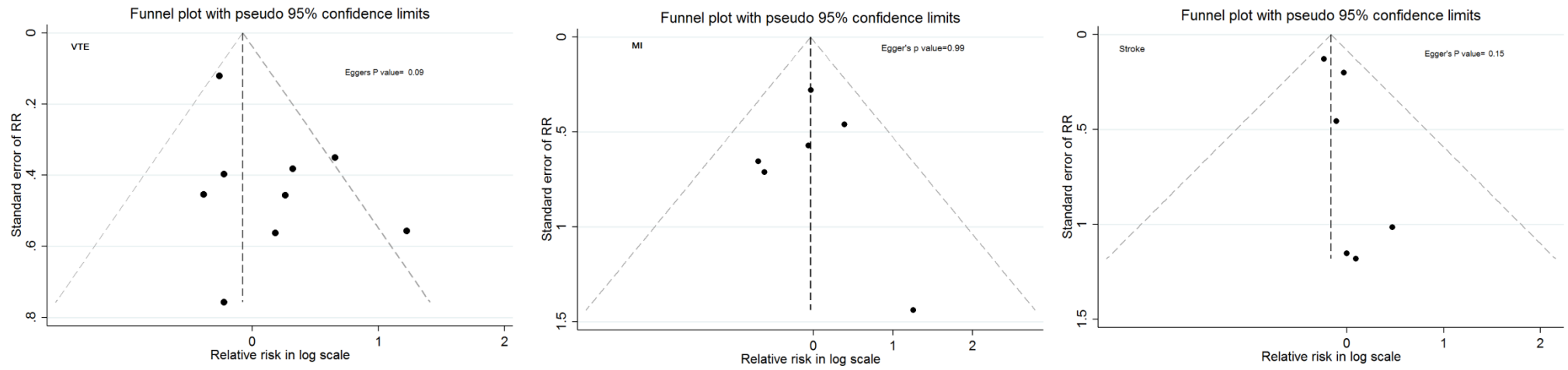


SUPPLEMENTAL MATERIAL

Supplemental figure 1: Search strategy used in this review.

(((((contraceptives, oral OR ((contraception OR contracept*) AND pill)) AND (progestin* OR progestational, hormones, synthetic OR progestogen* OR progesterone OR gestagen OR "progestin only" OR "progestogen only" OR "progestrogen only pill" OR minipill))) AND ((((((cardiovascular disease[MeSH Terms] OR heart disease OR stroke OR cerebrovascular disease OR cardiovascular disease OR coronary artery disease OR heart failure OR cardiovascular mortality OR coronary death OR CHD OR CVD OR cardiac death OR myocardial infarction OR angina))) OR ((diabetes OR diabetes mellitus OR DM OR T2DM OR T1DM))) OR (((("venous thromboembolism" OR VTE OR thromboembolism))) OR venous thromboembolism[MeSH Terms])) OR hypertension OR high blood pressure)))

Supplemental figure 2: Funnel plots for VTE, MI and stroke



The dotted lines show 95% confidence intervals around the overall summary estimate calculated using a random effect model; *P*-values using Egger's test were 0.09; 0.99; and 0.15 for effect of POC use on VTE, MI and stroke respectively.

Supplemental table 3: Characteristics of the studies that investigated the association between progestin-only contraception use and risk of Venous Thromboembolism.

Author	Study design	Location	Year of study	Age	No. of participants used POC		Adjusted relative risk of VTE for users v non-users OR(95% CI)	Route of administration	Type of POC used	Adjustment
					VT	no VT				
Barsoum et al, 2010	Nested case-control	USA	1988–2000	66.5 ± 20.2 (cases) 66.2 ± 20.1 (controls)	3	2	1.20 (0.4, 3.63)	Oral	Medroxyprogesterone acetate 5 or 10 mg, Megestrol acetate 80– 120 mg	BMI, recent hospitalization, recent surgery, nursing home confinement, trauma or fracture, active cancer, leg paresis, varicose veins
Heinemann et al, 1999	Case-control	Europe	1993-1996	16-44	7	54	0.68 (0.28, 1.66)	Oral	Progestin only pills, type and dosage not available	BMI
Bergendal et al, 2014	Case-control	Europe, Sweden	2003-2009	18-54	61	99	0.8 (0.4-1.9)	Oral	Levonorgestrel, Norethisterone, Lynestrenol	Smoking, BMI, immobilization
					47	23	2.2 (1.3-4.0)	Injectable	Medroxyprogesterone acetate	
					61	99	0.6 (0.4-1.0)	IUD	Levonorgestrel	
					25	35	0.9 (0.5-1.6)	Oral+ Implant	Desogestrel,Etonogestrel,Levonorgestrel	
WHO, 1998	Case-control	Worldwide	1989-1993	20-44	169	221	0.99 (0.54, 1.79)*	Oral, IUD, injectable	Levonorgestrel, Norethisterone, Lynestrenol, MPA	BMI
					21	63	1.82 (0.79-4.22)	Oral	d-Norgestrel 0.75 mg Anorethidrate dipropionate 7.5 mg	
					11	34	2.19 (0.66-7.26)	Injectable	dl-Norgestrel 3.0 mg Norethisterone 5.0 mg Depo medroxyprogesterone acetate , 150mg Norethisterone oenanthate, 200mg	
Vasilakis et al, 1999	Nested case-control	Europe, UK	1993-1997	<50	32	97	1.87 (0.86, 4.07)*	Pooled	Oral+Injectable	BMI, smoking
					7	6	2.4 (0.8, 6.5)	Oral+ IUD	Progestagens ≤0.5mg Injectable, 150mg Transdermal, 228mg Levonogestrel	
Vlieg et al, 2010	Case-control	Europe, Netherlands	1999-2004	18-50	4	4	3.4 (0.8-13.7)	Oral		Age, BMI, family history of deep vein VTE, smoking
					20	15	3.6 (1.8, 7.1)	Injectable	Depo medroxyprogesterone acetate, dose not available	
					3	26	0.3 (0.1, 1.1)	IUD	Levonogestrel	
Conard et al, 2004	Cohort	Europe, France	1992-1997	15-50	23	41	1.09 (0.1, 12.46)*	Pooled	DMPA, Levonogestrel	Age, thrombophilia and BMI
					3	99	0.8 (0.2, 3.9)	Oral	Chlormadinone acetate (CMA), a 17a-hydroxyprogesterone derivative, 10mg	
Vaillant-Roussel et al, 2011	Cohort	Europe, France	1995-2008	17-53	7	27	1.3 (0.5, 3)	Oral	Progestin only contraceptives, type or dosage not available	Age, thrombophilia and BMI
Lidegaard et al, 2012	Cohort	Europe, Denmark	2001-2010	15-49	15	NA	0.51 (0.23,1.14)	Oral	Norethisterone, Desogestrel	Age, calendar year, education
					55	NA	0.95 (0.65,1.38)	Intrauterine device	Levonorgestrel	
					70	NA	0.77 (0.44, 1.37)*	Pooled oral+ IUD	Norethisterone, Desogestrel, Levonorgestrel	

† Incidence rate ratio (from Poisson regression and Cox proportional hazard regression), results from Cox model shown

‡ HR obtained from Cox proportional hazard regression

*Incidence rate ratio (from Poisson regression)/ Summary measure for all progestin-only contraceptive users versus non-users calculated based on the results from different subgroups or oral
NA: no information in the original paper
IUD: intrauterine device

Supplemental table 4: Studies investigating the association of progestin-only pill with risk of Myocardial Infarction

Author	Study design	Location	Year of study	Age	No. of participants exposed to POC		Route of administration	Type of POC used	Type of MI	Adjusted relative risk of MI for users v non-users RR (95% CI)	Adjustment
					MI	No MI					
Heinemann et al, 1999	Case-control	Europe	1993-1996	16-44	7	17	Oral	Progestin only pills, type and dosage not available	MI	0.94(0.31, 2.91)	Age, HBP, diabetes, smoking, education
Dunn et al, 1999	Case-control	Europe, UK	1993-1995	16-44	9	49	Oral	Progestogen only	Fatal MI	1.48 (0.6, 3.65)	Age, smoking, BMI, HBP, diabetes, family history of MI
WHO, 1998	Case-control	Worldwide	1989-1993	20-44	3	6	Oral	d-Norgestrel 0.75 mg Anorethidrate dipropionate 7.5 mg dl-Norgestrel 3.0 mg Norethisterone 5.0 mg	Non-fatal MI	0.98 (0.16, 5.97)	Age, HBP, diabetes, smoking
					1	7	Injectable	Depo medroxyprogesterone acetate , 150mg Norethisterone oenanthate, 200mg			
							Pooled	oral+Injectable			
Petitti et al, 1998	Case-control	USA	1990	18-44	1	1	Implant	Levonorgestrel	MI	3.5 (0.2, 56.5)	Age
Thorogood et al, 1992	Case-control	UK	1986-1988	16-39	3	12	Oral	NA	Fatal MI	0.5 (0.14, 1.83)	Age, marital status
Lidegaard et al, 2012	Cohort	Denmark	1995-2009	15-49	13	NA	Oral	Pooled Norethindrone and Desogestrel	Non-fatal MI	0.97 (0.56, 1.68)	Age, education level, calendar year, hypertension, heart disease, diabetes, hyperlipidemia
					31	NA	IUD	Levonorgestrel			
					3	NA	Implant	NA			
					34	NA	Pooled	IUD +implant			
				46	NA	Pooled	Oral+ IUD +implant		1.06 (0.79,1.41)		
NA: no information in the original paper IUD: intrauterine device											

Supplemental table 5: Studies investigating the association of progestin-only pill with Stroke

Author	Study design	Location	Year of study	Age	No. of participants exposed to POC		Route of administration	POC Type	Type of Stroke	Adjusted relative risk of Stroke for users v non-users RR (95% CI)	Adjustment
					Stroke	No stroke					
Heinemann et al, 1999	Case-control	Europe	1993-1996	16-44	3	10	Oral	Progestin only pills, type and dosage not available	Ischemic	1.6 (0.2, 10.72)	HBP, alcohol, smoking
WHO , 1998	Case-control	Worldwide	1989-1993	20-44	54	151	Oral	d-Norgestrel 0.75 mg Anorethidrate dipropionate 7.5 mg dl-Norgestrel 3.0 mg Norethisterone 5.0 mg	All	1.07 (0.62, 1.86)	HBP, smoking, marital
					1	7	Injectable	Depo medroxyprogesterone acetate , 150mg Norethisterone oenanthate, 200mg		0.89 (0.53, 1.49)	
					55	158	Pooled	Oral and injectable		0.97 (0.64, 1.41)	
Petitti et al, 1998	Case-control	USA	1990	18-44	1	3	Implant	Levonorgestrel	All	1.0 (0.1, 9.2)	Age
Lidegaard et al, 1993	Case-control	Europe, Denmark	1990-1991	15-44	7	18	Oral	Minipill (progestogen)	Ischemic	0.9 (0.4, 2.4)	Age, education, smoking, migraine
Tzourio et al,1995	Case-control	Europe, France	1990-1993	18-44	1	4	Oral	Progestogen only	Ischemic	1.1 (0.1, 10.3)	Crude
Lidegaard et al, 2012	Cohort	Denmark	1995-2009	15-49	86	115 059 person-yr	Oral	Pooled Norethindrone and Desogestrel		0.97 (0.56, 1.68)*	Age, education level, calendar year, hypertension, heart disease, diabetes, hyperlipidemia
					45	184 875 person-yr	IUD	Levonorgestrel	Thrombotic	0.73 (0.54, 0.98)	
					3	24 954 person-yr	Implant	NA		0.88 (0.28, 2.72)	
					48	209 829 person-yr	Pooled	Implant+ IUD		0.74 (0.55,0.99)	
					130	324 888 person-yr	Pooled	Oral, IUD, injectable, implant		0.78 (0.61,1.01)	

NA: no information in the original paper
IUD: intrauterine device

Supplemental table 6: Showing cohort studies examining the association of progestin-only pill with Hypertension

Author	Study design	Location	Year of study	Age	No. of participants	POC used	Result	Adjustment
Spellacy and Birk et al, 1972	Cohort	USA	1972-74	16-45	415	Injectable: DMPA Oral: NG 0.075 mg, ethynodiol acetate 0.25 mg	Progestogen-only group using NG showed a significant fall in DBP	Age, height, weight, parity
Hall et al, 1980	Cohort	USA	1980-82	16-55	792	NET 0.35 mg	No association between minipill use and high BP	Age, weight
Wilson et al, 1984	Cohort	Scotland	1984-87	15-49	593	Norethisterone, Levonorgestrel , Injection: NET enanthate	No change or fall of blood pressure in progestogen-only methods NG use associated with fall in DBP, evident until after 2 years of follow-up	Smoking habits

Supplemental table 7: Showing a case-control study examining the association of progestin-only pill with Type II Diabetes

Author	Study design	Location	Year of study	Age	No. of participants	POC used	Outcome/Result	Adjustment
Kim et al, 2001	Case-control	USA	1998	18-50	Cases/Controls 284/570	DMPA	OR: 2.4 (95% CI, 1.3-4.6)	BMI
							OR: 2.1 (95% CI, 1.03-4.3)	Age, BMI, parity
							OR 1.6 (95%CI 0.77- 3.5)	Age, BMI, parity, gestational diabetes diagnosed after contraception given
International Collaborative Post-Marketing Surveillance of Norplant,2001	Cohort	Multicultural (8 countries)	1989-1997	Mean 28.8	16,021 women, 12 T2D cases	Norplant	RR: 2.42 (0.73-8.1)	Clinics, age, body weight