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## Appendix 1: Medline Search Strategy.

Concept	Search Strategy	Results
1	exp reproductive history/ or exp pregnancy/ or exp contraception behavior/ or exp Parity/	851996
2	exp Breast Feeding/	34875
3	exp hypertension, pregnancy-induced/ or exp eclampsia/ or exp hellp syndrome/ or exp pre-eclampsia/	33911
4	(pre-eclamp* or eclamp* or gestosis or tox?mia or (hypertens* and pregnan*) or (hypertens* disorder* adj2 prenancy) or gestation* hypertens* or transient hypertens* or maternal hypertens*).ti,ab.	36317
5	3 or 4	52448
6	(maternal placental syndrom?e* or placent* abrupti*).ti,ab.	1952
7	exp abortion, spontaneous/ or exp abortion, threatened/	35185
8	(pregnancy loss or miscarriage* or recurrent miscarriage* or foetal death or fetal death). ti,ab.	21811
9	7 or 8	49261
10	gestational diabetes.mp. or exp Diabetes, Gestational/	15248
11	(gdm or gestatio* diabet* or (diabet* adj2 pregn*) or ((impair* glucose tolerance or insulin resistanc* or pre-diabet*) and pregn*)).ti,ab.	18562
12	10 or 11	21200
13	(pre-matur* or prematur* or preterm or pre-term or LBW or low birth weight). ti,ab.	193847
14	exp Birth Weight/ or Birth weight.mp. or exp Infant, Small for Gestational Age/ or small for gestational age.mp. or exp Fetal Growth Retardation/	100480
15	13 or 14	249950
16	1 or 2 or 5 or 6 or 9 or 12 or 15	1048419
17	exp Polycystic Ovary Syndrome/ or Polycystic Ovary Syndrome*.mp.	15491
18	((sclerocystic or polycystic or micropolycystic) and ovar*) or (polycystic ovar* disease or polycystic ovar* syndro?me or PCO or PCOS or stein leventhal)).ti,ab.	19306
19	17 or 18	20881
20	endometri*.mp. or exp Endometriosis/ or exp HYSTERECTOMY, VAGINAL/ or exp HYSTERECTOMY/ or hysterectomy.mp. or oophorectomy.mp. or exp Ovariectomy/	153466
21	exp Contraceptives, Oral/ or exp Contraception/ or contracept*.mp.	103604
22	(birth control or family planning or hormon* method* or progest* or ethinyl estradiol).ti,ab.	118126
23	21 or 22	194628
24	exp menopause, premature/ or exp primary ovarian insufficiency/ or menarche.mp. or exp MENARCHE/	12196
25	19 or 20 or 23 or 24	353844
26	exp Cardiovascular Diseases/ or cardiovascular disease*.mp. or heart disease*.mp. or exp Heart Diseases/	2321196

27	(isch?mic heart or IHD or CHD or coronary artery or coronary heart or atheroscleros* or CVA or cerebrovascular event* or cerebrovascular accident or stroke or TIA or CV or CVD or heart failure).ti,ab.	696132
28	26 or 27	2505448
29	16 or 25	1320410
30	28 and 29	109156
31	MEDLINE.tw.	95359
32	systematic review.tw.	112686
33	meta-analysis.pt.	94442
34	intervention\$.ti.	123799
35	31 or 32 or 33 or 34	332105
36	30 and 35	2123

**Appendix 2: The Joanna Briggs Institute data extraction form for review for systematic reviews and research syntheses.**

<b>Study details</b>	
Author year	
Participants (characteristics/total number)	
Setting/context	
Description of interventions/ phenomena of interest.	
<b>Search details</b>	
Sources searched	
Range years of included studies	
Number of studies included	
Type of studies included	
Country of origin of included studies	
<b>Appraisal</b>	
Appraisal instruments used	
Appraisal rating	
<b>Analysis</b>	
Method of analysis	
Outcomes assessed	
Result /findings	
Significance/direction	
Heterogeneity	
Comments.	

Source: Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P. Methodology for JBI Umbrella Reviews. Joanna Briggs Inst Rev Man. 2014;1–34.

### Appendix 3. Citation matrices for reviews with overlapping associations.

#### A. Gestational diabetes

Systematic reviews: gestational diabetes mellitus (exposure)	Kramer 2019	Grandi 2019	Jing Li 2018	Hopman 2015
<b>Overlapping association</b>	Fatal and non-fatal cardiovascular disease	Fatal and non-fatal cardiovascular disease	Fatal and non-fatal cardiovascular disease	Fatal and non-fatal cardiovascular disease
<b>Primary Study</b>				
Carr 2206			X	X
Daly 2018	X			
Dawson 2009		X		
Freibert 2011				X
Fadl 2014	X			
Goueslard 2016	X	X	X	
Heida 2015		X		
Kaul 2015	X	X	X	
Kessous 2013	X	X	X	X
Mackenzie-Sampson 2018	X			
Pintaudi 2015		X		
Retnakaran and Shah 2017	X		X	
Savitz 2014	X	X		
Shah 2008		X	X	
Shostrom 2017			X	X
Tobias 2017	X			
<b>Total (No of publications per review)</b>	9	8	7	4
<b>Grand Total (N)</b>	<b>28</b>			
<b>Rows (r)</b>	<b>16</b>			
<b>Columns (c)</b>	<b>4</b>			
<b>Corrected covered area (CCA)</b>	<b>25%</b>			

Formula for calculating the corrected covered area,  $CCA (\%) = N - r / rc - r$

Where N = number of included publications (sum of checked boxes), r = number of rows (primary publications), c = number of columns (number of reviews).

## B. Preterm birth

Systematic review ID	Grandi 2019	Pensee Wu 2018	Robbins 2014	Grandi 2019	Pensee Wu 2018	Heida 2016	Robbins 2014	Heida 2016	Robbins 2014	Pense Wu 2018	Robbins 2014
<b>Overlapping associations</b>	Non-Fatal CVD	Non-Fatal CVD	Non-Fatal CVD	Fatal CVD	Fatal CVD	Fatal & non-fatal stroke	Fatal & non-fatal stroke	Fatal and non-fatal coronary heart disease	Fatal and non-fatal coronary heart disease	Fatal coronary heart disease	Fatal coronary heart disease
<b>Primary Study</b>											
Bonamy 2011	X	X					X				
Catov 2007		X	X								
Catov 2010	X	X			X	X					X
Cirillo 2015				X						X	
Davey Smith 2001					X						
Davey Smith 2005					X					X	
Freibert 2011		X									
Hastie 2011	X							X	X	X	X
Hovi 2014		X									
Irgens 2001						X					
Kessous 2013	X	X									
Lykke 2010	X			X	X			X			X
Nardi 2006	X		X						X	X	
Ngo 2015	X	X									
Ngo 2017	X										
Pell 2004						X	X				
Rich Edwards 2015				X						X	
Smith 2000											X
Smith 2001				X	X				X		X
Soh 2016	X										
Tanz 2017	X	X									
Wang 2011	X										
Wilkstrom 2005	X							X			
Total (No of publications per review)	12	8	2	4	5	3	2	3	3	5	5
Grand Total (N)	22			9		5		6		10	
Rows (r)	15			7		4		5		9	
Columns (c)	3			2		2		2		2	
<b>CCA</b>	<b>23.3%</b>			<b>28.6%</b>		<b>25%</b>		<b>20%</b>		<b>11.1%</b>	

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r:**

Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

### C. Pre-eclampsia

Systematic review ID	Grandi 2019	Pense Wu 2017	Grandi 2019	Pense Wu 2017	Grandi 2019	Pense Wu 2017	Grandi 2019	Pense Wu 2017
Overlapping associations	Fatal CVD	Fatal CVD	Non-Fatal coronary heart disease	Non-Fatal coronary heart disease	Non-fatal stroke	Non-fatal stroke	Fatal stroke	Fatal stroke
<b>Primary Study</b>								
Auger 2017					X			
Bhattacharya 2012				X	X	X		X
Funai 2005	X	X	X					
Gordin 2017				X				
Hannaford 1998					X			
Haukamaa 2009				X				
Hovsepian 2014						X		
Ingress 2001							X	
Iversen 2010	X		X					
Kaaja 2005				X				
Kestenbaum 2003								
Lin 2016					X			
Lin 2011 and Tang 2009		X		X	X	X		
Luoto 2008	X		X					
Lykke 2009 and Lykke 2010	X	X	X	X	X	X		
Mannisto 2013				X		X		
Mongraw Chaffin 2010	X		X					
Ray 2005								
Riise 2017	X		X					
Savitz 2014				X	X	X		
Sjaekerven 2012	X	X	X				X	X
Smith 2001	X		X					
Stuart 2013				X		X		
Tang 2009					X			
Wilkstrom 2005				X				
Wilson 2003	X		X		X		X	
Total (No of publications per review)	9	4	9	10	9	7	3	2
Grand Total (N)	13		19		16		5	
Rows (r)	10		18		12		4	
Columns (c)	2		2		2		2	
<b>CCA</b>	<b>30%</b>		<b>5.6%</b>		<b>33%</b>		<b>25%</b>	

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r:**

Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

#### D. Use of oestrogen containing pills in migraine

Systematic review	Sheikh 2017	Tepper 2016
<b>Overlapping associations</b>	Fatal CVD	Fatal CVD
<b>Primary Study</b>		
Collaborative group	X	X
Champaloux 2017	X	X
Chang 1999	X	X
Lidegaard 1995	X	X
MacClellan 2007		X
Nightingale 2004		X
Schwartz 1998	X	X
Tzurio 1995	X	X
Total (No of publications per review)	6	8
Grand Total (N)	14	
Rows (r)	8	
Columns (c)	2	
<b>CCA</b>	<b>75%</b>	

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r:**

Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).



## E. Early natural menopause

Systematic review	Muka 2016	Tao 2015	Gong 2015	Muka 2016	Tao 2015	Gong 2015	Muka 2016	Tao 2015	Gong 2015
<b>Overlapping associations</b>	Fatal CVD	Fatal CVD	Fatal CVD	Fatal coronary heart disease	Fatal coronary heart disease	Fatal coronary heart disease	Fatal stroke	Fatal stroke	Fatal stroke
<b>Primary Study</b>									
Cooper 1998		X		X	X	X	X	X	X
Cui 2006	X			X			X		
Gallagher 2011		X			X			X	
Hong 2007	X		X	X			X		X
Jacobsen 1999				X	X	X	X	X	X
Jacobsen 2004									
Li 2003			X						
Li S 2013	X	X	X						
Mondul 2005		X		X	X	X	X	X	X
Osserwarde 2005	X			X			X		
Snowdon 1989		X						X	
Tom 2012	X		X						
Wu 2014						X			X
Total (No of publications per review)	5	5	4	6	4	4	6	5	5
Grand Total (N)	14			14			16		
Rows (r)	10			8			9		
Columns (c)	3			3					
<b>CCA</b>	<b>20%</b>			<b>37.5%</b>			<b>38.9%</b>		

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation =  $CCA (\%) = N-r / rc-r$ :

Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

## F. Progesterone only Contraceptives

Systematic review	Glisic 2018	Tepper 2016	Glisic 2018	Tepper 2016
<b>Overlapping associations</b>	Myocardial infarction	Myocardial infarction	Stroke	Stroke
<b>Primary Study</b>				
Dunn 1999	X	X		X
Heinemann 1999	X	X	X	X
Lidegaard 1993			X	X
Lidegaard 2002				X
Lidegaard 2012	X	X	X	X
Petitti 1998	X	X	X	X
Poulter 1999		X		X
Thorogood 1991	X	X		
Tzourio 1995			X	X
WHO 1998		X	X	X
WHO 1999	X			
<b>Total (No of publications per review)</b>	6	6	6	9
<b>Grand Total (N)</b>	12		15	
<b>Rows (r)</b>	8		9	
<b>Columns (c)</b>	2		2	
<b>CCA</b>	<b>50%</b>		<b>66%</b>	

CCA = Corrected covered area. Calculation =  $CCA (\%) = \frac{N-r}{rc-r}$ :

Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

### G. Oral contraceptive use

Systematic review	Zhenlin Xu 2015	Peragallo 2013	Zhenlin Xu 2018	Peragallo 2013
<b>Overlapping associations</b>	Non-fatal ischaemic stroke	Non-fatal ischaemic stroke	Fatal & non-fatal haemorrhagic stroke	Non-fatal haemorrhagic stroke
<b>Primary Study</b>				
Carolei 1996	X			
CGSS 1973	X		X	
Chang 1999		X		X
Gallagher 2011			X	
Hannaford 1994	X			
Heinemann 1998	X			
Hirvonen 1990			X	
Inman 1979			X	
Kemmeren 2002	X			
Lewis 199		X		
Li 2006			X	
Lidegaard 1993	X			
Lidegaard 2002	X			
Lindegaard 2012	X			
Longstreth 1994			X	
Mant 1998	X	X		
Martinelli 2006	X			
Nightingale 2004	X			
Petitti 1978			X	
Petitti 1996	X	X	X	X
Pezzini 2007	X			
Schwartz 1997	X	X	X	X
RCGP 1983			X	
Siritho 2003		X		
Thorogood 1981			X	
Thorogood 1992			X	
Tzourio 1995	X			
WHO-1 1996	X		X	
WHO-2 1996	X		X	
Yang 2009	X	X	X	X
Total	18	7	15	4
Grand Total (N)	25		19	
Rows (r)	21		16	
Columns (c)	2		2	
<b>CCA</b>	<b>19%</b>		<b>18.75%</b>	

CCA = Corrected covered area. Calculation =  $CCA (\%) = N-r / rc-r$ :

Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

## H. Polycystic ovary syndrome

Systematic review ID	Tehrani 2019	Zhao 2016	Gilbert 2018
<b>Overlapping associations</b>	CVD	CVD	CVD
<b>Primary Study</b>			
Birdsall 1997		X	X
Cibula 2000		X	X
Ding 2018	X		
Glintborg 2015	X		
Hart 2014	X		
Ifitkhar 2012	X	X	X
Krentz 2007		X	X
Lo 2006	X		
Lunde 2007	X	X	X
Mani 2013	X	X	X
Merz 2016	X		
Meun 2018	X		
Okoroh 2015	X		
Pierpoint 1998	X		
Schmidt 2011	X	X	X
Shaw 2008			X
Sirmans 2014	X		
Solomon 2002		X	X
Wang 2011		X	X
Wild 2000	X	X	X
<b>Total</b>	14	10	11
<b>Grand Total (N)</b>	35		
<b>Rows (r)</b>	20		
<b>Columns (c)</b>	3		
<b>CCA</b>	37.5%		

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation =  $CCA (\%) = N-r / rc-r$ :

Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

## I. Oral contraceptive pills and risk of myocardial infarction

Systematic review	Roach 2015	Peragallo 2013
<b>Overlapping associations</b>	Fatal and non-fatal myocardial infarction	Non-fatal myocardial infarction
<b>Primary Study</b>		
Adam 1981	X	
Dunn 1999	X	X
Heinemann 1998/ Lewis 1997	X	X
Jick 1978	X	
Kemmeren 2002/Tanis 2001	X	X
Krueger 1980	X	
La Vecchia 1987	X	
Mann 1975a/Mann1975b	X	
Mann 1975b	X	
Mannt 1998		X
Margolis 2007		X
Rosenberg 2001	X	X
Rosenberg 1976a	X	
Schwartz 1997	X	
Shapiro 1979/ Slone 1981	X	
Sidney 1998	X	X
Tzourio 1995	X	
WHO collaboration 1997		X
Total	15	8
Grand Total (N)	23	
Rows (r)	18	
Columns (c)	2	
<b>CCA</b>	<b>27.8 %</b>	

CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r:**

Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

## J. Age at menarche

Systematic review	Xu Chen 2018	Charalampopoulos 2014	Xu Chen 2018	Charalampopoulos 2014	Xu Chen 2018	Charalampopoulos 2014
<b>Overlapping associations</b>	Fatal CVD	Fatal CVD	Fatal coronary heart disease	Fatal coronary heart disease	Fatal stroke	Fatal stroke
<b>Primary Study</b>						
Canoy 2014			X			
Chang 2011	X	X	X	X	X	X
Cui 2006	X	X	X	X	X	X
Gallagher 2011			X	X	X	X
Jacobsen 2009			X	X	X	X
Lakshman 2009	X	X				
Mueller 2012	X	X	X	X	X	X
Yang 2016	X					
Wu 2014	X		X		X	
Total (No of publications per review)	6	4	7	5	6	5
Grand Total (N)	10		12		11	
Rows (r)	6		7		6	
Columns (c)	2		2		2	
<b>CCA</b>	<b>66.7 %</b>		<b>71.4 %</b>		<b>83.3 %</b>	

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation =  $CCA (\%) = N-r / rc-r$ :  
 Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

## Appendix 4: Search strategy for newly published studies.

### A. Medline search strategy for breastfeeding and maternal risk of cardiovascular disease

Concept	Search terms	Results
1	exp Breast Feeding/	36904
2	exp LACTATION/	41793
3	exp Milk, Human/	18912
4	Breast fed.mp.	5692
5	Breastfe*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	26249
6	Lactat*.mp.	208342
7	Breast milk.mp.	12848
8	1 or 2 or 3 or 4 or 5 or 6 or 7	261289
9	exp Cardiovascular Diseases/	2343673
10	exp Coronary Artery Disease/	60319
11	Ischemic heart disease.mp.	25220
12	Ischaemic heart disease.mp.	8743
13	exp Myocardial Ischemia/	423937
14	exp Heart Failure/	118451
15	exp Stroke/	130429
16	9 or 10 or 11 or 12 or 13 or 14 or 15	2349619
17	8 and 16	18330
18	limit 17 to (female and humans and yr="2015 -Current")	999

### B. Medline search strategy for miscarriage and maternal risk of stroke

Concept	Search term	Results
1	exp Abortion, Spontaneous/	34727
2	exp Abortion, Habitual/	8097
3	Recurrent Abortion.mp.	614
4	Habitual Miscarriage.mp.	26
5	Miscarriage.mp.	10437
6	Foetal Death.mp.	442

7	exp Fetal Death/	29071
8	Pregnancy Loss.mp.	5979
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	68502
10	exp Cardiovascular Diseases/	2343673
11	exp Coronary Artery Disease/	60319
12	exp Myocardial Infarction/	172659
13	Heart Attack.mp.	4229
14	Coronary Heart Disease.mp.	48640
15	Ischemic Heart Disease.mp.	25220
16	Ischaemic Heart Disease.mp.	8743
17	exp Stroke/	130429
18	exp Ischemic Attack, Transient/	20112
19	Transient Ischaemic Attack.mp.	1829
20	Vascular Accident.mp.	902
21	Apoplexy.mp. or Stroke/	100350
22	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	2361615
23	9 and 22	4747
24	limit 23 to (humans and yr="2011 -Current")	977

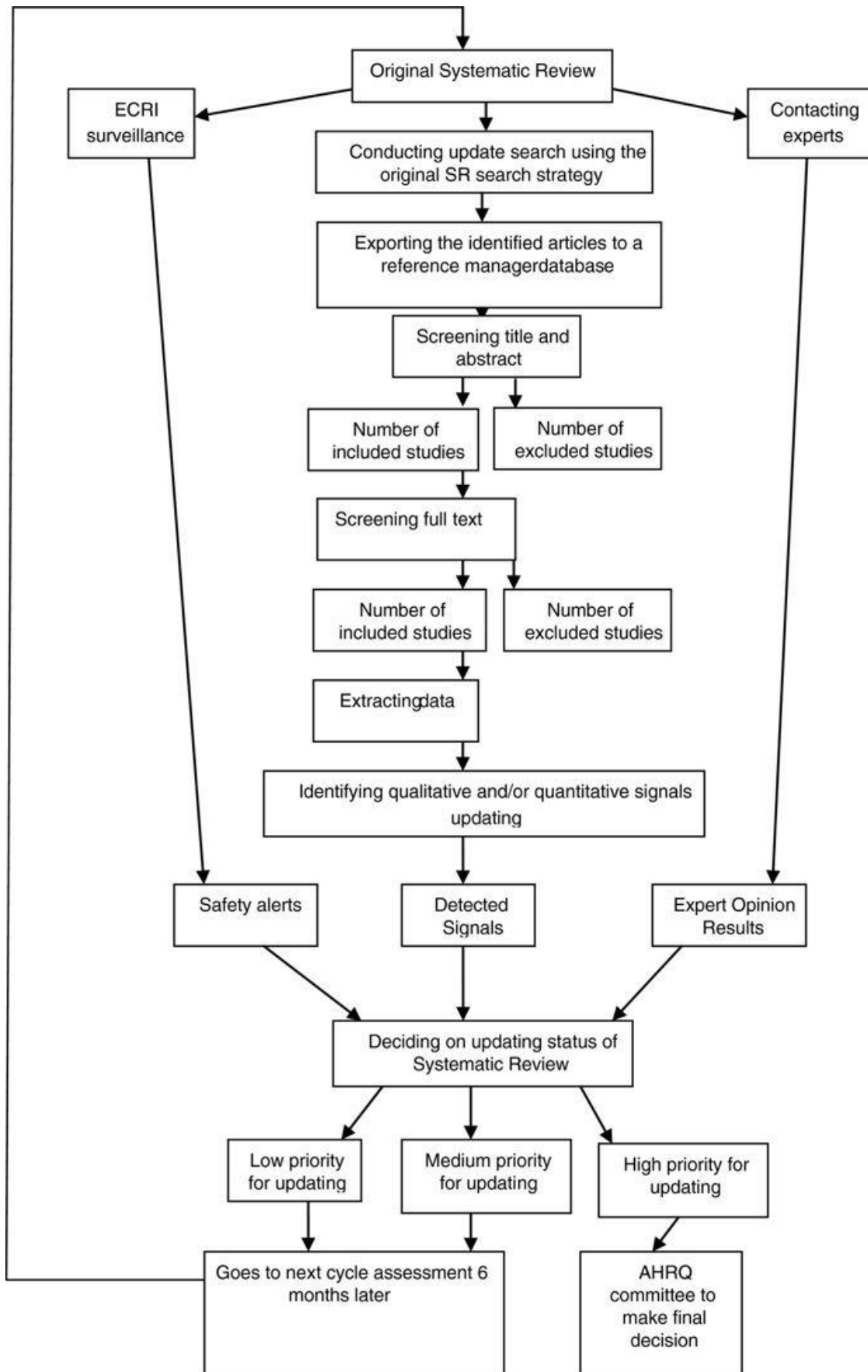
### C: Medline search strategy for gestational diabetes and maternal risk of stroke

Concept	Search terms	Results
1	exp Diabetes, Gestational/	12074
2	gestational diabetes.mp.	13910
3	gestational diabetes mellitus.mp.	7903
4	GDM.mp.	6883
5	1 or 2 or 3 or 4	17764
6	exp Cardiovascular Diseases/	2343673
7	exp Coronary Disease/	214889
8	exp Coronary Artery Disease/	60319
9	exp Myocardial Infarction/	172659
10	exp Coronary Artery Bypass/	52213
11	exp Endarterectomy, Carotid/	8644
12	exp Angina Pectoris/	43142
13	exp Stroke/	130429



14	exp Peripheral Vascular Diseases/	52535
15	PVD.mp.	2441
16	exp Peripheral Arterial Disease/	7203
17	PAD.mp.	23306
18	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	2380697
19	5 and 18	1480
20	limit 19 to yr="2016 -Current"	409

Appendix 5: Evaluation process for considering reviews for update



Ottawa's label	Ottawa method
	<b>Qualitative criteria for potentially invalidating signals</b>
A1	Opposing findings: a pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier
A2	Substantial harm: a pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision-making
A3	A superior new treatment: a pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm
	<b>Qualitative criteria for signals of major changes</b>
A4	Important changes in effectiveness short of 'opposing findings'
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or non-pivotal trial
	<b>Quantitative criteria signals of changes in evidence</b>
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent

RAND's label	RAND method indications for the need for an update
1	Original conclusion is still valid and this portion of the original report does not need updating. This conclusion was reached if we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid
2	Original conclusion is possibly out-of-date and this portion of the original report may need updating. This conclusion was reached if we found some new evidence that might change the CER conclusion, and/or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out-of-date
3	Original conclusion is probably out-of-date and this portion of the original report may need updating. This conclusion was reached if we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out-of-date
4	Original conclusion is out-of-date. This conclusion was reached if we found new evidence that rendered the CER conclusion out-of-date or no longer applicable; we classified the CER conclusion as out-of-date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce <i>prima facie</i> evidence that a conclusion was out-of-date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, and so on

Source (flow diagram and tables): Ahmadzai N, Newberry SJ, Maglione MA, Tsertsvadze A, Ansari MT, Hempel S, et al. A surveillance system to assess the need for updating systematic reviews. *Syst Rev.* 2013;2:104.

## Appendix 6: List of excluded studies and reasons for their exclusion

	1 <sup>st</sup> Author	Year	Title	Reason for Exclusion.
1.	Chakhtoura Z (1)	2011	Progesterone only contraceptive and risk of myocardial infarction: A meta-analysis.	Overlapping review outdated
2.	Chakhtoura Z (2)	2009	Progestogen-only contraceptives and the risk of stroke: a meta-analysis.	Overlapping review outdated
3.	Plu-Bureau (3)	2013	Hormonal contraceptives and arterial disease: an epidemiological update.	No Quality appraisal of primary studies Overlapping review outdated
4.	Khader YS (4)	2003	Oral contraceptives use and the risk of myocardial Infarction: a meta-analysis.	Overlapping review outdated
5.	Septer ARW	2001	Meta-analysis shows an increased incidence of stroke in persons using oral contraceptives.	Overlapping review outdated
6.	Gillum LA (5)	2000	Ischemic stroke risk with oral contraceptives: A meta-analysis	No quality appraisal of primary studies Overlapping outdated
7.	Johnston SC (6)	1998	Oral contraceptives and the risk of subarachnoid haemorrhage: a meta-analysis	No quality appraisal of primary studies Overlapping review outdated
8.	Xu B, Xu Z (7)	1996	Oral contraceptive and risk of disease.	Overlapping review outdated
9.	Katerndahl (8)	1992	Oral contraceptive use and cardiovascular disease risk: Is the relationship real or due to study bias?	Overlapping review outdated
10.	Novotna (9)	2002	M Arterial diseases in women using combined hormonal contraceptives. [in Czech language]	Overlapping review outdated
11.	Wu CQ (10)	2013	Drospirenone-containing oral contraceptive pills and the risk of venous and arterial thrombosis: a systematic review	No quality appraisal of primary studies
12.	Baillargeon JP (11)	2005	Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis	No quality appraisal of primary studies Overlapping review outdated
13.	Chans WS (12)	2004	Risk of stroke in women exposed to low dose oral contraceptives	No quality appraisal of primary studies
14.	Spitzer WO (13)	2002	Myocardial infarction and third generation oral contraceptives: aggregation of recent studies	No quality appraisal of primary studies

15	Leblanc ES (14)	1999	Benefits and risks of third-generation oral contraceptives	Overlapping review outdated Literature review No quality appraisal of primary studies
16	Luijken J (15)	2017	Association between age at menarche and cardiovascular disease: A systematic review on risk and potential mechanisms	No quality appraisal of primary studies
17	Anderson SA (16)	2014	Risk of coronary heart disease and risk of stroke in women with polycystic ovary syndrome: a systematic review and meta-analysis	Abstract; Inadequate information provided
18	Tomilson (17)	2010	Type 2 diabetes and cardiovascular disease in polycystic ovary syndrome: what are the risks, and can they be reduced?	Literature review
19	Wild RA (18)	2002	Polycystic ovary syndrome: a risk for coronary artery disease	Literature review of risk factors
20	Appiah D (19)	2016	Association of age at menopause with incident heart failure: A prospective cohort study and meta-analysis.	No quality appraisal of primary studies
21	Schwartz RH (20)	2017	the incidence of pregnancy-related stroke: A systematic review and meta-analysis	No comparator
22	Gibson (21)	2017	Incidence of myocardial infarction in pregnancy: A systematic review and meta-analysis of observational studies	No comparator
23.	Roth A (22)	1996	Acute myocardial infarction associated with pregnancy	Literature review Literature review
24.	Rosendaal NTA (23)	2017	Age at first birth and risk of later-life cardiovascular disease: a systematic review of the literature, its limitation, and recommendations for future research	No quality appraisal of primary studies. Literature review
25.	Bellamy L (24)	2007	Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis	Overlapping review outdated No quality appraisal of primary studies
26	McDonald (25)	2008	Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses	Overlapping review Outdated
27	Brown MC (26)	2013	Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis.	No quality appraisal
28	Li JW (27)	2014	Association of gestational diabetes mellitus (GDM) with subclinical atherosclerosis: a systemic review and meta-analysis	No hard-cardiovascular endpoints reported.

29	Huxley R (28)	2007	Is birth weight a risk factor for Ischaemic heart disease later in life?	Reports on future ischaemic heart disease as outcome among adults born with low birth weight
30	Poorthuis (29)	2017	MH Female- and Male-Specific Risk Factors for Stroke: A Systematic Review and Meta-analysis	No quality appraisal of primary studies
31	Feigin., VL (30)	2005	Risk factors for subarachnoid haemorrhage: an updated systematic review of epidemiological studies	Overlapping review outdated
32	Teunissen (31)	1996	Risk factors for subarachnoid haemorrhage: a systematic review	Overlapping review outdated
33	Aguilar Cordero (32)	2015	Breastfeeding as a method to prevent cardiovascular diseases in the mother and the child]. [in Spanish	No quality appraisal of primary studies
34	Davey Smith (33)	2007	Offspring birth weight and parental mortality: prospective observational study and meta-analysis	No quality appraisal of primary studies
35.	Sacco S (34)	2017	Contribution of hormonal contraceptive to the risk of ischaemic stroke in women with migraine: A meta-analysis of current data	Guideline/consensus statement
36	Wabnitz A (35)	2015	Bushnell C. Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature	Literature review No quality appraisal
37	Lameijer H (36)	2015	Ischaemic heart disease during pregnancy or post-partum: systematic review and case series.	No comparator
38.	Downes (37)	2017	Maternal, Labor, Delivery, and Perinatal Outcomes Associated with Placental Abruption: A Systematic Review.	No quality appraisal
39	Belbasis (38)	2016	Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses	No quality appraisal
40	Curtis (39)	2005	Use of combined oral contraceptives among women with migraine and nonmigraine headaches: a systematic review	Overlapping review outdated
41	Algra (40)	2012	Female risk factors for subarachnoid hemorrhage: a systematic review with emphasis on hormonal menstrual and reproductive factors	Overlapping review outdated
42	De Groot (41)	2011	PCOS coronary heart disease stroke and the influence of obesity: A systematic review and meta-analysis	Overlapping review outdated
43	M de Kleijin (42)	1999	Reproductive history and cardiovascular disease risk in postmenopausal women	Literature review

			A review of the literature	
44	Ganesh (43)	2015	Hypertensive disorders in pregnancy and future risk of stroke: A systematic review.	Abstract: inadequate information provided
45	Culwell (44)	2009	Safety of hormonal contraceptive use among women with systemic lupus erythematosus: A systematic review	No hard cardiovascular disease end points mentioned.
46	Riley (45)	2016	Hormonal contraceptive among electronic cigarette users and cardiovascular risk: a systematic review	No cardiovascular disease outcomes reported
47	Oliver-Williams (46)	2019	Future cardiovascular disease risk for women with a history of gestational hypertension: a systematic review and meta-analysis	Abstract; inadequate information
48	Stampfer (47)	1990	Past use of oral contraceptives and cardiovascular disease: a meta-analysis in the context of the Nurses' Health Study.	Overlapping review outdated
49	Atsma (48)	2006	Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis	Overlapping and outdated



## Appendix 7: AMSTAR 2 quality appraisal scores

Item No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall Rating
Charalampopoulos 2014	Yes	No	Yes	Partial Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Prentice and Vinner 2013	Yes	Partial Yes	No	Partial Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Xu Chen 2018	Yes	No	No	Partial Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Glisic 2018	Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Tepper 2018	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No MA	No MA	Yes	No	No MA	No	Low
Zhenlin Xu 2015	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Zhenlin Xu 2018	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Peragallo 2013	Yes	No	Yes	Partial Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Roach 2015	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Moderate
Horton 2014	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No MA	No MA	Yes	Yes	No MA	No	Low
Sheikh Hu 2016	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	No MA	No MA	Yes	Yes	No MA	Yes	Moderate
Tepper 2016 <sup>a</sup>	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No MA	No MA	Yes	Yes	No MA	No	Low
Tepper 2016 <sup>b</sup>	Yes	No	No	No	No	Yes	No	Yes	Yes	Yes	No MA	No MA	Yes	Yes	No MA	Yes	Low
Dragomann 2015	Yes	No	No	Partial Yes	Yes	No	No	Yes	Yes	Yes	No MA	No MA	Yes	Yes	No MA	Yes	Moderate
Curtis 2005	Yes	No	No	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Low
Gilbert 2018	Yes	Yes	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	No MA	No MA	Yes	Yes	No MA	Yes	Moderate
Zhous 2017	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate

Zhao 2016	Yes	No	No	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Roeters van Lennep, 2014	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Tao 2015	Yes	No	No	Partial Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Muka 2016a	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Muka 2016b	Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Gong 2016	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Oliver-Williams 2015	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Brouwers 2018	Yes	No	No	Partial Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Pensee Wu 2018	Yes	Yes	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Moderate
Jing Li 2018	Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Kramer 2019	Yes	Yes	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Hopmans 2015	Yes	No	No	Partial Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Pensee Wu 2017(HDP)	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Heidi 2014	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Robbins 2014	Yes	No	Yes	Partial Yes	Yes	No	No	Yes	Yes	No	No MA	No MA	Yes	No	No MA	Yes	Moderate
Haichen Lv 2015	Yes	No	No	Partial Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Li W 2018	Yes	No	No	Partial Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Nguyen 2017	Yes	Yes	No	Partial Yes	Yes	No	No	Yes	Yes	No	No MA	No MA	Yes	Yes	No MA	Yes	Moderate
Bojilin 2016	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	No MA	No MA	Yes	Yes	No MA	Yes	Moderate

Grandi 2019	Yes	Yes	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Dayan 2017	Yes	Yes	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Tehrani 2019	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

No MA= No meta-analysis.

Item 1: inclusion of PICO elements? Item 2: review methods established before conduct of review? Item 3: explanation for selection of study designs to be included in review? Item 4: use of a comprehensive search strategy? Item 5: selection of studies in duplicate? Item 6: data extraction in duplicate? Item 7: provision of list of excluded studies with justification for exclusion? Item 8: description of included studies in adequate detail? Item 9: satisfactory technique for risk of bias? Item 10: sources of funding for included studies reported? Item 11: proper methods for meta-analysis? Item 12: potential risk of bias in included studies discussed? Item 13: risk of bias accounted for in interpreting results? Item 14: heterogeneity discussed? Item 15: if meta-analysis conducted was publication bias discussed? Item 16: disclosure of funding or conflict of interest?

## Appendix 8: General characteristics of reviews with overlapping associations.

Index of overlapping associations	Study ID	AMSTAR 2 rating	Reproductive factor	Outcome	Synthesis type (number)	Corrected covered area (CCA)	Decision to retain ✓ = Yes ✗ = No
1	Peragallo 2013	Moderate	Current oral contraceptive pill use	Non-fatal ischaemic stroke	MA (8)	19% very high	✗
	Zhenlin Xu 2015	Moderate	Oral contraceptive use	Non-fatal ischaemic stroke	MA (18)		✓
2	Roach 2015	Moderate	Current combined oral contraceptive use	Fatal and non-fatal myocardial infarction	MA (11)	27.8% very high	✓ (Cochrane review)
	Peragallo 2013	Moderate	Current combined oral contraceptive use	Non-fatal myocardial infarction	MA (8)		✗
3	Zhenlin Xu	Moderate	Oral contraceptive use	Fatal and non-fatal haemorrhagic stroke	MA (15)	18.7% very high	✓
	Peragallo 2013	Moderate	Current combined oral contraceptive use	Non-fatal haemorrhagic stroke	MA (4)		✗
4	Glisic 2018	Moderate	Progesterone only pill use	Myocardial infarction	MA (8)	very high 50%	✓
	Tepper 2018	Low	Progesterone only pill use	Myocardial infarction	Narrative (7)		✗
5	Glisic 2018	Moderate	Progesterone only pill use	Stroke	MA (8)	very high 66%	✓
	Tepper 2016	Low	Progesterone only pill use	Stroke	Narrative (8)		
6	Sheikh 2017	Moderate	Oestrogen-containing contraceptives in migraine	Stroke	Narrative (6)	75% very high	✓
	Tepper 2016	Low	Hormonal contraceptive use in migraine	Stroke	Narrative (8)		✗
7	Muka 2016	Moderate	Age at menopause	Fatal CVD	MA (5)	very high 20%	✓
	Gong 2015	Low	Early natural menopause	Fatal CVD	MA (4)		✗
	Tao 2015	Moderate	Early Natural menopause	Fatal CVD	MA (5)		✗
8	Muka 2016	Moderate	Age at menopause	Fatal ischaemic heart disease	MA (6)	37.5% very high	✓
	Gong 2015	Low	Early natural menopause	Fatal ischaemic heart disease	MA (4)		✗
	Tao 2015	Moderate	Early natural menopause	Fatal ischaemic heart disease	MA (4)		✗
9	Muka 2016	Moderate	Age at menopause	Fatal stroke	MA (6)	38% very high	✓
	Gong 2015	Low	Early natural menopause	Fatal stroke	MA (5)		✗

	Tao 2015	Moderate	Early Natural menopause	Fatal stroke	MA (5)		✘
10	Grandi 2019	Moderate	Pre-eclampsia	Fatal CVD	MA (9)	30% very high	✓
	Pensee Wu 2017	Moderate	Pre-eclampsia	Fatal CVD	MA (4)		✘
11	Grandi 2019	Moderate	Pre-eclampsia	Non-fatal coronary heart disease	MA (9)	5.6% slight	✓
	Pensee Wu 2017	Moderate	Pre-eclampsia	Non-fatal coronary heart disease	MA (10)		✓
12	Grandi 2019	Moderate	Pre-eclampsia	Non-fatal stroke	MA (9)	33% very high	✓
	Pensee Wu 2017	Moderate	Pre-eclampsia	Non-fatal stroke	No MA (7)		✘
13	Grandi 2019	Moderate	Pre-eclampsia	Fatal stroke	No MA (3)	25% very high	✘
	Pensee Wu 2017	Moderate	Pre-eclampsia	Fatal stroke	MA (2)		✓
14	Kramer 2019	Moderate	Gestational diabetes mellitus	Fatal and non-fatal CVD	MA (9)	25% very high	✓
	Grandi 2019	Moderate	Gestational diabetes mellitus	Fatal and non-fatal CVD	MA (8)		✘
	Jing Li 2018	Moderate	Gestational diabetes mellitus	Fatal and non-fatal CVD	MA (7)		✘
15	Grandi 2019	Moderate	Pre-term birth	Non-fatal CVD	MA (12)	23% very high	✓
	Pensee Wu 2018	Moderate	Pre-term birth	Non-fatal CVD	MA (8)		✘
	Robbins 2014	Moderate	Pre-term birth	Non-fatal CVD	MA (2)		✘
16	Grandi 2019	Moderate	Pre-term birth	Fatal CVD	MA (4)	28.6% very high	✘
	Pense Wu 2019	Moderate	Pre-term birth	Fatal CVD	MA (5)		✓
17	Heida 2016	Moderate	Pre-term birth	Fatal and non-fatal stroke	MA (3)	25% very high	✓
	Robbins 2014	Moderate	Pre-term births	Fatal and non-fatal stroke	Narrative (2)		✘
18	Heida 2016	Moderate	Pre-term birth	Fatal and non-fatal coronary heart disease	MA (3)	20% very high	✓
	Robbins 2014	Moderate	Pre-term births	Fatal and non-fatal coronary heart disease	Narrative (3)		✘
19	Pense Wu 2018	Moderate	Pre-term birth	Fatal coronary heart disease	MA (5)	11% High	✓
	Robbins 2014	Moderate	Pre-term birth	Fatal coronary heart disease	Narrative 5		✘
20	Zhao 2016	Moderate	Polycystic ovary syndrome	Non-fatal CVD	MA (10)	37.5% High	✓
	Tehrani 2019	Low	Polycystic ovary syndrome	Non-fatal CVD	MA (9)		✓*

	Gilbert 2018	Moderate	Polycystic ovary syndrome	Non-fatal CVD	Narrative (2)		✖
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CVD = cardiovascular disease, MA = Meta-analysis.

\*The Tehrani paper was retained because, although there was overlap, it provided further information we considered clinically relevant.

## Appendix 9:

### A. List of studies included in analysis

#### Fertility-related reviews

1	Xu Chen (49)	2018	Age at menarche and risk of all cause and cardiovascular mortality: a systematic review and dose-response meta-analysis.
2	Prentice P (50)	2012	Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis
3	Glisic M (51)	2018	Association between progestin-only contraceptive use and cardiometabolic outcomes: A systematic review and meta-analysis
4	Xu Z (52)	2018	Association between oral contraceptive and risk of haemorrhagic stroke: A meta- analysis of observational studies.
5	Xu Z (53)	2015	Current use of oral contraceptives and the risk of first-ever ischemic stroke: A meta-analysis of observational studies
6	Roach (54)	2015	Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke
7	Horton (55)	2015	Combined hormonal contraceptive use among obese women and risk for cardiovascular events: A systematic review
8	Sheikh (56)	2016	Risk of Stroke Associated with Use of Oestrogen Containing Contraceptives in Women with Migraine: A Systematic Review
9	Tepper (57)	2016	Nonoral combined hormonal contraceptives and thromboembolism: a systematic review
10	Dragoman (58)	2015	Combined hormonal contraceptive use among women with known dyslipidaemias: a systematic review of critical safety outcomes
11	Curtis (59)	2006	Combined oral contraceptive use among women with hypertension: A systematic review.
12	Zhao L (60)	2016	Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): a meta-analysis.
13	Zhou Y (61)	2017	Association between polycystic ovary syndrome and the risk of stroke and all-cause mortality: insights from a meta-analysis

14	Tehrani (62)	2019	Cardiovascular events among reproductive and menopausal age women with polycystic ovary syndrome: a systematic review and meta-analysis
15	Muka T (63)	2016	Association of Age at Onset of Menopause and Time Since Onset of Menopause with Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis
16	Muka T (64)	2016	Association of vasomotor symptoms and other menopausal symptoms with risk of cardiovascular disease: A systematic review
17	Roeters (65)	2016	Cardiovascular disease risk in women with premature ovarian insufficiency: A systematic review and meta-analysis
18	Tao X-Y (66)	2016	Effect of primary ovarian insufficiency and early natural menopause on mortality
19	Dayan (67)	2017	Cardiovascular risk following fertility therapy
20	Nguyen B (68)	2017	Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review
<b>B</b>			<b>Adverse Pregnancy outcomes</b>
21	Oliver-Williams (69)	(2013)	Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis
22	Brouwers (70)	2018	Recurrence of pre-eclampsia and risk of future hypertension and cardiovascular diseases
23	Wu P (71)	2017	Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis.
24	Li J (72)	2018	Increased risk of cardiovascular disease in women with prior gestational diabetes: A systematic review and meta-analysis
25	Wu P (73)	2018	Preterm delivery and maternal cardiovascular disease future risk: A systematic review and meta-analysis
26	Heida KY (74)	2016	Cardiovascular disease risk in women with a history of spontaneous preterm delivery: A systematic review and meta-analysis
27	Robbins (75)	2014	History of preterm birth and subsequent cardiovascular disease: a systematic review



28	Haichen Lv, (76)	2015	Parity and Cardiovascular Disease Mortality: A Dose-Response Meta-Analysis of Cohort Studies
29	Wenzhen Li (77)	2018	Parity and risk of maternal cardiovascular disease: A dose–response meta-analysis of cohort studies
30	Kramer (78)	2019	Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis.
31	Grandi (79)	2019	Cardiovascular Disease-Related Morbidity and Mortality in Women with a History of Pregnancy Complications Systematic Review and Meta-Analysis
<b>Combined (Fertility related and adverse pregnancy outcomes)</b>			
32	Bolijn R (80)	2017	Reproductive factors in relation to heart failure in women: A systematic review

**B. List of contemporary reviews with overlapping associations excluded from analysis**

33	Gong D (81)	2015	Early age at natural menopause and risk of cardiovascular and all-cause mortality- A meta-analysis of prospective observational Studies
34	Hopmans (82)	2015	Increased risk of type II diabetes mellitus and cardiovascular disease after gestational diabetes mellitus: a systematic review
35	Gilbert (83)	2018	Comorbidities and complications of polycystic ovary syndrome: An overview of systematic reviews.
36	Tepper NK (84)	2016	Safety of hormonal contraceptives among women with migraine: A systematic review
37	Peragallo (85)	2013	Risk of acute thromboembolic events with oral contraceptive use: a systematic review and meta-analysis.
38	Tepper NK (86)	2016	Progestin-only contraception and thromboembolism: A systematic review.
39	Charalampopolous (87)	2014	Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis.

**Appendix 10: Newcastle Ottawa scale appraisal scores for newly published studies.**

<b>Study ID</b>	<b>Selection</b>	<b>Comparability</b>	<b>Exposure</b>	<b>Total Score</b>
Kirkegaard 2018	****	**	***	9 (high)
Peters 2016	***	*	**	7 (medium)
Peters 2017	***	*	***	7 (medium)
Jacobson 2018	**	**	***	7 (medium)
Nguyen 2019	***	**	***	8 (high)
Ranthe 2013 #	****	*	**	7 (medium)
Daly 2018 ##	****	*	**	7 (medium)
Rajaei 2019*	***	*	**	6* (low)

Score based on Newcastle Ottawa scale for cohort studies. \* = Newcastle Ottawa score for case-control study. # = newly published study on history of miscarriage and maternal risk of stroke, ## = newly published study on history of gestational diabetes mellitus and maternal risk of stroke.

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## **SUPPLEMENTARY TABLES**

**Supplementary Table 1. General characteristics of systematic reviews included in the umbrella review**

**Supplementary Table 2. Summary of main findings, existing guidelines and recommendations for clinical practice and research**

**Supplementary Table 3: Tabular presentation of findings: Meta-analysis**

**Supplementary Table 4. Tabular presentation of findings: Narrative syntheses**

**Supplementary Table 5: General study characteristic for studies evaluating the association between breastfeeding and maternal risk of cardiovascular disease**

**Supplementary Table 1. General characteristics of systematic reviews included in the umbrella review.**

Author/Year	Systematic review objective	Reproductive Factor	Comparator	Population source (number of participants)	Outcome	Study designs (number of studies)	Quality Appraisal Tool	Funding source
<b>Fertility-related factors</b>								
Xu Chen 2018 (76)	To clarify the dose-response relationship between age at menarche and all-cause mortality and cardiovascular disease mortality	Menarche	Reference category	General (2,341,769)	Cardiovascular disease mortality; ischaemic heart disease mortality; stroke mortality	Cohort (12)	NOS	National Natural Science Foundation China
Prentice and Viner (78)	To examine whether pubertal timing is related to long-term cardiovascular morbidity and mortality	Menarche before age of 12 years	Menarche after 12 years	General (NP)	Cardiovascular disease morbidity	Cohort (6) Case control (4)	CEBM	None
Glisic 2018 (72)	To determine impact of progesterone only contraceptive use on cardiometabolic outcomes (venous thromboembolism, myocardial infarction, stroke)	Progestin-only contraceptive	Non-users of progesterone only contraceptives	General (62,088)	Myocardial infarction; stroke	Cohort (7) Case-control (10) Nested case-control (2)	NOS	None
Zhenlin Xu 2015 (67)	Evaluate risk of ischaemic stroke associated with first ever use of any oral contraceptive pills and describe influence of oestrogen dose, progesterone, and study characteristics	Any oral contraceptive pill	Ever and never users of any oral contraceptive pill	General (1,701,114)	Ischaemic stroke	Cohort (3) Case-control (15)	NOS	National Natural Science Foundation of China
Zhenlin Xu 2018 (71)	To estimate risk of haemorrhagic stroke among current users of any oral contraceptive pill and how risk is affected by study characteristics	Any oral contraceptive pill	Ever and never users of any oral contraceptive pill	General (1,701,114)	Haemorrhagic stroke (subarachnoid haemorrhage and intracranial haemorrhage)	Cohort (5) Case-control (10)	NOS	National Natural Science Foundation of China

Roach 2015 (55)	To estimate myocardial infarction and ischaemic stroke in users and non- users of diverse types, generations, and doses of hormonal contraceptives	Combined oral contraceptive	Ever and never users of combined oral contraceptive	General (NP)	Myocardial infarction; stroke	Cohort (1) Case-control (23)	ROBIS	None
Horton 2016 (81)	To evaluate whether combined hormonal contraceptive use modifies the risk of acute myocardial infarction, stroke, venous thromboembolism, central venous thrombosis, in obese women and evaluate evidence of a dose-response relationship between BMI and venous thromboembolism	Combined oral contraceptive use in obese women	Combined oral contraceptive use in normal weight women; obese women not on combined oral contraceptive	Obese women (NP)	Acute myocardial infarction; stroke	Cohort (1) Case-control (11) Pooled studies (3)	U.S. Preventive Services Task Force	None
Sheikh Hu 2016 (74)	To assess whether risk of stroke is associated with oestrogen dose and whether there is synergism between migraine and combined hormonal contraceptives	Oestrogen-containing contraceptives	Not on oestrogen-containing contraceptives	Migraineurs (NP)	Stroke	Cohort (1) Case-control (11) Mixed cohort and case-control (2) Cross-sectional (1)	NOS GRADE	International Headache Academy
Tepper 2016 (79)	Risk of venous thromboembolism and arterial thromboembolism among women using non-oral combined hormonal contraceptives compared to women using combined oral contraceptives	Non-oral combined hormonal contraceptives (combined hormonal patch, ring and injectables)	Levonorgestrel and norgestrel containing combined oral contraceptives	General (NP)	Acute myocardial infarction; stroke	Cohort (4) Case-control (4)	U.S. Preventive Services Task Force	Department of Reproductive Health and Research, WHO
Dragoman 2015 (80)	To investigate whether combined hormonal contraceptives modify the risk of myocardial infarction, stroke,	Combined hormonal contraceptive pills, transdermal patches, vaginal rings and	Combined oral contraceptive use without dyslipidaemia	Women with dyslipidaemia (NP)	Acute myocardial infarction; cerebrovascular accident	Case-control (1) Cohort (1)	U.S. Preventive Services Task Force	Department of Reproductive Health and Research, WHO

	venous thromboembolism, pancreatitis among women with dyslipidaemia, and determine whether existing lipid abnormalities worsen with combined hormonal contraceptive use	injectables in dyslipidaemia patients						
Zhou 2017 (85)	To investigate the link between polycystic ovary syndrome and stroke, death from any cause and whether BMI might explain higher risk of stroke	Polycystic ovary syndrome	Women without polycystic ovary syndrome	General (237,647)	Stroke	Cohort (9)	NOS	None
Zhao 2016 (66)	Summarize evidence on the association between polycystic ovary syndrome and cardiovascular disease	Polycystic ovary syndrome	Women without polycystic ovary syndrome	General (104,392)	Cardiovascular disease; coronary heart disease	Cohort (5) Case-control (5)	NOS	None
Tehrani 2019 (70)	To investigate whether cardiovascular events are increased in women with polycystic ovary syndrome and explore difference in polycystic ovary syndrome events in reproductive age women compared to menopausal/aging women who had polycystic ovary syndrome during their younger ages	Polycystic ovary syndrome	Healthy women without polycystic ovary syndrome	General (NP)	Cardiovascular disease; cardiovascular mortality; coronary heart disease; stroke; heart failure	Cohort (12) Case-control (1) Cross-sectional (3)	NOS	National Institute for Medical Research Development (NIMAD)
Dayan 2017 (88)	Summarize data linking fertility therapy with subsequent cardiovascular disease	Fertility therapy, ovulation induction drugs, ovulation stimulation drugs, in vitro fertilization, intra-uterine insemination	Women without fertility therapy	General population (NP)	Coronary ischemia; cardiovascular death; cardiovascular hospitalisations; heart failure; myocardial	RCT (1) Cohort (2) Case-cohort (1)	ACROBAT-NRSI	Heart and Stroke Foundation of Canada Grant in Aid

					infarction; stroke and transient ischaemic attack			
Haichen Lv 2015 (89)	Quantitatively assess the association between parity and cardiovascular disease mortality by summarizing evidence from prospective studies	Ever Parity	Nulliparous	General (994,810)	Cardiovascular disease mortality	Cohort (10)	NOS	None
Wenzhen Li 2018 (90)	A meta-analysis of cohort studies to investigate the association between parity and cardiovascular disease risk	Ever parity	Nulliparous	General (3,089,929)	Cardiovascular disease morbidity	Cohort (10)	NOS	China Postdoctoral Science Foundation
Nguyen 2017 (91)	Examine association between breastfeeding and maternal cardiovascular disease risk factors and outcomes	Breastfeeding	Breastfeeding less than 7 months	General (NP)	Subclinical and clinical cardiovascular disease (prevalence, incidence, mortality); cardiovascular disease risk factors	RCT (1) Cohort (10) Cross-sectional (9)	An adapted 15-item checklist derived from checklists for the reporting of observational studies	None
Roeters van Lennep, 2014 (96)	To assess the relationship between premature ovarian insufficiency and risk of ischaemic heart disease, stroke and overall cardiovascular disease	Premature ovarian insufficiency	Women without premature ovarian insufficiency	General (190,588)	Ischaemic heart disease (fatal and non-fatal); stroke (fatal and non-fatal); total cardiovascular disease (fatal and non-fatal)	Cohort (10)	Downs and Black	Dutch Society of Medical Specialists
Tao 2015 (59)	To systematically evaluate the association of all-cause, cardiovascular disease and all cancer mortality in women with premature ovarian insufficiency and early natural menopause	Premature ovarian insufficiency (Menopause <40 yrs.) Early natural menopause (Menopause at 40-44 yrs.)	Menopause at >45 years	General (NP)	Cardiovascular disease mortality; ischaemic heart disease mortality; stroke mortality	Cohort (7)	NOS	None
Muka 2016 (57)	To systematically review and meta-analyse studies evaluating age at onset of menopause and time since	Early menopause	Menopause at age >45 years; menopause at age 50-54 years	General (342,284)	Ischaemic heart disease (fatal and non-fatal); stroke (fatal and non-fatal); cardiovascular	Cohort (24) Case-control (2) Cross-sectional (6)	NOS	Metagenetics

	onset of menopause and cardiovascular disease risk				disease (fatal and non-fatal)			
Muka 2016 (97)	To investigate the association between menopausal symptoms and cardiovascular disease	Vasomotor symptoms (hot flushes and night sweats) and menopausal symptoms (depression, panic attack, insomnia)	Women without menopausal symptoms	General (213,976)	Cardiovascular disease, coronary heart disease, stroke	Cohort (10)	NOS	Metagenics Inc
<b>Adverse pregnancy outcomes</b>								
Oliver-Williams 2015 (98)	To confirm or refute the association between miscarriage and future cardiovascular disease	History of miscarriages; history of recurrent miscarriages	Women without miscarriages	General (NP)	Coronary heart disease; stroke	Cohort (5) Case-control (5)	NOS	Medical Research Council (MRC) PhD Studentship
Brouwers 2018 (99)	To evaluate all evidence on the risk of developing future hypertension and cardiovascular disease after multiple pregnancies complicated by pre-eclampsia compared with pre-eclampsia in a single pregnancy followed subsequently by a normal pregnancy	Recurrent pre-eclampsia	A single episode of pre-eclampsia followed by uneventful pregnancies	General (52,544)	Cerebrovascular accident; ischaemic heart disease. thromboembolism, atherosclerosis; heart failure; fatal cardiovascular disease; hypertension or cardiovascular disease hospitalisation as an outcome	Cohort (6)	NOS	None
Pensee Wu 2017 (61)	To systemically evaluate and quantify the relationship between pre-eclampsia and future cardiovascular disease	Pre-eclampsia	Women without pre-eclampsia	General (6.4 million)	Heart failure; coronary heart disease (fatal and non-fatal); cardiovascular disease (fatal and non-fatal); stroke (fatal and non-fatal)	Cohort (18)  Cross-sectional (4)	NOS	North Staffordshire Heart Committee
Kramer 2019 (62)	Evaluate the impact of gestational diabetes on future incidence of cardiovascular disease.	Gestational diabetes	Women without gestational diabetes	General population (5,390,591)	Cardiovascular disease	Cohort (8) Case-control (1)	NOS	None

Jing Li 2018 (63)	To investigate the effect of diabetes mellitus on long-term cardiovascular disease risk	Gestational diabetes	Pregnant women without gestational diabetes	General (3,417,020)	Coronary artery disease; stroke	Cohort (7)	Moderate	Tianjin Medical University's Talent Recruitment Grant and the National 13 <sup>th</sup> 5-Year's Plan Grant of China
Pensee Wu 2018 (64)	To systematically evaluate the evidence on the association between preterm births and future maternal risk of cardiovascular disease	Preterm birth	Pregnant women without preterm birth	General (5,813,682)	Cardiovascular disease; cardiovascular disease death; coronary heart disease; coronary heart disease death; stroke; stroke death	Cohort (15) Case-control (3) Cross-sectional (1)	NOS	North Staffordshire Heart Committee
Heida 2014 (102)	To summarize evidence on the association between history of spontaneous preterm delivery and risk of ischaemic heart disease, stroke, and cardiovascular disease	Preterm birth	Uncomplicated pregnancies	General (4,172,204)	Fatal and non-fatal ischaemic heart disease, stroke, and cardiovascular disease	Cohort (10)	NOS	Quality fund (SKMS) of the Netherlands Association of Medical Specialists
Robbins 2014 (65)	Summarize evidence on preterm birth and cardiovascular disease morbidity or mortality	Preterm birth	Uncomplicated pregnancies	General	Fatal and non-fatal cardiovascular disease, stroke, ischaemic heart disease, atherosclerosis	Cohort (8) Cross-sectional (1) Cohort-nested case-control (1)	Community Guide's methods	None
Bolijn 2016 (87)	To provide an overview of the current evidence on the association between reproductive factors and risk of heart failure	Parity; gravidity. age at menopause; preterm delivery and small for gestational age; gestational diabetes; polycystic ovary syndrome; hysterectomy; hypertensive disorders of pregnancy; reproductive duration and age at first hormonal replacement therapy		General (NP)	Heart failure	RCT (1) Cohort (15) Case-control (2) Cross-sectional (3)	Quality assessment tools from the NHLBI and NIH	None

Grandi 2019 (60)	To determine an association between a broad array of pregnancy complications and cardiovascular disease	Hypertensive disorders of pregnancy; placental abruption; preterm birth; gestational diabetes; low birth weight; small for gestational age; stillbirth; miscarriage	Women without pregnancy complications	General (28,993,438)	Cardiovascular disease (coronary heart disease, cerebrovascular accident, myocardial infarction, coronary revascularization, transient ischaemic attack, stroke); cardiovascular disease mortality.	Cohort (73) Case-control (11)	ROBINS-I	Personal funding
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ACROBAT-NRSI A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions BMI = body mass index, CEBM = Centre for evidenced based medicine, GRADE = Grading of Recommendations, Assessment, Development and Evaluation, NHLBI = National Lung and Blood Institute, NIH = National Institute of Health, NP = not provided, NOS = Newcastle Ottawa Scale, RCT = randomized controlled trial, ROBINS-I = risk of bias in non-randomized studies – of interventions, ROBIS-I = risk of bias in systematic reviews, SKMS = Stichting Kwaliteitsgelden Medisch Specialisten (Quality Assurance Medical Specialists Foundation), WHO = World Health Organization.



Supplementary Table 2: Summary of main findings, existing guidelines and recommendations for clinical practice and research

Reproductive factor	Systematic review ID (AMSTAR 2 rating)	Primary study design (number)	Outcome by fatality type: Effect size (95% CI)	Mention of female-specific risk factors in the current UK (NICE/RCOG/FSRH) guidelines	Umbrella review comments
<b>Fertility-related factors</b>					
<b>Early menarche</b>					
	Prentice and Viner 2012(78) (Moderate)	Cohort (5)	Non-fatal composite cardiovascular disease: HR 1.15 (1.02 to 1.28)	No mention as part of cardiovascular disease risk assessment in any guidelines.	<p><b>Conclusion:</b> Early age at menarche was associated with cardiovascular disease risk.</p> <p><b>Recommendations:</b> (1) Recognition of early menarche as a risk enhancing factor for cardiovascular disease in cardiovascular disease prevention guidelines. (2) Periodic evaluation of cardiovascular disease risk factors among women history of early age at menarche</p>
	Xu Chen 2018(76) (Moderate)	Cohort (6)	Fatal Composite cardiovascular disease: RR 0.99 (0.98 to 1.01)		
		Cohort (7)	Fatal ischaemic heart disease; RR 0.97 (0.95 to 0.99)		
		Cohort (6)	Fatal stroke: RR 0.983 (0.954 to 1.012)		
<b>Hormonal contraceptives (oral)</b>					
<b>Oral contraceptive pills (includes either combined oral contraceptive or progesterone-only pills)</b>	Zhenlin Xu 2015(67) (Moderate)	Cohort (3), Case-control (15)	Non-fatal ischaemic stroke: OR 2.47 (2.04 to 2.99)	<p><b>FSRH (UK):</b>(112) Recommends women to be advised that current combined oral contraceptive use is associated with increased risk of myocardial infarction and stroke. The risk may be magnified when combined oral contraceptives are used in women with additional cardiovascular disease risks. Based on an out of date meta-analysis, the guideline notes that combined hormonal contraceptive</p>	<p><b>Conclusion:</b> Oral contraceptive pill use (combined oral contraceptives and progesterone-only contraceptives) compared to non-use was associated with increased risk of cardiovascular disease outcomes including haemorrhagic stroke. Progesterone-only contraceptive use was not associated with increased cardiovascular disease risk. Despite the increased risk in relative terms, the absolute risk for myocardial infarction (10.1/100000 person-years) and stroke (21/100000 person-years) among combined oral contraceptive users is low.(21)</p>
	Zhenlin Xu 2018(71) (Moderate)	Cohort (5) Case-control (10)	Non-fatal haemorrhagic stroke: OR 1.39 (1.05 to 1.83)		
<b>Combined oral contraceptive pills</b>	Roach(55) 2015 (Moderate)	Case-control (11)	Fatal and non-fatal myocardial infarction: RR 1.6 (1.3 to 1.9)		
		Case-control (10)	Fatal and non-fatal ischaemic stroke: RR 1.7 (1.5 to 1.9)		

<b>Progesterone only contraceptives</b>	Glisic 2018(72) (Moderate)	Cohort (1) Case-control (4)  Cohort (1) Case-control (4)	Non-fatal myocardial infarction, oral route: (progesterone-only contraceptives): RR 0.98 (0.66 to 1.47) Non-fatal stroke, oral formulation (progesterone-only contraceptives): RR 1.02 (0.72 to 1.44)	use is not associated with increased risk of haemorrhagic stroke.	<b>Recommendations:</b> An update of current guidelines is needed to reflect recent evidence that links current combined oral contraceptive use to increased risk of haemorrhagic stroke. Caution in the use of combined oral contraceptives among women with sex-specific risk factors for cardiovascular disease.
<b>Hormonal contraceptives (non-oral)</b>					
<b>Combined non-oral hormonal contraceptives (transdermal patch, vaginal and injectables)</b>	Tepper 2016(79) (Low)	Cohort (1) Case-control (1)  Cohort (1) Case-control (1)	Non-fatal myocardial infarction: OR 0.2 to OR 1.6; the null value of 1 crossed in all the included studies Non-fatal stroke: OR 0.8 to OR 1.2; the null value of 1 crossed in all the included studies	Evidence does not support an association between non-oral combined hormonal contraceptives and risk of myocardial infarction or stroke.	<b>Conclusion:</b> No association was found in the limited number of studies available  <b>Recommendations (future research):</b> Studies investigating the association between non-oral hormonal contraceptive use and cardiovascular disease risk are sparse. Well-conducted observational studies are needed to investigate the cardiovascular safety of non-oral forms of hormonal contraceptives.
<b>Progesterone only Contraceptives (injectable, and intra-uterine)</b>	Glisic 2018(72) (Moderate)	Cohort (1) Case-control (2)  Cohort (1) Case-control (2)	Non-fatal myocardial infarction, non-oral route (implants, injectable, intra-uterine): RR 1.10 (0.77 to 1.56) Non-fatal stroke, non-oral formulation (implants, injectable, intrauterine): RR 0.78 (0.60 to 1.00)		
<b>Hormonal contraceptive use among women with co-existing illness</b>					
<b>Oestrogen containing contraceptives (Oral, patch and ring) use among women with migraine</b>	Sheikh Hu 2016 (74) (Moderate)	Case-control (5) Mixed Cohort & Case-control (1)	Fatal and non-fatal ischaemic stroke: OR 2.08 to OR 16.9	<b>FSRH-UK MEC:</b> (113) Recommend caution in use of oestrogen-containing contraceptive pills among women with migraine, dyslipidaemia, obesity and hypertension as these are established risk factors for cardiovascular disease.	<b>Conclusion:</b> Combined oral contraceptive use among women with migraine, dyslipidaemia or hypertension compared to non-use among women without these conditions was associated with higher risks of cardiovascular disease.  <b>Recommendations (future research):</b> (1) No evidence regarding the cardiovascular safety of non-oral forms of combined hormonal contraceptive use (patch, ring or injectables) in pre-existing conditions that predispose to cardiovascular disease risk were identified from
<b>Combined hormonal contraceptives</b>	Dragoman 2015(80) (Moderate)	Case-control (1)  Cohort (1)	Non-fatal myocardial infarction: OR 25 (6 to 109) Non-fatal stroke: IRR 1.76 (1.51 to 2.06)		

(oral pills, transdermal patch, vaginal rings,) among women with dyslipidemia					the reviews. Well-conducted observational studies are needed to clarify their safety profile. (2) There was conflicting evidence on the association between combined hormonal contraceptive use in obese women compared to non-use in women of normal weight and the risk of cardiovascular disease outcomes. Well-designed observational studies are needed to clarify the cardiovascular disease risk posed by combined hormonal contraceptive use in obese women. (3) No evidence regarding the cardiovascular safety of progesterone-only contraceptive use among women with co-existing conditions that predispose to cardiovascular disease risk were identified. Well-conducted observational studies are needed to clarify their safety profile.
Combined hormonal oral pills, transdermal patch, vaginal rings,) contraceptive use in obese women	Horton 2016(81) (Low)	Case-control (3) Case-control (3)	Non-fatal myocardial infarction: OR 0.88 to OR 5.1 Non-fatal stroke: OR 0.59 to OR 4.6		
Combined oral contraceptive use among women with hypertension	Curtis 2006(84) (Low)	Case-control (4) Case-control (8)	Non-fatal myocardial infarction: OR 6 to OR 68. All studies reported statistically significant results Non-fatal ischaemic stroke: OR 3.1 to OR 14.5. All studies reported statistically significant results		
<b>Polycystic ovary syndrome</b>					
	Zhao 2016(66) (Moderate)	Cohort (5) Case-control (5)	Non-fatal cardiovascular disease: OR 1.30 (1.09 to 1.56)	<i>NICE/RCOG</i> :(114) Recognises cardiovascular disease risk factors are more prevalent among women with polycystic ovary syndrome. Recommends for prospective studies to investigate the association between polycystic ovary syndrome and cardiovascular disease risk.	<b>Conclusion:</b> Polycystic ovary syndrome was associated with an increased risk of cardiovascular disease outcomes  <b>Recommendation/future research:</b> (1) Inclusion of polycystic ovary syndrome as a risk enhancing factor for cardiovascular disease in current cardiovascular disease prevention guidelines. (2) Periodic assessment for cardiovascular disease risk factors among women with polycystic ovary syndrome. (3) No association was found between polycystic ovary syndrome and heart failure risk. Evidence was
		Cohort (2) Case-control (3)	Non-fatal ischaemic heart disease: OR 1.44 (1.13 to 1.84)		
	Zhou 2017(85) (Moderate)	Cohort (9)	Non-fatal stroke: OR 1.36 (1.09 to 1.7)		
	Bolijn 2017(87)	Cross-sectional study (1)	Non-fatal heart failure: OR 3.24 (0.53 to 19.94)		

	(Moderate)  Tehrani 2019(70) (Low)	Cohort (6) Cross-sectional study (1)  Cohort (1)	Non-fatal composite cardiovascular disease: HR 1.43 (1.27 to 1.61) in reproductive age polycystic ovary syndrome patients. Non-fatal composite cardiovascular disease: HR 1.03 (0.41 to 2.59) in menopausal age polycystic ovary syndrome patients		derived from a single cross-sectional with a small sample size leading to imprecise estimates. Well-designed observational studies are needed to investigate this association.
<b>Fertility therapy</b>					
<b>Fertility therapy (in-vitro fertilisation, intrauterine insemination)</b>	Dayan 2017(88) (Moderate)  Boliijn 2017(87) (Moderate)	Cohort (3) RCT (1)  Cohort (2)  Cohort (1)	Fatal and non-fatal cardiovascular disease: HR 0.91 (0.67 to 1.25)  Fatal and non-fatal stroke: HR 1.25 (0.96 to 1.63)  Fatal and non-fatal heart failure: HR 0.60 (0.30 to 1.22)	<b>NICE:</b> (115) Recommends providing patients with information on the long- term risks associated with fertility therapy. No mention of potential long-term cardiovascular disease risk.	<b>Conclusion:</b> Women on fertility therapy compared to those without fertility therapy were not at an increased risk of cardiovascular disease.  <b>Recommendations (future research):</b> Evidence was derived from few observational studies resulting in imprecise estimates. Prospective cohort studies are needed to investigate the long-term cardiovascular disease risk associated with fertility therapy.
<b>Parity</b>					
	Wenzhen Li 2018(90) (Moderate)  Haichen Lv 2015(89) (Moderate)	Cohort (9)  Cohort (6)	Non-fatal and fatal cardiovascular disease: RR 1.14 (1.09 to 1.18)  Fatal cardiovascular disease: RR 0.79 (0.60 to 1.06)	<b>NICE:</b> (116) No mention of long-term maternal cardiovascular disease risk and follow-up.	<b>Conclusion:</b> Higher parity compared to nulliparity was associated with morbidity but not mortality from cardiovascular disease. The dose-response analysis revealed a J-shaped association between parity and risk of cardiovascular disease outcomes with increasing parity linked to higher cardiovascular disease risk.  <b>Recommendations:</b> (1) Update of cardiovascular disease prevention guideline to recognise multiparity risk as a risk-enhancing

					factor for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women with high parity (>5).
<b>Breastfeeding*</b>					
	Nguyen 2017(91) (Moderate)	Cohort (9) Case-control (1)	Overall, ever breastfeeding and a longer lactation duration was associated with reduced risk of non-fatal and fatal cardiovascular disease outcomes.	NICE: No mention of cardiovascular benefits of breastfeeding.(116)	<b>Conclusion:</b> Breastfeeding and longer lactation duration is associated with decreased risk of cardiovascular disease. <b>Recommendations:</b> Breastfeeding information should be included within ante-natal clinics to advise women of the reduced risk.
<b>Premature ovarian insufficiency</b>					
	Roeters van Lennep 2014(96) (Moderate)	Cohort (2) Cohort (7) Cohort (7)	Fatal and non-fatal cardiovascular disease: HR 1.61 (1.22 to 2.12) Fatal and non-fatal ischaemic heart disease: HR 1.69 (1.29 to 2.21) Fatal and non-fatal stroke: HR 1.03 (0.88 to 1.99)	NICE:(117) Recognises that women with premature ovarian insufficiency are potentially at increased risk of cardiovascular disease complications. Recommends future research to clarify the long-term effects of premature ovarian insufficiency on psychological and physical health including cardiovascular disease.	<b>Conclusion:</b> Premature ovarian insufficiency was associated with an increased risk of cardiovascular disease. <b>Recommendations:</b> (1) Update of current guideline to reflect current evidence on the association between premature ovarian insufficiency and cardiovascular disease risk. (2) Periodic evaluation for the presence of cardiovascular disease risk factors among women with premature ovarian insufficiency.
	Tao 2015(59) (Moderate)	Cohort (7) Cohort (3) Cohort (4)	Fatal cardiovascular disease: RR 1.24 (0.98 to 1.58) Fatal ischaemic heart disease: RR 1.48 (1.02 to 2.16) Fatal stroke: RR 1.00 (0.86 to 1.16)		
<b>Menopause</b>					
<b>Early menopause (natural and surgical)</b>	Muka 2016(57) (Moderate)	Cohort (3) Cross-sectional study (2) Cohort (1) Cohort (4) Cross-sectional study (2)	Fatal cardiovascular disease: RR 1.19 (1.08 to 1.31)  Non-fatal cardiovascular disease: RR 1.56 (1.08 to 2.26) Fatal ischaemic heart disease: RR 1.11 (1.03 to 1.20)	NICE:(117) No mention on long-term maternal cardiovascular disease risk and follow up.	<b>Conclusion:</b> Early menopause and menopausal symptoms were associated with increased cardiovascular disease risk. <b>Recommendations:</b> (1) Update of current guideline to reflect current evidence on the association between early menopause and menopausal symptoms and cardiovascular disease risk. (2) Periodic evaluation for the

<b>Early natural menopause</b>	Bolijn 2017(87) (Moderate)	Cohort (5)	Non-fatal ischaemic heart disease: RR 1.50 (1.28 to 1.76)		presence of cardiovascular disease risk factors among women with early menopause.
		Cohort (4)	Fatal stroke: RR 0.99 (0.92 to 1.07)		
		Cross-sectional study (2)			
		Cohort (5)	Non-fatal stroke: 1.23 (0.98 to 1.53)		
		Cohort (2)	Non-fatal heart failure: HR 1.36 to HR 1.66		
<b>Menopausal symptoms</b>	Tao 2015(59) (Moderate)	Cohort (9)	Fatal cardiovascular disease: RR 1.10 (0.91 to 1.13)		
		Cohort (4)	Fatal ischaemic heart disease: RR 1.09 (1.00 to 1.18)		
		Cohort (5)	Fatal stroke: RR 0.94 (0.86 to 1.03)		
<b>Menopausal symptoms</b>	Muka 2016(97) (Moderate)	Cohort (4)	Fatal and non-fatal cardiovascular disease: RR 1.29 (0.98 to 1.71)		
		Cohort (7)	Fatal and non-fatal ischaemic heart disease: RR 1.18 (1.03 to 1.35)		
		Cohort (3)	Fatal and non-fatal stroke: RR 1.08 (0.89 to 1.32)		
<b>Adverse pregnancy outcomes</b>					
<b>Pregnancy loss</b>					
<b>Miscarriage</b>	Oliver-Williams 2013(98) (Moderate)	Cohort (3)	Fatal and non-fatal ischaemic heart disease: OR 1.45 (1.18 to 1.78)	<i>NICE:</i> No mention of long-term maternal cardiovascular disease risk.(118–120)	<b>Conclusion:</b> History of pregnancy loss (miscarriage and stillbirth) was associated with an increased risk of cardiovascular disease.  <b>Recommendations:</b> (1) Pregnancy loss (miscarriage and stillbirths) should be included in relevant guidelines as risk enhancing factors for cardiovascular disease. (2) Periodic
		Cohort (2)	Fatal and non-fatal stroke: OR 1.11 (0.72 to 1.69)		
	Grandi 2019(60) (Moderate)	Cohort (6)	Fatal and non-fatal cardiovascular disease: OR 0.83 to 2.69		

<b>Recurrent Miscarriage</b>	Oliver-Williams 2013(98) (Moderate)	Cohort (3) Case-control (4)	Fatal and non-fatal ischaemic heart disease: OR 1.99 (1.13 to 3.50)		evaluation of cardiovascular disease risk factors among women history of pregnancy loss.
<b>Stillbirth</b>	Grandi 2019(60) (Moderate)	Cohort (4) Cohort (4)	Non-fatal composite cardiovascular disease: OR 1.49 (1.08 to 2.06) Fatal composite cardiovascular disease: OR 2.23 (1.90 to 2.62)		
<b>Hypertensive disorders of pregnancy</b>					
<b>Pre-eclampsia</b>	Grandi 2019(60) (Moderate)	Cohort(16)	Non-fatal composite cardiovascular disease: OR 2.24 (1.72 to 2.93) for moderate pre-eclampsia	<i>NICE</i> :(121) Recognises that hypertensive disorders of pregnancy are associated with a 1.5-3-fold risk of cardiovascular disease outcomes. Women with hypertensive disorders of pregnancy should be advised on the increased cardiovascular disease risk. Recommends that such women should maintain a healthy lifestyle including avoiding smoking and maintaining an appropriate weight.	<b>Conclusion:</b> Hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension) were associated with an increased risk of cardiovascular disease.  <b>Recommendation:</b> Periodic evaluation of cardiovascular disease risk factors among women with history of hypertensive disorders of pregnancy.
		Cohort (6)	Non-fatal composite cardiovascular disease: OR 2.74 (2.48 to 3.04) for severe pre-eclampsia		
		Cohort (9)	Fatal composite cardiovascular disease: OR 1.73 (1.46 to 2.06)		
		Cohort (9)	Non-fatal cerebrovascular accident: OR 2.95 (1.10 to 7.90)		
	Pensee Wu 2017(61)(Moderate)	Cohort (4)	Fatal ischaemic heart disease: RR 2.10 (1.25 to 3.51)		
		Cohort (4)	Non-fatal stroke: OR 2.95 (1.10 to 7.90) Fatal stroke: RR 1.97 (0.80 to 4.88)		
		Cohort (4)	Non-fatal heart failure: RR 4.19 (2.09 to 8.38)		
<b>Recurrent pre-eclampsia</b>	Brouwers 2018(99) (Moderate)	Cohort (2)	Non-fatal ischaemic heart disease: RR 2.40 (2.15 to 2.68)		
		Cohort (2)	Non-fatal stroke: RR 1.69 (1.21 to 2.35)		
		Cohort (3)	Non-fatal Heart failure: RR 2.88 (2.23 to 3.72)		

<b>Gestational hypertension</b>	Grandi 2019(60) (Moderate)	Cohort (9) Cohort (4)	Non-fatal cardiovascular disease: RR 1.67 (1.28 to 2.19) Non-fatal stroke: RR 1.83 (0.79 to 4.22)		
<b>Gestational diabetes mellitus</b>	Kramer 2019(62) (Moderate)  Jing Li 2018(63) (Moderate)	Cohort (8) Case-control (1)  Cohort (4) Cohort (2)	Non-fatal and fatal cardiovascular disease: RR 1.98 (1.57 to 2.50)  Non-fatal coronary artery disease: RR 2.09 (1.56 to 2.80) Non-fatal stroke: RR 1.25 (1.07 to 1.48)	<i>NICE</i> :(122) No mention of maternal cardiovascular disease risk assessment and long-term follow-up.	<b>Conclusion:</b> History of gestational diabetes mellitus was associated with an increased risk of cardiovascular disease.  <b>Recommendations:</b> (1) Updating of current guidelines to include gestational diabetes as a risk enhancing factor for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women with a history of gestational diabetes.
<b>Placental abruption</b>	Grandi 2019(60) (Moderate)	Cohort (7)	Fatal and non-fatal composite cardiovascular disease: OR 1.82 (1.42 to 2.33)	<i>RCOG</i> :(123) No mention of maternal cardiovascular disease risk assessment and long-term follow-up .	<b>Conclusion:</b> History of placental abruption was associated with an increased risk of cardiovascular disease.  <b>Recommendations:</b> (1) Updating of guidelines to include placental abruption as a risk enhancing factor for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women with a history of placental abruption.
<b>Preterm birth</b>	Grandi 2019(60) (Moderate)  Pensee Wu 2018(64) (Moderate)	Cohort (12) Cohort (4)  Cohort (4) Cross-sectional study (1)	Non-fatal cardiovascular disease: OR 1.63 (1.39 to 1.93) Fatal cardiovascular disease: OR 1.93 (1.83 to 2.03)  Non-fatal ischaemic heart disease: RR 1.49 (1.38 to 1.60)	<i>NICE</i> :(124) No mention of maternal cardiovascular disease risk assessment and long-term follow-up.	<b>Conclusion:</b> Maternal history of preterm birth was associated with later risk of cardiovascular disease  <b>Recommendations:</b> (1) Updating of guidelines to include preterm birth as a risk enhancing factor for cardiovascular disease. (2) Periodic



<b>Recurrent preterm birth</b>	Heida 2014 (102) (Moderate)	Cohort (4)	Fatal ischaemic heart disease: RR 2.11 (1.87 to 2.36)		assessment of cardiovascular disease risk factors among women with a history of preterm births.
		Cohort (6)	Non-fatal stroke RR 1.65 (1.51 to 1.79)		
		Cohort (2)	Fatal stroke: RR 1.30 (0.94 to 1.80)		
		Cohort (4)	Fatal- and non-fatal cardiovascular disease: HR 2.01 (1.52 to 2.65)		
		Cohort (3)	Fatal and non-fatal ischaemic heart disease: HR 1.38 (1.22 to 1.57)		
		Cohort (3)	Fatal and non-fatal stroke: HR 1.71 (1.53 to 1.91)		
	Robbins 2014(65) (Moderate)	Cohort (2)	Fatal and non-fatal composite cardiovascular disease: HR 1.4 to HR 1.8		
<b>Low birth weight &amp; small for gestational age</b>					
	Grandi 2019(60) (Moderate)	Cohort (4)	Fatal and non-fatal composite cardiovascular disease: OR 1.29 (0.91 to 1.83)	<i>NICE</i> :(125) No mention of maternal cardiovascular disease risk assessment and long-term follow-up.	<b>Conclusion:</b> Maternal history of low birth weight and small for gestational age offspring was associated with increased cardiovascular disease risk.  <b>Recommendations:</b> (1) Updating of guidelines to include preterm birth as a risk enhancing factor for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women with a history of small for gestational age offspring.
	Grandi 2019(60) (Moderate)	Cohort (10)	Fatal and non-fatal composite cardiovascular disease: OR 1.09 to OR 3.50		

FSRH = Faculty of Sexual and Reproductive Health guidelines, FSRH-UK MEC = Faculty of Sexual and Reproductive Health guidelines, Faculty of Sexual and Reproductive Health, United Kingdom medical eligibility criteria, HR = hazard ratio, NICE = National Institute for Health and Care Excellence, OR = odds ratio, RCT = randomised controlled trial, RR = risk ratio, RCOG= Royal College of Obstetricians and Gynaecologists, \* = updated systematic review

Supplementary Table 3: Tabular presentation of findings: Meta-analysis.

Reproductive factor	Study identity Author/Year	Outcome	Secondary Analysis	No of studies included	Participants	Evidence synthesis	I <sup>2</sup> statistic	Overall evidence of publication bias	AMSTAR 2 rating	
<b>Fertility-related factors</b>										
<b>Early age at menarche</b>	Xu Chen 2018 (76)	Fatal ischaemic heart disease		7	NP	RR 0.969 (0.947-0.993)	44.9%	P = 0.573	Moderate	
				6	NP	RR 0.983 (0.954-1.012)	58.1%	P = 0.881		
				6	NP	RR 0.993 (0.975-1.012)	53.1%	P = 0.091		
	Prentice and Viner (78)	Non-fatal CVD		5	126,083	HR 1.15 (1.02-1.28)	47%	None	Moderate	
<b>Combined oral contraceptive</b>	Roach 2015 (55)	Fatal and non-fatal myocardial infarction		14	NP	RR 1.6 (1.3-1.9)	78.3%	Not assessed		
		Fatal and non-fatal stroke		13	NP	RR 1.7 (1.5 - 1.9)	78.3%			
		Fatal and non-fatal myocardial infarction and stroke	<u>Oestrogen dose</u>							
			20 µg	2	NP	RR 1.6 (1.4-1.8)	0.0%			
			30-40 µg	2	NP	RR 2.0 (1.4-3.0)	50.4%			
			>49 µg	2	NP	RR 2.4 (1.8-3.3)	29.6%			
			Fatal and non-fatal myocardial infarction and stroke	<u>Progestin generation</u>						
		1 <sup>st</sup>	7	NP	RR 1.2 (0.8-1.9)	69.4%				
		2 <sup>nd</sup>	8	NP	RR 1.1 (0.8-1.7)	82.0%				
		3 <sup>rd</sup>	6	NP	RR 1.1 (0.7-1.7)	79.9%				
<b>Oral contraceptive pills</b>	Xu 2015 (67)	Non-fatal ischaemic stroke		18	NP	RR 2.47 (2.04-2.99)	77.5%	None	Moderate	
				<u>Oestrogen dose</u>						
				20 µg	3	NP	OR 1.56 (1.36-1.79)	0.0%		
				30-40 µg	5	NP	OR 1.75 (1.61-1.89)	0.0%		
				<50 µg	11	NP	OR 1.97 (1.61-2.41)	68.4%		
				>50 µg	9	NP	OR 3.28 (2.49-4.32)	47.8%		
				Progesterone only pill	4	NP	OR 0.99 (0.71-1.37)	0.0%		
	<u>Progestin combined with &lt;50 µg oestrogen</u>									

			1 <sup>st</sup>	5	NP	OR 1.63 (0.97-2.75)	48.1%		
			2 <sup>nd</sup>	5	NP	OR 2.17 (1.59 -2.97)	68.8%		
			3 <sup>rd</sup>	5	NP	OR 2.01 (1.46-2.76)	65.4%		
			4 <sup>th</sup>	5	NP	OR 1.52 (1.23-1.89)	0.0%		
			<u>Progestin combined with all dose oestrogen</u>						
			1 <sup>st</sup> gen	8	NP	OR 2.71 (1.76-4.17)	50.4%		
			2 <sup>nd</sup> gen	8	NP	OR 2.23 (1.88-2.98)	71.9%		
			<u>Dyslipidaemia</u>						
			Yes	5	NP	OR 2.24 (1.65-3.05)	74.8%		
			No	13	NP	OR 2.59 (2.08-3.24)	60.6%		
			<u>Obesity</u>						
			Yes (BMI >27.3)	3	NP	OR 1.78 (0.24-13.26)	87.0%		
			No (BMI <27.3)	3	NP	OR 2.03 (1.43-2.87)	6.2%		
			<u>History of Migraine</u>						
			Yes	6	NP	OR 6.33 (2.35-17.05)	80.6%		
			No	6	NP	OR 2.55 (1.10-5.91)	80.4%		
			<u>Age</u>						
			>35 years	6	NP	OR 3.08 (1.82-5.23)	56.4%		
			<35 years	6	NP	OR 1.82 (1.38-2.39)	0.0%		
			<u>Smoking</u>						
			Current	7	NP	OR 4.90 (3.17-7.57)	42.3%		
			Non-current	7	NP	OR 2.59 (1.96-3.43)	12.5%		
			<u>Blood pressure</u>						
			Hypertensive	5	NP	OR 8.02 (5.53-11.64)	0.0%		
			Normotensive	5	NP	OR 2.73 (2.22-3.37)	5.3%		
	Xu 2018 (71)	Fatal and non-fatal haemorrhagic stroke		15	NP	OR 1.39 (1.05-1.83)	65.6%	None	Moderate
			<u>Stroke subtype</u>						
			Sub-arachnoid haemorrhage	10	NP	OR 1.60 (1.21-2.12)	41%		
			Intra-cranial haemorrhage	4	NP	OR 0.92 (0.33-2.54)	82.6%		
			<u>Outcome</u>						
			Morbidity	10	NP	OR 1.71 (1.82-2.29)	50.7%		
			Mortality	5	NP	OR 0.95 (0.59-1.50)	60.6%		
			<u>Oestrogen dose</u>						
			High	2	NP	OR 1.60 (1.12-2.27)	0.0%		
			Low	8	NP	OR 1.19 (0.86-1.66)	76.3%		

			<u>Progestin</u>						
			1st	3	NP	OR 0.91 (0.77-1.09)	0.0%		
			2nd	4	NP	OR 1.76 (1.25-2.48)	0.0%		
			3rd	4	NP	OR 1.70 (0.72-4.02)	-		
			<u>Migraine</u>						
			Ever	5	NP	OR 1.97 (1.19-3.27)	0.0%		
			Never	5	NP	OR 1.43 (0.84-2.43)	49.6%		
			<u>Smokers</u>						
			Current	6	NP	OR 4.52 (2.27-8.99)	80.8%		
			Non-current	5	NP	OR 1.35 (1.03-1.76)	0.0%		
			<u>Blood pressure</u>						
			Hypertensive	5	NP	OR 6.02 (1.50-24.25)	89.9%		
			Normotensive	3	NP	OR 1.37 (1.06-1.75)	0.0%		Moderate
<b>Progesterone only pills</b>	Glisic 2018 (72)	Non-fatal myocardial infarction		6	NP	RR 0.98 (0.66-1.47)	0%		
		Non- fatal stroke		6	NP	RR 1.02 (0.72-1.44)	0%		
<b>Polycystic ovary syndromme</b>	Zhous 2017 (85)	Non-fatal stroke		8	28,977	OR 1.36 (1.09-1.7)	44.7%		Moderate
			<u>BMI-adjusted</u>						
			Yes	5		OR 1.24 (0.98-1.59)	32.2%		
			No	3		OR 2.2 (1.25-3.88)	42.4%		
			<u>Polycystic ovary syndrome diagnosis</u>						
			Definite	5		OR 1.84 (1.14-2.99)	18.2%		
			Possible	3		OR 1.25 (0.97-1.61)	65.7%		
			<u>Mean age</u>						
			>50 years	5		OR. 1.31(1.04-1.65)	21.4%		
			<50 years	3		OR 2.03 (0.93-4.43)	55.5%		
			<u>Cohort type</u>						
			Retrospective	4		OR 2.29(1.43-3.67)	27.5%		
			Prospective	4		OR 1.17(0.91-1.51)	0%		
			<u>Sample size</u>						
			<10,000	5		OR 1.56(0.81-2.99)	15.3%		
			>10000	3		OR 1.33 (1.09-1.69)	74.2%		
			<u>Quality</u>						
			Low	4		OR 1.36 (1.03-1.79)	37.7%		
			High	4		OR 1.36 (0.94-1.97)	61.7%		
	Zhao 2016 (66)	Non-fatal CVD		10	104,392	OR 1.30 (1.09-1.56)	40%	None	Moderate

			<u>Type of CVD</u>						
			Non-fatal coronary heart disease	5	86,816	OR 1.44 (1.13-1.84)	59%		
			Non-fatal myocardial infarction	5	86,816	OR 1.01 (0.68-1.51)	0%		
	Tehrani 2019 (70)	Non-fatal CVD	<u>Age group of participants (Population based studies)</u>						Low
			Reproductive age group	12	NP	HR 1.429 (1.270-1.607)	73%		
			Menopausal age group	1	NP	HR 1.030 (0.410-2.588)	-		
<b>Fertility Therapy</b>	Dayan 2017 (88)	Fatal and non-fatal CVD		4	1,426,640	HR 0.91 (0.67-1.25)	36.6%	Not assessed	Moderate
<b>Ever Parity versus Nulliparous (Ref)</b>	Wenzhen Li 2018 (90)	Non-fatal CVD		13	3,089,929	RR 1.14 (1.09-1.18)	89.6%	None	Moderate
			<u>CVD type</u>						
			Coronary heart disease	7	NP	RR 1.14 (1.12-1.16)	51.1%		
			Ischaemic heart disease	2	NP	RR 1.23 (1.08-1.39)	0%		
			Stroke	4	NP	RR 1.08 (1.05-1.10)	0%		
			<u>BMI adjusted</u>						
			Yes	9	NP	RR 1.15 (1.10-1.21)	61.2%		
			No	4	NP	RR 1.11 (1.09-1.12)	64.1%		
			<u>Hypertension adjusted</u>						
			Yes	3	NP	RR 1.28 (1.16-1.42)	64.3%		
			No	10	NP	RR 1.11 (1.09-1.12)	51.1%		
			<u>Smoking adjusted</u>						
			Yes	9	NP	RR 1.15 (1.10-1.21)	61.2%		
			No	4	NP	RR 1.11 (1.09-1.12)	64.1%		
			<u>Diabetes adjusted</u>						
			Yes	9	NP	RR 1.15 (1.10-1.21)	61.2%		
			No	4	NP	RR 1.11 (1.09-1.12)	64.1%		
	Haichen Lv 2015 (89)	Fatal CVD		6	994,810	RR 0.79 (0.60-1.06)	90.9%	None	Moderate
<b>Premature ovarian insufficiency</b>	Roeters van Lennep, 2014 (96)	Fatal and non-fatal ischaemic heart disease		7	NP	HR 1.69 (1.29-2.21)	22%	Not assessed	Moderate
		Fatal and non-fatal stroke		7	NP	HR 1.03 (0.88-1.99)	0%		
		Fatal and non-fatal CVD		2	NP	HR 1.61 (1.22-2.12)	0%		

	Tao 2015 (59)	Fatal CVD		7	NP	RR 1.24(0.98-1.58)	0%		Moderate
		Fatal ischaemic heart disease		3	NP	RR 1.48(1.02-2.16)	0%		
<b>Early natural menopause</b>	Tao 2015 (59)	Fatal stroke		4	NP	RR 1.00 (0.86-1.16)	0%		
		Fatal CVD		9	NP	RR 1.10 (0.91-1.13)	29.4%		Moderate
		Fatal ischaemic heart disease		4	NP	RR 0.94 (0.86-1.03)	0%		
		Fatal stroke		5	NP	RR 1.31 (0.78-2.18)	77%		
<b>Early menopause &lt;45 years in comparison to women &gt; 45 years</b>	Muka 2016 (57)	Fatal CVD		5	65,653	RR 1.19 (1.08-1.31)	30%	None	Moderate
		Non-fatal coronary heart disease		5	50,125	RR 1.50 (1.28-1.76)	0%	None	
		Fatal coronary heart disease		6	130,284	RR 1.11 (1.03-1.20)	42%		
		Non-fatal stroke		5	49,246	RR 1.23 (0.98-1.53)	51%		
		Fatal stroke		6	143,833	RR 0.99 (0.92-1.07)	34%		
<b>Onset of menopause at 45-49 years vs women &gt; 50 years</b>	Muka 2016 (57)	Fatal CVD		4	62,995	RR 0.99 (0.92-1.07)	0%	None	Moderate
		Non-fatal coronary heart disease		2	36,483	RR 1.12 (0.95-1.31)	0%		
		Non-fatal stroke		2	41,347	RR 0.95 (0.74-1.23)	0%		
		Fatal coronary heart disease		3	121,444	RR 0.98 (0.93-1.04)	0%		
		Fatal stroke		5	129,041	RR 1.03 (0.91-1.16)	0%		
<b>Menopausal symptoms</b>	Muka 2016 (97)	Fatal and non-fatal coronary heart disease		7		RR 1.14 (0.98-1.34)	79%		Moderate
		Fatal and non-fatal stroke		Single study	60,027	RR 1.14(0.82-1.59)	N/A	None	
			<i>Type of menopausal symptom</i>						
		Fatal and non-fatal coronary heart disease	Vasomotor symptoms	2	70,814	RR 1.28 (1.08-1.52)	0%		

		Fatal and non-fatal coronary heart disease	Non-vasomotor symptoms	5		RR 1.14 (0.98-1.34)	5%		
<b>Adverse pregnancy outcomes</b>									
<b>Miscarriage</b>	Oliver-Williams (98)	Fatal and non-fatal coronary heart disease		8	517,504	OR 1.45 (1.18-1.78)	28.2%	Inconclusive	Moderate
		Fatal and non-fatal stroke		6	NP	OR 1.11 (0.72-1.69)	62.5%	Not assessed	
<b>Recurrent miscarriage</b>		Fatal and non-fatal coronary heart disease		7	NP	OR 1.99 (1.13-3.50)	63.8%	Present; p=0.028	
<b>Stillbirth</b>	Grandi 2019 (60)	Non-fatal CVD		4	NP	OR 1.49 (1.08-2.06)	0%	Not assessed	Moderate
		Fatal CVD		4	1,528,862	OR 2.23 (1.90-2.62)	0%	Not assessed	
<b>Pre-eclampsia</b>	Pensee Wu 2018 (61)	Non-fatal heart failure		4	1,986,285	RR 4.19 (2.09-8.38)	71%	Not assessed	Moderate
		Fatal coronary heart disease		4	677,378	RR 2.10 (1.25-3.51)	89%	Not assessed	
		Fatal stroke		2	NP	RR 1.97 (0.80-4.88)	86%	Not assessed	
		<i>CVD death</i>							
			Follow up time						
			<1 year						
			1-10 years	1	NP	RR 2.30 (1.65-3.20)			
			>10 years	3	NP	RR 2.21 (1.73-2.81)			
	Grandi 2019 (60)	Non-fatal coronary heart disease		9	NP	OR 1.73 (1.46-2.06)	99%	Not assessed	Moderate
		Non-fatal cerebrovascular accident		9	NP	OR 1.73 (1.46-2.06)	60.6%	Not assessed	
			<u>Severity</u>						
			Moderate	16	NP	OR 2.24 (1.72-2.93)	95%	Not assessed	
			Severe	6	2,282,470	OR 2.74 (2.48-3.04)	0%	Not assessed	
<b>Recurrent Pre-eclampsia</b>	Brouwers 2018 (99)	Non-fatal coronary heart disease		2	69,012	RR 2.40 (2.15-2.68)	0%	Not assessed	Moderate
		Non-fatal heart failure		3	61,757	RR 2.88 (2.23-3.72)	27%	Not assessed	
		cerebrovascular accident		2	9,585	RR 1.69 (1.21-2.35)	75%	Not assessed	
<b>Gestational hypertension</b>	Grandi 2019 (60)	Non-fatal cerebrovascular disease		4	61,757	RR 1.83 (0.79-4.22)	98.4%	Not assessed	Moderate
		Non-fatal CVD		9	3,204,633	RR 1.67 (1.28-2.19)	83.9%	Not assessed	

<b>Gestational diabetes mellitus</b>	Kramer 2019 (62)	Non-fatal and fatal CVD		9	5390591	RR 1.98 (1.57-2.50)	80.2%	Not assessed	Moderate
			Restricted to women who did not develop type 2 diabetes mellitus	5	2147236	RR 1.56 (1.04, 2.32)	98%	Not assessed	
	Jing Li 2018 (63)	Non-fatal coronary artery disease		4	3,079,357	RR 2.09 (1.56-2.80)	91.2%	None; p=0.43	Moderate
		Non-fatal stroke		2	1,516,323	RR 1.25 (1.07-1.48)	0%	None	
<b>Placental Abruption</b>	Grandi 2019 (60)	Fatal and non-fatal CVD		7	5,799,266	OR 1.82 (1.42-2.33)	66%	Not assessed	Moderate
<b>Preterm Birth</b>	Pensee Wu 2017 (64)	Non-fatal coronary heart disease		4	2,411,083	RR 1.49 (1.38-1.60)	54%	Not assessed	Moderate
		Fatal coronary heart disease		5	1,459,690	RR 2.11 (1.87-2.36)	0%	Not assessed	
		Stroke		5	1,499,386	RR 1.65 (1.51-1.79)	0%	Not assessed	
		Fatal stroke		2	699030	RR 1.30 (0.94-1.80)	66%	Not assessed	
	Grandi 2019 (60)	Non-fatal CVD		12	NP	OR 1.63 (1.39-1.93)	91.1%	Not assessed	Moderate
		Fatal CVD		4	372,199	OR 1.93 (1.83-2.03)	0%	Not assessed	
	Heida 2014 (102)	Fatal and non-fatal ischaemic heart disease		3	1,936,178	HR 1.38 (1.22-1.57)	74%	Not assessed	Moderate
		Fatal and non-fatal stroke		4	1,173,705	HR 1.71 (1.53-1.91)	0	Not assessed	
		Fatal- and non-fatal CVD		4	2,462,165	HR 2.01 (1.52-2.65)	77%	Not assessed	
<b>Low birth weight</b>	Grandi 2019 (60)	Fatal and non-fatal CVD		4	2,445,956	OR 1.29 (0.91-1.83)	96.5%	Not assessed	Moderate
			Sensitivity analyses	3	NP	OR 1.46 (1.11-1.91)	80.2%	Not assessed	

BMI = body mass index, CVD = cardiovascular disease, HR = hazard ratio, OR = odds ratio, NP = not provided, RR = risk ratio.



Supplementary Table 4. Tabular presentation of findings: Narrative syntheses.

Reproductive factor	Author Year	Outcome	No of participants	Narrative summary Effect estimate (95% CI)	Reviewer's conclusions	Overall AMSTAR 2 rating for Review
<b>Fertility-related factors</b>						
Combined oral contraceptive use in obese women	Horton 2016 (81)	Non- fatal myocardial infarction	2,432	<p><u>Tanis et al.</u>(82)            BMI &lt;27.3 kg/m<sup>2</sup> not on combined oral contraceptive: Ref            BMI &lt;27.3 kg/m<sup>2</sup> on combined oral contraceptive: OR 2.4 (1.6-3.5)            BMI ≥27.3 kg/m<sup>2</sup> not on combined oral contraceptive: OR 3.4 (2.2-5.3)            BMI ≥27.3 kg/m<sup>2</sup> on combined oral contraceptive: OR 5.1 (2.7-9.6)</p> <p><u>Sidney et al.</u>(166)            BMI ≥27.3 kg/m<sup>2</sup> not on combined oral contraceptive: Ref            BMI ≥27.3 kg/m<sup>2</sup> on combined oral contraceptive: OR 0.88 (0.33-2.36)</p>	Evidence that combined hormonal contraceptive use modifies risk of myocardial infarction among obese women is inconclusive.	Low
		Non-fatal stroke	2,683	<p><u>Kemmerman et al.</u>(167)            BMI &lt;27.3 kg/m<sup>2</sup> no combined oral contraceptive: Ref            BMI &lt;27.3 kg/m<sup>2</sup> on combined oral contraceptive: OR 2.2 (1.5-3.0)            BMI ≥ 27.3 kg/m<sup>2</sup> no combined oral contraceptive: OR 1.2 (0.7-2.2)            BMI ≥27.3 kg/m<sup>2</sup> on combined oral contraceptive: OR 4.6 (2.4-8.9)</p> <p><u>Schwartz et al.</u>(168)            BMI ≥ 27.3 kg/m<sup>2</sup> no combined oral contraceptive: Ref            BMI ≥27.3 kg/m<sup>2</sup> on combined oral contraceptive: ischemic stroke pooled OR 0.59 (0.16-2.12); haemorrhagic stroke pooled OR 1.06 (0.35-3.21)</p>	Evidence that combined hormonal contraceptive use modifies risk of stroke among obese women is inconclusive.	

Oestrogen-containing contraceptives use among women with migraine	Sheikh Hu 2016 (74)	Stroke	NP	<p><u>Oestrogen contraceptives in migraine</u> OR provided by 6 studies, point estimates ranged from 2.08-16.9. Studies were small and 95% CIs wide.</p> <p><u>Migraine with aura and on combined oral contraceptive Champaloux(169)</u> Compared to neither migraine nor contraceptive use: OR 6.1 (3.1-12.1) for migraine with aura on combined oral contraceptive; OR 1.8 (1.1-2.9) for migraine without aura on combined oral contraceptive</p>	<p>An increased risk of stroke among women with migraine and on oestrogen contraceptives.</p> <p>Studies on stroke risk among women with migraine with aura are required.</p>	Moderate
Combined non-oral hormonal contraceptives	Tepper 2016 (79)	Myocardial infarction stroke		<p><u>Jick et al.(170)</u> Acute myocardial infarction crude IRR 0.2 (0.004-1.7) Stroke crude IRR 1.2 (0.41-3.4)</p> <p><u>Dore et al (171)</u> Acute myocardial infarction OR 1.6 (0.4-6.5) Ischaemic stroke OR 0.8 (0.2-4.5)</p>	No increased risk of arteriothrombotic events (myocardial infarction and stroke) was observed among women using the patch compared to those using norgestimate combined oral contraceptives.	Moderate
Combined Hormonal contraceptives among women with dyslipidaemia	Dragoman 2015 (80)	Myocardial infarction Cerebrovascular accident	820,910	<p><u>Tanis et al (82)</u> Risk of myocardial infarction: Combined oral contraceptive non-use and hypercholesterolemia: OR 3.3 (1.6-6.8) Combined oral contraceptive use and hypercholesterolemia: OR 24.7 (5.6-108.5)</p> <p><u>Gronich et al.(83)</u> Risk of cerebrovascular accident: Combined oral contraceptive non-use and hypercholesterolemia: Ref Combined oral contraceptive use and hypercholesterolemia: crude IRR 1.76 (1.51-2.06)</p>	Evidence from observational studies of low quality suggests that myocardial infarction risk may be increased among combined oral contraceptive users with dyslipidaemia. In the unadjusted estimates combined oral contraceptive use among women with dyslipidaemia linked to an increased risk of stroke.	Moderate
Combined oral contraceptive use among women with hypertension	Curtis 2006 (84)	Myocardial infarction	3,523	<p><u>Croft and Hannaford(172)</u> No hypertension/no oral contraceptive use: Ref No hypertension/oral contraceptive use: OR 2.0 (1.1-3.9) Hypertension/no oral contraceptive use: OR 5.4 (2.6-11.2) Hypertension/oral contraceptive use: OR 7.7 (1.2-49.2)</p> <p><u>Tanis et al (82)</u></p>	Hypertensive users on oral contraceptive are at higher risk of myocardial infarction compared to normotensive non-oral contraceptive users.	Low

				<p>No hypertension/no oral contraceptive use: Ref  No hypertension/oral contraceptive use: OR 2.1 (1.5-3.1)  Hypertension/no oral contraceptive use: OR 5.1 (2.9-8.8)  Hypertension/oral contraceptive use: OR 6.1 (3.1-12.1)</p> <p><u>D'Avanzo(173)</u>  Never use of oral contraceptive normotensive: Ref  Hypertensive and oral contraceptive use: OR 28.4 (6.7-120.1)</p> <p><u>WHO developing countries(174)</u>  No hypertension/no oral contraceptive: Ref  No hypertension/oral contraceptive use: OR 3.66 (1.81-7.39)  Hypertension/no oral contraceptive use: OR, 9.52 (4.90-18.5)  Hypertension/oral contraceptive use: OR 15.3 (3.27-71.6)</p> <p><u>WHO European countries(174)</u>  No hypertension/no oral contraceptive: Ref  No hypertension/oral contraceptive use OR 3.85 (1.88-7.89)  Hypertension/no oral contraceptive: OR 5.43 (2.39-12.4)  Hypertension/oral contraceptive use: OR 68.1 (6.18-751)</p>		
	Curtis 2006 (84)	Stroke	NP	<p><u>Collaborative group (175)</u>  Hypertension/oral contraceptive use:  Borderline hypertension: OR 5.2 (2.3-12.0)  Moderate hypertension: OR 8.9 (3.5-22.8)  Severe hypertension: OR 13.6 (4.8-38.6)</p> <p><u>Lidegaard et al:(176–178)</u>  OR for hypertension 3.1 (p&lt;0.001)  OR for combined oral contraceptive 1.8 (1.1-2.9)</p> <p><u>WHO Developing countries(174)</u>  No hypertension/no oral contraceptive: Ref  No hypertension/oral contraceptive use: OR 2.73 (1.97-3.77)  Hypertension/no oral contraceptive use: OR 7.70 (5.36-11)  Hypertension/oral contraceptive use: OR 14.5 (5.36-39.0)</p> <p><u>WHO European countries(174)</u>  Hypertension/no oral contraceptive use: Ref</p>	Hypertensive users on oral contraceptive are at higher risk of stroke compared to normotensive non-oral contraceptive users.	Low

				<p>No hypertension/oral contraceptive use: OR 2.71 (1.47-4.99)  Hypertension/no oral contraceptive use: OR 4.59 (2.39-8.82)  Hypertension/oral contraceptive use: OR 10.7 (2.04-56.6)</p> <p><u>Heinemann et al.</u>(179)  No hypertension/no oral contraceptive use: Ref  Hypertension/oral contraceptive use: OR 3.92 (2.24-6.97)  Hypertension/no oral contraceptive use: OR 9.6 (3.25-30.57)  Hypertension/oral contraceptive use: OR 3.07 (0.85-11.05)</p> <p><u>Lidegaard et al 2002</u> (180)  30-40 µg of ethinyl estradiol combined oral contraceptive use OR 1.6 (1.3-2.0)  Hypertension OR 5.0 (3.3-7.4)</p> <p><u>Kemmeren et al</u> (167)  No hypertension/no oral contraceptive use: Ref  No hypertension/no oral contraceptive: OR 2.7(1.8-4.0)  Hypertension/no oral contraceptive use: OR 6.8 (3.7-12.2)  Hypertension/oral contraceptive use: OR 7.6 (3.5-26.3)</p> <p><u>Siritho et al.</u> (181)  Oral contraceptive use: OR 1.76 (0.86-3.61)  OR for hypertension: 2.18 (1.22-3.91)</p> <p><u>Nightingale and Farmer</u>(182)  Oral contraceptive use: OR 2.30 (1.15-4.59)  OR for hypertension: 4.61 (2.71-7.84)</p>		
Polycystic ovary syndrome	Bolijn 2017 (87)	Heart Failure	308	<u>Cheang et al.</u> (86) A cross-sectional study; did not find an increased risk of heart failure among women with polycystic ovary syndrome: OR 3.24 (0.53–19.94). The number of heart failure cases was small (n=5).	The number of heart failure events was small (n=5). Evidence was derived from a study of low methodological quality. Longitudinal studies of high quality recommended.	Moderate
Breastfeeding	Nguyen 2017 (91)	Non-fatal CVD	229,007	<u>Stuebe et al.</u> (92) Outcome: Self-reported myocardial infarction Exposure: Lifetime duration of breastfeeding in months No breastfeeding: Ref	Lifetime duration of breastfeeding >23 months linked to lower incidence of CVD.	Moderate

				<p>&gt;11–23 months: HR 0.93 (0.8-1.07) &gt;23 months: HR 0.77 (0.62-0.94)</p> <p><u>Schwarz et al.</u>(93) Outcome: Self-reported incidence of CVD Exposure: lactation duration in months Never breastfed: Ref 1–6 months: HR 1.03 (0.98, 1.08) 7–12 months: HR 0.97 (0.90, 1.04) 13–23 months: HR 0.98 (0.91-1.05) &gt;24 months: HR 0.93 (0.85-1.02)</p>		
Breastfeeding	Nguyen 2017 (91)	Fatal CVD	281,383	<p><u>Gallagher et al.</u>(94) Lactation duration, never (Ref) versus ever, in months: Ischaemic heart disease mortality: &lt;6 months: HR 0.70 (0.42-1.16) 7–12 months: HR 0.50 (0.33-0.76) 13–24 months: HR 0.67 (0.46-0.97) 25–36 months: HR 0.53 (0.36-0.79) 37–48 months: HR 0.71 (0.48-1.06) &gt;49 months: HR 0.78 (0.53-1.14)</p> <p>Ischaemic stroke: &lt;6 months: HR 1.02 (0.63-1.66) 7–12 months: HR 1.05 (0.72-1.54) 13–months: HR 0.90 (0.62-1.31) 25–36 months: HR 1.15 (0.79-1.67) 37–48 months: HR 1.21 (0.83-1.77) &gt;49 months: HR 1.20 (0.84-1.72)</p> <p>Hemorrhagic stroke: &lt;6 months: HR 0.84 (0.63-1.12) 7–12 months: HR 0.98 (0.79-1.22) 13–months: HR 1.01 (0.82-1.24) 25–36 months: HR 0.88 (0.71-1.09) 37–48 months: HR 1.02 (0.82-1.28) &gt;49 months: HR 1.05 (0.84-1.30)</p> <p><u>Natland et al.</u>(95)</p>	<p>Evidence suggests breastfeeding linked to lower mortality from ischaemic heart disease.</p> <p>No association was observed between lactation duration and mortality from ischaemic or hemorrhagic stroke.</p> <p>Norwegian women aged &lt;65 years and who never breastfeed</p>	Moderate

				<p>In Women &lt;65 years  Ever lactated: Ref  Nulliparous: HR 0.41 (0.16-1.04)  Never lactated: HR 2.86 (1.51-5.39)</p> <p>In women over &gt;65 years  Ever lactated: Ref  Nulliparous: HR 1.20 (1.0-1.44)  Never lactated: HR 1.11 (0.77-1.69)</p>	<p>were at a three-fold higher risk of mortality from CVD.</p> <p>No linear relationship was noted. Instead, evidence of a U-shaped association was observed between categories of lactation duration.</p>	
Early natural menopause	Bolijn 2017 (87)	Non-fatal heart failure	25,230	<p><u>Ebong et al.</u>(183)  Self-report of early menopause (&lt;45 years): HR 1.66 (1.01-2.73)</p> <p><u>Rahman et al.</u>(184)  Age at menopause:  50–54 years: Ref  40–45 years: HR 1.36 (1.16-1.60)  46–49 years: HR 1.13 (1.02-1.26)  ≥55 years: HR 1.03 (0.93-1.14)</p>	Two studies of good methodological quality suggested that early menopause is associated with heart failure risk.	Moderate
<b>Adverse pregnancy outcomes</b>						
Miscarriage	Grandi 2019 (60)	Fatal and non-fatal CVD		The effect estimates for 6 cohort studies (103,185–189) ranged from 0.91–2.69, while 1 case-control study(190) reported effect estimates of 0.83-1.17.	The definition of miscarriage was different across studies. The effect estimates varied across studies with some suggesting increased risk while others suggesting no risk.	Moderate
Gestational diabetes	Bolijn 2017 (87)	Non-fatal Heart failure	853,558	<p><u>Freibet et al.</u>(100)  HR 0.7 (0.3-1.9)</p> <p><u>Savitz et al.</u>(101)  OR 1.5 (1.0-2.2)</p>	Gestational diabetes was not associated with heart failure. Further research needed to clarify the association.	Moderate
Recurrent Preterm birth	Robbins 2014 (65)	Fatal and non-fatal CVD		<p><u>Catov et al.</u>(165)  CVD HR 1.4 (1.2-1.6)  Ischaemic heart disease HR 1.8(1.4-2.3)  Stroke HR 1.8 (1.4-2.2)  CVD death HR 2.1 (1.2-3.7)</p>		Moderate

				<u>Lykke et al.</u> (191) Ischaemic heart disease death HR 1.4 (1.0-1.8)		
Recurrent preterm birth	Bolijn (87)	Heart failure	1,322,615	<u>Freibert et al.</u> (100) No association between preterm delivery and heart failure risk; OR not provided.  <u>Lykke et al.</u> (191) Any preterm delivery was associated with heart failure risk; OR not provided.		Moderate
Small for gestational age	Grandi 2019 (60)	Fatal and non-fatal CVD	4,113,820	Effects estimates of ten studies ranged from 1.09-3.50.	Due to heterogeneity in exposure definition pooling was not possible. Overall small for gestational age was associated with an increased risk of CVD.	Moderate

BMI = body mass index, CVD = cardiovascular disease, HR = hazard ratio, IRR = incidence rate ratio, NP = not provided, OR = odds ratio, Ref = Reference, WHO = World Health Organization.

**Supplementary Table 5. General study characteristic for studies evaluating the association between breastfeeding and maternal risk of cardiovascular disease.**

Study ID/ (Setting)	Objective	Study design	Exposure/ comparator	Outcome	Effect size (95% CI)	Covariates	NOS quality
Stuebe 2009 (92) (USA)	Evaluate the association between lactation duration and maternal incident myocardial infarction	Prospective cohort Study (1986-2002) of 89326 parous women in the Nurses' health study	Cumulative lactation duration versus never breastfeeding	Non-fatal Myocardial infarction	Never breastfed: Ref >0-3 months: HR 1.01 (0.91-1.11) >3-6 months: HR 1 (0.88-1.14) >6-11 months: HR 1.02 (0.88-1.18) >11-23 months: HR 0.93 (0.8-1.07) >23 months: HR 0.77 (0.62-0.94)	Age, parity, history of stillbirth, BMI at age 18, birth weight of subject, parental history of myocardial infarction before age 60, diet quintile, physical activity, smoking, menopausal status, and use of aspirin, alcohol, multivitamins, and postmenopausal hormones	High
Schwarz 2009 (93) (USA)	To evaluate the dose-response relationship between the cumulative number of months women lactated and postmenopausal risk factors for cardiovascular disease	Cohort study of 139,681 postmenopausal women with > 1 live birth.	Lactation duration in months versus never breastfed.	Non-fatal composite CVD	Never breastfed: Ref 1-6 months: HR 1.03 (0.98-1.08) 7-12 months: HR 0.97 (0.90-1.04) 13-23 months: HR 0.98 (0.91-1.05) >24 months: HR 0.93 (0.85-1.02)	Age, race, parity, age at menopause, education, income, family history (of diabetes mellitus, myocardial infarction or stroke), physical activity, energy, cholesterol, fat, fibre, and sodium intakes, tobacco history, hormone replacement therapy use, aspirin use, multivitamin use.	High
Gallagher 2011 (94) (China)	Examine the association between a wide range of reproductive factors and CVD	A cohort (1989-2000) of 259,494 non-smoking female textile workers in Shanghai, China	Breastfeeding duration in months versus parous women who never breastfed	Fatal coronary heart disease	Never (with live birth): Ref <6 months: HR 0.70 (0.42-1.16) 7-12 months: HR 0.50 (0.33-0.76) 13- 24 months: HR 0.67 (0.46-0.97) 25-36 months: HR 0.53 (0.36-0.79) 37-48 months: HR 0.71 (0.48-1.06) ≥49 months: HR 0.78 (0.53-1.14)  Never (with live birth): Ref	Age, number of live births	Medium



				Fatal ischaemic stroke	<6 months: HR 1.02 (0.63-1.66) 7-12 months: HR 1.05 (0.72-1.54) 13- 24 months: HR 0.90 (0.62-1.31) 25-36 months: HR 1.15 (0.79-1.67) 37-48 months: HR 1.21 (0.83-1.77) ≥49 months: HR 1.20 (0.84-1.72)		
				Fatal haemorrhagic stroke	Never (with live birth): Ref <6 months: HR 0.84 (0.63-1.12) 7-12 months: HR 0.98 (0.79-1.22) 13-24 months: HR 1.01 (0.82-1.24) 25-36 months: HR 0.88 (0.71-1.09) 37-48 months: HR 1.02 (0.82-1.28) >49 months: HR 1.05 (0.84-1.30)		
Natland Fagerhaug 2013 (95) (Norway)	To investigate the association between lifetime lactation duration and cardiovascular disease mortality	A prospective cohort (1995-2010) of 21,889 women aged 30 to 85 years		Fatal composite CVD	<u>Younger women (under 65 years)</u> Ever lactated: Ref Never lactated: HR 2.86 (1.51-5.39) Nulliparous: HR 0.41 (0.16-1.04)  <u>Older women (over 65 years)</u> Ever lactated: Ref Never lactated: HR 1.11 (0.77-1.69) Nulliparous: HR 1.20 (1.00-1.44)	Age, smoking status, physical activity, education, marital status and parity	High
Nguyen* 2019 (106) (New South wales Australia)	Examine the association between breastfeeding and CVD hospitalization and death	Cohort study (2006-2014) of 100864 middle-aged (≥45 years) and parous women	Self-reported breastfeeding, never versus ever and average breastfeeding duration per child	Non-fatal composite CVD  Fatal CVD  Non-fatal CVD	<u>Breastfeeding history</u> Parous never breastfed: Ref Parous ever breastfed: HR 0.86 (0.78-0.96)  Parous never breastfed: Ref Parous ever breastfed: HR 0.66 (0.49-0.89)  <u>Average duration of breastfeeding per child</u> Never breastfed: Ref >0-6 months: HR 0.86 (0.78-0.96) >6-12 months: HR 0.85(0.75-0.97) >12 months: HR 0.89 (0.71-1.12)  Never breastfed: Ref >0-6 months: HR 0.69 (0.51-0.94) >6-12 months: HR 0.59 (0.41-0.84)	age, country of birth, educational level, marital status, area-level socio-economic status, BMI, smoking status, alcohol intake, physical activity multivitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes mellitus, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes	High

				Fatal CVD	> 12 months: HR 0.67 (0.28-1.57)	mellitus/recent treatment for diabetes mellitus	
Rajaei* 2019 (Stanford-USA) (107)	To evaluate the association between lactation duration and risk of developing non-fatal coronary artery disease	Hospital case-control study of 643 nulliparous and multiparous women aged 40-65 years	Exposure divided into two categories 1. Single longest duration of breastfeeding of all-live births 2. Total lifetime duration of breastfeeding	Non-fatal Coronary artery disease	<p><u>1. Single highest ever duration of breastfeeding across all live births</u> Never child/pregnant: Ref 1+ child, never breastfed: OR 1.79 (0.81-3.94) 1-4 months: OR 2.78 (1.43-5.39) 5-9 months: OR 1.04 (0.5-2.15) 10-18 months: OR 1.22 (0.63-2.37) 19+ months: OR 1.72 (0.69-4.26)</p> <p>Child and never breastfed: Ref 1-4 months: OR 1.57 (0.63-3.92) 5-9 months: OR 0.53 (0.2-1.39) 10-18 months: OR 0.71 (0.29-1.76) ≥19 months: OR 0.89 (0.29-2.76)</p> <p>1-4 months: Ref 5-9 months: OR 0.33 (0.14-0.8) 10-18 months: OR 0.47 (0.21-1.06) ≥19 months: OR 0.57 (0.2-1.65)</p> <p><u>2. Total (summed over all live births) lifetime duration of breastfeeding</u> Never child/pregnant: Ref 1+ child; never breastfed: OR 1.78 (0.81-3.9) 0-7 months: OR 2.16 (1.14-4.09) 8-15.5 months: OR 1.7 (0.85-3.41) 16-26 months: OR 1.03 (0.47-2.26) 26.5+ months: OR 1.24 (0.57-2.7)</p> <p>Never breastfed: Ref 0-7 months: OR 1.18 (0.48-2.86) 8-15.5 months: OR 0.88 (0.35-2.25) 16-26 months: OR 0.59 (0.21-1.63) 26.5 months: OR 0.71 (0.26-1.93)</p> <p>0-7 months: Ref</p>	Adjusted for age, race, BMI, tobacco use, hypertension, systolic blood pressure, hyperlipidaemia, total cholesterol, HDL, triglycerides, and diabetes.	Low

					8-15.5 months: OR 0.78 (0.34 -1.76) 16-26 months: OR 0.45 (0.17-1.16) ≥26.5 months: OR 0.62 (0.26-1.15)		
Jacobson* 2018 (108) USA	To assess the association between breastfeeding and risk of stroke and whether the association differs by ethnicity and race	Cohort study (1993-2010) 80191 parous women from the women's health observational study.	Never breastfeeding (< 1month) versus Ever-breastfeeding	Non-fatal Stroke	<u>Ever Breastfed</u> No: Ref Yes: HR 0.77 (0.70-0.84)  <u>Duration of breastfeeding</u> Never: Ref 1-6 months: HR 0.81 (0.74-0.90) 7-12 months: HR 0.75 (0.66-0.85) ≥13 months: HR 0.74 (0.65-0.83)	Adjusted for age, regional centre, extension study inclusion, race/ethnicity, education, parity, age at menarche, family history, exercise at baseline, Healthy Eating Index at baseline, smoking history, body mass index at baseline, and multivitamin use at baseline.	Medium
Kirkegaard* 2018 (109) Denmark	To examine how any, partial, and full breastfeeding duration were associated with maternal risk of hypertension and CVD and how pre-pregnancy BMI and waist circumference influenced the association	Cohort study (1996–2002) of 63260 women with live-born singleton infants	Breastfeeding for less than 4 months vs breastfeeding for > 4months	Non-fatal CVD	<u>Cardiovascular disease risk (18 months- 15 years postpartum):</u> Pre-pregnancy normal/ underweight: < 4 months: Ref 4-10 months: HR 0.68 (0.58-0.80) >10 months: HR 0.61 (0.52-0.73) Pre-pregnancy overweight/ obese: <4 months: Ref 4-10 months: HR 0.79 (0.64-0.98) >10 months: 0.88 (0.71-1.10) <u>Cardiovascular disease risk (7 years- 15 years postpartum):</u> <4 months: Ref 4-10 months: HR 0.77 (0.63-0.94) >10 months: HR 0.77 (0.62-0.96)	Adjusted for age, pre-pregnancy BMI, alcohol intake before the index pregnancy, socio-occupational status, dietary intake, physical activity, smoking, preterm birth, preeclampsia and diabetes during the index pregnancy and parity at 18 months postpartum.	High
Peters 2017* (111) China	To examine the long-term CVD effects of breastfeeding among Asian (Chinese) women)	Cohort study (2004-2016) of 289 573 Chinese women aged 30-79 years at baseline	Ever breastfeeding compared to never breastfeeding among parous women	Non-fatal CVD	<u>Lifetime lactation duration of breastfeeding among parous women</u> Never: HR 1.00 (0.95-1.06) >0-12 months: HR 0.96 (0.93-0.99) 12-24 months: HR 0.97 (0.95-0.99) 24-36 months: HR 0.96 (0.94-0.98) 36-48 months: HR 0.92 (0.89-0.94) >48 months: HR 0.91 (0.88-0.93)	Analyses are stratified by age at risk and study area, and adjusted for level of attained education, household income, smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes.	Medium

				Fatal CVD	Never: 1.00 (0.77 -1.29) >0-12 months: 0.88 (0.74-1.04) 12-24 months: 0.98 (0.87-1.09) 24-36 months: 0.93 (0.85-1.02) 36-48 months: 0.81 (0.74-0.89) >48 months: 0.86 (0.79-0.92)		
				Non-fatal coronary heart disease	Never: HR 1.00 (0.92-1.09) >0-12 months: HR 0.93 (0.89-0.99) 12-24 months: HR 0.92 (0.89-0.96) 24-36 months: HR 0.86 (0.83-0.89) 36-48 months: HR 0.86 (0.82-0.90) >48 months: HR 0.82 (0.79-0.86)		
				Non-fatal stroke	Outcome stroke Never: HR 1.00 (0.93-1.08) >0-12 months: HR 0.93 (0.89-0.97) 12-24 months: HR 0.93 (0.90-0.96) 24-36 months: HR 0.91 (0.88-0.94) 36-48 months: HR 0.86 (0.82-0.89) >48 months: HR 0.85 (0.82-0.89)		
Peters 2016* (110) European cohort	To assess the association between breastfeeding and risk of incident coronary heart disease	Cohort 8044 parous women	Ever breastfeeding compared to never breastfeeding	Non-fatal coronary heart disease	<u>Exposure lifetime duration of breastfeeding among parous women</u> Never breastfed: HR 1.00 (0.75-1.34) 0-3 months: HR 0.73 (0.60-0.89) 3-6 months: HR 0.68 (0.56- 0.83) 6-12 months: HR 0.69 (0.55 -0.87) 12-23 months: HR 0.63 (0.51-0.76) >23 months: HR 0.62 (0.45 -0.86)	Age at study entry and centre; attained education, smoking status, number of live born children (for breastfeeding analyses only); high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.	Medium

BMI = body mass index, CVD = Cardiovascular disease, HDL = high density lipoprotein, HR = hazard ratio, OR = odds ratio, Ref = reference. \* Newly published observational studies

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