

DARWIN EU - Non-steroidal anti-inflammatory drug and venous thromboembolism among women 15-49 years using hormonal contraceptives: population based self-controlled case series study from four European countries

Xintong Li¹, postdoctoral epidemiologist Xintong.li@ndorms.ox.ac.uk

Yuchen Guo¹, postdoctoral data scientist yguo.mimi@gmail.com

Xihang Chen¹, research assistant xihang.chen@ndorms.ox.ac.uk

Dr. Albert Prats-Urbe¹, Senior Clinical Research Fellow albert.prats-uribe@ndorms.ox.ac.uk

Anna Saura-Lazaro¹, Senior Researcher anna.sauralazaro@ndorms.ox.ac.uk

Agustina Giuliodori², Postdoctoral Researcher agiuliodori@idiapjgol.org

Anna Palomar-Cros², Postdoctoral Researcher apalomar@idiapjgol.org

Antonella Delmestri¹, lead health data scientist antonella.delmestri@ndorms.ox.ac.uk

Elvira Bräuner³, senior advisor ELVB@dkma.dk

Hedvig Nordeng^{4,5}, Professor h.m.e.nordeng@farmasi.uio.no

Irene López² PhD student ilopez@idiapjgol.org

Nhung TH Trinh⁴, senior researcher nthtrinh@uio.no

Saeed Hayati⁴, data scientist saeedha@uio.no

Susanne Bruun³, statistical programmer sbru@dkma.dk

Talita Duarte Salles^{2,6}, professor tduarte@idiapjgol.org

Martí Català Sabaté¹, Senior Researcher, marti.catalasabate@ndorms.ox.ac.uk

Daniel Prieto-Alhambra^{1,6}, Professor daniel.prietoalhambra@ndorms.ox.ac.uk

1. Health Data Sciences (HDS), Translational Sciences, Botnar Research Centre, University of Oxford, Oxford, UK.

2. Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)

3. Danish Medical Agency

4. Pharmacoepidemiology and Drug Safety Research Group, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway

5. Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway

6. Department of Medical Informatics, Erasmus University Medical Center

Background

Venous thromboembolism refers to the formation of a blood clot in a deep vein and is a potentially preventable cause of morbidity and mortality in women of reproductive age. 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. [1]

The use of non-steroidal anti-inflammatory drugs (NSAIDs) has also been linked to increased venous thromboembolism risk. NSAID use has been associated with a 1.5- to 2-fold increased risk of venous thromboembolism compared to non-users, with some studies indicating higher risks for specific agents such as diclofenac.[2]

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. [3] 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. The current study was commissioned via the Data Analysis and Real World Interrogation Network (DARWIN EU®)[4]. We therefore aimed to estimate the association between oral NSAID use and the incidence of venous thromboembolism among women aged 15-49 years on hormonal contraceptives.

Methods

We conducted a multinational self-controlled case-series study using routinely collected data from four European countries: the UK (Clinical Practice Research Datalink, CPRD GOLD)[5], Denmark (Danish Data Health Registries, DK-DHR)[6], Spain (the Information System for the Development of Research in Primary Care, SIDIAP)[7], and Norway (Norwegian Linked Health Registry data, NLHR)[8], all mapped to OMOP CDM. Women aged 15–49 years using HCs during 2014-2024 were included. The study population included women aged 15-49 years, using hormonal contraceptives at any point in the study period, with no history of venous or arterial thromboembolism, cancer (except non-melanoma skin cancer), thrombophilia, hysterectomy, bilateral oophorectomy, sterilisation, or infertility treatment before using hormonal contraceptives. The exposure of interest was concurrent use of oral NSAIDs during HCs. Use of paracetamol served as a negative control exposure.

We categorised person-time exposed to hormonal contraceptives into six intervals based on concomitant NSAID exposure: baseline (only exposed to hormonal contraceptives); pre-exposure to NSAIDs (2 weeks before starting NSAIDs, during exposure to hormonal contraceptives); NSAID initiation (first day of concomitant

hormonal contraceptive and NSAID use); main risk period (the first 7 days of concomitant hormonal contraceptive and NSAID use, extended risk period (day 8 to end of concomitant hormonal contraceptives and NSAIDs); and post-exposure to NSAIDs (30 days after stopping NSAIDs while still using hormonal contraceptives)[9]. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for deep vein thrombosis, pulmonary embolism, and composite VTE before, during, and after NSAIDs use, compared with HC use alone.

Results

Over 3 million women using hormonal contraceptives were included. Across all databases, IRRs increased before NSAID exposure, peaked on the day of initiation, remained elevated during use, and declined after exposure.

In Denmark, among women using high VTE risk HCs, IRRs were 3.70 (95% CI 1.93–7.12) before exposure, 14.47 (4.50–46.57) on the day of initiation, 12.29 (7.02–21.51) in the first week, 6.02 (3.50–10.37) during subsequent use, and 3.70 (2.17–6.30) after exposure. Similar patterns were observed in Norway (5.12 [3.16–8.28], 20.24 [8.82–46.48], 12.29 [7.82–19.32], 4.60 [3.03–7.00], and 3.35 [2.19–5.13], respectively), Spain (5.77 [1.62–20.50], 30.30 [3.99–230.28], 14.96 [4.23–52.87], 22.58 [6.42–79.48], and 3.83 [0.97–15.10]), and the UK (2.29 [0.61–8.58], 15.10 [5.77–39.48], 3.46 [1.00–12.04], and 1.48 [0.40–5.46]).] Similar findings were observed across NSAID types (ibuprofen, diclofenac, naproxen), HC subgroups, and sensitivity analyses.

Notably, paracetamol (negative control) showed similar risk patterns, magnitudes, and statistical significance across all time windows and databases. (Figure 1)

Conclusion

The elevated risk observed before and on the day of NSAID initiation, mirrored by the negative control paracetamol, suggests that the association is likely driven by NSAID indication rather than a causal medication. Although a small causal effect cannot be excluded, these findings suggest that concurrent use of NSAIDs and HCs does not substantially increase VTE risk beyond the underlying clinical factors.

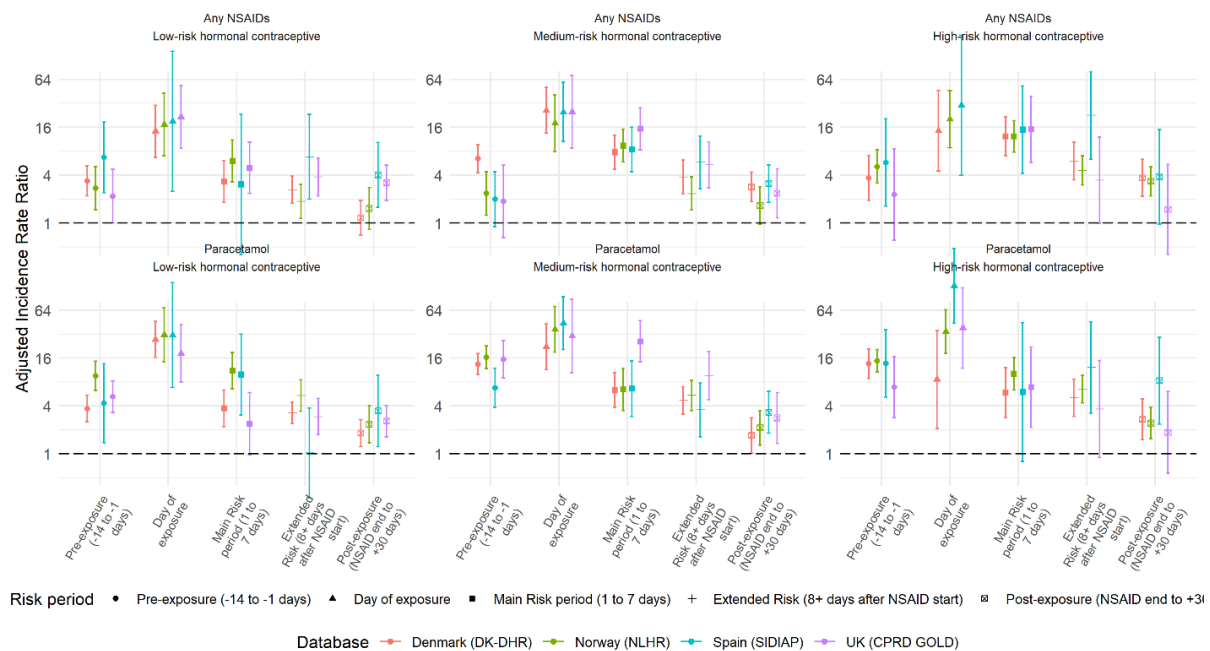


Figure 1. Adjusted incidence rate ratios (IRRs) of venous thromboembolism (VTE) during each pre-defined period of any NSAID (top panel) or paracetamol (bottom panel) use: pre-exposure, day of exposure, main risk period, extended risk period, and post-exposure period, for women using low-risk (left), medium-risk (middle), and high-risk (right) hormonal contraceptives (HC).

References

- 1 Pfeifer S, Butts S, Dumesic D, *et al.* Combined hormonal contraception and the risk of venous thromboembolism: a guideline. *Fertil Steril.* 2017;107:43–51.
- 2 Ungprasert P, Srivalli N, Wijarnpreecha K, *et al.* Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism: a systematic review and meta-analysis. *Rheumatology (Oxford).* 2015;54:736–42.
- 3 Meaidi A, Mascolo A, Sessa M, *et al.* Venous thromboembolism with use of hormonal contraception and non-steroidal anti-inflammatory drugs: nationwide cohort study. *BMJ.* 2023;e074450.
- 4 Home. 2025. <https://www.darwin-eu.org/> (accessed 4 November 2025)
- 5 Sanchez-Santos MT, Axson EL, Dedman D, *et al.* Data resource profile update: CPRD GOLD. *Int J Epidemiol.* 2025;54. doi: 10.1093/ije/dyaf077

- 6 Danish health data registries.
<https://catalogues.ema.europa.eu/node/1145/administrative-details> (accessed 28 July 2025)
- 7 Raventós B, Fernández-Bertolín S, Aragón M, *et al.* Transforming the Information System for research in Primary Care (SIDIAP) in Catalonia to the OMOP Common Data Model and its use for COVID-19 research. *Clin Epidemiol.* 2023;15:969–86.
- 8 Trinh NT, Houghtaling J, Bernal FL, *et al.* Harmonizing Norwegian registries onto OMOP common data model: Mapping challenges and opportunities for pregnancy and COVID-19 research. *Int J Med Inform.* 2024;191:105602.
- 9 Bykov K, Li H, Kim S, *et al.* Drug-drug interaction surveillance study: Comparing self-controlled designs in five empirical examples in real-world data. *Clin Pharmacol Ther.* 2021;109:1353–60.