (7.12%)	7,578 (2.87%)	1,837 (3.53%)
	Depression	N (%)	11,268 (6.88%)	13,523 (5.12%)	3,145 (6.04%)
	Asthma	N (%)	9,732 (5.94%)	15,629 (5.91%)	2,870 (5.51%)
	Hypertension	N (%)	7,300 (4.46%)	3,971 (1.50%)	1,257 (2.41%)
	Hyperlipidaemia	N (%)	5,984 (3.65%)	6,348 (2.40%)	1,767 (3.39%)
	Pneumonia	N (%)	4,788 (2.92%)	9,254 (3.50%)	1,371 (2.63%)
	Gastroesophageal reflux disease	N (%)	3,911 (2.39%)	4,453 (1.68%)	819 (1.57%)
	Osteoarthritis	N (%)	3,444 (2.10%)	3,337 (1.26%)	839 (1.61%)
	Gastrointestinal hemorrhage	N (%)	3,331 (2.03%)	4,240 (1.60%)	773 (1.49%)

			SIDIAP		
			Cohort name		
Variable name	Variable level	Estimate value	Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Psoriasis	N (%)	2,485 (1.52%)	3,713 (1.40%)	726 (1.39%)
	Hepatitis	N (%)	1,698 (1.04%)	1,666 (0.63%)	301 (0.58%)
	Inflammatory bowel disease	N (%)	748 (0.46%)	776 (0.29%)	215 (0.41%)
	Renal impairment	N (%)	562 (0.34%)	423 (0.16%)	114 (0.22%)
	Chronic liver disease	N (%)	513 (0.31%)	382 (0.14%)	104 (0.20%)
	Colitis	N (%)	411 (0.25%)	392 (0.15%)	111 (0.21%)
	Crohn's disease	N (%)	364 (0.22%)	414 (0.16%)	111 (0.21%)
	COPD	N (%)	362 (0.22%)	330 (0.12%)	101 (0.19%)
	Schizophrenia	N (%)	346 (0.21%)	381 (0.14%)	92 (0.18%)
	Rheumatoid arthritis	N (%)	298 (0.18%)	220 (0.08%)	56 (0.11%)
	Malignancy	N (%)	219 (0.13%)	254 (0.10%)	65 (0.12%)
	HIV	N (%)	195 (0.12%)	203 (0.08%)	58 (0.11%)
	Parkinson	N (%)	7 (0.00%)	6 (0.00%)	-
Medication use during the year prior to index	Antibacterials	N (%)	59,665 (36.44%)	96,166 (36.39%)	18,802 (36.12%)
	Antiinflammatory and antirheumatic products	N (%)	47,950 (29.28%)	88,139 (33.35%)	16,596 (31.88%)
	Psycholeptics	N (%)	24,137 (14.74%)	36,529 (13.82%)	7,792 (14.97%)
	Drugs for acid related disorders	N (%)	21,596 (13.19%)	28,989 (10.97%)	6,260 (12.03%)
	Drugs for obstructive airway diseases	N (%)	21,172 (12.93%)	35,187 (13.31%)	7,074 (13.59%)
	Antidepressants	N (%)	14,810 (9.04%)	20,110 (7.61%)	4,705 (9.04%)
	Opioids	N (%)	8,648 (5.28%)	13,720 (5.19%)	2,794 (5.37%)
	Antithrombotic agents	N (%)	7,417 (4.53%)	3,548 (1.34%)	862 (1.66%)
	Low molecular weight heparin	N (%)	7,257 (4.43%)	3,508 (1.33%)	835 (1.60%)
	Antifibrinolytic agents	N (%)	6,484 (3.96%)	5,179 (1.96%)	871 (1.67%)
	Antiepileptics	N (%)	5,500 (3.36%)	6,088 (2.30%)	1,468 (2.82%)

Variable name	Variable level	Estimate value	SIDIAP Cohort name Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Agents acting on the renin angiotensin system	N (%)	3,623 (2.21%)	1,469 (0.56%)	632 (1.21%)
	Drugs used in diabetes	N (%)	3,577 (2.18%)	2,441 (0.92%)	832 (1.60%)
	Beta blocking agents	N (%)	3,176 (1.94%)	2,145 (0.81%)	644 (1.24%)
	Second generation antipsychotics	N (%)	2,565 (1.57%)	3,448 (1.30%)	674 (1.29%)
	Lipid modifying agents	N (%)	1,609 (0.98%)	1,125 (0.43%)	527 (1.01%)
	Calcium channel blockers	N (%)	1,337 (0.82%)	616 (0.23%)	172 (0.33%)
	Drug diuretics	N (%)	1,188 (0.73%)	728 (0.28%)	354 (0.68%)
	Drug psychost	N (%)	845 (0.52%)	2,043 (0.77%)	349 (0.67%)
	Immunosuppressants	N (%)	721 (0.44%)	720 (0.27%)	185 (0.36%)
	Antineoplastic agents	N (%)	404 (0.25%)	466 (0.18%)	112 (0.22%)
	Antipsoriatics	N (%)	130 (0.08%)	227 (0.09%)	51 (0.10%)

* "-" means there was less than 5 counts in the cell and the number was suppressed.

12.3 Patient-level cohort characterisation: women using naproxen, ibuprofen, or diclofenac during hormonal contraceptives

This section includes the descriptive analyses results of Objective 1.

Tables 7-10 describe the characteristics of women who used naproxen during the HC, indexed on naproxen initiation. Characteristics for users of ibuprofen and diclofenac are available on the shiny app. Summary key characteristics at the time of naproxen initiation are summarised in this section.

Median age at initiation of NSAIDs among women on HC ranged from 22 (medium-risk HC starting naproxen, DK-DHR) to 40 (low-risk HC starting ibuprofen, DK-DHR database) years old. All the contributing data sources had well over the required 365 days of observation prior to NSAID initiation for all study participants, ranging from median 3,505 days (high-risk HC starting diclofenac, SIDIAP database) to 8,559 days (low-risk HC starting ibuprofen, DK-DHR database). Time in cohort was short, as based on NSAID treatment duration, ranging from 8 days (low- and medium-risk HC starting diclofenac or ibuprofen, SIDIAP database) to 101 days (medium-and high-risk HC starting naproxen, NLHR database).

The most common comorbidities were anxiety (prevalence ranging from 27-32% in CPRD GOLD, 13-19% in DK-DHR, 39-45% in NLHR, 34-38% in SIDIAP), depression (prevalence 20-32% in CPRD GOLD, 15-28% in DK-DHR, 15-16% in NLHR, 8-11% in SIDIAP), urinary tract infection (prevalence 18-19% in CPRD GOLD, 31-40% in DK-DHR, 3-4% in NLHR, 33-41% in SIDIAP) and asthma (prevalence 10-12% in CPRD GOLD, 25-27% in DK-DHR, 17-21% in NLHR, 8% in SIDIAP)

Medicine/s use was relatively uncommon, with the most common medicines including Antibacterials (prevalence 31% in low-risk HC starting naproxen, NLHR to 61% in high-risk HC starting ibuprofen, CPRD GOLD), drugs for acid related disorders, (prevalence 10% in medium -risk HC starting ibuprofen, NLHR to 43% in low-risk HC starting naproxen, CPRD GOLD), drugs for obstructive airway diseases (prevalence 16% in high-risk HC starting ibuprofen, DK-DHR to26% in high-risk HC starting naproxen, NLHR), psycholeptics (prevalence 8% in medium-risk HC starting naproxen, DK-DHR to 38% in low- and high-risk HC starting diclofenac, SIDIAP), opioids(prevalence 10% in medium-risk HC starting ibuprofen, SIDIAP to 52% in low-risk HC starting diclofenac, CPRD GOLD) , antidepressants(prevalence 10% in medium -risk HC starting naproxen, DK-DHR to 42% in low -risk HC starting naproxen, CPRD GOLD)

As compared to women initiating HC, women initiating NSAIDs during HC use were of older age, and had higher prevalence of comorbidities and medication use. For example, prevalence of anxiety was 23% and among women used low-risk HC, and was 26%, 28%, and 32% among women who initiated diclofenac, ibuprofen, and naproxen during low-risk HC in CPRD GOLD. There were 13% of women used opioids in the year prior among those used low-risk HC, and 52%, 44% and 43% among those initiated diclofenac, ibuprofen, and naproxen during low-risk HC in CPRD GOLD. In DK-DHR, 0.7% women had rheumatoid arthritis among those used low-risk HC, and 1.9%, 1.8%, and 2.6% among those initiated diclofenac, ibuprofen, and naproxen during low-risk HC. In NLHR, the prevalence of rheumatoid arthritis was 1.4% among those used low-risk HC, and was 2.1%, 4.3%, and 4.2% among those initiated diclofenac, ibuprofen, naproxen during low-risk HC.

Table 7. Characteristics of women at the time of naproxen initiation during low-, medium, and high-risk hormonal contraceptives: CPRD GOLD.

			CPRD GOLD		
			Cohort name		
Variable name	Variable level	Estimate value	Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
Number records	-	N	87,242	37,748	10,655
Number subjects	-	N	54,053	28,399	8,677
Age	-	Median [Q25 - Q75]	37 [30 - 44]	30 [24 - 37]	29 [24 - 35]
Days in observation prior to index date	-	Median [Q25 - Q75]	4,832 [3,010 - 6,271]	4,665 [2,615 - 6,114]	4,607 [2,443 - 6,108]
Length of NSAIDs use during HC	-	Median [Q25 - Q75]	28 [14 - 28]	28 [14 - 28]	28 [14 - 28]
Comorbidity any time prior to index	Anxiety	N (%)	28,103 (32.21%)	10,108 (26.78%)	2,974 (27.91%)
	Depression	N (%)	28,098 (32.21%)	8,710 (23.07%)	2,152 (20.20%)
	Urinary tract infectious disease	N (%)	16,871 (19.34%)	6,636 (17.58%)	1,877 (17.62%)
	Asthma	N (%)	9,777 (11.21%)	4,346 (11.51%)	1,109 (10.41%)
	Gastrointestinal hemorrhage	N (%)	5,510 (6.32%)	1,981 (5.25%)	533 (5.00%)
	Obesity	N (%)	4,746 (5.44%)	923 (2.45%)	129 (1.21%)
	Hypertension	N (%)	3,910 (4.48%)	684 (1.81%)	93 (0.87%)
	Psoriasis	N (%)	3,652 (4.19%)	1,358 (3.60%)	306 (2.87%)
	Osteoarthritis	N (%)	3,579 (4.10%)	975 (2.58%)	230 (2.16%)
	Diabetes	N (%)	3,191 (3.66%)	776 (2.06%)	133 (1.25%)
	Gastroesophageal reflux disease	N (%)	2,524 (2.89%)	753 (1.99%)	152 (1.43%)
	Pneumonia	N (%)	742 (0.85%)	236 (0.63%)	52 (0.49%)
	Hyperlipidaemia	N (%)	702 (0.80%)	138 (0.37%)	28 (0.26%)
	Rheumatoid arthritis	N (%)	617 (0.71%)	212 (0.56%)	27 (0.25%)
	Renal impairment	N (%)	610 (0.70%)	200 (0.53%)	25 (0.23%)

			CPRD GOLD		
			Cohort name		
Variable name	Variable level	Estimate value	Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
	Inflammatory bowel disease	N (%)	410 (0.47%)	146 (0.39%)	51 (0.48%)
	Malignancy	N (%)	363 (0.42%)	26 (0.07%)	7 (0.07%)
	COPD	N (%)	237 (0.27%)	41 (0.11%)	5 (0.05%)
	Crohn's disease	N (%)	190 (0.22%)	79 (0.21%)	17 (0.16%)
	Colitis	N (%)	183 (0.21%)	44 (0.12%)	23 (0.22%)
	Hepatitis	N (%)	84 (0.10%)	43 (0.11%)	7 (0.07%)
	Schizophrenia	N (%)	63 (0.07%)	23 (0.06%)	-
	Chronic liver disease	N (%)	51 (0.06%)	23 (0.06%)	-
	Parkinson	N (%)	9 (0.01%)	-	0 (0.00%)
	HIV	N (%)	5 (0.01%)	-	-
Medication use during the year prior to index	Antibacterials	N (%)	42,778 (49.03%)	19,126 (50.67%)	5,580 (52.37%)
	Opioids	N (%)	37,531 (43.02%)	14,631 (38.76%)	3,575 (33.55%)
	Drugs for acid related disorders	N (%)	37,377 (42.84%)	12,203 (32.33%)	3,265 (30.64%)
	Antidepressants	N (%)	36,610 (41.96%)	12,218 (32.37%)	3,104 (29.13%)
	Drugs for obstructive airway diseases	N (%)	20,301 (23.27%)	8,378 (22.19%)	2,344 (22.00%)
	Psycholeptics	N (%)	19,140 (21.94%)	7,044 (18.66%)	1,861 (17.47%)
	Beta blocking agents	N (%)	9,303 (10.66%)	3,144 (8.33%)	886 (8.32%)
	Antiepileptics	N (%)	7,709 (8.84%)	2,298 (6.09%)	442 (4.15%)
	Agents acting on the renin angiotensin system	N (%)	3,079 (3.53%)	474 (1.26%)	49 (0.46%)
	Antifibrinolytic agents	N (%)	3,057 (3.50%)	929 (2.46%)	307 (2.88%)
	Drugs used in diabetes	N (%)	2,509 (2.88%)	577 (1.53%)	145 (1.36%)
	Second generation antipsychotics	N (%)	1,762 (2.02%)	567 (1.50%)	107 (1.00%)
	Calcium channel blockers	N (%)	1,579 (1.81%)	306 (0.81%)	56 (0.53%)
	Lipid modifying agents	N (%)	1,384 (1.59%)	241 (0.64%)	54 (0.51%)

Variable name	Variable level	Estimate value	CPRD GOLD Cohort name: Naproxen - Low risk hormonal contraceptives	CPRD GOLD Cohort name: Naproxen - Medium risk hormonal contraceptives	CPRD GOLD Cohort name: Naproxen - High risk hormonal contraceptives
	Drug diuretics	N (%)	1,021 (1.17%)	201 (0.53%)	58 (0.54%)
	Immunosuppressants	N (%)	722 (0.83%)	302 (0.80%)	42 (0.39%)
	Antineoplastic agents	N (%)	669 (0.77%)	271 (0.72%)	49 (0.46%)
	Antithrombotic agents	N (%)	452 (0.52%)	126 (0.33%)	17 (0.16%)
	Antipsoriatics	N (%)	430 (0.49%)	165 (0.44%)	30 (0.28%)
	Low molecular weight heparin	N (%)	281 (0.32%)	90 (0.24%)	16 (0.15%)
	Drug psychost	N (%)	205 (0.23%)	99 (0.26%)	26 (0.24%)

* "-" means there was less than 5 counts in the cell and the number was suppressed.

Table 8 Characteristics of women at the time of naproxen initiation during low-, medium, and high-risk hormonal contraceptives: DK-DHR.

Variable name	Variable level	Estimate value	DK-DHR Cohort name: Naproxen - Low risk hormonal contraceptives	DK-DHR Cohort name: Naproxen - Medium risk hormonal contraceptives	DK-DHR Cohort name: Naproxen - High risk hormonal contraceptives
Number records	-	N	20,487	16,872	3,924
Number subjects	-	N	14,140	12,706	3,008
Age	-	Median [Q25 - Q75]	37 [27 - 43]	22 [18 - 27]	26 [21 - 33]
Days in observation prior to index date	-	Median [Q25 - Q75]	8,459 [7,397 - 9,510]	7,470 [6,563 - 8,376]	7,577 [7,060 - 8,297]
Length of NSAIDs use during HC	-	Median [Q25 - Q75]	25 [25 - 50]	25 [25 - 50]	25 [25 - 50]
Comorbidity any time prior to index	Urinary tract infectious disease	N (%)	8,206 (40.05%)	5,180 (30.70%)	1,252 (31.91%)
	Depression	N (%)	5,787 (28.25%)	2,603 (15.43%)	872 (22.22%)
	Asthma	N (%)	5,100 (24.89%)	4,627 (27.42%)	978 (24.92%)
	Pneumonia	N (%)	4,926 (24.04%)	3,782 (22.42%)	896 (22.83%)

			DK-DHR		
			Cohort name		
Variable name	Variable level	Estimate value	Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
	Obesity	N (%)	4,114 (20.08%)	1,258 (7.46%)	317 (8.08%)
	Anxiety	N (%)	3,900 (19.04%)	2,154 (12.77%)	597 (15.21%)
	Osteoarthritis	N (%)	1,871 (9.13%)	768 (4.55%)	210 (5.35%)
	Hypertension	N (%)	1,848 (9.02%)	352 (2.09%)	134 (3.41%)
	Psoriasis	N (%)	1,309 (6.39%)	819 (4.85%)	237 (6.04%)
	Diabetes	N (%)	1,036 (5.06%)	324 (1.92%)	127 (3.24%)
	Hyperlipidaemia	N (%)	565 (2.76%)	165 (0.98%)	45 (1.15%)
	Rheumatoid arthritis	N (%)	522 (2.55%)	269 (1.59%)	62 (1.58%)
	Gastrointestinal hemorrhage	N (%)	408 (1.99%)	161 (0.95%)	47 (1.20%)
	Gastroesophageal reflux disease	N (%)	386 (1.88%)	213 (1.26%)	58 (1.48%)
	Inflammatory bowel disease	N (%)	351 (1.71%)	179 (1.06%)	43 (1.10%)
	COPD	N (%)	251 (1.23%)	124 (0.73%)	40 (1.02%)
	Malignancy	N (%)	240 (1.17%)	26 (0.15%)	10 (0.25%)
	Schizophrenia	N (%)	235 (1.15%)	152 (0.90%)	60 (1.53%)
	Colitis	N (%)	226 (1.10%)	100 (0.59%)	19 (0.48%)
	Crohn's disease	N (%)	135 (0.66%)	90 (0.53%)	24 (0.61%)
	Hepatitis	N (%)	101 (0.49%)	27 (0.16%)	15 (0.38%)
	Parkinson	N (%)	56 (0.27%)	15 (0.09%)	-
	Renal impairment	N (%)	49 (0.24%)	28 (0.17%)	9 (0.23%)
	Chronic liver disease	N (%)	28 (0.14%)	12 (0.07%)	-
	HIV	N (%)	-	-	0 (0.00%)
Medication use during the year prior to index	Antibacterials	N (%)	8,961 (43.74%)	8,223 (48.74%)	1,858 (47.35%)
	Drugs for acid related disorders	N (%)	4,280 (20.89%)	2,143 (12.70%)	647 (16.49%)
	Drugs for obstructive airway diseases	N (%)	4,241 (20.70%)	3,095 (18.34%)	728 (18.55%)

Variable name	Variable level	Estimate value	DK-DHR Cohort name: Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
	Antidepressants	N (%)	3,365 (16.43%)	1,668 (9.89%)	553 (14.09%)
	Opioids	N (%)	2,984 (14.57%)	1,909 (11.31%)	609 (15.52%)
	Psycholeptics	N (%)	2,291 (11.18%)	1,346 (7.98%)	411 (10.47%)
	Antiepileptics	N (%)	1,845 (9.01%)	701 (4.15%)	228 (5.81%)
	Agents acting on the renin angiotensin system	N (%)	1,311 (6.40%)	321 (1.90%)	126 (3.21%)
	Beta blocking agents	N (%)	748 (3.65%)	363 (2.15%)	138 (3.52%)
	Second generation antipsychotics	N (%)	705 (3.44%)	504 (2.99%)	158 (4.03%)
	Drugs used in diabetes	N (%)	678 (3.31%)	251 (1.49%)	73 (1.86%)
	Drug psychost	N (%)	645 (3.15%)	576 (3.41%)	110 (2.80%)
	Immunosuppressants	N (%)	594 (2.90%)	364 (2.16%)	75 (1.91%)
	Drug diuretics	N (%)	562 (2.74%)	118 (0.70%)	59 (1.50%)
	Calcium channel blockers	N (%)	401 (1.96%)	108 (0.64%)	30 (0.76%)
	Lipid modifying agents	N (%)	398 (1.94%)	138 (0.82%)	43 (1.10%)
	Antifibrinolytic agents	N (%)	353 (1.72%)	90 (0.53%)	27 (0.69%)
	Antineoplastic agents	N (%)	352 (1.72%)	208 (1.23%)	43 (1.10%)
	Antithrombotic agents	N (%)	241 (1.18%)	81 (0.48%)	31 (0.79%)
	Antipsoriatics	N (%)	33 (0.16%)	13 (0.08%)	-
	Low molecular weight heparin	N (%)	16 (0.08%)	14 (0.08%)	-

* "-" means there was less than 5 counts in the cell and the number was suppressed.

Table 9. Characteristics of women at the time of naproxen initiation during low-, medium, and high-risk hormonal contraceptives: NLRH.

Variable name	Variable level	Estimate value	NLHR Cohort name: Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
Number records	-	N	58,550	27,977	21,702

Variable name	Variable level	Estimate value	NLHR Cohort name Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
Number subjects	-	N	43,879	21,859	16,333
Age	-	Median [Q25 - Q75]	33 [23 - 41]	26 [21 - 34]	29 [23 - 36]
Days in observation prior to index date	-	Median [Q25 - Q75]	4,958 [4,418 - 5,413]	4,613 [4,109 - 5,130]	4,644 [4,104 - 5,187]
Length of NSAIDs use during HC	-	Median [Q25 - Q75]	121 [51 - 121]	101 [28 - 121]	101 [51 - 121]
Comorbidity any time prior to index	Anxiety	N (%)	26,496 (45.25%)	11,006 (39.34%)	9,338 (43.03%)
	Asthma	N (%)	11,501 (19.64%)	5,693 (20.35%)	4,598 (21.19%)
	Depression	N (%)	9,070 (15.49%)	4,076 (14.57%)	3,536 (16.29%)
	Obesity	N (%)	8,051 (13.75%)	2,748 (9.82%)	2,274 (10.48%)
	Pneumonia	N (%)	6,708 (11.46%)	3,130 (11.19%)	2,675 (12.33%)
	Hypertension	N (%)	5,722 (9.77%)	1,615 (5.77%)	1,491 (6.87%)
	Gastrointestinal hemorrhage	N (%)	3,568 (6.09%)	1,399 (5.00%)	1,240 (5.71%)
	Psoriasis	N (%)	3,215 (5.49%)	1,346 (4.81%)	1,045 (4.82%)
	Diabetes	N (%)	3,151 (5.38%)	860 (3.07%)	711 (3.28%)
	Gastroesophageal reflux disease	N (%)	2,721 (4.65%)	1,102 (3.94%)	953 (4.39%)
	Osteoarthritis	N (%)	2,633 (4.50%)	964 (3.45%)	717 (3.30%)
	Rheumatoid arthritis	N (%)	2,428 (4.15%)	1,007 (3.60%)	790 (3.64%)
	Urinary tract infectious disease	N (%)	2,002 (3.42%)	935 (3.34%)	792 (3.65%)
	Malignancy	N (%)	685 (1.17%)	140 (0.50%)	164 (0.76%)
	Inflammatory bowel disease	N (%)	591 (1.01%)	224 (0.80%)	224 (1.03%)
	COPD	N (%)	567 (0.97%)	277 (0.99%)	231 (1.06%)
	Renal impairment	N (%)	353 (0.60%)	122 (0.44%)	73 (0.34%)
	Hepatitis	N (%)	348 (0.59%)	132 (0.47%)	86 (0.40%)

			NLHR		
			Cohort name		
Variable name	Variable level	Estimate value	Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
	Colitis	N (%)	328 (0.56%)	120 (0.43%)	121 (0.56%)
	Hyperlipidaemia	N (%)	302 (0.52%)	116 (0.41%)	110 (0.51%)
	Crohn's disease	N (%)	282 (0.48%)	119 (0.43%)	116 (0.53%)
	Schizophrenia	N (%)	234 (0.40%)	115 (0.41%)	62 (0.29%)
	Chronic liver disease	N (%)	218 (0.37%)	74 (0.26%)	63 (0.29%)
	HIV	N (%)	31 (0.05%)	10 (0.04%)	-
	Parkinson	N (%)	25 (0.04%)	24 (0.09%)	10 (0.05%)
Medication use during the year prior to index	Antibacterials	N (%)	18,334 (31.31%)	9,306 (33.26%)	7,310 (33.68%)
	Drugs for obstructive airway diseases	N (%)	13,838 (23.63%)	6,847 (24.47%)	5,557 (25.61%)
	Opioids	N (%)	13,415 (22.91%)	6,355 (22.72%)	5,054 (23.29%)
	Psycholeptics	N (%)	9,280 (15.85%)	4,386 (15.68%)	3,564 (16.42%)
	Antidepressants	N (%)	8,538 (14.58%)	3,876 (13.85%)	3,101 (14.29%)
	Drugs for acid related disorders	N (%)	7,728 (13.20%)	3,393 (12.13%)	2,808 (12.94%)
	Antiepileptics	N (%)	2,672 (4.56%)	1,102 (3.94%)	824 (3.80%)
	Drugs used in diabetes	N (%)	2,448 (4.18%)	701 (2.51%)	732 (3.37%)
	Agents acting on the renin angiotensin system	N (%)	2,438 (4.16%)	783 (2.80%)	709 (3.27%)
	Second generation antipsychotics	N (%)	2,108 (3.60%)	1,067 (3.81%)	770 (3.55%)
	Beta blocking agents	N (%)	2,009 (3.43%)	774 (2.77%)	756 (3.48%)
	Drug psychost	N (%)	1,660 (2.84%)	780 (2.79%)	662 (3.05%)
	Immunosuppressants	N (%)	959 (1.64%)	503 (1.80%)	364 (1.68%)
	Antifibrinolytic agents	N (%)	953 (1.63%)	397 (1.42%)	280 (1.29%)
	Lipid modifying agents	N (%)	819 (1.40%)	290 (1.04%)	205 (0.94%)
	Antineoplastic agents	N (%)	722 (1.23%)	416 (1.49%)	290 (1.34%)
	Antithrombotic agents	N (%)	693 (1.18%)	247 (0.88%)	185 (0.85%)

Variable name	Variable level	Estimate value	NLHR Cohort name Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
	Low molecular weight heparin	N (%)	588 (1.00%)	200 (0.71%)	156 (0.72%)
	Calcium channel blockers	N (%)	557 (0.95%)	167 (0.60%)	138 (0.64%)
	Drug diuretics	N (%)	484 (0.83%)	143 (0.51%)	182 (0.84%)
	Antipsoriatics	N (%)	13 (0.02%)	-	-

* "-" means there was less than 5 counts in the cell and the number was suppressed.

Table 10. Characteristics of women at the time of naproxen initiation during low-, medium, and high-risk hormonal contraceptives: SIDIAP.

Variable name	Variable level	Estimate value	SIDIAP Cohort name Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
Number records	-	N	21,836	42,955	4,884
Number subjects	-	N	15,671	30,644	3,734
Age	-	Median [Q25 - Q75]	35 [28 - 41]	28 [22 - 36]	32 [24 - 39]
Days in observation prior to index date	-	Median [Q25 - Q75]	4,331 [3,314 - 5,300]	4,343 [3,459 - 5,194]	3,839 [3,160 - 4,841]
Length of NSAIDs use during HC	-	Median [Q25 - Q75]	11 [6 - 21]	11 [6 - 21]	11 [6 - 21]
Comorbidity any time prior to index	Urinary tract infectious disease	N (%)	8,967 (41.07%)	16,776 (39.05%)	1,594 (32.64%)
	Anxiety	N (%)	8,326 (38.13%)	14,683 (34.18%)	1,806 (36.98%)
	Obesity	N (%)	5,274 (24.15%)	7,440 (17.32%)	986 (20.19%)
	Depression	N (%)	2,446 (11.20%)	3,543 (8.25%)	556 (11.38%)
	Asthma	N (%)	1,650 (7.56%)	3,334 (7.76%)	394 (8.07%)
	Diabetes	N (%)	1,617 (7.41%)	1,697 (3.95%)	226 (4.63%)
	Hypertension	N (%)	1,355 (6.21%)	1,017 (2.37%)	210 (4.30%)
	Hyperlipidaemia	N (%)	1,196 (5.48%)	1,525 (3.55%)	231 (4.73%)

			SIDIAP		
			Cohort name		
Variable name	Variable level	Estimate value	Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
	Osteoarthritis	N (%)	1,080 (4.95%)	1,215 (2.83%)	152 (3.11%)
	Gastroesophageal reflux disease	N (%)	869 (3.98%)	1,383 (3.22%)	148 (3.03%)
	Pneumonia	N (%)	768 (3.52%)	1,709 (3.98%)	192 (3.93%)
	Gastrointestinal hemorrhage	N (%)	683 (3.13%)	1,073 (2.50%)	101 (2.07%)
	Psoriasis	N (%)	425 (1.95%)	816 (1.90%)	89 (1.82%)
	Hepatitis	N (%)	247 (1.13%)	320 (0.74%)	47 (0.96%)
	Inflammatory bowel disease	N (%)	81 (0.37%)	94 (0.22%)	13 (0.27%)
	Malignancy	N (%)	75 (0.34%)	109 (0.25%)	16 (0.33%)
	COPD	N (%)	74 (0.34%)	82 (0.19%)	17 (0.35%)
	Chronic liver disease	N (%)	72 (0.33%)	70 (0.16%)	12 (0.25%)
	Renal impairment	N (%)	67 (0.31%)	93 (0.22%)	9 (0.18%)
	Rheumatoid arthritis	N (%)	62 (0.28%)	66 (0.15%)	13 (0.27%)
	Schizophrenia	N (%)	55 (0.25%)	73 (0.17%)	17 (0.35%)
	Crohn's disease	N (%)	43 (0.20%)	48 (0.11%)	11 (0.23%)
	Colitis	N (%)	35 (0.16%)	48 (0.11%)	-
	HIV	N (%)	31 (0.14%)	27 (0.06%)	12 (0.25%)
	Parkinson	N (%)	5 (0.02%)	-	0 (0.00%)
Medication use during the year prior to index	Antibacterials	N (%)	10,292 (47.13%)	21,328 (49.65%)	2,389 (48.91%)
	Psycholeptics	N (%)	7,388 (33.83%)	13,140 (30.59%)	1,621 (33.19%)
	Drugs for acid related disorders	N (%)	5,831 (26.70%)	9,582 (22.31%)	1,254 (25.68%)
	Drugs for obstructive airway diseases	N (%)	4,569 (20.92%)	9,490 (22.09%)	1,091 (22.34%)
	Antidepressants	N (%)	3,951 (18.09%)	6,333 (14.74%)	896 (18.35%)
	Opioids	N (%)	3,251 (14.89%)	5,399 (12.57%)	682 (13.96%)
	Antiepileptics	N (%)	1,776 (8.13%)	2,169 (5.05%)	359 (7.35%)

			SIDIAP		
			Cohort name		
Variable name	Variable level	Estimate value	Naproxen - Low risk hormonal contraceptives	Naproxen - Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives
	Antifibrinolytic agents	N (%)	858 (3.93%)	720 (1.68%)	87 (1.78%)
	Agents acting on the renin angiotensin system	N (%)	739 (3.38%)	434 (1.01%)	122 (2.50%)
	Beta blocking agents	N (%)	605 (2.77%)	618 (1.44%)	99 (2.03%)
	Second generation antipsychotics	N (%)	595 (2.72%)	786 (1.83%)	120 (2.46%)
	Antithrombotic agents	N (%)	530 (2.43%)	518 (1.21%)	77 (1.58%)
	Low molecular weight heparin	N (%)	517 (2.37%)	510 (1.19%)	75 (1.54%)
	Drugs used in diabetes	N (%)	505 (2.31%)	512 (1.19%)	104 (2.13%)
	Lipid modifying agents	N (%)	330 (1.51%)	293 (0.68%)	109 (2.23%)
	Drug diuretics	N (%)	252 (1.15%)	200 (0.47%)	60 (1.23%)
	Calcium channel blockers	N (%)	237 (1.09%)	115 (0.27%)	46 (0.94%)
	Drug psychost	N (%)	199 (0.91%)	483 (1.12%)	53 (1.09%)
	Antineoplastic agents	N (%)	133 (0.61%)	220 (0.51%)	36 (0.74%)
	Immunosuppressants	N (%)	105 (0.48%)	161 (0.37%)	24 (0.49%)
	Antipsoriatics	N (%)	17 (0.08%)	52 (0.12%)	9 (0.18%)

* "-" means there was less than 5 counts in the cell and the number was suppressed.

12.4 Patient-level cohort characterisation: women who used NSAIDs and had VTE event during HC

This section includes the descriptive analyses results of Objective 2.

In the SCCS analysis, in CPRD GOLD data, we identified a total of 172, 92, and 35 women who had VTE and used any NSAIDs during the use of low-, medium, and high-risk HC. The median age at VTE diagnosis was 40, 35, and 30 years among the low-, medium, and high-risk HC groups. Similar to the previous section, the most common comorbidities (any time prior to VTE event) in this population were anxiety, depression, and urinary tract infectious disease. Among the list of potential indications of NSAIDs, trauma/ fracture and surgery were the most common (Table 11). Some specific conditions were more common in these women than in the overall cohorts of NSAID and HC users described in previous sections. For example, cancer had a prevalence of 9.88 % in women with a VTE during use of low-risk HC, compared to 0.06-0.58% in the overall cohort of users of HC+NSAIDs. Since we excluded women with cancer when constructing the cohort of HC user, comorbidity of cancer was identified during HC use.

History of major surgery had a prevalence of 6.5-11.6% in women with a VTE, compared to 2.0-5.1% in the overall cohort of users of HC+NSAIDs.

In DK-DHR, we identified a total of 414, 244, and 142 women who had VTE and used any NSAIDs while on low-, medium and high-risk HC respectively. The median age at VTE diagnosis was 42, 27 and 34 years respectively. Common comorbidities include depression, anxiety, asthma, pneumonia, urinary tract infectious disease, and hypertension. Some specific conditions were more common in these women than in the overall cohorts of NSAID and HC users described in previous sections. For example, cancer had a prevalence of 8.2 % in women with a VTE during low-risk HC use, compared to 0.05-1.16% in the overall cohort of users of HC+NSAIDs. History of major surgery had a prevalence of 2.9-5.8% in women with a VTE, compared to 1.8-3.7% in the overall cohort of users of HC+NSAIDs.

In NLHR, we identified a total of 188, 212, and 243 women who had VTE event and used any NSAIDs during the use of low-, medium, and high-risk HC. The median age at VTE diagnosis was 35, 27, and 30 years among the low-, medium, and high-risk HC groups. Common comorbidities include depression, anxiety, asthma and pneumonia. Some specific conditions were more common in these women than in the overall cohorts of NSAID and HC users described in previous sections. For example, cancer had a prevalence of 2.5-12.2 % in women with a VTE, compared to 0.16-0.52% in the overall cohort of users of HC+NSAIDs.

In SIDIAP, we identified a total of 38, 130, and 23 women who had VTE event and used any NSAIDs during the use of low-, medium, and high-risk HC. The median age at VTE diagnosis was 38, 32, and 35 years among the low-, medium, and high-risk HC groups. Common comorbidities include anxiety, depression, obesity, and urinary tract infectious diseases.

Table 11. Characteristics of women with VTE and used any NSAIDs during hormonal contraceptive use (index on day of VTE).

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
CPRD GOLD					
Number subjects	-	N	172	92	35
Age	-	Median [Q25 - Q75]	40 [33 - 46]	35 [28 - 41]	30 [23 - 36]
Comorbidity any time prior to index	Depression	N (%)	85 (49.42%)	24 (26.09%)	8 (22.86%)
	Anxiety	N (%)	70 (40.70%)	26 (28.26%)	10 (28.57%)
	Urinary tract infectious disease	N (%)	52 (30.23%)	20 (21.74%)	6 (17.14%)
	Asthma	N (%)	28 (16.28%)	11 (11.96%)	-
	Obesity	N (%)	22 (12.79%)	5 (5.43%)	-
	Malignancy	N (%)	17 (9.88%)	0 (0.00%)	0 (0.00%)
	Pneumonia	N (%)	13 (7.56%)	-	-
	Diabetes	N (%)	12 (6.98%)	-	0 (0.00%)
	Gastrointestinal hemorrhage	N (%)	11 (6.40%)	8 (8.70%)	-
	Hypertension	N (%)	10 (5.81%)	-	0 (0.00%)
	Psoriasis	N (%)	9 (5.23%)	-	-
	Gastroesophageal reflux disease	N (%)	7 (4.07%)	-	0 (0.00%)
	Osteoarthritis	N (%)	6 (3.49%)	7 (7.61%)	0 (0.00%)
	COPD	N (%)	-	-	0 (0.00%)
	Chronic liver disease	N (%)	-	0 (0.00%)	0 (0.00%)
	Hepatitis	N (%)	-	0 (0.00%)	0 (0.00%)
	Hyperlipidaemia	N (%)	-	0 (0.00%)	-
	Renal impairment	N (%)	-	-	0 (0.00%)
	Colitis	N (%)	0 (0.00%)	-	0 (0.00%)
	Crohn's disease	N (%)	0 (0.00%)	-	0 (0.00%)
	HIV	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Parkinson	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Schizophrenia	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Risk factor of VTE any time prior	Trauma fracture	N (%)	34 (19.77%)	14 (15.22%)	5 (14.29%)
	Surgery	N (%)	20 (11.63%)	6 (6.52%)	-
	Cancer	N (%)	17 (9.88%)	0 (0.00%)	0 (0.00%)
	Lupus erythematosus	N (%)	-	0 (0.00%)	0 (0.00%)
	Rheumatoid arthritis	N (%)	-	-	0 (0.00%)
	Wheelchair reduced mobility	N (%)	-	0 (0.00%)	0 (0.00%)
	Behcets syndrome	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Edema of lower leg	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Hospitalisation	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Inflammatory bowel disease	N (%)	0 (0.00%)	-	0 (0.00%)
Medication use during the year prior to index	Antibacterials	N (%)	108 (62.79%)	56 (60.87%)	15 (42.86%)
	Antiinflammatory and antirheumatic products	N (%)	102 (59.30%)	72 (78.26%)	26 (74.29%)
	Antidepressants	N (%)	100 (58.14%)	37 (40.22%)	10 (28.57%)
	Opioids	N (%)	86 (50.00%)	46 (50.00%)	16 (45.71%)
	Drugs for acid related disorders	N (%)	85 (49.42%)	37 (40.22%)	9 (25.71%)
	Psycholeptics	N (%)	55 (31.98%)	19 (20.65%)	10 (28.57%)
	Drugs for obstructive airway diseases	N (%)	51 (29.65%)	22 (23.91%)	9 (25.71%)
	Antithrombotic agents	N (%)	44 (25.58%)	19 (20.65%)	5 (14.29%)
	Antiepileptics	N (%)	30 (17.44%)	11 (11.96%)	-
	Beta blocking agents	N (%)	24 (13.95%)	7 (7.61%)	6 (17.14%)
	Low molecular weight heparin	N (%)	18 (10.47%)	7 (7.61%)	-
	Antifibrinolytic agents	N (%)	11 (6.40%)	-	-

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Drugs used in diabetes	N (%)	11 (6.40%)	-	0 (0.00%)
	Agents acting on the renin angiotensin system	N (%)	10 (5.81%)	-	0 (0.00%)
	Second generation antipsychotics	N (%)	9 (5.23%)	-	0 (0.00%)
	Drug diuretics	N (%)	7 (4.07%)	-	-
	Lipid modifying agents	N (%)	5 (2.91%)	-	0 (0.00%)
	Antineoplastic agents	N (%)	-	-	0 (0.00%)
	Antipsoriatics	N (%)	-	-	0 (0.00%)
	Calcium channel blockers	N (%)	-	-	0 (0.00%)
	Immunosuppressants	N (%)	-	-	0 (0.00%)
DK-DHR					
Number subjects	-	N	414	244	142
Age	-	Median [Q25 - Q75]	42 [35 - 46]	27 [21 - 35]	34 [26 - 43]
Comorbidity any time prior to index	Urinary tract infectious disease	N (%)	166 (40.10%)	101 (41.39%)	44 (30.99%)
	Obesity	N (%)	150 (36.23%)	50 (20.49%)	23 (16.20%)
	Pneumonia	N (%)	149 (35.99%)	80 (32.79%)	59 (41.55%)
	Depression	N (%)	128 (30.92%)	57 (23.36%)	33 (23.24%)
	Asthma	N (%)	113 (27.29%)	72 (29.51%)	36 (25.35%)
	Anxiety	N (%)	81 (19.57%)	44 (18.03%)	21 (14.79%)
	Hypertension	N (%)	58 (14.01%)	10 (4.10%)	15 (10.56%)
	Osteoarthritis	N (%)	51 (12.32%)	14 (5.74%)	10 (7.04%)
	Malignancy	N (%)	33 (7.97%)	-	0 (0.00%)
	Psoriasis	N (%)	33 (7.97%)	13 (5.33%)	6 (4.23%)
	Diabetes	N (%)	26 (6.28%)	11 (4.51%)	-
	Hyperlipidaemia	N (%)	23 (5.56%)	8 (3.28%)	0 (0.00%)
	Gastrointestinal hemorrhage	N (%)	16 (3.86%)	6 (2.46%)	-
	COPD	N (%)	10 (2.42%)	5 (2.05%)	-

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Colitis	N (%)	10 (2.42%)	-	-
	Gastroesophageal reflux disease	N (%)	10 (2.42%)	5 (2.05%)	-
	Schizophrenia	N (%)	8 (1.93%)	10 (4.10%)	-
	Crohn's disease	N (%)	7 (1.69%)	-	-
	Renal impairment	N (%)	5 (1.21%)	-	0 (0.00%)
	Chronic liver disease	N (%)	-	0 (0.00%)	0 (0.00%)
	Hepatitis	N (%)	-	0 (0.00%)	0 (0.00%)
	Parkinson	N (%)	-	0 (0.00%)	-
	HIV	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Risk factor of VTE any time prior	Hospitalisation	N (%)	408 (98.55%)	232 (95.08%)	135 (95.07%)
	Trauma fracture	N (%)	77 (18.60%)	75 (30.74%)	31 (21.83%)
	Cancer	N (%)	34 (8.21%)	-	0 (0.00%)
	Surgery	N (%)	24 (5.80%)	7 (2.87%)	-
	Inflammatory bowel disease	N (%)	14 (3.38%)	5 (2.05%)	-
	Rheumatoid arthritis	N (%)	13 (3.14%)	-	-
	Lupus erythematosus	N (%)	-	-	0 (0.00%)
	Behcets syndrome	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Edema of lower leg	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Wheelchair reduced mobility	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Medication use during the year prior to index	Antibacterials	N (%)	197 (47.58%)	120 (49.18%)	75 (52.82%)
	Antiinflammatory and antirheumatic products	N (%)	192 (46.38%)	160 (65.57%)	108 (76.06%)
	Antithrombotic agents	N (%)	126 (30.43%)	60 (24.59%)	20 (14.08%)
	Opioids	N (%)	103 (24.88%)	51 (20.90%)	36 (25.35%)
	Drugs for acid related disorders	N (%)	97 (23.43%)	47 (19.26%)	31 (21.83%)
	Antidepressants	N (%)	90 (21.74%)	29 (11.89%)	21 (14.79%)

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Drugs for obstructive airway diseases	N (%)	84 (20.29%)	51 (20.90%)	23 (16.20%)
	Psycholeptics	N (%)	74 (17.87%)	33 (13.52%)	21 (14.79%)
	Antiepileptics	N (%)	46 (11.11%)	16 (6.56%)	12 (8.45%)
	Drug diuretics	N (%)	44 (10.63%)	5 (2.05%)	-
	Agents acting on the renin angiotensin system	N (%)	36 (8.70%)	7 (2.87%)	6 (4.23%)
	Antineoplastic agents	N (%)	31 (7.49%)	8 (3.28%)	-
	Second generation antipsychotics	N (%)	31 (7.49%)	18 (7.38%)	6 (4.23%)
	Beta blocking agents	N (%)	26 (6.28%)	8 (3.28%)	-
	Drugs used in diabetes	N (%)	20 (4.83%)	7 (2.87%)	-
	Lipid modifying agents	N (%)	18 (4.35%)	7 (2.87%)	0 (0.00%)
	Immunosuppressants	N (%)	16 (3.86%)	5 (2.05%)	-
	Calcium channel blockers	N (%)	15 (3.62%)	-	-
	Low molecular weight heparin	N (%)	11 (2.66%)	-	0 (0.00%)
	Antifibrinolytic agents	N (%)	5 (1.21%)	-	0 (0.00%)
	Antipsoriatics	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
NLHR					
Number subjects	-	N	188	212	243
Age	-	Median [Q25 - Q75]	35 [26 - 42]	27 [22 - 34]	30 [24 - 36]
Comorbidity any time prior to index	Anxiety	N (%)	92 (48.94%)	84 (39.62%)	116 (47.74%)
	Asthma	N (%)	41 (21.81%)	50 (23.58%)	59 (24.28%)
	Pneumonia	N (%)	40 (21.28%)	43 (20.28%)	42 (17.28%)
	Depression	N (%)	36 (19.15%)	32 (15.09%)	53 (21.81%)
	Hypertension	N (%)	32 (17.02%)	7 (3.30%)	21 (8.64%)
	Obesity	N (%)	29 (15.43%)	25 (11.79%)	38 (15.64%)
	Malignancy	N (%)	24 (12.77%)	10 (4.72%)	6 (2.47%)

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Gastrointestinal hemorrhage	N (%)	16 (8.51%)	14 (6.60%)	20 (8.23%)
	Diabetes	N (%)	14 (7.45%)	13 (6.13%)	8 (3.29%)
	Gastroesophageal reflux disease	N (%)	11 (5.85%)	8 (3.77%)	12 (4.94%)
	Osteoarthritis	N (%)	10 (5.32%)	7 (3.30%)	7 (2.88%)
	Psoriasis	N (%)	9 (4.79%)	7 (3.30%)	6 (2.47%)
	Urinary tract infectious disease	N (%)	8 (4.26%)	7 (3.30%)	13 (5.35%)
	COPD	N (%)	6 (3.19%)	-	6 (2.47%)
	Renal impairment	N (%)	6 (3.19%)	-	5 (2.06%)
	Chronic liver disease	N (%)	-	-	-
	Colitis	N (%)	-	-	-
	Crohn's disease	N (%)	-	0 (0.00%)	-
	Hepatitis	N (%)	-	-	-
	Hyperlipidaemia	N (%)	-	-	0 (0.00%)
	Parkinson	N (%)	-	-	0 (0.00%)
	Schizophrenia	N (%)	-	5 (2.36%)	0 (0.00%)
	HIV	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Risk factor of VTE any time prior	Hospitalisation	N (%)	126 (67.02%)	129 (60.85%)	143 (58.85%)
	Trauma fracture	N (%)	44 (23.40%)	51 (24.06%)	44 (18.11%)
	Cancer	N (%)	23 (12.23%)	10 (4.72%)	6 (2.47%)
	Rheumatoid arthritis	N (%)	11 (5.85%)	6 (2.83%)	5 (2.06%)
	Inflammatory bowel disease	N (%)	5 (2.66%)	-	6 (2.47%)
	Behcets syndrome	N (%)	-	0 (0.00%)	0 (0.00%)
	Lupus erythematosus	N (%)	-	0 (0.00%)	0 (0.00%)
	Edema of lower leg	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Surgery	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Wheelchair reduced mobility	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
Medication use during the year prior to index	Antiinflammatory and antirheumatic products	N (%)	115 (61.17%)	140 (66.04%)	175 (72.02%)
	Opioids	N (%)	86 (45.74%)	75 (35.38%)	90 (37.04%)
	Antibacterials	N (%)	76 (40.43%)	97 (45.75%)	97 (39.92%)
	Drugs for obstructive airway diseases	N (%)	61 (32.45%)	52 (24.53%)	68 (27.98%)
	Drugs for acid related disorders	N (%)	55 (29.26%)	36 (16.98%)	44 (18.11%)
	Antithrombotic agents	N (%)	49 (26.06%)	49 (23.11%)	77 (31.69%)
	Psycholeptics	N (%)	37 (19.68%)	35 (16.51%)	43 (17.70%)
	Antidepressants	N (%)	26 (13.83%)	33 (15.57%)	39 (16.05%)
	Antiepileptics	N (%)	21 (11.17%)	12 (5.66%)	9 (3.70%)
	Low molecular weight heparin	N (%)	17 (9.04%)	9 (4.25%)	9 (3.70%)
	Drugs used in diabetes	N (%)	14 (7.45%)	10 (4.72%)	9 (3.70%)
	Second generation antipsychotics	N (%)	11 (5.85%)	16 (7.55%)	7 (2.88%)
	Agents acting on the renin angiotensin system	N (%)	10 (5.32%)	-	8 (3.29%)
	Drug diuretics	N (%)	9 (4.79%)	-	-
	Antifibrinolytic agents	N (%)	8 (4.26%)	-	-
	Antineoplastic agents	N (%)	8 (4.26%)	10 (4.72%)	6 (2.47%)
	Beta blocking agents	N (%)	7 (3.72%)	-	10 (4.12%)
	Immunosuppressants	N (%)	7 (3.72%)	6 (2.83%)	5 (2.06%)
	Lipid modifying agents	N (%)	6 (3.19%)	-	-
	Calcium channel blockers	N (%)	-	-	-
	Antipsoriatics	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
SIDIAP					
Number subjects	-	N	38	130	23
Age	-	Median [Q25 - Q75]	38 [31 - 43]	32 [24 - 40]	35 [30 - 41]

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
Comorbidity any time prior to index	Anxiety	N (%)	21 (55.26%)	48 (36.92%)	11 (47.83%)
	Obesity	N (%)	16 (42.11%)	36 (27.69%)	11 (47.83%)
	Urinary tract infectious disease	N (%)	16 (42.11%)	53 (40.77%)	9 (39.13%)
	Depression	N (%)	8 (21.05%)	21 (16.15%)	8 (34.78%)
	Hyperlipidaemia	N (%)	7 (18.42%)	9 (6.92%)	-
	Asthma	N (%)	-	11 (8.46%)	-
	COPD	N (%)	-	0 (0.00%)	0 (0.00%)
	Diabetes	N (%)	-	6 (4.62%)	-
	Gastroesophageal reflux disease	N (%)	-	11 (8.46%)	-
	Gastrointestinal hemorrhage	N (%)	-	-	-
	Hepatitis	N (%)	-	-	-
	Hypertension	N (%)	-	6 (4.62%)	-
	Malignancy	N (%)	-	-	0 (0.00%)
	Osteoarthritis	N (%)	-	7 (5.38%)	-
	Pneumonia	N (%)	-	11 (8.46%)	-
	Schizophrenia	N (%)	-	0 (0.00%)	0 (0.00%)
	Chronic liver disease	N (%)	0 (0.00%)	-	0 (0.00%)
	Colitis	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Crohn's disease	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	HIV	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Parkinson	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Psoriasis	N (%)	0 (0.00%)	-	0 (0.00%)
	Renal impairment	N (%)	0 (0.00%)	-	0 (0.00%)
Risk factor of VTE any time prior	Hospitalisation	N (%)	31 (81.58%)	83 (63.85%)	17 (73.91%)
	Trauma fracture	N (%)	21 (55.26%)	40 (30.77%)	7 (30.43%)
	Cancer	N (%)	-	-	0 (0.00%)

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Lupus erythematosus	N (%)	-	0 (0.00%)	0 (0.00%)
	Rheumatoid arthritis	N (%)	-	0 (0.00%)	0 (0.00%)
	Behcets syndrome	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Edema of lower leg	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Inflammatory bowel disease	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Surgery	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Wheelchair reduced mobility	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Medication use during the year prior to index	Antiinflammatory and antirheumatic products	N (%)	25 (65.79%)	99 (76.15%)	19 (82.61%)
	Antibacterials	N (%)	18 (47.37%)	63 (48.46%)	14 (60.87%)
	Antithrombotic agents	N (%)	16 (42.11%)	42 (32.31%)	5 (21.74%)
	Antidepressants	N (%)	15 (39.47%)	25 (19.23%)	10 (43.48%)
	Psycholeptics	N (%)	14 (36.84%)	43 (33.08%)	13 (56.52%)
	Low molecular weight heparin	N (%)	13 (34.21%)	38 (29.23%)	5 (21.74%)
	Drugs for acid related disorders	N (%)	11 (28.95%)	30 (23.08%)	10 (43.48%)
	Drugs for obstructive airway diseases	N (%)	10 (26.32%)	31 (23.85%)	8 (34.78%)
	Antiepileptics	N (%)	9 (23.68%)	5 (3.85%)	5 (21.74%)
	Opioids	N (%)	8 (21.05%)	17 (13.08%)	7 (30.43%)
	Beta blocking agents	N (%)	5 (13.16%)	-	-
	Agents acting on the renin angiotensin system	N (%)	-	-	-
	Calcium channel blockers	N (%)	-	-	0 (0.00%)
	Drug diuretics	N (%)	-	-	-
	Drugs used in diabetes	N (%)	-	6 (4.62%)	-
	Lipid modifying agents	N (%)	-	-	-
	Second generation antipsychotics	N (%)	-	6 (4.62%)	-

Variable name	Variable level	Estimate value	Cohort name		
			Low risk hormonal contraceptives	Medium risk hormonal contraceptives	High risk hormonal contraceptives
	Antifibrinolytic agents	N (%)	0 (0.00%)	7 (5.38%)	0 (0.00%)
	Antineoplastic agents	N (%)	0 (0.00%)	-	-
	Antipsoriatics	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Immunosuppressants	N (%)	0 (0.00%)	-	0 (0.00%)

* "-" means there was less than 5 counts in the cell and the number was suppressed.

12.5 Main results

12.5.1 Objective 1. Drug utilisation of NSAIDs

Tables 12-15 below report results for the drug utilisation analyses of ibuprofen, diclofenac, and naproxen during hormonal contraceptive/s use in each database.

We observed that ibuprofen use was shorter than diclofenac, and naproxen. For example, the median length of ibuprofen use was 16 days, compared to 28 days for diclofenac and naproxen in CPRD GOLD.

In both Denmark and Norway, ibuprofen and diclofenac treatment had a similar duration, while naproxen was used for longer. For example, in NLHR (Norway) we observed a median duration of ibuprofen use of 16 days, 11 days for diclofenac. An exception was naproxen in NLHR, which was dispensed for a median of 101–121 days—likely reflecting a 3-month treatment duration consistent with requirements for chronic illness use.

In SIDIAP, the median treatment duration with NSAIDs was shorter than the other three databases, with medians for ibuprofen, diclofenac, and naproxen of 8, 8, and 11 days respectively.

In all four databases, the median number of prescriptions for ibuprofen, diclofenac, and naproxen was one.

Table 12. Drug utilization of ibuprofen, diclofenac, and naproxen during HC use in CPRD GOLD.

		CPRD GOLD								
		Cohort name								
Variable	Estimate	Ibuprofen - High risk hormonal contraceptives	Ibuprofen - Low risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Diclofenac- High risk hormonal contraceptives	Diclofenac- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives
number records	N	4,159	25,443	16,155	1,575	11,421	5,324	10,655	87,242	37,748
number subjects	N	3,660	18,790	13,341	1,359	8,291	4,398	8,677	54,053	28,399
number of prescription	Median (Q25 - Q75)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)
days prescribed	Median (Q25 - Q75)	16 (8 - 28)	16 (10 - 28)	16 (8 - 28)	28 (10 - 28)	28 (14 - 28)	28 (14 - 28)	28 (14 - 28)	28 (14 - 28)	28 (14 - 28)

Table 13. Drug utilization of ibuprofen, diclofenac, and naproxen in DK-DHR.

		DK-DHR								
		Cohort name								
Variable name	Estimate value	Ibuprofen - High risk hormonal contraceptives	Ibuprofen - Low risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Diclofenac-High risk hormonal contraceptives	Diclofenac- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives
number records	N	60,660	370,613	210,677	3,818	17,071	10,045	3,924	20,487	16,872
number subjects	N	37,482	169,591	126,651	2,835	10,927	7,586	3,008	14,140	12,706
number of prescription	Median (Q25 - Q75)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)
days prescribed	Median (Q25 - Q75)	16 (10 - 33)	20 (15 - 33)	16 (10 - 33)	15 (15 - 30)	15 (15 - 50)	15 (15 - 25)	25 (25 - 50)	25 (25 - 50)	25 (25 - 50)

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Table 14. Drug utilization of ibuprofen, diclofenac, and naproxen in NLHR.

		NLHR								
		Cohort name								
Variable name	Estimate value	Ibuprofen - High risk hormonal contraceptives	Ibuprofen - Low risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Diclofenac-High risk hormonal contraceptives	Diclofenac- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives
number records	N	29,894	69,093	37,625	31,171	76,668	39,812	21,702	58,550	27,977
number subjects	N	19,318	45,939	26,183	21,260	53,204	28,799	16,333	43,879	21,859
number of prescription	Median (Q25 - Q75)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)
days prescribed	Median (Q25 - Q75)	16 (16 - 34)	16 (16 - 34)	16 (16 - 34)	11 (11 - 21)	11 (11 - 21)	11 (11 - 21)	102 (51 - 121)	121 (51 - 121)	101 (27 - 121)

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Table 15. Drug utilization of ibuprofen, diclofenac, and naproxen in SIDIAP.

		SIDIAP								
		Cohort name								
Variable name	Estimate value	Ibuprofen - High risk hormonal contraceptives	Ibuprofen - Low risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Diclofenac-High risk hormonal contraceptives	Diclofenac- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Naproxen - High risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives
number records	N	16,939	68,754	142,917	2,243	8,535	14,724	4,884	21,836	42,955
number subjects	N	10,860	40,318	75,921	1,946	7,180	12,318	3,734	15,671	30,644
number of prescription	Median (Q25 - Q75)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)
days prescribed	Median (Q25 - Q75)	8 (6 - 14)	8 (6 - 14)	8 (6 - 14)	8 (6 - 14)	8 (6 - 14)	8 (6 - 14)	11 (6 - 21)	11 (6 - 21)	11 (6 - 21)

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We assessed the potential indication of NSAIDs therapy which are also risk factors of VTE during the use of HC, presented in tables 16-19.

Among all included potential indications, 0.5 – 1.6% women experienced of trauma or fracture in the 30 days before NSAID initiation in CPRD GOLD. In DK-DHR, 3.2 – 8.4% people had record of hospitalisation during the 30 days before NSAID use. In SIDIAP, 0.5 – 1.9% people had record of hospitalisation before NSAID use. In NLHR, 0.6 – 2.1% people had record of rheumatoid arthritis, and 1.2 – 3.4% had record of hospitalisation.

Most women initiating NSAIDs while on HC did not have a record of a potential indication for NSAID therapy which are also risk factors of VTE. This limited our ability to adjust for confounding by indication in the later SCCS analysis.

Table 16. Potential indication of NSAID use which are also risk factors of VTE during the 30-days prior to NSAID initiation among women used HCs.

Indication		Cohort name								
		Diclofenac- Low risk hormonal contraceptives	Ibuprofen- Low risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives	Diclofenac- High risk hormonal contraceptives	Ibuprofen- High risk hormonal contraceptives	Naproxen- High risk hormonal contraceptives
CPRD GOLD										
Number records	N	11,421	25,443	87,242	5,324	16,155	37,748	1,575	4,159	10,655
Behcet's syndrome	N (%)	0 (0.0 %)	0 (0.0 %)	-	0 (0.0 %)	0 (0.0 %)	-	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Cancer	N (%)	6 (0.1 %)	18 (0.1 %)	25 (0.0 %)	-	6 (0.0 %)	8 (0.0 %)	0 (0.0 %)	-	-
Edema of lower leg	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Inflammatory bowel disease	N (%)	0 (0.0 %)	-	7 (0.0 %)	-	-	-	0 (0.0 %)	0 (0.0 %)	-
lupus erythematosus	N (%)	0 (0.0 %)	0 (0.0 %)	5 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-
Rheumatoid arthritis	N (%)	-	12 (0.0 %)	36 (0.0 %)	-	-	23 (0.1 %)	0 (0.0 %)	-	-
Surgery	N (%)	35 (0.3 %)	98 (0.4 %)	67 (0.1 %)	9 (0.2 %)	14 (0.1 %)	18 (0.0 %)	-	8 (0.2 %)	7 (0.1 %)
Trauma/ fracture	N (%)	80 (0.7 %)	347 (1.4 %)	815 (0.9 %)	38 (0.7 %)	232 (1.4 %)	456 (1.2 %)	8 (0.5 %)	63 (1.5 %)	171 (1.6 %)
Wheelchair use/reduced mobility	N (%)	0 (0.0 %)	-	8 (0.0 %)	-	-	-	0 (0.0 %)	-	0 (0.0 %)

Indication		Cohort name								
		Diclofenac- Low risk hormonal contraceptives	Ibuprofen- Low risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives	Diclofenac- High risk hormonal contraceptives	Ibuprofen- High risk hormonal contraceptives	Naproxen- High risk hormonal contraceptives
Unknown*	N (%)	5,440 (47.6 %)	15,291 (60.1 %)	52,552 (60.2 %)	2,793 (52.5 %)	10,627 (65.8 %)	24,987 (66.2 %)	838 (53.2 %)	2,763 (66.4 %)	7,038 (66.1 %)
None$	N (%)	5,859 (51.3 %)	9,678 (38.0 %)	33,727 (38.7 %)	2,479 (46.6 %)	5,268 (32.6 %)	12,250 (32.5 %)	726 (46.1 %)	1,321 (31.8 %)	3,430 (32.2 %)
NLHR										
Number records	N	76,668	69,093	58,550	39,812	37,625	27,977	31,171	29,894	21,702
Behcet's syndrome	N (%)	-	-	-	0 (0.0 %)	-	-	0 (0.0 %)	-	-
Cancer	N (%)	149 (0.2 %)	168 (0.2 %)	76 (0.1 %)	27 (0.1 %)	29 (0.1 %)	16 (0.1 %)	36 (0.1 %)	40 (0.1 %)	12 (0.1 %)
Edema of lower leg	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
hospitalisation	N (%)	2,578 (3.4 %)	1,269 (1.8 %)	702 (1.2 %)	1,438 (3.6 %)	622 (1.7 %)	351 (1.3 %)	905 (2.9 %)	438 (1.5 %)	258 (1.2 %)
Inflammatory bowel disease	N (%)	92 (0.1 %)	81 (0.1 %)	78 (0.1 %)	77 (0.2 %)	43 (0.1 %)	40 (0.1 %)	37 (0.1 %)	52 (0.2 %)	40 (0.2 %)
lupus erythematosus	N (%)	14 (0.0 %)	50 (0.1 %)	28 (0.0 %)	-	10 (0.0 %)	5 (0.0 %)	5 (0.0 %)	7 (0.0 %)	-
Rheumatoid arthritis	N (%)	461 (0.6 %)	1,455 (2.1 %)	1,238 (2.1 %)	283 (0.7 %)	615 (1.6 %)	566 (2.0 %)	208 (0.7 %)	601 (2.0 %)	446 (2.1 %)
Surgery	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Trauma/ fracture	N (%)	416 (0.5 %)	530 (0.8 %)	277 (0.5 %)	211 (0.5 %)	274 (0.7 %)	150 (0.5 %)	176 (0.6 %)	242 (0.8 %)	130 (0.6 %)

Indication		Cohort name								
		Diclofenac- Low risk hormonal contraceptives	Ibuprofen- Low risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives	Diclofenac- High risk hormonal contraceptives	Ibuprofen- High risk hormonal contraceptives	Naproxen- High risk hormonal contraceptives
Wheelchair use/reduced mobility	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Unknown	N (%)	65,017 (84.8 %)	46,716 (67.6 %)	50,518 (86.3 %)	33,411 (83.9 %)	24,286 (64.5 %)	23,968 (85.7 %)	26,235 (84.2 %)	19,756 (66.1 %)	18,464 (85.1 %)
None	N (%)	8,039 (10.5 %)	18,941 (27.4 %)	5,679 (9.7 %)	4,400 (11.1 %)	11,787 (31.3 %)	2,902 (10.4 %)	3,598 (11.5 %)	8,802 (29.4 %)	2,366 (10.9 %)
SIDIAP										
Number records	N	76,668	69,093	58,550	39,812	37,625	27,977	31,171	29,894	21,702
Behcet's syndrome	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-	-	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Cancer	N (%)	10 (0.1 %)	82 (0.1 %)	11 (0.1 %)	7 (0.0 %)	104 (0.1 %)	22 (0.1 %)	0 (0.0 %)	10 (0.1 %)	-
Edema of lower leg	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
hospitalisation	N (%)	164 (1.9 %)	1,502 (2.2 %)	146 (0.7 %)	259 (1.8 %)	2,200 (1.5 %)	178 (0.4 %)	39 (1.7 %)	309 (1.8 %)	25 (0.5 %)
Inflammatory bowel disease	N (%)	-	20 (0.0 %)	6 (0.0 %)	-	13 (0.0 %)	-	0 (0.0 %)	-	0 (0.0 %)
lupus erythematosus	N (%)	-	11 (0.0 %)	-	-	11 (0.0 %)	7 (0.0 %)	-	0 (0.0 %)	0 (0.0 %)
Rheumatoid arthritis	N (%)	-	14 (0.0 %)	5 (0.0 %)	-	11 (0.0 %)	7 (0.0 %)	0 (0.0 %)	-	5 (0.1 %)

Indication		Cohort name								
		Diclofenac- Low risk hormonal contraceptives	Ibuprofen- Low risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives	Diclofenac- High risk hormonal contraceptives	Ibuprofen- High risk hormonal contraceptives	Naproxen- High risk hormonal contraceptives
Surgery	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Trauma/ fracture	N (%)	88 (1.0 %)	408 (0.6 %)	116 (0.5 %)	149 (1.0 %)	850 (0.6 %)	251 (0.6 %)	38 (1.7 %)	143 (0.8 %)	26 (0.5 %)
Wheelchair use/reduced mobility	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Unknown	N (%)	5,914 (69.3 %)	49,762 (72.4 %)	15,552 (71.2 %)	10,410 (70.7 %)	105,472 (73.8 %)	31,119 (72.4 %)	1,552 (69.2 %)	11,941 (70.5 %)	3,400 (69.6 %)
None	N (%)	2,380 (27.9 %)	17,133 (24.9 %)	6,013 (27.5 %)	3,922 (26.6 %)	34,428 (24.1 %)	11,376 (26.5 %)	620 (27.6 %)	4,574 (27.0 %)	1,429 (29.3 %)
DK-DHR										
Number records	N	17,071	370,613	20,487	10,045	210,677	16,872	3,818	60,660	3,924
Behcet's syndrome	N (%)	0 (0.0 %)	25 (0.0 %)	-	0 (0.0 %)	-	0 (0.0 %)	0 (0.0 %)	-	0 (0.0 %)
Cancer	N (%)	28 (0.2 %)	1,595 (0.4 %)	70 (0.3 %)	-	207 (0.1 %)	15 (0.1 %)	-	57 (0.1 %)	6 (0.2 %)
Edema of lower leg	N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
hospitalisation	N (%)	541 (3.2 %)	13,618 (3.7 %)	1,197 (5.8 %)	402 (4.0 %)	9,551 (4.5 %)	1,410 (8.4 %)	149 (3.9 %)	2,525 (4.2 %)	328 (8.4 %)
Inflammatory bowel disease	N (%)	47 (0.3 %)	762 (0.2 %)	49 (0.2 %)	20 (0.2 %)	428 (0.2 %)	45 (0.3 %)	14 (0.4 %)	152 (0.3 %)	-
lupus erythematosus	N (%)	-	173 (0.0 %)	16 (0.1 %)	-	60 (0.0 %)	13 (0.1 %)	0 (0.0 %)	18 (0.0 %)	-

Indication		Cohort name								
		Diclofenac- Low risk hormonal contraceptives	Ibuprofen- Low risk hormonal contraceptives	Naproxen- Low risk hormonal contraceptives	Diclofenac- Medium risk hormonal contraceptives	Ibuprofen- Medium risk hormonal contraceptives	Naproxen- Medium risk hormonal contraceptives	Diclofenac- High risk hormonal contraceptives	Ibuprofen- High risk hormonal contraceptives	Naproxen- High risk hormonal contraceptives
Rheumatoid arthritis	N (%)	74 (0.4 %)	1,641 (0.4 %)	138 (0.7 %)	32 (0.3 %)	567 (0.3 %)	76 (0.5 %)	16 (0.4 %)	187 (0.3 %)	13 (0.3 %)
Surgery	N (%)	-	590 (0.2 %)	12 (0.1 %)	0 (0.0 %)	85 (0.0 %)	-	-	30 (0.0 %)	-
Trauma/ fracture	N (%)	30 (0.2 %)	2,094 (0.6 %)	41 (0.2 %)	22 (0.2 %)	1,522 (0.7 %)	41 (0.2 %)	9 (0.2 %)	390 (0.6 %)	9 (0.2 %)
Wheelchair use/reduced mobility	N (%)	0 (0.0 %)	-	0 (0.0 %)	0 (0.0 %)	-	-	0 (0.0 %)	0 (0.0 %)	-
Unknown	N (%)	15,214 (89.1 %)	328,628 (88.7 %)	18,162 (88.7 %)	8,849 (88.1 %)	182,827 (86.8 %)	14,517 (86.0 %)	3,234 (84.7 %)	51,671 (85.2 %)	3,281 (83.6 %)
None	N (%)	1,161 (6.8 %)	23,179 (6.3 %)	874 (4.3 %)	725 (7.2 %)	16,028 (7.6 %)	785 (4.7 %)	399 (10.5 %)	5,822 (9.6 %)	290 (7.4 %)

*Unknown means that individual didn't have any of the previous listed conditions recorded in the corresponding time window, but had other condition recorded.

$None means that individual didn't have any conditions recorded in the data during the corresponding time window.

12.5.2 Objective 2. SCCS – any NSAIDs use

Any NSAIDs

In objective 2, we estimated the person-time, and number of events of each of the defined period [baseline period, the pre-exposure period, the NSAIDs exposure risk period (day of initiation, first 7 days on NSAIDs, and days after), and the post-exposure period]. We estimated the incidence rate ratios (IRRs) as compared to the base line period within each HC group in two models: the first model only adjusted for age as time-varying variable. In the second model, in addition to age, we also adjusted for seasonality and potential indication as time-varying confounders (Table 17, Figure 6).

Among women using low risk HC, we observed an increased adjusted IRR already in the pre-exposure period in all databases: adjusted IRRs for the 14 days pre-exposure were 2.18 [95%CI 1.00 - 4.77], 3.38 [2.19 - 5.22], 2.74 [1.46 - 5.12], and 6.71 [2.42 - 18.60] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRR peaked on the day of NSAIDs initiation, followed in the first 7 days of NSAIDs use (risk period 1), and then in the rest of time until end of NSAID use (risk period 2): adjusted IRRs for risk period 1 were 4.95 [95%CI 2.37 - 10.36], 3.33 [1.81 - 6.13], 6.03 [3.29 - 11.05], and 3.06 [0.40 - 23.38] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. As for risk period 2, the adjusted IRRs were 3.78 [2.19 - 6.53], 2.63 [1.78 - 3.87], 1.87 [1.14 - 3.08], and 6.80 [1.99 - 23.18] respectively. Post-exposure adjusted IRRs were 3.21 [1.93 - 5.35], 1.16 [0.71 - 1.91], 1.52 [0.83 - 2.78], and 4.03 [1.57 - 10.31] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively (Figure 6).

Among women used medium risk HC, increased adjusted IRR was observed on the pre-exposure period, the day of NSAID initiation, risk period 1, risk period 2, and the 30-days post-exposure period in all four databases. Adjusted IRRs for the pre-exposure were 1.87 [0.66 - 5.35], 6.47 [4.3- 9.67], 2.36 [1.26 - 4.41], and 1.99 [0.90 - 4.40] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 15.30 [8.33 - 28.09], 7.75 [4.73 - 12.71], 9.39 [5.84 - 15.11], and 8.40 [4.43 - 15.93] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 5.40 [2.77 - 10.52], 3.79 [2.32 - 6.22], 2.34 [1.45 - 3.78], and 5.80 [2.72 - 12.39] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 2.37 [1.17 - 4.82], 2.84 [1.86 - 4.35], 1.66 [0.96 - 2.86], and 3.13 [1.82 - 5.37]in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used high risk HC, we observed similar pattern that adjusted IRR was increased in the pre-exposure period, on day of NSAIDs exposure, on risk periods 1 and 2, and remained until the post-exposure period. Adjusted IRRs for the pre-exposure were 2.29 [0.61 - 8.58], 3.70 [1.93 - 7.12], 5.12 [3.16 - 8.28], and 5.77 [1.62 - 20.50] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 15.10 [5.77 - 39.48], 12.29 [7.02 - 21.51], 12.29 [7.82 - 19.32], and 14.96 [4.23 - 52.87] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 3.46 [1.00 - 12.04], 6.02 [3.50 - 10.37], 4.60 [3.03 - 7.00], and 22.58 [6.42 - 79.48] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were. 1.48 [0.40 - 5.46], 3.70 [2.17 - 6.30], 3.35 [2.19 - 5.13], and 3.83 [0.97 - 15.10] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

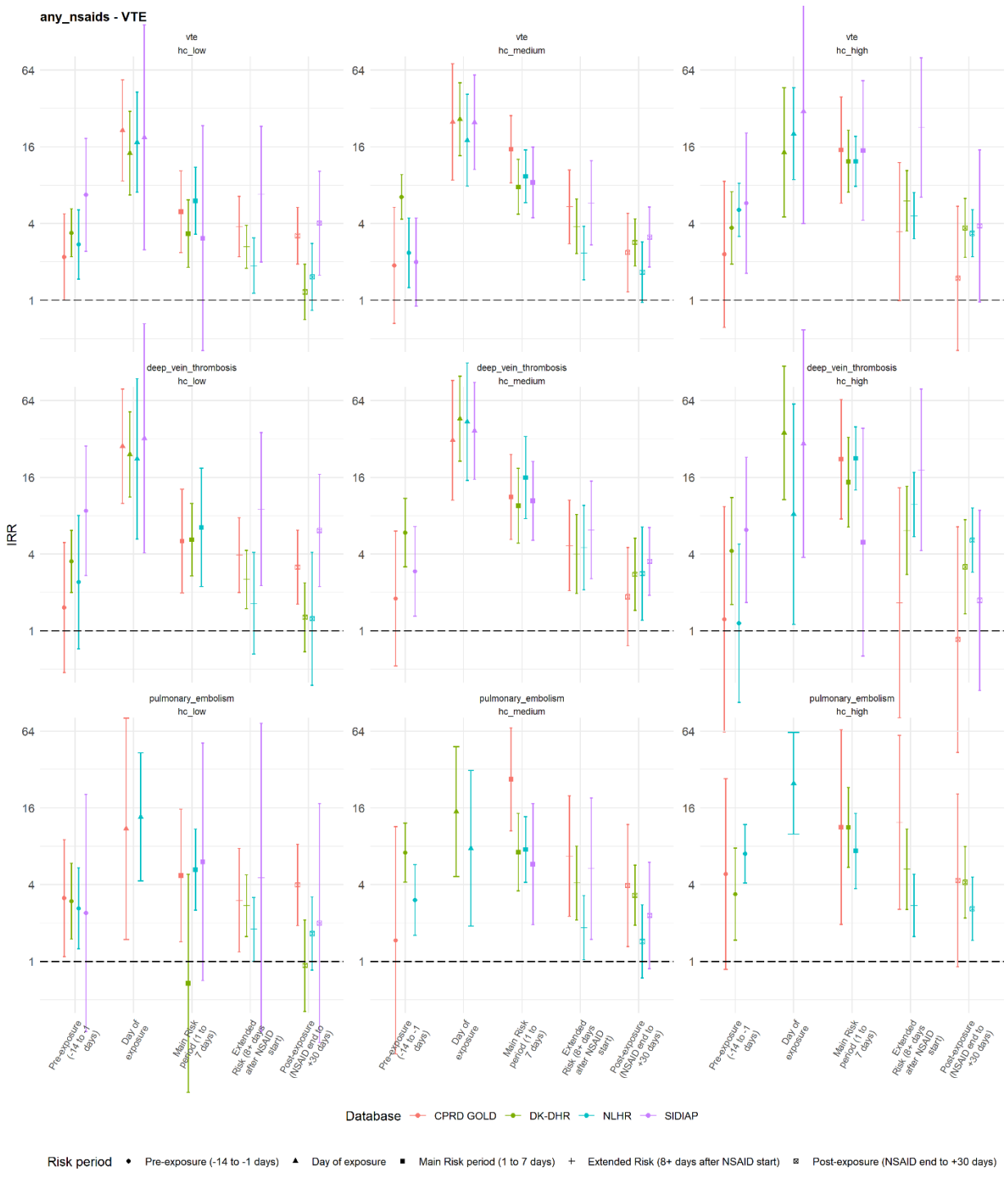

Figure 6. Adjusted incidence rate ratio (IRR) of VTE, pulmonary embolism, and deep vein thrombosis during each pre-defined period of any NSAIDs use. X-axis present the pre-exposure, day of exposure, main risk period, extended risk period, and post-exposure periods. Y-axis present the adjusted incidence rate ratio of each period. Rows: outcome of VTE, deep vein thrombosis, and pulmonary embolism. Columns: Low-, medium-, and high-risk HC.

Table 17. Adjusted incidence rate ratio (IRR) and event count of VTE during each pre-defined period of any NSAIDs use.

	CPRD GOLD			DK-DHR			NLHR			SIDIAP		
	Estimate value											
Variable level	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time
Low risk hormonal contraceptives												
Pre-exposure (-14 to -1 days)	2.18 [1.00 - 4.77]	7	4,408	3.38 [2.19 - 5.22]	23	16,111	2.74 [1.46 - 5.12]	11	5,697	6.71 [2.42 - 18.60]	5	1,187
Day of exposure	21.50 [8.63 - 53.57]	5	323	14.24 [6.68 - 30.32]	7	1,190	17.37 [7.04 - 42.84]	5	421	18.97 [2.49 - 144.64]	-	86
Main Risk period (1 to 7 days)	4.95 [2.37 - 10.36]	8	2,244	3.33 [1.81 - 6.13]	11	8,088	6.03 [3.29 - 11.05]	12	2,914	3.06 [0.40 - 23.38]	-	540
Extended Risk (8+ days after NSAID start)	3.78 [2.19 - 6.53]	20	9,868	2.63 [1.78 - 3.87]	34	36,458	1.87 [1.14 - 3.08]	23	21,750	6.80 [1.99 - 23.18]	-	1,592
Post-exposure (NSAID end to +30 days)	3.21 [1.93 - 5.35]	19	9,078	1.16 [0.71 - 1.91]	17	34,664	1.52 [0.83 - 2.78]	12	11,714	4.03 [1.57 - 10.31]	6	2,456
Baseline	-	113	202,824	-	322	836,417	-	125	198,886	-	21	34,837
Medium risk hormonal contraceptives												
Pre-exposure (-14 to -1 days)	1.87 [0.66 - 5.35]	-	1,789	6.47 [4.33 - 9.67]	33	5,315	2.36 [1.26 - 4.41]	11	5,464	1.99 [0.90 - 4.40]	7	4,186
Day of exposure	25.00 [8.74 - 71.51]	-	139	26.27 [13.58 - 50.80]	10	393	18.00 [7.87 - 41.20]	6	404	24.89 [10.59 - 58.52]	6	312
Main Risk period (1 to 7 days)	15.30 [8.33 - 28.09]	17	969	7.75 [4.73 - 12.71]	20	2,656	9.39 [5.84 - 15.11]	21	2,769	8.40 [4.43 - 15.93]	12	1,966

	CPRD GOLD			DK-DHR			NLHR			SIDIAP		
	Estimate value											
Variable level	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time
Extended Risk (8+ days after NSAID start)	5.40 [2.77 - 10.52]	16	5,401	3.79 [2.32 - 6.22]	22	8,794	2.34 [1.45 - 3.78]	27	17,023	5.80 [2.72 - 12.39]	13	10,389
Post-exposure (NSAID end to +30 days)	2.37 [1.17 - 4.82]	11	3,791	2.84 [1.86 - 4.35]	28	10,719	1.66 [0.96 - 2.86]	15	11,139	3.13 [1.82 - 5.37]	19	8,489
Baseline	-	40	51,388	-	130	205,002	-	132	187,008	-	73	112,948
High risk hormonal contraceptives												
Pre-exposure (-14 to -1 days)	2.29 [0.61 - 8.58]	-	679	3.70 [1.93 - 7.12]	11	3,218	5.12 [3.16 - 8.28]	21	5,922	5.77 [1.62 - 20.50]	-	815
Day of exposure	0.00 [0.00 - Inf]	-	50	14.47 [4.50 - 46.57]	-	241	20.24 [8.82 - 46.48]	6	436	30.30 [3.99 - 230.28]	-	63
Main Risk period (1 to 7 days)	15.10 [5.77 - 39.48]	9	338	12.29 [7.02 - 21.51]	17	1,627	12.29 [7.82 - 19.32]	25	3,013	14.96 [4.23 - 52.87]	-	398
Extended Risk (8+ days after NSAID start)	3.46 [1.00 - 12.04]	5	1,511	6.02 [3.50 - 10.37]	24	5,486	4.60 [3.03 - 7.00]	44	20,560	22.58 [6.42 - 79.48]	5	1,531
Post-exposure (NSAID end to +30 days)	1.48 [0.40 - 5.46]	-	1,252	3.70 [2.17 - 6.30]	19	6,286	3.35 [2.19 - 5.13]	29	12,175	3.83 [0.97 - 15.10]	-	1,502
Baseline	-	15	10,597	-	68	101,862	-	118	200,023	-	9	15,651

Negative control exposure

In the analysis of the negative control exposure, paracetamol use showed similar associations as with any NSAID use. In all four databases, we observed elevated adjusted IRRs in the 14-day pre-exposure period, peaking on the day of paracetamol initiation, and then still high on the exposure periods 1 (first week), 2 (from day 8 until end of paracetamol therapy), and post-exposure period. See Figure 7 for full detailed results.

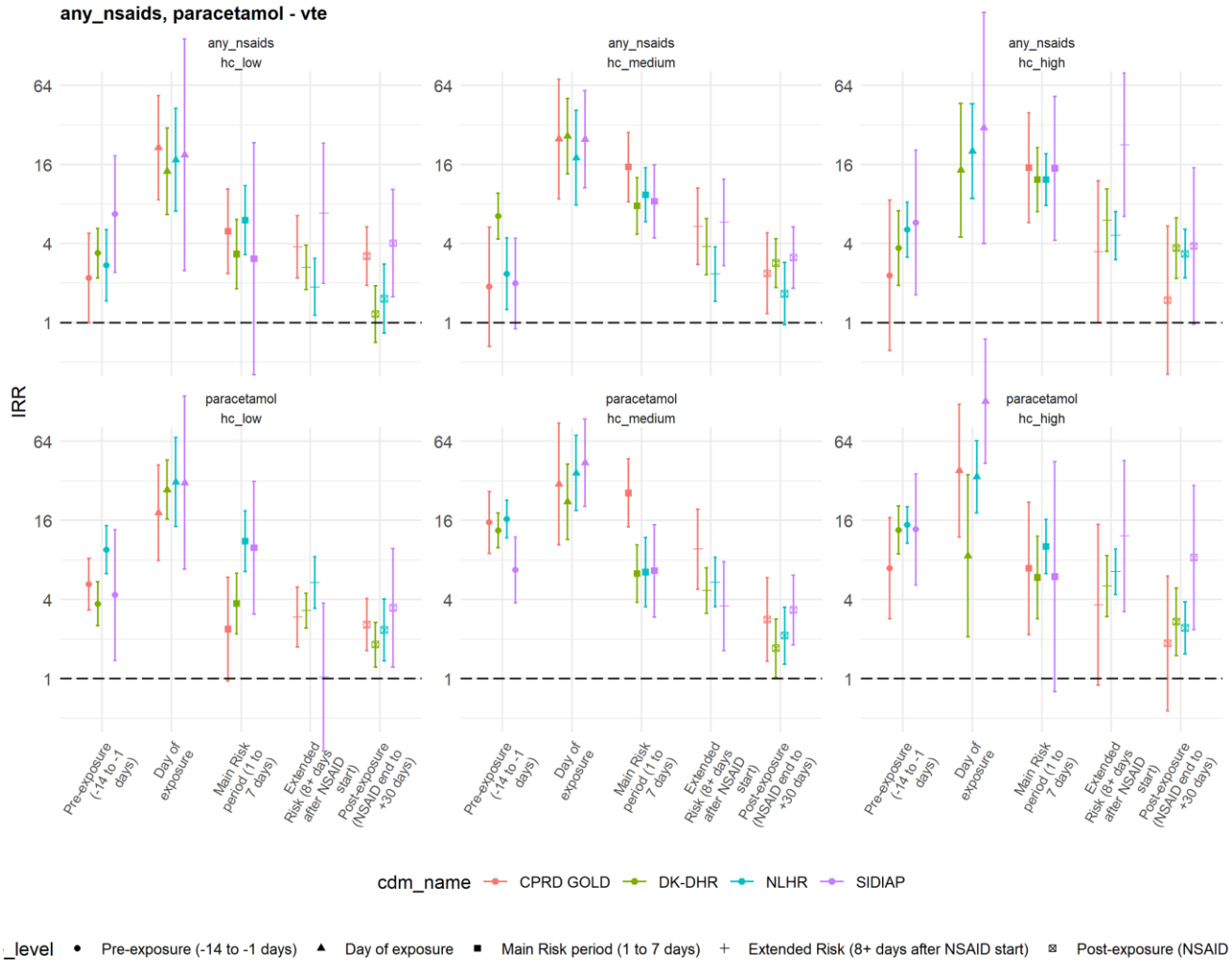

Figure 7 Adjusted incidence rate ratio (IRR) of VTE during each pre-defined period of any NSAIDs (top panel) or paracetamol (bottom panel) use**.**

PE, DVT

In addition to VTE as a composite, we also analysed PE and DVT) as individual outcomes. (Table 18)

Among women using low-risk HC, the adjusted IRRs of PE for the pre-exposure were 3.13 [1.09 - 8.98], 2.96 [1.49 - 5.88], 2.60 [1.25 - 5.41], and 2.40 [0.28 - 20.48] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP

respectively. Adjusted IRRs during risk period 1 were 4.71 [1.42 - 15.65], 0.67 [0.09 - 4.83], 5.24 [2.52 - 10.92], and 6.04 [0.71 - 51.74] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were [1.18 - 7.67], 2.73 [1.56 - 4.78],1.79 [1.01 - 3.17], and 4.54 [0.28 - 73.80] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 97 [1.91 - 8.28], 0.93 [0.41 - 2.12], 1.65 [0.85 - 3.21], and 2.00 [0.23 - 17.28] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Adjusted IRRs of DVT for the pre-exposure were 1.52 [0.47 - 4.94], 3.50 [2.00 - 6.12], 2.41 [0.72 - 8.03], and 8.75 [2.71 - 28.20] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 5.05 [1.98 - 12.88], 5.19 [2.70 - 9.96], and 6.48 [2.23 - 18.84] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 3.92 [2.00 - 7.68], 2.52 [1.49 - 4.27], 1.64 [0.66 - 4.12], and 9.00 [2.26 - 35.87]in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 6.15], 1.27 [0.68 - 2.38], 1.24 [0.37 - 4.14], and 6.12 [2.22 - 16.85]in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used medium-risk HC, the adjusted IRRs of PE for the pre-exposure were 1.46 [0.19 - 11.39], 7.13 [4.18 - 12.15], 3.03 [1.60 - 5.74], and 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 26.85 [10.60 - 68.01], 7.19 [3.58 - 14.46], 7.53 [4.16 - 13.63], and 5.79 [1.94 - 17.28] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 6.69 [2.25 - 19.90], 4.12 [2.11 - 8.02], 1.84 [1.03 - 3.28], 5.34 [1.49 - 19.11] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 3.93 [1.31 - 11.84], 3.30 [1.92 - 5.67], 1.43 [0.74 - 2.78], 2.29 [0.87 - 5.99] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Adjusted IRRs of DVT for the pre-exposure were 1.79 [0.53 - 6.07], 5.88 [3.17 - 10.90], 0.00 [0.00 - Inf], and 2.92 [1.30 - 6.59] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 11.22 [5.20 - 24.23], 9.57 [4.87 - 18.81], 15.91 [7.59 - 33.37], and 10.45 [5.13 - 21.28] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 4.67 [2.06 - 10.58], 4.00 [1.96 - 8.18], 4.49 [2.10 - 9.62], and 6.19 [2.56 - 14.94] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 0.85 [0.76 - 4.49], 2.77 [1.45 - 5.31], 2.80 [1.21 - 6.50], and 3.50 [1.90 - 6.45] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used high-risk HC, the adjusted IRRs of PE for the pre-exposure were 4.85 [0.87 - 27.13], 3.37 [1.47 - 7.71], 6.98 [4.13 - 11.82], 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 11.28 [1.95 - 65.36], 11.22 [5.46 - 23.05], and 7.36 [3.73 - 14.51] in CPRD GOLD, DK-DHR, NLHR respectively. Adjusted IRRs during risk period 2 were 2.32 [2.56 - 59.26], 5.27 [2.55 - 10.90], 2.75 [1.57 - 4.82] in CPRD GOLD, DK-DHR, NLHR respectively. During the 30-days post-exposure period, adjusted IRRs were 4.31 [0.90 - 20.53], 4.17 [2.18 - 7.97], 2.58 [1.46 - 4.58] in CPRD GOLD, DK-DHR, NLHR respectively.

Adjusted IRRs of DVT for the pre-exposure were 1.23 [0.16 - 9.43], 4.23 [1.61 - 11.11], 1.15 [0.27 - 4.77], and 6.19 [1.66 - 23.01] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 22.20 [7.55 - 65.24], 14.63 [6.50 - 32.92], 22.50 [12.71 - 39.82], and 4.96 [0.63 - 38.74] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 1.66 [0.21 - 13.24], 6.12 [2.76 - 13.58], 9.79 [5.49 - 17.45], 18.27 [4.25 - 78.59] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 0.85 [0.11 - 6.55], 3.18 [1.36 - 7.44], 5.14 [2.88 - 9.17], and 1.73 [0.34 - 8.81] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Table 18. Adjusted incidence rate ratio (IRR) of pulmonary embolism, and deep vein thrombosis during each pre-defined period of any NSAIDs use.

	CPRD GOLD		DK-DHR		NLHR		SIDIAP	
	Estimate value							
Variable level	IRR (95%CI)	Number events	IRR (95%CI)	Number events	IRR (95%CI)	Number events	IRR (95%CI)	Number events
Low risk hormonal contraceptives - Deep vein thrombosis								
Pre-exposure (-14 to -1 days)	1.52 [0.47 - 4.94]	-	3.50 [2.00 - 6.12]	14	2.41 [0.72 - 8.03]	-	8.75 [2.71 - 28.20]	-
Day of exposure	27.99 [9.96 - 78.71]	-	24.17 [11.21 - 52.12]	7	22.30 [5.24 - 94.94]	-	32.35 [4.09 - 255.77]	-
Main Risk period (1 to 7 days)	5.05 [1.98 - 12.88]	5	5.19 [2.70 - 9.96]	10	6.48 [2.23 - 18.84]	-	0.00 [0.00 - Inf]	-
Extended Risk (8+ days after NSAID start)	3.92 [2.00 - 7.68]	14	2.52 [1.49 - 4.27]	18	1.64 [0.66 - 4.12]	7	9.00 [2.26 - 35.87]	-
Post-exposure (NSAID end to +30 days)	3.16 [1.62 - 6.15]	11	1.27 [0.68 - 2.38]	11	1.24 [0.37 - 4.14]	-	6.12 [2.22 - 16.85]	6
Baseline	-	67	-	191	-	41	-	14
Medium risk hormonal contraceptives - Deep vein thrombosis								
Pre-exposure (-14 to -1 days)	1.79 [0.53 - 6.07]	-	5.88 [3.17 - 10.90]	14	0.00 [0.00 - Inf]	-	2.92 [1.30 - 6.59]	7
Day of exposure	31.20 [10.58 - 92.00]	-	46.13 [21.42 - 99.37]	8	43.62 [15.11 - 125.89]	-	37.02 [15.44 - 88.79]	6
Main Risk period (1 to 7 days)	11.22 [5.20 - 24.23]	10	9.57 [4.87 - 18.81]	11	15.91 [7.59 - 33.37]	10	10.45 [5.13 - 21.28]	10
Extended Risk (8+ days after NSAID start)	4.67 [2.06 - 10.58]	10	4.00 [1.96 - 8.18]	11	4.49 [2.10 - 9.62]	12	6.19 [2.56 - 14.94]	10
Post-exposure (NSAID end to +30 days)	1.85 [0.76 - 4.49]	7	2.77 [1.45 - 5.31]	12	2.80 [1.21 - 6.50]	7	3.50 [1.90 - 6.45]	15
Baseline	-	28	-	66	-	37	-	52
High risk hormonal contraceptives - Deep vein thrombosis								

Variable level	CPRD GOLD		DK-DHR		NLHR		SIDIAP	
	Estimate value							
	IRR (95%CI)	Number events	IRR (95%CI)	Number events	IRR (95%CI)	Number events	IRR (95%CI)	Number events
Pre-exposure (-14 to -1 days)	1.23 [0.16 - 9.43]	-	4.23 [1.61 - 11.11]	5	1.15 [0.27 - 4.77]	-	6.19 [1.66 - 23.01]	-
Day of exposure	0.00 [0.00 - Inf]	-	35.77 [10.72 - 119.39]	-	8.22 [1.12 - 60.25]	-	29.38 [3.76 - 229.47]	-
Main Risk period (1 to 7 days)	22.20 [7.55 - 65.24]	8	14.63 [6.50 - 32.92]	8	22.50 [12.71 - 39.82]	19	4.96 [0.63 - 38.74]	-
Extended Risk (8+ days after NSAID start)	1.66 [0.21 - 13.24]	-	6.12 [2.76 - 13.58]	11	9.79 [5.49 - 17.45]	26	18.27 [4.25 - 78.59]	-
Post-exposure (NSAID end to +30 days)	0.85 [0.11 - 6.55]	-	3.18 [1.36 - 7.44]	7	5.14 [2.88 - 9.17]	18	1.73 [0.34 - 8.81]	-
Baseline	-	10	-	32	-	46	-	9
Low risk hormonal contraceptives - Pulmonary embolism								
Pre-exposure (-14 to -1 days)	3.13 [1.09 - 8.98]	-	2.96 [1.49 - 5.88]	9	2.60 [1.25 - 5.41]	8	2.40 [0.28 - 20.48]	-
Day of exposure	10.97 [1.48 - 81.09]	-	0.00 [0.00 - Inf]	0	13.60 [4.28 - 43.25]	-	0.00 [0.00 - Inf]	-
Main Risk period (1 to 7 days)	4.71 [1.42 - 15.65]	-	0.67 [0.09 - 4.83]	-	5.24 [2.52 - 10.92]	8	6.04 [0.71 - 51.74]	-
Extended Risk (8+ days after NSAID start)	3.01 [1.18 - 7.67]	7	2.73 [1.56 - 4.78]	17	1.79 [1.01 - 3.17]	17	4.54 [0.28 - 73.80]	-
Post-exposure (NSAID end to +30 days)	3.97 [1.91 - 8.28]	10	0.93 [0.41 - 2.12]	6	1.65 [0.85 - 3.21]	10	2.00 [0.23 - 17.28]	-
Baseline	-	49	-	146	-	95	-	8
Medium risk hormonal contraceptives - Pulmonary embolism								
Pre-exposure (-14 to -1 days)	1.46 [0.19 - 11.39]	-	7.13 [4.18 - 12.15]	19	3.03 [1.60 - 5.74]	11	0.00 [0.00 - Inf]	-
Day of exposure	0.00 [0.00 - Inf]	-	14.96 [4.63 - 48.41]	-	7.70 [1.89 - 31.46]	-	0.00 [0.00 - Inf]	-

Variable level	CPRD GOLD		DK-DHR		NLHR		SIDIAP	
	Estimate value							
	IRR (95%CI)	Number events	IRR (95%CI)	Number events	IRR (95%CI)	Number events	IRR (95%CI)	Number events
Main Risk period (1 to 7 days)	26.85 [10.60 - 68.01]	9	7.19 [3.58 - 14.46]	10	7.53 [4.16 - 13.63]	13	5.79 [1.94 - 17.28]	-
Extended Risk (8+ days after NSAID start)	6.69 [2.25 - 19.90]	7	4.12 [2.11 - 8.02]	12	1.84 [1.03 - 3.28]	18	5.34 [1.49 - 19.11]	-
Post-exposure (NSAID end to +30 days)	3.93 [1.31 - 11.84]	5	3.30 [1.92 - 5.67]	18	1.43 [0.74 - 2.78]	10	2.29 [0.87 - 5.99]	6
Baseline	-	13	-	66	-	105	-	34
High risk hormonal contraceptives; - Pulmonary embolism								
Pre-exposure (-14 to -1 days)	4.85 [0.87 - 27.13]	-	3.37 [1.47 - 7.71]	7	6.98 [4.13 - 11.82]	19	0.00 [0.00 - Inf]	-
Day of exposure	0.00 [0.00 - Inf]	-	0.00 [0.00 - Inf]	0	24.92 [9.94 - 62.51]	5	NA*	-
Main Risk period (1 to 7 days)	11.28 [1.95 - 65.36]	-	11.22 [5.46 - 23.05]	11	7.36 [3.73 - 14.51]	10	NA*	-
Extended Risk (8+ days after NSAID start)	12.32 [2.56 - 59.26]	5	5.27 [2.55 - 10.90]	13	2.75 [1.57 - 4.82]	23	NA*	-
Post-exposure (NSAID end to +30 days)	4.31 [0.90 - 20.53]	-	4.17 [2.18 - 7.97]	14	2.58 [1.46 - 4.58]	15	NA*	-
Baseline	-	5	-	40	-	83	-	-

* "-" means there was less than 5 events in that cell and the number was suppressed.

NA: Statistic model gave unrealistic estimates due to small sample size and overdispersion.

SCCS assumptions

In section "9.9.2 Main statistical methods -SCCS", we explained the assumptions of the SCCS method.

We examined the assumption of "subsequent exposures should not appreciably be affected by previous events" by plotting the distribution of the interval between exposure and event time. If a peak or trough in events prior to exposure is apparent, the presence of short-term event-dependent exposures is indicated.

We examined the assumption of "event-dependent observation periods" by using the histograms of the times from event to end of observation, for those whose observation times are censored, and those are not separately. If a spike is apparent close to zero in the censored data histogram, the presence of event-dependent observation periods is indicated.

In the diagnostics of SCCS assumptions, we did not find evidence of violation of these SCCS assumptions. Figure 8 reports the analysis of DK-DHR data as an example:

- The first column from the left represents the number of VTE events in exposed cases (Y axis) over days since NSAIDs initiation (X axis). We observed that there was a spike around day 0, suggested that short-term event-dependent exposures may exist. In the analysis, we included a pre-exposure period to estimate the association during that period.
- The second column represents the number of people under observation (Y axis) over time since NSAIDs initiation (X). We observed that the number of people in observation was symmetrical/similar before and after day 0 of NSAID initiation. This suggested that exposure to NSAIDs didn't impact the observation period.
- The third and fourth columns represent the intervals from event (e.g. VTE) to end of observation in uncensored cases (third column), and in censored cases (rightmost column). Death after VTE was very rare, with both histograms showing similar shapes. This suggested that there's no evidence of violation of the "event-dependent observation periods" assumption.

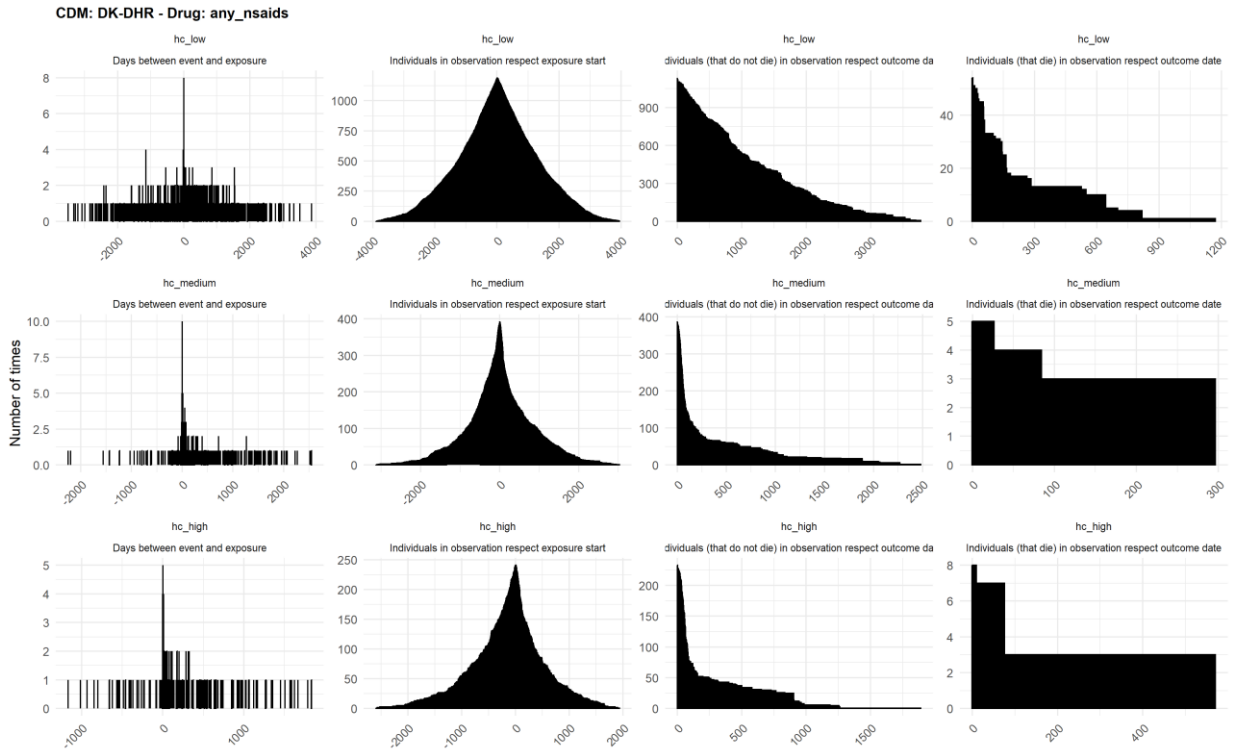

Figure 8. Diagnostics plot for SCCS assumption: Any NSAIDs use in DK-DHR.

Results from other databases are presented in the tab 'SCCS Plot Assumptions' of the online shiny app.

12.5.3 Objective 3. SCCS – individual NSAID ingredient use

In the analysis of the association between individual NSAIDs (diclofenac, ibuprofen, and naproxen) wider confidence intervals were reported due to low outcome counts. However, we observed similar trends as those seen for the analyses of 'any NSAIDs' (Objective 2) reported above (Figures 9-11).

Diclofenac

Among women used low-risk HC, adjusted IRRs of VTE during the pre-exposure were 6.41 [1.30 - 31.53], 1.55 [0.21 - 11.48], 3.77 [1.61 - 8.81], and 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 5.96 [0.72 - 49.67], 3.27 [0.44 - 24.24], 3.80 [1.18 - 12.22], and 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 3.21 [0.51 - 20.05], 2.47 [0.69 - 8.81], 1.32 [0.38 - 4.55], and 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 4.14 [1.05 - 16.29], 0.00 [0.00 - Inf], 1.80 [0.77 - 4.21], and 4.54 [0.50 - 41.66] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used medium-risk HC, adjusted IRRs of VTE during the pre-exposure were 0.00 [0.00 - Inf], 10.96 [2.29 - 52.53], 1.53 [0.47 - 4.93], and 8.40 [2.47 - 28.55]in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 0.00 [0.00 - Inf], 8.22 [1.02 - 65.98], 13.25 [7.03 - 24.96], and 22.43 [7.46 - 67.43] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 0.00 [0.00 - Inf], 0.00 [0.00 - Inf], 1.78 [0.42 - 7.52], and 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 5.59 [1.25 - 25.08], 1.64 [0.20 - 13.54], 1.94 [0.88 - 4.27], and 2.84 [0.66 - 12.27] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used high-risk HC, number of events were below 5 in all pre-defined periods in CPRD GOLD, DK-DHR, and SIDIAP, which led to very wide confidence intervals. In NLHR, the adjusted IRRs of VTE during the pre-exposure period, risk period 1, risk period 2, and post-exposure period were 1.60 [0.49 - 5.16], 11.32 [5.80 - 22.12], 3.96 [1.60 - 9.79], and 2.72 [1.39 - 5.30] respectively.

Ibuprofen

Among women used low-risk HC, adjusted IRRs of VTE during the pre-exposure were 1.77 [0.24 - 12.97], 3.69 [2.37 - 5.75], 5.52 [2.31 - 13.18], 7.66 [2.45 - 23.91] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 7.49 [1.79 - 31.30], 3.78 [2.05 - 6.97], 13.30 [5.84 - 30.29], 4.45 [0.58 - 34.34] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 4.39 [1.29 - 14.93], 2.84 [1.89 - 4.28], 2.90 [1.00 - 8.44], 2.28 [0.24 - 21.54] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were4.70 [1.81 - 12.22], 1.17 [0.69 - 1.99], 1.30 [0.40 - 4.23], 3.28 [0.94 - 11.44] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used medium-risk HC, adjusted IRRs of VTE during the pre-exposure were 9.42 [2.55 - 34.89], 6.60 [4.34 - 10.03], 5.41 [2.51 - 11.65], 1.23 [0.38 - 4.03] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 25.81 [7.85 - 84.87], 8.36 [5.03 - 13.89], 8.83 [3.72 - 20.97], 7.58 [3.32 - 17.33] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 19.87 [5.50 - 71.82], 4.21 [2.51 - 7.07], 1.14 [0.32 - 4.06], 1.76 [0.41 - 7.46] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 3.00 [0.73 - 12.39], 3.05 [1.97 - 4.73], 1.60 [0.63 - 4.08], 2.93 [1.50 - 5.75] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used high-risk HC, adjusted IRRs of VTE during the pre-exposure were 11.21 [2.87 - 43.89], 4.34 [2.30 - 8.21], 10.14 [5.28 - 19.48], 3.11 [0.33 - 29.06] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP

respectively. Adjusted IRRs during risk period 1 were 21.80 [5.57 - 85.26], 12.45 [6.97 - 22.21], 9.48 [3.93 - 22.85], 5.58 [0.62 - 50.11] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 4.60 [0.68 - 31.12], 5.25 [2.93 - 9.43], 4.94 [2.17 - 11.24], 6.76 [0.67 - 68.08] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 0.00 [0.00 - Inf], 3.75 [2.16 - 6.50], 3.23 [1.58 - 6.62], 2.72 [0.52 - 14.23] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Naproxen

In DK-DHR, no VTE event was observed during the pre-exposure, day of exposure, and the first 7 days of exposure in low-and high-risk HC user groups, precluding analysis. In SIDIAP, the number of VTE events during use of low-risk HC and naproxen was too low for SCCS analyses.

Among women used low-risk HC, adjusted IRRs of VTE during the pre-exposure were 2.11 [0.83 - 5.33], 0.00 [0.00 - Inf], 0.65 [0.09 - 4.76], 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 5.07 [2.15 - 11.96], 0.00 [0.00 - Inf], 6.73 [2.62 - 17.29], 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 3.33 [1.69 - 6.54], 0.74 [0.10 - 5.65], 0.99 [0.48 - 2.05], 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 2.96 [1.57 - 5.59], 2.60 [0.61 - 11.01], 1.14 [0.35 - 3.70], 4.88 [0.99 - 24.10]in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used medium-risk HC, adjusted IRRs of VTE during the pre-exposure were 0.71 [0.10 - 5.30], 2.77 [0.35 - 21.79], 2.14 [0.65 - 6.99], 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 15.27 [7.32 - 31.83], 0.00 [0.00 - Inf], 7.09 [2.75 - 18.26], 6.61 [1.55 - 28.19] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 3.13 [1.25 - 7.87], 1.81 [0.38 - 8.58], 1.35 [0.65 - 2.80], 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 1.75 [0.66 - 4.66], 1.06 [0.13 - 8.57], 1.49 [0.53 - 4.23], 2.80 [0.96 - 8.19]in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

Among women used high-risk HC, adjusted IRRs of VTE during the pre-exposure were 0.00 [0.00 - Inf], 0.00 [0.00 - Inf], 3.93 [1.51 - 10.23], 10.06 [1.05 - 96.06] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 1 were 15.76 [5.30 - 46.90], 0.00 [0.00 - Inf], 13.95 [6.52 - 29.85], 0.00 [0.00 - Inf] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Adjusted IRRs during risk period 2 were 4.28 [1.13 - 16.27], 17.35 [2.74 - 109.97], 2.17 [1.16 - 4.07], 4.09 [0.11 - 154.53] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. During the 30-days post-exposure period, adjusted IRRs were 3.14 [0.85 - 11.54], 12.32 [1.25 - 121.64], 0.39 [0.05 - 2.84], 3.18 [0.29 - 35.27] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively.

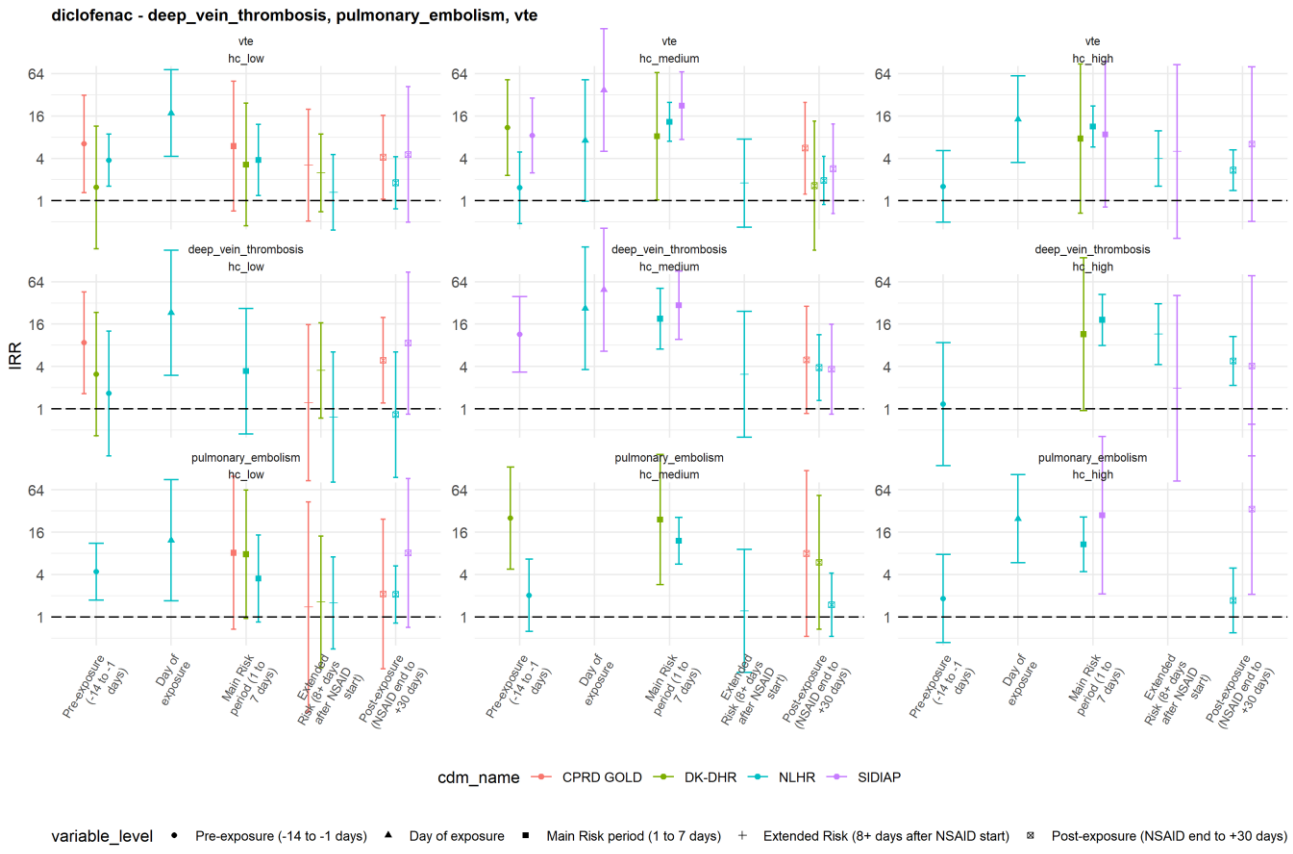

Figure 9. Adjusted IRR of VTE, deep vein thrombosis, and pulmonary embolism and use of diclofenac.

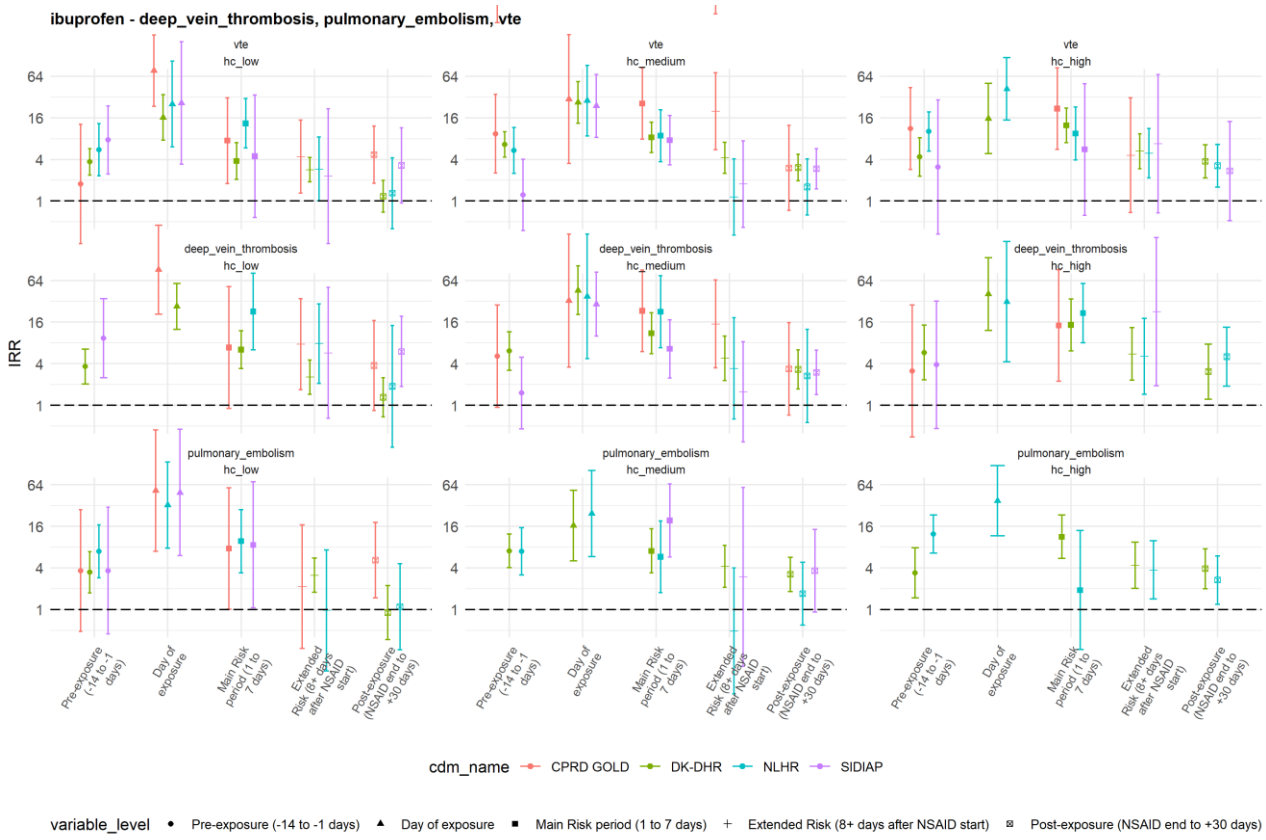

Figure 10. Adjusted IRR of VTE, deep vein thrombosis, and pulmonary embolism and use of ibuprofen.

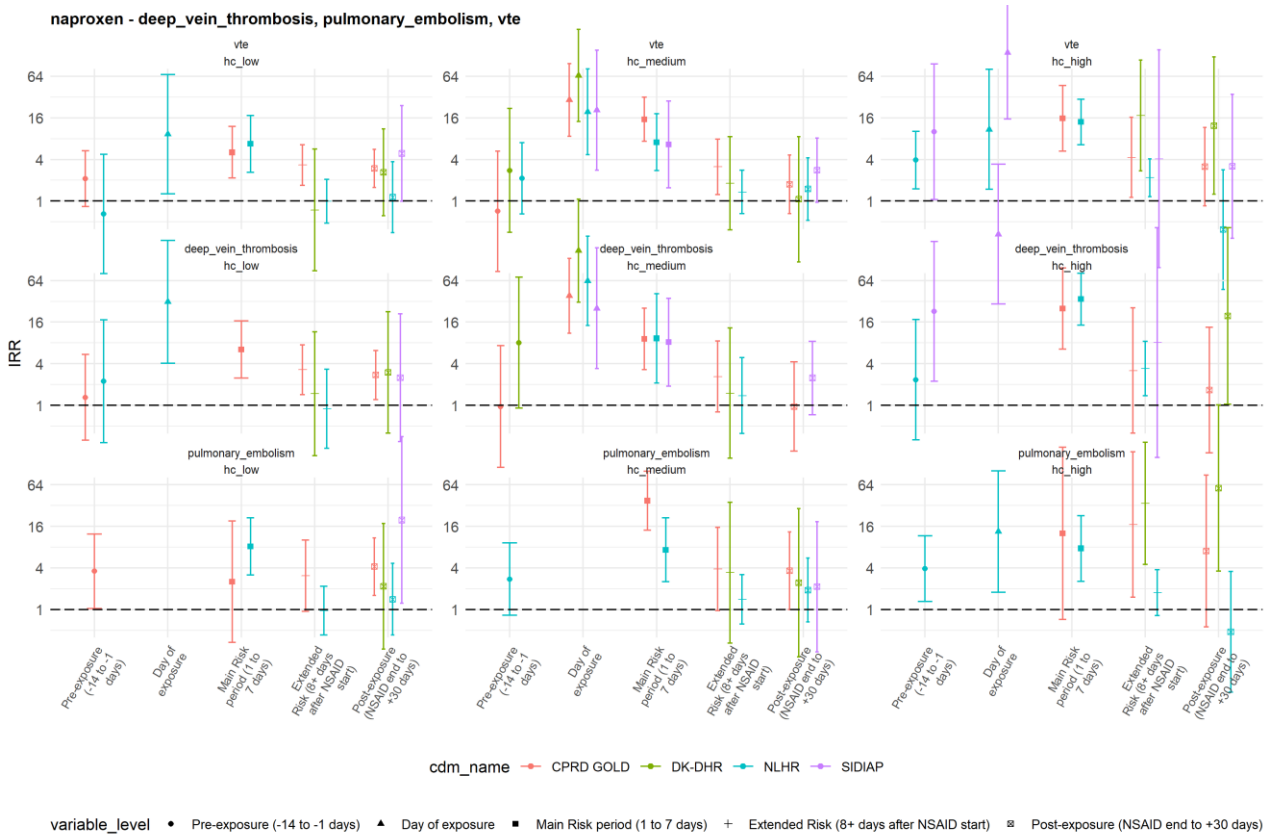

Figure 11. Adjusted IRR of VTE, deep vein thrombosis, and pulmonary embolism and use of naproxen.

12.6 Other analysis

We conducted two sensitivity analyses.

In the **first** sensitivity analysis where we exclude individual who died within 90 days after a VTE event, very few individuals were excluded. The IRR estimates were very similar to the main analysis(Figure 12, Table 19).

In the **second** sensitivity analysis, we excluded individuals with a record of cancer/ hospitalisation/ fracture/ major surgery/ trauma during the 6 months prior to a VTE event. Among women who used low-risk hormonal contraceptives, this led to the exclusion of 21, 207, 83, and 12 participants from CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively (Figure 12, Table 19). The resulting IRRs had wider confidence intervals but similar findings: adjusted IRRs during risk period 1 were 5.51 [2.61 - 11.62], 4.18 [1.93 - 9.03], 5.38 [2.30 - 12.60], and 3.70 [0.47 - 28.97] in CPRD GOLD, DK-DHR, NLHR, and SIDIAP. (Figure 12, Tables 19-21) During risk period 2 (from second week until end of NSAID use). Among women using medium-risk HC, this led to the exclusion of 6, 139, 107, 50 participants from CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. Increased IRR was observed on the pre-exposure period, day of NSAID exposure, risk periods 1 and 2, and the post-exposure period in all four databases. Finally, in women on high-risk HC , this led to the exclusion of 2, 98, 120, and 10 participants from CPRD GOLD, DK-DHR, NLHR, and SIDIAP respectively. We observed similar patterns as the main analysis. However, estimates were of wide confidence intervals due to sample size.

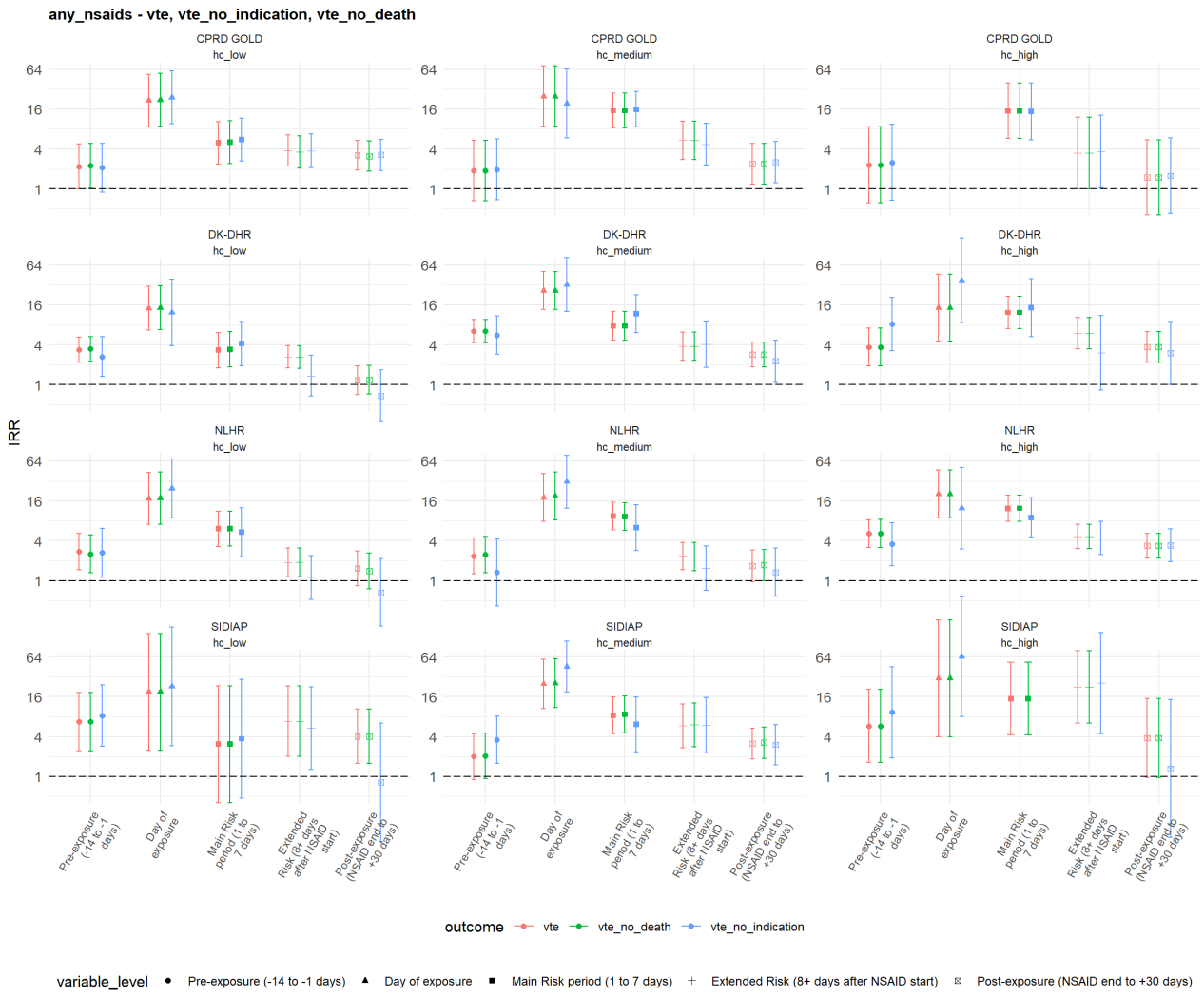

Figure 12. Sensitivity analysis: Adjusted IRR of VTE and any NSAIDs use.

Table 19. Adjusted IRR of VTE in sensitivity analyses and any NSAIDs use among women used low risk hormonal contraceptives.

Outcome	Low risk hormonal contraceptives											
	CPRD GOLD			DK-DHR			NLHR			SIDIAP		
	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time
Pre-exposure (-14 to -1 days)												
VTE (main analysis)	2.18 [1.00 - 4.77]	7	4,408	3.38 [2.19 - 5.22]	23	16,111	2.74 [1.46 - 5.12]	11	5,697	6.71 [2.42 - 18.60]	5	1,187
VTE exclude death case (Sensitivity 1)	2.23 [1.02 - 4.88]	7	4,324	3.46 [2.24 - 5.35]	23	15,835	2.52 [1.31 - 4.85]	10	5,669	6.71 [2.42 - 18.60]	5	1,187
VTE exclude potential indication (sensitivity 2)	2.08 [0.89 - 4.83]	6	3,932	2.66 [1.34 - 5.28]	9	7,944	2.63 [1.13 - 6.14]	6	2,999	8.27 [2.83 - 24.21]	5	935
Day of exposure												
VTE (main analysis)	21.50 [8.63 - 53.57]	5	323	14.24 [6.68 - 30.32]	7	1,190	17.37 [7.04 - 42.84]	5	421	18.97 [2.49 - 144.64]	-	86
VTE exclude death case (Sensitivity 1)	21.95 [8.80 - 54.78]	5	317	14.57 [6.84 - 31.05]	7	1,169	17.53 [7.11 - 43.25]	5	419	18.97 [2.49 - 144.64]	-	86
VTE exclude potential indication (sensitivity 2)	23.89 [9.53 - 59.87]	5	289	12.30 [3.89 - 38.91]	-	582	24.57 [8.85 - 68.22]	-	220	22.83 [2.91 - 178.93]	-	68
Main Risk period (1 to 7 days)												
VTE (main analysis)	4.95 [2.37 - 10.36]	8	2,244	3.33 [1.81 - 6.13]	11	8,088	6.03 [3.29 - 11.05]	12	2,914	3.06 [0.40 - 23.38]	-	540
VTE exclude death case (Sensitivity 1)	5.05 [2.41 - 10.59]	8	2,203	3.41 [1.85 - 6.28]	11	7,941	6.09 [3.32 - 11.16]	12	2,900	3.06 [0.40 - 23.38]	-	540
VTE exclude potential indication (sensitivity 2)	5.51 [2.61 - 11.62]	8	2,006	4.18 [1.93 - 9.03]	7	4,002	5.38 [2.30 - 12.60]	6	1,519	3.70 [0.47 - 28.97]	-	424
Extended Risk (8+ days after NSAID start)												
VTE (main analysis)	3.78 [2.19 - 6.53]	20	9,868	2.63 [1.78 - 3.87]	34	36,458	1.87 [1.14 - 3.08]	23	21,750	6.80 [1.99 - 23.18]	-	1,592
VTE exclude death case (Sensitivity 1)	3.62 [2.07 - 6.33]	19	9,782	2.60 [1.75 - 3.85]	33	36,051	1.89 [1.14 - 3.11]	23	21,665	6.80 [1.99 - 23.18]	-	1,592
VTE exclude potential indication (sensitivity 2)	3.76 [2.08 - 6.79]	17	8,036	1.37 [0.67 - 2.78]	9	16,588	1.12 [0.52 - 2.39]	9	12,260	5.38 [1.28 - 22.59]	-	1,464
Post-exposure (NSAID end to +30 days)												

Outcome	Low risk hormonal contraceptives											
	CPRD GOLD			DK-DHR			NLHR			SIDIAP		
	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time
VTE (main analysis)	3.21 [1.93 - 5.35]	19	9,078	1.16 [0.71 - 1.91]	17	34,664	1.52 [0.83 - 2.78]	12	11,714	4.03 [1.57 - 10.31]	6	2,456
VTE exclude death case (Sensitivity 1)	3.12 [1.84 - 5.27]	18	8,898	1.19 [0.72 - 1.96]	17	34,082	1.40 [0.75 - 2.61]	11	11,684	4.03 [1.57 - 10.31]	6	2,456
VTE exclude potential indication (sensitivity 2)	3.26 [1.89 - 5.60]	17	8,112	0.68 [0.28 - 1.67]	5	17,091	0.66 [0.21 - 2.13]	-	6,180	0.81 [0.10 - 6.32]	-	1,935
Baseline												
VTE (main analysis)	-	113	202,824	-	322	836,417	-	125	198,886	-	21	34,837
VTE exclude death case (Sensitivity 1)	-	109	197,440	-	315	822,810	-	125	198,507	-	21	34,837
VTE exclude potential indication (sensitivity 2)	-	98	176,764	-	174	453,983	-	77	117,055	-	15	23,879

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Table 20. Adjusted IRR of VTE in sensitivity analyses and any NSAIDs use among women used medium risk hormonal contraceptives.

	Medium risk hormonal contraceptives											
	CPRD GOLD			DK-DHR			NLHR			SIDIAP		
Outcome	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time
Pre-exposure (-14 to -1 days)												
VTE (main analysis)	1.87 [0.66 - 5.35]	-	1,789	6.47 [4.33 - 9.67]	33	5,315	2.36 [1.26 - 4.41]	11	5,464	1.99 [0.90 - 4.40]	7	4,186
VTE exclude death case (Sensitivity 1)	1.87 [0.66 - 5.35]	-	1,789	6.47 [4.33 - 9.67]	33	5,315	2.47 [1.32 - 4.61]	11	5,394	2.04 [0.92 - 4.52]	7	4,102
VTE exclude potential indication (sensitivity 2)	1.97 [0.69 - 5.63]	-	1,674	5.60 [2.90 - 10.84]	12	2,332	1.33 [0.42 - 4.28]	-	2,782	3.57 [1.57 - 8.13]	7	2,830
Day of exposure												
VTE (main analysis)	25.00 [8.74 - 71.51]	-	139	26.27 [13.58 - 50.80]	10	393	18.00 [7.87 - 41.20]	6	404	24.89 [10.59 - 58.52]	6	312
VTE exclude death case (Sensitivity 1)	25.00 [8.74 - 71.51]	-	139	26.27 [13.58 - 50.80]	10	393	18.87 [8.26 - 43.12]	6	399	25.59 [10.88 - 60.19]	6	306
VTE exclude potential indication (sensitivity 2)	19.49 [5.88 - 64.52]	-	130	32.56 [12.72 - 83.36]	5	167	31.09 [12.37 - 78.17]	5	204	45.40 [18.72 - 110.12]	6	212
Main Risk period (1 to 7 days)												
VTE (main analysis)	15.30 [8.33 - 28.09]	17	969	7.75 [4.73 - 12.71]	20	2,656	9.39 [5.84 - 15.11]	21	2,769	8.40 [4.43 - 15.93]	12	1,966
VTE exclude death case (Sensitivity 1)	15.30 [8.33 - 28.09]	17	969	7.75 [4.73 - 12.71]	20	2,656	9.24 [5.69 - 15.00]	20	2,742	8.65 [4.56 - 16.41]	12	1,926
VTE exclude potential indication (sensitivity 2)	15.91 [8.60 - 29.45]	17	906	11.83 [6.13 - 22.82]	12	1,128	6.33 [2.86 - 14.01]	7	1,399	6.11 [2.35 - 15.88]	5	1,337
Extended Risk (8+ days after NSAID start)												

	Medium risk hormonal contraceptives											
	CPRD GOLD			DK-DHR			NLHR			SIDIAP		
Outcome	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time
VTE (main analysis)	5.40 [2.77 - 10.52]	16	5,401	3.79 [2.32 - 6.22]	22	8,794	2.34 [1.45 - 3.78]	27	17,023	5.80 [2.72 - 12.39]	13	10,389
VTE exclude death case (Sensitivity 1)	5.40 [2.77 - 10.52]	16	5,401	3.79 [2.32 - 6.22]	22	8,794	2.30 [1.41 - 3.74]	26	16,871	6.00 [2.80 - 12.84]	13	10,328
VTE exclude potential indication (sensitivity 2)	4.73 [2.30 - 9.71]	13	4,851	4.06 [1.82 - 9.07]	8	2,485	1.54 [0.71 - 3.32]	9	7,773	5.97 [2.28 - 15.60]	8	6,851
Post-exposure (NSAID end to +30 days)												
VTE (main analysis)	2.37 [1.17 - 4.82]	11	3,791	2.84 [1.86 - 4.35]	28	10,719	1.66 [0.96 - 2.86]	15	11,139	3.13 [1.82 - 5.37]	19	8,489
VTE exclude death case (Sensitivity 1)	2.37 [1.17 - 4.82]	11	3,791	2.84 [1.86 - 4.35]	28	10,719	1.71 [0.99 - 2.96]	15	11,019	3.22 [1.88 - 5.54]	19	8,309
VTE exclude potential indication (sensitivity 2)	2.54 [1.24 - 5.20]	11	3,536	2.27 [1.09 - 4.72]	9	4,676	1.34 [0.57 - 3.12]	6	5,771	3.00 [1.50 - 6.03]	11	5,859
Baseline												
VTE (main analysis)	-	40	51,388	-	130	205,002	-	132	187,008	-	73	112,948
VTE exclude death case (Sensitivity 1)	-	40	51,388	-	130	205,002	-	131	186,520	-	72	112,463
VTE exclude potential indication (sensitivity 2)	-	38	47,461	-	59	92,633	-	75	105,351	-	43	68,136

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Table 21. Adjusted IRR of VTE in sensitivity analyses and any NSAIDs use among women used high risk hormonal contraceptives.

	High risk hormonal contraceptives											
	CPRD GOLD			DK-DHR			NLHR			SIDIAP		
Outcome	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time
Pre-exposure (-14 to -1 days)												
VTE (main analysis)	2.29 [0.61 - 8.58]	-	679	3.70 [1.93 - 7.12]	11	3,218	5.12 [3.16 - 8.28]	21	5,922	5.77 [1.62 - 20.50]	-	815
VTE exclude death case (Sensitivity 1)	2.29 [0.61 - 8.58]	-	679	3.70 [1.93 - 7.12]	11	3,218	5.15 [3.18 - 8.33]	21	5,894	5.77 [1.62 - 20.50]	-	815
VTE exclude potential indication (sensitivity 2)	2.51 [0.67 - 9.42]	-	651	8.23 [3.23 - 20.93]	6	1,140	3.53 [1.67 - 7.49]	8	3,223	9.33 [1.91 - 45.52]	-	465
Day of exposure												
VTE (main analysis)	0.00 [0.00 - Inf]	-	50	14.47 [4.50 - 46.57]	-	241	20.24 [8.82 - 46.48]	6	436	30.30 [3.99 - 230.28]	-	63
VTE exclude death case (Sensitivity 1)	0.00 [0.00 - Inf]	-	50	14.47 [4.50 - 46.57]	-	241	20.35 [8.86 - 46.73]	6	434	30.30 [3.99 - 230.28]	-	63
VTE exclude potential indication (sensitivity 2)	0.00 [0.00 - Inf]	-	48	37.68 [8.67 - 163.72]	-	83	12.43 [3.01 - 51.28]	-	235	64.24 [7.96 - 518.33]	-	35
Main Risk period (1 to 7 days)												
VTE (main analysis)	15.10 [5.77 - 39.48]	9	338	12.29 [7.02 - 21.51]	17	1,627	12.29 [7.82 - 19.32]	25	3,013	14.96 [4.23 - 52.87]	-	398
VTE exclude death case (Sensitivity 1)	15.10 [5.77 - 39.48]	9	338	12.29 [7.02 - 21.51]	17	1,627	12.35 [7.86 - 19.42]	25	2,999	14.96 [4.23 - 52.87]	-	398
VTE exclude potential indication (sensitivity 2)	14.72 [5.45 - 39.73]	8	324	14.49 [5.30 - 39.67]	5	547	8.97 [4.51 - 17.81]	10	1,628	0.00 [0.00 - Inf]	-	216
Extended Risk (8+ days after NSAID start)												

	High risk hormonal contraceptives											
	CPRD GOLD			DK-DHR			NLHR			SIDIAP		
Outcome	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time	IRR (95%CI)	Number events	Person time
VTE (main analysis)	3.46 [1.00 - 12.04]	5	1,511	6.02 [3.50 - 10.37]	24	5,486	4.60 [3.03 - 7.00]	44	20,560	22.58 [6.42 - 79.48]	5	1,531
VTE exclude death case (Sensitivity 1)	3.46 [1.00 - 12.04]	5	1,511	6.02 [3.50 - 10.37]	24	5,486	4.61 [3.03 - 7.01]	43	19,647	22.58 [6.42 - 79.48]	5	1,531
VTE exclude potential indication (sensitivity 2)	3.67 [1.05 - 12.87]	5	1,503	3.04 [0.84 - 11.09]	-	1,526	4.40 [2.47 - 7.82]	20	8,158	25.77 [4.44 - 149.66]	-	1,061
Post-exposure (NSAID end to +30 days)												
VTE (main analysis)	1.48 [0.40 - 5.46]	-	1,252	3.70 [2.17 - 6.30]	19	6,286	3.35 [2.19 - 5.13]	29	12,175	3.83 [0.97 - 15.10]	-	1,502
VTE exclude death case (Sensitivity 1)	1.48 [0.40 - 5.46]	-	1,252	3.70 [2.17 - 6.30]	19	6,286	3.37 [2.20 - 5.15]	29	12,145	3.83 [0.97 - 15.10]	-	1,502
VTE exclude potential indication (sensitivity 2)	1.58 [0.42 - 5.92]	-	1,222	2.99 [1.00 - 8.91]	-	2,222	3.43 [1.94 - 6.05]	16	6,753	1.31 [0.12 - 14.39]	-	855
Baseline												
VTE (main analysis)	-	15	10,597	-	68	101,862	-	118	200,023	-	9	15,651
VTE exclude death case (Sensitivity 1)	-	15	10,597	-	68	101,862	-	117	198,778	-	9	15,651
VTE exclude potential indication (sensitivity 2)	-	14	10,333	-	26	45,591	-	67	112,673	-	6	11,458

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13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were be 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).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

14. DISCUSSION

14.1 Key results

In this multinational observational study, we first assessed the utilisation of NSAIDs among women aged 15 -49 used low-, medium, and high-risk HC. We observed that among women who were prescribed/ dispensed NSAIDs during HC, most only had one prescription/ dispensation of diclofenac, ibuprofen, or naproxen for a short treatment period of less than a month. Most women initiating prescription NSAIDs while on HC did not have a record of any potential indication for NSAID therapy which were also risk factors for VTE.

We applied the SCCS method to assess the association between NSAIDs use and VTE events among women using HC. We observed a positive association with VTE during NSAIDs exposure risk period. However, we also observed a counterintuitive positive association in the 2 weeks prior to NSAID initiation, and in most scenarios a remaining association in the post-exposure period after NSAID therapy cessation. Additionally, we observed a similar association in VTE risk before and during use of paracetamol, pre-defined by protocol as a negative control exposure. All our findings in the present study were consistent across four European databases, including nationwide linked health data from two Scandinavian countries (Denmark and Norway), primary care data from the UK, and primary care linked to hospital data from Catalonia, Spain.

Similar findings were seen for the association between individual NSAID ingredients under study (diclofenac, ibuprofen, and naproxen), albeit with wider confidence intervals due to reduced power. Similarly, the results for the association with individual thromboembolic events (DVT, PE) were in line with the main findings for the composite outcome (VTE), again with wider uncertainty due to smaller numbers of participants in the SCCS analyses.

Finally, two pre-specified sensitivity analyses reached similar conclusions as the main, confirming the robustness of our findings.

14.2 Limitations of the research methods

Misclassification in exposures of both NSAIDS and hormonal contraception is a general limitation in observational studies using routinely collected health data. Prescriptions and/or purchases of hormonal contraception differs from country to country. In Denmark and Norway, HC are only available through prescription. Conversely, in the UK, over-the-counter progestogen-only contraceptive pills became available in July 2021, classified as low VTE risk contraceptives. Apart from OTC use, contraceptives can also be prescribed in Sexual Health Clinics, therefore we might not be able to capture this information in the UK GP data (CPRD) available to us. In the latest NHS report of Sexual and Reproductive Health Services (Contraception), (11) the number of women using contraception services through the Sexual and

Reproductive Health Services (SRH) has decreased by half during the previous ten years. While no explanation was provided in the reports, the impact of decreased use through SRH could lead by either increased use through GP, or OTCs. In a previous study using the UK CPRD data to estimate the risk of VTE and oral contraceptives, the authors reported similar age-standardised rates of HC exposure as compared to survey data from the Office for National Statistics. (12). In Spain, only specific types of HC are included and reimbursed, while most HCs are purchased as OTC. For example, only since 2023, the long-acting reversible contraceptives for women and people who can get pregnant up to the age of 29 were included in the universal health care. Before that, HCs were only reimbursed (and therefore seen in the data) in Spain for women with additional indications, e.g. hyper- or dys-menorrhoea, hirsutism, polycystic ovaries, etc. Therefore, there is overall less risk of misclassification of use of HCs compared to NSAIDs. However, it is expected that misclassification of HC use could be higher for Spanish data compared to UK and best in Scandinavian data.

In the SCCS design, we only use observed data that include individuals who used HC and experienced both exposure and event and for whom data is available/captured. If some people experienced the event but weren't captured in the data, they won't be included in the analysis. Therefore, the misclassification of HC shouldn't bias the SCCS results, because SCCS is designed to compare time periods within the same individual. Our findings were remarkably consistent across all 4 databases, reassuring us on the potential impact of HC use misclassification in our SCCS analyses. However, the incomplete capture of HC use might affect the generalisability of the study results to the population group whose HC use was not captured in electronic health records or registries data.

NSAIDs like ibuprofen are commonly purchased (although at lower doses) as over the counter (OTC) in many countries. Misclassification of the NSAIDs exposure exists that during the "baseline" period, women could potentially be exposed to low-dose (OTC) NSAIDs, which would bias the effect estimates towards the null. However, misclassification may be less likely for diclofenac and naproxen, as diclofenac tablets are not available over the counter, and naproxen is only available OTC in limited pack sizes (maximum 20 tablets). In contrast, misclassification of paracetamol use is expected to be substantial, as it is widely available over the counter in large quantities without a prescription. This potential differential exposure misclassification may limit the appropriateness of paracetamol as a negative control, as it could underestimate actual exposure and bias comparisons with prescription-only NSAIDs.

In this study, we included only the first event of VTE. While this approach could solve the potential violation of event recurrence independence assumptions in SCCS, this decision in our study design limited our ability to estimate the risk of recurrent VTEs.

With the SCCS design, we assume that apart from the effect of age and seasonality, the baseline risk of DVT during the use of HC is constant. However, previous studies on HC have shown that the risk of VTE was higher during early stages after initiation, and decreased over time.(13,14) In the current study, we found that use of continuous HC episode had median length of around 1 year.

Our SCCS design adjusted for time-fixed confounding by indication. However, time-variable confounding remains a challenge. Due to the scarcity of recording of NSAID indications that are also risk factors of VTE in all 4 databases, we had a limited ability to adjust for time-varying confounding by indication. Some of the common indications for NSAIDs in young women similar to our participants include conditions that are known to increase VTE risk, like COVID-19, other viral infections, trauma/fracture, and surgery. To assess residual/unmeasured confounding, we used paracetamol as the negative control exposure, and observed a similar association in VTE risk before and during use of paracetamol, suggested the observed excess risk (increased IRR) between NSAIDs and VTE is subjected to confounding, highlighted the importance of using negative controls is observational study.

In the current study, the precision of our estimates was affected by the relatively few event/exposures contributing to the analysis. Although point estimates showed elevated IRR, the 95%CIs of some IRR were very wide and crossed the null.

Our study is based on routinely collected health data, also known as Real World Data (RWD). Despite many strengths, one key limitation of RWD is the lack of validation of individual events. Many previous studies have shown the high validity of VTE in all the contributing data sources. For example, validation studies of circulatory system disease including VTE showed 84-85% of cases identified from CPRD data had confirmed diagnosis.(15,16) Validation study with the Danish national patient registry data showed positive predictive value of 75% for VTE diagnoses coded at wards.(17)

14.3 Interpretation

In this study, we applied the SCCS method to assess the association between NSAIDs use and VTE events among women using HC. We observed a positive association of VTE during the 14 days before NSAID use, peaking on the day of NSAID initiation, to then decline in the first and subsequent weeks of NSAID use. The observed positive association remained observable in most scenarios during the 30-days after NSAID therapy cessation. Additionally, we observed similar patterns of positive association before, during and after the use of paracetamol, pre-defined per protocol as a negative control exposure.

While multiple studies have assessed the risk of VTE and use of HC or NSAIDs separately (1–3,18), very few studies have focused on the association between concomitant use of NSAIDs and HC and the risk of VTE events. Meaidi and colleagues recently reported on a nationwide historical cohort study of women of reproductive age (15-49 years) in Denmark during 1996-2017 using linked nationwide registries.(4) The study included over two million women, of whom 529,704 used NSAIDs while using hormonal contraception. In our study, we included the same Danish registries (mapped to the applied database DK-DHR) in the study period of 2014 -2023, and identified 183,586, 141,293, and 42,542 women who used any NSAIDs during low-, medium, and high-risk HC.

Follow-up time was then classified as NSAIDs use, HC use, concomitant use, and not use (of either HC or NSAIDs). Confounding control was conducted by censoring during the occurrence of temporary confounding factors. Time during pregnancy and six months after delivery or 12 weeks after other pregnancy terminations, eight weeks following hospital discharge, and eight weeks from the date of redemption of a prescription for tranexamic acid was censored. The analysis also adjusted for the following factors in the model: age, calendar time, educational level, hypertension, diabetes, polycystic ovary syndrome, endometriosis, migraine, systemic connective tissue disorders, and inflammatory polyarthropathies.

That previous study reported that use of NSAIDs alone was associated with a 7-fold increased incidence rate ratio of VTE compared to time when women not using either NSAIDs or HC. Additionally, the authors reported that, as compared to only using HC, contaminant use of NSAID and HC was associated with 11-fold excess incidence rate of VTE in women using high risk HC, an 8-fold increase in incidence rate when using medium risk HC, and a 4.5-fold increased incidence rate in users of low/no risk HC. There are some limitations that should be considered when interpreting these findings. First, the study design of comparing to “no medication use” time was essentially a historical comparison method, with suboptimal control for confounding by indication. Previous methodological research has shown that this lack of adjustment in historical cohort analyses leads to high type 1 error, with a high rate of false positive safety signals.(19,20) Secondly, while the authors censored follow-up time to control for confounding such as pregnancy and surgery-related hospitalisation, other major risk factors of VTE such as fracture, smoking, viral infection or obesity were not accounted for. Besides, during the censored follow-up time, over 2,000 events were excluded. These censoring could be informative as the exposure status of NSAID, and HC was unclear, which could increase the risk of selection bias. No specific efforts were made to identify or quantify the

potential impact of residual confounding. Incorporating approaches such as quantitative bias analysis or negative control exposure/outcome analyses—as recommended in the ENCePP methodological guidelines—could have provided additional insights into the robustness of the findings.(21)

In our study, we used a self-controlled design to assess within-individual associations between NSAID use and VTE. By design, the SCCS method accounts for time-fixed confounding by using the same person with an event (case) as their own control.(9) We further included VTE risk factors as time-varying covariates and adjusted for them in the adjusted SCCS models. Our analyses showed a positive association with VTE in all five pre-defined periods compared to periods when women used only HC, with the highest association observed on the day of NSAID initiation. In a sensitivity analysis where we excluded women with VTE events following a potential indication for NSAID use, 11%–50% of individuals were excluded from each database. Despite this, the resulting estimates followed a similar pattern to the main analysis.

We conducted the current study by three pre-defined HC groups by their risk of VTE as defined in previous literature: the high-risk HC included combined hormonal contraception of transdermal patch, vaginal ring, and oral tablets containing 50 µg ethinyl oestradiol. The medium-risk group included oral combined hormonal contraceptives with less than 50 ug ethinyl oestradiol or estradiol in combination with the progestins etynodiol, quingestanol, lynestrenol, megestrol, norethisterone, norgestrel, levonorgestrel, medroxyprogesterone, norgestimate, norelgestromin, nomegestrol, chlormadinone or dienogest, and medroxyprogesterone injection. The low-risk HC group included progestin only contraceptive, including oral, implant, and intrauterine devices. (1) Results from the SCCS analyses showed that the estimated IRRs were numerically higher during the periods of NSAID use among the medium- and high-risk HC group in most databases. However, we also observed similar patterns of elevated IRRs during the pre- and post-NSAID exposure windows within each of the HC group. These results suggested that the association between NSAID use and VTE might be modified by type of HC, highlighted the necessity of stratifying the analysis by HC risk-group.

Risk of VTE could also increase after viral infections including COVID-19.(22,23) In the current study, we used clinical as well as data-driven methods to characterise the cohort of women who used NSAIDs during HC. During the 30 days before NSAID use, pain including joint pain, as well as infectious disease/ viral infection were observed in some women.

In the current study, we also included paracetamol as a negative control exposure and observed a similar pattern of elevated IRR of the same magnitude as those detected in association with NSAIDs, suggesting the presence of residual confounding by indication. While we assume that there is no association between paracetamol use and VTE, some previous studies have suggested that paracetamol could increase cardiovascular risk through cyclooxygenase-2 inhibition.(24) However, there is no evidence on the association between paracetamol use and VTE. In a cohort analysis using data from the Women's Health Study (1993–2012) in the United States, Kinsey and colleagues reported an increased risk of VTE associated with NSAID use, but this association was null or attenuated when compared with paracetamol use.(18) The authors concluded that the observed increased VTE risk in observational studies may partly reflect differences in baseline risk among individuals requiring analgesics. However, drug use information in that study was self-reported based on annual surveys, potentially introducing recall bias and exposure misclassification. In the current study, we were able to define NSAID/paracetamol exposure based on prescription records, which allowed us to better capture the time of NSAID (and paracetamol) use.

14.4 Generalisability

In this study, we included women who used HC and NSAIDs identified through electronic health records or health registries. We were not able to capture those obtaining HC and/or NSAIDs over the counter. This could limit the generalisability of our findings, particularly for countries like Spain, where most hormonal

contraception is purchased OTC. However, our results were consistent across all 4 contributing databases, suggesting that any attributable risk/s is consistent across the study population.

15. CONCLUSION

In this study, with a SCCS analysis, we observed a positive association with VTE during any oral NSAIDs exposure risk period. However, we also observed a counterintuitive positive association in the 2 weeks prior to NSAID initiation, and in most scenarios a remaining association in the post-exposure period. Additionally, we observed a similar association in VTE risk before and during use of paracetamol, pre-defined by protocol as a negative control exposure. All these findings were consistent across four large databases from different parts of Europe.

Our results suggest that protopathic bias and residual unmeasured confounding may explain the observed association between NSAID use and VTE risk in women taking HC in this study. We observed the lack of recording of indication (for NSAIDs) in any of the contributing datasets, which limited our ability to adjust for it during our analyses. However, we cannot rule out the possibility that part of the observed excess risk may be directly linked to NSAID use.

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17. ANNEXES

Not applicable.