List of Supplementary Tables

Table 1 – Meta-Analyses Evaluating Risk of HIV Transmission with Depot medroxyprogesterone acetate (DMPA)

Meta-analysis	# Included studies	Pooled Adj. OR or HR (95% CI)
Ralph et al. 2015	10 (longitudinal)	HR 1.40 (1.16–1.69)
Morrison et al. 2015	18 (longitudinal)	HR 1.50 (1.24–1.83)
Brind et al. 2015	8 (cross-sectional)	OR 1.41 (1.15–1.73)
Brind et al. 2015	16 (longitudinal)	HR 1.49 (1.28–1.73)

Table 2 – Individual Studies of the Effects of DMPA HIV Transmission

Study	Yr.(s) of study	Pop. size	Nation and locale	Subject source	Months of follow-up	Follow-up interval (months)	Type of data shown	HR or IRR (95% CI)	Weight (%)
Crook 2014	2005–2009	8,663	S Africa, Uganda, Tanzania, Zambia	Microbicide trial sero-disc. couples	12	1	Inv. Prob. W'ted HR	1.45 (1.09–1.93)	16.39
McCoy 2013	2003–2007	4,913	South Africa, Zimbabwe	Diaphragm/gel HIV prev. trial	24	3	MV HR	1.22 (0.85–1.76)	13.20
Morrison 2012	2004–2007	5,567	South Africa	General population	9–24	3	MSM HR	1.27 (0.93–1.73)	15.32
Wand 2012	Not reported	2,236	Durban, S. Africa	>90% from microbicide trial	Not reported	3	MV HR	2.02 (1.37–2.99)	12.22
Heffron 2012	2004–2010	3,790	7 African nations	Sero-discordant couples	12–24	3	MSM HR	3.93 (1.38–11.21)	2.81
Morrison 2007	1999–2004	6,109	Uganda, Zimbabwe, Thailand	Family planning clinics	21.5	3	MSM HR	1.25 (0.88–1.77)	13.86
Myer 2007	2000–2004	4,073	Cape Town, So. Africa	General population	24	6,6, & 12	MV IRR	0.75 (0.33–1.69)	4.36
Kleinschmidt 2007	1999–2001	551	Orange Farm, So. Africa	Family planning clinic	12	3	MV HR	0.46 (0.06–3.66)	0.78
Baeten 2007	1993–1997	779	Mombasa, Kenya	CSW	120	1	MV HR	1.73 (1.28–2.34)	15.69
Kiddugavu 2003	1994–1999	5,117	Rakai, Uganda	General population	31	10	IRR, MLR	0.84 (0.41–1.72)	5.37

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Table 3 – Breast Cancer (Cohort Studies)

Study	Study Design	OR[1] Ever Use	RR[2] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Mørch et al. 2017	Cohort		1.2[3] (1.14–1.26)					1,797,932	*[4]	100%
Heikkinen et al. 2016	Cohort		1.37 (1.12–1.68)					7,000	20,000	100%
Lund et al. 2007	Cohort		1.33 (1.11–1.59)					11,777	23,676	96%
Poosari et al. 2014	Cohort		1.31 (0.65–2.65)					70	11,344	92%
Phipps et al. 2011	*[5]		0.80[6] (0.68–0.94)					5,194		92%
Brohet et al. 2007[7]	Cohort		1.47 (1.16–1.87)					846	747	88%
Thorbjarnardottir et al. 2014	Cohort		1.32 (1.02–1.70)					654	16,928	84%
Samson et al. 2017	Cohort		1.80[8] (1.29-2.55)					4816		83%
Rosenberg et al. 2010	Cohort		1.65 (1.19–2.30)					789	53,848	83%
Silvera et al. 2005	Cohort		0.88[9] (0.73–1.07)					1,707	25,611	78%
Hunter et al. 2010	Cohort		1.12 (0.95–1.33)		1.33 (1.03–1.73)			1,344	115,264	73%
			1.42[10] (1.05–1.94)							

[1] OR = odds ratio (95 % confidence interval).
[2] RR = relative risk (95 % confidence interval).
[3] Initiation before age 20, greater than 10 years of use and evaluation within 5 yrs. of stopping further increased the risk.
[4] Entire population of Denmark was the cohort.
[5] Concurrent randomized clinical trials and an observational study.
[6] Hazard ratio shown. Note that women started COCs after age 25, had been off COCs for many years.
[7] Evaluation in patients carrying BRCA mutations. Hazard ratios shown.
[8] Hazard ratio shown.
[9] Hazard ratio shown.
[10] Eight or more years of use.

Study	Study Design	OR[1] Ever Use	RR[2] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
			3.05[11] (2.00–4.66)							
Trivers et al. 2007[12]	Cohort			1.57 (0.95–2.61)				292[13]	1,264[14]	67%

[11] Levonorgestrel containing combined oral contraceptives.
[12] Looked at mortality in patients with breast cancer over 8-10 years depending on whether they were on COCs at the time of diagnosis or within one year.
[13] Deaths.
[14] Total cohort.

Table 4 – Breast Cancer (Case Control Studies)

Study	Study Design	OR[15] Ever Use	RR[16] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Dolle et al. 2009	Case control	2.5 (0.9-5.24)		4.2 (1.9-9.3)				898	961	100%
Lee et al. 2008	Case Case[17]	0.68 (0.33-1.38)						94	444	100%
Sweeney et al. 2007	Case control	1.27 (0.99-1.63)						2,318	2,515	100%
Beaber et al. 2014b	Case control	1.5 (1.1-2.2)						985	882	100%
Li et al. 2012[18]	Case control	2.2 (1.2-4.2)						1,028	919	96%
Beaber et al. 2014a	Case control			1.5[19] (1.3-1.9)				1,102	21,952	96%
Ichida et al. 2015	Case control			0.45 (0.22-0.90)				155	12,333	96%
Ma et al. 2010	Case control	2.87[20] (1.44-5.74)						1,197	2,015	95%
Folger et al. 2007	Case control	1.0[21] (0.8-1.1)						4575	4682	92%
Jernstrom et al. 2005	Case control					2.10 (1.32-3.33)		245	745	92%
Kotsopoulos et al. 2014[22]	Case control	1.45[23] (1.20-1.75)						2,492	2,492	88%
		1.19[24] (0.99-1.42)								
Figueiredo et al. 2010[25]	Case control					2.38 (0.72-7.83)		705	1,398	86%

[15] OR = odds ratio (95 % confidence interval).
[16] RR = relative risk (95 % confidence interval).
[17] BRCA1 and BRCA2 carriers with breast cancer.
[18] Population-based case-control of women 20-44 yo with recent DMPA use for at least 12 months.
[19] Use within the past year of COCs increases risk of breast cancer.
[20] Triple negative breast cancer if less than 18 yo on COCs.
[21] Evaluated short-term use only.
[22] Study of BRCA+ patients.
[23] <20 years old.
[24] 20-25 years old.
[25] Evaluation of BRCA1 and BRCA2 carriers; controls with unilateral breast cancer compared with contralateral cases.

Study	Study Design	OR[15] Ever Use	RR[16] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Veneroso et al. 2008	Case Case[26]	1.12 (1.03-1.23)						116	99	86%

Study	Study Design	OR[27] Ever Use	RR[28] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Ma et al. 2006	Case control	1.27[29] (0.75-2.14)				0.76 (0.49-1.18)		1,366	440	84%
		0.76[30] (0.49-1.18)								
Rosenberg et al. 2008	Case control	1.5[31] (1.2-1.8)						907	1,711	83%
Haile et al. 2006	Case control	0.77[32] (0.53-1.12)						195	497	83%
		1.62[33] (0.90-2.92)						128	307	
Milne et al. 2005	Case control	1.52 (1.22-1.91)						1156	815	83%
Amadou et al. 2013	Case control	1.68 (0 .67-4.21)						1,000	1,074	75%
Ozmen et al. 2009	Case control	0.60 (0.48-0.74)						1,492	2,167	74%
Delort et al. 2007	Population based[34]	1.84[35] (1.38-2.44)						934		71%
Beji et al. 2006	Case control	1.98 (1.38-2.85)						405	1,050	63%
Veisy et al. 2015	Case control	2.11 (1.44-3.08)						235	235	63%
Tehranian et al. 2010	Case control	2.83 (1.87-4.24)						321	321	58%

[26] Comparison of more aggressive with less aggressive cases.
[27] OR = odds ratio (95 % confidence interval).
[28] RR = relative risk (95 % confidence interval).
[29] ER-/PR-
[30] ER+/PR+
[31] OR for 5+ years of use.
[32] BRCA1+ patients.
[33] BRCA2+ patients.
[34] Population-based study of early onset breast cancer.
[35] OR for developing breast cancer 2 years earlier than non-users.

Study	Study Design	OR[27] Ever Use	RR[28] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Lumachi et al. 2010	Retrospective Review	2.06 (1.14-3.70)						404	408	33%

Table 5 – Breast Cancer (Meta-Analyses)

Study	Study Design	OR[36] Ever Use	RR[37] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Kahlenborn et al. 2006[38]	Meta-analysis	1.19 (1.09-1.29)						18,406	27,677	91%
		1.29[39] (1.20-1.40)								
		1.24[40] (0.92-1.67)								
		1.44[41] (1.28-1.62)								
Bethea et al. 2015	Meta-analysis	1.46[42] (1.18-1.81)						1,848	10,044	85%
		1.57[43] (1.22-1.43)						1,043	10,044	
		1.78[44] (1.25-2.53)						494	10,044	
Zhu et al. 2012	Meta-analysis	1.08[45] (0.99-1.17)								54%
Friebel et al. 2014[46]	Meta-analysis	1.36[47] (0.99-1.88)								27%
		1.51[48] (1.10-2.08)								
Moorman et al. 2013	Meta-analysis	1.21[49] (0.93-1.58)								

[36] OR = odds ratio (95 % confidence interval).
[37] RR = relative risk (95 % confidence interval).
[38] Limited to case-control studies from 1980-2004.
[39] Parous women.
[40] Nulliparous women.
[41] Use before first full term pregnancy among parous women.
[42] ER+
[43] ER-
[44] Triple negative.
[45] For each 5 years on COCs the risk increased by 7%, but statistical significance not achieved.
[46] Study limited to BRCA1 and BRCA2 mutation carriers.
[47] 1-3 years of use.
[48] >3 years of use.
[49] 8 studies on BRCA1+ or BRCA2+ patients and breast cancer risk with CSC use.

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Table 6 – Cervical Cancer

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Roura et al. 2016	Cohort Study		1.1[1] (0.9–1.3)		1.8[10] (1.4–2.4)		1[10] (0.9–1.3)	1,065	306,971	94%
			1.6[2] (1.1–2.3)		2.2[8] (1.3–4.0)		1.6[8] (1.1–2.2)	261	306,971	
Leslie et al. 2014	Case Control Study	1.35[3] (0.99-1.85)						219	2,300	87%
McFarlane-Anderson et al. 2008	Case Control Study	1.59[4] (0.87-2.82)						240	102	83%
		2.48[5] (1.30-4.74)								
Vanakankovit et al. 2008	Case Control Study	1.49 (0.79-2.64)						60	180	76%
Wilson et al. 2013	Case Control Study	1.22 (0.96–1.56)						724	3,479	76%
Matos et al. 2005	Case Control Study	1.3 (0.8–3.1)						140	157	47%
International Collaboration 2007[6]	Meta-analysis	1.05[7] (1.04–1.07)						16,573	35,509	97%
	<5 years of use	0.96 (0.04)[8]								
	5-9 years of use	1.2 (0.05)5								
	10+ years of use	1.56 (0.08)5								
	<5 years of use	1.07 (0.08)[9]						7,227	19,335	
	5+ years of use	1.22 (0.11)6								
Moreno 2002[10]	Meta-analysis							1676	255	95%
	Invasive cervical cancer (ICC)	1.29 (0.88-1.91)								
	ICC 5+ years of use	4.01 (2.01-8.02)								

[1] Includes Cervical Intraepithelial Neoplasia Grade 3, carcinoma in situ and invasive cervical cancer.
[2] Analysis limited to invasive cervical cancer.
[3] Study limited to HIV+ women.
[4] Combined hormonal contraceptives.
[5] Progesterone only contraceptives.
[6] Meta-analysis of 24 studies (15 cohort and 9 case-control studies).
[7] Relative risk per year of use for current users of combined hormonal contraceptives.
[8] Floating standard error shown for users of combined hormonal contraceptives.
[9] Progestin only contraceptives. Floating standard error shown. The 95% CI for 5+ years of use is 1.01-1.46.
[10] Pooled data from 8 case-control studies of invasive cervical cancer and 2 of carcinoma in situ, analyzing only the subset positive for Human Papilloma Virus DNA in cervical cells.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
	In situ carcinoma (ISC)	1.42 (0.99-2.04)								
	ISC 5+ years of use	3.42 (2.13-5.48)								

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Table 7 – Individual Studies of the Effects of COCs on the Development of Crohn's Disease

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Khalili et al. 2013[1]	Cohort		1.43 (1.08-1.90)		2.82 (1.65—4.82)		1.39 (1.05—1.85)	315	117,060	93%
García Rodríguez et al. 2005[2]	Cohort				1.94 (0.85–4.45)		1.04 (0.50–2.17)	171	10,000	88%
Logan and Kay 1989	Cohort		1.7 (0.88—3.2)					42	45,958	54%
Vessey et al. 1986[3]	Cohort				1.33			18	17,014	46%
Boyko et al. 1994	Case-control		2 (1.0—3.7)					91	169	94%
Katschinski 1993[4]	Case-control				2.5 (0.75—4.6)					93%
Katschinski 1993[5]	Case-control				3.1 (1.1-6.7)					93%
Lashner et al. 1989	Case-control	1 (0.46—2.16)		0.73 (0.34—1.59)		1.8 (0.61—5.29)		51	51	88%
Lesko et al. 1985[6]	Case-control		1.7 (1.0—3.2)					57	2189	83%
Sandler et al. 1992	Case-control		1.49 (0.99—2.26)					184	217	81%
Persson et al. 1993	Case-control		1.7 (0.9—3.2)					152	305	81%
Halfvarson et al. 2006[7]	Case-control				1.5 (0.4—5.3)			102	102	75%
Lowe et al. 2009[8]	Case-control		1.05					21,172	754,6131	74%
Ng et al. 2012[9]	Case-control	4						125	125	74%

[1] Hazard ratios (RR adjusted for time).
[2] OR increased with duration of use.
[3] Authors' calculation adjusted for smoking.
[4] Adjusted RR for 1-3 years prior to disease onset.
[5] Adjusted RR for >3 years prior to disease onset.
[6] RR is from multiple logistic regression analysis.
[7] Monozygotic and dizygotic twins.
[8] Adjusted incidence rate ratio.
[9] Twins study.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
		(1.1—14.2)								
Ng et al. 2012[10]	Case-control	9.04 (1.11–73.6)								74%
Sicilia et al. 2001	Case-control	2.8 (1.01—7.77)						103	103	71%
Corrao et al. 1998	Case-control ever use			3.4 (1.0—11.9)		1.8 (0.4—7.3)		225	225	67%
Katschinski 1993[11]	Case-control		4.3 (1.3-14.4)					83	83	57%
Han et al. 2010	Case-control		0.66 (0.38—1.15)					315	536	52%
Calkins et al. 1986[12]	Case-control	1.14 (0.44—2.96)						66	67	42%
Calkins et al. 1986[13]	Case-control	1.6 (0.59—4.37)						66	71	42%
Vcev et al. 2015	Case-control	0.28 (0.03—2.46)						11	42	31%
Cornish et al. 2008	Meta-analysis				1.46 (1.26—1.70)		1.04 (0.816—.340)	1251	74,564	91%
Cornish et al. 2008[14]	Meta-analysis				1.58 (1.07—2.40)					91%
Godet et al. 1995[15]	Meta-analysis		1.44 (1.12—1.86)					531	49,156	82%

[10] Multivariate analysis.
[11] RR for use >3 years.
[12] Hospital controls.
[13] Neighborhood controls.
[14] High quality studies.
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Table 8 – Individual Studies of the Effects of COCs on the Development of Ulcerative Colitis

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Khalili et al. 2013[1]	Cohort		1.18 (0.92—1.52)		1.22 (0.74—2.07)		1.18 (0.91—1.52)	392	116,983	93%
García Rodríguez et al. 2005	Cohort				1.58 (0.71–3.52)		0.67 (0.32–1.39)	222	10,000	88%
Logan and Kay 1989	Cohort		1.3 (0.82—2.0)					78	45,922	54%
Vessey et al. 1986[2]	Cohort				2.1			31	17,001	46%
Boyko et al 1994	Case-control		1.7 (1.1—2.7)					211	341	94%
Lashner et al. 1990	Case-control	0.86 (0.40—1.85)		0.7 (0.27—1.83)		1.14 (0.41—.15)		46	46	81%
Sandler et al. 1992[3]	Case-control		1.1 (0.65—1.85)					89	217	81%
Persson et al. 1993	Case-control		1.7 (0.8—3.3)					145	305	81%
Halfvarson et al. 2006[4]	Case-control				0.6 (0.1–2.5)			125	125	75%
Ng et al. 2012[5]	Case-control	0.43 (0.11—1.66)						125	125	74%
Parrello et al. 1997[6]	Case-control	3.11 (1.54—6.3)						536	755	67%
Corrao et al. 1998	Case-control			1.6 (0.9—3.0)		1.3 (0.6—2.8)		594	594	67%
Calkins et al. 1986[7]	Case-control	0.62 (0.11—3.42)						35	32	42%
Calkins et al. 1986[8]	Case-control	0.57 (0.11—2.88)						35	38	42%

[1] Hazard ratios (RR adjusted for time).
[2] Authors' calculation, adjusted for smoking.
[3] Interaction with smoking notes, higher RR in smokers (2.49).
[4] Monozygotic and dizygotic twins.
[5] Twins studies.
[6] Unclear how the calculation was done.
[7] Hospital controls.
[8] Neighborhood controls.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Vcev et al. 2015	Case-control	0.75 (0.30–1.88)						62	42	31%
Cornish et al. 2008	Meta-analysis				1.28 (1.06–1.54)		1.07 (0.702–1.640)	883	74,932	91%
Cornish et al. 2008[9]	Meta-analysis				1.24 (0.999–1.54)					91%
Godet et al. 1995[10]	Meta-analysis		1.29 (0.94–1.77)					851	49,875	82%

[9] High quality studies.
[10] Adjusted for smoking.

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Table 9 – Individual Studies of the Effects of COCs on the Development of Systemic Lupus Erythematosus

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Costenbader et al. 2007[1]	Cohort		1.5 (1.1–2.1)				1.7 (1.2-2.3)	262	238,046	96%
Costenbader et al. 2007[2]	Cohort		1.6 (1.1-2.2)				1.6 (1.1-2.2)	164	102,882	96%
Costenbader et al. 2007[3]	Cohort		2.3 (1.0-5.0)				2.3 (1.1-5.2)	98	107,854	96%
Bernier et al. 2009	Cohort		1.19 (0.98-1.45)		1.54 (1.15-2.07)		1.06 (0.85-1.33)	786	7817	96%
Bernier et al. 2009[4]	Cohort				2.52 (1.14-5.57)			786	7817	96%
Bernier et al. 2009[5]	Cohort				1.45 (1.06-1.99)			786	7817	96%
Sanchez-Guerrero et al. 1997	Cohort		1.4 (0.9-2.1)					99	121,546	88%
Sanchez-Guerrero et al. 1997[6]	Cohort		1.9 (1.1-3.3)					58	121,587	88%
Cooper et al. 2002	Case-control			1.5 (0.8–2.7)		1.3 (0.8–2.0)		240	321	92%
Strom et al. 1994	Case-control	0.8 (0.5-1.4)						195	143	73%
Zonana-Nacach et al. 2002[7]	Case-control	2.1 (1.18-3.6)						130	130	61%
Grimes et al. 1985	Case-control			0.5 (0.11-2.3)				109	109	58%

[1] Pooled RR from the Nurses' Health Study (NHS) and NHS II.
[2] RR from the NHS (data collection through 1976).
[3] RR from NHS II (data collection through 1989).
[4] RR for short term use (starting COCs within ≤3 months).
[5] RR for long term use (starting COCs over 3 months previously with current use ongoing).
[6] Using most stringent definition of systemic lupus erythematosus.
[7] Paper written in Spanish. OR is for use of oral contraceptives for more than one year.

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Table 10 – Studies of Chemical Contraceptives and Depression, Mood Disorders and Suicides

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
Skovlund 2016 incl /Worley	Prospective Cohort Incident Depression – COCs		1.1[92] (1.08-1.14)				1,061,997
	Incident Depression – POCs		1.2[93] (1.04-1.31)				
	First use of Antidepressants – COCs		1.23[94] (1.22-1.25)				
	First use of Antidepressants – POCs		1.3[95] (1.27-1.40)				
Skovlund 2018 incl /Worley	Prospective Cohort						475,802
	Prospective Cohort Suicide attempts		1.97[96] (1.85-2.10)				
	Suicides		3.08[97] (1.34-7.08)				
Gregory 2018	NCHA survey					146,938	202,759
	Ever Diagnosed with Depression	1.558 (1.506-1.612)					
	Academic performance affected by depression	1.282 (1.245-1.321)					
Keyes 2013	COC reduced depression among women 25-34 years of age.[98] 4 waves of L-Hanes			-1.04[99] (-1.73 - -0.35)		3224	1219
	Suicide attempts			0.38 (0.15-0.97)			
Toffol 2011	Population/choice			-0.988[101] (-1.917 – -0.059)			2,310

[92] First diagnosis of depression for combined oral contraceptive users.
[93] First diagnosis of depression for all progestin-only method users.
[94] First use of an antidepressant for combined oral contraceptive users.
[95] First use of an antidepressant for all progestin-only method users.
[96] Hazard ratio for suicide attempts; all hormonal contraceptives.
[97] Hazard ratio for suicides; all hormonal contraceptives.
[98] "The presence of depressive symptoms during the past 7 days was assessed in all waves using the Center for Epidemiologic Studies Depression Scale (CES-D)."
[99] β statistic shown.
[101] β statistic shown for the Beck Depression Inventory (BDI). None of the other parameters assessed was statistically significant (including any psychiatric diagnosis, alcohol dependence, major depressive episode or disorder, dysthymic disorder, or anxiety disorder).

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
	Cross sectional 30-54 yrs. of age[100]						
Toffol 2012	Population-based cross-sectional study[102]			-0.42 (--1.79 - -0.04)[103]			8,586
Svendal 2012[104]	Population-based cross-sectional study					40	458
	POC Use – mood disorder			3.0 (1.1-7.8)			
	COC Use – mood disorder			0.3 (0.1-0.9)			
Horibe 2018	Retrospective[105]					253	6,157,897
	Post-partum depression w/ levonorgestrel			12.5 (8.7-18)			
	Post-partum depression w/ etonogestrel			14.0 (8.5-22.8)			
	Post-partum depression w/ sertraline & drospirenone			5.4 (2.7-10.9)			
Singata-Madliki 2016	Single-blind randomized controlled trial of post-partum DMPA vs. copper IUD			[106]		111[107]	117[108]

[100] "The associations between the current use of COCs and the LNG-IUS, and their duration versus mood symptoms [Beck Depression Inventory (BDI)], psychological well-being [(General Health Questionnaire-12 (GHQ-12)] and recent psychiatric diagnoses [(Composite International Diagnostic Interview (CIDI)] were examined among women who participated in the Finnish-population-based Health 2000 study." "Overall, hormonal contraception was well tolerated with few significant effects on psychological well-being."

[102] Data were collected in the context of the National FINRISK Study Survey, a cross-sectional population-based health survey carried out in Finland every 5 years since 1972. For the purpose of this study, data collected in the years 1997, 2002 and 2007 were analyzed for ages 25–54. OC vs. LNG. inconsistent questions between surveys, BDI, recall bias, etc. "Presence of somatic and psychological symptoms was assessed by asking the participants how often (often, sometimes, not at all) in the previous month they had had one or more out of 13 symptoms." Also administered the Beck Depression Inventory-13. "A negative association between the current use of COCs and Beck Depression Inventory-13 (BDI-13) score was found. Some other negative associations, all characterized by a small effect size, were detected between current use of COCs and the BDI items feelings of dissatisfaction, feelings of uselessness, irritability, lost interest in people and lost appetite."

[103] Results for the BDI-13 shown. Other parameters (including BDI-21, low mood last year, anhedonia last year, recent diagnosis of depression and recent other psychiatric diagnosis) did not reach statistical significance.

[104] Women in Australia 20-50 years of age. Evaluated for the occurrence of mood disorders, including major depressive disorder (MDD), minor depression, bipolar disorder, dysthymia, mood disorder due to a general medical condition and substance induced mood disorder.

[105] Data is from the FDA Adverse Event Reporting System (FAERS) database. Reporting Odds Ratios (ROR) are shown.

[106] Beck Depression Inventory (BDI-II) and the Edinburgh Postnatal Depression Scale (EPDS) evaluated. The one-month EPDS depression scores were statistically significantly higher in the DMPA arm compared with the IUD arm (p=0.04). Three-month BDI-II scores were significantly higher in the DMPA arm than in the IUD arm (p=0.002) and, according to the BDI-II but not the EPDS, more women in the DMPA arm had major depression at this time-point (8 vs 2; p=0.05).

[107] 111 randomized to DMPA.

[108] 117 randomized to IUDs.

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
Kulkarni 2005[109]	Case-control pilot study COCs vs non-users			p=0.001 depression for all scales[110]		26	32
Roberts 2017	Retrospective cohort study[111]			With Dx of depression[112]	w/anti depressant use[113]	31,506[114]	44,022[115]
	Norethindrone-only pills			0.56 (0.49-0.64)	0.58 (0.52-0.64)		
	Levonorgestrel intrauterine system			0.65 (0.52–0.82)	1.01 (0.87–1.18)		
	Etonogestrel subdermal implant			1.01 (0.83–1.22)	1.22 (1.06–1.41)		
	Ethinyl estradiol/ norgestimate (pill)			0.89 (0.70–1.14)	1.02 (0.85–1.22)		
	Ethinyl estradiol/norethindrone (pill)			0.82 (0.59–1.12)	0.88 (0.69–1.13)		
	Ethinyl estradiol/etonogestrel (ring)			1.09 (0.80–1.50)	1.45 (1.16–1.80)		
Tsai 2010	Retrospective chart review[116]	DMPA	Controls			55	192
	Mean EPDS scores at 6 weeks postpartum	5.02	6.17				
Griksiene 2011	Case-control study[117]	[118]				23[119]	20[120]

[109] Assessment tools included three depression rating scales: Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAMD) and Montgomery-Asberg Depression Rating Scale (MADRS); also used the Global Assessment of Functioning (GAF) Scale.

[110] ANOVA of GAF, BDI, HAMD &MADR scales all significantly different.

[111] Post-partum depression with hormonal contraception.

[112] Adjusted hazard ratios shown.

[113] Adjusted hazard ratios shown.

[114] Number on hormonal contraceptives.

[115] Number not on hormonal contraceptives.

[116] Depot medroxyprogesterone in the immediate post-partum period and depression. Evaluated the Edinburgh Postnatal Depression Scale (EPDS).

[117] Verbal fluency and mental rotation (spatial perception) are affected by progestins w/androgenic or antiandrogenic properties.

[118] Naturally cycling women performed better on verbal fluency task as compared to OC users. Subjects who used the third generation (androgenic) COCs generated significantly fewer words as compared to new generation (anti-androgenic) OC users and non-users. The third generation OC users demonstrated significantly longer RT in MRT task as compared to non-users. The MRT, verbal fluency and mood parameters did not depend on the phase of menstrual cycle.

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Table 11 – Individual Studies of the Effects of COCs on the Development of Multiple Sclerosis

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Hernán et al. 2000[121]	Cohort		1.1 (0.9-1.5)		1 (0.6-1.6)		1.2 (0.9-1.5)	313	237,318	90%
Thorogood et al. 1998[122]	Cohort				1.2 (0.7-2.0)		1.3 (0.9-2.0)	114	46,000	75%
Villard-Mackintosh et al. 1993	Cohort		0.8 (0.5-1.4)					63	16,969	65%
Hellwig et al. 2016	Case-control	1.51 (1.12-2.03)		1.47 1.05-2.05		1.55 (1.20-2.00)		400	3804	92%
Kotzamani et al. 2012	Case-control	1.6 (1.1-2.4)						254	314	81%
Alonso et al. 2005[123]	Case-control	0.6 (0.4-1.0)		0.5 (0.3-1.2)		0.6 (0.4-1.0)		106	1001	77%

[121] NHS I and II cohorts.

[122] Funded by drug companies that make HCs.

[123] OC use over the 3 years prior to the index date. Limited to women ≤50 years of age.

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Table 12 – Individual Studies of the Effects of Contraceptives on the Development of Osteoporotic Fractures

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
Cooper 1993[124]	Cohort	COCs		1.20 (1.08-1.34)		1365	46,000	All fractures
Vessey 1998[125]	Cohort	COCs		1.5 (1.1-2.1)		1308	17,032	First fracture: radius or ulna
Vessey 1998[126]	Cohort	COCs		1.2 (1.1-1.4)				First fracture: all sites
Vessey 1998[127]	Cohort	COCs		2.5 (1.5-4.0)				First fracture: radius or ulna
Vessey 1998[128]	Cohort	COCs		1.3 (1.1-1.5)				First fracture: all sites
Vessey 1998[129]	Cohort	COCs		5.7 (p=0.017)				First fracture: radius or ulna
Vessey 1998[130]	Cohort	COCs		11.2 (p<0.001)				First fracture: all sites
Barad 2005[131]	Cohort	OCs[132]		1.07 (1.01–1.15)		4,674	80,947	First fracture
Barad 2005[133]	Cohort	OCs		1.15 (1.04-1.27)		4,674	80,947	First fracture
Barad 2005[134]	Cohort	OCs		1.09 (0.97–1.23)		4,674	80,947	First fracture
Lanza 2013[135]	Retrospective cohort study	DMPA[136]		1.41 (1.35–1.47)		11,822	312,395	Incident fractures

[124] From the Royal College of General Practitioners (RCGP) Oral Contraception Study.
[125] OC use > 97 months vs no use. Recruited age 25 to 39 years; followed to 45 years.
[126] OC use > 97 months vs no use. Recruited age 25 to 39 years; followed to 45 years.
[127] Interval since use: 73 to 96 months vs no use (radius or ulna). Recruited age 25 to 39 years; followed to 45 years.
[128] < 12 months vs no use (all fractures). Recruited age 25 to 39 years; followed to 45 years.
[129] X^2 trend.
[130] X^2 trend.
[131] Recruited age 50 to 74 years; OC use: any vs none.
[132] The patients were asked about oral contraceptive use, which likely was predominantly COCs but was not broken down with regard to COCs or POCs.
[133] Among women without any postmenopausal hormone treatment, past OC use for 5 years or less.
[134] Among women without any postmenopausal hormone treatment, past OC use for more than 5 years.
[135] They note that, "Although DMPA users experienced more fractures than nonusers, this association may be the result of confounding by a pre-existing higher risk for fractures in women who chose DMPA for contraception." However, this is based on analysis of relatively few fractures prior to DMPA use.
[136] Depot medroxyprogesterone acetate = DMPA.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
	Past use[137]	DMPA		1.32 (1.24–1.41)				Incident fractures
	Recent use[138]	DMPA		1.41 (1.31–1.50)				Incident fractures
	Current use[139]	DMPA		1.51 (1.41–1.61)				Incident fractures
Tuppurainen 1993[140]	Case-control	OCs	1.21 (0.93-1.57)			629	13,100	All fractures
Tuppurainen 1993[141]	Case-control	OCs	1.35 (0.88-2.05)			210	13,100	Wrist fractures
O'Neill 1996	Case-control	OCs	0.3 (0.1-0.9)			62	116	Distal forearm fractures only Population controls
O'Neill 1996	Case-control	OCs	0.7 (0.2-2.4)			62	50	Distal forearm fractures only Fall controls
Michaëlsson 1999[142]	Case-control	Any[143]	0.75 (0.59–0.96)			1327	3312	Hip fractures
Vestergaard 2006[144]	Case-control	OCs	<0.3 DDD/day	0.3–0.99 DDD/day	1+ DDD/day	64,548	193,641	Any fracture in the year 2000
	<25 years[145]	OCs	0.97 (0.91–1.03)	0.96 (0.92–1.01)	0.92 (0.86–0.98)			Any fracture in the year 2000
	25-49 years	OCs	0.91 (0.82–1.00)	0.90 (0.77–1.05)	0.87 (0.64–1.18)			Any fracture in the year 2000
	50+ years	OCs	0.92 (0.77–1.10)	0.69 (0.45–1.05)	0.62 (0.27–1.41)			Any fracture in the year 2000
Vestergaard 2008a[146]	Case-control	OCs	<0.3 DDD/day	0.3–0.99 DDD/day	1+ DDD/day	64,548	193,641	Any fracture in the year 2000
	<15	OCs	1.02 (0.75–1.37)	1.17 (1.01–1.37)	0.97 (0.85–1.11)			Any fracture in the year 2000

[137] Active DMPA use based on the interleaving of active 90-day exposures generated by each injection.
[138] Recent exposure is 640 or fewer days after the last active exposure.
[139] Past exposure begins after "recent" exposure (641 or more days after the last active exposure).
[140] Oral contraceptive use for 6+ years.
[141] Oral contraceptive use for 6+ years.
[142] No significant correlation was seen with duration of use, time since last use or time between last use and menopause.
[143] Any type of chemical contraceptive was evaluated, not separated as COCs or POCs.
[144] "The exposure time for oral contraceptives may thus maximally have spanned 5 years (from January 1, 1996, to December 31, 2000)." This and the other Vestergaard study are not useful as they do not take into account remote use or cumulative lifetime use. ORs shown.
[145] Defined daily dosages = DDD.
[146] Similar to Vestergaard 2006; only looked at use within the past 5 years. A younger group examined here. ORs shown.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
	15.1-17	OCs	1.22 (1.02–1.47)	1.14 (1.00–1.30)	1.04 (0.90–1.19)			Any fracture in the year 2000
	17.1-19	OCs	0.97 (0.87–1.09)	0.93 (0.84–1.02)	1.02 (0.89–1.18)			Any fracture in the year 2000
	>19	OCs	0.99 (0.93–1.05)	1.00 (0.93–1.08)	0.88 (0.78–0.99)			Any fracture in the year 2000
Vestergaard 2008b[147]	Case-control	DMPA	1.44 (1.01–2.06)			64,548	193,641	Any fracture in the year 2000 DMPA use
Wei 2011[148]	Cross-sectional		<5 years of use	5-10 years of use	>10 years of use		491	
		OCs	0.85 (0.45–1.58)	0.45 (0.21–0.93)	0.75 (0.36–1.54)			Presence of vertebral deformity
		OCs	0.96 (0.62–1.48)	0.63 (0.37–1.07)	0.94 (0.56–1.56)			Number of vertebral deformities
Meier 2010[149]	Case-control		Current Use	Past Use		17,527	70,130	Incident fracture
	1-2 DMPA Scripts	DMPA	1.18 (0.93–1.49)	1.17 (1.07–1.29)				Incident fracture
	3-9 DMPA scripts	DMPA	1.36 (1.15–1.60)	1.23 (1.11–1.36)				Incident fracture
	10+ DMPA scripts	DMPA	1.54 (1.33–1.78)	1.30 (1.09 –1.55)				Incident fracture
	1-2 COC Scripts	COCs	1.01 (0.87–1.18)	1.00 (0.95–1.07)				Incident fracture
	3-9 COC scripts	COCs	1.01 (0.94 –1.09)	0.99 (0.94 –1.04)				Incident fracture
	10+ COC scripts	COCs	1.09 (1.03–1.16)	1.03 (0.97–1.10)				Incident fracture
Memon 2011[150]	Case-control	COCs	1.05 (0.86-1.29)			651	1302	Any fracture
Kyvernitakis 2017[151]	Case-control		OR Current Use	OR Past Use		4189	4189	First-time fracture diagnosis
	1-2 DMPA scripts	DMPA	0.97 (0.51–1.86)	0.96 (0.73–1.26)				
	3-9 DMPA scripts	DMPA	2.41 (1.42–4.08)	1.14 (0.86–1.51)				
	10+ DMPA scripts	DMPA	1.46 (0.96–2.23)	1.55 (1.07–2.27)				

[147] Similar to Vestergaard 2006; only looked at use within the past 5 years. DMPA examined here. ORs shown.

[148] Small cross-sectional study. ORs shown.

[149] Females aged 20–44 years with an incident fracture diagnosis between 1995 and 2008.

[150] Nested case-control study of the Cooper study from the Royal College of General Practitioners (RCGP) Oral Contraception Study. Last OC use > 10 years vs never.

[151] Women between 20 and 44 years of age with a first-time fracture diagnosis, matched with random controls using the Disease Analyzer database.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
	1-2 COC scripts	COCs	0.98 (0.73–1.31)	0.90 (0.77–1.05)				
	3-9 COC scripts	COCs	1.39 (1.12–1.73)	0.90 (0.78–1.03)				
	10+ COC scripts	COCs	1.07 (0.88–1.30)	1.04 (0.90–1.21)				

Osteoporotic Fracture References

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Table 13 – Effect of Chemical Contraceptives on Weight Gain

Study	Design	Comparison	N	Time	Weight change (Kg)	Fat mass change	Lean mass change	Comments
Pantoja 2010	Retrospec.	DMPA 150 vs CuIUC	758	1yr	1.76 vs-0.42*			
				2yr	3.1 vs 0.4*			Largest differences noted in normal and overweight BMI subgroups, minimal differences in obese BMI subgroup
				3yr	3.9 vs 0.8*			
Modesto 2015	Retrospec.	DMPA150 vs CuIUC	1277	1yr	1.3 vs 0.2*			
				4yr	3.5 vs 1.9*			
				10yr	6.6 vs 4.9*			Adjusted for years of school & # children. 20% loss @4yrs 84% @ 10yr.
Taneepanichuskul 1998	Retrospec.	DMPA 150 vs CuIUC	100	10yr	10.9 vs 11.2			Included women 37-50 years (no younger women)
Vickery 2013	Prospec.	DMPA 150 vs CuIUC	167	1yr	2.2 vs 0.16			CHOICE study subgroup
Dal'Ava 2014	Prospec.	DMPA 150 vs CuIUC	110	1yr	1.9vs 1.1	1.6 vs -0.9 (Kg)	0.3 vs 1.2 (kg)	Paired by age (+/-2yr) & weight (+/-2kg)
Dos Santos 2014	Prospec.	DMPA 150 vs CuIUC	71	1yr	1.4 vs 0.3	1.57 vs 0.52 (kg)	(0.31) vs (0.26) (kg)	Matched by age & BMI
								()= negative value
Studies comparing LNG IUC to non-hormonal contraceptive								
Study	**Design**	**Comparison**	**N**	**Time**	**Weight change (Kg)**	**Total body fat**	**Lean body mass**	
Dal'Ava 2012	Prospec.	LNG-IUC vs non-hormonal IUC	76	1yr	2.9 vs 1.4	2.5% vs -1.3%*	(1.4%) vs 1.0%*	Paired by age & BMI
Napolitano 2015	Prospec.	LNG IUC vs no method	60	1yr	0.6 vs (0.2)	1.1% vs (0.5%)*	(1.1%) vs 0.5*	
Vickery 2013	Prospec.	LNG-IUC vs Cu IUC	230	1yr	1.03 vs 0.16	nd	nd	

Modesto 2015	Retrospec.	LNG-IUC vs CuIUC	1204	1yr	0.7 vs 0.2	nd	nd	
				4yr	2.7 vs1.9			
				10yr	4.0 vs 4.9			
Studies comparing progestin-only COCs to non-hormonal								
Study	**Design**	**Comparison**	**N**	**Time**	**Weight change (Kg)**	**Total body fat**	**Lean body mass**	
Napolitano 2015	Prospec.	Desogestrel 75ug vs no hormonal	68	1yr	0.3 vs -0.2	1.1% vs -0.5%*	(2.8%) vs 0.5%*	
Studies comparing combined COCs to non-hormonal								
None found-								
Abstract from 2014 Cochrane review of combined oral contraceptives on weight gain: "We found 49 trials that met our inclusion criteria. The trials included 85 weight change comparisons for 52 distinct contraceptive pairs (or placebos). *The four trials with a placebo or no intervention group did not find evidence supporting a causal association* between combination oral contraceptives or a combination skin patch and weight change. Most comparisons of different combination contraceptives showed no substantial difference in weight. In addition, discontinuation of combination contraceptives because of weight change did not differ between groups where this was studied. Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD003987.								

* Significant difference ($p<0.05$).

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Table 14 – Relative Risk of Venous Thromboembolism in Current Users of Different Combined Hormonal Contraceptives as Compared with Nonusers Unless Otherwise Specified

Study	Data Sampling Period	VTE (number)	COCs with levonorgestrel RR (95% CI)	COCs with desogestrel/gestodene RR (95% CI)	COCs with drospirenone RR (95% CI)
Blomenkamp 1995	1988 - 1992	126	3.8 (1.7 - 8.4)	8.7 (3.9 - 19.3)	-
WHO 1995a, 1995b	1989 - 1993	433	3.6 (2.5 - 5.1)	7.4 (4.2 - 12.9)	-
Jick 1995	1991 - 1994	80	1 (reference)	1.8 (1.0 - 3.2)	-
Spitzer 1996	1991 - 1995	471	3.7 (2.2 - 6.2)	6.7 (3.4 - 13.0)	-
Lewis 1999	1993 - 1995	502	2.9 (1.9 - 4.2)	2.3 (1.5 - 3.5)	-
Farmer 1997	1991 - 1995	85	3.1‡ (2.1 - 4.5)	5.0‡ (3.7 - 6.5)	-
Todd 1999	1992 - 1997	99	1 (reference)	1.4 (0.7 - 2.8)	-
Bloemenkamp 1999	1994 - 1998	185	3.7 (1.9 - 7.2)	5.6 (not given)	-
Parkin 2000	1990 - 1998	26	5.1 (1.2 - 21.4)	14.9 (3.5 - 64.3)	-
Lidegaard 2002	1994 - 1998	987	2.9 (2.2 - 3.8)	4.0 (3.2 - 4.9)	-
Dinger 2007	2000 - 2004	118	1 (reference)	1.3 (NA)	1.0 (0.6 - 1.8)
Vlieg 2009	1999 - 2004	1524	3.6 (2.9 - 4.6)	7.3 (5.3 - 10.0)/5.6 (3.7 - 8.4)	6.3 (2.9 - 13.7)
Lidegaard 2009	1995 - 2005	4213	2.0 (1.8 - 2.3)	3.6 (3.3 - 3.8)	4.0 (3.3 - 4.9)
Dinger 2010	2002 - 2008	680	1 (reference)	NA	1.0 (0.6 - 1.8)
Parkin 2011	2002 - 2009	61	1 (reference)	NA	2.7 (1.5 - 4.7)
Jick 2011	2002 - 2008	186	1 (reference)	NA	2.8 (2.1 - 3.8)
Lidegaard 2011	2001 - 2009	4246	2.2 (1.7 - 2.8)	4.2 (3.6 - 4.9)	4.5 (3.9 - 5.1)
Confirmed only	2001 - 2009	2707	2.9 (2.2 - 3.8)	6.8 (5.7 - 8.1)	6.3 (5.4 - 7.5)
FDA Kaiser 2011	2001 - 2007	625	1 (reference)	NA	1.5 (1.2 - 1.9)
Gronich 2011	2002 - 2008	518	1 (reference)	1.4 (0.9 - 2.1)	1.7 (1.0 - 2.7)
Lidegaard 2012	2001 - 2010	5287	3.2 (2.7 - 3.8)	6.5 (4.7 - 8.9)*	NA
Dinger 2014	2005 - 2010	162	1 (reference)	NA	0.8 (0.5 - 1.6)

‡ Absolute risk per 10,000 years.
* Vaginal ring with the third-generation progestin etonogestrel.

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Table 15 – Relative Risk of Thrombotic Stroke and Myocardial Infarction among Users of Selected Types of Combined Oral Contraception with Ethinyl Estradiol at a Dose of 30 to 40 µg, as Compared with Nonusers, According to Duration of Use (from Lidegaard 2012).

		Thrombotic Stroke		Myocardial infarction	
Duration of use	No. of person-yrs.	No. of events	Relative Risk (95% CI)	No. of events	Relative Risk (95% CI)
<1 year	987,564	213	1.90 (1.64–2.20)	86	1.85 (1.48–2.31)
1-4 years	992,825	194	1.55 (1.33–1.80)	108	1.99 (1.63–2.43)
>4 years	399,461	173	1.93 (1.65–2.26)	91	2.11 (1.70–2.62)

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