WILEY

ENABLING DISCOVERY | POWERING EDUCATION | SHAPING WORKFORCES

Pregnancy and Periodontitis : E-learning

Periodontitis Knowledge Hub

Are you aware of the fact that maintaining optimal oral health is crucial for the mother and the newborn?

Assess your knowledge on pregnancy and periodontitis with our e-learning module for healthcare practitioners, developed by a panel of experts to aid earlier diagnosis and better patient outcomes.

Visit the knowledge hub to access e-learning modules:

Pregnancy & Periodontitis

Cognitive Decline & Periodontitis

Cardiovascular Diseases & Periodontitis

Diabetes & Periodontitis

Access now

This Knowledge Hub is supported by Oral B.

Accepted: 13 June 2022

DOI: 10.1111/1471-0528.17268

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Use of combined oral contraceptives and risk of venous thromboembolism in young women: a nested case–control analysis using German claims data

Tania Schink[1] | **Christina Princk**[1] | **Malte Braitmaier**[2] | **Ulrike Haug**[1,3]

[1]Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany

[2]Department of Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany

[3]Faculty of Human and Health Sciences, University of Bremen, Bremen, Germany

Correspondence
Tania Schink, Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Achterstr. 30, 28359 Bremen, Germany.
Email: schink@leibniz-bips.de

Funding information
Federal Institute for Drugs and Medical Devices (Bundesinstitut fuer Arzneimittel und Medizinprodukte, BfArM), Grant/Award Number: V-18283/68605/2019-2020

Abstract

Objective: To compare the risk of venous thromboembolism (VTE) among young women for nine combined oral contraceptives (COCs), including progestogens with an as yet unclear risk of VTE such as chlormadinone and nomegestrol, using COCs containing levonorgestrel with low ethinylestradiol (<50 µg) as a reference.

Design: Case–control study nested in a cohort of new users of COCs.

Setting: German claims data.

Population: A total of 1166 cases of VTE matched to 11 660 controls nested in a cohort of 677 331 girls and young women aged 10–19 years with one or more COCs dispensed between 2005 and 2017 after a 1-year period without any COCs.

Methods: Confounder-adjusted odds ratios (aORs) of VTE associated with current use of the respective COCs were calculated using conditional logistic regression.

Main outcome measures: Venous thromboembolism (VTE), defined as a diagnosis of pulmonary embolism or deep vein thrombosis.

Results: Compared with levonorgestrel with low ethinylestradiol (<50 µg), the risk of VTE was increased two-fold for COCs containing dienogest (aOR 2.23, 95% CI 1.77–2.80), cyproterone (aOR 2.15, 95% CI 1.43–3.25), chlormadinone (aOR 2.06, 95% CI 1.58–2.68), desogestrel (aOR 1.93, 95% CI 1.44–2.61) and drospirenone (aOR 1.89, 95% CI 1.41–2.55), and increased five-fold for gestodene (aOR 5.05, 95% CI 1.23–20.74). For norgestimate and nomegestrol, the point estimates suggest a two-fold increased risk (aOR 1.90, 95% CI 0.62–5.81) and 40% increased risk (aOR 1.41, 95% CI 0.52–3.81), respectively.

Conclusions: Our study confirms that levonorgestrel with low ethinylestradiol (<50 µg) is the COC associated with the lowest risk of VTE and suggests that for chlormadinone the risk of VTE is two times higher, and thus in the same range as for desogestrel and drospirenone.

KEYWORDS
chlormadinone, combined oral contraceptives, levonorgestrel, nomegestrol, venous thromboembolism

1 | INTRODUCTION

Combined oral contraceptives (COCs), which are widely used by women of childbearing age, are well known to be associated with an increased risk of venous thromboembolism (VTE). Several studies demonstrated that the type of progestogen is one of the key factors determining the risk of VTE. After a critical review of the available evidence, in 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded that levonorgestrel, norethisterone and norgestimate have the lowest risk, with between five and seven VTE events per year in 10 000 women. The risk for etonogestrel and norelgestromin was higher, with between six and 12 VTE events per year in 10 000 women, and the highest risk was observed for drospirenone, gestodene and desogestrel, with between nine and 12 VTE events per year in 10 000 women.[1]

A systematic review and meta-analysis published in 2018 confirmed that COCs containing levonorgestrel had the lowest risk of VTE. COCs containing cyproterone acetate, desogestrel, dienogest, drospirenone or gestodene were associated with a 1.5–2.0-fold increased risk of VTE compared with COCs containing levonorgestrel. For dienogest, however, the results were based on only two studies, only one of which was rated as being of good quality. The review by Dragoman et al. did not include a study on the risk of VTE associated with the progestogens chlormadinone and nomegestrol and, to the best of our knowledge, no such study has been published so far.[2]

To shed further light on this topic, we compared the risk of VTE and its entities deep vein thrombosis (DVT) and pulmonary embolism (PE) for different types of COC in young women based on German claims data using COCs containing levonorgestrel with low ethinylestradiol (<50μg) as reference. Of particular interest were COCs with an as yet unclear risk of VTE, i.e. COCs containing the progestogens chlormadinone and nomegestrol.

2 | METHODS

2.1 | Data source

We used the German Pharmacoepidemiological Research Database (GePaRD), which is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on drug dispensing as well as outpatient (i.e. from general practitioners and specialists) and inpatient services and diagnoses. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented. Diagnoses in GePaRD are coded according to the International Classification of Diseases, 10th revision, German modification (ICD-10-GM).[3]

The suitability of GePaRD for pharmacoepidemiological research has been demonstrated by various types of pharmacoepidemiological studies investigating the risks of medications,[4–8] including a study on the risk of VTE in cancer patients treated with epoetins or blood transfusions.[9] During the study period (2005–2017), COCs were reimbursable in Germany only up to the 20th birthday (i.e. for those aged 19 years or younger), therefore information on COCs in GePaRD is limited to girls and young women.

2.2 | Study design and study population

The study was designed as a case–control analysis nested in a cohort of new users of COCs. The study period started on 1 January 2005 and ended on 31 December 2017. The study cohort included all girls and young women between 10 and 19 years of age with at least one COC dispensed during the study period after a 1-year period without any dispensing ('new users'). The following exclusion criteria were applied: (i) less than 1 year of continuous insurance before the first dispensing of a COC found in the database; (ii) a previous diagnosis of DVT or PE any time before entry to the cohort; (iii) a diagnosis of cancer in the 3 years before entry to the cohort; and (iv) pregnancy in the 3 months before entry to the cohort. Entry to the cohort was defined as the date of dispensing of a COC when all inclusion and exclusion criteria were fulfilled. Exit from the cohort was defined as the first of the following dates: (i) occurrence of VTE (DVT/PE); (ii) start of pregnancy; (iii) diagnosis of cancer; (iv) end of the year when the cohort member turned 19 years of age; (v) end of insurance (including death); or (vi) end of the study period, i.e. 31 December 2017.

2.3 | Definition of cases and controls

Venous thromboembolism was defined as a diagnosis of PE (ICD-10-GM code I26.-) or DVT (I80.1, I80.2, I80.3, I80.81, I80.9, I81 and I82.-, excluding I82.1). For PE only hospital main discharge diagnoses were included, and the date of the PE event (index date) was set to the admission date of the respective hospitalisation. For DVT, outpatient diagnoses were also included if accompanied by the dispensing of an anticoagulant within the same quarter because DVT might also be treated in the outpatient setting only. The date of the DVT event (index date) was set to the admission date of the respective hospitalisation (inpatient diagnosis) or the prescription date of the respective dispensing (relevant to events coded in the outpatient setting only).

For each case, ten controls were matched by statutory health insurance provider and age at index date (±1 year), using risk set sampling with time in cohort as the time axis to ensure the follow-up period was similar to the corresponding case. Eligible controls hospitalised for any reason

at the index date of the case were excluded from the set of potential controls. Cases were eligible to be selected as a control before their index date and controls could be selected more than once.[10]

2.4 | Assessment of exposure

Exposure included all COCs available in Germany during the study period. The COCs dispensed were selected based on the Anatomical Therapeutic Chemical (ATC) Classification System groups G03AA, G03AB, G03HB01, G03FA and G03FB.

In the main analysis, we assumed that a woman started using the respective COC at the dispensing date and did not shorten the 28-day cycle. Thus, the start of the exposure period was set to the dispensing date and the supply was calculated as the number of defined daily doses (DDDs) of the respective dispensing. Exposure at index date was defined as supply overlapping with the index date.

2.5 | Assessment of potential confounding factors

Age, risk factors for VTE, other comorbidities, potential other (off-label) indications, lifestyle factors and co-medication were assessed at baseline (with appropriate review periods) as potential confounding factors or effect modifiers (as far as available in claims data). Co-medication was additionally assessed on index date. Educational attainment was used as a proxy for socio-economic status (SES) and overall health awareness. In Germany, family members with no income of their own (e.g. students) are insured with one of their parents (i.e. the main insurant). As the girls/young women in the cohort probably had not yet received their final degree and their behaviour was probably (still) influenced by the SES of their parental home, the educational attainment of the main insurant was used preferentially; for details, see Table S1.

2.6 | Statistical analysis

In the main analysis, Confounder-adjusted odds ratios (aORs) of VTE, as well as DVT and PE, associated with the current use of the respective progestogen were calculated using conditional logistic regression and levonorgestrel with low ethinylestradiol (<50 µg) as a reference.

To assess potential effect modification, analyses were additionally stratified by age (≤17 years vs >17 years), SES (no formal degree/degree unknown vs basic secondary degree vs further education), diagnosis of obesity, diagnosis of chronic comorbidity, acute infection, immobilisation at index date and ethinylestradiol content (<30 µg, 30 µg, >30 µg).

To assess the robustness of our results, we conducted the following sensitivity analyses:

1. excluding girls/young women with a history of anticoagulant use or anticoagulant use on index date, as this might indicate a previous history or higher risk of VTE;
2. excluding girls/young women with codes for oophorectomy, hysterectomy or sterilisation, which are common exclusion criteria in other studies;
3. excluding girls/young women with codes for selected chronic or acute comorbidities increasing the risk of VTE and immobilisation, to restrict the analysis to 'idiopathic' cases;
4. not considering cases diagnosed more than 90 days after entry to the cohort, to analyse the risk within the first 90 days of starting COCs.

Additional sensitivity analyses were performed to assess the impact of potential misclassification of exposure as girls/young women may not have started exposure at the dispensing date or may have shortened the recommended 28-day cycle by skipping the 7-day break. In these analyses, the following additional criteria were used to classify girls/young women as being exposed:

- index date had to be 28 days or more after dispensing date (to account for potential delay in starting);
- supply had to overlap the index date by 14 days or more (to account for potential shorter cycles, which would result in an overestimation of the duration of supply).

To assess the potential impact of the confounding factor 'smoking', which is hardly captured in claims data, on the association between COCs and VTE a bias analysis was performed. Based on the method proposed by Greenland,[11] expanded to exposures with more than two groups, externally adjusted odds ratios of the association between COCs and VTE were estimated for a range of values regarding the prevalence of smoking. For these analyses, we assumed that the prevalence of smoking in the target population was about 16.6%.[12] To mimic various scenarios for differential prevalence of smoking between exposure groups, we multiplied this value by 0.5, 0.75, 1.25 and 1.5 for the reference group (levonorgestrel with ethinylestradiol) and calculated the resulting prevalence in the other exposure groups, so that the overall prevalence of 16.6% remained. The strength of the association between smoking and the occurrence of VTE in the target population was assumed to be 1.3.[13]

3 | RESULTS

Between 1 January 2005 and 31 December 2017, 1 005 809 girls and young women aged between 10 and 19 years with at least one COC dispensed were identified in GePaRD. Of those, 228 713 (22.7%) were excluded as they had fewer than 365 days of continuous insurance before entry to the cohort, 96 935 (9.6%) did not have a 1-year period without a COC being dispensed, 405 (0.04%) had a previous history of VTE,

477 (0.05%) had a diagnosis of cancer in the 3 years before entry to the cohort and 1948 (0.2%) were pregnant in the 3 months before entry to the cohort.

Thus, 677 331 girls and young women were finally included in the new user cohort. Among those, 1166 cases of VTE (969 DVT and 213 PE, and 16 girls/young women had both a DVT and PE on the same day) occurred during the study period. The median age of cases was 18 years. All cases could be matched to ten controls. Further characteristics of cases and controls are presented in Table 1.

No cases of VTE were observed during current use of norelgestromin or norethisterone. For all other progestogens, an increased aOR of VTE was observed, compared with levonorgestrel with low ethinylestradiol (<50 µg) as reference (Table 2). The highest aOR was observed for gestodene (aOR 5.05, 95% CI 1.23–20.74). Current use of a COC containing chlormadinone was associated with a 2.06-fold increased risk of VTE (95% CI 1.58–2.68) and current use of nomegestrol was associated with an increased risk of 1.41 (95% CI 0.52–3.81).

The aORs for the effect of current use of individual progestogen on DVT were similar to those for VTE, whereas the aORs regarding PE tended to be higher (Figure 1).

Stratified analyses did not suggest effect modification by age, diagnosis of an acute infection or immobilisation/recent trauma (Figure S1). The aORs were, however, higher in girls and young women with lower SES, compared with those with higher SES, and in girls and young women with a diagnosis indicating obesity, compared with girls and young women without such a code. In girls and young women with diagnostic codes indicating a chronic comorbidity, aORs were lower than in those without such codes. Confidence intervals, however, overlapped between strata.

Table S2 presents aORs of VTE stratified by the quantity of ethinylestradiol. In our study the majority of progestogens were predominantly combined with low ethinylestradiol content and their aORs were similar in the main and stratified analyses. For norgestimate, however, which in our study was always combined with ethinylestradiol >30 µg, the risk was no longer elevated (aOR 1.02, 95% CI 0.16–6.39) when ethinylestradiol content was taken into account (Table S2). Sensitivity analyses showed that aORs for individual progestogens did not change after the exclusion of girls and young women who used anticoagulants on the index day (7.2%) or who had a previous oophorectomy, hysterectomy or sterilisation (0.7%) (Figure 2). Risk of VTE for the more commonly used progestogens was higher in idiopathic cases, i.e. cases without a diagnosis of a risk factor of VTE (20.8%). Only 12.5% of the VTE cases occurred in the first 3 months after entry to the cohort and the respective aORs were lower. Confidence intervals, however, overlapped with those of the main analysis.

Sensitivity analyses regarding exposure showed that aORs tended to be higher if we accounted for a potentially later start of exposure than the dispensing date (Figure S2) and were comparable with the main analysis when accounting for a potential shortening of the 28-day cycle.

TABLE 1 Characteristics of cases and controls

	Cases	Controls
	n = 1166	*n* = 11 660
Age at index day (years)		
Mean (±SD)	17.63 (1.24)	17.55 (1.16)
Median (Q1–Q3)	18 (17–19)	18 (17–18)
Min.–max.	13–19	12–19
Socio-economic status[a]		
Further education	431 (36.96%)	4257 (36.51%)
Basic secondary degree	618 (53.00%)	6182 (53.02%)
Degree unknown or no formal degree	117 (10.03%)	1221 (10.47%)
Comorbidity		
Coronary heart disease[b]	8 (0.69%)	70 (0.60%)
Ischaemic stroke or transient ischaemic attack (TIA)[b]	4 (0.34%)	19 (0.16%)
Hypertension[b,c]	53 (4.55%)	291 (2.50%)
Antihypertensives[c]	21 (1.80%)	135 (1.16%)
Other cardiac disease[b]	158 (13.55%)	969 (8.31%)
Hyperlipidaemia[b,c]	66 (5.66%)	334 (2.86%)
Coagulation disorders[b]	123 (10.55%)	167 (1.43%)
Other blood disease[b]	2 (0.17%)	2 (0.02%)
Diabetes[b]	27 (2.32%)	161 (1.38%)
Antidiabetics[c]	5 (0.43%)	9 (0.08%)
Insulin[c]	7 (0.60%)	42 (0.36%)
Migraine with aura[b]	45 (3.86%)	221 (1.90%)
Inflammatory/autoimmune disease[b]	85 (7.29%)	445 (3.82%)
Asthma/chronic obstructive pulmonary disease (COPD)[b]	240 (20.58%)	2173 (18.64%)
Varicose veins in lower extremities[b]	33 (2.83%)	64 (0.55%)
Chronic kidney disease[b]	8 (0.69%)	34 (0.29%)
Acute infection[d]	615 (52.74%)	5136 (44.05%)
Lifestyle factors		
Obesity[b]	240 (20.58%)	1127 (9.67%)
Smoking[b]	48 (4.12%)	296 (2.54%)
Alcohol abuse[b]	21 (1.80%)	264 (2.26%)
Immobilisation and trauma		
Paresis[d]	17 (1.46%)	43 (0.37%)
Hospitalisation ≥2 nights[e]	235 (20.15%)	481 (4.13%)
Operation[e]	160 (13.72%)	373 (3.20%)
Fractures and traumata[d]	33 (2.83%)	61 (0.52%)
Co-medication		
Antiplatelets and antithrombotics[c]	17 (1.46%)	6 (0.05%)
Acetylsalicylic acid (ASS)[c]	1 (0.09%)	1 (0.01%)
Non-steroidal anti-inflammatory drugs (NSAIDs)[c]	118 (10.12%)	218 (1.87%)

TABLE 1 (Continued)

	Cases	Controls
	n = 1166	*n* = 11 660
Glucocorticoids and other corticoids[c]	11 (0.94%)	28 (0.24%)
Antidepressants[c]	17 (1.46%)	92 (0.79%)
Antipsychotics[c]	10 (0.86%)	21 (0.18%)
Triptanes[c]	0 (0.00%)	4 (0.03%)
Potential other indication		
Acne[b]	564 (48.37%)	5082 (43.58%)
Androgenetic alopecia[b]	5 (0.43%)	60 (0.51%)
Menstrual disorders[b]	916 (78.56%)	8847 (75.87%)
Hirsutism[b]	22 (1.89%)	144 (1.23%)
Endometriosis[b]	4 (0.34%)	31 (0.27%)
Polycystic ovarian syndrome[b]	35 (3.00%)	160 (1.37%)
Exclusion criteria in other studies		
Infertility[f]	7 (0.60%)	45 (0.39%)
Hysterectomy[f]	0 (0.00%)	0 (0.00%)
Ovariectomy[f]	1 (0.09%)	3 (0.03%)

[a]Educational attainment of main insurant.
[b]Diagnosis at any time before or on index day.
[c]Dispensing overlapping with index day.
[d]Diagnosis or procedure in the 180 days before or on the index day.
[e]In the 180 days before or on the index day.
[f]Any time before the index day.

Bias analyses showed that the potential impact of the only partly observed confounding factor 'smoking' is expected to be small. Even a large difference in the proportion of smokers between exposure groups changed the aORs only minimally (Table S3).

4 | DISCUSSION

4.1 | Main findings

Based on a cohort of more than half a million girls and young women initiating the use of a COC, we were able to compare the risk of VTE, and its components DVT and PE, for nine individual progestogens, including chlormadinone and nomegestrol with an as yet unclear risk of VTE. Our study confirms that levonorgestrel with low ethinylestradiol (<50 µg) is the COC with the lowest risk of VTE. Compared with levonorgestrel with low ethinylestradiol (<50 µg), the risk of VTE was increased two-fold for COCs containing chlormadinone, cyproterone, desogestrel, dienogest, and drospirenone, and increased five-fold for gestodene. For norgestimate and nomegestrol, the point estimates suggested a two-fold and a 40% increased risk, respectively, but confidence intervals overlapped the null value of 1, and for norgestimate the aOR was close to 1 when the ethinylestradiol content was considered.

4.2 | Interpretation

To our knowledge, this study is the first to present estimates on the risk of VTE for COCs containing the fourth-generation progestogens chlormadinone and nomegestrol, even though the sample size for nomegestrol was limited. For chlormadinone, we found a risk of VTE in the same range as for the third-generation progestogens desogestrel and drospirenone.

With respect to the third-generation dienogest, evidence has been limited so far.[2] Based on two studies on dienogest (one of which was rated as being of poor quality), Dragoman et al. estimated a 1.5-fold increased risk of VTE for this progestogen compared with levonorgestrel, which is somewhat lower than in our study. Regarding cyproterone, desogestrel, and drospirenone, our results indicating a two-fold increased risk compared with levonorgestrel are in line with the meta-analysis by Dragoman et al. as well as the large, thoroughly conducted nested case–control study based on data from QResearch and Clinical Practice Research Datalink (CPRD) published by Vinogradova et al.[14] Our point estimates for gestodene and norgestimate were both somewhat higher than those observed by Dragoman et al. and Vinogradova et al., but because of the small number of observed cases for these progestogens the confidence intervals were wide and overlapped the estimates of the other studies.[2,14]

In the interpretation of this study, it must be noted that we could only include girls and young women up to the age of 19 years, as COCs were only reimbursable up to the 20th birthday during the study period. The risk estimates observed in our study thus refer to this young population and it is not clear whether they can be extrapolated to women aged 20 years or older, where incidences of VTE are increasing and the aetiology of VTE might differ. However, in our analyses stratified by age (≤17 years vs >17 years), the relative risks were comparable across age strata, suggesting that at least in these young women age is not an effect modifier. The study of Vinogradova et al.,[14] comparing risk estimates between age groups 15–24 years and 25–49 years, found only small differences across age strata, suggesting that in this population age is not an effect modifier either. They reported slightly lower odds ratios for the younger group than for the older group, but emphasised that the overall pattern of risk stayed in line with the main analysis.

4.3 | Strengths and limitations

As is the case for all studies based on secondary data, this analysis has limitations inherent to the data source, which we addressed by comprehensive sensitivity analyses. Not all potential confounding factors could be assessed in the desired detail in the database, e.g. body mass index and family history of VTE were not available. The ICD-10-GM coding

TABLE 2 Confounder-adjusted odds ratios (aORs) with 95% confidence intervals (95% CI) for the effect of current use of individual progestogens on the risk of venous thromboembolism

	Cases	Controls	aOR[a]
	n = 1166	*n* = 11 660	(95% CI)
Current use of:			
Levonorgestrel with <50 µg ethinylestradiol	145 (12.4%)	2367 (20.3%)	(ref.)
Norgestimate (with ethinylestradiol)	4 (0.3%)	42 (0.4%)	1.90 (0.62–5.81)
Desogestrel (with ethinylestradiol)	85 (7.3%)	760 (6.5%)	1.93 (1.44–2.61)
Dienogest	250 (21.4%)	1801 (15.4%)	2.23 (1.77–2.80)
with ethinylestradiol	249 (21.4%)	1767 (12.4%)	2.26 (1.80–2.84)
with estradiol	1 (0.1%)	34 (0.3%)	0.28 (0.03–2.46)
Drospirenone (with ethinylestradiol)	87 (7.5%)	733 (6.3%)	1.89 (1.41–2.55)
Gestodene (with ethinylestradiol)	3 (0.3%)	10 (0.1%)	5.05 (1.23–20.74)
Chlormadinone (with ethinylestradiol)	135 (11.6%)	1069 (9.2%)	2.06 (1.58–2.68)
Nomegestrol (with estradiol)	5 (0.4%)	61 (0.5%)	1.41 (0.52–3.81)
Cyproterone (with ethinylestradiol)	36 (3.1%)	282 (2.4%)	2.15 (1.43–3.25)
Norelgestromin (with ethinylestradiol)	0 (0.0%)	1 (0.0%)	–
Norethisterone (with ethinylestradiol)	0 (0.0%)	0 (0.0%)	–
Potential confounding factors			
Age at cohort entry			1.19 (1.08–1.30)
Cardiovascular diseases[b]	195 (16.7%)	1216 (10.4%)	1.36 (1.13–1.63)
Coagulation disorders and other blood diseases[c]	125 (10.7%)	169 (1.4%)	7.36 (5.61–9.66)
Diabetes or use of antidiabetics or insulin	28 (2.4%)	166 (1.4%)	1.19 (0.75–1.87)
Migraine with aura	45 (3.9%)	221 (1.9%)	1.93 (1.33–2.79)
Varicose veins of lower extremities	33 (2.8%)	64 (0.5%)	5.28 (3.28–8.50)
Obesity	240 (20.6%)	1127 (9.7%)	2.19 (1.85–2.60)
Paresis, hospitalisation, surgery, fractures or trauma	294 (25.2%)	752 (6.4%)	4.27 (3.60–5.05)
Current use of ASA, antiplatelets, antithrombotics or DOACs	17 (1.5%)	7 (0.1%)	12.88 (4.85–34.23)
Current use of NSAIDs	118 (10.1%)	218 (1.9%)	4.67 (3.58–6.10)
Current use of glucocorticoids or other corticoids	11 (0.9%)	28 (0.2%)	2.45 (1.11–5.41)
Current use of antidepressants or antipsychotics	24 (2.1%)	106 (0.9%)	1.44 (0.88–2.37)

Note: All potential confounding factors listed were included in the model.

Abbreviations: ASA, acetylsalicylic acid; DOACs, direct oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]aORs above 1 indicate an increased risk of VTE.

[b]Coronary heart disease, hypertension, atrial fibrillation and flutter, cardiac arrhythmia, congenital heart defects, valvular heart disease, heart failure, peripheral arterial diseases, or use of antihypertensives.

[c]Thrombophilia, other coagulation disorders, sickle cell anaemia or haemolytic uremic syndrome.

system, however, allows coding of obesity (E66.-). Stratified analyses did not indicate substantial effect modification by obesity, but case numbers were low in the subgroup of girls/young women who were obese (20% of cases), making the results less reliable than in the main analysis including all women. Information on the risk factor of smoking is also rather limited in the claims data, but bias analyses revealed that the potential impact of the unobserved confounding factor 'smoking' is small. Even a large difference between the proportions of smokers in the exposure groups would not substantially change the risk estimates. Confounding by indication or channelling of girls and young women with a certain risk profile to certain drugs cannot be excluded. Stratification by risk factors and educational attainment as a proxy for SES has shown that the effects remained the same in these more homogenous patient groups, which implies that the observed increased risk is unlikely to be explained by channelling alone.

The analysis is based on dispensing data, and thus we did not have information on when the girls and young women actually started using the respective drugs, which depends on the menstrual cycle or whether the 28-day cycle was shortened. To address these uncertainties, we performed two sensitivity analyses accounting for a potentially later

BJOG An International Journal of Obstetrics and Gynaecology

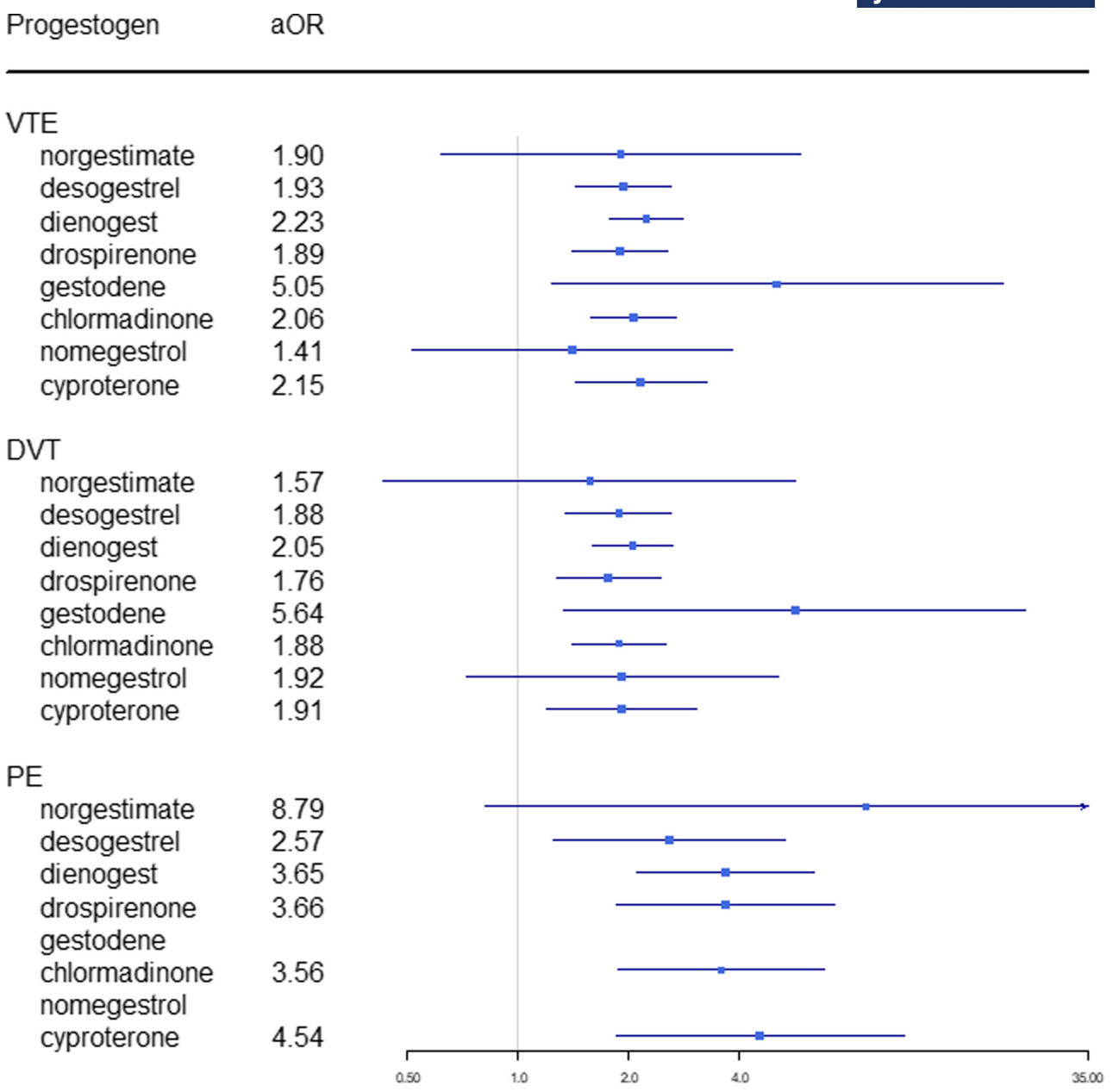

FIGURE 1 Confounder-adjusted odds ratios (aORs) for the effect of current use of individual progestogens on venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE), using levonorgestrel with <50 μg ethinylestradiol as a reference.

start of exposure than the dispensing date and a potential shortening of the 28-day cycle. Risk estimates for the first analysis were slightly higher, whereas estimates for the second analysis were slightly lower. However, the changes were only minor, so both analyses suggest that our results are robust with respect to both types of misclassification of exposure.

Potential misclassification of the outcome also needs to be considered. For the definition of PE we only used main discharge diagnoses, which are assumed to have a high validity as they are based on all information (including laboratory tests and imaging results) collected during the hospital stay, and are subject to regular inspections because of their importance for reimbursement. For DVT, we also considered outpatient diagnosis as this condition may not lead to hospitalisation, but we combined outpatient diagnosis codes with information on treatment to minimise misclassification. To avoid recurrent VTE being classified as incident VTE, we excluded all girls and young women with a previous VTE. With these measures we assume that the outcome definition had a very high level of specificity and that the risk estimates were thus not biased through misclassification of the outcome. Owing to data privacy rules in Germany, this cannot be ascertained by linking insurants with their medical charts. The validity of our outcome definition is also supported by the fact that the VTE rates in our cohort were comparable with those expected according to the rates reported by the EMA.[15]

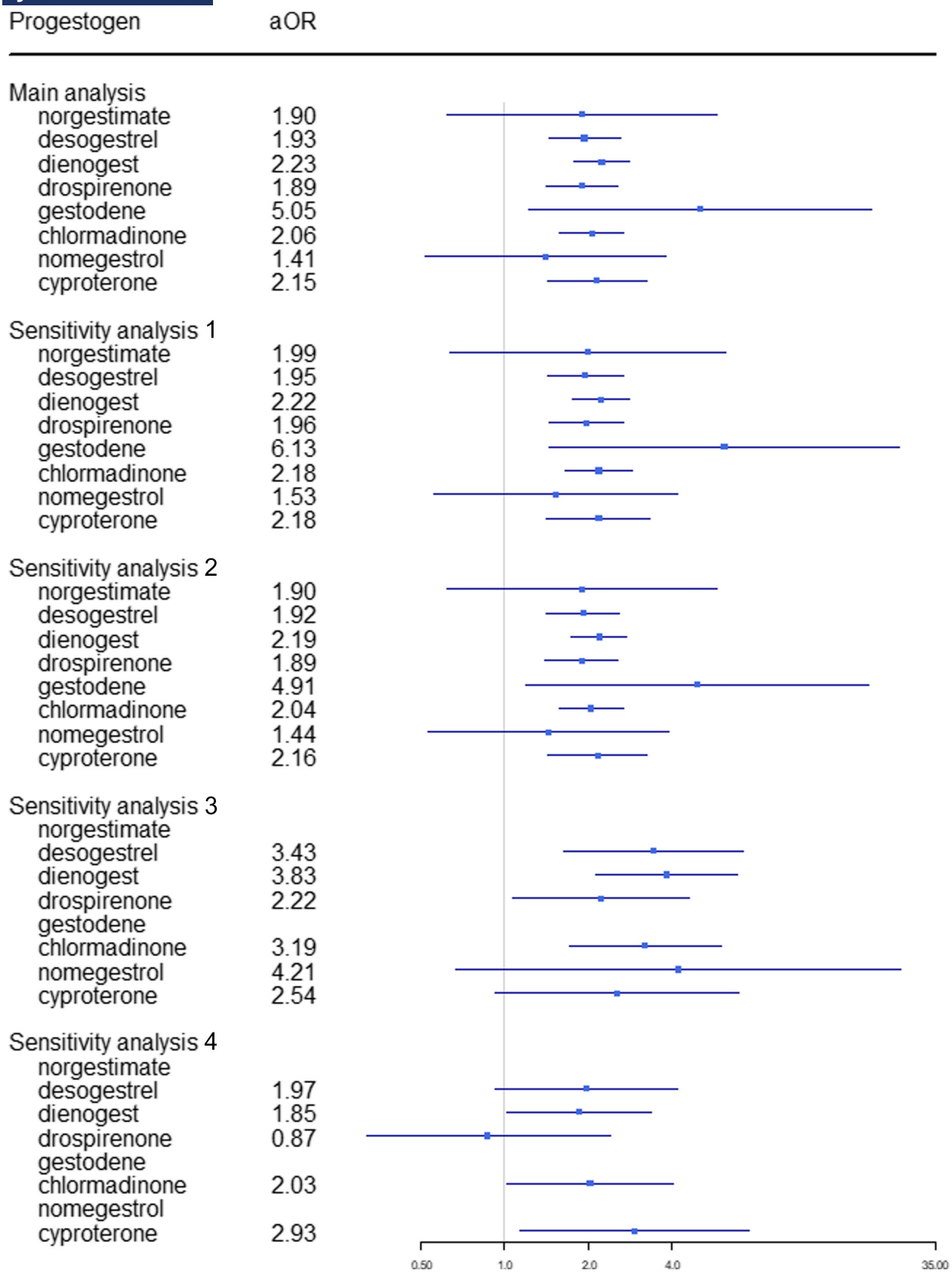

FIGURE 2 Confounder-adjusted odds ratios (aORs) for the effect of current use of individual progestogens on venous thromboembolism (VTE) in the main analysis compared with various sensitivity analyses (sensitivity analyses: 1, exclusion of girls/young women who used anticoagulants; 2, exclusion of girls/women with oophorectomy, hysterectomy or sterilization; 3, exclusion of comorbidity increasing the risk of VTE; 4, only cases occurring within 90 days after entry to the cohort considered).

The risk of VTE is not only influenced by the type of progestogen, but also by the level of ethinylestradiol. Comparison of different progestogens without taking the ethinylestradiol content into account might bias the results if one progestogen is usually combined with higher ethinylestradiol as the reference. In our study this was observed for norgestimate, where the point estimate regarding risk of VTE was no longer elevated when ethinylestradiol content was considered.

The strengths of our study are the size and representativeness of the study population, the absence of recall and non-responder bias, the new-user active comparator design and the comprehensive sensitivity and bias analyses, showing that the results are robust with respect to exposure assumptions, uncertainties regarding confounding, changes in exclusion criteria and restriction to idiopathic cases.

5 | CONCLUSION

Our study confirms that levonorgestrel with low ethinylestradiol (<50 μg) is the COC with the lowest risk of VTE, and it suggests that for chlormadinone, the risk of VTE is two times higher and thus in the same range as for the third-generation progestogen desogestrel and the fourth-generation progestogen drospirenone.

AUTHOR CONTRIBUTIONS

TS: study concept and design; analysis and interpretation of data; drafting the article; critical revision of the article. CP: interpretation of data; critical revision of the article. MB: analysis; critical revision of the article. UH: drafting the article; critical revision of the article.

ACKNOWLEDGEMENTS

We thank the statutory health insurance providers AOK Bremen/Bremerhaven, DAK-Gesundheit, Die Techniker (TK) and hkk Krankenkasse for contributing the data for this analysis. We would also like to thank Anja, Gabbert, Marieke Niemeyer and Sandra Ulrich for programming the analysis data sets and Simon Klau for the validation of the statistical program code. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

This study was funded by the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM).

CONFLICT OF INTERESTS

All authors are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts post-authorisation safety studies (PASSs) requested by health authorities and financed by the pharmaceutical industry. These PASSs are performed in line with the ENCePP Code of Conduct, which means that the design and conduct as well as the interpretation and publication are not influenced by the pharmaceutical industry. The study presented was not funded by the pharmaceutical industry. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

As we are not the owners of the data we are not legally entitled to grant access to the data of the German Pharmacoepidemiological Research Database. In accordance with German data protection regulations, access to the data is granted only to BIPS employees on the BIPS premises and in the context of approved research projects. Third parties may only access the data in cooperation with BIPS and after signing an agreement for guest researchers at BIPS.

ETHICS APPROVAL

In Germany, the use of health insurance data for scientific research is regulated by the Code of Social Law. All health insurance providers involved, as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen, as their responsible authorities, approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias the results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

ORCID

Tania Schink https://orcid.org/0000-0002-0224-1866
Malte Braitmaier https://orcid.org/0000-0001-7534-4068

REFERENCES

1. European Medicines Agency. Assessment report for combined hormonal contraceptives containing medicinal products (EMA/739865/2013). London: European Medicines Agency; 2014.
2. Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. Int J Gynaecol Obstet. 2018;141(3):287–94.
3. Haug U, Schink T. German Pharmacoepidemiological Research Database (GePaRD). In: Sturkenboom M, Schink T, editors. Databases for pharmacoepidemiological research. Cham: Springer; 2020. p. 119–24.
4. Pisa FE, Reinold J, Kollhorst B, Haug U, Schink T. Individual antidepressants and the risk of fractures in older adults: a new user active comparator study. Clin Epidemiol. 2020;12:667–78.
5. Schafer W, Princk C, Kollhorst B, Schink T. Antidepressants and the risk of hemorrhagic stroke in the elderly: a nested case-control study. Drug Saf. 2019;42(9):1081–9.
6. Pisa FE, Reinold J, Kollhorst B, Haug U, Schink T. Antidepressants and the risk of traumatic brain injury in the elderly: differences between individual agents. Clin Epidemiol. 2019;11:185–96.
7. Thone K, Kollhorst B, Schink T. Non-steroidal anti-inflammatory drug use and the risk of acute myocardial infarction in the general German population: a nested case-control study. Drugs Real World Outcomes. 2017;4(3):127–37.

8. Jobski K, Kollhorst B, Garbe E, Schink T. The risk of ischemic cardio- and cerebrovascular events associated with oxycodone-naloxone and other extended-release high-potency opioids: a nested case-control study. Drug Saf. 2017;40(6):505–15.
9. Douros A, Jobski K, Kollhorst B, Schink T, Garbe E. Risk of venous thromboembolism in cancer patients treated with epoetins or blood transfusions. Br J Clin Pharmacol. 2016;82(3):839–48.
10. Rothman K, Greenland S, Lash TL. Case-control studies. In: Rothman K, Greenland S, Lash TL, editors. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 111–27.
11. Greenland S. Basic methods for sensitivity analysis of biases. Int J Epidemiol. 1996;25(6):1107–16.
12. BZgA. Repräsentativerhebung. 2018 [cited 2020 July 07]; Available from: https://www.dhs.de/suechte/tabak
13. Cheng YJ, Liu ZH, Yao FJ, Zeng WT, Zheng DD, Dong YG, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med. 2013;10(9):e1001515.
14. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2015;350:h2135.
15. Schink T, Princk C, Haug U. Risiko venöser Thromboembolien bei Einnahme von kombinierten hormonalen Kontrazeptiva. Bulletin zur Arzneimittelsicherheit. 2021;2:13–6.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schink T, Princk C, Braitmaier M, Haug U. Use of combined oral contraceptives and risk of venous thromboembolism in young women: a nested case–control analysis using German claims data. BJOG. 2022;00:1–10. https://doi.org/10.1111/1471-0528.17268