ESC European Society of Cardiology

European Heart Journal Open (2022) **2**, 1–10
https://doi.org/10.1093/ehjopen/oeac065

ORIGINAL ARTICLE
Epidemiology and prevention

The risk of cardiovascular diseases after miscarriage, stillbirth, and induced abortion: a systematic review and meta-analysis

Harry Kyriacou[1,†], Abdulrahman Al-Mohammad[1,†], Charlotte Muehlschlegel[1,†], Lowri Foster-Davies[1], Maria Eduarda Ferreira Bruco[2], Chloe Legard[2], Grace Fisher[1], Fiona Simmons-Jones[3], and Clare Oliver-Williams [4,5,6,7,*]

[1]School of Clinical Medicine, Addenbrooke's Hospital, Hills Rd, Cambridge CB2 0SP, UK; [2]Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK; [3]Health Education East of England, 2.4- Vicotria House, Capital Park, Fulbourn, Cambridge, CB21 5XB, UK; [4]Cardiovascualr Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge Papworth Road, Cambridge Biomedical Campus, Cambridge, CB2 0BB, UK; [5]Homerton College, University of Cambridge, Hills Rd, Cambridge CB2 8PH, UK; [6]Biostatistics Research Group, Department of Health Sciences, University of Leicester, George Davies Centre, University Rd, Leicester LE1 7RH, UK; and [7]Central Bedfordshire Council, Priory House, Chicksands, Monks Walk, Shefford SG17 5TQ, UK

Received 3 June 2022; revised 26 September 2022; online publish-ahead-of-print 5 October 2022

Handling Editor: Magnus Bäck

Aims

Miscarriage and stillbirth have been included in cardiovascular disease (CVD) risk guidelines, however heterogeneity in exposures and outcomes and the absence of reviews assessing induced abortion, prevented comprehensive assessment. We aimed to perform a systematic review and meta-analysis of the risk of cardiovascular diseases for women with prior pregnancy loss (miscarriage, stillbirth, and induced abortion).

Methods and results

Observational studies reporting risk of CVD, coronary heart disease (CHD), and stroke in women with pregnancy loss were selected after searching MEDLINE, Scopus, CINAHL, Web of Knowledge, and Cochrane Library (to January 2020). Data were extracted, and study quality were assessed using the Newcastle-Ottawa Scale. Pooled relative risk (RR) and 95% confidence intervals (CIs) were calculated using inverse variance weighted random-effects meta-analysis.

Twenty-two studies involving 4 337 683 women were identified. Seven studies were good quality, seven were fair and eight were poor. Recurrent miscarriage was associated with a higher CHD risk (RR = 1.37, 95% CI: 1.12–1.66). One or more stillbirths was associated with a higher CVD (RR = 1.41, 95% CI: 1.09–1.82), CHD (RR = 1.51, 95% CI: 1.04–1.29), and stroke risk (RR = 1.33, 95% CI: 1.03–1.71). Recurrent stillbirth was associated with a higher CHD risk (RR = 1.28, 95% CI: 1.18–1.39). One or more abortions was associated with a higher CVD (RR = 1.04, 95% CI: 1.02–1.07), as was recurrent abortion (RR = 1.09, 95% CI: 1.05–1.13).

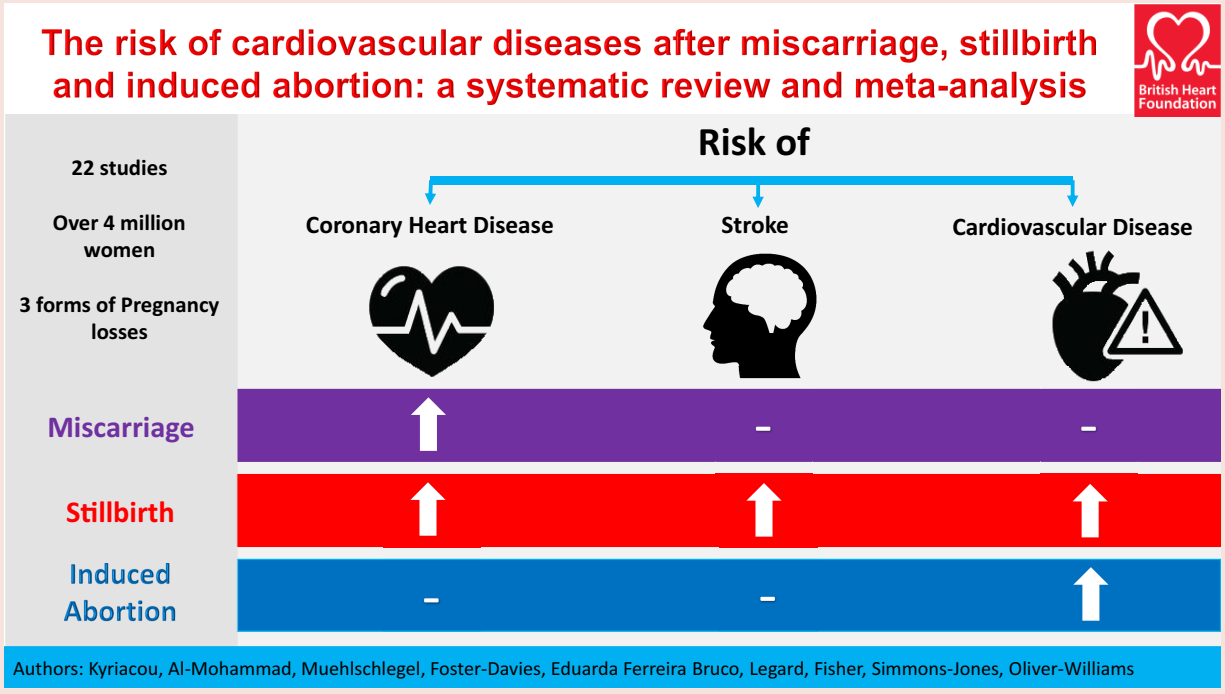
Conclusion

Women with previous pregnancy loss are at a higher CVD, CHD, and stroke risk. Early identification and risk factor management is recommended. Further research is needed to understand CVD risk after abortion.

* Corresponding author. Tel: +44 (0) 1223 748653, Email: cto21@cam.ac.uk
† Joint lead authors.

© The Author(s) 2022. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Graphical Abstract



Keywords Systematic review • Cardiovascular disease • Stillbirth • Miscarriage • Abortion

Introduction

Cardiovascular disease (CVD) is the leading cause of death among women. Understanding of female-specific risk factors has increased,[1] allowing appropriate risk stratification and prevention, accurate counselling, and early intervention. This is reflected by inclusion of miscarriage and stillbirth in recent CVD risk guidelines for women.[1] However, these recommendations provide limited indication of the magnitude of risk associated with stillbirth or miscarriage, and do not differentiate between different exposures (history of miscarriage and recurrent miscarriage, or history of stillbirth and recurrent stillbirth) and different outcomes [coronary heart disease (CHD), stroke, and CVD].

Further evidence gaps remain. To the authors' knowledge, no previous review has assessed the cardiovascular outcomes for women with prior abortions. In spite of induced abortion (henceforth known as 'abortion') being common; there were 209 917 abortions in England & Wales in 2020 and 1% of women aged 15–44 in the US underwent legally reported abortions in 2019.[2,3] Similarly, no previous review has assessed the risk of CHD after stillbirth, which affects 1.8% of babies worldwide (0.3% in developed countries).[4] Inclusion of miscarriage in this review, which has been reviewed previously,[5,6] facilitates comprehensive comparison of the magnitude of CVD, CHD, and stroke risk across different forms of pregnancy loss.

Therefore, we comprehensively examined CVD, CHD, and stroke risk for women with prior miscarriage, stillbirth, or abortion. This gives a comprehensive picture of the heterogeneity of cardiovascular risks across different forms of pregnancy loss and furthers the discussion of whether the cessation of a pregnancy in and of itself, as opposed to the pathophysiology underlying miscarriage and stillbirth, contributes to CVD.

Methods

Study design

This systematic review of studies explored the relationship between pregnancy loss and risk of cardiovascular outcomes in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[7] statement and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[8] protocol (see Supplementary material online, *Tables S1–S3*). It was registered with PROSPERO (CRD42020167587) and a protocol was published.[9]

Study selection

The following databases were systematically searched for relevant articles up to January 2020: MEDLINE (through PubMed), Scopus, CINAHL, Web of Knowledge, and the Cochrane Library. No time restrictions were applied. Medical search headings and open text fields were used to identify articles. Exposure search terms included: 'Miscarriage', 'Recurrent Miscarriage', 'Fetal Death', 'Stillbirth', 'Induced Abortion', and 'Abortion'. Outcome search terms were: 'Cardiovascular Disease', 'Coronary Heart Disease', 'Stroke', and 'Transient Ischaemic Attack'. Full search terms are given in Supplementary material online, *Table S4*. The PubMed search was restricted to humans. Reference lists of relevant articles were also searched.

To be included, articles had to assess the association between one form of pregnancy loss and a cardiovascular outcome in otherwise healthy women. Papers evaluating ectopic pregnancies, neonatal death, or combinations of pregnancy loss were excluded to minimize heterogeneity.

Exposures were categorized as a history of pregnancy loss, where one or more miscarriages, stillbirths, or abortions was considered exposed; or recurrent pregnancy loss, defined as at least two or more miscarriages, stillbirths, or abortions. This created six exposure groups: (i) history of one or more miscarriages, (ii) recurrent (two or more) miscarriages, (iii) history of one or more stillbirths, (iv) recurrent stillbirths, (v) history of one or more abortions, and (vi) recurrent abortions. The comparison group was women who had not experienced the relevant pregnancy losses.

CVD, CHD, angina, myocardial infarction, overall stroke, ischaemic and haemorrhagic stroke, and transient ischaemic attacks (TIA) were outcomes of interest. Outcomes were segregated into overall CVD; CHD (including CHD diagnoses and coronary artery bypass graft); and stroke (including ischaemic and haemorrhagic stroke with or without TIA).

Cohort or case-control studies were included. Where raw data was provided but not association measures, the data were used to calculate an unadjusted estimate. The decision to include studies was hierarchical; study titles, abstracts, and finally the full text were assessed.

Some identified papers used data from the same individuals and assessed the same exposure-outcome combinations in multiple publications. When this occurred, the article containing the greater number of participants or, if that was not applicable, the article with more detailed analytic information was selected. When an article provided risk estimates for subgroups of an exposure, e.g. early miscarriage and late miscarriage, the analysis with the largest number of individuals was included.

Data extraction

The literature search and data extraction were conducted by eight individuals. Information was collected using a pre-designed data extraction form which included: lead author, publication year, study design, population studied, exposure and outcome assessed, the number of cases and non-cases, the association measure, point estimate and 95% confidence intervals (CIs), and any adjustment/stratification/matching variables. Each study was reviewed for inclusion/exclusion by two independent reviewers. Differences were discussed and resolved by a third reviewer (F.S.-J. or C.O.-W.).

Study quality and quality of evidence across studies

Three authors assessed study quality using the Newcastle-Ottawa Scale,[10] which judged articles on the selection criteria of participants, comparability of cases and controls, and exposure or outcome assessment. The final score was converted to Agency for Healthcare Research and Quality (AHRQ) standards.[11] Discrepancies between authors were adjudicated by C.O.-W.

The strength of the evidence from each meta-analysis was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[12] This was applied where two or more studies evaluated the same outcome. As all studies were observational, the initial rating was low quality. It is downgraded for each serious study limitation [risk of bias (RoB), indirectness of evidence, serious inconsistency, effect estimate imprecision, or publication bias]. Evidence was upgraded for: a large effect magnitude [relative risk (RR) > 2 or <0.5], dose-response gradient, and if all residual confounding would reduce the magnitude of effect.

The following significantly associated exposure-outcome combinations were included in the GRADE assessment: history of stillbirth and CVD, recurrent miscarriage and CHD, history of stillbirth and CHD, recurrent stillbirth and CHD, and history of stillbirth and stroke.

Statistical analysis

To conduct meta-analyses, at least two studies evaluating the same exposure-outcome combination was needed. If only one study was found, results were included in the narrative review alone.

The inverse variance weighted random-effects meta-analysis combined odds ratios (ORs), RRs, and hazard ratios (HRs) to produce a pooled RR and 95% CI, under the rare outcome assumption. The Hartung-Knapp-Sidik-Jonkman (HKSJ) model was used to allow for between-study heterogeneity as clear differences between studies were identified, such as ethnicity. Cochrane χ^2 statistic and the I^2 statistic assessed heterogeneity. Forest plots displayed individual and summary risk estimates.

Sensitivity analyses

To assess the impact of different statistical models on the results, sensitivity analyses were conducted using only studies that performed Cox proportional hazards regression models, as this was the most common statistical method.

Separately, meta-analyses were rerun with fixed-effects models to assess the results' consistency and provide an estimation of the relationship specifically in the populations studied.

Several studies assessed the risk of stroke subtypes (intracerebral haemorrhage and ischaemic stroke). To assess risk of any stroke outcome, meta-analyses were conducted that combined risk estimates for overall stroke and stroke subtypes.

Stratified analyses were conducted to evaluate (i) differential adjustment levels by excluding poorly adjusted studies, and (ii) the impact of confounding and bias in individual studies by the exclusion of poor-quality studies according to AHRQ standards.

Small study effects were evaluated through funnel plots and Egger tests for meta-analyses including at least 10 studies.[13]

All tests were two-tailed and P values of <0.05 were considered statistically significant. STATA software package (version 14.2; Stata Corp, College Station, TX) and R version 4.1.2 (R Foundation, Vienna, Austria, www.r-project.org) were used for statistical analyses.

Results

The search identified 22 034 papers; 21 922 were excluded during abstract screening. The remaining 112 papers were reviewed in full. Twenty-two articles, with 4 337 683 women, were included (*Figure 1*). *Table 1* summarizes the studies included in the systematic review. Sixteen cohort studies[15,16,18,19,21,24,26,27,29–34,28] and six case-control studies were identified.[14,20,22,23,25,35] In total, 355 745 women had one or more miscarriages, 54 613 women had one or more stillbirths, and 262 847 women had one or more abortions. Studies were conducted in Europe (12 studies),[14,15,20–22,24,25,29,31–34] North America (4 studies),[1,17,28,35] and Asia (6 studies).[16,18,19,23,26,30]

Pregnancy loss was self-reported or ascertained through medical records, registry data, or health insurance claims. Based on the AHRQ standards, seven studies were judged to be of good quality (low RoB), seven studies were fair quality (moderate RoB), and eight were poor quality (high RoB) (see Supplementary material online, *Tables S5 and S6*).

In cohort studies, 17.1% women had a history of miscarriage, 2.4% had recurrent miscarriages, 1.4% reported a history of stillbirth, 0.4% had recurrent stillbirths, 38.8% reported a history of abortion, and 17.9% had recurrent abortions.

Figure 2 summarises the results of the meta-analyses.

Cardiovascular disease

Eight studies examined CVD risk. Three studies,[30,31,34] including 630 214 women, examined CVD risk associated with a history of miscarriage and four studies,[19,30,31,34] including 712 403 women, assessed risk associated with recurrent miscarriages (see Supplementary material online, *Table S7*). Six studies,[16,24–26,30,31] including 2 400 480 women, and three studies,[27,30,31] including 654 540 women, assessed risk associated with a history of stillbirth and recurrent stillbirths, respectively (see Supplementary material online, *Table S8*). One study[30] assessed risk associated with a history of abortion (302 669 women), and recurrent abortions (total number of women not reported) (see Supplementary material online, *Table S9*).

Supplementary material online, *Figure S1* shows the results of the CVD systematic review and meta-analyses. Meta-analyses found no evidence for a higher CVD risk in women with a history of one or more miscarriages, RR = 1.02 (0.91–1.15); with moderate levels of between-study heterogeneity (I^2 = 57.9%, P = 0.093). There was some indication that women with a history of recurrent miscarriage were at higher

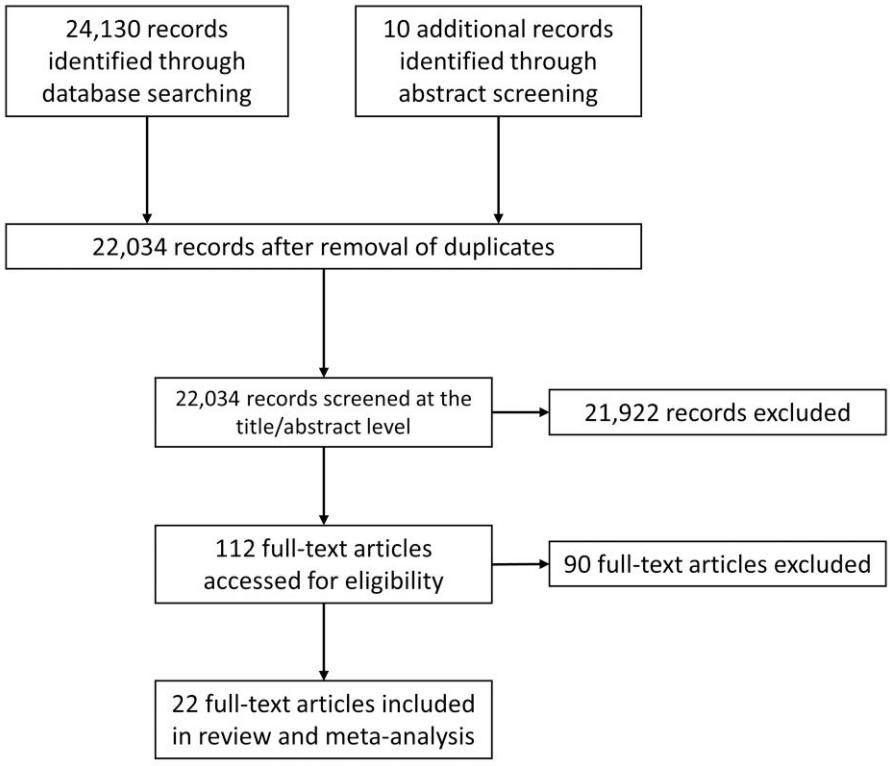


Figure 1 Flowchart of study selection.

CVD risk, RR = 1.29 (0.98–1.71). High levels of between-study heterogeneity were found (I^2 = 84.0%, $P < 0.001$). Higher CVD risk was found for women with a history of stillbirth, RR = 1.41 (1.09–1.82), but there was limited evidence of a higher risk for women with recurrent stillbirth, RR = 1.57 (0.49–5.02). High levels of between-study heterogeneity were found in both meta-analyses, (I^2 = 82.0%, $P < 0.001$ and I^2 = 78.8%, $P = 0.009$, respectively).

One study assessed CVD risk with a history of abortion or recurrent abortion. Higher risk was found for a history of abortion and recurrent abortion: RR = 1.04 (1.02–1.07) and RR = 1.09 (1.05–1.13), respectively.

Excluding studies that were minimally adjusted or excluding poor-quality studies had little impact on findings (see Supplementary material online, *Figures S2 and S3*, respectively). Conducting fixed-effects meta-analyses to estimate risk specifically in the populations studied found all forms of pregnancy loss were associated with a higher CVD, although the risk was lower for history of stillbirth, RR = 1.10 (1.06–1.14) and a positive association with recurrent stillbirth was found, RR = 1.19 (1.06–1.33) (see Supplementary material online, *Table S10*). When analyses were limited to studies that had performed the Cox proportional hazards regression model, results were broadly consistent (see Supplementary material online, *Figure S4*).

Coronary heart disease

Seventeen studies examined CHD risk. Eleven studies,[14,17,20,21,25,30–35] including 1 788 781 women, examined CHD risk associated with history of miscarriage and 13 studies,[14,17,21,22,24,27,28,30–35] including 175 064 women, assessed risk associated with recurrent miscarriages (see Supplementary material online, *Table S11*). Eight studies,[16,21,25,27,28,30–32] including 1 769 309 women, and four studies,[18,27,30,31] including 871 207 women, assessed risk associated a history of stillbirth and recurrent stillbirths, respectively (see Supplementary material online, *Table S12*). Four studies,[14,21,22,30] including 296 116 women, and four studies,[14,18,24,30] including 537 769 women, assessed risk associated with a history of abortion and recurrent abortions, respectively (see Supplementary material online, *Table S13*).

Supplementary material online, *Figure S5* shows the results of the CHD systematic review and meta-analyses. There was non-significant evidence of a higher CHD risk associated with a history of one or more miscarriages, RR = 1.17 (0.99–1.27) with moderate levels of between-study heterogeneity (I^2 = 41.5%, $P = 0.072$). Women with recurrent miscarriages were at significantly higher risk, RR = 1.37 (1.12–1.66) with little evidence of between-study heterogeneity (I^2 = 20.6%, $P = 0.235$). Higher CHD risk was found for women with a history of stillbirth, RR = 1.51 (1.04–2.19), and women with recurrent stillbirth, RR = 1.28 (1.18–1.39). High levels of between-study heterogeneity were found in the history of stillbirth meta-analysis (I^2 = 89.6%, $P < 0.001$), but no evidence of between-study heterogeneity in the recurrent stillbirth meta-analysis (I^2 = 0.0%, $P = 0.956$). No increased CHD risk was noted for women with a history of abortion, RR = 1.08 (0.85–1.38), nor for women with recurrent abortion, RR = 0.94 (0.57–1.55). There was no evidence of between-study heterogeneity in the history of abortion meta-analysis (I^2 = 0.0%, $P = 0.460$), but high levels were identified for recurrent abortion (I^2 = 68.1%, $P = 0.026$).

Excluding studies that were minimally adjusted or excluding poor-quality studies had little impact on findings (see Supplementary material online, *Figures S6 and S7*, respectively). Results of fixed-effects meta-analyses to estimate the relationships specifically in the populations studied found positive associations between all forms of pregnancy loss and CHD (see Supplementary material online, *Table S14*),

Table 1 Summary of studies included in the systematic review

Study (country)	Study design	Total *n*	Follow-up	Outcome(s)	Exposure(s)	Quality[a]
Bertuccio *et al.* 2007[14] (Italy)	Hospital case-control	1715	NA	Acute MI	Hx of abortion, miscarriage; Recurrent abortion (2+), miscarriage (2+)	Poor
Bonamy *et al.* 2011[15] (Sweden)	Retrospective cohort	923 686	11.8 years	CVD event/hospitalization	Hx of stillbirth	Good
Calderon-Margalit *et al.* 2007[16] (Israel)	Retrospective cohort	25 118	36.5 years	CHD mortality	Hx of stillbirth	Good
				CVD mortality	Hx of stillbirth	
Cooper *et al.* 1999[17] (USA)	Prospective cohort	867	52 years	MI, angioplasty, heart bypass, CHD mortality	Hx of miscarriage; Recurrent miscarriage (2+)	Poor
Gallagher *et al.* 2011[18] (China)	Prospective cohort	267 400	11 years	CHD	Recurrent abortion (2+), stillbirth (2+)	Fair
				Haemorrhagic stroke	Recurrent abortion (2+), miscarriage (2+), stillbirth (2+)	
Kessous *et al.* 2014[19] (Israel)	Retrospective cohort	99 285	11.2 years	Cardiovascular hospitalizations	Recurrent miscarriage (≥3)	Fair
Kharazmi *et al.* 2010[20] (Finland)	Community case-control	3937	NA	MI	Hx of miscarriage	Good
				Stroke	Hx of miscarriage	
Kharazmi *et al.* 2011[21] (Germany)	Prospective cohort	11 518	10.8 years	MI	Hx of abortion, miscarriage, stillbirth; Recurrent miscarriage (≥4)	Good
				Stroke	Hx of abortion, miscarriage, stillbirth; Recurrent abortion (4+), miscarriage (4+)	
La Vecchia *et al.* 1987[22] (Italy)	Hospital case-control	576	NA	MI	Hx of abortion; Recurrent miscarriage (2+)	Poor
Lin *et al.* 2018[23] (Taiwan)	Nested case-control	72 750	7.6 years	IHD	Recurrent abortion (2+), miscarriage (2+)	Poor
Lykke *et al.* 2010[24] (Denmark)	Retrospective cohort	782 287	14.8 years	CVD mortality	Hx of stillbirth	Poor
Maino *et al.* 2016[25] (The Netherlands)	Hospital case-control	1126	NA	Ischaemic stroke	Hx of miscarriage (early), stillbirth	Poor
				MI	Hx of miscarriage (early), stillbirth	
Pariente *et al.* 2014[26] (Israel)	Retrospective cohort	99 280	25 years	CVD hospitalization	Hx of stillbirth; Recurrent stillbirth (2+)	Poor
Parikh *et al.* 2016[27] (USA)	Prospective cohort	72 982	12 years	CHD	Hx of stillbirth (1+); Recurrent miscarriage (5+), stillbirth (2+)	Good
Parker *et al.* 2014[28] (USA)	Prospective cohort	77 701	7.7 years	CHD	Hx of stillbirth; Recurrent miscarriage (2+)	Fair
				Stroke	Hx of miscarriage (1); stillbirth; Recurrent miscarriage (2+)	
Pell *et al.* 2004[29] (Scotland)	Retrospective cohort	119 668	14–19 years	All stroke and TIA	Hx of abortion (prior to 1st live birth), miscarriage (prior to 1st live birth)	Fair
Peters *et al.* 2017[30] (China)	Prospective cohort	289 573	7.1 years	CHD	Hx of abortion, miscarriage, stillbirth; Recurrent abortion (3+), miscarriage (3+), stillbirth (3+)	Fair
				CVD	Hx of abortion, miscarriage, stillbirth; Recurrent abortion (3+), miscarriage (3+), stillbirth (3+)	
				Stroke	Hx of abortion, miscarriage, stillbirth; Recurrent abortion (3+), miscarriage (3+)	
Peters *et al.* 2018[31] (UK)	Prospective cohort	267 440	7.1 years	Incident CHD	Hx of miscarriage, stillbirth; Recurrent miscarriage (2+), stillbirth (2+)	Fair
				Incident CVD	Hx of miscarriage, stillbirth; Recurrent miscarriage (2+), stillbirth (2+)	
				Incident stroke	Hx of miscarriage, stillbirth, Recurrent miscarriage (2+), stillbirth (2+)	

Continued

Table 1 *Continued*

Study (country)	Study design	Total *n*	Follow-up	Outcome(s)	Exposure(s)	Quality[a]
Ranthe *et al.* 2013[32] (Denmark)	Prospective cohort	1 031 279	15.5 years	Cerebral infarctions MI	Hx of miscarriage, stillbirth; Recurrent miscarriage (4+) Hx of miscarriage, stillbirth; Recurrent miscarriage (4+)	Good
Smith *et al.* 2003[33] (Scotland)	Retrospective cohort	129 290	18 years	CHD	Hx of miscarriage (1 + prior 1st live birth); Recurrent miscarriage (3 + prior 1st live birth)	Fair
Wagner *et al.* 2015[34] (Scotland)	Retrospective cohort	60 105	17 years	Cerebrovascular disease IHD Total CVD or cardiac surgery	Hx of miscarriage (1+) Consecutive miscarriage (≥3); Non-consecutive miscarriage Consecutive miscarriage (≥3); Hx of miscarriage	Good
Winkelstein *et al.* 1958[35] (USA)	Community case-control	100	NA	MI and positive ECG findings	Hx of miscarriage; Recurrent miscarriage (3+)	Poor

Number of studies = 22.
CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; Hx, history; IHD, ischaemic heart disease; MI, myocardial infarction; *n*, number of women; NA, not applicable; TIA, transient ischaemic attack; UK, United Kingdom; USA, United States of America.
[a]Study quality determined using the Agency for Healthcare Research and Quality (AHRQ) standards.

although CHD risk associated with a history of stillbirth was diminished, RR = 1.09 (1.03–1.16). When analyses were limited to studies that had performed the Cox proportional hazards regression model, results were broadly consistent, except for the history of stillbirth analysis, which was no longer significant, HR = 1.57 (0.91–2.71) (see Supplementary material online, *Figure S8*).

Stroke

Eight studies examined overall stroke risk. Seven studies[20,21,28–32,34] including 1 853 783 women examined overall stroke risk associated with a history of miscarriage and five studies[21,28,30–32] including 1 748 656 women assessed risk associated with recurrent miscarriages (see Supplementary material online, *Table S15*). Six studies[21,28,30–32] including 1 646 726 women and two studies[30,31] including 557 013 women assessed risk associated with a history of stillbirth and recurrent stillbirth, respectively (see Supplementary material online, *Table S16*). Three studies[21,29,30] including 413 509 women and two studies[21,30] including 298 715 women assessed risk in women with a history of abortion and recurrent abortions, respectively (see Supplementary material online, *Table S17*).

Supplementary material online, *Figure S9* shows the results of the systematic review and meta-analyses of stroke risk. Meta-analysis did not find a higher stroke risk in women with a history of one or more miscarriages, RR = 1.05 (0.88–1.25) with moderate levels of between-study heterogeneity ($I^2 = 66.0\%$, $P = 0.007$). Women with recurrent miscarriage were also not at higher risk, RR = 1.05 (0.89–1.24), with no evidence of between-study heterogeneity ($I^2 = 0.0\%$, $P = 0.421$). Higher stroke risk was found for women with a history of stillbirth, RR = 1.33 (1.03–1.71), with high levels of between-study heterogeneity ($I^2 = 74.6\%$, $P = 0.001$). This was not found in the meta-analysis of recurrent stillbirth, RR = 1.17 (0.05–24.76), with moderate levels of between-study heterogeneity ($I^2 = 59.6\%$, $P = 0.116$). No higher stroke risk was found for women with a history of abortion, RR = 1.05 (0.92–1.21), or recurrent abortion, RR = 1.18 (0.06–30.09), with no evidence of between-study heterogeneity in either meta-analysis ($I^2 = 0.0\%$, $P = 0.671$) and ($I^2 = 0.0\%$, $P = 0.389$), respectively.

When studies that assessed either ischaemic or haemorrhagic stroke alone[18,25] were included in the meta-analysis the findings did not change (see Supplementary material online, *Figure S10*).

Excluding poorly adjusted studies had little impact on the findings (see Supplementary material online, *Figure S11*) nor did restricting analyses to studies at low RoB (see Supplementary material online, *Figure S12*). Conducting fixed-effects meta-analyses to estimate the relationships specifically in the overall populations found some differences (see Supplementary material online, *Table S18*). The exceptions were a significantly higher risk was found for history of miscarriage, RR = 1.06 (1.02–1.09), history of abortion, RR = 1.04 (1.01–1.07), and recurrent abortion, RR = 1.09 (1.04–1.15), as well as a diminished association for a history of stillbirth, RR = 1.10 (1.04–1.15). When analyses were limited to studies that had performed the Cox proportional hazards regression model, results were broadly consistent with the random-effects model, except for the history of stillbirth analysis, which was no longer significant, HR = 1.36 (0.92–2.01) (see Supplementary material online, *Figure S13*).

Small study effects

Neither of the funnel plots for CHD risk associated with a history of miscarriage and recurrent miscarriage showed asymmetry (Egger test, $P = 0.325$ and $P = 0.209$, respectively) (see Supplementary material online, *Figures S14 and S15*).

GRADE assessment

Downgrading due to RoB, inconsistency and imprecision resulted in low to very low evidence in all meta-analyses except recurrent

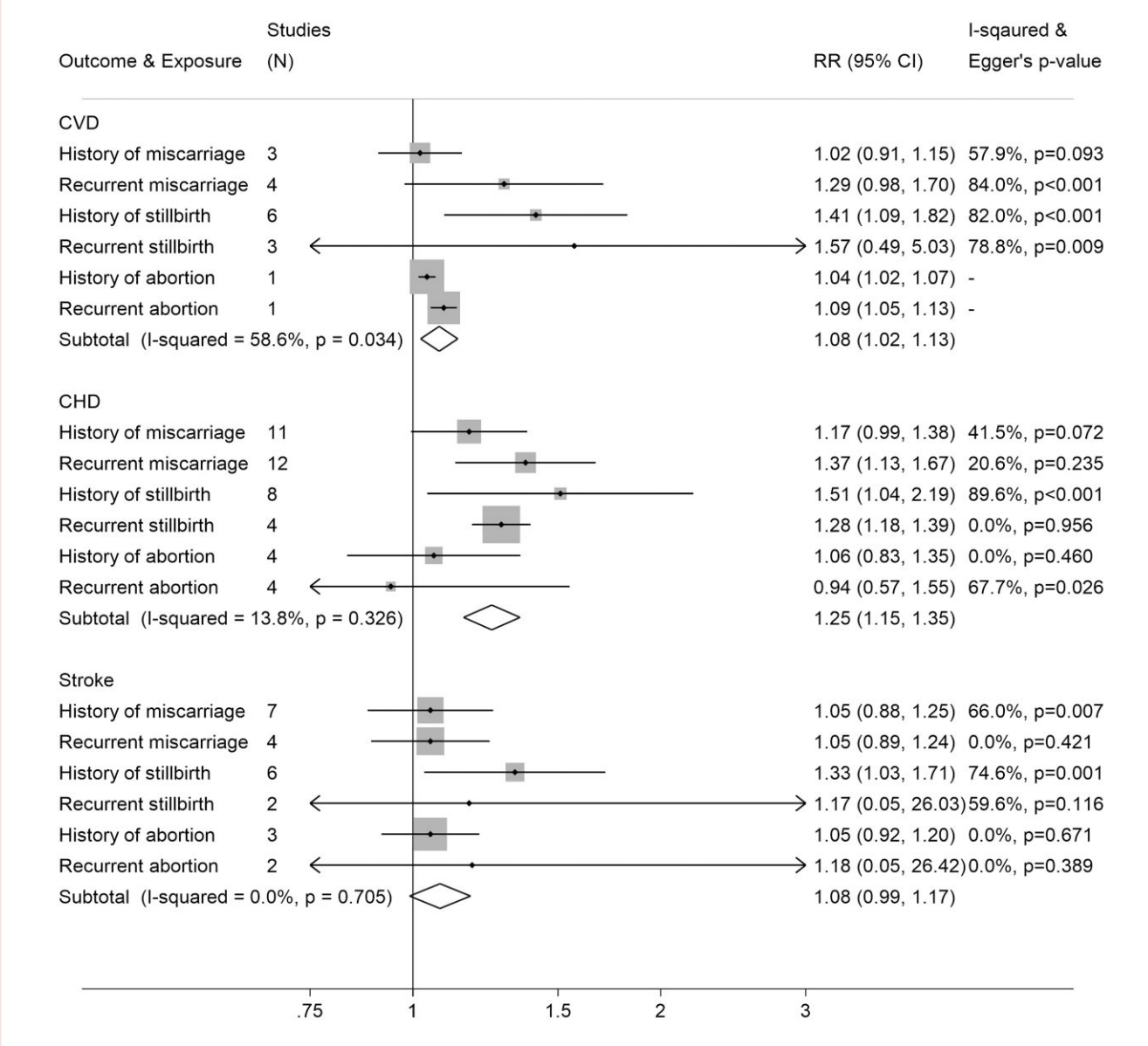


Figure 2 Summary of random-effects meta-analyses of pregnancy loss and risk of cardiovascular disease, coronary heart disease and stroke. CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; RR, relative risk.

miscarriage and CHD, which was rated as moderate due to a dose-response relationship (recurrent miscarriage is associated with a higher risk than a history of miscarriage) (see Supplementary material online, *Table S19*).

Discussion

Main findings

This is, to our knowledge, the first meta-analysis comprehensively investigating the associations between pregnancy loss and future CVD risk. We identified a higher CVD risk for women with a history of stillbirth, and a history of recurrent abortion. Higher CHD risk was found for women with a history of recurrent miscarriage, a history of one or more stillbirths or recurrent stillbirth. Higher stroke risk was found for women with a history of stillbirth.

Strengths and limitations

This review has multiple strengths. It evaluated several forms of pregnancy loss and CVD, providing a comprehensive picture. It employed a wide-ranging search strategy of five databases, and it included over 4.3 million women across three continents.

However, limitations remain. Although five databases were searched without language or time restrictions relevant studies may have been missed. Additionally, some pregnancy losses may have been unreported. Miscarriage, for example, can often go undetected in early pregnancy. It is also a sensitive topic which some women may not want to disclose. The same applies to abortion, which can carry a social stigma and may be achieved by unconventional means due to accessibility issues. This may have led to underestimates of exposed women, resulting in differential misclassification, which would bias results towards the null. Geographical diversity of healthcare models, medical standards and legislature, may also mean that this review's results are

not generalisable to all settings, despite the inclusion of studies from three continents.

Residual confounding may have impacted the findings, although the exclusion of poorly adjusted studies had little impact on the results. Pregnancy complications should be considered as potential confounders of the association between pregnancy loss and CVD. Many pregnancy complications are associated with pregnancy loss and CVD.[36,37] Few studies adjusted for pregnancy complications, although the one study that did found adjustment had little impact on the association between miscarriage and CHD.[33] Between-study heterogeneity was noted in some meta-analyses, although the exclusion of poor-quality studies had little impact on this. Other factors which may be responsible for this include: (i) population differences, such as differential inclusion of premenopausal women who may experience subsequent pregnancy loss; (ii) differential case ascertainment and case definitions for CHD and stroke; and (iii) varying adjustment levels.

Interpretation

The American Heart Association and the American College of Obstetricians and Gynecologists recommend CVD screening starting in the first 3 months post-partum for women with adverse pregnancy outcomes including any history of miscarriage or stillbirth.[1,38] This review's findings underscore that recurrent miscarriage should be explicitly included in guidelines. It also highlights the question of how easily women who have experienced miscarriages can be identified for screening, as women may not approach medical professionals when miscarrying.

Some differences between the random-effects model and the fixed-effects model were noted. The fixed-effects model estimates the relationships specifically in the populations studied, while random-effects models estimate the association in the underlying population. In CVD and CHD analyses, all forms of pregnancy loss were associated with a higher risk in fixed-effects models, although the point estimates were comparable between models. The difference in significance is likely due to the random-effects model having less power, but this emphasizes the need for further research into the cardiovascular implications of pregnancy loss to accurately ascertain the presence and magnitude of the risk.

The aetiological links underlying the observed associations between miscarriage and CHD, and stillbirth and CVD, warrant further discussion. Women who experience miscarriage or stillbirth may have a pre-existing predisposition to CVD that unmasks itself during pregnancy, leading to pregnancy loss. This theory is supported by multiple joint risk factors for miscarriage or stillbirth and CVD, including body mass index,[39,40] and chronic maternal disorders, such as diabetes,[41,42] polycystic ovary syndrome,[43,44] and chronic kidney disease.[45,46] Alternatively, or in addition, the physiological changes that occur during pregnancy, especially pregnancies that end in stillbirth and miscarriage, may have long-term consequences on maternal health.

Several reviews have investigated CVD risk after stillbirth or miscarriage.[5,6] The results of this meta-analysis are in line with prior reviews and build upon them by including abortion. Induced abortion was hypothesised to represent a natural control for miscarriages. An increased risk of CVD was found for women with a history of recurrent abortion in a single study. This finding may be because the cessation of a pregnancy in and of itself, as opposed to the pathophysiology underlying miscarriage, may contribute to CVD risk. Alternatively, women who access abortions may be more likely to have pre-existing medical conditions that predispose them to developing CVD. For example, women who have type 1 diabetes may be more likely to have an abortion[47] and are at a higher CVD risk.[42] Alternatively, residual confounding may have led to the observed association.

Recent research using a large low-income American population also adds to the weight of evidence linking abortion to cardiovascular outcomes.[48] After adjusting for multiple confounders, women whose first pregnancy ended in either miscarriage or abortion were 18% more likely to develop CVD and more likely to have a haemorrhagic stroke compared with women with only live births. Unfortunately, the American study ($n = 1\,157\,980$) did not segregate the results associated with miscarriage and abortion separately. In the present meta-analysis, a significantly higher risk of stroke was not found for either abortion or miscarriage, though higher risks were identified in two individual studies. Given this and the findings of our meta-analysis, more research is required to fully elucidate the nature and mechanisms underlying associations between abortion and CVD.

Conclusion

Women with a history of any form of pregnancy loss are at higher CVD risk. This study highlights the potential CVD burden for women with prior pregnancy loss, emphasising the need for risk-factor screening and early management after pregnancy loss.

Lead author biography

Dr H. Kyriacou, Dr A. Al-Mohammad, and Dr C. Muehlschlegel are joint first authors and studied medicine at the University of Cambridge. Dr Harry Kyriacou, MBBChir BA (Hons) is currently a postgraduate doctor training at Guy's and St Thomas' NHS Foundation Trust. Dr Abdulrahman Al-Mohammad, MBBChir BA (Hons) is currently a foundation trainee doctor at Barking, Havering and Redbridge University Hospitals NHS Trust. Dr Charlotte Muehlschlegel, MBBChir BA (Hons) is currently a foundation trainee doctor at University College London Hospitals NHS Foundation Trust.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

F.S.-J. and C.O.-W. conceived and designed the study including the search strategy. H.K., A.A.-M., C.M., L.F.-D., F.S.-J., and C.O.-W. were involved in project development. H.K., A.A.-M., C.M., L.F.-D., M.E.F.B., and F.S.-J. were involved in abstract/full-text screening. All authors were involved in data extraction and study quality assessment. C.O.-W., H.K. and A.A.-M. performed the data analysis. The manuscript was written and edited by H.K., A.A.-M., C.M., L.F.-D., F.S.-J., and C.O.-W. All authors have read the final manuscript and given approval for publication.

Funding

C.O.-W. received funding from Homerton College, University of Cambridge. This work was supported by core funding from the UK Medical Research Council (MR/L003120/1), the British Heart Foundation (RG/13/13/30194; RG/18/13/33946), and the National Institute for Health Research (Cambridge Biomedical Research Centre at the Cambridge University Hospitals NHS Foundation Trust). F.S-J receives funding from Health Education England, the University of East Anglia and University of Cambridge. The funders had no role in the development of the systematic review. The authors confirm that the data supporting the

findings of this study are available within the article [and/or] its supplementary materials.

Conflict of interest: C.O-W received payment for a lecture from the American Heart Assoication. F.S-J is an honorary Associate Lecturer in Public Health at Anglia Ruskin University and a Member of Faculty of Public Health Equality, Diversity and Inclusion Committee (both roles are unpaid).

References

1. Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, Gunderson EP, Stuart JJ, Vaidya D. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. *Circulation* 2021;**143**:E902–E916.
2. Kortsmit K, Mandel MG, Reeves JA, Clark E, Pagano HP, Nguyen A, Petersen EE, Whiteman MK. Abortion surveillance—United States, 2019. *MMWR Surveill Summ* 2021;**70**:1–29.
3. Department of Health & Social Care. Abortion statistics, England and Wales: 2020—GOV.UK. https://www.gov.uk/government/statistics/abortion-statistics-for-england-and-wales-2020/abortion-statistics-england-and-wales-2020 (3 June 2022).
4. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, Flenady V, Frøen JF, Qureshi ZU, Calderwood C, Shiekh S, Jassir FB, You D, McClure EM, Mathai M, Cousens S, Kinney MV, de Bernis L, Heazell A, Leisher SH, Azad K, Rahman A, El-Arifeen S, Day LT, Saha SL, Alam S, Wangdi S, Ilboudo TF, Zhu J, Liang J, Mu Y, Li X, Zhong N, Kyprianou T, Allvee K, Gissler M, Zeitlin J, Bah A, Jawara L, Lack N, Herandez FM, More NS, Nair N, Tripathy P, Kumar R, Newtonraj A, Kaur M, Gupta M, Varghese B, Isakova J, Phiri T, Hall JA, Curteanu A, Manandhar D, Hukkelhoven C, Dijs-Elsinga J, Klungsøyr K, Poppe O, Barros H, Correia S, Tsiklauri S, Cap J, Podmanicka Z, Szamotulska K, Pattison R, Hassan AA, Musafili A, Kujala S, Bergstrom A, Langhoff-Roos J, Lundqvist E, Kadobera D, Costello A, Colbourn T, Fottrell E, Prost A, Osrin D, King C, Neuman M, Hirst J, Rubayet S, Smith L, Manktelow BN, Draper ES. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016;**387**:587–603.
5. Oliver-Williams CT, Heydon EE, Smith GCS, Wood AM. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. *Heart* 2013;**99**:1636–1644.
6. Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, Adderley NJ. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. *BMJ* 2020;**371**:m3502.
7. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–2012.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, Atkins D, Barbour V, Barrowman N, Berlin JA, Clark J, Clarke M, Cook D, D'Amico R, Deeks JJ, Devereaux PJ, Dickersin K, Egger M, Ernst E, Gøtzsche PC, Grimshaw J, Guyatt G, Higgins J, Ioannidis JPA, Kleijnen J, Lang T, Magrini N, McNamee D, Moja L, Mulrow C, Napoli M, Oxman A, Pham B, Rennie D, Sampson M, Schulz KF, Shekelle PG, Tovey D, Tugwell P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.
9. Muehlschlegel C, Kyriacou H, Al-Mohammad A, Foster-Davies LA, Simmons-Jones F, Oliver-Williams C. The risk of cardiovascular disease in women after miscarriage, stillbirth, and therapeutic abortion: a protocol for a systematic review and meta-analysis. *Syst Rev* 2020;**9**:234.
10. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;**25**:603–605.
11. Viswanathan M, Ansari M, Berkman N, Chang S, Hartling L, McPheeters L, Santaguida P, Shamliyan T, Singh K. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.Rockville, MD: Agency for Healthcare Research and Quality; 2008.
12. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE Guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol* 2011;**64**:380–382.
13. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–634.
14. Bertuccio P, Tavani A, Gallus S, Negri E, La Vecchia C. Menstrual and reproductive factors and risk of non-fatal acute myocardial infarction in Italy. *Eur J Obstet Gynecol Reprod Biol* 2007;**134**:67–72.
15. Bonamy AKE, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. *Circulation* 2011;**124**:2839–2846.
16. Calderon-Margalit R, Friedlander Y, Yanetz R, Deutsch L, Manor O, Harlap S, Paltiel O. Late stillbirths and long-term mortality of mothers. *Obstet Gynecol* 2007;**109**:1301–1308.
17. Cooper G, Ephross S, Weinberg C, Bair D, Whelan E, Sandler D. Menstrual and reproductive risk factors for ischemic heart disease—PubMed. *Epidemiology* 1999;**10**:255–259.
18. Gallagher LG, Davis LB, Ray RM, Psaty BM, Gao DL, Checkoway H, Thomas DB. Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai, China. *Int J Epidemiol* 2011;**40**:1510–1518.
19. Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Holcberg G, Sheiner E. Recurrent pregnancy loss: a risk factor for long-term maternal atherosclerotic morbidity? *Am J Obstet Gynecol* 2014;**211**:414.e1–414.e11.
20. Kharazmi E, Fallah M, Luoto R. Miscarriage and risk of cardiovascular disease. *Acta Obstet Gynecol Scand* 2010;**89**:284–288.
21. Kharazmi E, Dossus L, Rohrmann S, Kaaks R. Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). *Heart* 2011;**97**:49–54.
22. La Vecchia C, Decarli A, Franceschi S, Gentile A, Negri E, Parazzini F. Menstrual and reproductive factors and the risk of myocardial infarction in women under fifty-five years of age. *Am J Obstet Gynecol* 1987;**157**:1108–1112.
23. Lin TB, Hsieh MF, Hou YC, Hsueh YL, Chang HP, Tseng YT. Long-term physical health consequences of abortion in Taiwan, 2000 to 2013: a nationwide retrospective cohort study. *Medicine (Baltimore)* 2018;**97**:e11785.
24. Lykke JA, Langhoff-Roos J, Lockwood CJ, Triche EW, Paidas MJ. Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery. *Paediatr Perinat Epidemiol* 2010;**24**:323–330.
25. Maino A, Siegerink B, Algra A, Martinelli I, Peyvandi F, Rosendaal FR. Pregnancy loss and risk of ischaemic stroke and myocardial infarction. *Br J Haematol* 2016;**174**:302–309.
26. Pariente G, Shoham-Vardi I, Kessous R, Sergienko R, Sheiner E. Is stillbirth associated with long-term atherosclerotic morbidity? *Am J Obstet Gynecol* 2014;**211**:416.e1–416.e12.
27. Parikh NI, Jeppson RP, Berger JS, Eaton CB, Kroenke CH, Leblanc ES, Lewis CE, Loucks EB, Parker DR, Rillamas-Sun E, Ryckman KK, Waring ME, Schenken RS, Johnson KC, Edstedt-Bonamy AK, Allison MA, Howard BV. Reproductive risk factors and coronary heart disease in the Women's Health Initiative Observational Study. *Circulation* 2016;**133**:2149–2158.
28. Parker DR, Lu B, Sands-Lincoln M, Kroenke CH, Lee CC, O'Sullivan M, Park HL, Parikh N, Schenken RS, Eaton CB. Risk of cardiovascular disease among postmenopausal women with prior pregnancy loss: the women's health initiative. *Ann Fam Med* 2014;**12**:302–309.
29. Pell JP, Smith GCS, Walsh D. Pregnancy complications and subsequent maternal cerebrovascular events: a retrospective cohort study of 119,668 births. *Am J Epidemiol* 2004;**159**:336–342.
30. Peters SAE, Yang L, Guo Y, Chen Y, Bian Z, Tian X, Chang L, Zhang S, Liu J, Wang T, Chen J, Li L, Woodward M, Chen Z, Collins R, Peto R, Avery D, Bennett D, Chang Y, Chen Y, Chen Z, Clarke R, Du H, Fan X, Gilbert S, Hacker A, Holmes M, Iona A, Kartsonaki C, Kerosi R, Kong L, Kurmi O, Lancaster G, Lewington S, McDonnell J, Mei W, Millwood I, Nie Q, Radhakrishnan J, Rafiq S, Ryder P, Sansome S, Schmidt D, Sherliker P, Sohoni R, Turnbull I, Walters R, Wang J, Wang L, Yang X, Chen G, Han B, Hou C, Lv J, Pei P, Qu S, Tan Y, Yu C, Zhou H, Pang Z, Gao R, Wang S, Liu Y, Du R, Zang Y, Cheng L, Zhang H, Lv S, Wang J, Hou W, Yin J, Jiang G, Liu S, Pang Z, Zhou X, Yang L, He H, Yu B, Li Y, Mu H, Xu Q, Dou M, Ren J, Du J, Wang S, Hu X, Wang H, Chen J, Fu Y, Fu Z, Wang X, Dong H, Weng M, Zheng X, Li Y, Li H, Li C, Wu M, Zhou J, Tao R, Yang J, Shen J, Hu Y, Lu Y, Gao Y, Ma L, Zhou R, Tang A, Jin J, Tang Z, Chen N, Huang Y, Li M, Meng J, Pan R, Jiang Q, Qing J, Zhang W, Liu Y, Wei L, Zhou L, Chen N, Yang J, Guan H, Wu X, Zhang N, Chen X, Tang X, Luo G, Li J, Chen X, Wang J, Sun Q, Ge P, Ren X, Dong C, Zhang H, Mao E, Wang X, Liu G, Zhu B, Zhou G, Feng S, Fan L, Gao Y, He T, Jiang L, Sun H, He P, Hu C, Lv Q, Zhang X, Yu M, Hu R, Fang L, Wang H, Qian Y, Wang C, Xie K, Chen L, Pan Y, Pan D, Huang Y, Chen B, Jin D, Liu H, Fu Z, Xu Q, Xu X, Xiong Y, Jia W, Li X, Zhang L, Qiu Z. Pregnancy, pregnancy loss, and the risk of cardiovascular disease in Chinese women: findings from the China Kadoorie Biobank. *BMC Med* 2017;**15**:148.
31. Peters SAE, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. *Heart* 2018;**104**:1069–1075.
32. Ranthe MF, Andersen EAW, Wohlfahrt J, Bundgaard H, Melbye M, Boyd HA. Pregnancy loss and later risk of atherosclerotic disease. *Circulation* 2013;**127**:1775–1782.
33. Smith GCS, Pell JP, Walsh D. Spontaneous loss of early pregnancy and risk of ischaemic heart disease in later life: retrospective cohort study. *BMJ* 2003;**326**:423–424.
34. Wagner MM, Bhattacharya S, Visser J, Hannaford PC, Bloemenkamp KWM. Association between miscarriage and cardiovascular disease in a Scottish cohort. *Heart* 2015;**101**:1954–1960.
35. Winkelstein W, Stenchever MA, Lilienfeld AM. Occurrence of pregnancy, abortion, and artificial menopause among women with coronary artery disease: a preliminary study. *J Chronic Dis* 1958;**7**:273–286.
36. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Ray JG, Nerenberg K, Platt RW. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. *Circulation* 2019;**139**:1069–1079.

37. Oliver-Williams C, Fleming M, Wood A, Smith G. Previous miscarriage and the subsequent risk of preterm birth in Scotland, 1980–2008: a historical cohort study. *BJOG* 2015;**122**:1525–1534.
38. Brown HL, Warner JJ, Gianos E, Gulati M, Hill AJ, Hollier LM, Rosen SE, Rosser ML, Wenger NK. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists: a presidential advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. *Circulation* 2018;**137**:e843–e852.
39. Ng KYB, Cherian G, Kermack AJ, Bailey S, Macklon N, Sunkara SK, Cheong Y. Systematic review and meta-analysis of female lifestyle factors and risk of recurrent pregnancy loss. *Sci Rep* 2021;**11**.
40. Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, Gupta PC, Ramadas K, Inoue M, Tsugane S, Tamakoshi A, Gao YT, Yuan JM, Shu XO, Ozasa K, Tsuji I, Kakizaki M, Tanaka H, Nishino Y, Chen CJ, Wang R, Yoo KY, Ahn YO, Ahsan H, Pan WH, Chen CS, Pednekar MS, Sauvaget C, Sasazuki S, Yang G, Koh WP, Xiang YB, Ohishi W, Watanabe T, Sugawara Y, Matsuo K, You SL, Park SK, Kim DH, Parvez F, Chuang SY, Ge W, Rolland B, McLerran D, Sinha R, Thornquist M, Kang D, Feng Z, Boffetta P, Zheng W, He J, Potter JD. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. *BMJ* 2013;**347**:f5446.
41. Mackin ST, Nelson SM, Kerssens JJ, Wood R, Wild S, Colhoun HM, Leese GP, Philip S, Lindsay RS. Diabetes and pregnancy: national trends over a 15 year period. *Diabetologia* 2018;**61**:1081–1088.
42. Huxley RR, Peters SAE, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015;**3**:198–206.
43. Sha T, Wang X, Cheng W, Yan Y. A meta-analysis of pregnancy-related outcomes and complications in women with polycystic ovary syndrome undergoing IVF. *Reprod Biomed Online* 2019;**39**:281–293.
44. Zhang J, Xu JH, Qu QQ, Zhong GQ. Risk of cardiovascular and cerebrovascular events in polycystic ovarian syndrome women: a meta-analysis of cohort studies. *Front Cardiovasc Med* 2020;**7**:552421.
45. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;**108**:2154–2169.
46. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ* 2008;**336**:211–215.
47. Sjöberg L, Kaaja R, Gissler M, Tuomilehto J, Tiitinen A, Pitkäniemi J. Termination of pregnancy and sterilisation in women with childhood-onset type 1 diabetes. *Diabetologia* 2017;**60**:2377–2383.
48. Tsulukidze M, Reardon D, Craver C. Elevated cardiovascular disease risk in low-income women with a history of pregnancy loss. *Open Heart* 2022;**9**:e002035.