Recurrent miscarriage and the subsequent risk of cardiovascular disease

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Association between miscarriage and cardiovascular disease in a Scottish cohort

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Abstract

Objective To assess if miscarriage, whether consecutive or not, is associated with an increased risk of subsequent cardiovascular disease.

Methods A cohort study was performed using women with at least one miscarriage or live birth recorded from 1950 - 2010 in the Aberdeen Maternity and Neonatal Databank. The exposed groups consisted of women with non-consecutive, two consecutive or ≥ three consecutive miscarriages; the unexposed group consisted of all women with at least one live birth and no miscarriages. Women were linked to Scottish Morbidity Records for hospital admissions for cardiovascular conditions, cardiac surgery and death registrations. Main outcome measures were ischemic heart disease, cerebrovascular disease and a composite outcome of any disease of circulatory system. A sensitivity analysis was performed dividing the women into those who had one, two or ≥ three miscarriages irrespective of these were consecutive or not.

Results After excluding women with pre-existing hypertension, type one diabetes mellitus, kidney disease and 'disease of circulatory system', 60105 women were analysed; 9419 with non-, 940 with two, 167 with ≥ three consecutive miscarriages and 49579 with no miscarriage. In the multivariate analyses a significant association was found between ischemic heart disease and women with two {Hazard Ratios (HR) 1.75 (95% confidence interval (CI) 1.22-2.52-1.72)} or ≥ three {HR 3.18 (95%CI 1.49-6.80-4.51)} consecutive miscarriages. Similar patterns of risk were observed in the sensitivity analysis.

Conclusions Women with a history of two or more miscarriages, irrespective of whether consecutive or not, appear to have an increased risk of ischemic heart disease.

INTRODUCTION

Globally, cardiovascular disease(CVD) is a major cause of premature mortality in women[1]. There is increasing evidence that women with adverse pregnancy outcomes are at increased risk of CVD[2]. A history of preeclampsia, gestational diabetes or pregnancy-induced hypertension is mentioned as a major risk factor for cardiovascular disease in women in the American Heart Association guideline[3]. The association between recurrent miscarriage and CVD is less clear[4 5].

Approximately 15% of clinically recognized pregnancies fail to result in a live birth[6]. Recurrent miscarriage is commonly defined as three or more consecutive pregnancy losses before 22 weeks' gestation[7] and affects 0.5 to 3% of fertile couples[8]. Recurrent miscarriage is a highly heterogeneous condition. Possible etiologic factors include genetic disorders, uterine anomalies, endocrine factors, maternal autoimmune disorders, metabolic disorders, maternal thrombophilia and lifestyle factors[9]. An underlying cause may be identified in 25-50% of cases.

CVD and recurrent miscarriage share risk factors such as smoking and obesity[10]. Further endothelial dysfunction has been hypothesized as the underlying link between recurrent miscarriage, preeclampsia, IUGR and future cardiovascular events[11]. It is possible therefore that recurrent miscarriage is a first sign of subsequent CVD in women. Early identification of women at increased risk of CVD from their reproductive history may enable them to benefit from screening and preventive interventions[12].

A recently published meta-analysis found an association between recurrent miscarriage and coronary heart disease: pooled odds ratio 1.99 (1.13 to 3.50)[4]. However clinical heterogeneity between studies was evident. The effect of recurrent miscarriage on cerebrovascular disease could not be pooled due to the small number of primary studies. A large cohort study, not included in the meta-analysis, reported an association[5].

We report here a retrospective cohort study with a long follow-up which assessed if miscarriage (consecutive or not) is associated with an increased risk of subsequent CVD.

METHODS

Data sources and record linkage: The Aberdeen Maternity and Neonatal Databank (AMND) has recorded and stored information on all pregnancy-related events occurring in a geographically defined population living in Aberdeen Scotland from 1950 to the present date. Data were extracted for all women with at least one singleton live birth or miscarriage from 1950 until 2010. These women were linked using probabilistic record linkage to Scottish Morbidity Record (SMR 01) to identify any hospital admissions (SMR data available since 1968) for cardiovascular conditions and to the National Register of Scotland (NRS) for death registrations (up to 2013). After linkage the dataset was anonymised.

To ensure confidentiality, the linked dataset was managed by the Grampian Data Safe Haven, a facility providing a secure environment for the safe linkage, analysis, management and storage of datasets containing non-consented clinical data.

Study design: In this retrospective cohort study, the women were grouped according to their reproductive history into four mutually exclusive groups: no miscarriage, non-consecutive miscarriage, two consecutive miscarriages and three or more consecutive miscarriages. Women with miscarriages could have had one or more live births prior to, or after, their consecutive or non-consecutive miscarriages. The non-consecutive miscarriage group consisted of women with one miscarriage or more than one miscarriage that were not consecutive. Women experiencing miscarriage(s) formed the exposed cohorts while those without a history of miscarriage and at least one live birth comprised the unexposed cohort (reference group).

The AMND uses the International Classification of Disease-version 9 (ICD-9) to code events. Miscarriage in this study refers to spontaneous loss of pregnancy before 24 weeks of gestation.

Outcome: The primary outcomes of interest were arterial CVD identified by admission to hospital or death from ischemic heart disease (ICD-9 411, 413-414, ICD-10 I20-I25), cerebrovascular disease (ICD-9 430-438, ICD-10 I60-I69, G45), or a composite outcome of any disease of the circulatory system, defined as admission to hospital or death due to diseases of the circulatory system ((ICD-9 390-459 ICD-10 I00-I99, G45) or cardiac surgery (OPCS4 Classification of Surgical Operations and Procedures: K40 saphenous vein graft replacement of coronary artery, K51 diagnostic transluminal operations on coronary artery, K65 catheterisation of heart, K75 percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery).

In a separate sensitivity analysis we divided the women into those who had one, two or three or more miscarriages irrespective of whether these events were consecutive or not. Subgroup analyses were performed dividing the women into those with consecutive and non-consecutive miscarriages (2 or more) and primary and secondary consecutive miscarriages. Primary miscarriages were defined as miscarriages without a prior live birth. Secondary miscarriages as miscarriages after a prior live birth. For all analyses women with pre-existing cardiovascular related disease were excluded. Pre-existing disease was defined as disease before entry time in the cohort (see statistical analysis below); divided into pre-existing hypertension, pre-existing type one diabetes, kidney disease and any disease of the circulatory system.

Definition of covariates:

Baseline characteristics and covariates were obtained from AMND. Gravidity, parity and primary versus secondary miscarriages were retrieved. Birth dates were collected, as well as dates of pregnancy events and dates of the cardiovascular outcome. Maternal age was defined as age at the time of last pregnancy event or age at first, second consecutive

or third consecutive miscarriage, depending on the reproductive history. Self-reported smoking habits are coded in AMND at the time of the first antenatal clinic visit. As a covariate 'ever' or 'never' smoked were used. Socio economic deprivation is coded in the AMND using the husband/ partner's social class according to the Registrar General's occupation based social class[13]. The social class was divided into two categories: class 1-3a- 'non manual', class 3b to 5- 'manual'. Body mass index (BMI) was measured at first antenatal visit. For each woman a mean BMI (using information from all pregnancies) was calculated.

Statistical analyses

All data were extracted, linked and entered into SPSS (Statistical Package for Social Science; SPSS Inc., Chicago, IL) version 21.0. Statistical comparisons of baseline characteristics between the exposed and unexposed groups were done using independent samples t-test, the χ^2 test or Fisher's exact test, as appropriate. P-values of 0.05 or less were used to indicate statistical significance. Kaplan-Meier's curves of survival from cardiovascular events of interest were constructed for each of the exposure groups, including log rank tests. To calculate the event-free survival, univariate and multivariate analyses were done by Cox regression analysis. Hazard ratios (HR) were calculated with 95% confidence intervals (CIs). Time since exposure in years was used as underlying time variable. Entry time was defined as the year of the last pregnancy event for women in the unexposed cohort. Depending on their reproductive history, the entry time for women in the exposed cohort was year of first miscarriage, second consecutive miscarriage or third consecutive miscarriage. End time was defined as the date of the cardiovascular event, or in case no event occurred January 2013. The following covariates were included in the adjusted analyses: maternal age at entry time and BMI (as continuous variables), social class and smoking (as categorical variables). All of the covariates used for adjustment were significantly associated with CVD. A complete case analysis was performed, as well as a Cox regression using multiple imputation for the missing values (creating five different 'complete' datasets using maternal age, BMI, social class, smoking).

Power calculation

A power calculation was performed *a priori* in nQuery advisor using the smallest exposed cohort. The prevalence of CVD in women aged 55-64 in Scotland is 15.3%[14]. Assuming the same prevalence in the unexposed cohort, using a 2 sided test with 90% power at 5% significance level, to detect a clinically relevant HR of 2.0 we would need 177 in the smallest exposed cohort and 705 in the unexposed group.

RESULTS

We identified 65227 women who had a pregnancy ending in miscarriage and/or live birth between 1950 and 2010 (Figure 1). A total of 5122 women had some pre-existing cardiovascular related disease.

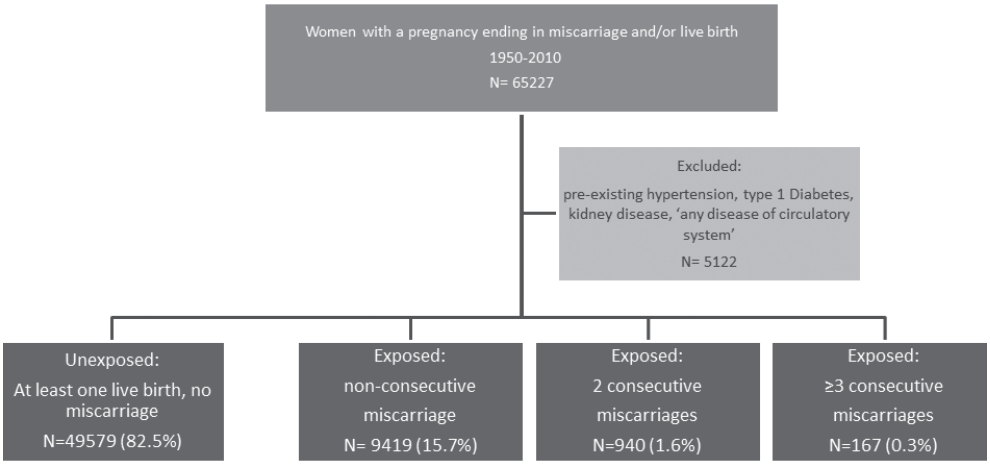


Figure 1 Flow chart selection of cohort

Table 1 Pre–existing morbidity in 65227 women; divided in women experiencing consecutive miscarriages and women with live birth and no miscarriages

	no miscarriages	non-consecutive miscarriage	2 consecutive miscarriages	≥3 consecutive miscarriages
	N=53646	N=10297	N=1083	N=201
Pre-existing hypertension (%)	2182 (4.1)	512 (5.0) (p<0.01)	77 (7.1) (p<0.01)	21 (10.4) (p<0.01) (p=0.10)[a]
Pre-existing type one diabetes mellitus 1 (%)	328 (0.6)	67 (0.7) (p=0.64)	11 (1.0) (p=0.21)	3 (1.5) (p=0.20) (p=0.55)[a]
Pre-existing kidney disease (%)	936 (1.7)	167 (1.6) (p=0.38)	24 (2.2) (p=0.33)	4 (2.0) (p=0.85) (p=0.84)[a]
Pre-existing diseases of the circulatory system (including cardiac surgery) (%)	866 (1.6)	177 (1.7) (p=0.44)	38 (3.5) (p<0.01)	10 (5.0) (p<0.01) (p=0.31)[a]

p- values refer to comparisons between miscarriage group and no miscarriage group.
[a]Comparison between 2 and ≥3 consecutive miscarriages

The prevalence of pre-existing hypertension was higher in women with miscarriages compared to women with no miscarriages, the prevalence of pre-existing diseases of the circulatory system was higher in women with consecutive miscarriages compared to women with no miscarriages (Table 1). Women with pre-existing disease were excluded from all analyses, leaving 60105 women; 9419 women with none, 940 women with two and 167 women with three or more consecutive miscarriages, and 49579 women with at least one live birth and no miscarriages.

The exposed and unexposed groups differed at baseline on maternal age; women in the non-consecutive miscarriage group being younger and women in the two and ≥ three miscarriage groups older than the no miscarriage group (Table 2).

Table 2 Comparison of characteristics between women experiencing consecutive miscarriages and women with live birth and no miscarriages

	no miscarriages	non-consecutive miscarriage	2 consecutive miscarriages	≥3 consecutive miscarriages
	N=49579	N=9419	N=940	N=167
Maternal age mean(SD)[a]	27.92(5.43) N=49532	27.51(6.51) (p<0.01) N=9127	29.75(6.52) (p<0.01) N=938	31.50(6.71) (p<0.01) N=167
BMI mean(SD)	24.52(4.39) N=47862	24.92(4.63) (p<0.01) N=6043	24.81(4.62) (p=0.09) N=708	24.64(4.06) (p=0.77) N=124
RGCS non manual (%)[b] missing (%)	17242 (43.3) 9789 (19.7)	2325 (43.9) (p=0.40) 4128 (43.8)	338 (51.9) (p< 0.01) 289 (30.7)	48 (43.2) (p=0.99) 56 (33.5)
Smoking (ever) (%)[b] missing (%)	14896 (36.6) 8883 (17.9)	2603 (38.7) (p<0.01) 2695 (28.6)	325 (40.3) (p=0.03) 134 (14.3)	54 (37.8) (p=0.77) 24 (14.4)
Gravidity mean(SD)	1.78 (0.92)	2.60(1.46) (p<0.01)	3.96(1.56) (p<0.01)	4.90(1.52) (p<0.01)
Parity mean(SD)	1.59 (0.72)	1.27(1.15) (p<0.01)	1.50(1.13) (p=0.03)	1.29(1.05) (p<0.01)
Primary miscarriages (%)	-------	6552 (69.6)	609 (64.8)	117 (70.1)
At least one continuing pregnancy (%)	49579 (100)	6219 (66.0) (p<0.01)	725 (77.1) (p<0.01)	123 (73.7) (p<0.01)

p- values refer to comparisons between miscarriage group and no miscarriage group.
[a]maternal age at last pregnancy or miscarriage, depending on exposure
[b]percentage without missing
BMI= body mass index; RGSC= Registrar General Social Class

Mean BMI was higher in the exposed groups, although only significantly so in the non-consecutive miscarriage group. Women in the miscarriage groups were more likely to be 'ever smokers' than those with no miscarriages, significantly so for the non-consecutive and two consecutive miscarriage groups. Significantly more women in the two consecutive miscarriage group were of 'non-manual' socio-economic status than those in the no miscarriage group, although this variable was missing for a large proportion of women in each group.

Median follow-up time was 17 years (range 0-62 years). An association was found on univariate analysis between two or three consecutive miscarriages and most cardiovascular endpoints examined (tables 3-5).

Table 3 Survival analysis Ischemic Heart Disease

	no miscarriages	non-consecutive miscarriage	2 consecutive miscarriages	≥3 consecutive miscarriages
	N= 49579	N=9419	N=940	N=167
Events N (%)	1440 (2.9)	272 (2.9)	30 (3.2)	7 (4.2)
Person-years[a]	1006	192	15	3
Univariate HR (95% CI)	1.0	0.92 (0.81-1.05)	2.24 (1.56-3.22)	4.00 (1.90-8.42)
Multivariate[b,c] HR (95% CI)	1.0	1.28 (0.96-1.72)	2.40 (1.28-4.51)	3.80 (0.94-15.33)
Missing[d] (%)		(38.5)	(31.3)	(30.8)
Multivariate[b,e] HR (95% CI)	1.0	0.99 (0.87-1.13)	1.75 (1.22-2.52)	3.18 (1.49-6.80)

[a]Person-years in thousands
[b]Adjusted for maternal age, body mass index, social class, smoking
[c]Complete case analysis
[d]Percentage of cases with missing covariates; exposed and unexposed group together
[e]Multiple imputation model, model includes maternal age, body mass index, social class, smoking
HR: Hazard ratio; CI: confidence interval

Table 4 Survival analysis Cerebrovascular Disease

	no miscarriages	non- consecutive miscarriage	2 consecutive miscarriages	≥3 consecutive miscarriages
	N= 49579	N=9419	N=940	N=167
Events N (%)	826 (1.7)	139 (1.5)	14 (1.5)	3 (1.8)
Person-years[a]	1010	193	15	3
Univariate HR (95% CI)	1.0	0.82 (0.68-0.98)	1.71 (1.01-2.90)	2.53 (0.81-7.86)
Multivariate[b,c] HR (95% CI)	1.0	1.12 (0.77-1.64)	1.27 (0.47-3.41)	--
Missing[d] (%)		(38.5)	(31.3)	(30.8)
Multivariate[b,e] HR (95% CI)	1.0	0.88 (0.73-1.05)	1.30 (0.77-2.22)	--

[a]Person-years in thousands
[b]Adjusted for maternal age, body mass index, social class, smoking
[c]Complete case analysis
[d]Percentage of cases with missing covariates; exposed and unexposed group together
[e]Multiple imputation model, model includes maternal age, body mass index, social class, smoking
HR: Hazard ratio; CI: confidence interval

Figure 2 shows the event free survival for ischemic heart disease for the unexposed and exposed groups. In the multivariate Cox regression analysis between consecutive miscarriages and ischemic heart disease (Table 3), the HR in the ≥three miscarriage group was 3.18 (95%CI 1.49-6.80) (multiple imputation model). Results from the Cox regression analysis between consecutive miscarriages and cerebrovascular disease can be found in Table 4. We were unable to perform multivariate analyses for women experiencing ≥ three consecutive miscarriages because of small numbers.

Table 5 Survival analysis Diseases of the Circulatory System (including cardiac surgery)

	no miscarriages	non- consecutive miscarriage	2 consecutive miscarriages	≥3 consecutive miscarriages
	N= 49579	N=9419	N=940	N=167
Events N (%)	6841 (13.8)	1207 (12.8)	126 (13.4)	23 (13.8)
Person-years[a]	957	184	14	2
Univariate HR (95% CI)	1.0	0.88 (0.83-0.94)	1.53 (1.28-1.82)	1.70 (1.13-2.56)
Multivariate[b,c] HR (95% CI)	1.0	1.19 (1.08-1.31)	1.29 (1.00-1.66)	1.32 (0.73-2.40)
Missing[d] (%)		(38.5)	(31.3)	(30.8)
Multivariate[b,e] HR (95% CI)	1.0	0.97 (0.91-1.03)	1.34 (1.12-1.60)	1.38 (0.91-2.09)

[a]Person-years in thousands
[b]Adjusted for maternal age, body mass index, social class, smoking
[c]Complete case analysis
[d]Percentage of cases with missing covariates; exposed and unexposed group together
[e]Multiple imputation model, model includes maternal age, body mass index, social class, smoking
HR: Hazard ratio; CI: confidence interval

Table 6 Survival analysis Ischemic Heart Disease – groups divided by total number of miscarriages

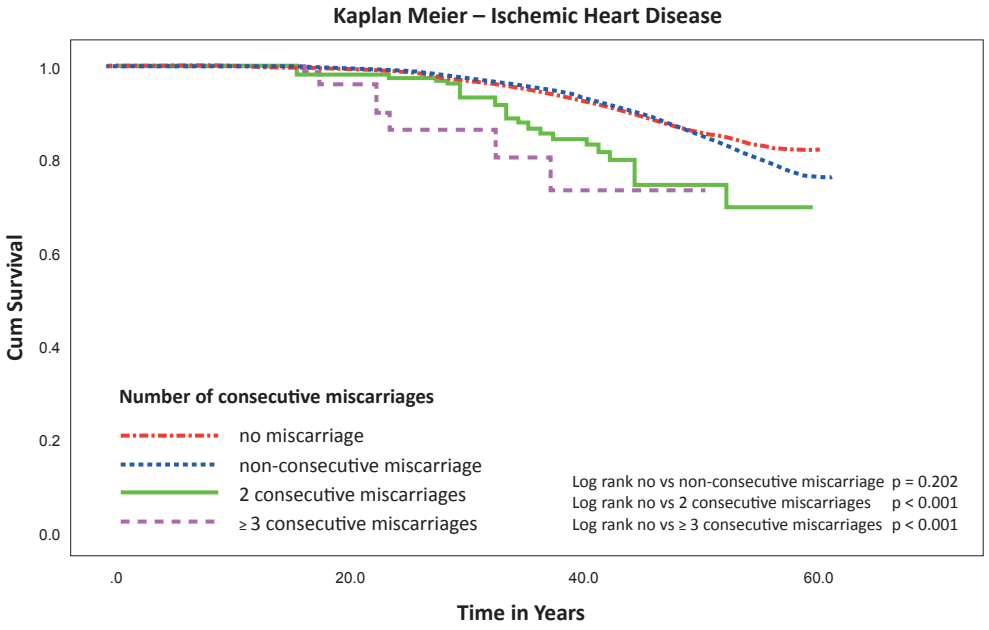
	no miscarriages	1 miscarriage	2 miscarriages	≥3 miscarriages
	N= 49579	N=9022	N=1222	N=282
Events N (%)	1440 (2.9)	262 (2.9)	36 (2.9)	11 (3.9)
Person-years[a]	1006	184	19	4
Univariate HR (95% CI)	1.0	0.90(0.79-1.03)	2.38(1.71-3.32)	4.35(2.40-7.89)
Multivariate[b,c] HR (95% CI)	1.0	1.22(0.90-1.67)	2.16(1.21-3.84)	5.65(2.32-13.78)
Missing[d] (%)		(38.3)	(31.4)	(30.8)
Multivariate[b,e] HR (95% CI)	1.0	0.97 (0.85-1.11)	1.82 (1.30-2.54)	3.18 (1.76-5.78)

[a]Person-years in thousands
[b]Adjusted for maternal age, body mass index, social class, smoking
[c]Complete case analysis
[d]Percentage of cases with missing covariates; exposed and unexposed group together
[e]Multiple imputation model, model includes maternal age, body mass index, social class, smoking
HR: Hazard ratio; CI: confidence interval

In the model looking at diseases of the circulatory system, HRs remained significantly elevated after multivariate analyses in the two consecutive miscarriage group; whereas statistical significance was lost in the ≥ three consecutive miscarriage group (Table 5).

Sensitivity analysis: A sensitivity analysis was performed using data whereby women were allocated to groups according to the total number of miscarriages, irrespective of whether these were consecutive or not (Table 6, supplementary data). In this analysis there were 9022 women in the one miscarriage group, 1222 in the two miscarriages group and 282 in the ≥three miscarriages group. The results were consistent with those described above; univariate analyses found increasing HR's by number of miscarriages, for each cardiovascular endpoint examined. This association remained significant in the multivariate analysis for ischemic heart disease (Table 6) and diseases of the circulatory

system.



Life Tables for Ischemic Heart Disease

Consecutive miscarriages

TIME	0 YEARS	10 YEARS	20 YEARS	30 YEARS	40 YEARS	50 YEARS	60 YEARS
no miscarriage	49579	34927	21458	12116	6544	4047	492
non-consecutive miscarriage	9419	6831	3397	2110	1394	813	196
2 consecutive miscarriages	940	605	239	130	64	24	1
≥ 3 consecutive miscarriages	167	115	42	17	9	2	-

Figure 2 Kaplan–Meier estimate: event–free survival for ischaemic heart disease

Subgroup analyses (supplementary data): Hazard ratios of ischemic heart disease and diseases of the circulatory system were lower in the women with consecutive miscarriages compared to the women with 2 or more non-consecutive miscarriage in the multivariate (multiple imputation) model. No significant difference was found in the subgroup analysis comparing women with primary and secondary consecutive miscarriages, for each cardiovascular endpoint examined.

DISCUSSION

Main findings

Our data suggest that women with a history of two or more miscarriages, irrespective of whether consecutive or not, have an increased risk of ischemic heart disease.

Strengths and limitations

To our knowledge, this study has the longest follow-up compared to other studies on this topic [5 15 16], giving time for CVD to develop. Another strength was the ability to exclude women with relevant pre-existing morbidity (type one diabetes, hypertension and kidney disease) from the analysis. Unfortunately information about type 2 diabetes was not available. Data about exposure was recorded prospectively, and information about outcome was collected from two national datasets, thereby eliminating recall bias. The quality of data collected from hospital admissions is periodically assessed, the accuracy of SMR 01 data was 88% for Main Condition [17]. Inaccuracy of outcome and wrong linkage (possibility of 3%) [18], is unlikely to introduce bias as collection of these data and linkage was done blind to the exposure status of the women. We are confident that complete reproductive histories of the women were captured in the AMND thereby minimising the possibility of misclassification according to the number of miscarriages. Previous studies have found that data from the AMND is more than 90% accurate regarding the studied exposure variables of miscarriage assessed by case note review[19] (www.abdn.ac.uk/amnd). The covariates like BMI were collected at time of exposure, by health care personnel who were blind to any outcome at that time, adding validity to the measurement.

Since the patient population is exclusively from Scotland our findings may not be applicable to other populations, for example as a result of genetic differences. Misclassification of exposure could have occurred if miscarriages were underreported (more likely to occur during the earlier years of the Databank before the widespread use of ultrasound or improved pregnancy tests). If this is the case, women who experienced miscarriages could have been placed in the no miscarriage group, and our risk estimation could have been underestimated. Bias could have been introduced due to missing data about smoking habits and social class. Women who have had an ongoing pregnancy were less likely to have missing data, because variables were better recorded at their antenatal visits. To reduce the risk of bias due to missing data we performed both complete case analysis and multiple imputation.

Each of the univariate HRs for different endpoints in the non-consecutive miscarriage group was less than one. This is likely to have been because these women were younger at exposure (first miscarriage) than women in the unexposed group (last pregnancy). When age was adjusted for the direction of effect changed. We defined maternal age in

the unexposed group as age at last pregnancy because from this point women could not become part of the exposed groups; they were no longer at risk for miscarriage.
Some women experience a complication during pregnancy, such as preeclampsia, placental abruption, IUGR or pre-term delivery, events which may increase their risk of CVD later in life[2 20]. A substantial proportion of the women in the miscarriage groups had no ongoing pregnancy, so did not have the chance to develop pregnancy complications. We did not adjust for history of complications of pregnancy since it is unclear whether these events are on the causal pathway between miscarriage and CVD[19 21]. If they are not, and if there are important differences in the prevalence of these complications, the effect of not making an adjustment will be to bias the effect towards null and therefore any effect seen in our analysis is likely to be an underestimate.

Interpretation
Our findings concur with the meta-analysis by Oliver-Williams et al[4], which included 10 studies investigating the association between miscarriage and coronary heart disease However, comparability between case-control studies in the meta-analysis was moderate and 6 of the included studies had no or minimal adjustment for confounding factors[4]. Due to the small number of studies available, the meta-analysis was unable to examine the association between recurrent miscarriage and cerebrovascular disease[4]. Our data suggest (on univariate analysis) an increased risk of cerebrovascular disease for women with two and ≥ three consecutive miscarriages. An association between miscarriage and cerebral infarction was seen in a large cohort study[5]. Although our estimates are based on relatively small numbers they can contribute to future meta-analyses.
Any higher risk of CVD later in life in women with consecutive miscarriages is probably multifactorial in aetiology. It is noteworthy that we observed an association between consecutive miscarriages and pre-existing cardiovascular related disease such as; hypertension, and diseases of circulatory system (including cardiac surgery). This suggests that miscarriage and CVD share either common risk factors or mechanism(s) of effect or both. One of the mechanisms involved may be related to the metabolic syndrome, as research suggests an association between miscarriage and insulin resistance and obesity[22]. Antiphospholipid syndrome is known to be a risk factor for women experiencing miscarriage, as well as CVD[23]. Another contribution to aetiology could be genetic; several papers describe a higher risk of miscarriage in women with a family history of miscarriage[24 25] and Smith et al 2011[26] found an increased risk of CVD in parents of women who had recurrent miscarriage.
Most of previous studies has focused on whether total number of miscarriages, rather than the consecutive nature of the events, is associated with future risk of cardiovascular disease.
We focused on the consecutive nature, as in the clinic recurrent miscarriage is mostly defined as three or more consecutive miscarriages. Also from a pathophysiological point

of view consecutive miscarriages are interesting, since it is more likely that a maternal factor plays a role[9]. Ranthe described an increased risk of cerebral infarction and renovascular hypertension in women with consecutive compared to non-consecutive miscarriages[5]. In our paper similar patterns of risk were observed when the data were examined by number of consecutive miscarriages or total number of miscarriages, irrespective of whether consecutive or not. In subgroup analyses, risks for ischemic heart disease and diseases of the circulatory system were lower in women with consecutive miscarriages compared to women with 2 or more non-consecutive miscarriages. This suggests that the number of miscarriage (2 or more) is more important than the consecutive nature of events. Although, it is important to recognise that these subgroup analyses had more limited statistical power than our main analysis. The American Heart Association advises monitoring and control of risk factors postpartum in women with a history of hypertensive complications of pregnancy[3]. As the HR for ischemic heart disease in women with two or more miscarriages is comparable with the HR for CVD in women with hypertensive disorders of pregnancy[20] we think that a comparable approach for women with two or more miscarriages is justified.

Conclusion

Women who have experienced miscarriages appear to have an increased risk of ischemic heart disease, suggesting its importance as an independent risk indicator. Miscarriage may also be an important risk indicator for other cardiovascular outcomes. We suggest that women who have experienced two or more miscarriages, irrespective of whether consecutive or not, should be made aware of an increased cardiovascular risk and advised appropriate risk factor modifications. Work is needed to determine whether women with such a history will benefit from these screening and preventative interventions.

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Supplementary data

Sensitivity analyses; groups divided by total number of miscarriages:

Table 7 Survival analysis Cerebrovascular Disease – groups divided by total number of miscarriages

	no miscarriages N= 49579	1 miscarriage N=9022	2 miscarriages N=1222	≥3 miscarriages N=282
Events N (%)	826 (1.7)	138 (1.5)	13 (1.1)	5 (1.8)
Person-years[a]	1010	185	19	4
Univariate HR (95% CI)	1.0	0.83(0.69-0.99)	1.38(0.80-2.39)	2.90(1.20-6.98)
Multivariate[b,c] HR (95% CI)	1.0	1.15 (0.79-1.69)	1.18(0.49-2.88)	--
Missing[d] (%)		(38.5)	(31.3)	(30.8)
Multivariate[b,e] HR (95% CI)	1.0	0.89 (0.74-1.06)	1.03 (0.59-1.77)	2.07 (0.86-5.01)

[a]Person-years in thousands
[b]Adjusted for maternal age, body mass index, social class, smoking
[c]Complete case analysis
[d]Percentage of cases with missing covariates; exposed and unexposed group together
[e]Multiple imputation model, model includes maternal age, body mass index, social class, smoking
HR: Hazard ratio; CI: confidence interval.

Table 8 Survival analysis Diseases of the Circulatory System (including cardiac surgery) – groups divided by total number of miscarriages

	no miscarriages N= 49579	1 miscarriage N=9022	2 miscarriages N=1222	≥3 miscarriages N=282
Events N (%)	6841 (13.8)	1155 (12.8)	152 (12.5)	45 (16)
Person-years[a]	957	177	18	4
Univariate HR (95% CI)	1.0	0.87 (0.82-0.93)	1.53 (1.30-1.79)	2.23 (1.66-2.99)
Multivariate[b,c] HR (95% CI)	1.0	1.19 (1.08-1.32)	1.22 (0.97-1.53)	1.68 (1.13-2.49)
Missing[d] (%)		(38.5)	(31.3)	(30.8)
Multivariate[b,e] HR (95% CI)	1.0	0.95 (0.89-1.01)	1.32 (1.12-1.55)	1.72 (1.28-2.31)

[a]Person-years in thousands
[b]Adjusted for maternal age, body mass index, social class, smoking
[c]Complete case analysis
[d]Percentage of cases with missing covariates; exposed and unexposed group together
[e]Multiple imputation model, model includes maternal age, body mass index, social class, smoking
HR: Hazard ratio; CI: confidence interval

Subgroup –analyses:

Table 9 Survival analysis – Consecutive miscarriages vs Non–Consecutive miscarriages

		Non-consecutive miscarriages (2 or more) N= 397	Consecutive miscarriages (2 or more) N= 1107
Ischemic Heart Disease	Events N (%)	10 (2.5)	12 (3.3)
	Univariate HR (95% CI)	1.0	0.74 (0.37-1.50)
	Multivariate[a,b] HR (95% CI)	1.0	0.47 (0.15-1.49)
	Missing[c] (%)		(33.0)
	Multivariate[b,d] HR (95% CI)	1.0	0.45 (0.21-0.97)
Cerebrovascular Disease	Events N (%)	1 (0.3)	17 (1.5)
	Univariate HR (95% CI)	1.0	3.70 (0.49-28.00)
	Multivariate[a,b] HR (95% CI)	1.0	1.19 (0.10-14.70)
	Missing[c] (%)		(33.0)
	Multivariate[b,d] HR (95% CI)	1.0	2.71 (0.34-21.48)
Diseases of the Circulatory System (including cardiac surgery)	Events N (%)	48 (12.2)	149 (13.5)
	Univariate HR (95% CI)	1.0	0.79 (0.57-1.09)
	Multivariate[a,b] HR (95% CI)	1.0	0.72 (0.45-1.14)
	Missing[c] (%)		(33.0)
	Multivariate[b,d] HR (95% CI)	1.0	0.63 (0.44-0.89)

[a]Adjusted for maternal age, body mass index, social class, smoking
[b]Complete case analysis
[c]Percentage of cases with missing covariates; groups together
[d]Multiple imputation model, model includes maternal age, body mass index, social class, smoking
HR: Hazard ratio; CI: confidence interval

Table 10 Survival analysis – Primary vs Secondary consecutive miscarriages

		Primary consecutive miscarriages N=726	Secondary consecutive miscarriages N= 381
Ischemic Heart Disease	Events N (%)	25 (3.4)	12 (3.1)
	Univariate HR (95% CI)	1.0	1.18 (0.59-2.38)
	Multivariate[a,b] HR (95% CI)	1.0	1.07 (0.32-3.60)
	Missing[c] (%)		(36.9)
	Multivariate[b,d] HR (95% CI)	1.0	1.25 (0.61-2.56)
Cerebrovascular Disease	Events N (%)	14 (1.9)	3 (0.8)
	Univariate HR (95% CI)	1.0	0.61 (0.17-2.19)
	Multivariate[a,b] HR (95% CI)	1.0	0.73 (0.05-10.84)
	Missing[c] (%)		(36.9)
	Multivariate[b,d] HR (95% CI)	1.0	0.61 (0.17-2.19)
Diseases of the Circulatory System (including cardiac surgery)	Events N (%)	95 (13.1)	54 (14.2)
	Univariate HR (95% CI)	1.0	1.30 (0.93-1.82)
	Multivariate[a,b] HR (95% CI)	1.0	1.21 (0.75-1.94)
	Missing[c] (%)		
	Multivariate[b,d] HR (95% CI)	1.0	1.24 (0.88-1.74)

[a]Adjusted for maternal age, body mass index, social class, smoking
[b]Complete case analysis
[c]Percentage of cases with missing covariates; groups together
[d]Multiple imputation model, model includes maternal age, body mass index, social class, smoking
HR: Hazard ratio; CI: confidence interval