

Supplementary Tables

Table A: Nationwide data sources used and definitions of variables of interest.

Variables	Data source	Period	Classification	Definition
Exclusion/Censoring criteria				
Any venous thromboembolism	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	G951F, H348E, H348F, I26, I636, I676, I8001-9, I81-2, O032, O037, O042, O047, O072, O077, O082, O223, O225, O882, O871, O873, 28944, 321, 37703, 450, 45100, 45108-9, 45190, 45192, 45199, 452-3, 59323, 671, 67399
Any arterial thrombosis				G951G, H341A, H341B, I21, I240, I513, I630-5, I638, I639, I64, I74, K550C, K550H, N280A, N280, 37702, 410, 433-4, 444
Cancer, except non-melanoma skin cancer				C, 14-20 - except C44, 173
Thrombophilia				D685, D686
Hysterectomy	The Danish National Patient Registry	1977-2017	The Danish Classification of Surgical Procedures & The Nordic Medico-Statistical Committee Classification of Surgical Procedures	KLCC10, KLCC11, KLCC20, KLCD, 61000, 61020, 61040, 61050, 61100, 72110, 72230, 72650
Bilateral oophorectomy				KLAE2, KLAFF1, 60120, 60121, 60320, 70210, 70310
Second unilateral oophorectomy				KLAE, KLAFF0, 60100, 60300, 60101, 70200
Sterilisation				KLG, 60800, 60810, 60820, 60830, 60840
Infertility treatment	The Danish Register of Medicinal Product Statistics	1995-2017	The Anatomical Therapeutic Chemical Classification System	G03G
Confounding factors other than age and calendar time				
Polycystic ovary syndrome	The Danish National Patient Register	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	E282, 25690
Endometriosis				N80, 6253
Hypertension	The Danish Register of Medicinal Product Statistics	1995-2017	The Anatomical Therapeutic Chemical Classification System	C02A, C02B, C02C, C02DA, C02DB, C02DD, C02DG, C02L, C03A, C03B, C03D, C03E, C03X, C07A, C07B, C07C, C07D, C07F, C08, C08G, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Diabetes mellitus	The Danish National Patient Register & The Danish Register of Medicinal Product Statistics	1977-2017 & 1995-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision & The Anatomical Therapeutic Chemical Classification System	A10
Migraine				G43, 346 & N02C
Systemic connective	The Danish	1997-	The International	M3, 446

tissue disorders Inflammatory polyarthropathies	National Patient Register	2017	Classification of Diseases and Related Health Problems, 10th & 8th revision	M05-14, 71
Pregnancy	The Register of Legally Induced Abortions & The Danish Medical Birth Register & The Danish National Patient Register	1973- 2017 & 1973- 2017 & 1977- 2017	The International Classification of Diseases and Related Health Problems, 10th revision	Each observation in the Danish Medical Birth Register and The Register of Legally Induced Abortion included as a pregnancy & O00-8
Surgery	The Danish National Patient Register	1977- 2017	The Nordic Medico- Statistical Committee Classification of Surgical Procedures	Each surgical procedure registered with a hospital stay of ≥ 24 hours
Tranexamic acid	The Danish National Register of Medicinal Product Statistics	1995- 2017	The Anatomical Therapeutic Chemical Classification System	B02AA02
Educational level	The Education Register	1981- 2017	-	Elementary school only, secondary school only, skilled worker, theoretical education, theoretical education with research qualifications
Body-mass index	The Danish Medical Birth Register	2004- 2017	-	Weight in kilogram divided by height in m to power of two: <18.5, 18.5-25, >25-30, >30
Smoking status	The Danish Medical Birth Register	1991- 2017	-	Yes/no

Table B: Hormonal contraception available during the study period

Hormonal contraception	Anatomical Therapeutic Chemical code
High risk of venous thromboembolic event	
<i>Combined products</i>	
Oral	
50 micrograms ethinyl oestradiol	
Norethisterone	G03AA01, G03AA03, G03AA05
Levonorgestrel	G03AA07
20-40 micrograms ethinyl oestradiol	
Desogestrel	G03AA09, G03AB05
Gestodene	G03AA10, G03AB06
Drospirenone	G03AA12
Cyproterone	G03HB01
Patch	
33.9 micrograms ethinyl oestradiol/24 h	
Norelgestromine	G03AA13
Vaginal Ring	
15 micrograms ethinyl oestradiol/24 h	
Etonogestrel	G02BB01
Medium risk of venous thromboembolic event	
<i>Combined products</i>	
Oral	
20-40 micrograms ethinyl oestradiol	
Norethisterone	G03AA01, G03AA05, G03AB04
Levonorgestrel	G03AA07, G03AB03
Norgestimate	G03AA11
Natural oestrogen	
Dienogest	G03AB08
Nomegestrol acetate	G03AA14
<i>Progestin-only</i>	
Injection	
Medroxyprogesterone	G03AC06
Low/no risk of venous thromboembolic event	
<i>Progestin-only</i>	
Oral	
Norethisterone	G03AC01, G03AC02
Levonorgestrel	G03AC03
Desogestrel	G03AC09
Implant	
Etonogestrel	G03AC08
Intrauterine device	
Levonorgestrel	G02BA03

Table C: NSAIDs available during the study period

NSAID	Anatomical Therapeutic Chemical code
Aceclofenac	M01AB16
Celecoxib	M01AH01
Dexibuprofen	M01AE14
Dexketoprofen	M01AE17
Diclofenac*	M01AB05, M01AB55
Etodolac	M01AB08
Etoricoxib	M01AH05
Fenbufen	M01AE05
Fenoprofen	M01AE04
Flurbiprofen	M01AE09
Ibuprofen**	M01AE01, M01AE51
Indomethacin	M01AB01
Ketoprofen	M01AE03
Ketorolac	M01AB15
Lornoxicam	M01AC05
Meloxicam	M01AC06
Nabumetone	M01AX01
Naproxen	M01AE02, M01AE52
Parecoxib	M01AH04
Phenylbutazone	M01AA01
Piroxicam	M01AC01
Rofecoxib	M01AH02
Sulindac	M01AB02
Tenoxicam	M01AC02
Tiaprofenic acid	M01AE11
Tolfenamic acid	M01AG02
Tolmetin	M01AB03

* Diclofenac 12.5 mg tablets were available over-the-counter in 2007-2008

** Ibuprofen 200 mg tablets were available over-the-counter throughout the study period.

Table D: *Exclusion and censoring criteria for a sub-population of “healthy” women*

Variable	Data source	Period of availability	Classification	Definition
<u>Exclusion/Censoring criteria</u>				
Any venous thromboembolism	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	G951F, H348E, H348F, I26, I636, I676, I8001-9, I81-2, O032, O037, O042, O047, O072, O077, O082, O223, O225, O882, O871, O873, 28944, 321, 37703, 450, 45100, 45108-9, 45190, 45192, 45199, 452-3, 59323, 671, 67399
Any arterial thrombosis	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	G951G, H341A, H341B, I21, I240, I513, I630-5, I638, I639, I64, I74, K550C, K550H, N280A, N280, 37702, 410, 433-4, 444
Any cardiovascular disease other than thrombosis	The Danish National Patient Registry & The Danish National Registry of Medicinal Product Statistics	1977-2017 & 1995-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision & The Anatomical Therapeutic Chemical Classification System	(minus the codes for thromboses) I01-99, 391-458 & C
Diabetes mellitus	The Danish National Registry of Medicinal Product Statistics	1995-2017	The Anatomical Therapeutic Chemical Classification System	A10
Cancer	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	C, 14-20
Musculoskeletal disorders	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	M, 71-3
Liver disease	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	K70-7, 570-3
Chronic kidney disease/dialysis	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th revision & The Danish Classification System for Non-Surgical Procedures	N18-9 & BJFD, 92390,92400,94300,94340

Thrombophilia	The Danish National Patient Registry	1994-2017	The International Classification of Diseases and Related Health Problems, 10th revision	D685, D686
Endometriosis	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	N80, 6253
Polycystic ovary syndrome	The Danish National Patient Registry	1977-2017	The International Classification of Diseases and Related Health Problems, 10th & 8th revision	E282, 25690
Thyroid disease	The Danish National Registry of Medicinal Product Statistics	1995-2017	The Anatomical Therapeutic Chemical Classification System	H03
Use of tranexamic acid	The Danish National Registry of Medicinal Product Statistics	1995-2017	The Anatomical Therapeutic Chemical Classification System	B02AA02
Use of anticoagulative medication	The Danish National Registry of Medicinal Product Statistics	1995-2017	The Anatomical Therapeutic Chemical Classification System	B01
Hysterectomy	The Danish National Patient Registry	1977-2017	The Danish Classification of Surgical Procedures & The Nordic Medico-Statistical Committee Classification of Surgical Procedures	KLCC10, KLCC11, KLCC20, KLCD, 61000, 61020, 61040, 61050, 61100, 72110, 72230, 72650
Bilateral oophorectomy	The Danish National Patient Registry	1977-2017	The Danish Classification of Surgical Procedures & The Nordic Medico-Statistical Committee Classification of Surgical Procedures	KLAE2, KLA1, 60120, 60121, 60320, 70210, 70310
Second unilateral oophorectomy	The Danish National Patient Registry	1977-2017	The Danish Classification of Surgical Procedures & The Nordic Medico-Statistical Committee Classification of Surgical Procedures	KLAE1, KLA1, 60100, 60300, 60101, 70200
Use of hormone therapy	The Danish National Registry of Medicinal Product Statistics	1995-2017	The Anatomical Therapeutic Chemical Classification System	G03C, G03F, G03HB01 (only the drug by the product name Climen)
Infertility treatment	The Danish National Registry of Medicinal Product Statistics	1995-2017	The Anatomical Therapeutic Chemical Classification System	G03G

Table E: Use of ibuprofen, diclofenac, and naproxen in the cohort according to drug unit size stratified on hormonal contraception use

	NSAID use only	Concomitant use of NSAID and		
		High-risk hormonal contraception	Medium-risk hormonal contraception	Low/no-risk hormonal contraception
Ibuprofen				
Total no. of person-years	28,586	11,294	5039	4394
	<i>Column percentage of total no. of person-years</i>			
20 mg	0.0	0.0	0.0	0.0
200 mg	3.4	2.6	4.9	5.8
400 mg	44.0	42.5	49.9	47.8
600 mg	52.6	55.4	45.5	46.4
800 mg	2.2	1.7	1.6	2.0
Diclofenac				
Total no. of person-years	11,162	4431	1480	1074
	<i>Column percentage of total no. of person-years</i>			
12.5 mg	6.2	4.3	4.0	6.0
25 mg	0.9	0.7	0.7	0.6
50 mg	64.2	69.0	67.5	60.5
75 mg	9.6	9.0	8.6	11.4
100 mg	19.1	17.0	19.3	22.1
Naproxen				
Total no. of person-years	3426	1266	499	273
	<i>Column percentage of total no. of person-years</i>			
25 mg	0.6	0.3	0.4	0.5
125 mg	0.0	0.0	0.0	0.1
250-375 mg	23.4	21.3	20.2	16.5
500-550 mg	75.9	78.4	78.8	82.8
750 mg	0.4	0.2	0.2	0.3
1000 mg	0.1	0.0	0.0	0.0

Table F: Mode of administration of purchased hormonal contraception according to exposure status

Exposure	No. of Person-Yr	Mode of Administration of Hormonal Contraception				
		Oral	Patch	Vaginal Ring	Injection	Intrauterine system
		<i>Row percentage of total no. of person-years</i>				
Hormonal contraception use only						
High-risk hormonal contraception	4,298,461	97.6	0.3	2.1		
Medium-risk hormonal contraception	1,852,352	98.7			1.3	
Low/no-risk hormonal contraception	1,116,421	20.8				4.9 74.3
Concomitant use of hormonal contraception and NSAIDs						
High-risk hormonal contraception and any NSAID	20,036	97.2	0.4	2.4		
Medium-risk hormonal contraception and any NSAID	8073	97.8			2.2	
Low/no-risk hormonal contraception and any NSAID	6497	5.6				5.0 89.4

Table G: Adjusted incidence rate ratios of venous thromboembolism according to hormonal contraception use only, NSAID use only, and concomitant use of hormonal contraception and NSAIDs with non-use as the reference in the subpopulation of “healthy” women *

Exposure	No. of Person-Yr	No. of Events	Adjusted Incidence Rate Ratio** (95% CI)
Non-use of hormonal contraception and NSAIDs	8,596,336	1085	1.0 (Reference)
Hormonal contraception use only			
High-risk hormonal contraception	2,602,196	1322	5.7 (5.2 to 6.2)
Medium-risk hormonal contraception	1,088,425	382	4.1 (3.6 to 4.6)
Low/no-risk hormonal contraception	348,161	51	1.1 (0.8 to 1.5)
NSAID use only			
Any	17,060	37	15.0 (10.8 to 20.8)
Ibuprofen	9245	19	14.3 (9.1 to 22.5)
Diclofenac	3830	13	22.9 (13.2 to 39.5)
Naproxen	1533	0	-
Concomitant use of hormonal contraception and NSAIDs			
High-risk hormonal contraception and any NSAID	7920	87	111.7 (89.6 to 139.3)
Medium-risk hormonal contraception and any NSAID	3021	13	43.2 (25.0 to 74.6)
Low/no-risk hormonal contraception and any NSAID	1079	<3	13.0 (3.2 to 51.9)

* Exclusion and censoring criteria defined in Table S4

** Adjusted for age, calendar time, and educational level

Table H: Adjusted incidence rate ratios of venous thromboembolism with use of NSAIDs compared to non-use according to hormonal contraception use for different sensitivity analyses.

Exposure	Main analysis*	Only confirmed diagnoses*	Including diagnoses given in the emergency room*	Only 15-39-year-old women*	Sub-population of healthy women only**	NSAID exposure window of 30 days from prescription redemption*
Non-use of NSAIDs and hormonal contraception	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
NSAID use only	7.2 (6.0 to 8.5)	7.9 (6.5 to 9.6)	7.4 (6.4 to 8.7)	7.9 (5.9 to 10.6)	15.0 (10.8 to 20.8)	4.8 (4.4 to 5.4)
High-risk hormonal contraception use only	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
High-risk hormonal contraception and NSAIDs	11.0 (9.6 to 12.6)	11.7 (10.1 to 13.3)	11.0 (9.6 to 12.5)	12.9 (11.0 to 15.1)	19.6 (15.8 to 24.4)	6.4 (5.9 to 7.0)
Medium-risk hormonal contraception use only	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Medium risk hormonal contraception and NSAIDs	7.9 (5.9 to 10.6)	8.9 (6.7 to 12.0)	7.9 (6.0 to 10.2)	7.9 (5.5 to 11.5)	10.5 (6.1 to 18.3)	4.9 (4.0 to 5.9)
Low/no-risk hormonal contraception use only	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Low/no-risk hormonal contraception and NSAIDs	4.5 (2.6 to 8.1)	5.6 (3.1 to 10.3)	4.6 (2.7 to 7.6)	5.5 (2.5 to 12.5)	3.2 (0.8 to 12.7)	2.4 (1.6 to 3.5)

Results from main analysis shown in first column for easier comparison.

Only confirmed diagnoses: Diagnoses given following relevant imaging or followed by prescription redemption of an anticoagulant

* Incidence rate ratios adjusted for age, calendar time, educational level, hypertension, diabetes, polycystic ovary syndrome, endometriosis, migraine, systemic connective tissue disorders, and inflammatory polyarthropathies.

** Only including women without any history of cardiovascular disorder, diabetes, liver disease, chronic kidney disease, endometriosis, polycystic ovary syndrome, migraine, musculoskeletal disorder, cancer, thrombophilia, use of anticoagulants, thyroid disease, use of tranexamic acid, hysterectomy, bilateral oophorectomy, hormone therapy, and infertility treatment (Supplementary Table SD).