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Systemic hormonal contraception and risk of venous thromboembolism

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Abstract

Introduction: The increased risk of venous thromboembolism associated with the use of hormonal contraception is well recognized, but evidence regarding hormonal contraception containing natural estradiol is limited. This study aimed to assess the associations between the patterns of use of different systemic hormonal contraceptives and the risk of venous thromboembolism during 2017–2019.

Material and Methods: All fertile-aged women (15–49 years) living in Finland in 2017 and using hormonal contraception in 2017 and their 1:1 age- and residence-matched controls not using hormonal contraception in 2017 (altogether 587 559 women) were selected from the Prescription Centre. All incident venous thromboembolism cases during 2018–2019 and their 4:1 age-matched controls were further analyzed in a prospective nested case–control design to assess the associations between the use (starting, stopping, continuous vs no use) of different hormonal contraception types and venous thromboembolism.

Results: Altogether, 1334 venous thromboembolism cases occurred during the follow-up period (incidence rate 1.14 per 1000 person-years, 95% confidence interval [CI] 1.08–1.20), with an incidence rate ratio of hormonal contraception vs no hormonal contraception use of 1.42 (95% CI 1.27–1.58). Compared with non-use, starting the use of gestodene and ethinylestradiol (adjusted odds ratio [aOR] 2.85; 95% CI 1.62–5.03), drospirenone and ethinylestradiol (aOR 1.55; 95% CI 0.98–2.44), desogestrel and ethinylestradiol (aOR 1.97; 95% CI 0.99–3.92), and transdermal patch releasing norelgestromin and ethinylestradiol (aOR 5.10; 95% CI 1.12–23.16), as well as continuing the use of gestodene and ethinylestradiol (aOR 2.60; 95% CI 1.61–4.21), drospirenone and ethinylestradiol (aOR 1.55; 95% CI 1.02–2.37), cyproterone-acetate and estrogen/ethinylestradiol (aOR 1.66; 95% CI 1.06–2.61), and vaginal ring releasing etonogestrel and ethinylestradiol (aOR 3.27; 95% CI 1.95–5.48) were associated with venous thromboembolism risk. Regarding the type of estrogen, the highest risk was

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associated with current use (vs non use in the previous 180 days) of ethinylestradiol-containing preparations (aOR 2.20; 95% CI 1.82–2.65), followed by estradiol-containing preparations (aOR 1.39; 95% CI 1.04–1.87) with no risk for progestin-only hormonal contraception. Current use of estradiol-containing preparations was not associated with venous thromboembolism risk after exclusion of cyproterone-acetate and estrogen/ethinylestradiol (aOR 1.05; 95% CI 0.66–1.66).

Conclusions: An increased risk of venous thromboembolism is associated with ethinylestradiol-containing combined preparations. The use of estradiol-containing combined preparations confers only a slightly increased risk, possibly driven by cyproterone-containing combined oral contraceptives, whereas the use of progestin-only contraception is not associated with venous thromboembolism.

K E Y W O R D S
estradiol, ethinylestradiol, hormonal contraception, nested case–control, progestin-only contraception, venous thromboembolism

1 | INTRODUCTION

The increased risk of venous thromboembolism (VTE) associated with the use of combined hormonal contraception (CHC) is well recognized and has been widely characterized.[1–4] The risk is modified by the dose of estrogen (especially concerning ethinylestradiol [EE]) and the type of progestin.[5–7] Preparations containing the lowest doses of EE (i.e., 20 μg) combined with testosterone-derived progestins (i.e., norethisterone or levonorgestrel) confer the lowest risk of VTE. Conversely, higher doses of EE are associated with a higher risk of VTE, especially when combined with third-generation progestin (i.e., desogestrel, etonogestrel and gestodene) or fourth-generation progestin (i.e., drospirenone). Accordingly, several guidelines recommend low-dose second-generation combined preparations as starting preparations of CHC.[8–10] Moreover, the importance of identifying women who have an increased risk of VTE before starting hormonal contraception (HC) is emphasized in all guidelines on HC.

In part because of this increased risk of VTE associated with EE, the newest combined oral contraceptives (COCs) contain either natural estradiol or estradiol-valerate. The effects of estradiol on the coagulation system are presumed to be lower.[11–13] Nevertheless, evidence concerning the risk of VTE associated with COC-containing natural estradiol is limited to one study reporting a risk similar to or lower than that associated with other COCs.[14] In contrast with CHC, the risk of VTE is not increased during the use of progestin-only contraceptives.[15] Thus, the various progestin-only contraceptive methods can also be used in women at increased risk of VTE.

In the present study, we measured the overall incidence of VTE over 1 year of follow-up and assessed the associations between the use of different types of currently used systemic hormonal contraceptives vs the risk of VTE by analyzing recent (i.e., 2017–2019) high-quality registry data from Finland. In addition, we studied the risk of VTE in relation to different patterns of HC use (i.e., no use, recently stopped using, recently started using, or continuous use).

Key message

Combined hormonal contraception containing ethinylestradiol, in combination with either third-generation progestins or drospirenone, is associated with the highest risk of venous thromboembolism compared with estradiol-containing and progestin-only oral contraception. Estradiol-containing combined preparations confer only a slightly increased risk, possibly driven by the cyproterone-acetate and estrogen/ethinylestradiol contraceptives.

2 | MATERIAL AND METHODS

2.1 | Study population and design

This work is part of a larger register-based study of HC use in Finland, described in detail elsewhere.[16] Briefly, the population was selected using the unique personal identification number that is given at birth or at immigration to each person permanently residing in Finland. The original group of HC users was selected from the Prescription Centre in the Kanta Services[17] and included all fertile-aged women (15–49 years) with at least one redeemed prescription for HC (anatomical therapeutic chemical [ATC] codes: G02B, "contraceptives for topical use"; G03A, "hormonal contraceptives for systemic use"; G03HB, "antiandrogens and estrogens") in 2017 (n = 294 445). The same-sized control group of HC non-users included women matched by age and municipality of residence with no redeemed HC prescriptions in 2017. A total of 89 women who received a prescription with ATC code G03AD (i.e., emergency contraception, which is usually available without prescription in Finland) and their matched control individuals were excluded from the analyses, leaving a final population of 294 356 HC users and a reference group of the same size. As such, the initial

study population included 52% of the fertile-aged women living in Finland in 2017. The HC use of all these women was followed up by means of the Prescription Centre until the end of 2019.

The follow-up started on January 1, 2018, and ended on December 31, 2019; thus, the maximum length of follow-up was 2 years. The primary endpoint event of this study was a first hospitalization (as recorded in the Care Register of Health Care) due to one of the following causes: pulmonary embolism (International Classification of Diseases, Tenth Revision [ICD-10] code I26), cerebral infarction owing to cerebral venous non-pyogenic thrombosis (I63.6), or deep vein thrombosis (DVT), including thrombophlebitis of lower extremities (I80.0–I80.9), portal thrombosis (I81), thrombosis of caval vein (I82.2), thrombosis of renal vein (I82.3), and unspecified DVT (I82.8 and I82.9). Death, emigration, or end of follow-up were defined as censoring events. We excluded individuals with an endpoint event before the start of follow-up (years 2016 and 2017; N = 1153).

The overall study consists of two parts: a cohort study to examine the incidence of VTE and a nested case–control study to explore the VTE risk due to HC use. Altogether, the study population for the incidence study included 587 559 women. The incidence study was used as a sampling frame for the nested case–control study, which was constructed based on the incident VTE cases (N = 1334). We selected four controls for each case, matched by year of birth. To evaluate the credibility of the results, we used other external causes of accidental injury (ICD-10 W00-W99, X00-X39, and X50-X59) as a negative control outcome.[18] Accidental poisonings by and exposure to noxious substances (X40–X49) were excluded from this analysis as they may be associated with suicidal behavior.

2.2 | The register data and variables

We obtained information on sociodemographic characteristics of all the study members on December 31, 2017 (age, municipality of residence, civil status, socioeconomic group, highest level of education, annual income) from Statistics Finland. Information on cancer diagnoses was obtained from the Finnish Cancer Registry. We obtained special reimbursement rights for the following chronic diseases from the Social Insurance Institution of Finland: diabetes, multiple sclerosis, epilepsy, connective tissue diseases, ulcerative colitis, and Crohn's disease.[19] Based on these data, we selected the following baseline variables as covariates: marital status, socioeconomic status, education, indicator of cancer diagnosis (no/yes) before start of follow-up, and specific indicators for chronic diseases (no/yes).

Information on prescribed and redeemed medications for each person living in Finland is stored in the Prescription Centre, a centralized database in the Kanta Services. The recorded data include, among others, the product ATC code, date of prescription and of purchase, and the prescribed amount in defined daily dose. In addition to selection of the initial study population based on redeemed HC prescriptions in 2017, the Prescription Centre was used to gather information on their pattern of HC use in the period 2018–2019. Use of HC was assumed if at least two prescriptions were redeemed in a

180-day period. Only ATC codes with at least five individuals in all categories were used in statistical analyses.

In the incidence study, only an indicator of baseline (during year 2017) HC usage (no HC use vs HC use) was considered. In the nested case–control design, we defined a categorical variable for each substance, as follows: non-user (no use in the 360 days before the VTE event), previous user (use 179–360 days before, no use 1–180 days before the event), starter (no use 179–360 days before, use 1–180 days before the event), and continuous user (use during the whole period of 360 days before the event).

The systemic HC methods of interest that were available in Finland in 2018 and their use are summarized in Supporting Information Table S1 and Table S2. We excluded the users of contraceptive implants and the levonorgestrel-releasing intrauterine system as they can be used for up to 3 or 5 years and are often provided free of charge by individual communities, not necessitating individual prescription. Thus, they are only partly covered in the Prescription Centre database. Additionally, users of the COC-containing levonorgestrel and EE, norgestimate and EE, dienogest and EE, and levonorgestrel-only oral preparations were excluded from further analyses because of the small numbers of users and associated VTE cases.

2.3 | Statistical analyses

The incidence rates of VTE according to HC use were described using Kaplan–Meier curves, and incidence rate comparison was conducted using Poisson regression.

To take matching into account in the nested case–control design, we used a conditional logistic regression model. In addition to a model without any covariates, we fitted the following models: model 1 controlled for marital status, socioeconomic status, education, and cancer diagnosis, and model 2 was model 1 additionally controlled for chronic diseases. Because the case and control groups were matched by year of birth, age was not included as a covariate in the models. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

All the analyses were performed with R software version 3.5.1.[20]

2.4 | Ethical approval

The study was reviewed by the Ethics Committee of the Faculty of Medicine, University of Helsinki (3/2018; March 29, 2018). Because this was a register-based study, no individual consent was needed.

3 | RESULTS

During the follow-up, 1.173 million person-years were cumulated and 1334 VTE cases observed, with an overall incidence rate of 1.14 (95% CI 1.08–1.20) per 1000 person-years.

Altogether, 838 cases of thrombosis of lower extremities, 293 pulmonary embolism, 188 caval vein thrombosis, eight portal thrombosis, and seven cerebral venous thrombosis occurred. In the 2017 group of HC non-users, we observed 552 cases of VTE, corresponding to an incidence rate of 0.94 per 1000 person-years (95% CI 0.86–1.02), compared with 782 VTE cases (incidence rate 1.33; 95% CI 1.24–1.43) in the HC users group. The incidence rate ratio of HC vs no-HC users was 1.42 (1.27–1.58). The incidence of VTE increased with age, with the highest incidence rate ratio in the group aged 40–44 years (5.01; 3.83–6.57, with the age class 15–19 years as the reference category) (Supporting Information Figure S1 and Table S3).

Baseline characteristics of the population for the nested case–control study are reported in Table 1. When each substance of interest was analyzed separately in the nested case–control design, compared with the respective non-user groups, the risk of VTE was higher for those who started or continued the use of gestodene and EE (adjusted OR [aOR] 2.87; 95% CI 1.68–4.91 and aOR 2.35; 95% CI 1.51–3.68, respectively) and drospirenone and EE (aOR 1.59; 95% CI 1.06–2.38; and aOR 1.48; 95% CI 1.00–2.18, respectively). No difference was found for previous users (aOR 1.30; 95% CI 0.52–3.26; and aOR 0.82; 95% CI 0.40–1.71). Similarly, women who began using desogestrel and EE, and the transdermal patch releasing norelgestromin and EE, had a higher VTE risk (aOR 1.90; 95% CI 1.01–3.56; and aOR 5.27; 95% CI 1.16–23.88, respectively) than did non-users. Moreover, continuous use of vaginal ring releasing etonogestrel and EE (aOR 3.12; 95% CI 1.94–5.04), and of cyproterone-acetate and estrogen/EE (aOR 1.88; 95% CI 1.20–2.71) was associated with a higher risk of VTE, with no difference between starters or previous users and non-users. We observed no associations between the use of other preparations and VTE (Table 2).

When only considering current use (in the previous 180 days) vs no use (in the previous 180 days) of different categories of CHC, the highest risk was associated with EE-containing preparations (aOR 2.20; 95% CI 1.82–2.65); the overall risk associated with current use of estradiol-containing COCs was 1.39 (95% CI 1.04–1.87), although it reduced to non-significance after exclusion of cyproterone-acetate and estrogen/EE contraceptives (aOR 1.05; 95% CI 0.66–1.66). On the other hand, current use of progestin-only HC was not associated with a higher risk of VTE than non-use of HC (Figure 1 and Table 3).

When accidental injuries were used as a negative control outcome, we found a lower risk for accidents for women starting gestodene and EE (aOR 0.25; 95% CI 0.11–0.57) and those starting (aOR 0.69; 95% CI 0.49–0.97) or continuing (aOR 0.67; 95% CI 0.46–0.99) drospirenone and EE. We detected no other associations between the use of any HC types and accident incidence (Supporting Information Table S4).

4 | DISCUSSION

The main finding of our study is a higher risk of VTE associated with current use of HC. Specifically, we found that the use of CHC containing EE in combination with either third-generation progestins or drospirenone was associated with approximately a two- to four-fold increased risk of VTE compared with non-use of HC. In contrast, whereas the use of pooled estradiol-containing combined preparations was associated with a slightly increased risk of VTE, possibly driven by the cyproterone-acetate and estrogen/EE contraceptives, the use of various individual estradiol-containing combined preparations or progestin-only contraception was not associated with an altered risk of VTE. The risk associated with second-generation progestin-containing contraceptives was not assessed in this study.

Our analytical approach also allowed us to examine the duration of the effects of HC use on the risk of VTE. Specifically, for both the combination of gestodene and EE and of drospirenone and EE, as well as for the vaginal ring releasing etonogestrel and EE, previous users (i.e., at least 6 months after stopping use) and non-users experienced a similar risk of VTE. Conversely, the risk during the first 6 months of use of EE-containing combined preparations was similar to or slightly higher than during their continuous use.

The overall incidence of VTE in our population (1.14 per 1000 person-years) and increased frequency with age correspond to previously reported figures.[21,22] Interestingly, our detected incidence of VTE among non-users of HC was higher (9.4 per 10 000 woman-years) than that reported previously in Denmark (2.1/10 000 woman-years).[1,2] The time difference between the two studies (data from 2018 to 2019 in our current work and from 2001 to 2010 in the Danish studies), growing awareness of the risk factors for VTE, along with the increasing use of high-resolution diagnostic imaging techniques, may partly explain this apparent growing trend in VTE.[22] Another possible contributing factor to the high incidence of VTE in the control group compared with previous studies is the increasing prevalence of overweight and obesity in the population.[23]

The higher risk of VTE that we observed for women using CHC agrees with previously reported findings. According to a previous meta-analysis, the use of COCs containing EE and different generations of progestogens increases the risk of VTE compared with non-use (relative risk 3.5; 95% CI 2.9–4.3).[21] This figure is higher than the risk associated with current use of EE-containing CHCs in our study (relative risk 2.30; 95% CI 1.87–2.83). Possible explanations for this difference may include the use of very recent data (years 2018 and 2019) in the present study, whereas the cited meta-analysis is based on data from 1995 to 2010. In addition, the current guidelines, including the Finnish national guideline on contraception, take the risk factors for VTE into account and advise HC prescription accordingly.[24] This may have, in part, decreased this observed risk of VTE. However, when considering progestin-only preparations separately, combined preparations containing EE, and combined preparations containing natural estradiol or estradiol valerate, the highest risk was conferred by current use (vs no use) of EE-containing CHCs (2.20; 95% CI 1.82–2.65), with only small associations in relation to estradiol-containing oral contraceptives.

A key finding of our study is that none of the individual combined preparations containing natural estradiol or estradiol valerate were associated with an altered risk of VTE, with the exception

TABLE 1 Basic characteristics of the nested case–control study of venous thromboembolism

	Controls	Cases	
N	**5336**	**1334**	**p-Value**
Marital status			
Unmarried	2974 (55.7)	725 (54.3)	0.135
Married	1862 (34.9)	464 (34.8)	
Divorced	478 (9.0)	134 (10.0)	
Widowed	14 (0.3)	9 (0.7)	
Other	8 (0.1)	<5 (NA)	
Socioeconomic group			
Self-employed	221 (4.2)	56 (4.2)	0.001
Upper-level employees	852 (16.1)	176 (13.3)	
Lower-level employees	1937 (36.6)	475 (35.8)	
Manual workers	754 (14.2)	192 (14.5)	
Students	663 (12.5)	159 (12.0)	
Pensioners	111 (2.1)	54 (4.1)	
Others	498 (9.4)	133 (10.0)	
Unknown	261 (4.9)	81 (6.1)	
Education			
Upper secondary	2335 (43.8)	622 (46.6)	0.003
Post-secondary non-tertiary	44 (0.8)	17 (1.3)	
Short-cycle tertiary	260 (4.9)	65 (4.9)	
Bachelor	1162 (21.8)	258 (19.3)	
Master	761 (14.3)	148 (11.1)	
Doctoral	52 (1.0)	11 (0.8)	
Missing[a]	722 (13.5)	213 (16.0)	
Age group, years			
15–19	276 (5.2)	69 (5.2)	1.000
20–24	800 (15.0)	200 (15.0)	
25–29	932 (17.5)	233 (17.5)	
30–34	876 (16.4)	219 (16.4)	
35–39	912 (17.1)	228 (17.1)	
40–44	896 (16.8)	224 (16.8)	
45–49	644 (12.1)	161 (12.1)	
Cancer before baseline	46 (0.9)	49 (3.7)	<0.001
Diabetes at baseline	73 (1.4)	33 (2.5)	0.006
Multiple sclerosis at baseline	15 (0.3)	10 (0.7)	0.024
Epilepsy at baseline	51 (1.0)	9 (0.7)	0.418
Connective tissue diseases at baseline	86 (1.6)	44 (3.3)	<0.001
Ulcerative colitis or Crohn's disease at baseline	62 (1.2)	25 (1.9)	0.055

School dropouts as N (%). NA, not applicable.
[a] Including, for example, missing information on education other than of primary school level, school dropouts.

of a slightly increased risk (1.50; 95% CI 1.04–2.18) in association with current use of cyproterone and estrogen (which, however, includes both EE- and estradiol-containing preparations). Previous studies that have examined specific estradiol-containing preparations showed that dienogest and estradiol valerate carried a lower VTE risk than other COCs (hazard ratio 0.4–0.5).[14,25] To the best of our knowledge, this is the first study to compare the risk singularly at a national level and to compare several different CHCs, including different estradiol-containing preparations. Our results are further supported by the lack of higher VTE risk in association with current use of pooled estradiol-containing combined preparations after exclusion of cyproterone-containing COCs, possibly explained by the different estrogen modulation of cyproterone compared with progestins. This hypothesis is confirmed by the observation that the pooled risk for the complete natural estrogen (but not when excluding cyproterone acetate) group became significant only after adjustment, suggesting a negative confounding possibly related to the use of cyproterone-containing COCs.

COCs containing third-generation progestins (i.e., desogestrel, etonogestrel, and gestodene) and drospirenone are used more commonly in Finland than in other Nordic countries (Supporting Information Table S1).[26] The risk of VTE associated with these preparations was increased approximately two- to threefold. In previous studies, the risk of VTE associated with the use of these preparations has been rather similar. In the present analysis, the risk of VTE associated with the use of COCs containing gestodene and EE was higher than with preparations containing desogestrel or drospirenone. The VTE risk associated with drospirenone-containing preparations has been widely discussed. This may have resulted in preferential prescription of preparations containing third generation progestins to women at increased risk of VTE, potentially explaining the higher risk of VTE seen in the present study. As combined preparations containing levonorgestrel are rarely used in Finland, we could not assess the associated risk of VTE in the present study.

In contrast to COCs, parenteral administration of contraceptive steroids, especially by means of contraceptive patch releasing EE and norelgestromin, and vaginal ring with etonogestrel and EE, was associated with a significantly higher risk of VTE (5.27; 95% CI 1.16–23.88 in patch starters; 3.12; 95% CI 1.94–5.04 in continuous users of ring). Even higher risks of VTE during the use of the contraceptive ring (6.5; 95% CI 4.7–8.9) and patch (7.9; 95% CI 3.5–17.7) have been published from Denmark.[2] The higher risk associated with contraceptive patch may be due to a release rate of 34 μg/d of EE from the patch. In addition, it may be speculated that parenteral administration of combined contraception is presumed safer and thus prescribed to women at increased risk of VTE. However, given the infrequent use in Finland (Table S1) and the consequent small number of cases among users of parenterally administered contraceptives, these results must be considered with caution.

Interestingly, the high rates of VTE associated with current or continuous use of, in particular, EE-containing CHCs appeared to reverse after interruption of use, with similarly low rates in previous users and non-users. This observation supports previous evidence that the risk of VTE associated with the use of CHC is highest in the first year of use[27] and further confirms its reversibility after interruption.[28]

TABLE 2 Nested case–control study

N		Controls 5336	Cases 1334	Univariate	Model 1	Model 2
Combined hormonal contraceptives						
Desogestrel and ethinylestradiol[a]	No	5261 (98.6)	1299 (97.4)	(Reference)	(Reference)	(Reference)
	Start	30 (0.6)	15 (1.1)	2.00 (1.08–3.72)	2.00 (1.07–3.73)	1.90 (1.01–3.56)
	Continuous	28 (0.5)	12 (0.9)	1.77 (0.88–3.54)	1.87 (0.92–3.79)	1.89 (0.93–3.83)
	Quit	17 (0.3)	8 (0.6)	1.93 (0.82–4.52)	2.23 (0.94–5.32)	2.25 (0.94–5.40)
Gestodene and ethinylestradiol[a]	No	5225 (97.9)	1271 (95.3)	(Reference)	(Reference)	(Reference)
	Start	34 (0.6)	24 (1.8)	2.87 (1.70–4.87)	3.00 (1.76–5.12)	2.87 (1.68–4.91)
	Continuous	57 (1.1)	33 (2.5)	2.42 (1.56–3.76)	2.46 (1.58–3.83)	2.35 (1.51–3.68)
	Quit	20 (0.4)	6 (0.4)	1.23 (0.49–3.06)	1.29 (0.51–3.23)	1.30 (0.52–3.26)
Drospirenone and ethinylestradiol[a]	No	5088 (95.4)	1251 (93.8)	(Reference)	(Reference)	(Reference)
	Start	96 (1.8)	36 (2.7)	1.55 (1.04–2.30)	1.60 (1.07–2.40)	1.59 (1.06–2.38)
	Continuous	107 (2.0)	38 (2.8)	1.45 (0.99–2.13)	1.46 (0.99–2.15)	1.48 (1.00–2.18)
	Quit	45 (0.8)	9 (0.7)	0.82 (0.40–1.68)	0.82 (0.40–1.69)	0.82 (0.40–1.71)
Norelgestromin and ethinylestradiol patch	No	5322 (99.7)	1324 (99.3)	(Reference)	(Reference)	(Reference)
	Start	<5 (NA)	<5 (NA)	5.33 (1.19–23.83)	5.22 (1.15–23.65)	5.27 (1.16–23.88)
	Continuous	7 (0.1)	<5 (NA)	2.33 (0.68–7.99)	2.25 (0.65–7.76)	2.25 (0.65–7.75)
	Quit	<5 (NA)	<5 (NA)	2.09 (0.38–11.48)	2.20 (0.39–12.25)	2.26 (0.40–12.59)
Nomegestrol and estradiol	No	5251 (98.4)	1317 (98.7)	(Reference)	(Reference)	(Reference)
	Start	24 (0.4)	<5 (NA)	0.67 (0.23–1.92)	0.71 (0.25–2.07)	0.63 (0.22–1.84)
	Continuous	32 (0.6)	7 (0.5)	0.87 (0.38–1.98)	0.91 (0.40–2.09)	0.88 (0.38–2.03)
	Quit	29 (0.5)	6 (0.4)	0.83 (0.34–1.99)	0.86 (0.35–2.09)	0.84 (0.35–2.05)
Dienogest and estradiol-valerate	No	5280 (99.0)	1316 (98.7)	(Reference)	(Reference)	(Reference)
	Start	29 (0.5)	8 (0.6)	1.11 (0.51–2.43)	1.12 (0.51–2.47)	1.13 (0.51–2.49)
	Continuous	19 (0.4)	6 (0.4)	1.27 (0.51–3.17)	1.45 (0.58–3.67)	1.39 (0.55–3.54)
	Quit	8 (0.1)	<5 (NA)	2.00 (0.60–6.64)	2.00 (0.58–6.96)	2.07 (0.60–7.19)
Etonogestrel and ethinylestradiol vaginal ring	No	5232 (98.1)	1286 (96.4)	(Reference)	(Reference)	(Reference)
	Start	43 (0.8)	13 (1.0)	1.24 (0.66–2.33)	1.24 (0.65–2.36)	1.27 (0.67–2.41)
	Continuous	48 (0.9)	31 (2.3)	2.73 (1.71–4.36)	3.16 (1.96–5.09)	3.12 (1.94–5.04)
	Quit	13 (0.2)	<5 (NA)	1.28 (0.42–3.93)	1.48 (0.48–4.57)	1.45 (0.47–4.49)
Progestin-only oral contraceptives						
Norethisterone	No	5306 (99.4)	1331 (99.8)	(Reference)	(Reference)	(Reference)
	Start	6 (0.1)	<5 (NA)	0.67 (0.08–5.54)	0.75 (0.09–6.29)	0.90 (0.11–7.55)
	Continuous	20 (0.4)	<5 (NA)	0.40 (0.09–1.71)	0.43 (0.10–1.87)	0.44 (0.10–1.88)
	Quit	<5 (NA)	<5 (NA)	[c]	[c]	[c]
Desogestrel	No	4958 (92.9)	1252 (93.9)	(Reference)	(Reference)	(Reference)
	Start	151 (2.8)	29 (2.2)	0.75 (0.50–1.13)	0.74 (0.49–1.12)	0.74 (0.49–1.12)
	Continuous	166 (3.1)	40 (3.0)	0.95 (0.67–1.36)	0.95 (0.66–1.36)	0.92 (0.64–1.32)
	Quit	61 (1.1)	13 (1.0)	0.84 (0.46–1.54)	0.85 (0.46–1.56)	0.85 (0.46–1.58)
Antiandrogen and estrogen						
Cyproterone and estrogen[b]	No	5195 (97.4)	1286 (96.4)	(Reference)	(Reference)	(Reference)

The strengths of the study include the use of Finnish register data of proven high quality.[29,30] The identification of VTE cases was based on the diagnostic codes from specialist healthcare between 2017 and 2019. A national guideline on the management of DVT was introduced in Finland in late 2016.[31] Based on this guideline, the diagnosis of DVT requires, besides clinical symptoms, verification by means of imaging studies. Thus, inclusion of false positives in our case group is unlikely. The nested case–control design has been shown

TABLE 2 (Continued)

		Controls	Cases			
N		5336	1334	Univariate	Model 1	Model 2
Start		31 (0.6)	5 (0.4)	0.65 (0.25–1.66)	0.69 (0.27–1.79)	0.71 (0.27–1.85)
	Continuous	81 (1.5)	34 (2.5)	1.69 (1.13–2.52)	1.84 (1.22–2.76)	1.80 (1.20–2.71)
	Quit	29 (0.5)	9 (0.7)	1.25 (0.59–2.64)	1.18 (0.55–2.54)	1.19 (0.55–2.57)

Note: Frequency, and percentage in parenthesis. Odds ratios and 95% confidence intervals based on conditional logistic regression models. One substance in a model at a time. Usage of drugs in respect with event day: no = no use in past 360 days; quit = no use in past 180 days, use in 181–360 days before the event; start = use in past 180 days, no use in 181–360 days before the event; continuous = use in 360 days before the event. Multivariate model 1 adjusted with the following covariates: marital status, socioeconomic status, education, and cancer. Model 2 is model 1 further adjusted with chronic diseases. NA, not available
[a]Includes both 20 and 30 μg ethinylestradiol-containing preparations.
[b]Includes both ethinylestradiol- and estradiol-containing preparations. The use of combined oral contraceptives containing cyproterone and estradiol accounted for approximately 14% of the cyproterone and estrogen preparations during the period 2017–2019.
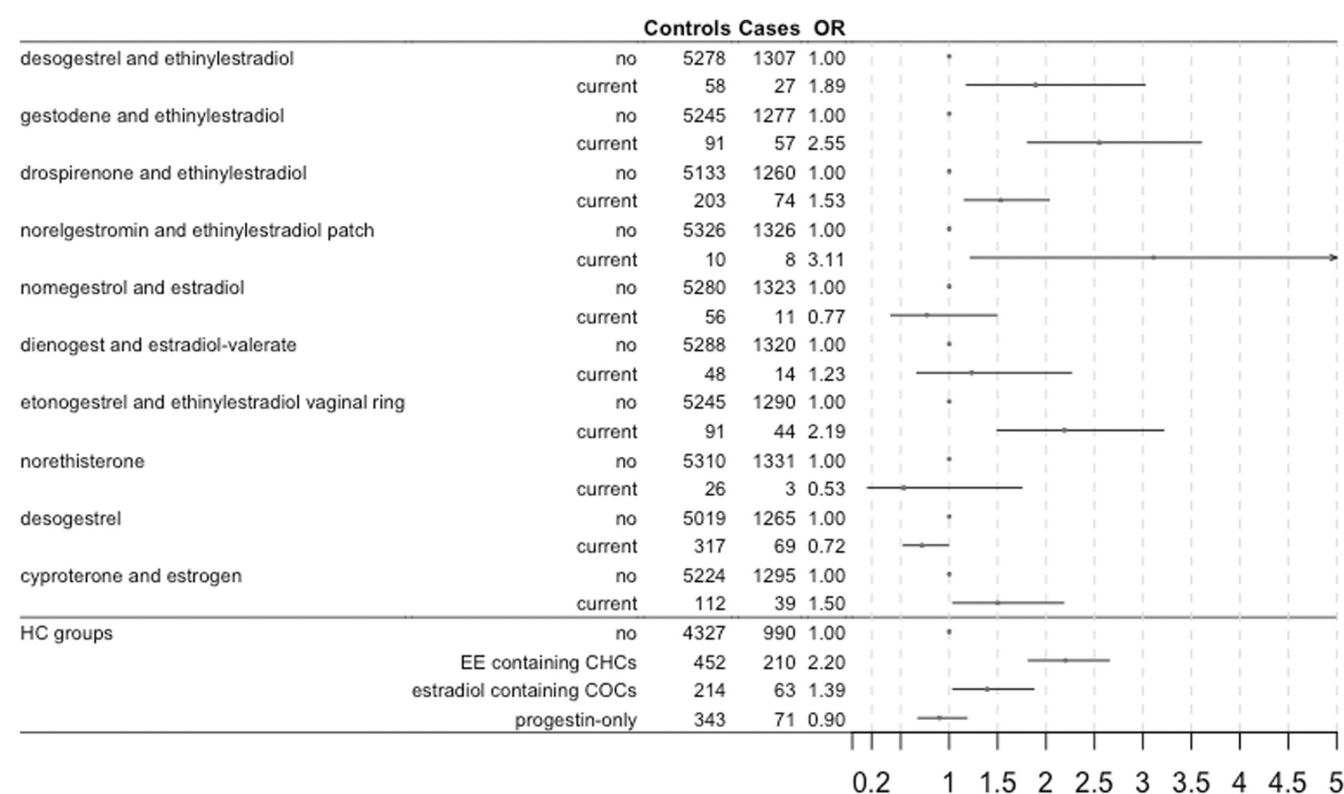[c]Not estimable.

FIGURE 1 Adjusted ORs for hormonal contraceptives. Multivariate model 2 adjusted with the following covariates: marital status, socioeconomic status, education, cancer, and chronic diseases. One substance in the model at a time. Usage of drugs with respect to event day: no = no use in past 180 days; current = use in past 180 days. CHCs, combined hormonal contraceptives; COCs, combined oral contraceptives; EE, ethinylestradiol; ORs, odds ratios.

to produce unbiased estimates and to be free from the weaknesses of ordinary case–control design. It uses correct sampling of controls that takes the follow-up time into account.[32,33] In addition, the control women were matched by age. Another methodological strength of our study is that we have included analyses of negative control outcome, a widely used and recommended approach in pharmacoepidemiology.[34] Both these methodological choices support the conclusion that the association between CHC use and VTE incidence is probably causal, although not totally free of bias due to confounding.

We lacked information on several important background factors. Importantly, neither body mass index (BMI) nor smoking habits are included in any of the registries used. The Finnish national guideline on contraception lists smoking, age ≥35 years, and BMI ≥30 kg/m^2 as relative contraindications to CHC use. If more than one of these factors is present, the contraindication becomes absolute.[23] Thus, it is likely that women at high risk of DVT are not included in the cohort of CHC users. Additionally, some of our controlling variables (e.g., education, socioeconomic status) are known proxies for BMI and

TABLE 3 Nested case–control study of venous thromboembolism

		Controls	Cases			
N		5336	1334	Univariate	Model 1	Model 2
Combined hormonal contraceptives						
Desogestrel and ethinylestradiol	No	5278 (98.9)	1307 (98.0)	(Reference)	(Reference)	(Reference)
	Current	58 (1.1)	27 (2.0)	1.89 (1.19–3.00)	1.93 (1.21–3.09)	1.89 (1.18–3.02)
Gestodene and ethinylestradiol	No	5245 (98.3)	1277 (95.7)	(Reference)	(Reference)	(Reference)
	Current	91 (1.7)	57 (4.3)	2.59 (1.85–3.64)	2.66 (1.89–3.75)	2.55 (1.81–3.60)
Drospirenone and ethinylestradiol	No	5133 (96.2)	1260 (94.5)	(Reference)	(Reference)	(Reference)
	Current	203 (3.8)	74 (5.5)	1.50 (1.14–1.98)	1.53 (1.15–2.03)	1.53 (1.16–2.03)
Norelgestromin and ethinylestradiol patch	No	5326 (99.8)	1326 (99.4)	(Reference)	(Reference)	(Reference)
	Current	10 (0.2)	8 (0.6)	3.20 (1.26–8.11)	3.11 (1.22–7.94)	3.11 (1.22–7.96)
Nomegestrol and estradiol	No	5280 (99.0)	1323 (99.2)	(Reference)	(Reference)	(Reference)
	Current	56 (1.0)	11 (0.8)	0.78 (0.41–1.50)	0.83 (0.43–1.59)	0.77 (0.40–1.49)
Dienogest and estradiol-valerate	No	5288 (99.1)	1320 (99.0)	(Reference)	(Reference)	(Reference)
	Current	48 (0.9)	14 (1.0)	1.17 (0.64–2.14)	1.24 (0.68–2.28)	1.23 (0.67–2.26)
Etonogestrel and ethinylestradiol vaginal ring	No	5245 (98.3)	1290 (96.7)	(Reference)	(Reference)	(Reference)
	Current	91 (1.7)	44 (3.3)	2.02 (1.39–2.93)	2.19 (1.50–3.20)	2.19 (1.50–3.21)
Progestin-only oral contraceptives						
Norethisterone	No	5310 (99.5)	1331 (99.8)	(Reference)	(Reference)	(Reference)
	Current	26 (0.5)	<5 (NA)	0.46 (0.14–1.52)	0.51 (0.15–1.68)	0.53 (0.16–1.75)
Desogestrel	No	5019 (94.1)	1265 (94.8)	(Reference)	(Reference)	(Reference)
	current	317 (5.9)	69 (5.2)	0.86 (0.66–1.13)	0.74 (0.54–1.01)	0.72 (0.53–0.99)
Antiandrogen and estrogen						
Cyproterone and estrogen	No	5224 (97.9)	1295 (97.1)	(Reference)	(Reference)	(Reference)
	Current	112 (2.1)	39 (2.9)	1.40 (0.97–2.01)	1.52 (1.05–2.20)	1.50 (1.04–2.18)
HC groups						
	No	4327 (81.1)	990 (74.2)	(Reference)	(Reference)	(Reference)
	EE containing CHCs	452 (8.5)	210 (15.7)	2.12 (1.76–2.55)	2.23 (1.85–2.69)	2.20 (1.82–2.65)
	Estradiol containing COCs	214 (4.0)	63 (4.7)	1.31 (0.98–1.75)	1.43 (1.07–1.92)	1.39 (1.04–1.87)
	Progestin-only	343 (6.4)	71 (5.3)	0.91 (0.69–1.18)	0.91 (0.70–1.20)	0.90 (0.68–1.18)
HC groups after exclusion of cyproterone and estrogen	No	4439 (83.2)	1029 (77.1)	(Reference)	(Reference)	(Reference)
	EE containing CHCs	452 (8.5)	210 (15.7)	2.08 (1.73–2.50)	2.18 (1.81–2.63)	2.15 (1.78–2.59)
	Estradiol containing COCs	102 (1.9)	24 (1.8)	1.03 (0.65–1.62)	1.10 (0.69–1.74)	1.05 (0.66–1.66)
	Progestin-only	343 (6.4)	71 (5.3)	0.89 (0.68–1.17)	0.90 (0.68–1.18)	0.88 (0.67–1.16)

Note: Frequency, and percentage in parenthesis. Odds ratios and 95% confidence intervals based on conditional logistic regression models. One substance in a model at a time. Usage of drugs in respect with event day: no = no use in past 180 days; current = use in past 180 days. Multivariate model 1 adjusted with the following covariates: marital status, socioeconomic status, education, and cancer. Model 2 is model 1 further adjusted for chronic diseases. NA, not applicable.

Abbreviation: CHC, combined HC; COC, combined oral contraception; EE, ethinylestradiol; HC, hormonal contraception.

smoking.[35,36] Another limitation arose from the lack of information on the exact contraceptive preparations used, which precluded any analyses on the effect of different doses of EE, known to influence the risk of VTE.[5-7] Additionally, analyses on individual preparations may be limited by the small number of cases in some groups (e.g., parenteral contraceptives). Moreover, the category of cyproterone and estrogen contains both EE- and estradiol-based combinations. However, based on Finnish sales data,[37] the use of COCs containing cyproterone and

estradiol accounted for approximately 14% of the cyproterone and estrogen preparations during the period 2017–2019.

5 | CONCLUSION

The overall elevated risk of VTE associated with the use of modern systemic HC was lower than that published previously. The increased

risk was associated with EE-containing combined preparations, and especially with start of the use of contraceptive patch. The use of estradiol-containing combined preparations was associated with a slightly increased risk of VTE only if all preparations were combined, but no change in risk was evident for individual preparations or after exclusion of cyproterone-acetate–containing COCs. There was no altered risk of VTE associated with progestin-only contraception.

AUTHORS CONTRIBUTION

OH and JH conceptualized the study. JH performed the data analysis. OH, ET, TP, AB, AL, and JH contributed to interpretation of the results. OH, ET, and JH drafted the manuscript. OH, ET, TP, AB, AL, and JH critically revised the manuscript and gave final approval of the version to be published.

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OH serves occasionally on advisory boards for Bayer AG, Gedeon Richter, HRA-Pharma, Sandoz A/S, and Vifor Pharma and has designed and lectured at educational events for these companies. ET, TP, AB, AL, and JH have no conflicts of interest.

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