Does self-reported pregnancy loss identify women at risk of an adverse cardiovascular phenotype in later life? Insights from UK Biobank

Einah Elmahi, Mihir M. Sanghvi, Alexander Jones, Christina Y. L. Aye, Adam J. Lewandowski, Nay Aung, Jackie A. Cooper, Jose Miguel Paiva, Elena Lukaschuk, Stefan K. Piechnik, Stefan Neubauer, Steffen E. Petersen, Paul Leeson

1 Oxford Cardiovascular Clinical Research Facility, Radcliffe Department of Medicine, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom
2 William Harvey Research Institute, NIHR Biomedical Research Centre at Barts, Queen Mary University of London, Charterhouse Square, London, Unite Kingdom
3 Department of Paediatrics, Children's Hospital, John Radcliffe, University of Oxford, Oxford, United Kingdom
4 The Nuffield Department of Women's & Reproductive Health, Medical Science Division, University of Oxford, Oxford, United Kingdom
5 Oxford Centre for Clinical Magnetic Resonance Research, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom

‡ Einas Elmahi and Mihir M. Sanghvi are joint first Authors on this work.
* paul.leeson@cardiov.ox.ac.uk

Abstract

Introduction

Cardiovascular disease (CVD) is more common in women who have had pregnancy complications such as spontaneous pregnancy loss. We used cross-sectional data from the UK Biobank Imaging Enhancement Study to determine whether pregnancy loss is associated with cardiac or vascular remodelling in later life, which might contribute to this increased risk.

Methods

Pregnancy history was reported by women participating in UK Biobank between 2006 and 2010 at age 40–69 years using a self-completed touch-screen questionnaire. Associations between self-reported spontaneous pregnancy loss and cardiovascular measures, collected in women who participated in the Imaging Enhancement Study up to the end of 2015, were examined. Cardiac structure and function were assessed by magnetic resonance (CMR) steady-state free precession imaging at 1.5 Tesla. Carotid intima-media thickness (CIMT) measurements were taken for both common carotid arteries using a CardioHealth Station. Statistical associations with CMR and carotid measures were adjusted for age, BMI and other cardiovascular risk factors.

Results

Data were available on 2660 women of whom 111 were excluded because of pre-existing cardiovascular disease and 30 had no pregnancy information available. Of the remaining
2519, 446 were nulligravid and 2073 had a history of pregnancies, of whom 622 reported at least one pregnancy loss (92% miscarriages and 8% stillbirths) and 1451 reported no pregnancy loss. No significant differences in any cardiac or carotid parameters were evident in women who reported pregnancy loss compared to other groups (Table 1).

Conclusion
Women who self-report pregnancy loss do not have significant differences in cardiac structure, cardiac function, or carotid structure in later life to explain their increased cardiovascular risk. This suggests any cardiovascular risks associated with pregnancy loss operate through other disease mechanisms. Alternatively, other characteristics of pregnancy loss, which we were not able to take account of, such as timing and number of pregnancy losses may be required to identify those at greatest cardiovascular risk.

Introduction
Spontaneous pregnancy loss is the most common and least studied complication of pregnancy, with 32% of all conceptions (clinically and non-clinically apparent pregnancy loss) resulting in loss of the fetus and about 15% of all clinically-recognized pregnancies failing to survive to delivery [1, 2]. A history of pregnancy loss (miscarriage and stillbirth) is linked to coronary artery disease (CAD) in later life[3]. In a meta-analysis of ten cohort and case-control studies, women with a history of a single pregnancy loss were reported to have 45% increased risk of CAD but not of other CVD or stroke, while the risk in women with recurrent pregnancy loss was doubled [4, 5]. Women who had more than three miscarriages had a nine-fold greater risk of myocardial infarction (MI) and those who had a stillbirth were nearly three times as likely to experience a coronary disease event [6]. The risk of future MI associated with pregnancy loss appears to be independent of other atherosclerotic cardiovascular disease (ASCVD) risk factors and directly proportional to the number of pregnancy losses [6, 7]. Deeper understanding of mechanisms that underpin these associations is therefore required if optimal ways to protect the future cardiovascular health of those who suffer pregnancy loss are to be identified[8].

Non-invasive measures of cardiovascular structure and function have demonstrable value in prediction of future CVD risk and are not entirely determined by the existence of traditional risk factors, such as hypertension. Abnormal cardiovascular magnetic resonance (CMR) measures of left ventricular (LV) geometry and LV hypertrophy (LVH) describe a cardiac phenotype that adds supplemental risk to that predicted by traditional cardiovascular risk factors [9]. Carotid intima-media thickness (CIMT) provides an assessment of the severity of vascular wall changes associated with an individual risk profile. Therefore, we used these early markers of cardiovascular risk to investigate whether pregnancy loss was associated with a high-risk cardiovascular phenotype in a large cross-sectional cohort of women from the UK Biobank Imaging Enhancement Study. The hypothesis was that the known association of pregnancy loss with cardiovascular disease risk, which is not explained by traditional risk factors, might be in part explained by abnormal cardiac and vascular re-modelling.

Material and methods
Ethical approval
The UK Biobank study has been approved by the—North West—Haydock Research Ethics Committee (REC reference: 16/NW/0274). The committee gave a favourable ethical opinion of
the UK Biobank research and has also confirmed that the favourable ethical opinion applies to all research projects conducted in the UK using tissue or data supplied by the tissue bank, provided that the release of the tissue or data complies with the committee’s specific conditions.

Table 1. Participant characteristics.

| Variable                        | No History of Pregnancy Loss (n = 1451 [57%]) | History of Pregnancy Loss (n = 622 [24.7%]) | Nulligravid (n = 446 [17.7%]) | P (ANOVA) |
|---------------------------------|---------------------------------------------|--------------------------------------------|--------------------------------|-----------|
| **BMI (Kg/m²)**                 | 26.1 ± 4.5                                  | 26.5 ± 4.6                                 | 26.1 ± 5.0                    | 0.1       |
| Systolic BP (mmHg)              | 134.0 ± 18.8                                | 134.0 ± 19.1                               | 129.4 ± 17.4                  | <0.001    |
| Diastolic BP (mmHg)             | 77.6 ± 9.8                                  | 77.5 ± 10.0                                | 76.6 ± 9.8                    | 0.2       |
| Hypercholesterolemia (Y/N)     | 14.1% (204)                                 | 15.4% (96)                                 | 12.8% (57)                    | 0.5       |
| Diabetes (Y/N)                 | 3.2% (46)                                   | 3.5% (22)                                  | 4.9% (22)                     | 0.2       |
| Caucasian Ethnicity (Y/N)      | 97.8% (1419)                                | 96.6% (601)                                | 97.5% (435)                   | 0.3       |
| Height (cm)                    | 163.1 ± 6.5                                 | 163.0 ± 6.1                                | 164.6 ± 6.9                   | <0.001    |
| Current smoker (Y/N)           | 3.3% (47)                                   | 4.1% (25)                                  | 3.6% (16)                     | 0.7       |
| Regular alcohol (Y/N)          | 37.7% (541)                                 | 37.1% (229)                                | 40.3% (179)                   | 0.5       |
| Accelerometry score (mean vector magnitude) | 28.4 ± 8.5                  | 28.7 ± 9.6                                | 28.4 ± 9.0                    | 0.8       |
| Townsend score                  | -2.10 ± 2.66                                | -2.0 ± 2.6                                 | -1.33 ± 2.8                   | <0.001    |
| Annual household income (£)    |                                             |                                           |                               |           |
| <18,000                         | 16.8% (226)                                 | 16.5% (96)                                 | ?                             |           |
| 18–30,999                       | 30.4% (409)                                 | 29.4% (171)                                | ?                             |           |
| 31–51,999                       | 28.0% (377)                                 | 29.7% (173)                                | ?                             |           |
| 52–100,000                      | 19.2% (258)                                 | 18.0% (105)                                | ?                             |           |
| >100,000                        | 5.6% (76)                                   | 6.4% (37)                                  | ?                             |           |
| Qualifications (degree/professional) | 58.7% (851)                   | -2.0 ± 2.6                                 | ??????                      |           |
| Aspirin use (Y/N)               | 4.8% (70)                                   | -2.0 ± 2.6                                 | 17.8% (76)                    | 0.6       |
| Number of live births—Median (IQR) | 2 (2–3)                                      | -2.0 ± 2.6                                 | 31.9% (136)                   | <0.001    |
| Number of live births—Median (IQR) | 0 (0–0)                                      | -2.0 ± 2.6                                 | 29.7% (127)                   | 0.95      |

https://doi.org/10.1371/journal.pone.0223125.T001

Study population

We studied 2,660 women, aged 40–69 years, from the UK Biobank Imaging Enhancement Study population (Fig 1). These women were assessed in 22 UK centres to provide socioeconomic and ethnic heterogeneity and an urban-rural mix. The UK Biobank study protocol is described in detail elsewhere [10].

As the aim of this study was to see whether pregnancy loss is associated with subclinical changes in cardiovascular structure and function i.e. before the development of CVD, women with a prior diagnosis of CAD were excluded from the analysis. All participants were asked to sign a written informed consent for imaging assessment.

Information on material deprivation, social deprivation, socioeconomic class and education were collected using the touch-screen self-administered questionnaire. Other information such as smoking and alcohol consumption, medical and reproductive history (including pregnancy history and any history of spontaneous pregnancy loss or stillbirth) were also included in the questionnaire, along with questions that allowed participants to be ranked according to their level of physical activity (vigorous, moderate and walking).

Baseline physical measurements were taken. Blood pressure (BP) was measured twice (a minute apart) using the Omron HEM-7015IT digital blood pressure monitor (recommended by the British Hypertension Society). Weight and height were measured using Tanita BC-418 MA body composition analysers and Seca 202 height measures, respectively.
The women were categorised into three groups, according to their reproductive history: (1) women with a history of pregnancy without loss; (2) women with a history of pregnancy loss; and (3) nulligravid women.

**CMR imaging protocol and analysis**

Each participant underwent a CMR protocol without pharmacological stressor or contrast agent. Cardiac measurements were made using balanced steady-state free precession (bSSFP) CMR imaging at 1.5 Tesla (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) [11] that included a complete short axis (SA) stack of bSSFP cines to allow assessment of volumes left ventricular function. The analysis in this study utilizes the manual analysis by two independent core labs according to standardized processing guidelines (https://jcmr-online.biomedcentral.com/articles/10.1186/s12968-017-0327-9).

**CIMT scanning protocol**

Ultrasound images of the common carotid arteries were obtained in short and long axes from low in the neck up to the jaw, at least to the level of the carotid bifurcation using a CardioHealth
Station (Panasonic Healthcare Corporation of North America, Newark, NJ, 19 USA), with a 9MHz linear array transducer. CIMT was measured at two angles for each carotid (150°/120° right and 210°/240° left) and the mean, maximum and minimum CIMT tracking for each carotid was recorded [12].

Statistical analysis
Prior to analysis, all dependent variables were assessed for normality using histograms and quartile-quartile plots. Natural logarithmic transformation was used where necessary to satisfy assumptions of normality. Outliers were defined as measurements more than three interquartile ranges below the first quartile or above the third quartile and were excluded.

We examined the impact of pregnancy loss, being pregnant without any previous miscarriages and never being pregnant on cardiac structure and function using regression models fitted for each cardiac (dependent) variable. Results are presented unadjusted and then adjusted by multiple regression for age, ethnicity, height, body mass index, systolic blood pressure, diastolic blood pressure, smoking, alcohol use, self-reported raised cholesterol, presence of diabetes, Townsend deprivation score, income, qualifications, live births, aspirin use, and physical activity as determined by accelerometer data. We used the same independent covariates in models examining relationships between pregnancy status and left-sided CIMT, right-sided CIMT and average CIMT.

Differences in means between groups were assessed by t-test or ANOVA, as appropriate, and differences in percentages were assessed using chi-squared tests.

The total proportion of data missing is 3.7% and 47.5% of the participants have missing data on at least one variable. Multiple imputations by chained equations (MICE) were used to impute missing data in 60 datasets, as follows. Predictive mean matching with five nearest neighbours was used for continuous variables and logistic regression for binary variables. All variables used in the analysis models were included in the imputation. Plots were examined to assess convergence and plausibility of estimates. The analysis was run on the 60 individual datasets and the results were pooled. The fraction of missing information for the pregnancy coefficients ranges from 0.009 (LVEF) to 0.088 (LAMaxV) indicating low variability between imputed datasets i.e. the observed data is providing adequate information about the missing data (Madley-Dowd et al.).

Descriptive statistics for continuous variables were presented as mean ± standard deviation or median and interquartile range (IQR), with categorical variables presented as number (percentage).

The ANOVA p values for CMR and CIMT measures were calculated from the F-statistics and reflect the overall between-group variability.

Results
Study population
Demographics for women with a history of pregnancy without loss (n = 1451), those with a history of pregnancy loss (n = 662), and nulligravidae (n = 446) are presented in Table 1 compared to nulligravidae. Women with a history of pregnancy were older, less educated and had a lower socioeconomic class. The significant difference in systolic blood pressure detected between all groups did not remain after adjustment for age and body mass index (BMI).

Cardiac parameters measured using CMR imaging
Cardiac indices measured for all groups are presented in Table 2. No significant differences were detected in CMR parameters between the groups after adjustment for potential confounders (Table 3).
Table 2. Unadjusted CMR cardiac geometry.

| Variable     | Pregnancy Status       | Means ± SE     | P value (ANOVA) |
|--------------|------------------------|----------------|-----------------|
| LVEDV (ml)   | Pregnancy Loss         | 124.0 ± 22.2   |                 |
|              | No pregnancy           | 125.9 ± 21.9   | 0.075           |
|              | Pregnancy (no loss)    | 123.1 ± 22.7   |                 |
| LVESV (ml)   | Pregnancy Loss         | 48.5 ± 12.1    |                 |
|              | No pregnancy           | 49.5 ± 12.0    | 0.017           |
|              | Pregnancy (no loss)    | 47.6 ± 12.5    |                 |
| LVSV (ml)    | Pregnancy Loss         | 74.5 ± 14.4    |                 |
|              | No pregnancy           | 75.6 ± 14.1    | 0.363           |
|              | Pregnancy (no loss)    | 74.5 ± 14.4    |                 |
| LVEF (%)     | Pregnancy Loss         | 60.4 ± 6.0     |                 |
|              | No pregnancy           | 60.4 ± 5.6     | 0.177           |
|              | Pregnancy (no loss)    | 60.9 ± 5.9     |                 |
| LVM (g)      | Pregnancy Loss         | 73.0 ± 14.1    |                 |
|              | No pregnancy           | 72.4 ± 13.7    | 0.501           |
|              | Pregnancy (no loss)    | 72.2 ± 14.2    |                 |
| LAMaxV (ml)  | Loss                   | 60.8 ± 16.5    |                 |
|              | No pregnancy           | 62.5 ± 18.1    | 0.051           |
|              | Pregnancy (no loss)    | 60.1 ± 18.3    |                 |
| LV Mass: Volume | Loss               | 0.59 ± 0.10   |                 |
| (Ratio in g/ml) | No pregnancy       | 0.58 ± 0.10   | 0.079           |
|              | Pregnancy (no loss)    | 0.59 ± 0.10    |                 |

CIMT measurements

Table 4 shows CIMT unadjusted measurements for both carotids (taken at different angles) for all groups with no significant differences identified between the groups before or after adjustment for potential confounders (Table 5).

Discussion

To our knowledge, this is the first study to investigate the relationship between self-reported pregnancy loss and maternal cardiovascular structure and function. Women with a greater burden of pregnancy loss have been found to have increased CVD risk in later life. In this large population of CVD-free women, we found no associations between pregnancy loss and later measures of cardiovascular geometry or function to explain that risk.

It has been proposed that pregnancy loss and CVD share a common pathophysiological mechanism and genetic predisposition and this suggestion has been supported by the observation that parents of women with recurrent pregnancy loss have a higher incidence of CAD [13].

Pregnancy loss and CVD also share common risk factors such as insulin resistance[14] and chronic kidney disease[15]. Endothelial dysfunction is also central to the development of atherosclerosis[16] and Germain et al. (2006) [17] hypothesised that endothelial dysfunction caused placentation defects in women who experienced recurrent pregnancy loss. The persistence of this dysfunction after a complicated pregnancy has therefore been proposed as a potential link with future cardiovascular events and recurrent pregnancy loss has been associated...
with lower endothelium-dependent as well as endothelium-independent vasodilatation. These observations have led some to postulate that women with a history of pregnancy loss may have underlying cardiovascular, microvascular, and/or homeostatic dysfunctions, which in turn lead to pregnancy complications during reproductive years and CAD in later life.

Therefore, it is reasonable to expect that women with a history of pregnancy loss might exhibit subclinical cardiac remodelling that influences their cardiovascular mortality and morbidity.

Some measures of cardiac remodelling, such as increased left ventricular mass (LVM), are known risk factors for CVD and adverse cardiovascular events [18, 19]. For example, Levy D et al [20] demonstrated that LVM increments of 50g/m (even within normal limits for mass)
are associated with 1.6x greater relative risk of CVD in women. Such LVM increases raise myocardial oxygen demand and reduce coronary blood supply reserve, resulting in supply-demand mismatch, which is associated with a higher risk of CAD. LVM normalised to cardiac volume (as a ratio) has been strongly associated with coronary events in asymptomatic individuals who are free of clinically apparent CVD [21]. Similarly, increased left atrial volume (LAV) in the context of sinus rhythm is a marker of left ventricular diastolic dysfunction and an established risk factor for CVD.

These markers of cardiac remodelling and function were measured using CMR, which is the gold standard technique for evaluating cardiac structure and function and detecting subclinical disease [22, 23]. Despite this, we detected no association of either pregnancy or pregnancy loss with cardiac geometry or function, when compared to a control group of similar women who had not been pregnant.

The incidence of failed pregnancies prior to becoming clinically recognised (diagnosed by urinary HCG) is far more than the incidence of spontaneous pregnancy loss in clinically recognised pregnancies[24–26]. As we used recall, women who experienced early pregnancy loss without a clinically recognised pregnancy, may have underreported very early pregnancy loss, which could have diluted associations with cardiac geometry. However, the evidence of association between pregnancy loss and higher risk of future CVD described in previous studies is also based on pregnancy loss reported by the women themselves.

Furthermore, early pregnancy loss is common [27] and its aetiology is usually different to that of mid and late trimester losses, being more commonly due to fetal chromosomal defects than due to abnormal placentation, for example [28]. Therefore, the overall impact of pregnancy loss on cardiac and vascular structure and function in this cohort could be diluted by the presence of other mechanisms unrelated to adverse cardiovascular outcomes.

We also measured carotid intima-media thickness (CIMT), a subclinical marker of vascular ageing / atherosclerosis that has been shown to reflect CVD risk profile and predict risk of future disease[29]. However, we were unable to demonstrate any significant differences between groups in CIMT measured at different angles. Diluted

Limitations

Pregnancy loss-timing (in gestational weeks) was not available making it impossible to examine the effect of the different stages of pregnancy loss (early and late) separately in this study.

Table 5. CIMT measurements adjusted for potential confounders.

| Carotid Artery | Pregnancy Status | Means (SE) | P        |
|---------------|-----------------|------------|----------|
| (measurement angle) |                  | (ANOVA)    |          |
| **Left (120°, 150°)** | Pregnancy Loss | 640.9 (102.1) |          |
|                  | No pregnancy    | 619.0 (96.2) | 0.066    |
|                  | Pregnancy (no loss) | 636.2 (102.0) |      |
| **Right (210°, 240°)** | Pregnancy Loss | 640.7 (111.6) |          |
|                  | No pregnancy    | 627.1 (98.0) | 0.415    |
|                  | Pregnancy (no loss) | 636.2 (105.2) |      |
| **Average measures** | Pregnancy Loss | 638.1(96.3) |          |
|                  | No pregnancy    | 621.7(85.6) | 0.201    |
|                  | Pregnancy (no loss) | 632.5(91.0) |        |

Associations adjusted for age, ethnicity, height, BMI, SBP, DBP, smoking, alcohol, raised cholesterol, diabetes, Townsend score, income, qualifications, live births, aspirin use, exercise (accelerometer).

https://doi.org/10.1371/journal.pone.0223125.t005
this may have diluted our ability to detect effects of, for example, vascular dysfunction driving both late pregnancy loss (through abnormal placentation) and later maternal cardiac remodelling and vascular disease.

There is a higher risk of CVD in women with any history of pregnancy loss but, this risk is substantially higher in women with a history of more than three losses. The number of women with higher than 3 pregnancy losses in our cohort was small and a specific impact of a high number of pregnancy losses could not be studied.

Also, there was a lack of some reproductive information which could potentially impact the incidence of CVD in women such as, early menarche, contraception use, infertility, early age at first birth, early menopause, HRT treatment, and hysterectomy.

This study was cross-sectional and, therefore, unable to assess the impact of pregnancy loss on cardiac geometry over time, with varying time periods between the pregnancy loss and our assessment of participants. Finally, no information was available on other pregnancy complications linked to future CVD such as hypertensive disorders of pregnancy, preterm birth and gestational diabetes, so we cannot comment on other possible explanations for the known link between pregnancy loss and future CVD risk.

Despite these limitations, a broad heterogeneity of socioeconomic and ethnic groups, in a large study population, in which a range of potential confounders have been measured and gold-standard measures of subclinical CVD are available should increase confidence that valid scientific inferences can be drawn from the lack of association between a history of pregnancy loss and cardiac remodeling, which is likely to be generalisable to the wider population.

Conclusion

Women who self-report pregnancy loss do not have significant differences in cardiac structure, cardiac function, or carotid structure in later life to explain their increased cardiovascular risk. This suggests any cardiovascular risks associated with pregnancy loss operate through other disease mechanisms. Alternatively, other characteristics of pregnancy loss, which we were not able to take account of, such as timing and number of pregnancy losses may be required to identify those at greatest cardiovascular risk.

Acknowledgments

AL and SEP acknowledge support from the National Institute for Health Research (NIHR) Cardiovascular Biomedical Research Centre at Barts and from the “SmartHeart” EPSRC programme grant (www.nihr.ac.uk; EP/P001009/1). SN, PL and SKP are supported by the Oxford NIHR Biomedical Research Centre and the Oxford British Heart Foundation Centre of Research Excellence.

This project was enabled through access to the MRC eMedLab Medical Bioinformatics infrastructure, supported by the Medical Research Council (www.mrc.ac.uk; MR/L016311/1).

Disclosures

SEP provides consultancy to Circle Cardiovascular Imaging Inc., Calgary, Canada and Servier.

Author Contributions

Conceptualization: Einas Elmahi, Alexander Jones, Paul Leeson.

Data curation: Nay Aung.

Formal analysis: Mihir M. Sanghvi.
Investigation: Nay Aung, Jackie A. Cooper, José Miguel Paiva, Elena Lukaschuk.
Methodology: Mihir M. Sanghvi, Nay Aung, Jackie A. Cooper, Steffen E. Petersen.
Supervision: Alexander Jones, Steffen E. Petersen, Paul Leeson.
Validation: Einas Elmahi, Paul Leeson.
Visualization: Einas Elmahi, Alexander Jones, Paul Leeson.
Writing – original draft: Einas Elmahi.
Writing – review & editing: Alexander Jones, Christina Y. L. Aye, Adam J. Lewandowski, Stefan K. Piechnik, Stefan Neubauer, Steffen E. Petersen, Paul Leeson.

References

1. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertility and Sterility. 2003; 79(3):577–84. https://doi.org/10.1016/s0015-0282(02)04694-0 PMID: 12620443
2. Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. Reviews in obstetrics and gynecology. 2009; 2(2):76. PMID: 19609401
3. Peters SA, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart. 2018;heartjnl-2017-312289.
4. Oliver-Williams CT, Heydon EE, Smith GC, Wood AM. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. Heart. 2013; 99(22):1636–44. https://doi.org/10.1136/heartjnl-2012-303237 PMID: 23539554
5. Peters SA, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart. 2018. https://doi.org/10.1136/heartjnl-2017-312289 PMID: 29335253
6. 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(1):49–54. https://doi.org/10.1136/heartjnl-2012-303237 PMID: 23539554
7. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129 290 births. The Lancet. 2001; 357(9273):2002–6.
8. Gholizadeh L, Davidson P. More similarities than differences: an international comparison of CVD mortality and risk factors in women. Health care for women international. 2007; 29(1):3–22.
9. Bluemke D, Mann D, Burke G, Lima J, Muntner P, Barr RG, et al. Association of Left Ventricular Hypertrophy With Incident Hypertension: The Multi-Ethnic Study of Atherosclerosis. American Journal of Epidemiology. 2011; 173(8):898–905. https://doi.org/10.1093/aje/kwq509 PMID: 21422061
10. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine. 2015; 12(3):e1001779. https://doi.org/10.1371/journal.pmed.1001779 PMID: 25826379
11. Petersen SE, Matthews PM, Francis JM, Robson MD, Zemrak F, Boubertakh R, et al. UK Biobank’s cardiovascular magnetic resonance protocol. Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance. 2016; 18:8. Epub 2016/02/03. https://doi.org/10.1186/s12968-016-0227-4 PMID: 26830817; PubMed Central PMCID: PMC4736703.
12. Coffey S, Lewandowski AJ, Garratt S, Meijer R, Lynum S, Bedi R, et al. Protocol and quality assurance for carotid imaging in 100,000 participants of UK Biobank: development and assessment. Eur J Prev Cardiol. 2017; 24(17):1799–806. Epub 2017/09/20. https://doi.org/10.1177/2047487317732273 PMID: 28925747.
13. Smith GC, Wood AM, Pell JP, Hattie J. Recurrent miscarriage is associated with a family history of ischaemic heart disease: a retrospective cohort study. BJOG : an international journal of obstetrics and gynaecology. 2011; 118(5):557–63. Epub 2011/01/20. https://doi.org/10.1111/j.1471-0528.2010.02890.x PMID: 21244619.
14. Celik N, Evsen MS, Sak ME, Soydinc E, Gul T. Evaluation of the relationship between insulin resistance and recurrent pregnancy loss. Ginekologia polska. 2011; 82(4):272–5. Epub 2011/07/05. PMID: 21721463.
15. Jungers P, Chauveaud D, Choukroun G, Moynot A, Skhiri H, Houillier P, et al. Pregnancy in women with impaired renal function. Clinical nephrology. 1997; 47(5):281–8. Epub 1997/05/01. PMID: 9181274.
16. Frick M, Weidinger F. Endothelial function: a surrogate endpoint in cardiovascular studies? Current Pharmaceutical Design. 2007; 13(17):1741–50. Epub 2007/06/23. https://doi.org/10.2174/13816120778031211 PMID: 17584104.

17. Germain AM, Romanik MC, Guerra I, Solari S, Reyes MS, Johnson RJ, et al. Endothelial Dysfunction. Hypertension. 2007; 49(1):90–5. https://doi.org/10.1161/HYP.0000251522.18094.d4 PMID: 17116761

18. Rodriguez CJ, Lin F, Sacco RL, Jin Z, Boden-Albala B, Homma S, et al. Prognostic Implications of Left Ventricular Mass Among Hispanics. The Northern Manhattan Study. 2006; 48(1):87–92. https://doi.org/10.1161/j.amjcard.1998.10.203 PMID: 20214617.

19. Desai CS, Bartz TM, Gott diener JS, Lloyd-Jones DM, Gardin JM. Usefulness of Left Ventricular Mass and Geometry for Determining 10-Year Prediction of Cardiovascular Disease in Adults > 65 Years of Age (From the Cardiovascular Health Study). The American journal of cardiology. 2016; 118(1):2148–55. https://doi.org/10.1016/j.amjcard.2016.06.016 PMID: 27547831; PubMed Central PMCID: PMC4988901.

20. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study. New England Journal of Medicine. 1990; 322(22):1561–6. https://doi.org/10.1056/NEJM199005313222223 PMID: 2139921.

21. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. Journal of the American College of Cardiology. 2008; 52(25):2148–55. https://doi.org/10.1016/j.jacc.2008.09.014 PMID: 19095132

22. Salerno M, Sharif B, Arheden H, Kumar A, Axel L, Li D, et al. Recent Advances in Cardiovascular Magnetic Resonance: Techniques and Applications. Circulation Cardiovascular imaging. 2017; 10(6). Epub 2017/06/15. https://doi.org/10.1161/circimaging.116.003951 PMID: 28611116; PubMed Central PMCID: PMC5777859.

23. Jordan JH, Todd RM, Vasu S, Hundley WG. Cardiovascular Magnetic Resonance in the Oncology Patient. JACC Cardiovascular Imaging. 2018; 11(8):1150–72. Epub 2018/08/11. https://doi.org/10.1016/j.jcmg.2018.09.004 PMID: 30092971; PubMed Central PMCID: PMC6242266.

24. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. The New England journal of medicine. 1988; 319(4):189–94. Epub 1988/07/28. https://doi.org/10.1056/NEJM198807283190401 PMID: 3393170.

25. Wang X, Chen C, Wang L, Chen D, Guang W. French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril. 2003; 79(3):577–84. Epub 2003/03/07. https://doi.org/10.1016/s0015-0282(02)04694-0 PMID: 12620443.

26. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertil Steril. 1996; 65(3):503–9. Epub 1996/03/01. PMID: 8774277.

27. Lang K, Nuevo-Chiquero A. Trends in self-reported spontaneous abortions: 1970–2000. Demography. 2012; 49(3):989–1000. https://doi.org/10.1073/s13524-012-0113-6 PMID: 22718315.

28. Ranthe MF, Boyd HA. Miscarriage and cardiovascular disease. Heart. 2015; 101(24):1933–4. https://doi.org/10.1136/heartjnl-2015-308383 PMID: 26385454

29. Eikendal AL, Groenewegen KA, Anderson TJ, Britton AR, Engström G, Evans GW, et al. Common carotid intima-media thickness relates to cardiovascular events in adults aged<45 years. Hypertension. 2015:HYPERTENSIONHA. 114.04658.