

Appendix 1. Search strategy

(Contraceptive Agents, Female/ OR exp Contraceptives, Oral/ OR exp Intrauterine Devices, Medicated/) OR ((Levonorgestrel/ OR Ethinyl Estradiol-Norgestrel Combination/ OR exp Progesterone/ OR exp Progestins/) and (contracept* OR birth control).ti,ab,kf,hw.) OR ((progest* OR Levonorgestrel OR ethinylestradiol OR estradiol OR Norgestrel OR etonogestrel OR oral OR pill OR tablet OR hormon* OR steroid OR inject* OR depo* OR medroxyprogesterone OR dmpa OR net-en OR norethisterone enanthate OR patch* OR transdermal OR implant* OR long acting OR intravaginal OR intra-vaginal OR ring* OR post coital OR postcoital) AND (contracept* OR birth control)).ti,ab,kf,hw. OR (norplant* OR (intrauterine ADJ2 device*) OR (intra-uterine ADJ2 device*) OR (intrauterine ADJ2 contracept*) OR (intrauterine ADJ2 system*) OR (intra-uterine ADJ2 contracept*) OR (intra-uterine ADJ2 system*) OR LNG-IUS OR IUD? OR IUS OR IUCD? OR (extrauterine ADJ2 coil*) OR (extra uterine ADJ2 coil*) OR (intravaginal ADJ2 ring*) OR (intra-vaginal ADJ2 ring*) OR (vaginal ADJ2 ring*) OR depo provera OR sayana press OR ortho evra OR xulane OR nuvaring OR mirena OR liletta OR kyleena OR Skyla OR implanon OR nexplanon OR jadelle OR uniplant OR sino-implant OR levoplant OR sinoplant OR cyclofem OR lunelle OR mesigyna or cyclo provera OR cycloprovera).ti,ab,kf,hw.

AND

exp thrombophilia/ OR exp antithrombins/ OR protein S/ OR protein C/ OR protein C deficiency/ OR protein S deficiency/ OR prothrombin/ OR Mutation/ OR "Methylenetetrahydrofolate Reductase (NADPH2)"/ OR exp Hyperhomocysteinemia/ OR (thromboph* OR thrombogenic OR prothromb* OR antithromb* OR hypercoagula* OR 5 Leiden OR V Leiden OR protein S OR protein C OR g20210a OR 20201A OR factor V OR

antiphospholipid OR anti-phospholipid OR anticardiolipin OR anti-cardiolipin OR lupus

anticoagulant* OR anti beta2 glycoprotein OR anti-beta-2-glycoprotein OR

methylenetetrahydrofolate reductase OR methylene tetrahydrofolate reductase OR methylene-thf
reductase OR MTHFR OR hyperhomocysteinemia*).ti,ab.

Appendix 2. Evidence on thrombosis risk with use of hormonal contraception among women with factor V Leiden mutation

Author, year, location, funding	Study design, period of data collection	Population	Contraception exposure and comparison	Outcome	Results																									
Vandenbroucke, 1994 [1] Netherlands Funded by Netherlands Heart Foundation	Case-control 1988-1993 3 anticoagulation clinics	Women ages 15-49 Cases: first DVT, from clinic files (N=155; 35 with factor V Leiden [86% heterozygous]) Controls: friends or partners of cases, matched by age (N=169; 6 with factor V Leiden [all heterozygous]) Exclusions: pregnant, postpartum, postmenopausal Thrombophilia diagnosed by blood tests	OC within 1 month of event (type not specified) (N=109 cases, 65 controls) Non-use (never and previous use) Self report (interview)	DVT Confirmed by “objective diagnosis” at anticoagulation clinic	<table><tr><th>Factor V Leiden</th><th>OC</th><th>Cases/controls</th><th>VTE crude RR (95% CI)</th></tr><tr><td>Yes</td><td>Non-use</td><td>10/4</td><td>Ref</td></tr><tr><td>Yes</td><td>Use</td><td>25/2</td><td>5.0 (0.8-31.8)</td></tr><tr><td>Heterozygous</td><td>Use</td><td>22/2</td><td>5.5 (0.84-36)</td></tr></table> <table><tr><th>Factor V Leiden</th><th>OC</th><th>VTE incidence per 10,000 person-years^a</th></tr><tr><td>Yes</td><td>Non-use</td><td>5.7</td></tr><tr><td>Yes</td><td>Use</td><td>28.5</td></tr></table> ^a Denominator was number of people in geographic region in same age group	Factor V Leiden	OC	Cases/controls	VTE crude RR (95% CI)	Yes	Non-use	10/4	Ref	Yes	Use	25/2	5.0 (0.8-31.8)	Heterozygous	Use	22/2	5.5 (0.84-36)	Factor V Leiden	OC	VTE incidence per 10,000 person-years ^a	Yes	Non-use	5.7	Yes	Use	28.5
Factor V Leiden	OC	Cases/controls	VTE crude RR (95% CI)																											
Yes	Non-use	10/4	Ref																											
Yes	Use	25/2	5.0 (0.8-31.8)																											
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Factor V Leiden	OC	VTE incidence per 10,000 person-years ^a																												
Yes	Non-use	5.7																												
Yes	Use	28.5																												
Anderson, 1998 [2] Denmark Funded by Helsefonden, Danish Medical Research Council, Danish National Research Foundation	Case-control 1985-end date not stated 10 hospitals in 2 counties	Women ages 18-49 Cases: first VTE (N=67; 19 with factor V Leiden [zygosity not reported]) Controls: blood donors from same region and similar age, matched 1:2 (N=134; 11 with factor V Leiden [zygosity not reported]) Exclusions: hx VTE, pregnant or postpartum, surgery/trauma within last 3 months, superficial thrombosis, malignancy, immobilization, lupus, Crohn disease.	COC 3 months before admission (N=16 with factor V Leiden) Non-use (N=14 with factor V Leiden) Hospital records and patient interview with picture prompts, some confirmed by physician	DVT +/- PE Identified by ICD code Confirmed by imaging or anticoagulant treatment	<table><tr><th>Factor V Leiden</th><th>COC</th><th>Cases/controls</th><th>VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>20/97</td><td>Ref</td></tr><tr><td>Yes</td><td>Non-use</td><td>5/9</td><td>2.6 (0.7-9.1)</td></tr><tr><td>Yes</td><td>1st and 2nd gen</td><td>9/1</td><td>64.7 (6.0-693.8)</td></tr><tr><td>Yes</td><td>3rd gen</td><td>5/1</td><td>29.6 (1.9-456.1)</td></tr></table>	Factor V Leiden	COC	Cases/controls	VTE crude OR (95% CI)	No	Non-use	20/97	Ref	Yes	Non-use	5/9	2.6 (0.7-9.1)	Yes	1 st and 2 nd gen	9/1	64.7 (6.0-693.8)	Yes	3 rd gen	5/1	29.6 (1.9-456.1)					
Factor V Leiden	COC	Cases/controls	VTE crude OR (95% CI)																											
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Yes	3 rd gen	5/1	29.6 (1.9-456.1)																											

		ulcerative colitis, heart failure Thrombophilia diagnosed by blood tests																							
Martinelli, 1999 [3] Italy Funding not stated	Case control 1995-1998 Thrombosis center	Women ages 15-48 Cases: referred to center with first DVT (N=134; 21 with factor V Leiden [92% heterozygous]) Controls: partners or friends of cases (N=179; 5 with factor V Leiden [all heterozygous]) Exclusions: hx thrombosis, cancer, autoimmune disorders, pregnant or postpartum Thrombophilia diagnosed by blood tests	COC use ≤ 2 wks before DVT or blood draw (N=87) Non-use, not further clarified Self report (questionnaire)	DVT “Objectively documented”, referred to thrombosis center	<table><tr><th>Factor V Leiden</th><th>COC</th><th>Cases/controls</th><th>DVT crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>35/127</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>52/41</td><td>4.6 (2.6-8.0)</td></tr><tr><td>Yes</td><td>Non-use</td><td>2/3</td><td>2.4 (0.4-15.1)</td></tr><tr><td>Yes</td><td>Current use</td><td>11/2</td><td>20.0 (4.2-94.3)</td></tr></table>	Factor V Leiden	COC	Cases/controls	DVT crude OR (95% CI)	No	Non-use	35/127	Ref	No	Current use	52/41	4.6 (2.6-8.0)	Yes	Non-use	2/3	2.4 (0.4-15.1)	Yes	Current use	11/2	20.0 (4.2-94.3)
Factor V Leiden	COC	Cases/controls	DVT crude OR (95% CI)																						
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Yes	Non-use	2/3	2.4 (0.4-15.1)																						
Yes	Current use	11/2	20.0 (4.2-94.3)																						
Emmerich, 2001 [4] Netherlands, Italy, France Funding not stated	Case control Poort: years not stated [5] Cattaneo: 1995-1997 [6] Alhenc-Gelas: 1995-1997 [7] Pooled analysis of 3 studies with OC information [5-7]	Women ages 15-49 Cases: at least 1 VTE (N=517) (Poort: affected families and anticoagulation clinics; Cattaneo: thrombosis center; Alhenc-Gelas: hospital) (N with Factor V Leiden mutation not reported [$>90\%$ heterozygous]) Controls: age-matched (N=518) (Poort: population controls ID'd by cases; Cattaneo: population controls from same area and “same cultural background”; Alhenc-Gelas: outpatient clinic)	Poort: Current OC use, ascertainment not stated Cattaneo: contraceptive use not described Alhenc-Gelas: Current OC use (“oestrogens” mentioned), patient interview Non-use	DVT +/- PE Poort: recruited from anticoagulation clinic Cattaneo: confirmed by imaging Alhenc-Gelas: confirmed by imaging	<table><tr><th>Factor V Leiden</th><th>OC</th><th>VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>Ref</td></tr><tr><td>No</td><td>Use</td><td>2.29 (1.72-3.04)</td></tr><tr><td>Yes</td><td>Non-use</td><td>5.88 (3.52-9.82)</td></tr><tr><td>Yes</td><td>Use</td><td>10.25 (5.69-18.45)</td></tr></table>	Factor V Leiden	OC	VTE crude OR (95% CI)	No	Non-use	Ref	No	Use	2.29 (1.72-3.04)	Yes	Non-use	5.88 (3.52-9.82)	Yes	Use	10.25 (5.69-18.45)					
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		(N with Factor V Leiden mutation not reported [>90% heterozygous]) Thrombophilia diagnosed by blood tests																																								
Spannagl, 2000 [8] Germany Funded by Schering AG	Case control 1995-1997 Multiple hospitals and outpatient facilities	Women ages 15-49 Cases: VTE (N=80; 17 with factor V Leiden) Controls: randomly sampled from database of ongoing population-based study, matched by 5-yr age group (N=406; 37 with factor V Leiden) 98% heterozygous (1 homozygous for Factor V Leiden, case status not specified) Thrombophilia diagnosed by blood tests	Current OC use (type not specified) (N=165) Non-use (never or past use) Self report (questionnaire)	DVT +/- PE All VTE (N=80) “Definite” VTE: confirmed by imaging and/or anticoagulant therapy (N=65) “Idiopathic” VTE: excluded pregnant or hx VTE (N=62)	<table><tr><th>Factor V Leiden^a</th><th>OC</th><th>Cases/controls</th><th>All VTE aOR^b (95% CI)</th></tr><tr><td>Yes</td><td>Non-use</td><td>5/27</td><td>Ref</td></tr><tr><td>Yes</td><td>Use</td><td>12/10</td><td>6.5 (1.6-26.9)</td></tr></table> <table><tr><th>Factor V Leiden^a</th><th>OC</th><th>All VTE aOR^b (95% CI)</th><th>Definite VTE aOR^b (95% CI)</th><th>Idiopathic VTE aOR^b (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>Ref</td><td>Ref</td><td>Ref</td></tr><tr><td>No</td><td>Use</td><td>2.6 (1.5-4.5)</td><td>2.7 (1.4-5.0)</td><td>4.1 (2.1-7.8)</td></tr><tr><td>Yes</td><td>Non-use</td><td>1.7 (0.6-4.8)</td><td>1.6 (0.5-5.6)</td><td>1.3 (0.2-10.5)</td></tr><tr><td>Yes</td><td>Use</td><td>6.4 (2.8-14.3)</td><td>7.0 (2.8-17.2)</td><td>10.2 (3.8-27.6)</td></tr></table> ^a All heterozygous except 1 subject ^b Adjusted for varicose veins, family history VTE, BMI	Factor V Leiden ^a	OC	Cases/controls	All VTE aOR ^b (95% CI)	Yes	Non-use	5/27	Ref	Yes	Use	12/10	6.5 (1.6-26.9)	Factor V Leiden ^a	OC	All VTE aOR ^b (95% CI)	Definite VTE aOR ^b (95% CI)	Idiopathic VTE aOR ^b (95% CI)	No	Non-use	Ref	Ref	Ref	No	Use	2.6 (1.5-4.5)	2.7 (1.4-5.0)	4.1 (2.1-7.8)	Yes	Non-use	1.7 (0.6-4.8)	1.6 (0.5-5.6)	1.3 (0.2-10.5)	Yes	Use	6.4 (2.8-14.3)	7.0 (2.8-17.2)	10.2 (3.8-27.6)
Factor V Leiden ^a	OC	Cases/controls	All VTE aOR ^b (95% CI)																																							
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No	Non-use	Ref	Ref	Ref																																						
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Yes	Use	6.4 (2.8-14.3)	7.0 (2.8-17.2)	10.2 (3.8-27.6)																																						
Legnani, 2002 [9] Italy Funding not stated	Case control 1994-2000 Thrombosis clinic	Women of “reproductive age” Cases: at least 1 VTE referred to clinic (N=301; 56 with factor V Leiden [all heterozygous]) Controls: healthy women from general population, same geographical area (N=650; 19 with factor V Leiden [all heterozygous]) Exclusions: VTE during pregnancy or postpartum	COC use at time of DVT or at time of blood sampling Non-use, not further clarified Self report (patient interview)	DVT +/- PE Confirmed by imaging	<table><tr><th>Factor V Leiden</th><th>COC</th><th>Cases/controls</th><th>VTE aOR^a (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>118/444</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>86/166</td><td>2.4 (1.7-3.5)</td></tr><tr><td>Yes</td><td>Non-use</td><td>30/15</td><td>8.9 (4.4-18.2)</td></tr><tr><td>Yes</td><td>Current use</td><td>26/4</td><td>41.0 (13.5-125)</td></tr></table> ^a Adjusted for age and other thrombophilic defects	Factor V Leiden	COC	Cases/controls	VTE aOR ^a (95% CI)	No	Non-use	118/444	Ref	No	Current use	86/166	2.4 (1.7-3.5)	Yes	Non-use	30/15	8.9 (4.4-18.2)	Yes	Current use	26/4	41.0 (13.5-125)																	
Factor V Leiden	COC	Cases/controls	VTE aOR ^a (95% CI)																																							
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Yes	Current use	26/4	41.0 (13.5-125)																																							

		Thrombophilia diagnosed by blood tests																							
Martinelli, 2003 [10] Italy Funded by Ministero dell'Universita e della Ricerca Scientifica e Tecnologica	Case control 1991-2002 Thrombosis center	Women of reproductive age Cases: first CVT (N=80; N with Factor V Leiden and zygosity not reported) Controls: partners or friends of cases, matched on age (N=148; N with Factor V Leiden and zygosity not reported) Exclusions: hx thrombosis Thrombophilia diagnosed by blood tests	OC use (type not specified) ≤2 wks before thrombosis or blood draw (N=100) Non-use, not further clarified Self report (questionnaire)	CVT Confirmed by medical records, imaging, and neurologist	<table><tr><td>Factor V Leiden</td><td>OC</td><td colspan="2">CVT crude OR (95% CI)</td></tr><tr><td>No</td><td>Non-use</td><td colspan="2">Ref</td></tr><tr><td>Yes</td><td>Current use</td><td colspan="2">30.0 (3.4-263.0)</td></tr></table>	Factor V Leiden	OC	CVT crude OR (95% CI)		No	Non-use	Ref		Yes	Current use	30.0 (3.4-263.0)									
Factor V Leiden	OC	CVT crude OR (95% CI)																							
No	Non-use	Ref																							
Yes	Current use	30.0 (3.4-263.0)																							
Sidney, 2004 [11] United States Funded by National Heart Lung and Blood Institute	Case control 1998-2000 Kaiser Permanente Northern and Southern California	Women ages 18-44 Cases: VTE (N=153 with thrombophilia testing; 18 with factor V Leiden [zygosity not reported]) Controls: women randomly selected from same healthcare plan, matched by 5-yr age band (N=312 with thrombophilia testing; 6 with factor V Leiden [zygosity not reported]) Exclusions: pregnant, hx VTE Thrombophilia diagnosed by blood tests	Current COC (<50 mcg estrogen) (N=134) Non-current use (included past use, recency not stated) Self-report by subject or proxy (for cases only), included pictures of COCs for identification	DVT +/- PE Identified by hospital or outpatient records and claims, or outpatient anticoagulation Confirmed by imaging (included definite or probable VTE)	<table><tr><td>Factor V Leiden</td><td>COC</td><td>Cases/controls</td><td>VTE aOR^a (95% CI)</td></tr><tr><td>No</td><td>Non-use</td><td>76/244</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>59/61</td><td>3.20 (2.04-5.03)</td></tr><tr><td>Yes</td><td>Non-use</td><td>8/3</td><td>8.42 (2.18-32.56)</td></tr><tr><td>Yes</td><td>Current use</td><td>10/3</td><td>11.32 (3.00-42.81)</td></tr></table> ^a Adjusted for age	Factor V Leiden	COC	Cases/controls	VTE aOR ^a (95% CI)	No	Non-use	76/244	Ref	No	Current use	59/61	3.20 (2.04-5.03)	Yes	Non-use	8/3	8.42 (2.18-32.56)	Yes	Current use	10/3	11.32 (3.00-42.81)
Factor V Leiden	COC	Cases/controls	VTE aOR ^a (95% CI)																						
No	Non-use	76/244	Ref																						
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Yes	Non-use	8/3	8.42 (2.18-32.56)																						
Yes	Current use	10/3	11.32 (3.00-42.81)																						
Slooter, 2005 [12]	Case control (RATIO study)	Women ages 18-49	Current OC (type not specified) (within 1	Ischemic stroke	<table><tr><td>Factor V Leiden</td><td>OC</td><td>Cases/controls</td><td>Stroke aOR^a (95% CI)</td></tr></table>	Factor V Leiden	OC	Cases/controls	Stroke aOR ^a (95% CI)																
Factor V Leiden	OC	Cases/controls	Stroke aOR ^a (95% CI)																						

Netherlands	1990-2001	Cases: hospitalized with first stroke (N=193; 14 with factor V Leiden [zygosity not reported])	month before index date) (N=373)	Confirmed by imaging	<table><tr><td>No</td><td>Non-use</td><td>83/463</td><td>Ref</td></tr><tr><td>No</td><td>Use</td><td>82/254</td><td>2.6 (1.7-4.0)</td></tr><tr><td>Yes</td><td>Non-use</td><td>2/24</td><td>0.4 (0.1-1.9)</td></tr><tr><td>Yes</td><td>Use</td><td>12/16</td><td>11.2 (4.3-29.0)</td></tr></table>	No	Non-use	83/463	Ref	No	Use	82/254	2.6 (1.7-4.0)	Yes	Non-use	2/24	0.4 (0.1-1.9)	Yes	Use	12/16	11.2 (4.3-29.0)
No	Non-use	83/463	Ref																		
No	Use	82/254	2.6 (1.7-4.0)																		
Yes	Non-use	2/24	0.4 (0.1-1.9)																		
Yes	Use	12/16	11.2 (4.3-29.0)																		
Funded by Netherlands Heart Foundation, Brain Foundation Netherlands	9 hospitals	Controls: no history of heart disease, stroke, or peripheral vascular disease, identified by random digit dialing, matched by age, residence, and year (N=767; 42 with factor V Leiden [zygosity not reported])	Non-use (previous or never use)		^a Adjusted for age, year, residence																
		Exclusions: transient ischemic attack, hemorrhagic stroke, CVT, carotid artery dissection, hx cardiovascular or cerebrovascular disease, terminal illness, aphasia, cognitive impairment, non-Dutch speaking	Self report (mailed questionnaire), included pictures of OCs for identification																		
		Thrombophilia diagnosed by blood tests																			
Martinelli, 2006 [13]	Case control	Women of “fertile age”	OC use (over half using COCs) ≤2 wks before stroke (N=110)	Ischemic stroke	<table><tr><td>Factor V Leiden</td><td>OC</td><td>Stroke aOR^a (95% CI)</td></tr><tr><td>No</td><td>Non-use</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>2.1 (1.3-3.6)</td></tr><tr><td>Yes</td><td>Non-use</td><td>1.4 (0.3-7.3)</td></tr><tr><td>Yes</td><td>Current use</td><td>12.9 (1.3-133.7)</td></tr></table>	Factor V Leiden	OC	Stroke aOR ^a (95% CI)	No	Non-use	Ref	No	Current use	2.1 (1.3-3.6)	Yes	Non-use	1.4 (0.3-7.3)	Yes	Current use	12.9 (1.3-133.7)	
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Yes	Non-use	1.4 (0.3-7.3)																			
Yes	Current use	12.9 (1.3-133.7)																			
Italy	1994-2005	Cases: first ischemic stroke (N=105; 6 with factor V Leiden [all heterozygous])	Non-use, not further clarified	Ascertained by medical records, confirmed by imaging or neurologist	^a Adjusted for age, education level, hypertension, hypercholesterolemia, obesity, and smoking																
Funding not stated	Thrombosis center	Controls: healthy, unrelated partners or friends of patients (N=293; 7 with factor V Leiden [all heterozygous])	Self report (questionnaire)																		
		Exclusions: hx thrombosis																			

		Thrombophilia diagnosed by blood tests																																											
Kuipers, 2009 [14] Netherlands Funded by Netherlands Heart Foundation, Dutch Cancer Foundation, United Kingdom government, European Commission	Case control 1999-2004 6 anticoagulant clinics	Women from MEGA study with travel at least 4 hrs within 8 wks before index date Cases: women with VTE from anticoagulant clinic records (N=200; N with Factor V Leiden and zygosity not reported) Controls: partners of patients (N=134; N with Factor V Leiden and zygosity not reported) Exclusions: non-Dutch speaking, severe psych problems, no partner Thrombophilia diagnosed by blood tests	OC (type not specified) (N=61) Non-use presumed Questionnaire	First DVT +/- PE Confirmed by imaging	<table><tr><th>Factor V Leiden</th><th>OC</th><th>VTE aOR* (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>Ref</td></tr><tr><td>No</td><td>Use</td><td>5.0 (2.1-12.1)</td></tr><tr><td>Yes</td><td>Non-use</td><td>4.5 (1.9-10.4)</td></tr><tr><td>Yes</td><td>Use</td><td>18.3 (2.0-171)</td></tr></table> *Adjusted for age and sex	Factor V Leiden	OC	VTE aOR* (95% CI)	No	Non-use	Ref	No	Use	5.0 (2.1-12.1)	Yes	Non-use	4.5 (1.9-10.4)	Yes	Use	18.3 (2.0-171)																									
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Yes	Non-use	4.5 (1.9-10.4)																																											
Yes	Use	18.3 (2.0-171)																																											
Bergendal, 2014 [15] Sweden Funded by Janssen-Cilag, Novartis, Organon, Schering, Wyeth, AFA Insurance, Center for Gender Medicine Karolinska Institutet, Medical Products Agency	Case control 2003-2009 43 hospitals in Sweden	Women ages 18-54 Cases: first DVT or PE, inpatient and outpatient (N=948; 223 with factor V Leiden [96% heterozygous]) Controls: from Swedish population register, matched by birth year (N=902; 70 with factor V Leiden [91% heterozygous]) Exclusions: hx thrombosis, pregnant or postpartum in last 3 months, current malignancy (hx malignancy included only if disease-free for 5 yrs)	Current CHC (COC, patch, ring; >95% COC) ≤3 mo of index date Current POC (LNG-IUDs, ETG or LNG implants (52), DMPA, POPs) ≤3 mo of index date Non-use Self report (phone interview)	DVT +/- PE Confirmed by imaging and anticoagulant treatment	<table><tr><th>Factor V Leiden</th><th>CHC</th><th>Cases/controls</th><th>VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>No HC use</td><td>378/525</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>221/91</td><td>3.4 (2.5-4.5)</td></tr><tr><td>Yes</td><td>No HC use</td><td>101/55</td><td>2.6 (1.8-3.7)</td></tr><tr><td>Yes</td><td>Current use</td><td>89/6</td><td>20.6 (8.9-58)</td></tr></table> <table><tr><th>Factor V Leiden</th><th>POC</th><th>Cases/controls</th><th>VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>No HC use</td><td>378/525</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>107/54</td><td>1.0 (0.7-1.3)</td></tr><tr><td>Yes</td><td>No HC use</td><td>101/55</td><td>2.6 (1.8-3.7)</td></tr><tr><td>Yes</td><td>Current use</td><td>35/9</td><td>5.4 (2.5-13)</td></tr></table>	Factor V Leiden	CHC	Cases/controls	VTE crude OR (95% CI)	No	No HC use	378/525	Ref	No	Current use	221/91	3.4 (2.5-4.5)	Yes	No HC use	101/55	2.6 (1.8-3.7)	Yes	Current use	89/6	20.6 (8.9-58)	Factor V Leiden	POC	Cases/controls	VTE crude OR (95% CI)	No	No HC use	378/525	Ref	No	Current use	107/54	1.0 (0.7-1.3)	Yes	No HC use	101/55	2.6 (1.8-3.7)	Yes	Current use	35/9	5.4 (2.5-13)
Factor V Leiden	CHC	Cases/controls	VTE crude OR (95% CI)																																										
No	No HC use	378/525	Ref																																										
No	Current use	221/91	3.4 (2.5-4.5)																																										
Yes	No HC use	101/55	2.6 (1.8-3.7)																																										
Yes	Current use	89/6	20.6 (8.9-58)																																										
Factor V Leiden	POC	Cases/controls	VTE crude OR (95% CI)																																										
No	No HC use	378/525	Ref																																										
No	Current use	107/54	1.0 (0.7-1.3)																																										
Yes	No HC use	101/55	2.6 (1.8-3.7)																																										
Yes	Current use	35/9	5.4 (2.5-13)																																										

		Thrombophilia diagnosed by blood tests			Exclusion of obese and severely immobilized women from models did not substantially change results																				
Khialani, 2020 [16]	Case control (MEGA study)	Women ages 18-49	COC (30 mcg estrogen) within year before index date (N=1772)	DVT +/- PE	<table><tr><th>Factor V Leiden</th><th>COC</th><th>Cases/controls</th><th>VTE aOR^a (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>266/745</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>800/463</td><td>5.5 (4.6-6.7)</td></tr><tr><td>Yes</td><td>Non-use</td><td>28/52</td><td>1.7 (1.1-2.6)</td></tr><tr><td>Yes</td><td>Current use</td><td>176/24</td><td>19.3 (13.9-26.8)</td></tr></table> ^a Adjusted for age	Factor V Leiden	COC	Cases/controls	VTE aOR ^a (95% CI)	No	Non-use	266/745	Ref	No	Current use	800/463	5.5 (4.6-6.7)	Yes	Non-use	28/52	1.7 (1.1-2.6)	Yes	Current use	176/24	19.3 (13.9-26.8)
Factor V Leiden	COC	Cases/controls	VTE aOR ^a (95% CI)																						
No	Non-use	266/745	Ref																						
No	Current use	800/463	5.5 (4.6-6.7)																						
Yes	Non-use	28/52	1.7 (1.1-2.6)																						
Yes	Current use	176/24	19.3 (13.9-26.8)																						
Netherlands	1999-2004	Cases: first VTE from anticoagulant clinic records (N=1426; 204 with factor V Leiden [zygosity not reported])	Nonhormonal use (N=1420)	Confirmed by imaging																					
Funding not stated	6 anticoagulant clinics	Controls: partners of patients or recruited by random digit dialing, matched on age (N=1777; 76 with factor V Leiden [zygosity not reported])	Self report (questionnaire)																						
		Exclusions: non-Dutch speaking, severe psych problems, postmenopausal, pregnant or 4 wks postpartum																							
		Thrombophilia diagnosed by blood tests																							

aOR, adjusted odds ratio; BMI, body mass index; CHC, combined hormonal contraception; CI, confidence interval; COC, combined oral contraception; CVT, cerebral venous thrombosis; DMPA, Depot medroxyprogesterone acetate; DVT, deep venous thrombosis; ETG, etonogestrel; ICD, International Classification of Disease; IUD, intrauterine device; LNG, levonorgestrel; MEGA, Multiple Environmental and Genetic Assessment; OC, oral contraception; OR, odds ratio; PE, pulmonary embolism; POC, progestin-only contraception; POP, progestin-only pill; RATIO, Risk of Arterial Thrombosis In relation to Oral contraceptives; VTE, venous thromboembolism.

Appendix 3. Evidence on thrombosis risk with use of hormonal contraception among women with prothrombin gene mutation

Author, year, location, funding	Study design, period of data collection	Population	Contraception exposure and comparison	Outcome	Results																				
Martinelli, 1998 [17] Italy Funding not stated	Case control 1991-1997 Thrombosis center	Women of reproductive age Cases: referred to center with first CVT (N=27; 7 with PT mutation [all heterozygous]) Controls: partners or friends of cases, matched on age, geographic origin, level of education (N=93; 2 with PT mutation [all heterozygous]) Exclusions: pregnant or postpartum, postmenopausal, hx thrombosis Thrombophilia diagnosed by blood tests	OC use (type not specified) ≤2 wks before thrombosis or blood draw (N=52) Non-use, not further clarified Self report (questionnaire)	CVT Confirmed by medical records, imaging, and neurologist	<table><tr><th>PT mutation^a</th><th>OC</th><th>Cases/controls</th><th>CVT crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>3/64</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>17/27</td><td>13.4 (3.5-51.3)</td></tr><tr><td>Yes</td><td>Non-use</td><td>0/1</td><td>--^b</td></tr><tr><td>Yes</td><td>Current use</td><td>7/1</td><td>149.3 (31.0-711.0)</td></tr></table> ^a All heterozygous ^b Not able to be calculated, no CVT in non-users with mutation	PT mutation ^a	OC	Cases/controls	CVT crude OR (95% CI)	No	Non-use	3/64	Ref	No	Current use	17/27	13.4 (3.5-51.3)	Yes	Non-use	0/1	-- ^b	Yes	Current use	7/1	149.3 (31.0-711.0)
PT mutation ^a	OC	Cases/controls	CVT crude OR (95% CI)																						
No	Non-use	3/64	Ref																						
No	Current use	17/27	13.4 (3.5-51.3)																						
Yes	Non-use	0/1	-- ^b																						
Yes	Current use	7/1	149.3 (31.0-711.0)																						
Martinelli, 1999 [3] Italy Funding not stated	Case control 1995-1998 Thrombosis center	Women ages 15-48 Cases: referred to center with first DVT (N=134; 12 with PT mutation [all heterozygous]) Controls: partners or friends of cases (N=179; 6 with PT mutation [all heterozygous]) Exclusions: hx thrombosis, cancer, autoimmune disorders, pregnant or postpartum	COC use ≤2 wks before DVT or blood draw (N=87) Non-use, not further clarified Self report (questionnaire)	DVT “Objectively documented”, referred to thrombosis center	<table><tr><th>PT mutation</th><th>COC</th><th>Cases/controls</th><th>DVT crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>35/127</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>52/41</td><td>4.6 (2.6-8.0)</td></tr><tr><td>Yes</td><td>Non-use</td><td>3/4</td><td>2.7 (0.6-12.7)</td></tr><tr><td>Yes</td><td>Current use</td><td>9/2</td><td>16.3 (3.4-79.1)</td></tr></table>	PT mutation	COC	Cases/controls	DVT crude OR (95% CI)	No	Non-use	35/127	Ref	No	Current use	52/41	4.6 (2.6-8.0)	Yes	Non-use	3/4	2.7 (0.6-12.7)	Yes	Current use	9/2	16.3 (3.4-79.1)
PT mutation	COC	Cases/controls	DVT crude OR (95% CI)																						
No	Non-use	35/127	Ref																						
No	Current use	52/41	4.6 (2.6-8.0)																						
Yes	Non-use	3/4	2.7 (0.6-12.7)																						
Yes	Current use	9/2	16.3 (3.4-79.1)																						

		Thrombophilia diagnosed by blood tests																							
Emmerich, 2001 [4] Netherlands, Italy, France Funding not stated	Case control Poort: years not stated Cattaneo: 1995-1997 Alhenc-Gelas: 1995-1997 Pooled analysis of 3 studies with OC information (Poort, Cattaneo, Alhenc-Gelas)	Women ages 15-49 Cases: at least 1 VTE (N=517) (Poort: affected families and anticoagulation clinics; Cattaneo: thrombosis center; Alhenc-Gelas: hospital) (N with PT gene mutation not reported [>90% heterozygous]) Controls: age-matched (N=518) (Poort: population controls ID'd by cases; Cattaneo: population controls from same area and "same cultural background"; Alhenc-Gelas: outpatient clinic) (N with PT gene mutation not reported [>90% heterozygous]) Thrombophilia diagnosed by blood tests	Poort: Current OC use, ascertainment not stated Cattaneo: contraceptive use not described Alhenc-Gelas: Current OC use ("oestrogens" mentioned), patient interview Non-use	First or recurrent DVT +/- PE Poort: recruited from anticoagulation clinic Cattaneo: confirmed by imaging Alhenc-Gelas: confirmed by imaging	<table><tr><th>PT gene mutation</th><th>OC</th><th>VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>Ref</td></tr><tr><td>No</td><td>Use</td><td>2.29 (1.72-3.04)</td></tr><tr><td>Yes</td><td>Non-use</td><td>3.21 (1.44-7.15)</td></tr><tr><td>Yes</td><td>Use</td><td>7.14 (3.39-15.04)</td></tr></table>	PT gene mutation	OC	VTE crude OR (95% CI)	No	Non-use	Ref	No	Use	2.29 (1.72-3.04)	Yes	Non-use	3.21 (1.44-7.15)	Yes	Use	7.14 (3.39-15.04)					
PT gene mutation	OC	VTE crude OR (95% CI)																							
No	Non-use	Ref																							
No	Use	2.29 (1.72-3.04)																							
Yes	Non-use	3.21 (1.44-7.15)																							
Yes	Use	7.14 (3.39-15.04)																							
Legnani, 2002 [9] Italy Funding not stated	Case control 1994-2000 Thrombosis clinic	Women of "reproductive age" Cases: at least 1 VTE referred to clinic (N=301; 29 with PT mutation [all heterozygous]) Controls: healthy women from general population, same geographical area (N=650; 20 with PT mutation [all heterozygous])	COC use at time of DVT or at time of blood sampling (N=313) Non-use, not further clarified Self report (patient interview)	DVT +/- PE Confirmed by imaging	<table><tr><th>PT mutation</th><th>COC</th><th>Cases/controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>118/444</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>86/166</td><td>2.4 (1.7-3.5)</td></tr><tr><td>Yes</td><td>Non-use</td><td>11/18</td><td>2.0 (0.8-4.8)</td></tr><tr><td>Yes</td><td>Current use</td><td>18/2</td><td>58.6 (12.8-267)</td></tr></table> *Adjusted for age and other thrombophilic defects	PT mutation	COC	Cases/controls	VTE aOR* (95% CI)	No	Non-use	118/444	Ref	No	Current use	86/166	2.4 (1.7-3.5)	Yes	Non-use	11/18	2.0 (0.8-4.8)	Yes	Current use	18/2	58.6 (12.8-267)
PT mutation	COC	Cases/controls	VTE aOR* (95% CI)																						
No	Non-use	118/444	Ref																						
No	Current use	86/166	2.4 (1.7-3.5)																						
Yes	Non-use	11/18	2.0 (0.8-4.8)																						
Yes	Current use	18/2	58.6 (12.8-267)																						

		Exclusions: VTE during pregnancy or postpartum Thrombophilia diagnosed by blood test																							
Martinelli, 2003 [10] Italy Funded by Ministero dell'Universita e della Ricerca Scientifica e Tecnologica	Case control 1991-2002 Thrombosis center	Women of reproductive age Cases: referred to center with first CVT (N=80; N with Factor V Leiden and zygosity not reported) Controls: partners or friends of cases, matched on age (N=148; N with Factor V Leiden and zygosity not reported) Exclusions: hx thrombosis Thrombophilia diagnosed by blood tests	OC use (type not specified) ≤2 wks before thrombosis or blood draw (N=100) Non-use, not further clarified Self report (questionnaire)	CVT Confirmed by medical records, imaging, and neurologist	<table><tr><th>PT mutation</th><th>OC</th><th>CVT crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>Ref</td></tr><tr><td>Yes</td><td>Current use</td><td>79.3 (10.0-629.4)</td></tr></table>	PT mutation	OC	CVT crude OR (95% CI)	No	Non-use	Ref	Yes	Current use	79.3 (10.0-629.4)											
PT mutation	OC	CVT crude OR (95% CI)																							
No	Non-use	Ref																							
Yes	Current use	79.3 (10.0-629.4)																							
Sidney, 2004 [11] United States Funded by National Heart Lung and Blood Institute	Case control 1998-2000 Kaiser Permanente Northern and Southern California	Women ages 18-44 Cases: VTE (N=153 with thrombophilia testing; 8 with PT mutation [zygosity not reported]) Controls: women randomly selected from same healthcare plan, matched by 5-yr age band (N=312 with thrombophilia testing; 4 with PT mutation [zygosity not reported]) Exclusions: pregnant, hx VTE	Current COC (<50 mcg estrogen) (N=134) Non-current use (included past use, recency not stated) Self-report by subject or proxy (for cases only), included pictures of COCs for identification	DVT +/- PE Identified by hospital or outpatient records and claims, or outpatient anticoagulation Confirmed by imaging (included definite or probable VTE)	<table><tr><th>PT mutation</th><th>COC</th><th>Cases/controls</th><th>VTE aOR^a (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>69/223</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>62/58</td><td>3.64 (2.30-5.77)</td></tr><tr><td>Yes</td><td>Non-use</td><td>5/2</td><td>8.43 (1.60-44.41)</td></tr><tr><td>Yes</td><td>Current use</td><td>3/2</td><td>5.10 (0.83-31.18)</td></tr></table> ^a Adjusted for age	PT mutation	COC	Cases/controls	VTE aOR ^a (95% CI)	No	Non-use	69/223	Ref	No	Current use	62/58	3.64 (2.30-5.77)	Yes	Non-use	5/2	8.43 (1.60-44.41)	Yes	Current use	3/2	5.10 (0.83-31.18)
PT mutation	COC	Cases/controls	VTE aOR ^a (95% CI)																						
No	Non-use	69/223	Ref																						
No	Current use	62/58	3.64 (2.30-5.77)																						
Yes	Non-use	5/2	8.43 (1.60-44.41)																						
Yes	Current use	3/2	5.10 (0.83-31.18)																						

		Thrombophilia diagnosed by blood tests																																											
Martinelli, 2006 [13] Italy Funding not stated	Case control 1994-2005 Thrombosis center	Women of “fertile age” Cases: first ischemic stroke (N=105; 5 with PT mutation [all heterozygous]) Controls: healthy, unrelated partners or friends of patients (N=293; 15 with PT mutation [all heterozygous]) Exclusions: hx thrombosis Thrombophilia diagnosed by blood tests	OC use (over half using COCs) ≤2 wks before stroke (N=110) Non-use, not further clarified Self report (questionnaire)	Ischemic stroke Ascertained by medical records, confirmed by imaging or neurologist	<table><tr><th>PT mutation</th><th>OC</th><th>Stroke aOR^a (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>2.2 (1.3-3.7)</td></tr><tr><td>Yes</td><td>Non-use</td><td>0.5 (0.1-2.5)</td></tr><tr><td>Yes</td><td>Current use</td><td>3.1 (0.4-23.3)</td></tr></table> ^a Adjusted for age, education level, hypertension, hypercholesterolemia, obesity, and smoking	PT mutation	OC	Stroke aOR ^a (95% CI)	No	Non-use	Ref	No	Current use	2.2 (1.3-3.7)	Yes	Non-use	0.5 (0.1-2.5)	Yes	Current use	3.1 (0.4-23.3)																									
PT mutation	OC	Stroke aOR ^a (95% CI)																																											
No	Non-use	Ref																																											
No	Current use	2.2 (1.3-3.7)																																											
Yes	Non-use	0.5 (0.1-2.5)																																											
Yes	Current use	3.1 (0.4-23.3)																																											
Bergendal, 2014 [15] Sweden Funded by Janssen-Cilag, Novartis, Organon, Schering, Wyeth, AFA Insurance, Center for Gender Medicine Karolinska Institutet, Medical Products Agency	Case control 2003-2009 43 hospitals in Sweden	Women ages 18-54 Cases: first DVT or PE, inpatient and outpatient (N=948; 55 with PT gene mutation [95% heterozygous]) Controls: from Swedish population register, matched by birth year (N=902; 27 with PT gene mutation [96% heterozygous]) Exclusions: hx thrombosis, pregnant or postpartum in last 3 months, current malignancy (hx malignancy included only if disease-free for 5 yrs) Thrombophilia diagnosed by blood tests	Current CHC (COC, patch, ring: >95% COC) ≤3 mo of index date Current POC (LNG-IUDs, ETG or LNG implants (52), DMPA, POPs) ≤3 mo of index date Non-use Self report (phone interview)	DVT +/- PE Confirmed by imaging and anticoagulant treatment	<table><tr><th>PT gene mutation</th><th>CHC</th><th>Cases/controls</th><th>VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>No HC use</td><td>459/556</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>273/97</td><td>3.4 (2.6-4.5)</td></tr><tr><td>Yes</td><td>No HC use</td><td>21/15</td><td>1.7 (0.8-3.6)</td></tr><tr><td>Yes</td><td>Current use</td><td>29/2</td><td>17.6 (4.4-152)</td></tr></table> <table><tr><th>PT gene mutation</th><th>POC</th><th>Cases/controls</th><th>VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>No HC use</td><td>459/556</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>133/154</td><td>1.0 (0.8-1.4)</td></tr><tr><td>Yes</td><td>No HC use</td><td>21/15</td><td>1.7 (0.8-3.6)</td></tr><tr><td>Yes</td><td>Current use</td><td>6/10</td><td>0.7 (0.2-2.2)</td></tr></table> Exclusion of obese and severely immobilized women from models did not substantially change results	PT gene mutation	CHC	Cases/controls	VTE crude OR (95% CI)	No	No HC use	459/556	Ref	No	Current use	273/97	3.4 (2.6-4.5)	Yes	No HC use	21/15	1.7 (0.8-3.6)	Yes	Current use	29/2	17.6 (4.4-152)	PT gene mutation	POC	Cases/controls	VTE crude OR (95% CI)	No	No HC use	459/556	Ref	No	Current use	133/154	1.0 (0.8-1.4)	Yes	No HC use	21/15	1.7 (0.8-3.6)	Yes	Current use	6/10	0.7 (0.2-2.2)
PT gene mutation	CHC	Cases/controls	VTE crude OR (95% CI)																																										
No	No HC use	459/556	Ref																																										
No	Current use	273/97	3.4 (2.6-4.5)																																										
Yes	No HC use	21/15	1.7 (0.8-3.6)																																										
Yes	Current use	29/2	17.6 (4.4-152)																																										
PT gene mutation	POC	Cases/controls	VTE crude OR (95% CI)																																										
No	No HC use	459/556	Ref																																										
No	Current use	133/154	1.0 (0.8-1.4)																																										
Yes	No HC use	21/15	1.7 (0.8-3.6)																																										
Yes	Current use	6/10	0.7 (0.2-2.2)																																										

Tufano, 2014 [18]	Case control	Ages not stated	OC use (type not specified) (current or within 1 month before entering study) (type not specified) (N=43)	CVT	<table><tr><th>PT mutation</th><th>OC</th><th colspan="2">VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td colspan="2">Ref</td></tr><tr><td>No</td><td>Use</td><td colspan="2">6.12 (2.83-13.23)</td></tr><tr><td>Yes</td><td>Non-use</td><td colspan="2">--^a</td></tr><tr><td>Yes</td><td>Use</td><td colspan="2">48.53 (5.57-422.56)</td></tr></table>	PT mutation	OC	VTE crude OR (95% CI)		No	Non-use	Ref		No	Use	6.12 (2.83-13.23)		Yes	Non-use	-- ^a		Yes	Use	48.53 (5.57-422.56)	
PT mutation	OC	VTE crude OR (95% CI)																							
No	Non-use	Ref																							
No	Use	6.12 (2.83-13.23)																							
Yes	Non-use	-- ^a																							
Yes	Use	48.53 (5.57-422.56)																							
Italy	1997-2012	Cases: admitted with CVT (N=41; N with PT mutation and zygosity not reported)	Non-use (not further described)	Confirmation not stated (admitted to hospital for CVT)	*Not reported																				
Funding not stated	Center for coagulation disorders	Controls: healthy friends and partners of cases, same ethnic background, matched by age (N=134; N with PT mutation and zygosity not reported)	Ascertainment not described																						
		Exclusions: none stated																							
		Thrombophilia diagnosed by blood tests																							
Momot, 2019 [19]	Nested case control	Women ages 18-45	CHC use	VTE or ATE	<table><tr><th>PT mutation</th><th>CHC</th><th>Cases/controls</th><th>Thrombosis crude OR (95% CI)</th></tr><tr><td>Yes</td><td>Non-use</td><td>19/92</td><td>Ref</td></tr><tr><td>Yes</td><td>Current use</td><td>13/16</td><td>4.7 (1.89-11.54)</td></tr></table>	PT mutation	CHC	Cases/controls	Thrombosis crude OR (95% CI)	Yes	Non-use	19/92	Ref	Yes	Current use	13/16	4.7 (1.89-11.54)								
PT mutation	CHC	Cases/controls	Thrombosis crude OR (95% CI)																						
Yes	Non-use	19/92	Ref																						
Yes	Current use	13/16	4.7 (1.89-11.54)																						
Russia	2012-2017	Cases: women with thrombosis (N=32 with PT mutation [zygosity not reported])	Non-use, not further clarified	Method of confirmation not stated																					
Funding not stated	Location of patients not stated	Controls: women without thrombosis (N=108 with PT mutation [zygosity not reported])	Method of ascertainment not stated																						
		Exclusions: autoimmune dz including APLS, factor V Leiden mutation, AT deficiency, protein C deficiency, protein S deficiency																							
		Thrombophilia diagnosed by blood tests																							
Khialani, 2020 [16]	Case control (MEGA study)	Women ages 18-49	COC (30 mcg estrogen) within year before index date (N=1772)	DVT +/- PE	<table><tr><th>PT mutation</th><th>COC</th><th>Cases/controls</th><th>VTE aOR^a (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>275/785</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>925/481</td><td>6.2 (5.1-7.5)</td></tr><tr><td>Yes</td><td>Non-use</td><td>19/12</td><td>4.9 (2.5-9.4)</td></tr></table>	PT mutation	COC	Cases/controls	VTE aOR ^a (95% CI)	No	Non-use	275/785	Ref	No	Current use	925/481	6.2 (5.1-7.5)	Yes	Non-use	19/12	4.9 (2.5-9.4)				
PT mutation	COC	Cases/controls	VTE aOR ^a (95% CI)																						
No	Non-use	275/785	Ref																						
No	Current use	925/481	6.2 (5.1-7.5)																						
Yes	Non-use	19/12	4.9 (2.5-9.4)																						
Netherlands	1999-2004	Cases: first VTE from anticoagulant clinic records (N=1426; 70		Confirmed by imaging																					
Funding not stated																									

	6 anticoagulant clinics	with PT mutation [zygosity not reported] Controls: partners of patients or recruited by random digit dialing, matched on age (N=1777; 18 with PT mutation [zygosity not reported]) Exclusions: non-Dutch speaking, severe psychiatric problems, postmenopausal, pregnant or 4 wks postpartum Thrombophilia diagnosed by blood tests	Nonhormonal use (N=1420) Self report (questionnaire)		Yes	Current use	51/6	24.0 (13.6-42.3)
					^a Adjusted for age			

aOR, adjusted odds ratio; APLS, antiphospholipid syndrome; AT, antithrombin; ATE, arterial thromboembolism; CHC, combined hormonal contraception; CI, confidence interval; COC, combined oral contraception; CVT, cerebral venous thrombosis; DMPA, Depot medroxyprogesterone acetate; DVT, deep venous thrombosis; ETG, etonogestrel; IUD, intrauterine device; LNG, levonorgestrel; MEGA, Multiple Environmental and Genetic Assessment; OC, oral contraception; OR, odds ratio; PE, pulmonary embolism; POC, progestin-only contraception; POP, progestin-only pill; PT, prothrombin; VTE, venous thromboembolism.

Appendix 4. Evidence on thrombosis risk with use of hormonal contraception among women with antithrombin deficiency

Author, year, location, funding	Study design, period of data collection	Population	Contraception exposure and comparison	Outcome	Results																								
Pabinger, 1994 [20] Austria, Germany, Switzerland Funded by Schering	Retrospective cohort 1964-1991 8 coagulation labs and thrombosis units	Women with hereditary thrombophilia (at least one relative with same deficiency) (age range not stated) Cohort: ever use of OCs (N=15 with antithrombin III deficiency [all heterozygous]) Controls: never use of OCs, selected from computer list, matched 1:1 by age (N=15 with antithrombin III deficiency [all heterozygous]) Exclusions: current use of anticoagulants Thrombophilia diagnosed by blood tests, different by site	Current OC use (type not specified) Self or physician report (questionnaire filled in by patient or physician)	DVT, PE, SVT, arm vein thrombosis, or CVT Confirmed by imaging, hospitalization plus anticoagulation, or clinical symptoms (SVT)	<table><tr><th>AT deficiency</th><th>OC</th><th>VTE/Total N</th><th colspan="3">VTE incidence^a</th></tr><tr><td></td><td></td><td></td><th>Per patient year</th><th>After 12 mos</th><th>After 60 mos</th></tr><tr><td>Yes</td><td>Never users</td><td>1/15</td><td>3.4%</td><td>0%</td><td>17%</td></tr><tr><td>Yes</td><td>Current users</td><td>10/15</td><td>27.5%</td><td>48%</td><td>77%</td></tr></table> ^a Difference between groups statistically significant (Wilcoxon test p=0.004, Log-Rank test p=0.005)	AT deficiency	OC	VTE/Total N	VTE incidence ^a						Per patient year	After 12 mos	After 60 mos	Yes	Never users	1/15	3.4%	0%	17%	Yes	Current users	10/15	27.5%	48%	77%
AT deficiency	OC	VTE/Total N	VTE incidence ^a																										
			Per patient year	After 12 mos	After 60 mos																								
Yes	Never users	1/15	3.4%	0%	17%																								
Yes	Current users	10/15	27.5%	48%	77%																								
Van Vlijmen, 2007 [21] Netherlands Funding not stated	Retrospective cohort Years not stated 1 hospital	Women ages 15-50 Cohort: women with thrombophilia using COCs (N=11 with AT deficiency [zygosity not reported]) Controls: family members with thrombophilia not using COCs (N=22 with AT deficiency [zygosity not reported])) Exclusions: none stated	COC within 3 months of event Never use Self report (questionnaire)	VTE Confirmed by imaging or anticoagulant therapy	<table><tr><th>AT deficiency</th><th>COC</th><th>VTE/Total N</th><th>VTE annual incidence, % (95% CI)</th></tr><tr><td>No</td><td>Never use</td><td>0/13</td><td>0% (0-1.3)</td></tr><tr><td>No</td><td>Use</td><td>0/17</td><td>0% (0-0.38)</td></tr><tr><td>Yes</td><td>Never use</td><td>6/22</td><td>1.77% (0.7-3.9)</td></tr><tr><td>Yes</td><td>Use</td><td>3/11</td><td>5.14% (1.1-15.0)</td></tr></table>	AT deficiency	COC	VTE/Total N	VTE annual incidence, % (95% CI)	No	Never use	0/13	0% (0-1.3)	No	Use	0/17	0% (0-0.38)	Yes	Never use	6/22	1.77% (0.7-3.9)	Yes	Use	3/11	5.14% (1.1-15.0)				
AT deficiency	COC	VTE/Total N	VTE annual incidence, % (95% CI)																										
No	Never use	0/13	0% (0-1.3)																										
No	Use	0/17	0% (0-0.38)																										
Yes	Never use	6/22	1.77% (0.7-3.9)																										
Yes	Use	3/11	5.14% (1.1-15.0)																										

		Thrombophilia diagnosed by blood tests			
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AT, antithrombin; CI, confidence interval; COC, combined oral contraception; CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; OC, oral contraception; PE, pulmonary embolism; SVT, superficial venous thrombosis; VTE, venous thromboembolism.

Appendix 5. Evidence on thrombosis risk with use of hormonal contraception among women with protein C deficiency

Author, year, location, funding	Study design, period of data collection	Population	Contraception exposure and comparison	Outcome	Results																								
Pabinger, 1994 [20] Austria, Germany, Switzerland Funded by Schering	Retrospective cohort 1964-1991 8 coagulation labs and thrombosis units	Women with hereditary thrombophilia (at least one relative with same deficiency) (age range not stated) Cohort: ever use of OCs (N=16 with protein C deficiency [all heterozygous]) Controls: never use of OCs, selected from computer list, matched 1:1 by age (N=16 with protein C deficiency [all heterozygous]) Exclusions: current use of anticoagulants Thrombophilia diagnosed by blood tests, different by site	Current OC use (type not specified) Self or physician report (questionnaire filled in by patient or physician)	DVT, PE, SVT, arm vein thrombosis, or CVT Confirmed by imaging, hospitalization plus anticoagulation, or clinical symptoms (SVT)	<table><tr><th>Protein C deficiency</th><th>OC</th><th>VTE/Total N</th><th colspan="3">VTE incidence^a</th></tr><tr><td></td><td></td><td></td><th>Per patient year</th><th>After 12 mos</th><th>After 60 mos</th></tr><tr><td>Yes</td><td>Never user</td><td>4/16</td><td>6.9%</td><td>0%</td><td>60%</td></tr><tr><td>Yes</td><td>Current user</td><td>8/16</td><td>11.95%</td><td>12%</td><td>38%</td></tr></table> ^a Difference between groups not statistically significant (Wilcoxon test p=0.3, Log-Rank test p=0.6)	Protein C deficiency	OC	VTE/Total N	VTE incidence ^a						Per patient year	After 12 mos	After 60 mos	Yes	Never user	4/16	6.9%	0%	60%	Yes	Current user	8/16	11.95%	12%	38%
Protein C deficiency	OC	VTE/Total N	VTE incidence ^a																										
			Per patient year	After 12 mos	After 60 mos																								
Yes	Never user	4/16	6.9%	0%	60%																								
Yes	Current user	8/16	11.95%	12%	38%																								
Van Vlijmen, 2007 [21] Netherlands Funding not stated	Retrospective cohort Years not stated 1 hospital	Women ages 15-50 Cohort: women with thrombophilia using COCs (N=24 with protein C deficiency [zygosity not reported])) Controls: family members with thrombophilia not using COCs (N=14 with protein C deficiency [zygosity not reported]))	COC within 3 months of event Never use Self report (questionnaire)	VTE Confirmed by imaging or anticoagulant therapy	<table><tr><th>Protein C deficiency</th><th>COC</th><th>VTE/Total N</th><th>VTE annual incidence, % (95% CI)</th></tr><tr><td>No</td><td>Never use</td><td>1/13</td><td>0.34% (0-1.9)</td></tr><tr><td>No</td><td>Use</td><td>1/37</td><td>0.29% (0-1.7)</td></tr><tr><td>Yes</td><td>Never use</td><td>5/14</td><td>2.23% (0.7-5.2)</td></tr><tr><td>Yes</td><td>Use</td><td>7/24</td><td>7.06% (2.8-14.5)</td></tr></table>	Protein C deficiency	COC	VTE/Total N	VTE annual incidence, % (95% CI)	No	Never use	1/13	0.34% (0-1.9)	No	Use	1/37	0.29% (0-1.7)	Yes	Never use	5/14	2.23% (0.7-5.2)	Yes	Use	7/24	7.06% (2.8-14.5)				
Protein C deficiency	COC	VTE/Total N	VTE annual incidence, % (95% CI)																										
No	Never use	1/13	0.34% (0-1.9)																										
No	Use	1/37	0.29% (0-1.7)																										
Yes	Never use	5/14	2.23% (0.7-5.2)																										
Yes	Use	7/24	7.06% (2.8-14.5)																										

		Exclusions: none stated Thrombophilia diagnosed by blood tests			
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CI, confidence interval; COC, combined oral contraception; CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; OC, oral contraception; PE, pulmonary embolism; SVT, superficial venous thrombosis; VTE, venous thromboembolism.

Appendix 6. Evidence on thrombosis risk with use of hormonal contraception among women with protein S deficiency

Author, year, location, funding	Study design, period of data collection	Population	Contraception exposure and comparison	Outcome	Results																								
Pabinger, 1994 [20] Austria, Germany, Switzerland Funded by Schering	Retrospective cohort 1964-1991 8 coagulation labs and thrombosis units	Women with hereditary thrombophilia (at least one relative with same deficiency) (age range not stated) Cohort: ever use of OCs (N=17 with protein S deficiency [all heterozygous]) Controls: never use of OCs, selected from computer list, matched 1:1 by age (N=17 with protein S deficiency [all heterozygous]) Exclusions: current use of anticoagulants Thrombophilia diagnosed by blood tests, different by site	Current OC use (type not specified) Self or physician report (questionnaire filled in by patient or physician)	DVT, PE, SVT, arm vein thrombosis, or CVT Confirmed by imaging, hospitalization plus anticoagulation, or clinical symptoms (SVT)	<table><tr><th>Protein S deficiency</th><th>OC</th><th>VTE/Total N</th><th colspan="3">VTE incidence^a</th></tr><tr><td></td><td></td><td></td><th>Per patient year</th><th>After 12 mos</th><th>After 60 mos</th></tr><tr><td>Yes</td><td>Never users</td><td>5/17</td><td>8.6%</td><td>0%</td><td>37%</td></tr><tr><td>Yes</td><td>Current users</td><td>6/17</td><td>6.5%</td><td>0%</td><td>15%</td></tr></table> ^a Difference between groups not statistically significant (Wilcoxon test p=0.5, Log-Rank test p=0.4)	Protein S deficiency	OC	VTE/Total N	VTE incidence ^a						Per patient year	After 12 mos	After 60 mos	Yes	Never users	5/17	8.6%	0%	37%	Yes	Current users	6/17	6.5%	0%	15%
Protein S deficiency	OC	VTE/Total N	VTE incidence ^a																										
			Per patient year	After 12 mos	After 60 mos																								
Yes	Never users	5/17	8.6%	0%	37%																								
Yes	Current users	6/17	6.5%	0%	15%																								
Van Vlijmen, 2007 [21] Netherlands Funding not stated	Retrospective cohort Years not stated 1 hospital	Women ages 15-50 Cohort: women with thrombophilia using COCs (N=21 with protein S deficiency [zygosity not reported])) Controls: family members with thrombophilia not using COCs (N=9 with protein S deficiency [zygosity not reported]))	COC within 3 months of event Never use Self report (questionnaire)	VTE Confirmed by imaging or anticoagulant therapy	<table><tr><th>Protein S deficiency</th><th>COC</th><th>VTE/Total N</th><th>VTE annual incidence, % (95% CI)</th></tr><tr><td>No</td><td>Never use</td><td>1/16</td><td>0.27% (0-1.9)</td></tr><tr><td>No</td><td>Use</td><td>2/25</td><td>1.01% (0.1-3.6)</td></tr><tr><td>Yes</td><td>Never use</td><td>1/9</td><td>0.46% (0.01-2.5)</td></tr><tr><td>Yes</td><td>Use</td><td>3/21</td><td>2.42% (0.5-7.1)</td></tr></table>	Protein S deficiency	COC	VTE/Total N	VTE annual incidence, % (95% CI)	No	Never use	1/16	0.27% (0-1.9)	No	Use	2/25	1.01% (0.1-3.6)	Yes	Never use	1/9	0.46% (0.01-2.5)	Yes	Use	3/21	2.42% (0.5-7.1)				
Protein S deficiency	COC	VTE/Total N	VTE annual incidence, % (95% CI)																										
No	Never use	1/16	0.27% (0-1.9)																										
No	Use	2/25	1.01% (0.1-3.6)																										
Yes	Never use	1/9	0.46% (0.01-2.5)																										
Yes	Use	3/21	2.42% (0.5-7.1)																										

		Exclusions: none stated Thrombophilia diagnosed by blood tests			
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CI, confidence interval; COC, combined oral contraception; CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; OC, oral contraception; PE, pulmonary embolism; SVT, superficial venous thrombosis; VTE, venous thromboembolism.

Appendix 7. Evidence on thrombosis risk with use of hormonal contraception among women with multiple inherited thrombophilias

Author, year, location, funding	Study design, period of data collection	Population	Contraception exposure and comparison	Outcome	Results																				
Emmerich, 2001 [4] Netherlands, Italy, France Funding not stated	Case control Poort: years not stated [5] Cattaneo: 1995-1997 [6] Alhenc-Gelas: 1995-1997 [7] Pooled analysis of 3 studies with OC information [5-7]	Women ages 15-49 Cases: at least 1 VTE (N=517) (Poort: affected families and anticoagulation clinics; Cattaneo: thrombosis center; Alhenc-Gelas: hospital) (N with thrombophilias not reported [all heterozygous]) Controls: age-matched (N=518) (Poort: population controls ID'd by cases; Cattaneo: population controls from same area and "same cultural background"; Alhenc-Gelas: outpatient clinic) (N with thrombophilias not reported [all heterozygous]) Thrombophilia diagnosed by blood tests	Poort: Current OC use, ascertainment not stated Cattaneo: contraceptive use not described Alhenc-Gelas: Current OC use ("oestrogens" mentioned), patient interview Non-use	First or recurrent DVT +/- PE Poort: recruited from anticoagulation clinic Cattaneo: confirmed by imaging Alhenc-Gelas: confirmed by imaging	<table><tr><th>Factor V Leiden plus PT gene mutation</th><th>OC</th><th>VTE crude OR (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>Ref</td></tr><tr><td>No</td><td>Use</td><td>2.29 (1.72-3.04)</td></tr><tr><td>Yes</td><td>Non-use</td><td>14.67 (3.47-62.03)</td></tr><tr><td>Yes</td><td>Use</td><td>16.97 (3.95-72.80)</td></tr></table>	Factor V Leiden plus PT gene mutation	OC	VTE crude OR (95% CI)	No	Non-use	Ref	No	Use	2.29 (1.72-3.04)	Yes	Non-use	14.67 (3.47-62.03)	Yes	Use	16.97 (3.95-72.80)					
Factor V Leiden plus PT gene mutation	OC	VTE crude OR (95% CI)																							
No	Non-use	Ref																							
No	Use	2.29 (1.72-3.04)																							
Yes	Non-use	14.67 (3.47-62.03)																							
Yes	Use	16.97 (3.95-72.80)																							
Legnani, 2002 [9] Italy Funding not stated	Case control 1994-2000 Thrombosis clinic	Women of "reproductive age" Cases: at least 1 VTE referred to clinic (N=301; 8 with factor V Leiden and PT mutation [all heterozygous]) Controls: healthy women from general population, same geographical area	COC use at time of DVT or at time of blood sampling (N=313) Non-use, not further clarified Self report (patient interview)	DVT +/- PE Confirmed by imaging	<table><tr><th>Factor V Leiden plus PT gene mutation</th><th>COC</th><th>Cases/controls</th><th>VTE aOR^a (95% CI)</th></tr><tr><td>No</td><td>Non-use</td><td>118/444</td><td>Ref</td></tr><tr><td>No</td><td>Current use</td><td>86/166</td><td>2.4 (1.7-3.5)</td></tr><tr><td>Yes</td><td>Non-use</td><td>1/0</td><td>--^b</td></tr><tr><td>Yes</td><td>Current use</td><td>7/1</td><td>86.5 (10.0-747)</td></tr></table> ^aAdjusted for age and other thrombophilic defects ^bNot able to be calculated, no VTE in non-users with mutations	Factor V Leiden plus PT gene mutation	COC	Cases/controls	VTE aOR ^a (95% CI)	No	Non-use	118/444	Ref	No	Current use	86/166	2.4 (1.7-3.5)	Yes	Non-use	1/0	-- ^b	Yes	Current use	7/1	86.5 (10.0-747)
Factor V Leiden plus PT gene mutation	COC	Cases/controls	VTE aOR ^a (95% CI)																						
No	Non-use	118/444	Ref																						
No	Current use	86/166	2.4 (1.7-3.5)																						
Yes	Non-use	1/0	-- ^b																						
Yes	Current use	7/1	86.5 (10.0-747)																						

		(N=650; 1 with factor V Leiden and PT mutation [all heterozygous]) Exclusions: VTE during pregnancy or postpartum Thrombophilia diagnosed by blood test			
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aOR, adjusted odds ratio; CI, confidence interval; COC, combined oral contraception; DVT, deep venous thrombosis; OC, oral contraception; OR, odds ratio; PE, pulmonary embolism; PT, prothrombin; VTE, venous thromboembolism.

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