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Hormonal Contraception and the Development of Autoimmunity
A Review of the Literature

Supplemental Material

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Table 1. Individual Studies of the Effects of Combined Hormonal Contraceptives on the Development of Rheumatoid Arthritis

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
Hernandez-Avila et al 1990	Cohort study		0.9 (0.6-1.4)				0.9 (0.6-1.3)	115	116,445	94%
Pedersen et al 2007[3]	Frequency-matched case-control study	1.1 (0.76-1.6)						366	478	92%
Brennan and Silman 1994	Case-control monozygotic twins		0.25 (0.03-2.24)					35	35	90%
Brennan and Silman 1994	Case-control dizygotic twins		0.75 (0.17-3.35)					31	31	90%
Brennan and Silman 1994	Case-control population controls		0.43 (0.17-1.09)					60	160	90%
Brennan et al 1997[4]	Nested case-control study	1.11 (0.48-2.54)		0.15 (0.1-2.3)				69	69	90%
Karlson et al 2004[5]	Cohort study		1.1 (0.9-1.3)					674	110,026	90%
Pikwer et al 2009[6]	Nested case-control	1.03 (0.63 - 1.67)						136	544	90%
Hazes et al 1990	Case-control in sibs		0.41 (0.16-1.09)					86	118	89%
del Junco et al 1985	Population-based case-control study		1.1 (0.7-1.7)		1.3 (0.7-2.4)		1 (0.6-1.7)	182	182	88%
Moskowitz et al 1990	Case-control				2 (0.97-4.21)		1 (0.4-2.2)	71	280	88%
Doran et al 2004	population based case-control study	0.56 (0.34 - 0.92)		1 (0.40-2.52)				445	445	88%
Pedersen et al 2006[7]	Case-control	1.24 (0.91 - 1.71)		1 (0.57 - 1.76)				366	478	87%
Pedersen et al 2006[14]	Case-control ACP+	1.65 (1.06 - 2.57)						209	477	87%
Pedersen et al 2006[14]	Case-control ACP-	1.19 (0.68 - 2.07)						103	477	87%
Spector et al 1990[8]	Case-control vs. OA	0.56 (0.29-1.12)						150	157	85%
Spector et al 1990[7]	Case-control vs. population	0.6 (0.30-1.17)						150	180	85%

[1] OR = odds ratio
[2] RR = relative risk
[3] The sample size is large enough to detect ORs of 1.5–2 . OR is my calculation. Study population overlap with Pedersen et al 2006.
[4] Rheumatoid arthritis cases only, very few with current OC use. Current use excluded from analyses as only 3 versus 5 cases versus controls.
[5] Notes that breast feeding is protective.
[6] Notes that breast feeding is protective.
[7] Same population as Pedersen 2007. ACP = anti-citrullinated protein antibody.
[8] Only considered oral contraceptive use prior to the age of 35.

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
Berglin et al 2010	Case-control		0.79 (0.45-1.38)					70	280	85%
Merlino et al 2003[9]	Prospective cohort		1 (0.67 – 1.50)					158	31,178	84%
Jorgensen et al 1996[10]	Case-control <5 years of use		0.713 (0.41 - 1.23)					176	145	80%
Jorgensen et al 1996[9]	Case-control >5 years of use		0.76 (0.5 - 1.14)							80%
Vandenbroucke et al 1982	Case-control		0.42 (0.27-0.65)		0.45 (0.28-0.75)		0.4 (0.22-0.72)	228	302	79%
Pope et al 1999	Case-control	0.6 (0.1-3.1)						34	68	79%
Linos et al 1983[11]	Case-control		1.7 (0.8-3.5)					229	458	78%
Allebeck et al 1984[12]	Case-control		0.7 (0.40 - 1.24)					76	152	78%
Hannaford et al 1990[13]	Prospective cohort study				0.82 (0.59 - 1.15)		0.94 (0.72 - 1.22)	23,000	23,000	78%
Adab et al 2014	Cohort[14]	1.14 (0.91-1.40)						669	6,654	78%
Adab et al 2014	Cohort[15]	1.18 (0.84-1.67)						247	7,076	78%
van Zeben et al 1990[16]	Case-control		0.72 (0.27-1.89)					173	378	75%
Rodríguez et al 2009	Cohort study			0.85 (0.45-1.60)		0.81 (0.46-1.41)		579	4,234	71%
Vessey et al 1987	Cohort study	1.12 (0.79-1.79)						78	16,954	68%
Darwish and Armenian 1987	Case-control	1.29 (0.64-2.58)						100	100	65%
Wingrave and Kay 1978[17]	Cohort study		0.49 (0.28-0.88)					94	46,000	59%
Hazes et al 1989	Case-control		0.39		0.58			135	378	48%

[9] Women aged 55-69.
[10] Confounded that OCP use was strongly associated with year of mother's birth and rheumatoid arthritis patients were older.
[11] Overlaps with Del Junco.
[12] Defined those on OCPs for less than a year as non-users.
[13] Results likely skewed by age of current users versus patients.
[14] Physician diagnosis of rheumatoid arthritis or pain/swelling of ≥ 3 joints including wrist. Notes that breast feeding is protective.
[15] Physician diagnosis of rheumatoid arthritis or pain/swelling of ≥ 3 joints including wrist and ≥ 1 ACR definition. Notes that breast feeding is protective.
[16] Overlaps with Hazes 1990 and focuses on severe disease.
[17] Clear skewing in the age of rheumatoid arthritis cases. This study was funded by pharmaceutical companies which sell hormonal contraceptives.

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
			(0.24-0.63)		(0.32-1.04)					
Hernandez-Avila et al 1989	Cohort study						1 (0.7-1.3)	217	Not stated	31%

Table 2. Meta-analyses of Studies of the Effects of Combined Hormonal Contraceptives on the Development of Rheumatoid Arthritis

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
Romieu et al 1989	Meta-analysis case-control studies	0.79 (0.58-1.08)		0.98 (0.34-2.77)		0.73 (0.49-1.08)		1447	2314	90%
Romieu et al 1989	Meta-analysis Longest duration of use in case-control studies	0.65 (0.39-1.08)						NA[1]	NA[1]	90%
Spector and Hochberg 1990	Meta-analysis	0.73 (0.61-0.85)						1634	181,841	89%
Spector and Hochberg 1990	Meta-analysis case-control studies	0.6 (0.48-0.75)						1245	2028	89%
Spector and Hochberg 1990	Meta-analysis cohort studies	0.88 (0.70-1.12)						389	179,813	89%
Pladevall-Vila et al 1996	Meta-analysis		0.84 (0.66-1.08)		0.93 (0.66-1.32)			1177	142,225	89%
Pladevall-Vila et al 1996	Meta-analysis case-control studies		0.73 (0.65-0.85)					367	31,655	89%
Pladevall-Vila et al 1996	Meta-analysis cohort studies		0.95 (0.81-1.12)					810	110,570	89%
Pladevall-Vila et al 1996	Meta-analysis population-based studies		1.11 (0.80-1.54)					924	NA[1]	89%
Pladevall-Vila et al 1996	Meta-analysis hospital-based studies		0.71 (0.37-1.37)					589	NA[1]	89%

[1] NA = not available

Table 3. Individual Studies of the Effects of Combined Hormonal Contraceptives 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
Boyko et al 1994	Case-control		2 (1.0-3.7)					91	169	94%
Katschinski 1993[1]	Case-control				2.5 (0.75-4.6)					93%
Katschinski 1993[2]	Case-control				3.1 (1.1-6.7)					93%
Khalili et al 2013[3]	Cohort		1.43		2.82 (1.65 - 4.82)		1.39 (1.05 - 1.85)	315	117,060	93%
Cornish et al 2008	Meta-analysis				1.46 (1.26-1.70)		1.04 (0.816-1.340)	1251	74,564	91%
Cornish et al 2008[4]	Meta-analysis				1.58 (1.07-2.40)					91%
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%
García Rodríguez et al 2005[5]	Cohort				1.94 (0.85–4.45)		1.04 (0.50–2.17)	171	10,000	88%
Lesko et al 1985[6]	Case-control		1.7 (1.0-3.2)					57	2189	83%
Godet et al 1995[7]	Meta-analysis		1.44 (1.12 - 1.86)					531	49,156	82%
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[8]	Case-control				1.5 (0.4–5.3)			102	102	75%
Lowe et al 2009[9]	Case-control		1.05					21,172	754,6131	74%
Ng et al 2012[10]	Case-control	4 (1.1–14.2)						125	125	74%
Ng et al 2012[11]	Case-control	9.04 (1.11–73.6)								74%

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

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
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[12]	Case-control		4.3 (1.3-14.4)					83	83	57%
Logan and Kay 1989	Cohort		1.7 (0.88 – 3.2)					42	45,958	54%
Han et al 2010	Case-control		0.66 (0.38 - 1.15)					315	536	52%
Vessey et al 1986[13]	Cohort				1.33			18	17,014	46%
Calkins et al 1986[14]	Case-control	1.14 (0.44-2.96)						66	67	42%
Calkins et al 1986[15]	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%

[12] RR for use >3 years.
[13] Authors calculation, adjusted for smoking.
[14] Hospital controls.
[15] Neighborhood controls.

Table 4. Individual Studies of the Effects of Combined Hormonal Contraceptives 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
Boyko et al 1994	Case-control		1.7 (1.1-2.7)					211	341	94%
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%
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[2]	Meta-analysis				1.24 (0.999-1.54)					91%
García Rodríguez et al 2005	Cohort				1.58 (0.71–3.52)		0.67 (0.32–1.39)	222	10,000	88%
Godet et al 1995[3]	Meta-analysis		1.29 (0.94 - 1.77)					851	49,875	82%
Lashner et al 1990	Case-control	0.86 (0.40-1.85)		0.7 (0.27-1.83)		1.14 (0.41-3.15)		46	46	81%
Sandler et al 1992[4]	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[5]	Case-control				0.6 (0.1–2.5)			125	125	75%
Ng et al 2012[6]	Case-control	0.43 (0.11-1.66)						125	125	74%
Parrello et al 1997[7]	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%
Logan and Kay 1989	Cohort		1.3 (0.82-2.0)					78	45,922	54%
Vessey et al 1986[8]	Cohort				2.1			31	17,001	46%
Calkins et al 1986[9]	Case-control	0.62 (0.11-3.42)						35	32	42%

[1] Hazard ratios (RR adjusted for time).
[2] High quality studies.
[3] Adjusted for smoking.
[4] Interaction with smoking notes, higher RR in smokers (2.49).
[5] Monozygotic and dizygotic twins.
[6] Twins studies.
[7] Unclear how the calculation was done.
[8] Authors calculation, adjusted for smoking.
[9] Hospital 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
Calkins et al 1986[10]	Case-control	0.57 (0.11-2.88)						35	38	42%
Vcev et al 2015	Case-Control	0.75 (0.30 - 1.88)						62	42	31%

[10] Neighborhood controls.

Table 5. Individual Studies of the Effects of Combined Hormonal Contraceptives 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%
Cooper et al 2002	Case-control			1.5 (0.8–2.7)		1.3 (0.8–2.0)		240	321	92%
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%
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 cHCs within ≤3 months).
[5] RR for long term use (starting cHCs 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.

Table 6. Individual Studies of the Effects of Combined Hormonal Contraceptives 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
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%
Hernán et al 2000[1]	Cohort		1.1 (0.9-1.5)		1 (0.6-1.6)		1.2 (0.9-1.5)	313	237,318	90%
Kotzamani et al 2012	Case-control	1.6 (1.1-2.4)						254	314	81%
Alonso et al 2005[2]	Case-control	0.6 (0.4-1.0)		0.5 (0.3-1.2)		0.6 (0.4-1.0)		106	1001	77%
Thorogood et al 1998[3]	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%

[1] NHS I and II cohorts.
[2] OC use over the 3 years prior to the index date. Limited to women ≤50 years of age.
[3] Funded by drug companies that make HCs.

Table 7. Individual Studies of the Effects of Combined Hormonal Contraceptives on the Development of Thyroid 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
Hyperthyroidism (Grave's Disease)										
Vestergaard et al 2002	Case-control	0.68 (0.49-0.93)						621	621	88%
Strieder et al 2003[1]	Case-control		0.169 (0.055-0.523)		0.356 (0.073-1.726)			15	759	70%
Frank and Kay 1978	Cohort				0.71		0.9	53	46,000	41%
Hypothyroidism (Autoimmune Thyroiditis)										
Vestergaard et al 2002	Case-control	0.86 (0.64-1.16)						411	411	88%
Strieder et al 2003[1]	Case-control		4.232 (0.552-32.425)		0.889 (0.375-2.104)			29	759	70%
Frank and Kay 1978	Cohort		1.17					26	46,000	41%

[1] Estrogen use not separated into hormone replacement therapy versus cHCs.

Table 8. Individual Studies of the Effects of Combined Hormonal Contraceptives on the Development of Dermatologic Conditions

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
Eczema										
Vessey et al 2000	Cohort		1.3 (1.0-1.6)		1.6 (1.2-2.1)		1 (0.8-1.4)	327	16,705	90%
Psoriasis										
Vessey et al 2000	Cohort		1.5 (1.0-2.4)		1.7 (1.0-2.9)		1.4 (0.8-2.4)	92	16,940	90%
Pemphigus										
Valikhani et al 2007	Case-control	1.78 (1.01-3.22)						210	205	53%
Scleroderma										
Pisa et al 2002[1]	Case-control	1.2[1] (0.5-3.2)						46	153	76%
Vulval Lichen Sclerosis										
Higgins and Cruickshank 2012	Case-control		0.7 (0.30 – 1.62)					92	66	61%
Günthert et al 2008[2]	Case-control	2.53 (1.12-5.75)						40	110	58%

[1] Use of OCs was the referent so the OR in the normal manner is 0.8.
[2] Analysis limited to oral contraceptives (OCs) with anti-androgenic activity. OR for all OCs infinity.

Table 9. Individual Studies of the Effects of Progesterone-Only Contraceptives on the Development of Autoimmune Diseases and Related Conditions

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
Dorsopathies										
International Collaborative 2001	Cohort	1.23 (0.99-1.53)						332	16,012	96%
Rheumatism Excluding the Back										
International Collaborative 2001	Cohort	4.71 (2.93 - 7.56)						114	15,907	96%
Arthropathies and Related Disorders										
International Collaborative 2001	Cohort	2.6 (1.34-5.05)						44	15,977	96%
Osteopathies/chondropathies/acquired muscular deformities										
International Collaborative 2001	Cohort	1.69 (0.87-3.27)						38	15,983	96%
Rheumatoid Arthritis										
International Collaborative 2001	Cohort	3.46 (0.72-16.6)						9	8044	96%
Eczema, contact dermatitis										
International Collaborative 2001	Cohort	3.53 (1.97-6.32)						62	15,959	96%
Pruritis and related conditions										
International Collaborative 2001	Cohort	2.21 (1.37-3.55)						75	15,946	96%
Alopecia										
International Collaborative 2001	Cohort	12.44 (1.60-96.6)						12	16,009	96%
Acne										
International Collaborative 2001	Cohort	7.48 (2.90-19.3)						35	15,986	96%
Urticaria										
International Collaborative 2001	Cohort	3.07 (1.21-7.81)						23	15,998	96%
Vulval Lichen Sclerosis										
Higgins and Cruickshank 2012	Case-control		0.19 (0.03 – 0.96)					92	66	61%

References

Adab P, CQ Jiang, E Rankin, YW Tsang, TH Lam, J Barlow, GN Thomas, WS Zhang, and KK Cheng. 2014. Breastfeeding practice, oral contraceptive use and risk of rheumatoid arthritis among Chinese women: the Guangzhou Biobank Cohort Study. *Rheumatology (Oxford)* 53: 860-66. doi: 10.1093/rheumatology/ket456. Epub 2014 Jan 6.

Allebeck, P., A. Ahlbom, K., and E. Allander. 1984. Do oral contraceptives reduce the incidence of rheumatoid arthritis? A pilot study using the Stockholm County medical information system. *Scandinavian Journal of Rheumatology* 13: 140-46.

Alonso, A., S.S. Jick, M.J. Olek, A. Ascherio, H. Jick, and M.A. Hernán. 2005. Recent use of oral contraceptives and the risk of multiple sclerosis. *Archives of Neurology* 62: 1362-65.

Bernier, M.O., Y. Mikaeloff, M. Hudson, and S. Suissa. 2009. Combined oral contraceptive use and the risk of systemic lupus erythematosus. *Arthritis and Rheumatism* 61: 476-81.

Berglin, E., H. Kokkonen, E. Einarsdottir, A. Agren, and S. Rantapää Dahlqvist. 2010. Influence of female hormonal factors, in relation to autoantibodies and genetic markers, on the development of rheumatoid arthritis in northern Sweden: a case-control study. *Scandinavian Journal of Rheumatology* 39: 454-60.

Brennan, P., and A.J. Silman. *American Journal of Epidemiology* 1994. An investigation of gene-environment interaction in the etiology of rheumatoid arthritis. 140: 453-60.

Brennan, P., C. Bankhead, A. Silman, and D. Symmons. 1997. Oral contraceptives and rheumatoid arthritis: results from a primary care-based incident case-control study. *Seminars in Arthritis and Rheumatism* 26: 817-23.

Boyko, E.J., M.K. Theis, T.L. Vaughan, and B. Nicol-Blades. 1994. Increased risk of inflammatory bowel disease associated with oral contraceptive use. *American Journal of Epidemiology* 140: 268-78.

Calkins, B.M., A.I. Mendeloff, and C. Garland. 1986. Inflammatory bowel disease in oral contraceptive users. *Gastroenterology* 91: 523–24.

Cooper, G.S., M.A. Dooley, E.L. Treadwell, E.W. St Clair, and G.S. Gilkeson. 2002. Hormonal and reproductive risk factors for development of systemic lupus erythematosus: results of a population-based, case-control study. *Arthritis and Rheumatism* 46: 1830-39.

Cornish, J.A., E. Tan, C. Simillis, S.K. Clark, J. Teare, and P.P. Tekkis. 2008. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *American Journal of Gastroenterology* 103: 2394-400.

Corrao, G., A. Tragnone, R. Caprilli, G. Trallori, C. Papi, A. Andreoli, M. Di Paolo, G. Riegler, G.P. Rigo, O. Ferraù, C. Mansi, M. Ingrosso, and D. Valpiani. 1998. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-

control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum (GISC). *International Journal of Epidemiology* 27: 397-404.

Costenbader, K.H., D. Feskanich, M.J. Stampfer, and E.W. Karlson. 2007. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis and Rheumatism* 56: 1251-62.

Darwish, M.J., and H.K. Armenian. 1987. A case-control study of rheumatoid arthritis in Lebanon. *International Journal of Epidemiology* 16: 420-24.

del Junco, D.J., J.F. Annegers, H.S. Luthra, C.B. Coulam, and L.T. Kurland. 1985. Do oral contraceptives prevent rheumatoid arthritis? *Journal of the American Medical Association* 254: 1938-41.

Doran, M.F., C.S. Crowson, W.M. O'Fallon, and S.E. Gabriel. 2004. The effect of oral contraceptives and estrogen replacement therapy on the risk of rheumatoid arthritis: a population based study. *Journal of Rheumatology* 31: 207-13.

Frank, P., and C.R. Kay. 1978. Incidence of thyroid disease associated with oral contraceptives. *British Medical Journal* 2: 1531.

García Rodríguez, L.A., A. González-Pérez, S. Johansson, and M.A. Wallander. 2005. Risk factors for inflammatory bowel disease in the general population. *Alimentary Pharmacology & Therapeutics* 22: 309–15.

Godet, P.G., G.R. May, and L.R. Sutherland. 1995. Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut* 37: 668-73.

Grimes, D.A., S.A. LeBolt, K.R. Grimes, and P.A. Wingo. 1985. Systemic lupus erythematosus and reproductive function: A case control study. *American Journal of Obstetrics and Gynecology* 153: 179-86.

Günthert, A.R., M. Faber, G. Knappe, S. Hellriegel, and G. Emons. 2008. Early onset vulvar Lichen Sclerosus in premenopausal women and oral contraceptives. *European Journal of Obstetrics Gynecology and Reproductive Biology* 137: 56-60. Epub 2007 Dec 4.

Halfvarson, J., T. Jess, A. Magnuson, S.M. Montgomery, M. Orholm, C. Tysk, V. Binder, and G. Järnerot. 2006. Environmental factors in inflammatory bowel disease: a co-twin control study of a Swedish-Danish twin population. *Inflammatory Bowel Disease* 12: 925-33.

Han, D.Y., A.G. Fraser, P. Dryland, and L.R. Ferguson. 2010. Environmental factors in the development of chronic inflammation: a case-control study on risk factors for Crohn's disease within New Zealand. *Mutation Research* 690: 116-22.

Hannaford, P.C., C.R. Kay, and S. Hirsch. 1990. Oral contraceptives and rheumatoid arthritis: new data from the Royal College of General Practitioners' oral contraception study. *Annals of the Rheumatic Diseases* 49: 744-46.

Hazes, J.M., B.A. Dijkmans, J.P. Vandenbroucke, R.R. De Vries, and A. Cats. 1989. Oral contraceptives and rheumatoid arthritis; further evidence for a protective effect independent of duration of pill use. *British Journal of Rheumatology* 28 Suppl 1: 34; discussion 42-45.

Hazes, J.M., A.J. Silman, R. Brand, T.D. Spector, D.J. Walker, and J.P. Vandenbroucke. 1990. Influence of oral contraception on the occurrence of rheumatoid arthritis in female sibs. *Scandinavian Journal of Rheumatology* 19: 306-10.

Hellwig, K., Chen, L.H., Stancyzk, F.Z., Langer-Gould, A.M. 2016. Oral Contraceptives and Multiple Sclerosis/Clinically Isolated Syndrome Susceptibility. *PLoS One*. 11:e0149094. doi: 10.1371/journal.pone.0149094.

Hernán, M.A., M.J. Hohol, M.J. Olek, D. Spiegelman, and A. Ascherio. 2000. Oral contraceptives and the incidence of multiple sclerosis. *Neurology* 55: 848-54.

Hernandez-Avila M, M.H. Liang, W.C. Willett, M.J. Stampfer, G.A. Colditz, B. Rosner, R.W. Chang, C.H. Hennekens, and F.E. Speizer. 1990. Exogenous sex hormones and the risk of rheumatoid arthritis. *Arthritis and Rheumatism* 33: 947-53.

Hernandez-Avila, M., Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, Chang RW, Hennekens CH, Speizer FE. 1989. Oral contraceptives, replacement oestrogens and the risk of rheumatoid arthritis. *British Journal of Rheumatology* 28 Suppl 1:31; discussion 42-45.

Higgins, C.A., and M.E. Cruickshank. 2012. A population-based case-control study of aetiological factors associated with vulval lichen sclerosus. *Journal of Obstetrics and Gynaecology* 32: 271-15. doi: 10.3109/01443615.2011.649320.

International Collaborative Post-Marketing Surveillance of Norplant. Corresponding authors: Farley, T.M.M. and I. Sivin. 2001. Post-marketing surveillance of Norplant contraceptive implants: II. non-reproductive health. *Contraception* 63: 187-20.

Jorgensen, C., M.C. Picot, C. Bologna, and J. Sany. 1996. Oral contraception, parity, breast feeding, and severity of rheumatoid arthritis. *Annals of the Rheumatic Diseases* 55: 94-98.

Katschinski, B. 1993. [Smoking and ovulation inhibitor in inflammatory bowel diseases]. *Medizinische Klinik (Munich, Germany)* 88 Suppl 1: 5-8.

Karlson, E.W., L.A. Mandl, S.E. Hankinson, and F. Grodstein. 2004. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis and Rheumatism* 50: 3458-67.

Khalili, H., L.M. Higuchi, A.N. Ananthakrishnan, J.M. Richter, D. Feskanich, C.S. Fuchs, and A.T. Chan. 2013. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. *Gut* 62: 1153-59.

Kotzamani, D., T. Panou, V. Mastorodemos, M. Tzagournissakis, H. Nikolakaki, C. Spanaki, and A. Plaitakis. 2012. Rising incidence of multiple sclerosis in females associated with urbanization. *Neurology* 78: 1728-35.

Lashner, B.A., S.V. Kane, and S.B. Hanauer. 1989. Lack of association between oral contraceptive use and Crohn's disease: a community-based matched case-control study. *Gastroenterology* 97: 1442-47.

Lashner, B.A., S.V. Kane, and S.B. Hanauer. 1990. Lack of association between oral contraceptive use and ulcerative colitis. *Gastroenterology* 99: 1032-36.

Lesko, S.M., D.W. Kaufman, L. Rosenberg, S.P. Helmrich, D.R. Miller, P.D. Stolley, and S. Shapiro. 1985. Evidence for an increased risk of Crohn's disease in oral contraceptive users. *Gastroenterology* 89: 1046-49.

Linos, A., J.W. Worthington, W.M. O'Fallon, and L.T. Kurland. 1983. Case-control study of rheumatoid arthritis and prior use of oral contraceptives. *Lancet* 1: 1299-300.

Logan, R.F., and C.R. Kay. 1989. Oral contraception, smoking and inflammatory bowel disease--findings in the Royal College of General Practitioners Oral Contraception Study. *International Journal of Epidemiology* 18: 105-07.

Lowe A.M., P.O. Roy, M. Poulin, P. Michel, A. Bitton, L. St Onge, and P. Brassard. 2009. Epidemiology of Crohn's disease in Quebec, Canada. *Inflammatory Bowel Disease* 15: 429–35.

Merlino, L.A., J.R. Cerhan, L.A. Criswell, T.R. Mikuls, and K.G. Saag. 2003. Estrogen and other female reproductive risk factors are not strongly associated with the development of rheumatoid arthritis in elderly women. *Seminars in Arthritis and Rheumatism* 33: 72-82.

Moskowitz, M.A., S.S. Jick, S. Burnside, W.J. Wallis, J.F. Dickson, J.R. Hunter, and H. Jick. 1990. The relationship of oral contraceptive use to rheumatoid arthritis. *Epidemiology* 1: 153-56.

Ng, S.C., S. Woodrow, N. Patel, J. Subhani, and M. Harbord. 2012. Role of genetic and environmental factors in British twins with inflammatory bowel disease. *Inflammatory Bowel Disease* 18: 725-36.

Pedersen, M., S. Jacobsen, P. Garred, H.O. Madsen, M. Klarlund, A. Svejgaard, B.V. Pedersen, J. Wohlfahrt, and M. Frisch. 2007. Strong combined gene-environment effects in anti-cyclic citrullinated peptide-positive rheumatoid arthritis: a nationwide case-control study in Denmark. *Arthritis and Rheumatism* 56: 1446-53.

Pedersen, M., S. Jacobsen, M. Klarlund, B.V. Pedersen, A. Wiik, J. Wohlfahrt, and M. Frisch. 2006. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. *Arthritis Research and Therapy* 8: R133.

Persson, P.G., C.E. Leijonmarck, O. Bernell, G. Hellers, and A. Ahlbom. 1993. Risk indicators for inflammatory bowel disease. *International Journal of Epidemiology* 22: 268-72.

Pikwer, M., U. Bergström, J.A. Nilsson, L. Jacobsson, G. Berglund, C. Turesson. 2009. Breast feeding, but not use of oral contraceptives, is associated with a reduced risk of rheumatoid arthritis. *Annals of the Rheumatic Diseases* 68: 526-30.

Pisa, F.E., M. Bovenzi, L. Romeo, A. Tonello, D. Biasi, L.M. Bambara, A. Betta, and F. Barbone. 2002. Reproductive factors and the risk of scleroderma: an Italian case-control study. *Arthritis and Rheumatism* 46: 451-56.

Pladevall-Vila, M., G.L. Delclos, C. Varas, H. Guyer, J. Brugués-Tarradellas, and A. Anglada-Arisa. 1996. Controversy of oral contraceptives and risk of rheumatoid arthritis: meta-analysis of conflicting studies and review of conflicting meta-analyses with special emphasis on analysis of heterogeneity. *American Journal of Epidemiology* 144: 1-14.

Pope, J.E., N. Bellamy, and A. Stevens. 1999. The lack of associations between rheumatoid arthritis and both nulliparity and infertility. *Seminars in Arthritis and Rheumatism* 28: 342-50.

Rodríguez, L.A., L.B. Tolosa, A. Ruigómez, S. Johansson, and M.A. Wallander. 2009. Rheumatoid arthritis in UK primary care: incidence and prior morbidity. *Scandinavian Journal of Rheumatology* 38: 173-77.

Romieu, I., M. Hernandez-Avila, and M.H. Liang. 1989. Oral contraceptives and the risk of rheumatoid arthritis: a meta-analysis of a conflicting literature. *British Journal of Rheumatology* 28 Suppl 1: 13-17; discussion 18-23.

Sanchez-Guerrero, J., E.W. Karlson, M.H. Liang, D.J. Hunter, F.E. Speizer, and G.A. Colditz. 1997. Past use of oral contraceptives and the risk of developing systemic lupus erythematosus. *Arthritis and Rheumatism* 40: 804-08.

Sandler, R.S., J.I. Wurzelmann, and C.M. Lyles. 1992. Oral contraceptive use and the risk of inflammatory bowel disease. *Epidemiology* 3: 374-78.

Sicilia, B., C. López Miguel, F. Arribas, J. López Zaborras, E. Sierra, and F. Gomollón. 2001. Environmental risk factors and Crohn's disease: a population-based, case-control study in Spain. *Digestive and Liver Disease* 33: 762-67.

Spector, T.D., E. Roman, A.J. Silman. 1990. The pill, parity, and rheumatoid arthritis. *Arthritis and Rheumatism* 33: 782-89.

Strieder, T.G., M.F. Prummel, Tijssen, J.G., E. Endert, and W.M. Wiersinga. 2003. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. *Clinical Endocrinology (Oxford)* 59: 396-401.

Strom, B.L., M.M. Reidenberg, S. West, E.S. Snyder, B. Freundlich, and P.D. Stolley. 1994. Shingles, allergies, family medical history, oral contraceptives, and other potential risk factors for systemic lupus erythematosus. *American Journal of Epidemiology* 140: 632-42.

Thorogood, M., and P.C. Hannaford. 1998. The influence of oral contraceptives on the risk of multiple sclerosis. *British Journal of Obstetrics and Gynaecology* 105: 1296-99.

Valikhani, M., S. Kavusi, C. Chams-Davatchi, M. Daneshpazhooh, M. Barzegari, M. Ghiasi, and R. Abedini. 2007. Pemphigus and associated environmental factors: a case-control study. *Clinical and Experimental Dermatology* 32: 256-60. Epub 2007 Mar 13.

Vandenbroucke, J.P., H.A. Valkenburg, J.W. Boersma, A. Cats, J.J. Festen, O. Huber-Bruning, and J.J. Rasker. 1982. Oral contraceptives and rheumatoid arthritis: further evidence for a preventive effect. *Lancet*. 2: 839-42.

van Zeben, D., J.M. Hazes, J.P. Vandenbroucke, B.A. Dijkmans, and A. Cats. 1990. Diminished incidence of severe rheumatoid arthritis associated with oral contraceptive use. *Arthritis and Rheumatism* 33: 1462-65.

Vcev A., Pezerovic D., Jovanovic Z., Nakic D., Vcev I., Majnarić L. 2015. A retrospective, case-control study on traditional environmental risk factors in inflammatory bowel disease in Vukovar-Srijem County, north-eastern Croatia, 2010. *Wiener Klinische Wochenschrift*. 127: 345-54.

Vessey, M., D. Jewell, A. Smith, D. Yeates, and K. McPherson. 1986. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age. *British Medical Journal (Clinical Research Edition)* 292: 1101-13.

Vessey, M.P., L. Villard-Mackintosh, and D. Yeates. 1987. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. *Contraception* 35: 457-64.

Vessey, M.P., R. Painter, and J. Powell. 2000. Skin disorders in relation to oral contraception and other factors, including age, social class, smoking and body mass index. Findings in a large cohort study. *British Journal of Dermatology* 143: 815-20.

Vestergaard, P., L. Rejnmark, J. Weeke, H.C. Hoeck, H.K. Nielsen, J. Rungby, P. Laurberg, and L. Mosekilde. 2002. Smoking as a risk factor for Graves' disease, toxic nodular goiter, and autoimmune hypothyroidism. *Thyroid* 12: 69-75.

Villard-Mackintosh, L., and M.P. Vessey. 1993. Oral contraceptives and reproductive factors in multiple sclerosis incidence. *Contraception* 47: 161-68.

Wingrave, S.J.,and C.R. Kay. 1978. Reduction in incidence of rheumatoid arthritis associated with oral contraceptives. *Lancet*. 1: 569-11.

Zonana-Nacach, A., L.M. Rodríguez-Guzmán, F.J. Jiménez-Balderas, A. Camargo-Coronel, J. Escobedo-de la Peña, and A. Fraga. 2002. [Risk factors associated with systemic lupus erythematosis in a Mexican population]. *Salud Pública de México* 44: 213-18.