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Okoth, Kelvin; Chandan, Joht; Marshall, Tom; Thangaratinam, Shakila; Thomas, G Neil; Nirantharakumar, Krishnarajah; Adderley, Nicola

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Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review

Kelvin Okoth,[1] Joht Singh Chandan,[1] Tom Marshall,[1] Shakila Thangaratinam,[1,2] G Neil Thomas,[1] Krishnarajah Nirantharakumar,[1,3,4] Nicola J Adderley[1]

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[2]Women's Health Research Unit, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[3]Institute of Metabolism and Systems Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
[4]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK

Correspondence to:
K Nirantharakumar
K.Nirantharan@bham.ac.uk
(or @Nirantharakumar on Twitter:
ORCID 0000-0002-6816-1279)

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ABSTRACT

OBJECTIVE

To consolidate evidence from systematic reviews and meta-analyses investigating the association between reproductive factors in women of reproductive age and their subsequent risk of cardiovascular disease.

DESIGN

Umbrella review.

DATA SOURCES

Medline, Embase, and Cochrane databases for systematic reviews and meta-analyses from inception until 31 August 2019.

REVIEW METHODS

Two independent reviewers undertook screening, data extraction, and quality appraisal. The population was women of reproductive age. Exposures were fertility related factors and adverse pregnancy outcomes. Outcome was cardiovascular diseases in women, including ischaemic heart disease, heart failure, peripheral arterial disease, and stroke.

RESULTS

32 reviews were included, evaluating multiple risk factors over an average follow-up period of 7-10 years. All except three reviews were of moderate quality. A narrative evidence synthesis with forest plots and tabular presentations was performed. Associations for composite cardiovascular disease were: twofold for pre-eclampsia, stillbirth, and preterm birth; 1.5-1.9-fold for gestational hypertension, placental abruption, gestational diabetes, and premature ovarian insufficiency; and less than 1.5-fold for early menarche, polycystic ovary syndrome, ever parity, and early menopause. A longer length of breastfeeding was associated with a reduced risk of cardiovascular disease. The associations for ischaemic heart disease were twofold or greater for pre-eclampsia, recurrent pre-eclampsia, gestational diabetes, and preterm birth; 1.5-1.9-fold for current use of combined oral contraceptives (oestrogen and progesterone), recurrent miscarriage, premature ovarian insufficiency, and early menopause; and less than 1.5-fold for miscarriage, polycystic ovary syndrome, and menopausal symptoms. For stroke outcomes, the associations were twofold or more for current use of any oral contraceptive (combined oral contraceptives or progesterone only pill), pre-eclampsia, and recurrent pre-eclampsia; 1.5-1.9-fold for current use of combined oral contraceptives, gestational diabetes, and preterm birth; and less than 1.5-fold for polycystic ovary syndrome. The association for heart failure was fourfold for pre-eclampsia. No association was found between cardiovascular disease outcomes and current use of progesterone only contraceptives, use of non-oral hormonal contraceptive agents, or fertility treatment.

CONCLUSIONS

From menarche to menopause, reproductive factors were associated with cardiovascular disease in women. In this review, presenting absolute numbers on the scale of the problem was not feasible; however, if these associations are causal, they could account for a large proportion of unexplained risk of cardiovascular disease in women, and the risk might be modifiable. Identifying reproductive risk factors at an early stage in the life of women might facilitate the initiation of strategies to modify potential risks. Policy makers should consider incorporating reproductive risk factors as part of the assessment of cardiovascular risk in clinical guidelines.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42019120076.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Risk factors specific to women are associated with cardiovascular disease

Individual reviews assessing the implications of these risk factors for cardiovascular disease have been published

Clarity on the quality of the evidence is lacking and on how the findings can be translated into public health and clinical practice

WHAT THIS STUDY ADDS

This study provides a comprehensive list of factors related to reproduction and adverse pregnancy outcomes and their association with cardiovascular disease

The review provides clarity on the quality of the evidence, identifies gaps in evidence and practice, and provides recommendations that could be incorporated into guidelines

Introduction

Globally, one third, or 17.9 million, of total annual deaths are attributable to cardiovascular disease.[1] The incidence of cardiovascular disease has declined since the middle of the last century, but less so in women than in men. In developed countries,[2-4] the incidence of cardiovascular disease has declined in older age groups (≥55), but has stagnated or increased in adults aged less than 55.[3 5] For instance, in the United States, the proportion of hospital admissions for acute myocardial infarction for adults aged less than 55 rose from 27% between 1995 and 1999 to 32% between 2010 and 2014.[6] The greatest increases were recorded in women aged 35-54.[6] In Western Australia, between 1996 and 2007, in adults aged 35-54, hospital admissions for acute myocardial infarctions increased by 4% in women but decreased by 0.2% in men.[4] Other temporal trend analyses have recorded similar increases in women aged 30-54.[6-9]

Although many commonalities exist, several differences between men and women in terms of risk factors for cardiovascular disease are apparent. Traditional risk factors for cardiovascular disease, such as smoking and diabetes, affect women more than men.[10 11] Beyond these traditional risk factors, risk factors specific to women, such as adverse pregnancy outcomes and fertility complications, are under recognised.[12] Women experiencing adverse pregnancy outcomes and issues related to fertility have been shown to often have early manifestations of vascular changes. Endothelial dysfunction has been shown to be prevalent in women with a history of pre-eclampsia and recurrent pregnancy loss, and could remain beyond pregnancy complications, predisposing these women to further vascular complications and serving as a prognostic marker for future cardiovascular disease.[13] Biochemical risk factors for cardiovascular disease, including raised concentrations of cholesterol, glucose, and triglycerides, have been shown to persist many years after a hypertensive disorder of pregnancy.[14] A better understanding of associations with these risk factors could be explored in future research to identify areas of modifiable risk in women to reduce their long term risk of cardiovascular disease.

In developed countries, up to a third of parous women experience one or more adverse pregnancy outcomes,[15] including hypertensive disorders of pregnancy, gestational diabetes mellitus, placental abruption, and low birth weight and preterm births.[16] Reproductive risk factors are not limited to the obstetric period. Globally, up to 10% of women are diagnosed with secondary infertility.[17] Common causes of secondary infertility, including polycystic ovary syndrome, premature ovarian insufficiency, endometriosis, and pelvic inflammatory disease, have been linked to an increased risk of cardiovascular disease.[18-20] Also, early age at menarche, early menopause, and use of hormonal contraceptive agents are associated with risk of cardiovascular disease.[21]

In the past three decades, the prevalence of adverse pregnancy outcomes has increased in some developed countries.[22-25] On average, young women could develop cardiovascular disease events as early as a decade after experiencing an adverse pregnancy outcome.[26 27] Young women who develop acute coronary syndromes have longer stays in hospital after admission, higher readmission rates, and higher mortality than men.[7 28] Moreover, women with pre-eclampsia have six times the risk of readmission for acute coronary syndromes at one year and tend to present with a more serious type of myocardial infarction than women without pre-eclampsia.[29] Prediction models for traditional risk factors for cardiovascular disease are less optimal in young adults.[30 31] Also, only 49% of primary care physicians in the US said they were confident in the assessment of the risk of cardiovascular disease in women.[32]

Adverse pregnancy outcomes and cardiovascular disease share common (traditional) risk factors, including hypertension, hyperglycaemia, and obesity. In a Norwegian cohort study, blood pressure and body mass index were linked to 77% of the excess risk of cardiovascular disease in women with hypertensive disorders of pregnancy.[33] Up to 15% of the risk of coronary heart disease in young women (aged <65) could not be accounted for by traditional risk factors.[34]

Several systematic reviews have looked at risk factors specific to women and cardiovascular disease but they evaluated different risk factors and different outcomes. An umbrella review is a review of existing systematic reviews and meta-analyses.[35]

The aim of the study was to conduct an umbrella review of systematic reviews evaluating the association between risk factors specific to women (adverse pregnancy outcomes and issues related to fertility) and cardiovascular disease outcomes. This umbrella review will provide decision makers with a consolidated source of high quality studies on this subject. This review will help in developing care pathways which consider a broader range of factors specific to women than are currently considered, in particular those risk factors that have the potential to be modified to reduce the risk of cardiovascular disease in women at high risk (such as those with pre-eclampsia, gestational diabetes, and polycystic ovary syndrome).[36-38] The results of this review are presented by the exposure of interest (over the life course of women) and by cardiovascular outcome.

Methods

An umbrella review is a narrative compilation of evidence for several related clinical questions from multiple systematic reviews and meta-analyses into one usable document with text, tables, and graphics. It aims to examine what is known and not known, and then to propose recommendations for practice and research.[39]

Objective, population, exposures, and comparator

In this review, we explored reproductive factors in women and their association with cardiovascular disease. The umbrella review followed the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the protocol was registered in PROSPERO (registration No CRD42019120076). The population included women of reproductive age.

Exposures were identified through a scoping search and consensus with an expert panel (clinicians and epidemiologists). The scoping search included search terms for women, cardiovascular disease, and risk factors, to identify relevant reproductive risk factors. These risk factors were related to fertility and adverse pregnancy outcomes. Factors related to fertility included: age at menarche; age at first pregnancy; age at first birth; early natural menopause; premature ovarian insufficiency; polycystic ovary syndrome; endometriosis; pelvic inflammatory disease; parity; gravidity; breastfeeding; use of hormonal contraceptive drugs; and fertility treatment. Adverse pregnancy outcomes included: pregnancy loss (miscarriage

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and stillbirth); hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension); low birth weight; small for gestational age; gestational diabetes; preterm birth; and placental abruption. The comparator group included women of reproductive age without the reproductive factor of interest (that is, controls or unexposed women).

Outcomes

Outcomes included: ischaemic heart disease; angina; myocardial infarction; coronary artery disease; cerebrovascular accident, including stroke and transient ischaemic attack; heart failure; peripheral arterial disease; and composite cardiovascular disease (ischaemic heart disease, cerebrovascular accident, heart failure, and peripheral arterial disease).

Study design

Systematic reviews or meta-analyses were included. A study qualified as a systematic review or meta-analysis if, at a minimum: it described the conduct of the systematic review in adequate detail; an attempt was made to identify all of the relevant primary studies in at least one database and a search strategy was provided; and it performed a quality appraisal of the primary studies included.[40]

Excluded were guidelines, narrative reviews, literature reviews, genetic studies, reviews looking at atherosclerosis or venous thromboembolism as an outcome, and reviews assessing the association between hormonal replacement treatment and cardiovascular disease.

Search strategy

Medline, Embase, and the Cochrane Database of Systematic Reviews were searched from inception until 31 August 2019 without language restrictions. The search strategy was developed around the key terms: menarche, OR hormonal contraceptives, OR polycystic ovary syndrome, OR menopause, OR endometriosis, OR hypertensive disorders of pregnancy, OR gestational diabetes, OR miscarriage, OR stillbirth, OR placental abruption, OR low birth weight, OR preterm birth, AND cardiovascular disease. The results were limited to systematic reviews and meta-analyses with a search filter.[41] Reference lists of eligible reviews and meta-analyses were searched for additional citations. Appendix 1 provides a detailed search strategy for the Medline database. This strategy was adapted for searching Embase and the Cochrane Database of Systematic Reviews.

Study selection and data extraction

Two reviewers (KO and JSC) independently carried out the study selection and data extraction from the eligible studies. Data extracted included: author, year of publication, number of participants, number and type of studies included, appraisal instrument used, method of analysis, outcomes assessed, heterogeneity, and findings. The study used the data extraction form recommended by the Joanna Briggs Institute (appendix 2).[42]

Quality assessment

The online AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) checklist was used to assess methodological quality and assign an overall rating for the reviews included.[43] Two reviewers (KO and JSC) rated the methodological quality of the reviews with the AMSTAR 2 quality appraisal instrument.[44] In the case of disagreements and failed consensus, a decision was reached by consulting a third reviewer (NJA).

The AMSTAR 2 quality assessment tool is a 16 item or domain checklist. Seven of these items are considered critical. Shortcomings in any of the critical domains could affect the overall validity of a review. The domains considered critical are: registration of the protocol before starting the review; conduct of an adequate search of the literature; providing justification for the exclusion of individual studies; satisfactory assessment of risk of bias in the studies included in the review; use of appropriate statistical methods in performing a meta-analysis; accounting for risk of bias when interpreting the results; and evaluation of the presence and effect of publication bias.[44]

Overlapping and outdated reviews

Associations assessed in two or more reviews overlapped if they evaluated the same exposure and outcome.[45] Incorporating results from reviews with overlapping associations could lead to the inclusion of primary studies more than once and result in biased findings and estimates.[46 47] Also, up to 50% of published systematic reviews are out of date after 5.5 years.[48] Reviews on cardiovascular disease topics have a shorter duration of currency (three years).[48] We categorised overlapping systematic reviews as outdated (reviews older than five years or published before 2013) and contemporary (reviews published after 2013). Overlapping reviews that were out of date were excluded at the full text screening stage.

For contemporary reviews found to have overlapping associations (that is, investigating the same exposure and outcome), a graphical cross tabulation (citation matrix) of the overlapping systematic reviews (in columns) and the included primary studies (in rows) was generated.[49] A citation matrix allows the degree of overlap to be quantified with a measure known as the corrected covered area (CCA).[45] CCA, expressed as a percentage, is calculated as (N−r)/(rc−r), where N is the number of publications included in evidence synthesis (or the number of ticked boxes in the citation matrix), r is the number of rows, and c is the number of columns. Overlap is categorised as very high (CCA >15%), high (CCA 11-15%), moderate (CCA 6-10%), or slight (CCA 0-5%).[45] CCA is a validated method of quantifying the degree of overlap between two or more reviews, and helps the decision process on how to deal with overlap when it is present.

All non-overlapping systematic reviews that met the inclusion criteria (Cochrane and non-Cochrane) were included in the analysis. Appendix 3 shows the citation matrices for all studies with some degree of overlap. Overlap between reviews was managed as follows:

- Where overlap involved evidence synthesis from Cochrane and non-Cochrane reviews, the Cochrane review was selected in preference.[50] A recent study examining the effect of different inclusion decisions on the comprehensiveness and complexity of overviews of reviews for healthcare interventions concluded that selecting the Cochrane review resulted in the least amount of data loss; also, Cochrane reviews were generally higher quality and tended to be more recent.[51]
- Where a high degree of overlap (CCA ≥11%) between two or more non-Cochrane reviews was found, preference was given to the review that (in hierarchical order): had the highest rating, and at a minimum was rated as moderate quality, assessed with the AMSTAR 2 quality assessment tool; was most recent; supplied pooled effect estimates or had conducted a meta-analysis; and had the highest number of studies or participants.[50]
- Where a slight or moderate degree of overlap (CCA ≤10%) was found, both reviews were retained, and the findings compared.

Data synthesis

Systematic reviews and meta-analyses that met the inclusion criteria formed the unit of analysis. Only data available from reviews were presented. Results from reviews were synthesised with a narrative synthesis, with tabular presentation of findings and forest plots for reviews that performed a meta-analysis. Summary tables describing review characteristics and findings were also presented.

Update of eligible reviews

The framework recommended by Garner et al[52] was used to determine whether an update was necessary. An existing review qualified for an update if all of the following were met:

- The review was widely cited and achieved a minimum rating of moderate with the AMSTAR 2 quality appraisal tool.[44] Reviews with low citations or a low quality rating were unsuitable for an update.
- With the key search terms from the search strategy of an existing review, a focused or abbreviated search of primary studies[53] identified newly published studies that met the inclusion criteria of the review.
- The findings from newly published studies would change the conclusion or credibility of the review.

Appendix 4 describes the search strategy used to identify newly published studies. With findings from newly published studies, we evaluated the effect of updating existing reviews which met the above eligibility criteria.[52] As proposed by Chung et al,[53] we relied on statistical methods (for reviews that conducted meta-analyses) and the informed opinion of subject experts (for reviews that did not perform meta-analyses).

In determining whether an original meta-analysis was out of date, newly published studies were sorted by sample size from the largest to the smallest. A fixed effect meta-analysis was then conducted by sequentially pooling (from the largest to the smallest) the effect estimate from newly published studies with the overall effect estimate of the original meta-analysis. The aim of this process was to identify whether a full update of the review was needed. An original meta-analysis was considered out of date if the addition of newly published studies resulted in a change of statistical significance or a change in the relative effect size by at least 50%.

Based on the opinion of subject experts (TM and ST), the reviews that did not perform a meta-analysis were classified as definitely out of date, probably out of date, possibly out of date, and still valid. A review that was ranked definitely out of date or probably out of date was considered a high priority for update.

If an update was considered necessary, the original methods used in the conduct of the existing review were replicated. Appendix 5 summarises the evaluation process for considering reviews for update.[54]

Patient and public involvement

No patients were involved in setting the umbrella review question, in conducting the study, or in interpreting and writing up the results. The umbrella review was unfunded and was used to answer a specific question, where patient and public involvement will take place later in the work. We plan to engage with local policy makers (National Institute for Health and Care Excellence, Royal College of Obstetricians and Gynaecologists, Clinical commissioning groups) and local charities (British Heart Foundation), and to disseminate the research through social media (twitter), a press release from the Institute of Applied Health Research, University of Birmingham, and sharing of the research findings at relevant conferences.

Results

Literature search

The search retrieved 11 345 articles. After removal of duplicates, and screening of titles and abstracts, 88 articles qualified for full text screening. Preliminary assessment of outdated overlapping reviews resulted in exclusion of 21 reviews. Applying the inclusion-exclusion criteria identified 39 reviews for the umbrella review. Figure 1 summarises the study selection process. Appendix 6 provides the list of excluded studies, with reason for exclusion, after screening of the titles and abstracts.

Methodological quality

Thirty two reviews were rated as moderate in quality and seven reviews were rated as low in quality (appendix 7). All seven low quality reviews did not

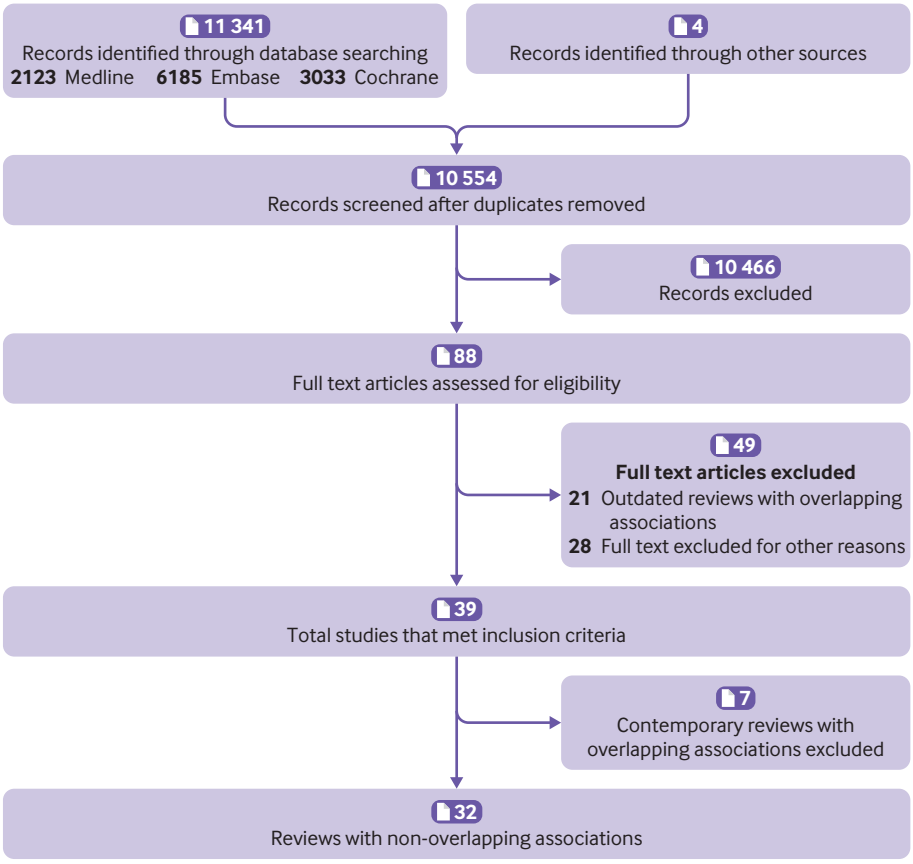

Fig 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

meet three of the seven domains considered critical: they had not stated that the review methods were established before conducting the review; they had not used a comprehensive search strategy; and they had not provided a list of excluded studies and the justification for their exclusion.[44]

Overlapping and non-overlapping associations

Twenty three reviews reported overlapping associations.[55-77] Overlapping associations included: current use of combined oral contraceptives and risk of myocardial infarction, n=2[55 56]; use of combined oral contraceptives and risk of ischaemic stroke, n=3[55-67]; use of combined oral contraceptives and risk of haemorrhagic stroke, n=2[56 71]; use of progesterone only pill and risk of stroke, n=2[72 73]; use of combined oral contraceptives in migraine and risk of stroke, n=2[74 75]; early menarche and mortality from cardiovascular disease, n=2[76 77]; early menopause and risk of fatal cardiovascular disease, n=3[57-59]; pre-eclampsia and risk of cardiovascular disease, n=2[60 61]; gestational diabetes and risk of cardiovascular disease, n=3[62 63 69]; preterm birth and risk of cardiovascular disease, n=3[60 64 65]; and polycystic ovary syndrome and risk of cardiovascular disease, n=3.[66 68 70] Appendix 8 describes the general characteristics of the reviews with overlapping associations, including the decision to retain or exclude an association from the analysis.

Appendix 3 provides an example of the assessment of the degree of overlap with a citation matrix. Appendix 9 lists the thirty two reviews with non-overlapping associations that were included in the analysis and the seven contemporary reviews that were excluded because of overlap.

Study characteristics of reviews with non-overlapping associations

Factors related to fertility investigated in the included reviews were use of hormonal contraceptive agents (n=9), fertility treatment (n=1), early menarche (n=2), polycystic ovary syndrome (n=3), menopause (n=4), parity (n=2), and breastfeeding (n=1). Adverse pregnancy outcomes included miscarriage (n=1), pre-eclampsia (n=2), gestational diabetes (n=2), preterm births (n=3), and multiple adverse pregnancy outcomes (n=1). One study reviewed risk factors related to fertility and adverse pregnancy outcomes but was limited to heart failure as an outcome (n=1). Of the 32 re-views included in the analyses, 24 conducted meta-analyses as the main form of evidence synthesis. The median length of follow-up was about 10 years for studies on risk factors related to fertility and 7.5 years for studies on adverse pregnancy outcomes. Supplementary table 1 summarises the general characteristics of the reviews and meta-analyses included in the umbrella review.

Table 1 | Summary findings for each reproductive risk factor and effect sizes for cardiovascular outcomes

Reproductive factors (related to fertility) and fatality type	Effect size (95% CI)			
	Composite cardiovascular disease	Ischaemic heart disease	Stroke	Heart failure
Early menarche				
Non-fatal	HR 1.15 (1.02 to 1.28)	—	—	—
Fatal	RR 0.99 (0.98 to 1.01)	RR 0.97 (0.95 to 0.99)	RR 0.98 (0.95 to 1.01)	—
Fatal and non-fatal	—	—	—	—
Oral contraceptive pill use				
Non-fatal	—	—	Ischaemic subtype, OR 2.47 (2.04 to 2.99)	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	Haemorrhagic subtype, OR 1.39 (1.05 to 1.83)	—
Current combined oral contraceptive use				
Non-fatal	—	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	—	Myocardial infarction, RR 1.6 (1.3 to 1.9)	Ischaemic subtype, RR 1.7 (1.5 to 1.9)	—
Progesterone only pill use				
Non-fatal	—	Myocardial infarction, RR 0.98 (0.66 to 1.47)	RR 1.02 (0.72 to 1.44)	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Combined oral contraceptives in obese women				
Non-fatal	—	Myocardial infarction, OR 0.88 to 5.1	OR 0.59 to 4.6	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Oestrogen containing contraceptives in women with migraine				
Non-fatal	—	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	Ischaemic subtype, OR 2.08 to 16.9	—
Combined oral contraceptives in women with dyslipidaemia				
Non-fatal	—	Myocardial infarction, OR 25 (6 to 109)	IRR 1.76 (1.51 to 2.06)	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Combined oral contraceptives in women with hypertension				
Non-fatal	—	Myocardial infarction, OR 6 to 68	Ischaemic subtype, OR 3.1 to 14.5	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Combined non-oral hormonal contraceptives				
Non-fatal	—	Myocardial infarction, OR 0.2 to OR 1.6	OR 0.8 to 1.2	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Polycystic ovarian syndrome				
Non-fatal	OR 1.30 (1.09 to 1.56)	OR 1.44 (1.13 to 1.84)	OR 1.36 (1.09 to 1.7)	OR 3.24 (0.53 to 19.94)
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Fertility treatment				
Non-fatal	—	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	HR 0.91 (0.67 to 1.25)	—	HR 1.25 (0.96 to 1.63)	—
Parity				
Non-fatal	RR 0.79 (0.60 to 1.06)	—	—	—
Fatal	RR 1.14 (1.09 to 1.18)	—	—	—
Fatal and non-fatal	—	—	—	—
Breastfeeding				
Non-fatal	HR 0.77 to 0.93	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Premature ovarian insufficiency				
Non-fatal	—	—	—	—
Fatal	RR 1.24 (0.98 to 1.58)	RR 1.48 (1.02 to 2.16)	RR 1.00 (0.86 to 1.16)	—
Fatal and non-fatal	HR 1.61 (1.22 to 2.12)	HR 1.69 (1.29 to 2.21)	HR 1.03 (0.88 to 1.99)	—

Table 1 | Continued

Reproductive factors (related to fertility) and fatality type	Effect size (95% CI)			
	Composite cardiovascular disease	Ischaemic heart disease	Stroke	Heart failure
Early menopause (natural and unnatural)				
Non-fatal	—	RR 1.50 (1.28 to 1.76)	-	HR 1.36 to 1.66
Fatal	RR 1.19 (1.08 to 1.31)	RR 1.11 (1.03 to 1.20)	RR 0.99 (0.92 to 1.07)	—
Fatal and non-fatal	—	—	—	—
Early natural menopause				
Non-fatal	—	—	—	—
Fatal	RR 1.01 (0.91 to 1.13)	RR 1.09 (1.00 to 1.18)	RR 0.94 (0.86 to 1.03)	—
Fatal and non-fatal	—	—	—	—
Menopausal symptoms				
Non-fatal	—	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	RR 1.29 (0.98 to 1.71)	RR 1.18 (1.03 to 1.35)	RR 1.08 (0.89 to 1.32)	—
Miscarriage				
Non-fatal	—	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	OR 0.83 to 2.69	OR 1.45 (1.18 to 1.78)	OR 1.11 (0.72 to 1.69)	—
Stillbirth				
Non-fatal	OR 1.49 (1.08 to 2.06)	—	—	—
Fatal	OR 2.23 (1.90 to 2.62)	—	—	—
Fatal and non-fatal	—	—	—	—
Pre-eclampsia				
Non-fatal	OR 2.24 (1.72 to 2.93)*; OR 2.74 (2.48 to 3.04)†	OR 1.73 (1.46 to 2.06)	OR 2.95 (1.10 to 7.90)	RR 4.19 (2.09 to 8.38)
Fatal	OR 1.73 (1.46 to 2.06)	RR 2.10 (1.25 to 3.51)	RR 1.97(0.80 to 4.88)	—
Fatal and non-fatal	—	—	—	—
Recurrent pre-eclampsia				
Non-fatal	—	RR 2.40 (2.15 to 2.68)	RR 1.69 (1.21 to 2.35)	RR 2.88 (2.23 to 3.72)
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Gestational hypertension				
Non-fatal	RR 1.67 (1.28 to 2.19)	—	RR 1.83 (0.79 to 4.22)	—
Fatal	—	—	—	—
Fatal and non-fatal	—	—	—	—
Gestational diabetes				
Non-fatal	—	RR 2.09 (1.56 to 2.80)	RR 1.25 (1.07 to 1.48)	—
Fatal	—	—	—	—
Fatal and non-fatal	RR 1.98 (1.57 to 2.50)	—	—	—
Placental abruption				
Non-fatal	—	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	OR 1.82 (1.42 to 2.33)	—	—	—
Preterm birth				
Non-fatal	OR 1.63 (1.39 to 1.93)	RR 1.49 (1.38 to 1.60)	RR 1.65 (1.51 to 1.79)	—
Fatal	OR 1.93 (1.83 to 2.03)	RR 2.11 (1.87 to 2.36)	RR 1.30 (0.94 to 1.80)	—
Fatal and non-fatal	HR 2.01 (1.52 to 2.65)	HR 1.38 (1.22 to 1.57)	HR 1.71 (1.53 to 1.91)	—
Recurrent preterm birth				
Non-fatal	—	—	—	—
Fatal	HR 2.1 (1.2 to 3.7)	—	—	—
Fatal and non-fatal	HR 1.4 (1.2 to 1.6)	HR 1.4 to 1.8	HR 1.8 (1.4 to 2.2)	—
Low birth weight				
Non-fatal	—	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	OR 1.29 (0.91 to 1.83)	—	—	—
Small for gestational age				
Non-fatal	—	—	—	—
Fatal	—	—	—	—
Fatal and non-fatal	OR 1.09 to 3.50	—	—	—

OR=odds ratio; HR=hazard ratio; RR=relative risk; IRR=incidence rate ratio.
*Moderate pre-eclampsia.
†Severe pre-eclampsia.

Summary findings

Supplementary table 2 provides a summary of the studies included in the umbrella review, with the main results, a summary of the relevant existing guidelines, and recommendations for future research and clinical practice. Table 1 shows the effect sizes for each reproductive factor and the risk of cardiovascular disease.

A life course approach was adopted where exposures are presented from menarche to menopause for risk factors related to fertility, and from miscarriage to low birth weight for adverse pregnancy outcomes.

Factors related to fertility

Early age at menarche

Early age at menarche (<12), compared with menarche after the age of 12, was associated with a risk of morbidity from composite cardiovascular disease (table 1).[78] No association between early age at menarche and mortality from cardiovascular disease was found.[76] When examined by subtype of cardiovascular disease, an association between early age at menarche and risk of mortality from ischaemic heart disease was seen, but no association with mortality from stroke.

Use of hormonal contraceptive agents

Oral contraceptives and non-oral forms of combined hormonal contraceptives were associated with an increased risk of arteriothrombotic events (table 1).[55 67 79]

Use of oral contraceptives

Current users of any oral contraceptive (combined oral contraceptives containing a combination of oestrogen and progesterone, or progesterone only pill) had an increased risk of stroke compared with non-current users.[67 71] The increase in risk was greater for ischaemic stroke[67] than haemorrhagic stroke.[71] The risk of both ischaemic and haemorrhagic stroke was greatest in women on higher doses of oestrogen, who had hypertension, were smokers, or were aged over 35 (supplementary table 3).

Current users of combined oral contraceptives had a greater risk of developing myocardial infarction and stroke than non-current users of combined oral contraceptives.[55] The same review[55] showed that the risk was increased in women on higher doses of oestrogen but was not related to the dose, generation, or type of progesterone (supplementary table 3). In contrast, no association was seen between current use of the progesterone only pill and risk of myocardial infarction or stroke.[72]

Use of non-oral contraceptive agents

Comparing users of non-oral combined hormonal contraceptive agents with users of combined oral contraceptives,[79] no association with the development of myocardial infarction (the results were not meta-analysed, but odds ratios from individual primary studies ranged from 0.2 to 1.6) or stroke (odds ratio 0.8 to 1.2) was seen but the review was rated as low quality (table 1 and supplementary table 4).

Use of hormonal contraceptive agents in women with coexisting medical illnesses

Use of hormonal contraceptive agents was associated with an additional risk of cardiovascular disease in women who had coexisting medical conditions.[74 80 81] The risk of stroke in women diagnosed with migraine was 2-16-fold greater for those taking combined hormonal contraceptive agents than those not taking combined hormonal contraceptives (table 1).[74] Similarly, in women with dyslipidaemia,[80] results derived from one primary study reported in the systematic review showed that users of combined hormonal contraceptive agents were at an increased risk of myocardial infarction[82] and cerebrovascular accident compared with non-users (table 1).[83] Use of combined oral contraceptives in women with hypertension women was associated with a much higher risk of myocardial infarction (odds ratio 6 to 68) and ischaemic stroke (odds ratio 3.1 to 14.5) than women with normal blood pressure taking non-combined oral contraceptives.[84] But use of combined hormonal contraceptives in women with a high body mass index (>27.3 kg/m^2) was not found to be a multiplicative or additive risk factor for the development of myocardial infarction or stroke (table 1).[81] Reviews assessing the association between the use of combined oral contraceptives in women with a high body mass index and the risk of myocardial infarction or stroke were rated as low quality (appendix 7).

Polycystic ovary syndrome

Women with polycystic ovary syndrome had a 1.3-fold greater risk of developing composite cardiovascular disease than women who did not have polycystic ovary syndrome (table 1).[66] This increased risk was maintained when examining ischaemic heart disease[66] and stroke[85] separately (supplementary table 3). Results from population based studies suggested that, compared with healthy controls, the risk of cardiovascular events was increased in young women in the reproductive age group with polycystic ovary syndrome (hazard ratio 1.43, 95% confidence interval 1.27 to 1.61); no association was seen in postmenopausal women with polycystic ovary syndrome (supplementary table 3)[70] but this review was rated as low quality. Based on the results of one cross sectional study,[86] no association was found between polycystic ovary syndrome and the risk of heart failure (table 1 and supplementary table 4).[87]

Fertility treatment

Women receiving fertility treatment (ovulation induction, in vitro fertilisation, and intrauterine insemination with drug treatment) had no greater risk of developing composite cardiovascular disease or stroke than infertile women not on fertility treatment.[88]

Parity

Mortality from composite cardiovascular disease was lower in ever parous women than nulliparous women (table 1).[89] In a dose-response analysis, the association between ever parity and mortality from composite cardiovascular disease followed a J shaped curve with the risk lowest at a parity of four. For non-fatal events,[90] however, the risk of composite cardiovascular disease was increased in ever parous women, with the risk increasing by 4% for each live birth.[90]

Breastfeeding

Evidence synthesised from four studies suggested that breastfeeding was associated with an overall reduction in maternal cardiovascular disease.[91] Reviewers presented only a narrative review, without a meta-analysis (supplementary table 4). Compared with women who did not breastfeed, two US cohort studies found that morbidity from myocardial infarction[92] and composite cardiovascular disease[93] was lower in women with a lifetime length of lactation of more than 12 months. In a cohort of Chinese women,[94] mortality from ischaemic heart disease but not stroke was lower in women who ever breastfed than in those who never breastfed. In a cohort of Norwegian women,[95] women aged 65 or younger and who never breastfed were at a higher risk of mortality from stroke than women who ever breastfed.

Menopause

Overall, women who experienced menopause earlier than age 40 (premature ovarian insufficiency) had a 1.6-fold risk of developing composite cardiovascular disease compared with women without premature ovarian insufficiency.[96] This association was related to the development of ischaemic heart disease[96]; no association was found with stroke. These findings were also reflected in the association with mortality risk from ischaemic heart disease, but not mortality from stroke or composite cardiovascular disease.[59]

Women who had experienced early (aged <45) menopause (natural and unnatural) had a 20% higher risk of mortality after cardiovascular disease than women who had experienced menopause at age 45 or older.[57] Specifically, an increased risk of developing ischaemic heart disease (fatal and non-fatal outcomes) but not stroke was seen.[57]

Early (aged <45) natural menopause was not associated with a risk of mortality from composite cardiovascular disease or stroke, but was associated with a risk of mortality as a result of ischaemic heart disease.[59] No association was seen between menopausal symptoms and risk of composite cardiovascular disease or stroke compared with women without menopausal symptoms[97] but the risk was increased for ischaemic heart disease.

Adverse pregnancy outcomes

Pregnancy loss (miscarriage and stillbirth)

A history of miscarriage was not associated with an increased risk of composite cardiovascular disease (table 1).[60] In a review exploring individual cardiovascular diseases, miscarriage was linked to a higher risk of ischaemic heart disease but not of stroke.[98] Women with a history of stillbirth had a greater risk of morbidity and mortality from composite cardiovascular disease than women with no history of stillbirth.[60]

Hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension)

Overall, women with a history of pre-eclampsia (both moderate and severe pre-eclampsia) were at an increased risk of mortality and morbidity from composite cardiovascular disease compared with those without a history of pre-eclampsia (table 1).[60] For subtypes of cardiovascular disease, a history of pre-eclampsia was associated with a higher odds of experiencing heart failure,[61] fatal ischaemic heart disease,[61] and non-fatal stroke,[60] but not fatal stroke.[61]

A small degree (CCA 5.6%) of overlap was noted between two reviews[60 61] that investigated the association between pre-eclampsia and the risk of morbidity from ischaemic heart disease (appendix 3). One review[61] searched for primary studies from 2005 only. The risk of non-fatal ischaemic heart disease in women with pre-eclampsia was 1.7-2-fold in the two reviews.[60 61]

In comparison with an episode of pre-eclampsia followed by a healthy pregnancy, a history of recurrent pre-eclampsia was associated with an increased risk of composite cardiovascular disease, coronary heart disease, heart failure, and cerebrovascular accident.[99] Gestational hypertension was linked to a greater risk of morbidity from composite cardiovascular disease but not stroke.[60]

Gestational diabetes mellitus

Women with a history of gestational diabetes had a greater risk of composite cardiovascular disease than those without gestational diabetes (table 1).[62] The risk was highest in the first decade after pregnancy.[62] When the analysis was limited to women who did not go on to develop diabetes mellitus after gestational diabetes, the risk was slightly less but remained statistically significant (supplementary table 3).[62] The risk persisted when analysed by subtype of cardiovascular disease (coronary artery disease and stroke).[63] Evidence of an association between gestational diabetes and heart failure[87] was inconclusive however (supplementary table 4).[100 101]

Placental abruption

A history of placental abruption was associated with a higher odds of composite cardiovascular disease.[60]

Preterm births

Preterm delivery was associated with an increased risk of fatal and non-fatal composite cardiovascular disease.[102 60] For subtypes of cardiovascular disease, the risk was increased in non-fatal ischaemic heart disease, fatal ischaemic heart disease, and non-fatal stroke.[64] The risk of composite cardiovascular disease was greater in women with multiple preterm births than in women with one preterm birth (table 1 and supplementary table 4).[65]

Low birth weight and small for gestational age

The risk of composite cardiovascular disease tended to be higher in women with babies of low birth weight than in women who delivered babies with an average birth weight (table 1).[60] Small for gestational age was linked to an increased risk of morbidity and mortality from maternal cardiovascular disease (odds ratio 1.09 to 3.50) (supplementary table 4).[60]

Reviews eligible for update

We considered three reviews for update: assessing breastfeeding and the risk of cardiovascular disease,[91] assessing miscarriage and the risk of stroke,[98] and assessing gestational diabetes and the risk of stroke.[63] Breastfeeding and the risk of cardiovascular disease was considered eligible for update because of conflicting evidence in the original review; findings for breastfeeding and the risk of cardiovascular disease risk are presented as a narrative summary in line with the method used in the original review. A meta-analysis was performed for miscarriage and the risk of stroke, and for gestational diabetes and the risk of stroke, to detect a signal indicating that the review would require a full update (as outlined above; eg, inclusion of a large new study that would result in a change to the conclusions of an existing review). After the meta-analysis, a full update was not considered necessary.

Miscarriage

A large (1 031 279 participants) Danish cohort study[103] noted that women who had a miscarriage were at a higher risk of stroke (incidence rate ratio 1.16, 95% confidence interval 1.07 to 1.25). Incorporating the results in the meta-analysis on the risk of stroke with those of the existing systematic review[98] did not alter the significance of the association between miscarriage and stroke. Figure 2 shows a forest plot of the results of the individual studies and the updated meta-analysis.[103-106]

Gestational diabetes

Two recent studies[107 108] found no association between gestational diabetes and the risk of stroke (hazard ratio 1.10, 95% confidence interval 0.75 to 1.61; incidence rate ratio 0.95, 95% confidence interval 0.51 to 1.77, respectively). When the results were incorporated into the meta-analysis on gestational diabetes and risk of stroke,[63] the association between gestational diabetes and risk of stroke was maintained (risk ratio 1.21, 95% confidence interval 1.05 to 1.40). Figure 3 shows a forest plot of the results of the individual studies and the updated meta-analysis.[107-110]

Breastfeeding

After the original review,[91] six newly published observational studies[111-116] (five cohort and one case-control study) examined the association between length of lactation and cardiovascular disease (table 2; supplementary table 5 provides more results for the primary studies in the original systematic review). The quality of the studies ranged from low to high (appendix 10). A longer length of breastfeeding was associated with a reduced risk of non-fatal composite cardiovascular disease compared with never breastfed in all three cohort studies.[111 114 116] Mortality from composite cardiovascular disease tended to be lower in women who breastfed for longer than in those who never breastfed, as assessed by two cohort studies.[111 116] Two cohort studies showed that a longer length of breastfeeding was associated with reduced morbidity from coronary heart disease compared with never breastfed.[115 116] In the case-control study, a U shaped association between length of breastfeeding and morbidity from coronary heart disease was seen, with the lowest risk in women who breastfed for 16-26 months over a total lifetime.[112] Longer length of breastfeeding versus never breastfed was associated with reduced morbidity from stroke in two cohort studies.[113 116] In summary, newly published observational studies support an inverse association between length of lactation and morbidity or mortality from cardiovascular disease.

Summary of results by cardiovascular outcome

Composite cardiovascular disease

Preterm birth, pre-eclampsia, and stillbirth were associated with a twofold increase in the risk of composite cardiovascular disease; premature ovarian insufficiency, placental abruption, gestational hypertension, and gestational diabetes mellitus were associated with a 1.5-1.9-fold increase in the risk; and polycystic ovary syndrome, early menopause, early menarche, and ever parity were associated with a less than 1.5-fold increase in risk. Breastfeeding for longer was associated with a reduced risk of cardiovascular disease. The forest plot (fig 4) shows the results for reviews that conducted a meta-analysis.[57 59 60 62 66 76 78 88-90 96 97 102]

No association was found between cardiovascular disease outcomes and fertility treatment, current use of the progesterone only pill, or use of non-oral hormonal contraceptive agents.

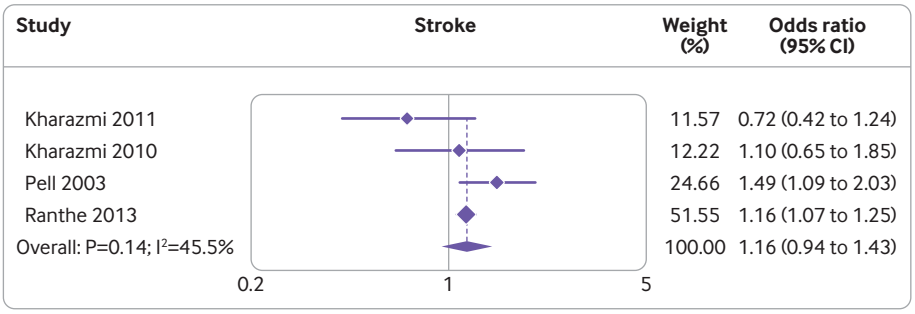

Fig 2 | Forest plot showing studies investigating the association between miscarriage and risk of stroke. Note, weights are from random effects analysis

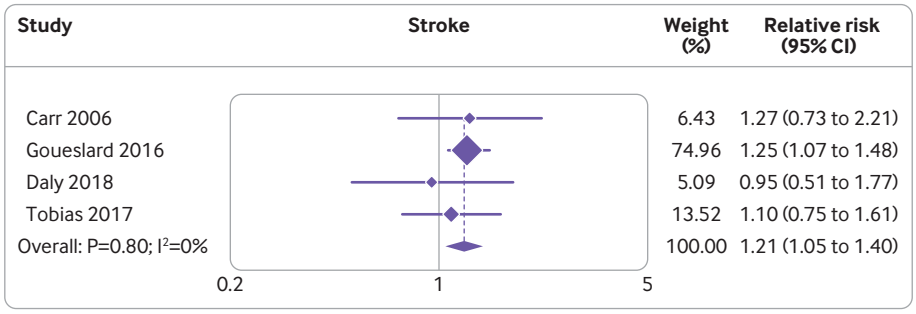

Fig 3 | Forest plot showing studies investigating the association between gestational diabetes and risk of stroke. Note, weights are from random effects analysis

Ischaemic heart disease

A history of maternal delivery of preterm infants, gestational diabetes, pre-eclampsia, and recurrent pre-eclampsia were associated with a twofold or more increase in the risk of ischaemic heart disease; current use of combined oral contraceptives (oestrogen and progesterone), premature ovarian insufficiency, early menopause, and recurrent miscarriage were associated with a 1.5-1.9-fold increased risk; and polycystic ovary syndrome, menopausal symptoms, and miscarriage were associated with a less than 1.5-fold increased risk (fig 5).[55 57 60 61 63 64 66 72 76 96-99 102]

Stroke

Current use of any oral contraceptives (combined oral contraceptives and progesterone only pill), recurrent pre-eclampsia, and pre-eclampsia were associated with a twofold or more increased risk of stroke; maternal delivery of preterm infants, gestational diabetes, and current use of combined oral contraceptives were associated with a 1.5-1.9-fold increase in risk; and polycystic ovary syndrome was associated with a less than 1.5-fold increase in risk (fig 6).[55 57 59 60 61 63 64 67 71 72 76 85 88 96-99 102]

Heart failure

Pre-eclampsia was associated with a fourfold increase in the risk of heart failure (fig 7).[61 99]

Discussion

This detailed umbrella review synthesised existing systematic reviews and meta-analyses into one user friendly document. The review has updated a previous systematic review on the association between breastfeeding and maternal cardiovascular outcomes, and identified gaps and proposed recommendations for research and practice, particularly with respect to relevant UK guidelines (National Institute for Health and Care Excellence, Royal College of Obstetricians and Gynaecologists, and Faculty of Sexual and Reproductive Healthcare).

Main findings

Evidence from the umbrella review suggests that current use of combined oral contraceptives, use of combined hormonal contraceptive agents in women with dyslipidaemia, use of combined hormonal contraceptive agents in women with hypertension, use of oestrogen containing pills in women with migraine, polycystic ovary syndrome, premature ovarian insufficiency, early menarche, early menopause, menopausal symptoms, parity, pre-eclampsia, recurrent pre-eclampsia, preterm births, gestational diabetes, gestational hypertension, miscarriages, stillbirths, placental abruption, and small for gestational age are associated with an increased risk of cardiovascular disease outcomes. The review on length of lactation and the recently published studies suggest that breastfeeding for longer reduces the risk of cardiovascular disease. Length of lactation might be a proxy for general health state but never breastfed was associated with vascular characteristics (larger arterial lumen and adventitial diameters) linked to a higher risk of cardiovascular disease independent of sociodemographic characteristics, health related behaviour, family history, and body mass index.[117 118] The evidence was inconclusive on the association between use of combined hormonal contraceptive agents in women with a high body mass index (>27.3) and the risk of cardiovascular disease outcomes. No association was found between current use of progesterone only contraceptives, use of non-oral combined hormonal contraceptive agents, or fertility treatment and the risk of cardiovascular disease outcomes. Reviews on endometriosis, pelvic inflammatory disease, and anaemia during pregnancy were absent.

Strengths and limitations

The umbrella review has many strengths. A comprehensive search strategy was used to identify relevant reviews. The methodological quality of the studies included in the review was assessed with the AMSTAR 2 tool. Where eligible, reviews were updated to ensure the evidence was current. Evaluation of CCA and reporting of the highest quality and most current review from reviews with overlapping associations were used to eliminate double counting. Methodological rigour in the conduct of the review was achieved by following PRISMA guidelines.

Several limitations arose. Lack of data, including missing metadata (number of participants and events), hindered the reporting of some elements of

Table 2 | Summary of primary observational studies (newly published) investigating the association between breastfeeding and risk of maternal cardiovascular disease

Study, setting, and objective	Study design and participants	Exposure and comparator	Outcome	Length of breastfeeding (effect size (95% CI))
Nguyen 2019,[111] New South Wales, Australia				
To examine the association between breastfeeding and hospital admission for cardiovascular disease and death	Cohort of 100 864 middle aged and parous women	Self-reported breastfeeding, never *v* ever and average breastfeeding duration per child	Non-fatal cardiovascular disease	Never breastfed (reference)
				0-6 months, HR 0.86 (0.78 to 0.96)
				6-12 months, HR 0.85 (0.75 to 0.97)
				>12 months, HR 0.89 (0.71 to 1.12)
			Fatal cardiovascular disease	Never breastfed (reference)
				0-6 months, HR 0.69 (0.51 to 0.94)
				6-12 months, HR 0.59 (0.41 to 0.84)
				>12 months, HR 0.67 (0.28 to 1.57)
Rajaei 2019,[112] Stanford, USA				
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	Exposure category 1: single longest duration of breastfeeding of all live births	Non-fatal coronary artery disease	Live delivery but never breastfed (reference)
				1-4 months, OR 1.57 (0.63 to 3.92)
				5-9 months, OR 0.53 (0.2 to 1.39)
				10-18 months, OR 0.71 (0.29 to 1.76)
				≥19 months, OR 0.89 (0.29 to 2.76)
				1-4 months (reference)
				5-9 months, OR 0.33 (0.14 to 0.8)
				10-18 months, OR 0.47 (0.21 to 1.06)
				≥19 months, OR 0.57 (0.2 to 1.65)
		Exposure category 2: total lifetime length of breastfeeding	Non-fatal coronary artery disease	Never breastfed (reference)
				0-7 months, OR 1.18 (0.48 to 2.86)
				8-15.5 months, OR 0.88 (0.35 to 2.25)
				16-26 months, OR 0.59 (0.21 to 1.63)
				26.5 months, OR 0.71 (0.26 to 1.93)
				0-7 months (reference)
				8-15.5 months, OR 0.78 (0.34 to 1.76)
				16-26 months, OR 0.45 (0.17 to 1.16)
				≥26.5 months, OR 0.62 (0.26 to 1.15)
Jacobson 2018,[113] USA				
To assess the association between breastfeeding and risk of stroke and whether the association differs by ethnicity or race	80 191 parous women from the Women's Health Observational Study	Never breastfed (<1 month) *v* ever breastfeeding	Non-fatal stroke	Never breastfed (reference)
				Ever breastfed, HR 0.77 (0.70 to 0.84)
		Length of breastfeeding		Never breastfed (reference)
				1-6 months, HR 0.81 (0.74 to 0.90)
				7-12 months, HR 0.75 (0.66 to 0.85)
				≥13 months, HR 0.74 (0.65 to 0.83)
Kirkegaard 2018,[114] Denmark				
To examine how any, partial, and full breastfeeding duration are associated with maternal risk of hypertension and cardiovascular disease and how pre-pregnancy body mass index and waist circumference influence the association	Cohort study of 63 260 women with liveborn singleton infants	Breastfeeding for less than 4 months *v* breastfeeding for >4 months (pre-pregnancy normal/underweight)	Non-fatal cardiovascular disease (18 months-15 years postpartum)	<4 months (reference)
				4-10 months, HR 0.68 (0.58 to 0.80)
				>10 months, HR 0.61 (0.52 to 0.73)
		Breastfeeding for less than 4 months *v* breastfeeding for >4 months (pre-pregnancy overweight/obese)		<4 months (reference)
				4-10 months, HR 0.79 (0.64 to 0.98)
				>10 months, HR 0.88 (0.71 to 1.10)
			Cardiovascular disease risk (7-15 years postpartum)	<4 months (reference)
				4-10 months, HR 0.77 (0.63 to 0.94)
				>10 months, HR 0.77 (0.62 to 0.96)

the umbrella review. Certain reproductive factors, including endometriosis, pelvic inflammatory disease, first trimester bleeding without miscarriage, and anaemia in pregnancy, have been linked to an increased risk of future cardiovascular disease events.[19 20 119-121] Systematic reviews on these exposures could not be identified, however, and therefore these factors were not incorporated in our analyses. Conversely, for some reproductive factors, including age at first birth,[122] evidence from a systematic review was identified, but because of inherent methodological shortcomings,[40] the review did not meet our inclusion criteria.

With the AMSTAR 2 quality appraisal instrument, some reviews were rated as low quality, and none of the reviews was rated as high in quality. Insufficient reporting by review authors rather than shortcomings of the review methods could have inadvertently led to a downgrading of the quality of the review. Also, the reviews included were necessarily based on observational evidence; consequently, as noted by Grandi et al,[60] the possibility of confounding remains because of unknown confounders or lack of adjustment for known confounders. The review by Grandi et al noted that a large number of studies failed to adjust for all key risk factors and therefore the results should be interpreted with caution. Misclassification of exposure or outcome status in the studies included in the review is also possible.

Methodological issues

The evidence in the umbrella review was from observational study designs which are prone to

Table 2 | Continued

Study, setting, and objective	Study design and participants	Exposure and comparator	Outcome	Length of breastfeeding (effect size (95% CI))
Peters 2017,[116] China				
To examine the long term effects of breastfeeding on cardiovascular disease in Asian (Chinese) Women	Cohort study of 289 573 Chinese women aged 30-79 at baseline	Lifetime lactation duration compared with never breastfed in parous women	Non-fatal composite cardiovascular disease	Never breastfed, HR 1.00 (0.95 to 1.06)
				0-12 months, HR 0.96 (0.93 to 0.99)
				12-24 months, HR 0.97 (0.95 to 0.99)
				24-36 months, HR 0.96 (0.94 to 0.98)
				36-48 months, HR 0.92 (0.89 to 0.94)
				>48 months, HR 0.91 (0.88 to 0.93)
			Fatal composite cardiovascular disease	Never breastfed, HR 1.00 (0.77 to 1.29)
				0-12 months, HR 0.88 (0.74 to 1.04)
				12-24 months, HR 0.98 (0.87 to1.09)
				24-36 months, HR 0.93 (0.85 to 1.02)
				36-48 months, HR 0.81 (0.74 to 0.89)
				>48 months, HR 0.86 (0.79 to 0.92)
			Non-fatal coronary heart disease	Never breastfed, HR 1.00 (0.92 to 1.09)
				0-12 months, HR 0.93 (0.89 to 0.99)
				12-24 months, HR 0.92 (0.89 to 0.96)
				24-36 months, HR 0.86 (0.83 to 0.89)
				36-48 months, HR 0.86 (0.82 to 0.90)
				>48 months, HR 0.85 (0.82 to 0.89)
			Non-fatal stroke	Never breastfed, HR 1.00 (0.93 to 1.08)
				0-12 months, HR 0.93 (0.89 to 0.97)
				12-24 months, HR 0.93 (0.90 to 0.96)
				24-36 months, HR 0.91 (0.88 to 0.94)
				36-48 months, HR 0.86 (0.82 to 0.89)
				>48 months, HR 0.85 (0.82 to 0.89)
Peters 2016,[115] European cohort				
To assess the association between breastfeeding and risk of incident coronary heart disease	Cohort of 8044 parous women	Lifetime duration of breastfeeding compared with never breastfed	Non-fatal coronary heart disease	Never breastfed, HR 1.00 (0.75 to 1.34)
				0-3 months HR 0.73 (0.60 to 0.89)
				3-6 months HR 0.68 (0.56 to 0.83)
				6-12 months HR 0.69 (0.55 to 0.87)
				12-23 months HR 0.63 (0.51 to 0.76)
				>23 months HR 0.62 (0.45 to 0.86)

OR=odds ratio; HR=hazard ratio.

residual confounding. In some instances, evidence was derived from one study or pooled studies which recorded a small number of events, leading to imprecise results. Also, some of the evidence was derived from cross sectional studies which are poor in determining temporal associations.

Several associations between reproductive factors and cardiovascular disease had a high degree of between study heterogeneity. Several reviews could not evaluate the presence of publication bias because of the small number of studies in the meta-analyses.[123] Information from some of the primary studies was self-reported, which might lead to potential misclassification and recall bias.

Relation to evidence based guidelines and other reviews

Factors related to fertility

Evidence presented in this review on combined hormonal contraceptive agents and combined oral contraceptives are in keeping with findings on the adverse effects of the use of hormonal contraceptive agents reported in current evidence based guidelines.[124] Also, the findings of this review agree with the consensus statement from the European Headache Federation, which reported that the risk of stroke was greater in women with migraine.[125] But caution should be exercised in the interpretation of findings on the use of combined oral contraceptives and the arteriothrombotic risk. Firstly, the between study heterogeneity was high. Secondly, publication bias was not always assessed so its presence cannot be ruled out.[55] Finally, results on current use of combined oral contraceptives in women with dyslipidaemia and current use of combined oral contraceptives in women with obesity were imprecise because they included a small number of studies. Although the absolute risk of cardiovascular disease associated with the use of combined oral contraceptives is low (about 10 per 100 000 person years for myocardial infarction and 21 per 100 000 person years for stroke),[21] a large proportion of women (up to 18% in Europe and North America in 2019) in the reproductive age group use contraceptive pills[126]; hence clinicians should discuss this risk with patients and ensure that women are aware of the association between the use of combined oral contraceptives and the increased risk of cardiovascular disease.

The evidence reported supports the results from an overview of reviews that investigated the association between polycystic ovary syndrome and system wide complications, including cardiovascular disease.[68] The overview summarised evidence from two systematic reviews.[66 127] Our review synthesised evidence from another three reviews, including one evaluating the risk of heart failure,[70 85 87] but no evidence of an

increased risk of heart failure in women with polycystic ovary syndrome was found. Results on the risk of heart failure were based on one cross sectional study that reported imprecise results. Moreover, cross sectional studies cannot be used to infer causality.

Guidelines on the prevention of cardiovascular disease recognise perimenopause and menopause as periods when women are vulnerable to cardiovascular disease.[128 129] In line with findings in the evidence based guideline on the management of women with premature ovarian insufficiency,[130] the evidence we evaluated reported an increased risk of ischaemic heart disease and cardiovascular disease associated with premature menopause. Also, early menopause and menopausal symptoms were associated with an increased risk of ischaemic heart disease.

Adverse pregnancy outcomes

Findings from our review are consistent with European and American evidence based guidelines on prevention of cardiovascular disease that highlighted pre-eclampsia, gestational diabetes, and preterm birth as adverse pregnancy outcomes that potentially increase the risk of cardiovascular disease.[131-134] Also, this review reports evidence of an increased risk of cardiovascular disease outcomes in women with stillbirths, small for gestational age offspring, and placental abruption. We reported that the increased risk of composite cardiovascular disease but not stroke was statistically significant (odds ratio 1.67, 95% confidence interval 1.28 to 2.19) in women with gestational hypertension. These findings are in keeping with a meta-analysis,[135] published beyond the time line of this review, which reported that women with gestational hypertension had an increased risk of composite cardiovascular disease (relative risk 1.73, 95% confidence interval 1.43 to 2.09), stroke (1.66, 0.99 to 2.79), coronary heart disease (1.56, 1.35 to 1.81), and heart failure (1.70, 1.43 to 2.02).

In an umbrella review,[136] an inverse association between birth weight and future maternal cardiovascular disease was reported (hazard ratio 0.75, 95% confidence interval 0.67 to 0.84, for every one standard deviation increase from the mean weight). An analysis reported in another review,[60] which excluded studies with self-reported low birth weight and those that reported less severe forms of cardiovascular disease, revealed a statistically significant association (odds ratio 1.46, 95% confidence interval 1.11 to 1.91) between low birth weight and cardiovascular disease,[60] in agreement with the findings of the umbrella review[136] (supplementary table 3).

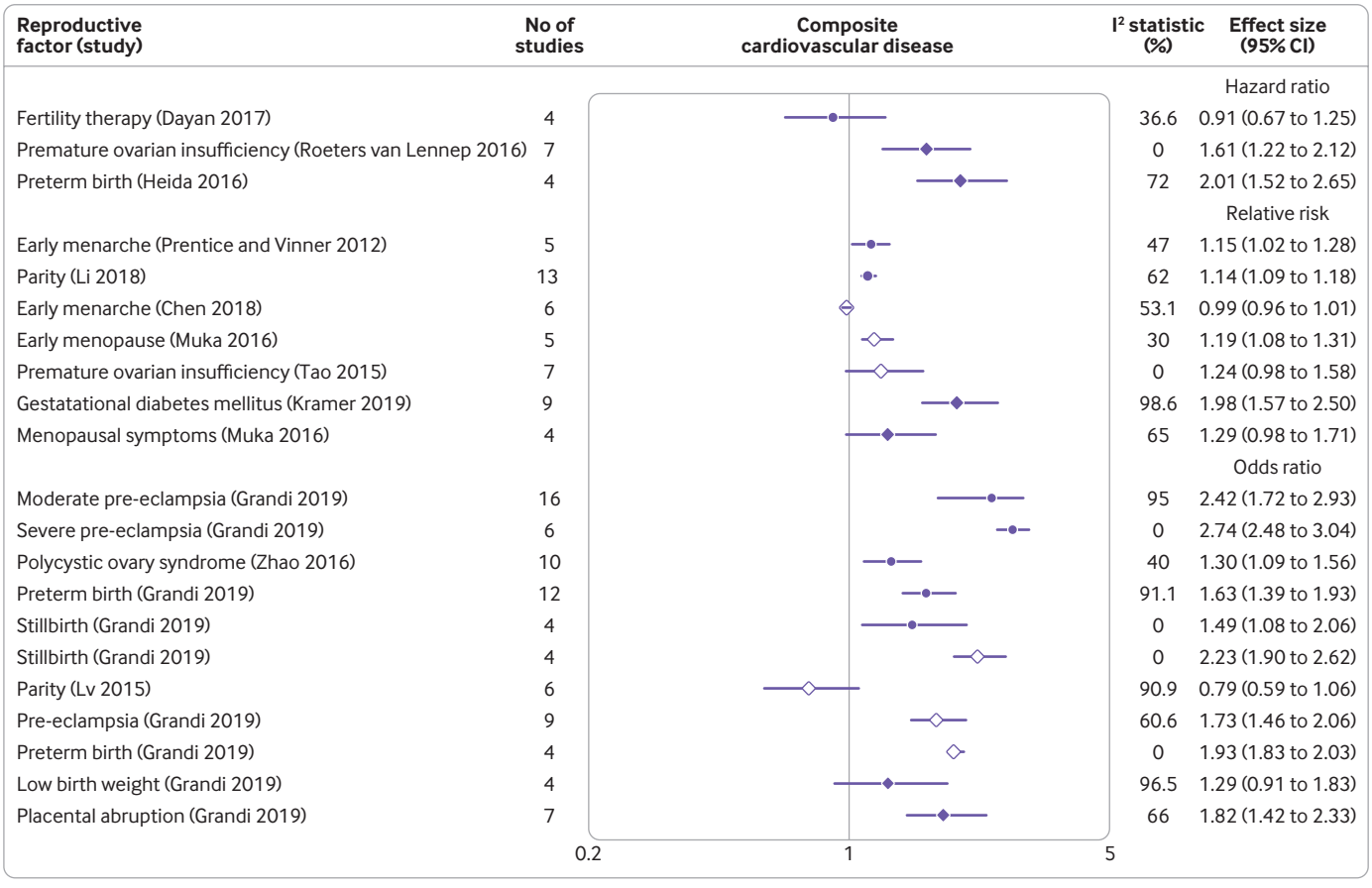

Fig 4 | Forest plot showing results of meta-analyses from reviews that investigated the association between various reproductive factors and risk of composite cardiovascular disease. Circles indicate non-fatal outcomes, open diamonds fatal outcomes, and filled diamonds combined fatal and non-fatal outcomes

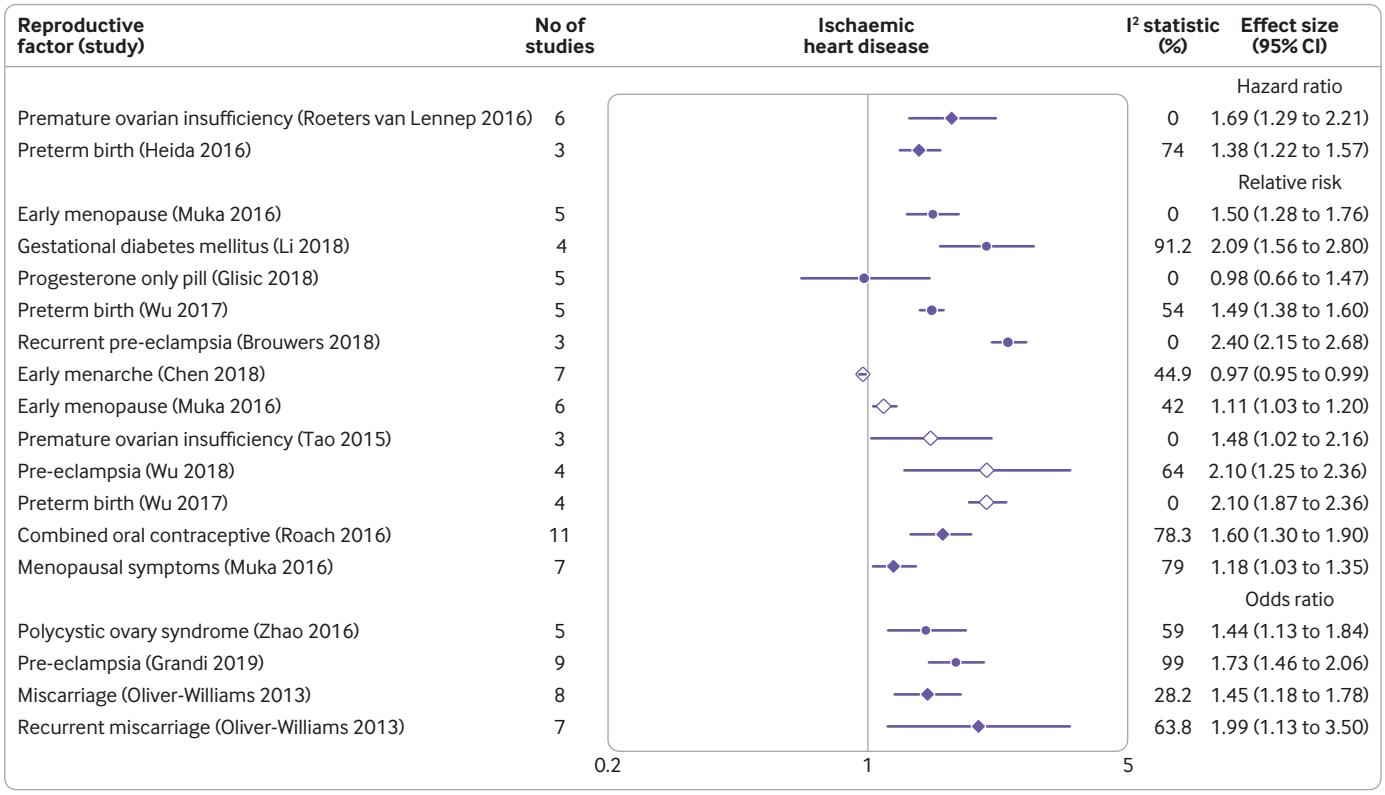

Fig 5 | Forest plot showing results of meta-analyses from reviews that investigated the association between various reproductive factors and risk of ischaemic heart disease. Circles indicate non-fatal outcomes, open diamonds fatal outcomes, and filled diamonds combined fatal and non-fatal outcomes

Biological plausibility

Multifactorial mechanisms might explain the increased risk of cardiovascular disease associated with various reproductive factors. Families of women with a history of reproductive complications were also at an increased risk of cardiovascular disease and so genetic predispositions could have a role.[137 138] Use of hormonal contraceptive agents might result in a homeostasis imbalance by favouring procoagulant factors and decreasing anticoagulant factors.[139] Metabolic derangements linked to the risk of cardiovascular disease, including weight gain, decreased insulin sensitivity, dyslipidaemia, and hypertension, are prevalent in women with risk factors for cardiovascular disease specific to women (eg, factors related to fertility and adverse pregnancy outcomes).[140-145] On the other hand, in young women aged 50 or younger, prolonged lactation was inversely linked to risk factors for cardiovascular disease, including total cholesterol, body mass index, waist circumference, and hypertension, which might be linked to the reduced risk of cardiovascular disease noted in these women.[146]

Endothelial dysfunction, which has been found in women with premature menopause and in those with adverse pregnancy outcomes, might trigger pregnancy complications and remain beyond these complications to predispose women to future cardiovascular disease.[13 147] Parity of four or more is associated with an increased risk of cardiovascular disease through an accelerated atherosclerotic process in both younger and older women.[148]

Implications for practice and public health

The implications for practice include early or routine screening and assessment for cardiovascular disease and risk factors; routine postpartum follow-up and monitoring, involving multidisciplinary healthcare professionals (eg, general practitioners, gynaecologists, cardiologists); improving education and awareness for patients and clinicians; and use of timely treatment.[149] A high proportion of women will encounter a clinician for the first time when planning for a family and during pregnancy. Obstetricians and gynaecologists should, therefore, be involved in the referral and follow-up of patients potentially at risk. A multidisciplinary approach between general practitioners, specialist physicians, and obstetricians and gynaecologists is recommended.[150] Likewise, educating practitioners in the primary care setting on the importance of taking a thorough reproductive history and recording factors related to fertility or adverse pregnancy outcomes is essential. Information from this history could prove crucial in identifying patients at high risk for prevention of cardiovascular disease and follow-up. Our previous study found insufficient reporting of gestational diabetes and screening for cardiovascular risk factors in these

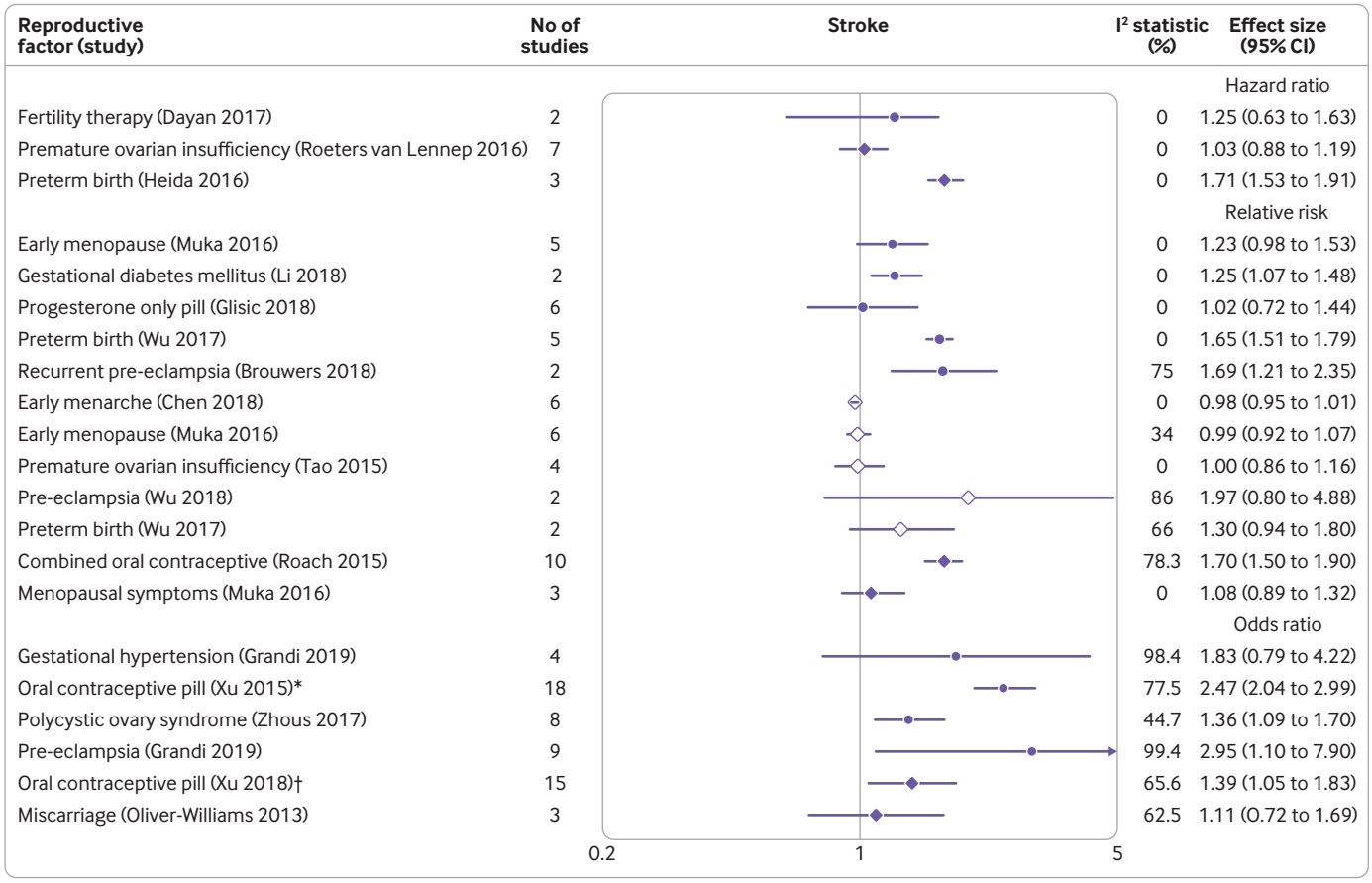

Fig 6 | Forest plot showing results of meta-analyses from reviews that investigated the association between various reproductive factors and risk of stroke. Circles indicate non-fatal outcomes, open diamonds fatal outcomes, and filled diamonds combined fatal and non-fatal outcomes. *Ischaemic stroke. †Haemorrhagic stroke

women.[108] Adverse pregnancy outcomes should be communicated to primary care and reported in primary care records so these factors can be used for future risk stratification, and patients recalled for risk assessment of cardiovascular disease.

Hospital episodes related to cardiovascular disease occurred in 381 458 women in the financial year 2017-18,[151] indicating an incidence of about 113.4 cardiovascular disease episodes per 10 000 women annually. A study focusing only on coronary heart disease suggested that 15% of coronary heart disease in women younger than 65 cannot be explained by existing risk factors.[34] Therefore, we believe that if we were to look at care pathways of women with reproductive risk factors, a large proportion of cardiovascular disease would be hypothetically preventable. But quantifying how much is preventable is difficult given that many of these risk factors might cluster together; also, how many of the risk factors are modifiable, and whether, if modified, a reduction in cardiovascular events will be seen is unclear. Nevertheless, screening for risk factors in these women and management of these reproductive risk factors might not only reduce the risk of cardiovascular disease as a result of the reproductive risk factors themselves, but also reduce the risk caused by traditional risk factors for cardiovascular disease (eg, improving care pathways for women with gestational diabetes will enable early identification of diabetes mellitus and also other risk factors, thereby reducing cardiovascular events).

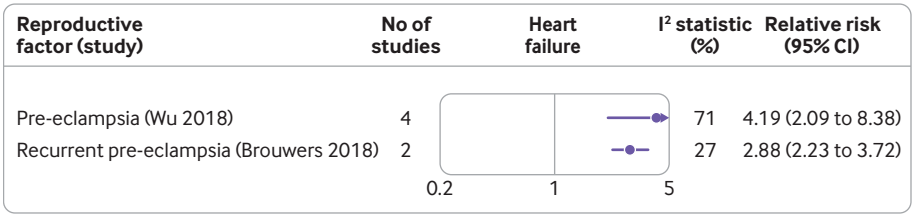

Fig 7 | Forest plot showing results of meta-analyses from reviews that investigated the association between various reproductive factors and risk of heart failure. Circles indicate non-fatal outcomes

Implications for future research

Several reproductive factors have been linked to an increased risk of ischaemic heart disease, stroke, and overall cardiovascular disease. These reproductive factors might be linked to the risk of peripheral arterial disease and heart failure, and therefore longitudinal studies are needed in this area.

Evidence from the review has suggested that women with adverse pregnancy outcomes are at risk of future cardiovascular disease outcomes. Current guidelines on prescription of contraceptives recommend a careful assessment of the eligibility for combined oral contraceptives in women with migraine, diabetes, and other existing conditions associated with a high risk of cardiovascular disease.[152] These guidelines do not include recommendations on the safety profile of the use of combined oral contraceptives in women with adverse pregnancy outcomes and other complications related to fertility. Also, the interaction between adverse pregnancy outcomes, factors related to fertility, and other conditions predominant in women (migraine, autoimmune diseases) that predispose to cardiovascular disease needs to be investigated.

That pregnancy complications act as a stress test that unmasks women who are at an increased risk of cardiovascular disease has been postulated.[153] Whether adverse pregnancy outcomes and reproductive factors related to fertility directly cause or act as stressors that reveal those who are already susceptible to cardiovascular disease needs to be determined. This information will help in starting preventive strategies early. Moreover, the mechanistic pathways between these reproductive factors and risk of cardiovascular disease need to be determined.[154]

Prediction models for traditional risk factors for cardiovascular disease could underestimate the true risk of cardiovascular disease in young women because they do not account for risk factors specific to women.[155] A recent systematic review on risk prediction models for cardiovascular disease in women noted that only 1.1% of the 260 articles included in the review investigated the added value of incorporating risk factors specific to women in risk prediction models.[156] Even in studies that evaluated the use of predictors specific to women, however, none included predictors such as hypertensive disorders of pregnancy, gestational diabetes, polycystic ovary syndrome, and premature ovarian insufficiency. The benefit of adding reproductive factors to risk prediction models for cardiovascular disease needs to be extensively evaluated.

Should the reproductive profile prove useful in the early prediction of cardiovascular disease, it would be equally essential to determine the effectiveness of intensive screening and monitoring.[157] Conventional risk factors for cardiovascular disease, including hypertension and body mass index, have been associated with an excess risk of cardiovascular disease in women with hypertensive disorders of pregnancy.[33] Determining whether women with reproductive profiles that place them at an increased risk of cardiovascular disease might be candidates for lifestyle changes, including statin treatment, is essential. Also, interventions to promote a healthy lifestyle, epidemiological data and trends, and randomised controlled trials that assess early intervention in women with risk factors should be evaluated.[149]

Conclusion

In summary, the evidence reported in this umbrella review suggests that, from menarche to menopause, the reproductive profile of women is associated with their future risk of cardiovascular disease. Large prospective studies are needed to confirm the association between current use of combined oral contraceptives in patients with obesity and the risk of cardiovascular disease. Similarly, prospective studies with a longer duration of follow-up are needed to investigate the association between reproductive factors and the risk of heart failure. A large proportion of unexplained risk of cardiovascular disease in women might be attributable to reproductive risk factors but the exact magnitude of the effect is unclear. Identification of reproductive risk factors at an early stage in the life course of women might facilitate the initiation of strategies to modify potential risks. Future research on the benefit of adding risk factors specific to women to prediction models for cardiovascular disease and on the mechanistic pathways that underlie the association between reproductive factors and cardiovascular disease is required. Policy makers should consider incorporating reproductive risk factors as part of the risk assessment for cardiovascular disease in clinical guidelines.

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The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Dissemination to participants is not possible as this is a review of existing evidence. Patients and the public will not be involved in dissemination of the findings.

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Web appendix: Appendices