Association of spontaneous abortion with all cause and cause specific premature mortality: prospective cohort study

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ABSTRACT

OBJECTIVE
To investigate the association of spontaneous abortion with the risk of all cause and cause specific premature mortality (death before the age of 70).

DESIGN
Prospective cohort study.

SETTING
The Nurses' Health Study II (1993-2017), United States.

PARTICIPANTS
101 681 ever gravid female nurses participating in the Nurses' Health Study II.

MAIN OUTCOMES MEASURES
Lifetime occurrence of spontaneous abortion in pregnancies lasting less than 6 months, determined by biennial questionnaires. Hazard ratios and 95% confidence intervals for all cause and cause specific premature death according to the occurrence of spontaneous abortion, estimated with time dependent Cox proportional hazards models.

RESULTS
During 24 years of follow-up, 2936 premature deaths were recorded, including 1346 deaths from cancer and 269 from cardiovascular disease. Crude all cause mortality rates were comparable for women with and without a history of spontaneous abortion (1.24 per 1000 person years in both groups) but were higher for women experiencing three or more spontaneous abortions (1.47 per 1000 person years) and for women reporting their first spontaneous abortion before the age of 24 (1.69 per 1000 person years). The corresponding age adjusted hazard ratios for all cause premature death during follow-up were 1.02 (95% confidence interval 0.94 to 1.11), 1.39 (1.03 to 1.86), and 1.27 (1.11 to 1.46), respectively. After adjusting for confounding factors and updated dietary and lifestyle factors, the occurrence of spontaneous abortion was associated with a hazard ratio of 1.19 (95% confidence interval 1.08 to 1.30) for premature mortality during follow-up. The association was stronger for recurrent spontaneous abortions (hazard ratio 1.59, 95% confidence interval 1.17 to 2.15 for three or more spontaneous abortions; 1.23, 1.00 to 1.50 for two; and 1.16, 1.05 to 1.28 for one compared with none), and for spontaneous abortions occurring early in a woman's reproductive life (1.32, 1.14 to 1.53 for age ≤23; 1.16, 1.01 to 1.33 for ages 24-29; and 1.12, 0.98 to 1.28 for age ≥30 compared with none). When cause specific mortality was evaluated, the association of spontaneous abortion with premature death was strongest for deaths from cardiovascular disease (1.48, 1.09 to 1.99). Spontaneous abortion was not related to premature death from cancer (1.08, 0.94 to 1.24).

CONCLUSIONS
Spontaneous abortion was associated with an increased risk of premature mortality, particularly death from cardiovascular disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Spontaneous abortion is one of the most common adverse outcomes of pregnancy, with an estimated prevalence of 12-24%

Whether spontaneous abortion is associated with a long term risk of premature death (before the age of 70) is unclear

WHAT THIS STUDY ADDS

Spontaneous abortion was associated with a greater risk of premature death, particularly from cardiovascular disease

The association was particularly strong for recurrent spontaneous abortions and spontaneous abortions occurring early in a woman's reproductive life

Spontaneous abortion could be an early marker of future health risk in women, including an increased risk of premature death

Introduction

Reducing a third of premature deaths from non-communicable diseases by 2030 is a United Nation's sustainable development goal.[1] Identifying risk factors for death from non-communicable disease to highlight priorities for intervention is needed urgently. Although traditional risk factors that affect both men and women (eg, tobacco use, overweight and obesity, and physical inactivity) explain most of the deaths from non-communicable diseases globally,[2] increasing evidence suggests that reproductive factors unique to women are associated with a greater risk of death from non-communicable diseases. Even if reproductive events do not increase the risk of death from non-communicable diseases, they could be useful as an early stress test of underlying risk factors that cause adverse reproductive outcomes and death from non-communicable diseases.[3 4]

Spontaneous abortion is one of the most common adverse outcomes of pregnancy, with an estimated prevalence of 12-24% in clinically recognized pregnancies.[5 6] Substantial evidence indicates that women with a history of spontaneous abortion have a greater risk of non-communicable diseases, including hypertension,[7] cardiovascular diseases,[7-11] and type 2 diabetes.[7 12 13] Evidence relating spontaneous abortion to mortality, however, is scant and inconsistent.[14-16] Major weaknesses of previous studies included retrospective assessment of spontaneous abortion in the long distant past, and lack of detailed data on various

relevant confounders (eg, pre-pregnancy body mass index, history of other pregnancy complications) and mediating lifestyle factors (body mass index, quality of diet, smoking status, and physical activity). Also, whether the association is influenced by the number of spontaneous abortions or age at first spontaneous abortion is unclear. To overcome these limitations, we investigated the associations of spontaneous abortion with all cause and cause specific premature death among participants of the Nurses' Health Study II. The Nurses' Health Study II is an ongoing prospective cohort study of women of reproductive age (aged 25-42 at baseline), with continuous follow-up spanning three decades and periodic update of reproductive characteristics and lifestyle and health related factors.[17]

Methods

Study population
The Nurses' Health Study II is an ongoing prospective cohort established in 1989 by recruiting 116 429 female nurses of reproductive age (25-42 years) living in one of 14 states in the United States.[17] Participants are followed by biennial questionnaires, which collect information on reproductive history, personal characteristics, lifestyle factors, and the occurrence of diseases.[17] Participants were eligible for inclusion in the current analysis if they had a pregnancy history at recruitment or reported a pregnancy during follow-up up to 2009 (n=101 852). We excluded participants who had missing data on date of birth (n=17), refused to report their history of spontaneous abortion (n=15), or who had died before 1993, the baseline year for this analysis (n=139). The total number of women included in our current analysis was 101 681.

Determination of reproductive history
In the 1993 questionnaire, participants reported their lifetime history of pregnancies, and spontaneous and induced abortions, in pregnancies lasting less than six months. Participants also reported age at these events in the age categories: <18, 18-20, 21-23, 24-26, 27-29, 30-34, and ≥35. In each subsequent biennial questionnaire up to 2009, participants reported any new pregnancies, or spontaneous and induced abortions, that occurred during the past two years. In 2009, when most participants had reached menopause, women also reported the outcome and year of all of their pregnancies, including those ending in spontaneous or induced abortion. Self-report of pregnancy loss, including stillbirth and spontaneous abortion, has been validated in other studies; the sensitivity of reporting a loss when one actually occurred was estimated as 75%.[18 19] Among women who completed the 2009 questionnaire in this cohort, the proportion of women who reported spontaneous abortion in the biennial questionnaires that were also identified as such in 2009 was 83.7% (15 558 of 18 594). Similarly, the proportion of women without a history of spontaneous abortion in the biennial questionnaires that were also confirmed as such in

2009 was 94.4% (45 953 of 48 671). To reduce recall bias, we only used spontaneous abortions reported in the biennial questionnaires to determine the occurrence of spontaneous abortions.

Determination of deaths
Deaths were identified by searching the National Death Index or state vital statistics records, or by reporting from close relatives or postal authorities. Deaths that occurred at ages younger than 70 were defined as premature.[20 21] Causes of death were established by autopsy reports, physician review of medical records, or death certificates, according to the International Classification of Diseases eighth revision (codes for cardiovascular disease and cancer were 390-458 and 140-207, respectively) (supplementary table S1). The validity of this method for determining the number of deaths has been assessed in a similar group of nurses from the Nurses' Health Study.[22] Briefly, all participants known to be alive from the Massachusetts death records were correctly confirmed by the National Death Index (n=224); of 346 participants known to be dead from the state death records, 96.5% of the true deaths were correctly identified by the National Death Index.

Assessment of covariates
A physician's diagnosis of gestational diabetes mellitus and hypertensive disorders of pregnancy were self-reported on the baseline questionnaire and updated every two years up to 2001.[23 24] Race or ethnicity, height, and body weight at age 18 were collected at baseline. Current body weight was collected at baseline and in the follow-up questionnaires. We calculated body mass index before pregnancy and during each follow-up cycle. Marriage status and parental history of myocardial infarction and stroke before the age of 60 were recorded at baseline and updated about every four years. Lifestyle factors, reproductive characteristics, and health related conditions (eg, smoking, menopausal status, use of oral contraceptives, use of aspirin, and pregnancy complications) were collected at baseline and updated every two years. Data on physical activity were recorded every four to six years from 1991. Usual dietary intake, including alcohol consumption, was assessed with a semi-quantitative food frequency questionnaire every four years from 1991.[17] Participants' overall quality of their diet was evaluated by calculating the Alternative Healthy Eating Index, 2010 version.[25] The reliability of self-reported gestational diabetes mellitus, hypertensive disorders of pregnancy, smoking habit, body weight, physical activity, and dietary intake has been validated in subgroups of participants from this cohort or similar nurses from the Nurses' Health Study.[26-28]

Data analysis
Women contributed person time from the date of return of the 1993 questionnaire or follow-up questionnaires when participants reported a pregnancy until death or the end of follow-up (30 June 2017), whichever

occurred first. Occurrence of spontaneous abortion was updated every two years from 1993 to 2009, and ever gravid participants without spontaneous abortion were regarded as the reference group. Participants were considered exposed to spontaneous abortion from the age of the first report of a spontaneous abortion.

Time dependent multivariable adjusted Cox proportional hazards models were constructed to estimate hazard ratios and 95% confidence intervals to explore the associations between spontaneous abortion, overall and according to the number of spontaneous abortions and age at first spontaneous abortion, and the risk of all cause and cause specific premature death, while simultaneously adjusting for time varying confounders and risk factors. To control as finely as possible for confounding by age, calendar time, and possible interactions between these two timescales, the models were jointly stratified by age in months (continuous) at the start of follow-up and the calendar year for the current questionnaire cycle.[29] Multivariable adjusted models included terms for race or ethnicity (white or other) and pre-pregnancy body mass index (<25, 25-29.9, or ≥30), and time varying gravidity (1, 2, 3, or ≥4), nulliparity (no or yes), marriage status (never v ever), history of gestational diabetes (no or yes), hypertensive disorders of pregnancy (no or yes), menopausal status (premenopausal, postmenopausal, or unsure or biologically uncertain), use of hormone treatment (never, past, or current), daily use of aspirin (no or yes), and parental history of myocardial infarction or stroke (no or yes). In a secondary multivariable model, we further adjusted for time varying lifestyle factors, including current body mass index (<23, 23-24.9, 25-29.9, or ≥30), smoking status (never, former, current 1-34 cigarettes/day, or current ≥35 cigarettes/day), physical activity (0, 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 hours/week), and Alternative Healthy Eating Index 2010 diet quality score (five categories). For the covariates with missing values (all <5%), an indicator for missing data was created.

We then tested for effect modification by gravidity, parity, pre-pregnancy body mass index, history of gestational diabetes mellitus and hypertensive disorders of pregnancy, parental history of cardiovascular disease, updated body mass index, quality score for diet, physical activity, and smoking status. Interaction on the multiplicative scale was assessed by conducting likelihood ratio tests and on the additive scale by calculating the relative excess risk caused by interaction.[25]

Several sensitivity analyses were conducted. First, we included never gravid women as a separate category to evaluate whether completing a pregnancy, rather than spontaneously losing a pregnancy, was responsible for the associations seen. Second, we jointly classified participants according to their history of spontaneous and induced abortion to explore whether the interruption of pregnancy, rather than the spontaneous loss of a pregnancy, was responsible for any observed relations. Third, we excluded women who were diagnosed with cancer (n=2788), type 2 diabetes (n=395), or cardiovascular disease (n=83) before 1993. Fourth, the comparison group was restricted to women whose pregnancies ended in a live birth only, by excluding women with other pregnancy outcomes (induced abortion, stillbirth, tubal or ectopic pregnancy) from the comparison group. Fifth, we excluded women who died as a result of complications of pregnancy, childbirth, and the puerperium. Sixth, we excluded women who did not return any follow-up questionnaires after 1993 (n=976). All data were analyzed with SAS 9.4 for UNIX (SAS Institute).

Patient and public involvement

This research was done without patient involvement. Patients and the public were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients and the public were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Among 101 681 gravid women, 25.6% (n=26 102) had at least one pregnancy ending in spontaneous abortion. Table 1 shows participants' age standardized characteristics in 1993 according to lifetime history of spontaneous abortion. Women who experienced spontaneous abortion were more likely than women who had not had a spontaneous abortion to use aspirin (2235 of 26 102 (8.56%) v 5195 of 75 579 (6.87%)), and to have a higher mean gravidity (3.34 (standard deviation 1.71) v 2.30 (1.22)) and higher prevalence of a parental history of myocardial infarction or stroke at baseline (7144 of 26 102 (27.37%) v 19 674 of 75 579 (26.03%)).

During 2 367 839 person years of follow-up, we reported 2936 premature deaths, including 1346 deaths from cancer and 269 from cardiovascular disease (supplementary table S1). Crude all cause mortality rates were comparable for women with and without a history of spontaneous abortion (1.24 per 1000 person years in both groups, fig 1), but were higher for women experiencing three or more spontaneous abortions (1.47 per 1000 person years, table 2) and for women reporting their first spontaneous abortion before the age of 24 (1.69 per 1000 person years, table 3). The corresponding age adjusted hazard ratios for all cause premature death during follow-up were 1.02 (95% confidence interval 0.94 to 1.11), 1.39 (1.03 to 1.86), and 1.27 (1.11 to 1.46), respectively. Differences in the risk of premature death were more evident after adjustment for gravidity (fig 1, table 2, and table 3) and were stronger after further adjustment for potential confounding factors and post-pregnancy dietary and lifestyle factors, particularly in analyses evaluating the relation between the number of spontaneous abortions (table 2) and age at first spontaneous abortion (table 3).

In the fully adjusted models, women who experienced a spontaneous abortion were 19% (8-30%) more

Table 1 | Age standardized baseline (1993) characteristics, according to occurrence of spontaneous abortion at baseline or during follow-up in 101 681 women (Nurses' Health Study II, 1993-2017)*

Characteristic	Spontaneous abortion	
	No (n=75 579)	Yes (n=26 102)
Age (years; mean (SD))†	38.85 (4.67)	38.32 (4.66)
Gravidity (mean (SD))	2.30 (1.22)	3.34 (1.71)
Parity (mean (SD))	1.88 (1.06)	1.97 (1.24)
Pre-pregnancy body mass index (mean (SD))	21.08 (2.86)	21.06 (2.86)
Total physical activity (hours/week; mean (SD))	2.76 (4.06)	2.78 (4.00)
Alcohol consumption (g/day; mean (SD))	3.03 (5.98)	2.96 (5.69)
AHEI-2010 dietary score (mean (SD))‡	47.57 (10.67)	48.01 (10.74)
Ever or currently married (No (%))	72 288 (95.65)	25 116 (96.22)
History of hypertensive disorders of pregnancy (No (%))	9668 (12.79)	3648 (13.98)
History of gestational diabetes (No (%))	3230 (4.27)	1369 (5.24)
Aspirin use (No (%))	5195 (6.87)	2235 (8.56)
Parental history of myocardial infarction or stroke (No (%))	19 674 (26.03)	7144 (27.37)
Race or ethnicity (No (%))		
Non-Hispanic white	69 112 (91.44)	24143 (92.49)
Non-Hispanic black	1427 (1.89)	382 (1.46)
Hispanic	1399 (1.85)	478 (1.83)
Other	3641 (4.82)	1099 (4.22)
Current body mass index (No (%))		
‹25	46 124 (61.03)	16 229 (62.18)
25-29.9	17 623 (23.32)	5798 (22.21)
≥30	11 832 (15.65)	4075 (15.61)
Smoking status (No (%))§		
Never	48 475 (64.75)	16 856 (64.74)
Past	17 723 (23.67)	6295 (24.18)
Current	8663 (11.58)	2885 (1.08)

SD=standard deviation; AHEI-2010= Alternative Healthy Eating Index 2010.
*Values are standardized to the age distribution of the study population.
†Value is not age adjusted.
‡Dietary score in 1991 was reported.
§784 women had missing data for smoking status.

likely to die prematurely than women who did not have a spontaneous abortion (fig 1). The multivariable adjusted hazard ratios for all cause premature death according to the number of spontaneous abortions were 1.59 (95% confidence interval 1.17 to 2.15) for three or more spontaneous abortions, 1.23 (1.00 to 1.50) for two spontaneous abortions, and 1.16 (1.05 to 1.28) for one spontaneous abortion relative to none (table 2). The multivariable adjusted hazard ratios for all cause premature mortality according to age at first spontaneous abortion were 1.32 (1.14 to 1.53) for women aged 23 or younger, 1.16 (1.01 to 1.33) for ages 24-29, and 1.12 (0.98 to 1.28) for age 30 or older relative to none (table 3). We found no evidence of effect modification of the relation between spontaneous abortion and premature death by reproductive characteristics, lifestyle factors, or body mass index (supplementary table S2).

In cause specific mortality analyses, spontaneous abortion was not related to death from cancer (hazard ratio 1.08, 95% confidence interval 0.94 to 1.24) but was associated with a greater risk of premature death from cardiovascular disease (1.48, 1.09 to 1.99) and of all other causes of death combined (1.25, 1.09 to 1.44) (fig 1). These relations were also stronger in women who had a greater number of spontaneous abortions and those who first experienced a spontaneous abortion early in their reproductive life (table 2 and table 3). In analyses where less common causes of death were disaggregated, spontaneous abortion was

associated with a greater risk of death attributed to diseases of the gastrointestinal system (1.97, 1.09 to 3.56) but not related to all other causes of death (table 4).

We then conducted a series of sensitivity analyses to evaluate the robustness of the findings and the possibility that the associations seen were not caused by spontaneous abortion itself. First, we performed an analysis where nulligravid women were included as a separate group to examine whether completing pregnancy was beneficial for mortality from cardiovascular disease rather than spontaneous abortion being detrimental. We found that nulligravidity was not related to death from cardiovascular disease in this analysis. Compared with gravid women who had never had a spontaneous abortion, the multivariable adjusted hazard ratio for premature death from cardiovascular disease was 1.47 (95% confidence interval 1.08 to 1.99) for gravid women with a history of spontaneous abortion and 1.21 (0.76 to 1.93) for nulligravid women. Second, to examine whether the termination of a pregnancy rather than spontaneous loss of a pregnancy was responsible for the association with death from cardiovascular disease, we conducted an analysis where induced abortion was classified as a separate comparison group. This analysis showed no relation between induced abortion and mortality from cardiovascular disease. Compared with gravid women who had never had a spontaneous or induced abortion, the multivariable adjusted hazard ratio for

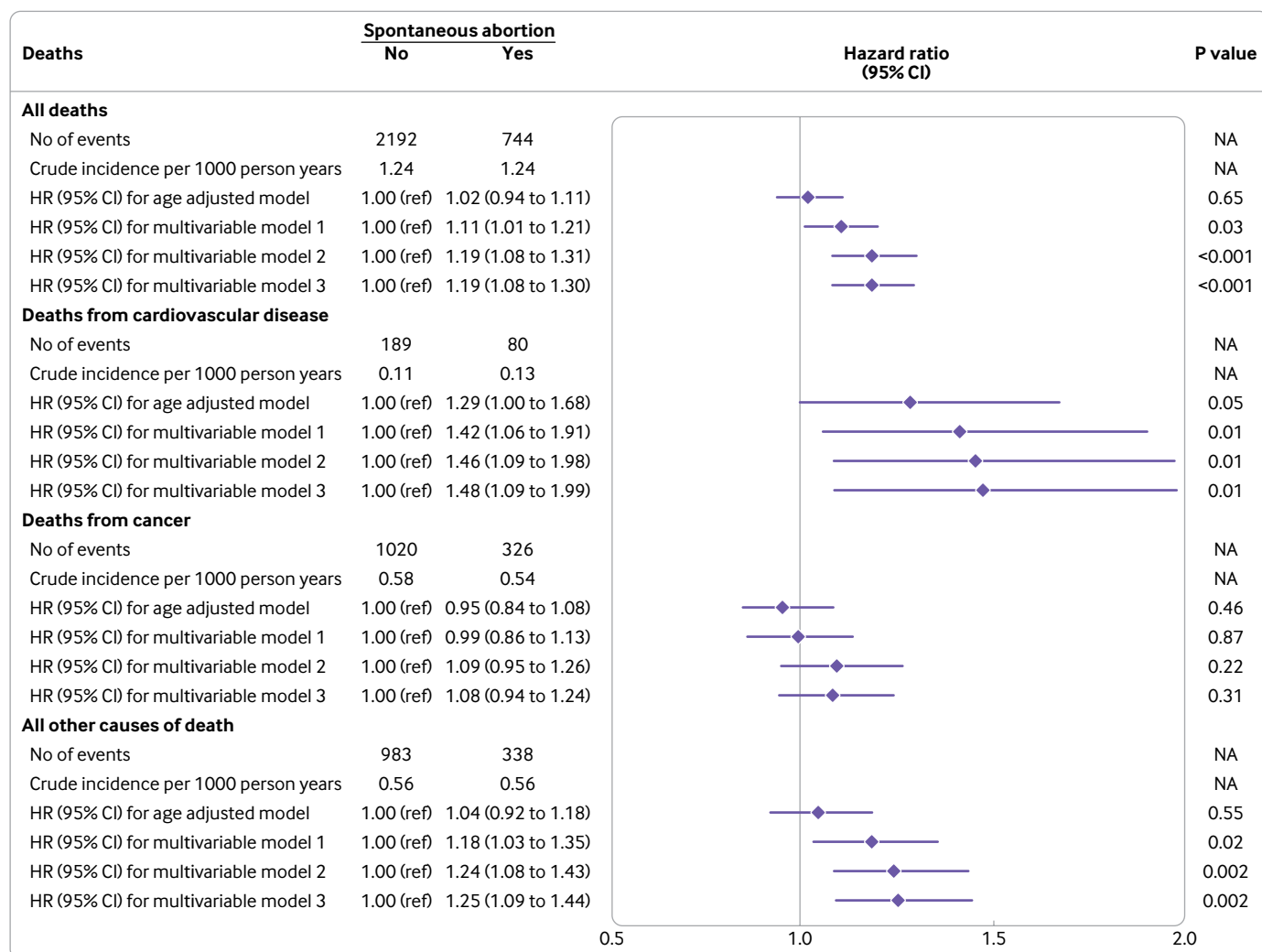| Deaths	Spontaneous abortion		Hazard ratio (95% CI)	P value
	No	Yes		
All deaths				
No of events	2192	744		NA
Crude incidence per 1000 person years	1.24	1.24		NA
HR (95% CI) for age adjusted model	1.00 (ref)	1.02 (0.94 to 1.11)		0.65
HR (95% CI) for multivariable model 1	1.00 (ref)	1.11 (1.01 to 1.21)		0.03
HR (95% CI) for multivariable model 2	1.00 (ref)	1.19 (1.08 to 1.31)		<0.001
HR (95% CI) for multivariable model 3	1.00 (ref)	1.19 (1.08 to 1.30)		<0.001
Deaths from cardiovascular disease				
No of events	189	80		NA
Crude incidence per 1000 person years	0.11	0.13		NA
HR (95% CI) for age adjusted model	1.00 (ref)	1.29 (1.00 to 1.68)		0.05
HR (95% CI) for multivariable model 1	1.00 (ref)	1.42 (1.06 to 1.91)		0.01
HR (95% CI) for multivariable model 2	1.00 (ref)	1.46 (1.09 to 1.98)		0.01
HR (95% CI) for multivariable model 3	1.00 (ref)	1.48 (1.09 to 1.99)		0.01
Deaths from cancer				
No of events	1020	326		NA
Crude incidence per 1000 person years	0.58	0.54		NA
HR (95% CI) for age adjusted model	1.00 (ref)	0.95 (0.84 to 1.08)		0.46
HR (95% CI) for multivariable model 1	1.00 (ref)	0.99 (0.86 to 1.13)		0.87
HR (95% CI) for multivariable model 2	1.00 (ref)	1.09 (0.95 to 1.26)		0.22
HR (95% CI) for multivariable model 3	1.00 (ref)	1.08 (0.94 to 1.24)		0.31
All other causes of death				
No of events	983	338		NA
Crude incidence per 1000 person years	0.56	0.56		NA
HR (95% CI) for age adjusted model	1.00 (ref)	1.04 (0.92 to 1.18)		0.55
HR (95% CI) for multivariable model 1	1.00 (ref)	1.18 (1.03 to 1.35)		0.02
HR (95% CI) for multivariable model 2	1.00 (ref)	1.24 (1.08 to 1.43)		0.002
HR (95% CI) for multivariable model 3	1.00 (ref)	1.25 (1.09 to 1.44)		0.002

Fig 1 | Adjusted hazard ratios and 95% confidence intervals for the risk of all cause and cause specific premature death (before age 70) according to the overall occurrence of spontaneous abortion in 101 681 women (Nurses' Health Study II, 1993-2017). In the age adjusted model, age in months (continuous) at the start of follow-up and calendar year of the current questionnaire cycle were included as stratification variables. Multivariable model 1 was further adjusted for time varying gravidity (1, 2, 3, or ≥4). Multivariable model 2 was further adjusted for white race or ethnicity (no or yes) and pre-pregnancy body mass index (<25, 25-29.9, or ≥30), and time varying nulliparity (no or yes), marriage status (never v ever or currently married), history of gestational diabetes (no or yes), hypertensive disorders of pregnancy (no or yes), menopausal status (premenopausal, postmenopausal, or unsure or biologically uncertain), use of hormone treatment (never, past, or current), daily use of aspirin (no or yes), and parental history of myocardial infarction or stroke (no or yes). Multivariable model 3 was further adjusted for time varying current body mass index (<23, 23-24.9, 25-29.9, or ≥30), smoking status (never, former, current 1-34 cigarettes/day, or current ≥35 cigarettes/day), physical activity (0, 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 hours/week), and Alternative Healthy Eating Index 2010 dietary score (five categories). NA=not available

premature death from cardiovascular disease was 1.59 (95% confidence interval 1.15 to 2.20) for women who ever had a spontaneous abortion but no induced abortions, 1.06 (0.70 to 1.62) for women who had ever had an induced abortion but no spontaneous abortions, and 1.01 (0.51 to 2.00) for women who had both spontaneous and induced abortions. The results of associations between spontaneous abortion and premature death were also substantially unchanged when we excluded women who received a diagnosis of cancer, type 2 diabetes, or cardiovascular disease before 1993, when the comparison group was restricted to women whose pregnancies ended in a live birth only, when we excluded deaths caused by complications of pregnancy, childbirth, and the puerperium, and when

we excluded women who never returned follow-up questionnaires (supplementary table S3).

Discussion
Principal findings
The results from this large longitudinal study, with a 24 year follow-up, indicated that spontaneous abortion was associated with a greater risk of all cause premature death, particularly for recurrent spontaneous abortions and spontaneous abortions occurring early in a woman's reproductive life. These associations were primarily because of an increased risk of death from cardiovascular disease, were independent of several shared risk factors (eg, body mass index, smoking, diet, and physical activity),

Table 2 | Adjusted hazard ratios for risk of all cause and cause specific premature mortality (before age 70), according to number of spontaneous abortions in 101 681 women (Nurses' Health Study II, 1993-2017)

No of spontaneous abortions	No of events	Crude incidence per 1000 person years	Adjusted hazard ratios (95% CI)			
			Age adjusted model*	Multivariable model 1†	Multivariable model 2‡	Multivariable model 3§
All deaths						
None	2192	1.24	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	584	1.24	1.00 (0.91 to 1.10)	1.08 (0.98 to 1.19)	1.17 (1.06 to 1.29)	1.16 (1.05 to 1.28)
2	114	1.17	1.02 (0.85 to 1.23)	1.16 (0.95 to 1.41)	1.22 (1.00 to 1.49)	1.23 (1.00 to 1.50)
≥3	46	1.47	1.39 (1.03 to 1.86)	1.58 (1.17 to 2.14)	1.61 (1.19 to 2.18)	1.59 (1.17 to 2.15)
P for trend	—	—	0.24	0.003	<0.001	<0.001
Deaths from cardiovascular disease						
None	189	0.11	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	60	0.13	1.21 (0.90 to 1.62)	1.34 (0.97 to 1.83)	1.39 (1.01 to 1.92)	1.40 (1.02 to 1.93)
2	15	0.15	1.59 (0.94 to 2.68)	1.84 (1.04 to 3.24)	1.78 (1.01 to 3.15)	1.82 (1.03 to 3.22)
≥3	5	0.16	1.84 (0.76 to 4.49)	2.16 (0.86 to 5.42)	2.00 (0.79 to 5.06)	1.96 (0.78 to 4.96)
P for trend	—	—	0.02	0.006	0.007	0.006
Deaths from cancer						
None	1020	0.58	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	262	0.56	0.96 (0.84 to 1.10)	0.99 (0.85 to 1.14)	1.09 (0.94 to 1.26)	1.07 (0.92 to 1.24)
2	52	0.53	0.99 (0.75 to 1.31)	1.05 (0.78 to 1.41)	1.17 (0.87 to 1.58)	1.16 (0.86 to 1.56)
≥3	12	0.38	0.76 (0.43 to 1.35)	0.82 (0.46 to 1.45)	0.90 (0.50 to 1.60)	0.89 (0.50 to 1.59)
P for trend	—	—	0.39	0.80	0.32	0.41
All other causes of death						
None	983	0.56	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	262	0.56	1.00 (0.88 to 1.15)	1.14 (0.98 to 1.32)	1.21 (1.04 to 1.40)	1.22 (1.05 to 1.42)
2	47	0.48	0.94 (0.70 to 1.27)	1.14 (0.84 to 1.55)	1.16 (0.85 to 1.59)	1.19 (0.87 to 1.62)
≥3	29	0.93	1.95 (1.35 to 2.83)	2.39 (1.62 to 3.51)	2.28 (1.55 to 3.36)	2.23 (1.51 to 3.28)
P for trend	—	—	0.12	<0.001	<0.001	<0.001

*Age in months (continuous) at the start of follow-up and calendar year of the current questionnaire cycle were included as stratification variables.
†Multivariable model 1 was further adjusted for time varying gravidity (1, 2, 3, or ≥4).
‡Multivariable model 2 was further adjusted for white race or ethnicity (no or yes) and pre-pregnancy body mass index (<25, 25-29.9, or ≥30), and time varying nulliparity (no or yes), marriage status (never v ever or currently married), history of gestational diabetes (no or yes), hypertensive disorders of pregnancy (no or yes), menopausal status (premenopausal, postmenopausal, or unsure or biologically uncertain), use of hormone treatment (never, past, or current), daily use of aspirin (no or yes), and parental history of myocardial infarction or stroke (no or yes).
§Multivariable model 3 was further adjusted for time varying current body mass index (<23, 23-24.9, 25-29.9, or ≥30), smoking status (never, former, current 1-34 cigarettes/day, or current ≥35 cigarettes/day), physical activity (0, 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 hours/week), and Alternative Healthy Eating Index 2010 dietary score (five categories).

and persisted in a series of sensitivity analyses aimed at isolating the role of spontaneous pregnancy losses from other factors. These findings highlight the growing literature showing that specific reproductive events and risk of chronic disease are linked over a woman's life course; a better understanding of their associations might lead to insights to prevent adverse reproductive outcomes and premature death.

Underlying mechanisms of the associations seen

The association between spontaneous abortion and cardiovascular disease might reflect shared mechanistic pathways that contribute to spontaneous abortion and to the development of cardiovascular disease and ultimately premature death. For instance, insulin resistance, chronic kidney disease, and immune disorders have been linked to both spontaneous abortion and the development of clinical risk factors for cardiovascular disease.[30-32] Likewise, endothelial dysfunction was related to spontaneous abortion by causing defects of the placenta,[33] and was also implicated in the pathogenesis of cardiovascular, microvascular, and homeostatic dysfunction.[34] Some genetic or epigenetic features might also predispose women to both spontaneous abortion and cardiovascular disease, which is supported by the finding that parents of women with recurrent spontaneous abortions have a higher incidence of coronary artery disease.[35] Also, that spontaneous abortion could trigger a cascade that, in turn, leads to premature death, potentially by interactions with established risk factors for cardiovascular disease, has been hypothesized.[36] In support of this hypothesis, Wagner and colleagues found that women with a history of recurrent pregnancy loss showed a proinflammatory state, manifested as increased levels of high sensitivity C reactive protein, that has been strongly associated with future risk of cardiovascular disease.[37] Further research is needed to understand the underlying mechanisms linking spontaneous abortion to premature death from cardiovascular disease.

Comparison with other studies

Previous epidemiological studies have reported an association between a history of spontaneous abortion and a greater risk of cardiovascular disease,[7-11 38-41] chronic hypertension,[7] and type 2 diabetes.[7 12 13] So far, however, few studies have assessed the association of spontaneous abortion with death. In a Danish register based study (n=1 001 266), Coleman and colleagues reported that women who had registered a spontaneous abortion exhibited an odds ratio for mortality of 3.06 (95% confidence interval 2.19 to 4.28) compared with women without a history of abortion.[14] In contrast, in a Japanese cohort of 54 652 women aged 40-79, Yamada and colleagues found that women with a history of self-reported pregnancy loss (stillbirth, spontaneous and induced abortions combined) had a

Table 3 | Adjusted hazard ratios for risk of all cause and cause specific premature mortality (before age 70), according to age at first spontaneous abortion in 101 681 women (Nurses' Health Study II, 1993-2017)

Age at first abortion	No of events	Crude incidence per 1000 person years	Adjusted hazard ratios (95% CI)			
			Age adjusted model*	Multivariable model 1†	Multivariable model 2‡	Multivariable model 3§
All deaths						
None	2192	1.24	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥30	274	1.09	0.93 (0.82 to 1.05)	1.00 (0.87 to 1.14)	1.08 (0.95 to 1.24)	1.12 (0.98 to 1.28)
24-29	254	1.17	0.97 (0.85 to 1.10)	1.06 (0.92 to 1.21)	1.16 (1.01 to 1.34)	1.16 (1.01 to 1.33)
≤23	216	1.69	1.27 (1.11 to 1.46)	1.39 (1.20 to 1.60)	1.41 (1.21 to 1.63)	1.32 (1.14 to 1.53)
P for trend	—	—	0.06	<0.001	<0.001	<0.001
Deaths from cardiovascular disease						
None	189	0.11	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥30	23	0.09	0.93 (0.60 to 1.43)	1.02 (0.65 to 1.60)	1.07 (0.68 to 1.68)	1.15 (0.73 to 1.82)
24-29	30	0.14	1.34 (0.91 to 1.97)	1.49 (0.99 to 2.25)	1.60 (1.05 to 2.42)	1.59 (1.05 to 2.41)
≤23	27	0.21	1.85 (1.23 to 2.77)	2.04 (1.33 to 3.14)	1.93 (1.25 to 2.98)	1.78 (1.15 to 2.76)
P for trend	—	—	0.004	<0.001	0.001	0.002
Deaths from cancer						
None	1020	0.58	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥30	145	0.58	1.05 (0.88 to 1.25)	1.08 (0.90 to 1.30)	1.21 (1.00 to 1.45)	1.20 (1.00 to 1.45)
24-29	102	0.47	0.82 (0.67 to 1.01)	0.85 (0.69 to 1.06)	0.96 (0.77 to 1.19)	0.95 (0.76 to 1.17)
≤23	79	0.62	1.00 (0.79 to 1.25)	1.03 (0.81 to 1.31)	1.10 (0.86 to 1.39)	1.05 (0.83 to 1.34)
P for trend	—	—	0.34	0.65	0.54	0.75
All other causes of death						
None	983	0.56	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥30	106	0.42	0.80 (0.65 to 0.97)	0.90 (0.73 to 1.10)	0.96 (0.77 to 1.18)	1.01 (0.82 to 1.24)
24-29	122	0.56	1.04 (0.86 to 1.26)	1.20 (0.99 to 1.47)	1.32 (1.08 to 1.61)	1.33 (1.09 to 1.63)
≤23	110	0.86	1.45 (1.19 to 1.77)	1.66 (1.35 to 2.05)	1.64 (1.33 to 2.02)	1.53 (1.24 to 1.89)
P for trend	—	—	0.01	<0.001	<0.001	<0.001

*Age in months (continuous) at the start of follow-up and calendar year of the current questionnaire cycle were included as stratification variables.
†Multivariable model 1 was further adjusted for time varying gravidity (1, 2, 3, or ≥4).
‡Multivariable model 2 was further adjusted for white race or ethnicity (no or yes) and pre-pregnancy body mass index (<25, 25-29.9, or ≥30), and time varying nulliparity (no or yes), marriage status (never v ever or currently married), history of gestational diabetes (no or yes), hypertensive disorders of pregnancy (no or yes), menopausal status (premenopausal, postmenopausal, or unsure or biologically uncertain), use of hormone treatment (never, past, or current), daily use of aspirin (no or yes), and parental history of myocardial infarction or stroke (no or yes).
§Multivariable model 3 was further adjusted for time varying current body mass index (<23, 23-24.9, 25-29.9, or ≥30), smoking status (never, former, current 1-34 cigarettes/day, or current ≥35 cigarettes/day), physical activity (0, 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 hours/week), and Alternative Healthy Eating Index 2010 dietary score (five categories).

lower risk of death from cardiovascular disease.[15] In a Chinese cohort of 267 400 female textile workers, ranging in age at enrolment from 30 to over 60, self-reported spontaneous abortion was not related to death from cardiovascular disease.[16] The major methodological weakness of these previous studies is that they determined the occurrence of spontaneous abortions by retrospective recall at one time point in the long distant past or by hospital register databases, which could result in misclassification because most spontaneous abortions do not result in hospital admission. Also, lack of detailed data on various relevant confounders (eg, gravidity, pre-pregnancy body mass index) and mediating lifestyle factors could lead to residual and unmeasured confounding.

We noticed an increasing trend of a higher risk of premature death with a greater number of spontaneous abortions. The Danish register based study also reported a growing trend of higher mortality rates with an increasing number of spontaneous abortions.[14] In the Japanese cohort, Yamada and colleagues reported a twofold higher risk of death from ischemic stroke in a young subgroup of participants (aged 40-59) who experienced two or more pregnancy losses than those with no history of pregnancy loss.[15] Recurrent spontaneous abortion is a major stressful event in a woman's life and has been associated with adverse mental health problems, such as depression and anxiety after the loss,[42] which are increasingly known as potential risk factors for all cause mortality and mortality related to cardiovascular disease.[43] The association between spontaneous abortion and all cause premature mortality was also stronger in women who experienced their first spontaneous abortion early in their reproductive life, suggesting that spontaneous abortion at an older age is more likely an indication of age related changes, such as chromosomal abnormalities and decreased ovarian function,[44 45] rather than an early sign of underlying physiopathology resulting in a greater risk of premature death.

Strengths and limitations
The strengths of our study include its prospective study design, large sample size, extensive follow-up period across most of the women's reproductive lifespan, and the availability of various reproductive characteristics, and lifestyle and health related factors that allowed us to control for confounding and examine effect modification.

Our study had several limitations. First, misclassification of the occurrence of spontaneous abortions cannot be entirely ruled out, even though self-reported spontaneous abortion has been found to be reliable in this study and in other cohorts.[18 19] Given our prospective design, however, misclassification should be non-differential with respect to mortality, which would tend to bias effect estimates toward the null. Second, observational studies such as ours can only

Table 4 | Adjusted hazard ratios for cause specific premature mortality (before age 70) for less common causes of death, according to overall occurrence of spontaneous abortion in 101 681 women (Nurses' Health Study II, 1993-2017)

Cause of death*	Spontaneous abortion	
	No	Yes
Infectious and parasitic diseases		
No of events	47	9
Crude incidence per 1000 person years	0.03	0.02
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	0.58 (0.27 to 1.28)
Respiratory disease		
No of events	51	27
Crude incidence per 1000 person years	0.03	0.05
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	1.67 (0.96 to 2.91)
Endocrine, nutritional, and metabolic diseases or immunity disorders		
No of events	38	10
Crude incidence per 1000 person years	0.02	0.02
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	0.94 (0.43 to 2.08)
Mental disorders		
No of events	34	9
Crude incidence per 1000 person years	0.02	0.02
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	0.79 (0.35 to 1.78)
Diseases of the nervous system and sense organs		
No of events	46	16
Crude incidence per 1000 person years	0.03	0.03
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	1.59 (0.80 to 3.14)
External causes (eg, accidents, injury, and poisoning)		
No of events	164	50
Crude incidence per 1000 person years	0.09	0.08
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	1.09 (0.76 to 1.56)
Suicide		
No of events	81	25
Crude incidence per 1000 person years	0.05	0.04
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	1.21 (0.73 to 1.99)
Gastrointestinal diseases		
No of events	44	21
Crude incidence per 1000 person years	0.02	0.04
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	1.97 (1.09 to 3.56)
Senility and ill defined diseases		
No of events	111	39
Crude incidence per 1000 person years	0.06	0.07
Multivariable adjusted hazard ratio (95% CI)†	1.00 (reference)	1.40 (0.92 to 2.11)

*Only conditions with 40 or more deaths were included.
†Models were adjusted for white race or ethnicity (no or yes) and pre-pregnancy body mass index (<25, 25-29.9, or ≥30), and time varying age (continuous), gravidity (1, 2, 3, or ≥4), nulliparity (no or yes), marriage status (never v ever or currently married), history of gestational diabetes (no or yes), hypertensive disorders of pregnancy (no or yes), menopausal status (premenopausal, postmenopausal, or unsure or biologically uncertain), use of hormone treatment (never, past, or current), daily use of aspirin (no or yes), parental history of myocardial infarction or stroke (no or yes), current body mass index (<23, 23-24.9, 25-29.9, or ≥30), smoking status (never, former, current 1-34 cigarettes/day, or current ≥35 cigarettes/day), physical activity (0, 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 hours/week), and Alternative Healthy Eating Index 2010 dietary score (five categories).

demonstrate an association, not causality. Whether experiencing the spontaneous loss of a pregnancy merely unmasks pre-existing risks or instead triggers or accelerates the development of premature death is not known. We found that induced abortion had no association with death from cardiovascular disease, however, suggesting that spontaneous abortion is more likely to be a marker than a cause of premature death. Because randomizing women to experience spontaneous loss of a pregnancy is not possible (or ethical, if it were possible), data from high quality observational studies with extended follow-up are, and are likely to remain, the best possible evidence to look at the association between spontaneous abortion and the risk of premature death. Third, although analyses where induced abortions were considered in a separate comparison group were supportive of our hypothesis, this specific analysis should be interpreted with caution as we are unsure of the validity of self-

reports of induced abortions in the United States at the time the data were collected, which might have been influenced by cultural views of induced abortion. Fourth, because most of our cohort was non-Hispanic white women and all participants shared a profession and similar educational qualifications, our findings might not be applicable to other racial or ethnic groups and populations with lower educational attainment. Last, we had only a few cases for many of the causes of death, which limited our power to generate accurate estimates for causes of death other than from all cancers and from all cardiovascular disease combined.

Conclusions
We found that spontaneous abortion, particularly recurrent spontaneous abortions and spontaneous abortions occurring early in a woman's reproductive life, was associated with an increased risk of premature death. The greater risk of all cause premature mortality

associated with spontaneous abortion was mainly a result of a higher risk of death from cardiovascular disease. Our results suggest that spontaneous abortion could be an early marker of future health risk in women, including premature death. More research is needed to establish how spontaneous abortion is related to women's long term health and the mechanisms underlying these relations.

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Dissemination to participants and related patient and public communities: Study participants are periodically updated on findings from the study through multiple channels, including a yearly newsletter, the study website, and social media feeds.

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Web appendix: Supplemental material