

Combined oral contraceptives and risk of venous thromboembolism: nested case–control studies using the QResearch and the CPRD databases

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Web appendix: Supplementary tables

Table 1 READ and ICD10 codes for venous thromboembolism

READ codes		ICD10 codes
F051.00	Thrombosis of central nervous system venous sinuses	I26 - Pulmonary embolism
F051000	Thrombosis cavernous sinus	I260 - Pulmonary embolism with mention of acute cor pulmonale
F051100	Thrombosis of superior longitudinal sinus	I269 - Pulmonary embolism without mention of acute cor pulmonale
F051200	Thrombosis lateral sinus	I636 - Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
F051300	Thrombosis transverse sinus	I81 - Portal vein thrombosis
F051z00	Thrombosis of central nervous system venous sinus NOS	I81X - Portal vein thrombosis
F423811	Retinal vein thrombosis	I82 - Other venous embolism and thrombosis
G401	Pulmonary embolism	I820 - Budd-Chiari syndrome
G401-1	Infarction - pulmonary	I822 - Embolism and thrombosis of vena cava
G401-2	Pulmonary embolus	I823 - Embolism and thrombosis of renal vein
G4011	Recurrent pulmonary embolism	I828 - Embolism and thrombosis of other specified veins
G676	Nonpyogenic venous sinus thrombosis	I829 - Embolism and thrombosis of unspecified vein
G801-1	Deep vein thrombosis	
G801-2	Deep vein thrombosis, leg	
G801-3	DVT - Deep vein thrombosis	
G801-99	Deep venous thrombosis - leg	
G801C	Deep vein thrombosis of leg related to air travel	
G801D	Deep vein thrombosis of lower limb	
G801D-99	Deep venous thrombosis - leg	
G801E	Deep vein thrombosis of leg related to intravenous drug use	
G801F	Deep vein thrombosis of peroneal vein	
G801G	Recurrent deep vein thrombosis	
G820	Budd - Chiari syndrome (hepatic vein thrombosis)	
G820-1	Hepatic vein thrombosis	
G822	Embolism and thrombosis of the vena cava	
G823	Embolism and thrombosis of the renal vein	
G824.00	Axillary vein thrombosis	
G825.00	Thrombosis of subclavian vein	
G826.00	Thrombosis of internal jugular vein	

G827	Thrombosis of external jugular vein	
G82y.00	Other embolism and thrombosis	
G82z.00	Embolism and thrombosis NOS	
G82z0	Venous embolism NOS	
G82z1	Venous thrombosis NOS	
G82zz00	Embolism and thrombosis NOS	

Table 2 Baseline characteristics in combined oral contraceptive users and non-users, cases and controls by database (CPRD or QResearch)

	CPRD				QResearch			
	Cases non-users	Controls non-users	Cases users	Controls users	Cases non-users	Controls non-users	Cases users	Controls users
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
total N	3161	14617	1901	5021	3401	16927	2099	5469
Age band at index date								
15-24	7.0 (221)	9.4 (1368)	21.8 (415)	22.5 (1128)	4.7 (160)	7.4 (1250)	15.9 (333)	16.2 (885)
25-34	19.2 (606)	18.8 (2753)	36.0 (684)	38.1 (1913)	18.5 (628)	20.7 (3512)	37.9 (795)	38.0 (2077)
35-39	17.3 (547)	17.8 (2600)	16.8 (320)	16.6 (833)	17.0 (577)	17.2 (2914)	19.8 (415)	19.1 (1043)
40-44	24.0 (760)	24.7 (3617)	15.5 (295)	13.4 (675)	26.4 (898)	25.5 (4324)	16.2 (341)	16.4 (895)
45-49	32.5 (1027)	29.3 (4279)	9.8 (187)	9.4 (472)	33.5 (1138)	29.1 (4927)	10.2 (215)	10.4 (569)
Ethnicity								
White	34.4 (1087)	31.8 (4654)	38.6 (734)	38.0 (1907)	60.3 (2050)	56.2 (9507)	63.6 (1336)	62.0 (3393)
Not recorded	61.2 (1934)	63.4 (9263)	58.7 (1115)	59.5 (2986)	28.5 (969)	32.7 (5531)	31.0 (651)	32.6 (1785)
Black	2.1 (66)	1.4 (208)	0.7 (13)	0.6 (29)	5.8 (198)	3.5 (594)	1.7 (35)	1.6 (86)
Asian	1.6 (49)	2.2 (324)	1.0 (19)	1.0 (51)	2.8 (96)	5.2 (885)	1.8 (38)	2.3 (128)
Other	0.8 (25)	1.1 (168)	1.1 (20)	1.0 (48)	2.6 (88)	2.4 (410)	1.9 (39)	1.4 (77)
Body Mass Index (kg/m²)								
15-24	30.5 (964)	42.9 (6266)	41.5 (789)	50.0 (2508)	29.2 (994)	41.5 (7019)	43.3 (909)	52.6 (2876)
25-29	21.6 (683)	21.6 (3154)	24.1 (459)	23.2 (1163)	20.3 (689)	19.1 (3236)	24.4 (513)	22.6 (1237)
30+	33.5 (1059)	17.5 (2559)	25.0 (475)	15.8 (794)	26.6 (906)	14.6 (2465)	20.2 (425)	13.4 (731)
not recorded	14.4 (455)	18.0 (2638)	9.4 (178)	11.1 (556)	23.9 (812)	24.9 (4207)	12.0 (252)	11.4 (625)
Smoking status								
non-smoker	48.3 (1527)	53.9 (7873)	55.7 (1059)	55.2 (2772)	41.7 (1419)	46.2 (7822)	46.4 (973)	47.3 (2588)

ex-smoker	16.9 (535)	16.1 (2354)	18.4 (349)	18.7 (941)	21.6 (735)	21.1 (3579)	26.0 (545)	25.1 (1373)
current light smoker	6.3 (200)	5.4 (785)	6.3 (119)	8.0 (403)	14.0 (476)	11.2 (1891)	15.0 (314)	14.8 (812)
current moderate smoker	14.8 (468)	11.0 (1602)	13.8 (262)	11.8 (592)	8.1 (277)	6.1 (1026)	7.0 (147)	7.4 (407)
current heavy smoker	8.4 (264)	4.6 (671)	3.7 (70)	3.1 (157)	5.2 (178)	2.9 (485)	3.3 (70)	2.5 (136)
not recorded	5.3 (167)	9.1 (1332)	2.2 (42)	3.1 (156)	9.3 (316)	12.5 (2124)	2.4 (50)	2.8 (153)
Use of alcohol								
no use	21.0 (663)	18.9 (2766)	18.5 (351)	14.9 (750)	24.2 (822)	20.3 (3442)	19.0 (398)	16.0 (873)
ex-use	6.4 (203)	4.4 (640)	5.3 (100)	4.6 (229)	6.7 (229)	5.0 (850)	6.6 (138)	6.0 (327)
light (up to 2 units/day)	46.9 (1482)	49.1 (7173)	52.4 (997)	54.7 (2748)	29.5 (1003)	31.7 (5373)	36.4 (763)	36.4 (1992)
moderate/heavy (3+ units/day)	5.4 (172)	5.1 (746)	4.3 (82)	4.8 (240)	16.8 (570)	17.8 (3007)	19.1 (400)	21.3 (1166)
not recorded	20.3 (641)	22.5 (3292)	19.5 (371)	21.0 (1054)	22.8 (777)	25.1 (4255)	19.1 (400)	20.3 (1111)
Non-idiopathic patients	50.6 (1599)	26.0 (3803)	41.1 (781)	30.6 (1537)	50.1 (1704)	25.5 (4311)	41.8 (878)	28.9 (1580)
Co-morbidities								
Asthma	19.4 (613)	11.8 (1726)	18.7 (356)	16.0 (804)	18.7 (637)	11.2 (1903)	19.0 (399)	14.4 (790)
Congestive cardiac disease	0.5 (17)	0.0 (5)	0.2 (3)	0.0 (0)	0.3 (11)	0.0 (3)	0.1 (2)	0.0 (2)
Rheumatoid arthritis	1.5 (47)	0.6 (93)	1.5 (28)	0.6 (28)	2.7 (92)	0.8 (138)	1.5 (31)	0.9 (49)
Systemic lupus erythematosus	0.6 (19)	0.1 (18)	0.4 (8)	0.1 (4)	0.9 (30)	0.1 (22)	0.2 (5)	0.1 (3)
Renal disease	1.4 (43)	0.2 (27)	0.3 (5)	0.2 (8)	1.5 (52)	0.3 (52)	0.5 (10)	0.2 (13)
Stroke	1.0 (31)	0.1 (21)	0.7 (13)	0.0 (1)	1.0 (34)	0.2 (42)	0.8 (16)	0.1 (6)
Chronic obstructive pulmonary disease	0.8 (25)	0.2 (28)	0.1 (1)	0.0 (2)	0.8 (26)	0.2 (29)	0.3 (6)	0.0 (2)
Coronary vascular disease	1.3 (42)	0.3 (41)	0.5 (10)	0.2 (9)	1.9 (63)	0.4 (69)	0.9 (19)	0.1 (8)
Coagulation disturbances	0.3 (8)	0.0 (6)	0.2 (3)	0.1 (3)	0.2 (6)	0.0 (5)	0.3 (7)	0.0 (1)
Varicose veins	3.3 (103)	1.8 (269)	2.1 (40)	0.9 (45)	3.3 (111)	1.8 (307)	1.9 (40)	1.0 (52)
Hypertension	8.4 (267)	4.0 (585)	2.7 (52)	2.3 (113)	8.0 (272)	4.2 (706)	2.7 (57)	2.3 (125)
Cancer	9.0 (283)	1.1 (160)	2.6 (50)	0.4 (20)	8.9 (303)	1.0 (175)	2.9 (60)	0.5 (29)
Inflammatory bowel disease	2.0 (62)	0.6 (85)	1.8 (34)	0.7 (33)	1.8 (61)	0.7 (116)	1.9 (39)	0.5 (27)

Conditions in the last 6 months								
Infection	18.6 (589)	9.3 (1361)	19.7 (375)	13.4 (672)	16.9 (574)	8.1 (1379)	17.8 (374)	11.8 (647)
Surgery or leg/hip fracture	1.4 (45)	0.1 (10)	0.5 (9)	0.1 (6)	1.1 (39)	0.1 (19)	0.6 (12)	0.1 (5)
Hospital admission	1.7 (54)	0.2 (35)	0.9 (18)	0.3 (13)	4.7 (161)	1.1 (187)	3.0 (62)	1.1 (61)
Indications for hormonal contraceptive use								
Acne	9.4 (296)	10.1 (1477)	18.0 (342)	16.5 (830)	7.3 (247)	7.4 (1252)	12.7 (267)	12.5 (681)
Menstrual disorders	37.8 (1196)	30.5 (4451)	34.2 (651)	32.7 (1640)	28.7 (977)	22.5 (3814)	24.8 (520)	24.3 (1327)
Hirsutism	2.0 (64)	1.2 (178)	2.3 (43)	1.6 (82)	1.1 (37)	1.1 (180)	1.8 (38)	0.9 (49)
Polycystic ovary syndrome	3.0 (94)	2.1 (311)	4.2 (80)	2.4 (122)	2.5 (84)	2.5 (418)	4.1 (86)	2.1 (117)

Table 3 Number of cases and controls exposed to different terms and different types of combined oral contraceptives by analysis and database

	All cases/controls	With anticoagulants cases/controls	Idiopathic cases/controls	Non-idiopathic cases/controls	15-24 years old cases/controls	25-49 years old cases/controls
CPRD						
Total N cases/controls	5062/19638	2533/9882	2630/7632	1658/2566	636/2496	4426/17142
Norethisterone						
No exposure	4927/19297	2461/9702	2547/7501	1619/2523	618/2414	4309/16883
29 to 365days	39/96	20/49	26/35	12/14	3/21	36/75
Up to 28days	96/245	52/131	57/96	27/29	15/61	81/184
Levonorgestrel						
No exposure	4386/17703	2184/8973	2219/6889	1491/2302	437/1918	3949/15785
29 to 365days	155/484	89/226	90/188	40/65	49/147	106/337
Up to 28days	521/1451	260/683	321/555	127/199	150/431	371/1020
Norgestimate						
No exposure	4902/19146	2445/9634	2541/7425	1610/2506	594/2366	4308/16780
29 to 365days	38/122	17/67	17/44	14/13	11/42	27/80
Up to 28days	122/370	71/181	72/163	34/47	31/88	91/282
Desogestrel						
No exposure	4864/19342	2396/9737	2507/7503	1612/2520	598/2426	4266/16916
29 to 365days	33/68	24/32	16/29	11/12	8/21	25/47
Up to 28days	165/228	113/113	107/100	35/34	30/49	135/179
Gestodene						
No exposure	4965/19450	2465/9799	2568/7546	1631/2538	620/2464	4345/16986
29 to 365days	19/39	11/22	10/18	8/5	5/8	14/31
Up to 28days	78/149	57/61	52/68	19/23	11/24	67/125
Drospirenone						
No exposure	4896/19359	2425/9734	2530/7513	1609/2537	590/2403	4306/16956
29 to 365days	27/79	14/40	14/41	7/6	8/29	19/50
Up to 28days	139/200	94/108	86/78	42/23	38/64	101/136
Cyproterone						
No exposure	4888/19364	2429/9750	2525/7517	1614/2526	586/2403	4302/16961
29 to 365days	36/82	21/33	22/32	11/11	13/30	23/52

Up to 28days	138/192	83/99	83/83	33/29	37/63	101/129
QResearch						
Total N cases/controls	5500/22396	2956/11933	2871/8937	1822/2903	493/2135	5007/20261
Norethisterone						
No exposure	5353/22016	2877/11726	2778/8772	1792/2864	468/2073	4885/19943
29 to 365days	38/121	22/64	19/48	9/13	9/23	29/98
Up to 28days	109/259	57/143	74/117	21/26	16/39	93/220
Levonorgestrel						
No exposure	4805/20502	2587/10967	2450/8145	1642/2687	364/1718	4441/18784
29 to 365days	155/483	72/227	88/190	43/66	41/103	114/380
Up to 28days	540/1411	297/739	333/602	137/150	88/314	452/1097
Norgestimate						
No exposure	5307/21916	2840/11692	2751/8736	1770/2838	446/2034	4861/19882
29 to 365days	33/128	17/65	16/53	12/16	11/25	22/103
Up to 28days	160/352	99/176	104/148	40/49	36/76	124/276
Desogestrel						
No exposure	5298/22043	2837/11749	2754/8792	1764/2859	459/2073	4839/19970
29 to 365days	39/91	24/52	19/40	16/12	10/13	29/78
Up to 28days	163/262	95/132	98/105	42/32	24/49	139/213
Gestodene						
No exposure	5356/22152	2852/11801	2789/8838	1773/2878	475/2101	4881/20051
29 to 365days	29/62	22/40	16/27	8/7	5/9	24/53
Up to 28days	115/182	82/92	66/72	41/18	13/25	102/157
Drospirenone						
No exposure	5371/22152	2876/11820	2788/8852	1788/2875	471/2072	4900/20080
29 to 365days	27/74	17/37	15/28	8/9	5/14	22/60
Up to 28days	102/170	63/76	68/57	26/19	17/49	85/121
Cyproterone						
No exposure	5345/22125	2870/11801	2785/8828	1770/2862	457/2064	4888/20061
29 to 365days	35/84	13/37	20/30	10/14	5/20	30/64
Up to 28days	120/187	73/95	66/79	42/27	31/51	89/136

Table 4 Full model by database

	CPRD		QResearch		Combined analysis	
	Adjusted odds ratios (95% CI)	P- value	Adjusted odds ratios (95% CI)	P- value	Adjusted odds ratios (95% CI)	P- value
Contraceptive use						
Norethisterone /no use in the last year	1.00		1.00		1.00	
current use	2.30 (1.78 to 2.99)	<0.001	2.82 (2.21 to 3.60)	<0.001	2.56 (2.15 to 3.06)	<0.001
past use	1.29 (0.84 to 1.96)	0.246	0.93 (0.61 to 1.42)	0.752	1.09 (0.81 to 1.47)	0.6
Levonorgestrel / no use in the last year	1.00		1.00		1.00	
current use	2.23 (1.97 to 2.52)	<0.001	2.52 (2.24 to 2.84)	<0.001	2.38 (2.18 to 2.59)	<0.001
past use	1.10 (0.89 to 1.37)	0.391	1.30 (1.05 to 1.60)	0.014	1.20 (1.03 to 1.39)	0.02
Norgestimate / no use in the last year	1.00		1.00		1.00	
current use	1.96 (1.56 to 2.46)	<0.001	3.15 (2.56 to 3.89)	<0.001	2.53 (2.17 to 2.96)	<0.001
past use	1.23 (0.82 to 1.85)	0.327	1.00 (0.66 to 1.52)	0.992	1.11 (0.83 to 1.49)	0.5
Desogestrel / no use in the last year	1.00		1.00		1.00	
current use	4.43 (3.54 to 5.55)	<0.001	4.15 (3.34 to 5.15)	<0.001	4.28 (3.66 to 5.01)	<0.001
past use	1.65 (1.02 to 2.67)	0.040	1.61 (1.06 to 2.47)	0.027	1.63 (1.19 to 2.24)	0.003
Gestodene / no use in the last year	1.00		1.00		1.00	
current use	3.14 (2.32 to 4.24)	<0.001	4.07 (3.14 to 5.26)	<0.001	3.64 (3.00 to 4.43)	<0.001
past use	1.75 (0.94 to 3.25)	0.078	1.69 (1.03 to 2.78)	0.037	1.71 (1.16 to 2.52)	0.006
Drospirenone / no use in the last year	1.00		1.00		1.00	
current use	4.36 (3.39 to 5.60)	<0.001	3.86 (2.93 to 5.08)	<0.001	4.12 (3.43 to 4.96)	<0.001
past use	1.23 (0.75 to 2.02)	0.410	1.42 (0.86 to 2.36)	0.174	1.32 (0.93 to 1.88)	0.1
Cyproterone / no use in the last year	1.00		1.00		1.00	
current use	4.13 (3.22 to 5.31)	<0.001	4.42 (3.41 to 5.73)	<0.001	4.27 (3.57 to 5.11)	<0.001

past use	1.47	(0.95 to 2.28)	0.085	1.21	(0.77 to 1.90)	0.408	1.34	(0.98 to 1.83)	0.07
Any oral progestogen only / no use in the last year	1.00			1.00			1.00		
current use	1.31	(1.12 to 1.53)	<0.001	1.43	(1.23 to 1.67)	<0.001	1.37	(1.23 to 1.53)	<0.001
past use	0.78	(0.61 to 1.00)	0.052	0.87	(0.67 to 1.14)	0.307	0.82	(0.68 to 0.99)	0.03
Any non-oral hormonal contraceptive / no use in the last year	1.00			1.00			1.00		
current use	1.79	(1.42 to 2.27)	<0.001	1.66	(1.41 to 1.96)	<0.001	1.70	(1.49 to 1.95)	<0.001
past use	1.51	(1.08 to 2.11)	0.015	1.33	(1.00 to 1.77)	0.053	1.40	(1.13 to 1.75)	0.002
Switch in the last month	1.96	(1.40 to 2.74)	<0.001	1.83	(1.33 to 2.52)	<0.001	1.89	(1.50 to 2.38)	<0.001
Confounders									
Body mass index (kg/m ²)	1.06	(1.06 to 1.07)	<0.001	1.06	(1.06 to 1.07)	<0.001	1.06	(1.06 to 1.07)	<0.001
Smoking status / non-smoker	1.00			1.00			1.00		
Ex-smoker	1.03	(0.93 to 1.13)	0.569	1.07	(0.98 to 1.17)	0.129	1.05	(0.98 to 1.12)	0.1
Current light smoker	1.17	(1.01 to 1.36)	0.034	1.36	(1.22 to 1.50)	<0.001	1.29	(1.19 to 1.41)	<0.001
Current moderate smoker	1.48	(1.33 to 1.64)	<0.001	1.36	(1.20 to 1.55)	<0.001	1.43	(1.32 to 1.55)	<0.001
Current heavy smoker	1.75	(1.51 to 2.03)	<0.001	1.87	(1.58 to 2.22)	<0.001	1.80	(1.61 to 2.02)	<0.001
Co-morbidities									
Asthma	1.35	(1.23 to 1.48)	<0.001	1.47	(1.34 to 1.60)	<0.001	1.41	(1.32 to 1.50)	<0.001
Congestive cardiac disease	6.29	(2.15 to 18.36)	<0.001	4.51	(1.45 to 14.08)	0.009	5.38	(2.47 to 11.74)	<0.001
Rheumatoid arthritis	2.02	(1.45 to 2.82)	<0.001	2.28	(1.76 to 2.96)	<0.001	2.18	(1.78 to 2.68)	<0.001
SLE	3.87	(2.02 to 7.43)	<0.001	4.84	(2.70 to 8.67)	<0.001	4.38	(2.83 to 6.77)	<0.001
Renal disease	4.05	(2.46 to 6.65)	<0.001	2.59	(1.70 to 3.93)	<0.001	3.12	(2.26 to 4.29)	<0.001
Stroke	4.34	(2.37 to 7.95)	<0.001	1.15	(0.58 to 2.30)	0.688	2.45	(1.55 to 3.86)	<0.001
COPD	2.22	(1.21 to 4.09)	0.010	2.64	(1.52 to 4.57)	<0.001	2.44	(1.63 to 3.68)	<0.001
Coronary vascular disease	2.79	(1.75 to 4.44)	<0.001	2.71	(1.56 to 4.70)	<0.001	2.75	(1.93 to 3.93)	<0.001
Coagulation disturbances	6.34	(2.42 to 16.64)	<0.001	10.92	(3.79 to 31.46)	<0.001	8.12	(3.98 to 16.55)	<0.001
Varicose veins	2.06	(1.65 to 2.57)	<0.001	2.01	(1.62 to 2.49)	<0.001	2.03	(1.74 to 2.37)	<0.001
Hypertension	1.30	(1.11 to 1.53)	0.001	1.22	(1.04 to 1.42)	0.012	1.26	(1.13 to 1.41)	<0.001

Cancer	8.90	(7.26 to 10.90)	<0.001	8.72	(7.18 to 10.60)	<0.001	8.81	(7.65 to 10.13)	<0.001
Inflammatory bowel disease	3.68	(2.72 to 4.98)	<0.001	2.73	(2.05 to 3.63)	<0.001	3.14	(2.55 to 3.86)	<0.001
Recent conditions in the last 6 months									
Infection	1.80	(1.64 to 1.98)	<0.001	1.77	(1.61 to 1.94)	<0.001	1.78	(1.67 to 1.91)	<0.001
Surgery	15.42	(8.37 to 28.40)	<0.001	6.09	(3.53 to 10.50)	<0.001	9.19	(6.12 to 13.80)	<0.001
Hospital admission	4.39	(2.86 to 6.74)	<0.001	3.09	(2.48 to 3.84)	<0.001	3.32	(2.73 to 4.04)	<0.001
Co-morbidities associated with hormonal contraceptives' use									
Polycystic ovary syndrome	1.07	(0.87 to 1.31)	0.512	0.91	(0.75 to 1.11)	0.376	0.99	(0.86 to 1.14)	0.9
Use of alcohol / no use	1.00			1.00			1.00		
Ex-use	0.99	(0.84 to 1.17)	0.914	0.91	(0.79 to 1.05)	0.213	0.95	(0.85 to 1.05)	0.3
Light use	0.81	(0.74 to 0.90)	<0.001	0.85	(0.77 to 0.93)	<0.001	0.83	(0.77 to 0.89)	<0.001
Moderate and heavy use	0.86	(0.72 to 1.02)	0.076	0.82	(0.74 to 0.92)	<0.001	0.83	(0.76 to 0.91)	<0.001
Ethnicity / White	1.00			1.00			1.00		
Black	1.48	(1.09 to 2.00)	0.011	1.46	(1.21 to 1.77)	<0.001	1.47	(1.25 to 1.72)	<0.001
Asian	0.75	(0.56 to 1.01)	0.062	0.59	(0.48 to 0.73)	<0.001	0.64	(0.54 to 0.76)	<0.001
Other	0.75	(0.52 to 1.09)	0.132	1.12	(0.89 to 1.40)	0.324	1.01	(0.83 to 1.22)	1.0

Current use – used at index date or last use in the 1 to 28 days prior to the index date; Past use – use between 29 and 365 days prior to the index date

Table 5 Duration of exposure to combined oral contraceptives in current users in cases and controls, compared to non-exposure in the last year by database

Type of contraceptive	CPRD			QResearch			Combined analysis	
	Cases/ Controls	Adjusted* Odds ratio (95%CI)		Cases/ Controls	Adjusted* Odds ratio (95%CI)		Pooled Odds ratio (95%CI)	P-value
Norethisterone								
Short term	22/46	2.48 (1.40 to 4.38)		26/34	4.49 (2.57 to 7.85)		3.36 (2.25 to 5.00)	<0.001
Long term	74/199	2.26 (1.69 to 3.02)		83/225	2.54 (1.93 to 3.32)		2.40 (1.97 to 2.93)	<0.001
Levonorgestrel								
Short term	138/263	3.12 (2.48 to 3.93)		134/225	3.68 (2.90 to 4.67)		3.38 (2.86 to 3.99)	<0.001
Long term	383/1188	2.03 (1.77 to 2.33)		406/1186	2.29 (2.01 to 2.62)		2.16 (1.97 to 2.38)	<0.001
Norgestimate								
Short term	31/81	2.04 (1.30 to 3.19)		37/78	2.87 (1.87 to 4.39)		2.44 (1.79 to 3.32)	<0.001
Long term	91/289	1.94 (1.50 to 2.51)		123/274	3.24 (2.56 to 4.10)		2.57 (2.16 to 3.06)	<0.001
Desogestrel								
Short term	41/45	4.84 (3.02 to 7.77)		35/60	3.60 (2.27 to 5.70)		4.16 (2.99 to 5.78)	<0.001
Long term	124/183	4.31 (3.35 to 5.56)		128/202	4.31 (3.38 to 5.49)		4.31 (3.62 to 5.14)	<0.001
Gestodene								
Short term	16/28	3.04 (1.55 to 5.98)		17/24	4.68 (2.38 to 9.18)		3.78 (2.34 to 6.09)	<0.001
Long term	62/121	3.17 (2.27 to 4.42)		98/158	3.97 (3.01 to 5.23)		3.62 (2.93 to 4.47)	<0.001
Drospirenone								
Short term	34/40	4.26 (2.56 to 7.10)		27/43	3.78 (2.22 to 6.43)		4.02 (2.79 to 5.82)	<0.001
Long term	105/160	4.42 (3.34 to 5.86)		75/127	3.87 (2.83 to 5.31)		4.17 (3.38 to 5.14)	<0.001
Cyproterone								
Short term	41/56	3.52 (2.25 to 5.49)		31/36	5.50 (3.22 to 9.39)		4.22 (3.00 to 5.94)	<0.001
Long term	97/136	4.45 (3.31 to 5.97)		89/151	4.17 (3.12 to 5.58)		4.30 (3.50 to 5.29)	<0.001

* Adjusted for body mass index, smoking status, alcohol consumption, ethnicity, chronic and acute conditions, use of other hormonal contraceptives

Short term – less than 84 days, Long term – 84 or more days

Table 6 Odds ratios for current use of combined oral contraceptives, unadjusted and adjusted for different confounders (% of change compared to unadjusted) by database

	Norethisterone	Levonorgestrel	Norgestimate	Desogestrel	Gestodene	Drospirenone	Cyproterone
	OR (% change)	OR (% change)	OR (% change)	OR (% change)	OR (% change)	OR (% change)	OR (% change)
CPRD							
Unadjusted for confounders*	1.81	1.83	3.54	2.61	1.58	3.55	3.50
Individual adjustment:							
Polycystic ovary syndrome	1.82 (0.37)	1.84 (0.52)	3.54 (-0.21)	2.61 (0.10)	1.59 (0.69)	3.49 (-1.74)	3.34 (-4.58)
Ethnicity	1.82 (0.10)	1.83 (0.24)	3.57 (0.78)	2.62 (0.22)	1.59 (0.62)	3.58 (0.69)	3.51 (0.28)
Alcohol consumption	1.83 (0.68)	1.87 (2.02)	3.61 (1.79)	2.66 (1.73)	1.61 (2.04)	3.65 (2.81)	3.52 (0.70)
All chronic conditions	1.98 (9.30)	1.93 (5.48)	3.76 (6.19)	2.83 (8.35)	1.69 (7.07)	3.73 (4.95)	3.64 (4.21)
All acute conditions	1.85 (2.01)	1.85 (1.21)	3.58 (1.06)	2.59 (-1.01)	1.59 (0.80)	3.61 (1.50)	3.47 (-0.69)
Body mass index	1.98 (9.36)	1.97 (7.83)	3.86 (8.94)	2.86 (9.41)	1.71 (8.57)	3.92 (10.25)	3.75 (7.36)
Smoking status	1.89 (4.33)	1.90 (3.71)	3.71 (4.72)	2.66 (1.97)	1.64 (3.65)	3.67 (3.23)	3.69 (5.64)
NHS Guidelines risk factors#	2.28 (25.86)	2.19 (19.47)	4.32 (22.04)	3.09 (18.25)	1.92 (21.60)	4.23 (18.92)	4.12 (17.90)
Full model	2.30 (26.94)	2.23 (21.95)	4.43 (25.12)	3.14 (20.08)	1.96 (24.32)	4.36 (22.63)	4.13 (18.21)
QResearch							
Unadjusted for confounders*	2.3	2.16	2.57	3.45	3.52	3.23	3.77
Individual adjustment:							
Polycystic ovary syndrome	2.30 (0.16)	2.16 (0.20)	2.57 (0.01)	3.44 (-0.21)	3.52 (0.07)	3.20 (-0.87)	3.68 (-2.32)
Ethnicity	2.30 (0.17)	2.16 (-0.13)	2.57 (-0.20)	3.47 (0.54)	3.49 (-1.02)	3.22 (-0.16)	3.76 (-0.31)
Alcohol consumption	2.32 (0.87)	2.21 (2.42)	2.64 (2.58)	3.57 (3.40)	3.62 (2.85)	3.30 (2.15)	3.79 (0.61)
Townsend quintile	2.38 (3.47)	2.20 (2.02)	2.64 (2.75)	3.51 (1.80)	3.68 (4.40)	3.39 (5.09)	3.83 (1.66)
All chronic conditions	2.50 (8.99)	2.31 (6.83)	2.76 (7.20)	3.61 (4.76)	3.64 (3.47)	3.47 (7.58)	4.04 (7.17)
All acute conditions	2.33 (1.38)	2.12 (-1.91)	2.62 (2.08)	3.47 (0.75)	3.48 (-1.14)	3.17 (-1.94)	3.72 (-1.42)
Body mass index	2.44 (6.26)	2.35 (8.82)	2.83 (9.97)	3.70 (7.25)	3.85 (9.36)	3.58 (10.89)	3.99 (5.97)
Smoking status	2.40 (4.41)	2.19 (1.68)	2.63 (2.17)	3.57 (3.52)	3.61 (2.41)	3.30 (2.12)	3.87 (2.59)
NHS Guidelines risk factors#	2.77 (20.60)	2.45 (13.62)	3.06 (19.22)	4.04 (17.14)	3.98 (13.09)	3.73 (15.57)	4.33 (14.76)
Full model without Townsend quintile	2.82 (22.71)	2.52 (16.77)	3.15 (22.73)	4.15 (20.23)	4.07 (15.47)	3.86 (19.44)	4.42 (17.34)

Full model with Townsend quintile	2.85 (24.08)	2.54 (17.70)	3.18 (23.87)	4.15 (20.33)	4.17 (18.49)	3.92 (21.48)	4.47 (18.46)
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*) The unadjusted model contains all hormonal contraceptive (past and current use), cases were matched to controls by age, general practice and calendar year

#) All factors listed in NHS Guidelines as affecting risk (chronic and acute conditions, body mass index and smoking status)

Table 7 Proportion of cases currently exposed to different types of combined oral contraceptives by presence or absence of anticoagulation treatment and by database excluding cases who died, comparison with extract from [Lidegaard BMJ 2011;343:d6423] Table3

Oral contraceptive exposure	CPRD		QResearch		Danish study	
	Anticoagulation treatment		Anticoagulation treatment		Anticoagulation treatment	
	No records	Recorded	No records	Recorded	No records	Recorded
No exposure	54% (2000)	46% (1728)	50% (2001)	50% (1992)	45% (808)	55% (1004)
Norethisterone	47% (44)	53% (50)	49% (52)	51% (55)	20% (2)	80% (8)
Levonorgestrel	50% (261)	50% (256)	46% (243)	54% (289)	26% (44)	74% (123)
Norgestimate	42% (51)	58% (71)	39% (61)	61% (96)	28% (46)	72% (119)
Desogestrel	32% (52)	68% (112)	42% (68)	58% (94)	16% (33)	84 (168)
Gestodene	27% (21)	73% (57)	29% (33)	71% (80)	22% (163)	78% (575)
Drospirenone	33% (45)	67% (93)	39% (39)	61% (61)	26% (70)	74% (196)
Cyproterone	40% (55)	60% (81)	40% (47)	60% (71)	19% (21)	81% (88)
Total alive cases	51%(2,529)	49%(2,448)	48%(2,544)	52%(2,738)	34% (1,187)	66% (2,281)

Table 8 Current exposure to combined oral contraceptives compared to non-exposure and to levonorgestrel: analysis for non-idiopathic cases and controls by database

Type of contraceptive	CPRD		QResearch		Combined analysis	
	Adjusted [#] Odds ratio (95%CI)	P-value	Adjusted [#] Odds ratio (95%CI)	P-value	Pooled Odds ratio (95%CI)	P-value
No use in the last year	1.00		1.00		1.00	
Norethisterone	2.06 (1.13 to 3.78)	0.02	2.46 (1.26 to 4.81)	0.009	2.23 (1.42 to 3.50)	<0.001
Levonorgestrel	1.45 (1.08 to 1.95)	0.01	2.39 (1.77 to 3.22)	<0.001	1.86 (1.51 to 2.29)	<0.001
Norgestimate	1.84 (1.09 to 3.12)	0.02	1.95 (1.16 to 3.27)	0.01	1.89 (1.31 to 2.74)	<0.001
Desogestrel	2.13 (1.19 to 3.81)	0.01	3.95 (2.33 to 6.69)	<0.001	2.99 (2.02 to 4.42)	<0.001
Gestodene	1.97 (0.98 to 3.97)	0.06	6.05 (3.23 to 11.32)	<0.001	3.67 (2.30 to 5.86)	<0.001
Drospirenone	4.75 (2.61 to 8.64)	<0.001	4.17 (2.17 to 8.00)	<0.001	4.47 (2.88 to 6.95)	<0.001
Cyproterone	2.23 (1.22 to 4.09)	0.009	3.81 (2.15 to 6.75)	<0.001	2.96 (1.95 to 4.48)	<0.001
Levonorgestrel	1.00		1.00		1.00	
Norethisterone	1.42 (0.74 to 2.73)	0.3	1.03 (0.50 to 2.10)	0.9	1.23 (0.76 to 1.99)	0.4
Norgestimate	1.27 (0.71 to 2.26)	0.4	0.81 (0.46 to 1.43)	0.5	1.01 (0.68 to 1.51)	1.0
Desogestrel	1.47 (0.78 to 2.75)	0.2	1.65 (0.93 to 2.94)	0.09	1.56 (1.02 to 2.39)	0.04
Gestodene	1.36 (0.65 to 2.86)	0.4	2.53 (1.30 to 4.92)	0.006	1.92 (1.17 to 3.15)	0.010
Drospirenone	3.27 (1.73 to 6.19)	<0.001	1.74 (0.88 to 3.46)	0.1	2.44 (1.53 to 3.90)	<0.001
Cyproterone	1.54 (0.81 to 2.92)	0.2	1.59 (0.86 to 2.97)	0.1	1.57 (1.00 to 2.45)	0.05

[#] Adjusted for body mass index, smoking status, alcohol consumption, ethnicity, chronic and acute conditions, use of other hormonal contraceptives

Table 9 Current exposure to combined oral contraceptives compared to non-exposure and to levonorgestrel: analysis for QResearch patients with Townsend score data.

	Cases/ Controls	Adjusted* Odds ratio (95%CI) in reference with no use	Adjusted* Odds ratio (95%CI) in reference to levonorgestrel use	P-value
Total N cases/controls	5490/22323			
No use in the last year		1.00		
Norethisterone	109/259	2.85 (2.24 to 3.64)	1.13 (0.87 to 1.47)	0.3
Levonorgestrel	539/1409	2.52 (2.23 to 2.84)	1.00	
Norgestimate	160/352	3.18 (2.58 to 3.93)	1.26 (1.00 to 1.59)	0.05
Desogestrel	163/262	4.13 (3.32 to 5.14)	1.64 (1.30 to 2.08)	<0.001
Gestodene	115/181	4.14 (3.20 to 5.35)	1.64 (1.25 to 2.16)	<0.001
Drospirenone	102/170	3.91 (2.97 to 5.14)	1.55 (1.16 to 2.07)	0.003
Cyproterone	120/186	4.42 (3.41 to 5.74)	1.76 (1.33 to 2.31)	<0.001

* Adjusted for body mass index, smoking status, alcohol consumption, ethnicity, chronic and acute conditions, use of other hormonal contraceptives and for Townsend score quintile

Table 10 Current exposure to combined oral contraceptives compared to non-exposure and to levonorgestrel: analysis for QResearch patients identified through general practice records

	Cases/ Controls	Adjusted* Odds ratio (95%CI) in reference with no use	Adjusted* Odds ratio (95%CI) in reference to levonorgestrel use	P-value
Total N cases/controls	5088/20674			
No use in the last year				
Norethisterone	106/240	2.96 (2.30 to 3.79)	1.12 (0.86 to 1.46)	0.4
Levonorgestrel	518/1319	2.64 (2.34 to 2.99)	1.00	
Norgestimate	155/326	3.33 (2.68 to 4.13)	1.26 (1.00 to 1.59)	0.05
Desogestrel	156/239	4.51 (3.60 to 5.66)	1.71 (1.34 to 2.18)	<0.001
Gestodene	109/168	4.17 (3.19 to 5.43)	1.58 (1.19 to 2.09)	0.002
Drospirenone	97/155	4.14 (3.11 to 5.49)	1.56 (1.16 to 2.11)	0.003
Cyproterone	118/176	4.73 (3.63 to 6.16)	1.79 (1.35 to 2.36)	<0.001

* Adjusted for body mass index, smoking status, alcohol consumption, ethnicity, chronic and acute conditions, use of other hormonal contraceptives.

Table 11 Current exposure to combined oral contraceptives compared to non-exposure and to levonorgestrel: analysis for CPRD patients identified with hospital admission, mortality and general practice data

	Cases/ Controls	Adjusted* Odds ratio (95%CI) in reference with no use	Adjusted* Odds ratio (95%CI) in reference to levonorgestrel use	P-value
Total N cases/controls	2989/11597			
No use in the last year		1.00		
Norethisterone	58/138	2.55 (1.81 to 3.60)	1.26 (0.87 to 1.82)	0.2
Levonorgestrel	278/815	2.03 (1.72 to 2.40)	1.00	
Norgestimate	69/213	1.90 (1.41 to 2.57)	0.94 (0.67 to 1.30)	0.7
Desogestrel	100/119	5.05 (3.74 to 6.82)	2.48 (1.79 to 3.45)	<0.001
Gestodene	48/86	3.33 (2.25 to 4.94)	1.64 (1.08 to 2.48)	0.02
Drospirenone	66/108	3.84 (2.70 to 5.45)	1.89 (1.30 to 2.74)	<0.001
Cyproterone	91/115	4.55 (3.30 to 6.27)	2.24 (1.59 to 3.16)	<0.001

* Adjusted for body mass index, smoking status, alcohol consumption, ethnicity, chronic and acute conditions, use of other hormonal contraceptives