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A Nationwide Partner Comparison Cohort Study

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ORIGINAL RESEARCH

Pregnancy Loss and the Risk of Myocardial Infarction, Stroke, and All-Cause Mortality: A Nationwide Partner Comparison Cohort Study

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BACKGROUND: Pregnancy loss has been associated with myocardial infarction, stroke, and all-cause mortality in women through unknown mechanisms. The aim of this study was to examine these associations in women and their male partners.

METHODS AND RESULTS: In this register-based cohort study, all people born between 1957 and 1997, residing in Denmark between 1977 and 2017, and with a registered partner of the opposite sex were eligible for inclusion. Male partners through cohabitation, marriage, or paternity constituted the male cohort. Exposure to pregnancy loss was categorized as follows: 0, 1, 2, or ≥3 pregnancy losses. The outcomes of interest were myocardial infarction, stroke, and all-cause mortality. The Cox proportional hazards model estimated hazard ratios (HRs), adjusted for age, calendar year, parity, and parental history of myocardial infarction or stroke.

During follow-up, 1 112 507 women experienced 4463 events of myocardial infarction compared with 13 838 events among 1 120 029 male partners. With the no pregnancy loss group as reference, the adjusted HRs of myocardial infarction in the female cohort after 1, 2, and ≥3 pregnancy losses were as follows: 1.1 (95% CI, 1.0–1.2), 1.3 (95% CI, 1.1–1.5), and 1.4 (95% CI, 1.1–1.8), respectively. In the male partner cohort, the corresponding estimates were 1.0 (95% CI, 1.0–1.1), 1.1 (95% CI, 1.0–1.2), and 1.0 (95% CI, 0.8–1.2), respectively. The outcome of stroke showed similar results. Pregnancy loss was not significantly associated with increased mortality in either sex.

CONCLUSIONS: Pregnancy loss or stillbirth was significantly associated with myocardial infarction and stroke in women but not their male partners. Pregnancy loss or stillbirth was not significantly associated with all-cause mortality in women or male partners.

Key Words: epidemiology ■ miscarriage ■ myocardial infarction ■ pregnancy loss ■ stroke

Several studies have linked women experiencing pregnancy loss with later cardiovascular disease[1–5] and diabetes.[6,7] Most studies show statistically significant positive associations, and some demonstrate a dose-response pattern (ie, the more pregnancy losses, the greater the risk of disease) and stronger association if losses occurred at a young age. Other studies have found an increased mortality after pregnancy loss,[8,9] although one investigation did not.[10] Studies have failed to disentangle the pathways leading from pregnancy

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*These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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CLINICAL PERSPECTIVE

What Is New?

- In this nationwide cohort study, pregnancy loss or stillbirth was significantly associated with later myocardial infarction and stroke in women but not in male partners, although the risk of death was not significantly impacted in either sex.

What Are the Clinical Implications?

- Pregnancy loss may be an important female-specific risk factor for later cardiovascular disease, although the mechanism explaining the link remains elusive.

loss to these adverse outcomes, and none have, to our knowledge, assessed the corresponding risk in men. Some authors have proposed a preceding factor, such as vascular pathology, immunological mechanism, or genetic risk variant, might increase the risk of both pregnancy loss and later disease.[1,2,8,11] Slight increases in risk of pregnancy loss have been found in both women and men with obesity or autoimmune disease[12–15]; thereby, pregnancy loss may be an early marker of later disease in both sexes. However, pregnancy loss may also be associated with changes in lifestyle factors that are tied to later disease.[16] Experiencing ≥1 pregnancy losses is traumatic for some couples, and has been associated with stress, depression, and posttraumatic stress disorder in women and men,[17–21] which, in turn, may increase the risk of cardiovascular and metabolic disorders.[22] Some previous studies[1,2,8] have adjusted for available lifestyle factors; however, residual confounding may nevertheless persist.[23]

A female-male comparison design has previously been used by Lawlor et al, assessing the influence of parity on the long-term risk of coronary heart disease.[24] The study found a "J"-shaped association, with higher morbidity among women and men with low and high offspring numbers, albeit to a slightly higher degree in women. The authors concluded that lifestyle factors linked to parity could lead to obesity and coronary heart disease in both women and men.

This study aimed to assess the risk of myocardial infarction, stroke, and all-cause mortality by increasing numbers of pregnancy loss for women and their male partners. The results may aid in the current understanding of the disease pathways and assess whether long-term mortality is impacted.

METHODS

Because of regulations by the Danish Health Data Authority, individual-level data cannot be made available by the authors. Aggregated data can be made available on reasonable request to the corresponding author.

Study Population

In this nationwide register-based cohort study, women and men born between 1957 and 1997, living in Denmark between 1977 and 2017, and registered with a partner of opposite sex were eligible for inclusion. Immigrants fulfilling these criteria were included if they immigrated before the age of 20 years. Male partners were identified through 3 sources: (1) the registry of cohabitation provided by Statistics Denmark, where partnership was defined as 2 adults of opposite sex with an age difference of <15 years who were living together, (2) partnership through marriage registered in the Civil Registration System,[25] and (3) partnership through registration of a common child in the Medical Birth Register.[26] Partnership between 2 people of opposite sex was assumed to continue until another partner was registered. Using these criteria, a male partner could be identified for 85.1% of pregnancies registered during the study period. During follow-up, 40.3% of men changed partners. A secondary analysis censored men if changes in partnership occurred after the first registered partnership.

The dates of birth, death, immigration, and emigration were extracted for both the women and men from the Civil Registration System, available since 1968. Women and male partners free of an outcome of interest were included at the age of 12 years, age at immigration, age of partnership, or start of follow-up (January 1, 1977), whichever came last. In both cohorts, people were censored at age of emigration, end of follow-up (December 31, 2017), or an event of interest (myocardial infarction, stroke, or death, depending on analysis), whichever came first. For a list of registers and definitions used, see Table S1. The project was approved by the Danish Health Data Authority. No approval from an ethical committee or institutional review board, or informed consent from study subjects, is needed for register-based studies in Denmark.

Exposure

The exposure of interest was the number of pregnancy losses, defined as a registered spontaneous abortion, missed abortion, or blighted ovum in the National Patient Register.[27] A specific diagnosis of recurrent pregnancy loss counted as 3 consecutive pregnancy losses, as this was the definition used in Denmark during the study period. The number of pregnancies experienced by a woman after inclusion was summed in a time-dependent manner. Pregnancy history was grouped by the number of losses (categories: 0, 1, 2, and ≥3), number of stillbirths (categories: 0 and ≥1), and number

of live births (categories: 0, 1, 2, and ≥3). If changes in partnering occurred, men's pregnancy history was the pregnancies of the women he was partnered to. For example, if a man's first and second partner each miscarried once while he was their partner, he was registered with 2 pregnancy losses, whereas each woman was registered with 1 pregnancy loss. Exposure to stillbirth was also evaluated and defined as a registered stillbirth in the Medical Birth Register.[26] A set of restriction periods between pregnancies was defined as a pregnancy loss that could lead to multiple clinical contacts (for details, see Data S1).

Outcome

The first outcome of interest was incident myocardial infarction identified in the National Patient Register using the following discharge diagnoses codes: *International Classification of Diseases, Eighth Revision* (*ICD-8*), code 410 and *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes I21 and I22. The second outcome of interest was the incident diagnosis of stroke, defined by *ICD-8* codes 433, 434, and 436 and *ICD-10* codes I63 and I64. The third outcome of interest was all-cause mortality, defined by the date of death registered in the Civil Registration System.

Covariates

Covariates were likewise defined time dependently. The main analyses adjusted for the following confounders: attained age used as the underlying time axis, calendar year (categories: 1977–1989, 1990–1999, 2000–2009, and 2010–2017), bachelor's degree obtained (categories: yes, no, and unknown), and parental history of the outcome of interest (myocardial infarction or stroke, depending on analysis). Parental history was determined by examining if a subject's mother or listed father was registered with the outcome of interest (categories: yes, no, or unknown). In case data about educational level or one or both parents were missing, people were assigned to the unknown category.

Statistical Analysis

The numbers of pregnancy losses, stillbirths, and live births were summarized by outcome of interest in the female and male partner cohorts separately. Crude incidence rates per 10 000 person-years were calculated. Crude and adjusted Cox proportional hazards models estimated hazard ratios (HRs) with 95% CIs for each outcome.[28] The proportional hazards assumption was assessed in plots of scaled Schoenfeld residuals (Figure S1), showing linearity and zero slope for all predictor variables. The effect per pregnancy loss was estimated using the number of pregnancy losses experienced as a numerical variable, and the test for trend was the Wald statistic for the covariate. Risk factors for cardiovascular disease were summarized by exposure group at a landmark during follow-up where the majority had concluded their reproductive period. This landmark was set to 40 years of age, and differences between groups were compared using the χ^2 test.

Sensitivity Analyses

Sensitivity analyses were performed to assess the robustness of the primary results and estimate the effect of consecutive pregnancy losses. First, men were censored if changes in partnering occurred. Second, analyses were further adjusted for available lifestyle and mediating factors for the subgroup with these data available using complete case analysis. Lifestyle factors included pregestational body mass index (in kilograms per meters squared) and smoking status and were registered during pregnancies ending in a live or stillbirth, from 1997 and 2004, respectively. Mediating factors included depression, diabetes, dyslipidemia, and hypertension, identified as fulfilling relevant medication in the National Prescription Register, available since 1995.[29] Third, the effect of 2 or 3 consecutive versus nonconsecutive pregnancy losses was assessed. Last, the impact of low age at first pregnancy loss was examined (categories: ≤23, 24–29, and ≥30 years).

All programming was conducted in *R* version 4.1.0.[30] Survival analyses were modeled using the *survival* package version 3.2-11.[31] $P<0.05$ was considered statistically significant.

Patient and Public Involvement

Patients were not involved in the design, conduct, reporting, or dissemination plans of this study.

RESULTS

Myocardial Infarction

Of 1 112 563 women eligible for inclusion, 1 112 507 women were included for the outcome of myocardial infarction. Of 1 120 352 male partners eligible for inclusion, 1 120 029 were included. The time at risk in the female cohort was 20 991 441 years, compared with 20 499 166 years in the male partner cohort. The median age at inclusion was 22.2 years in the female cohort (interquartile range [IQR], 20.2–24.9 years) and 24.2 years in the male cohort (IQR, 21.9–27.2 years). The median follow-up time was 19.5 years (IQR, 9.8–28.5 years) in the female cohort and 19.1 years (IQR, 9.5–27.5 years) in the male cohort. In the female cohort, 314 519 (28.3%) women were in the study population after the age of 50 years, and 132 257 (11.9%) were in the study population after the age of 55 years.

During follow-up, 4463 women were registered with an incident myocardial infarction, compared with 13 838 in the male partner cohort. The median age at diagnosis was 46.3 years (IQR, 40.7–51.0 years) in the female cohort and 47.1 years (IQR, 41.6–51.8 years) in the male partner cohort. The median time from first registered pregnancy loss to myocardial infarction was 16.0 years (IQR, 10.5–21.7 years) in the female cohort. The adjusted HR of myocardial infarction was significantly elevated among women after ≥2 pregnancy losses or stillbirth, whereas the adjusted HRs were not significantly elevated among male partners, as seen in Figure 1.

Stroke

A total of 1 112 048 women and 1 119 936 male partners were included in the cohorts for the outcome of stroke, as seen in Figure 2. During follow-up, 8499 women and 11 276 male partners were diagnosed with incident stroke at median ages of 44.0 (IQR, 37.1–49.5) and 47.4 (IQR, 41.6–52.2) years, respectively. In the female cohort, the adjusted HR of stroke was significantly elevated after 1 or 3 pregnancy losses and borderline significant after 2 pregnancy losses, compared with no pregnancy losses. In the male cohort, the adjusted HR of stroke was not

Covariate	Events	Person-years	Incidence rate*	Crude HR (95% CI)	Adjusted HR (95% CI)†	p for trend
Myocardial infarction						
Female cohort n = 1,112,507						
Pregnancy losses‡						
0	3,655	18,407,096	2.0	1	1	
1	605	2,086,504	2.9	1.04 (0.95-1.13)	1.09 (0.997-1.19)	
2	132	338,000	3.9	1.24 (1.04-1.47)	1.29 (1.08-1.53)	<0.001
≥3	71	159,840	4.4	1.38 (1.09-1.75)	1.41 (1.11-1.79)	
Stillbirths						
0	4,423	20,908,929	2.1	1	1	
≥1	40	82,511	4.8	1.75 (1.28-2.39)	1.68 (1.23-2.29)	
Live births						
0	1,228	8,111,135	1.5	1	1	
1	1,174	4,925,486	2.4	0.99 (0.92-1.08)	0.97 (0.90-1.05)	
2	1,419	5,876,029	2.4	0.77 (0.71-0.83)	0.77 (0.71-0.84)	<0.001
≥3	642	2,078,791	3.1	0.85 (0.77-0.94)	0.85 (0.77-0.94)	
Male partner cohort n = 1,120,029						
Partner pregnancy losses‡						
0	11,479	17,946,349	6.4	1	1	
1	1,846	2,065,693	8.9	0.98 (0.93-1.03)	1.01 (0.96-1.06)	
2	356	331,098	10.8	1.04 (0.94-1.16)	1.08 (0.97-1.20)	0.46
≥3	157	156,025	10.1	0.97 (0.83-1.13)	0.99 (0.84-1.16)	
Partner stillbirths						
0	13,760	20,417,710	6.7	1	1	
≥1	78	81,455	9.6	1.04 (0.84-1.30)	1.02 (0.81-1.27)	
Partner live births						
0	3,283	7,822,083	4.2	1	1	
1	3,587	4,976,043	7.2	1.01 (0.96-1.06)	1.01 (0.97-1.06)	
2	4,697	5,586,551	8.4	0.86 (0.82-0.90)	0.90 (0.86-0.94)	0.006
≥3	2,271	2,114,488	10.7	0.91 (0.86-0.96)	0.94 (0.89-1.00)	

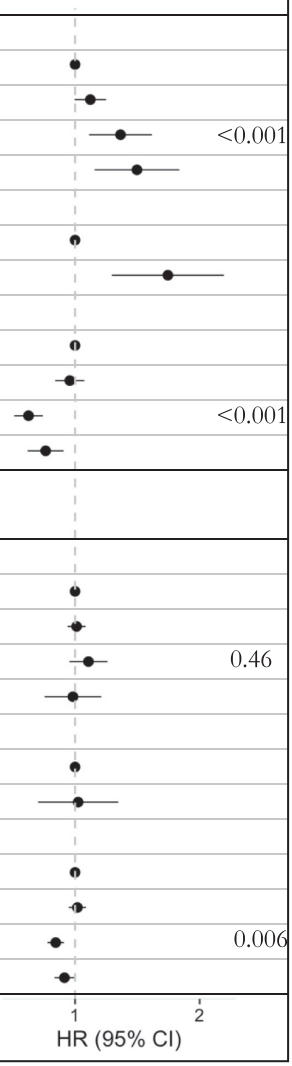

Figure 1. Pregnancy History and Risk of Later Myocardial Infarction in Women and Male Partners. HR indicateshazard ratio. *Incidence rate per 10 000 person-years. †Estimated using a Cox proportional hazards model. Analyses adjusted for number of live births, stillbirths, parental history of myocardial infarction, calendar period, and age. ‡Pregnancy loss defined as the spontaneous demise of fetus before gestational week 28 until 2004, and before gestational week 22 after 2004.

Covariate	Events	Person-years	Incidence rate*	Crude HR (95% CI)	Adjusted HR (95% CI)†	p for trend
Stroke						
Female cohort n = 1,112,048						
Pregnancy losses‡						
0	6,998	18,374,030	3.8	1	1	
1	1,150	2,080,870	5.5	1.10 (1.03-1.17)	1.15 (1.08-1.22)	
2	206	336,947	6.1	1.10 (0.95-1.26)	1.15 (0.997-1.32)	<0.001
≥3	145	159,001	9.1	1.61 (1.37-1.90)	1.65 (1.39-1.94)	
Stillbirths						
0	8,437	20,868,522	4.0	1	1	
≥1	62	82,325	7.5	1.48 (1.16-1.91)	1.43 (1.11-1.83)	
Live births						
0	2,578	8,098,955	3.2	1	1	
1	2,167	4,914,410	4.4	0.95 (0.90-1.01)	0.91 (0.85-0.96)	
2	2,648	5,863,373	4.5	0.77 (0.73-0.81)	0.73 (0.69-0.77)	<0.001
≥3	1,106	2,074,109	5.3	0.81 (0.75-0.87)	0.75 (0.70-0.81)	
Male partner cohort n = 1,119,936						
Partner pregnancy losses‡						
0	9,397	17,965,591	5.2	1	1	
1	1,517	2,068,910	7.3	1.00 (0.95-1.06)	1.05 (0.99-1.11)	
2	241	332,067	7.3	0.88 (0.77-1.00)	0.93 (0.82-1.06)	0.96
≥3	121	156,338	7.7	0.93 (0.77-1.11)	0.96 (0.80-1.15)	
Partner stillbirths						
0	11,204	20,441,233	5.5	1	1	
≥1	72	81,674	8.8	1.20 (0.95-1.51)	1.20 (0.95-1.51)	
Partner live births						
0	2,997	7,825,496	3.8	1	1	
1	3,002	4,982,511	6.0	0.95 (0.90-1.00)	0.94 (0.89-0.99)	
2	3,571	5,594,843	6.4	0.75 (0.71-0.79)	0.75 (0.72-0.79)	<0.001
≥3	1,706	2,120,057	8.1	0.78 (0.74-0.83)	0.79 (0.74-0.84)	

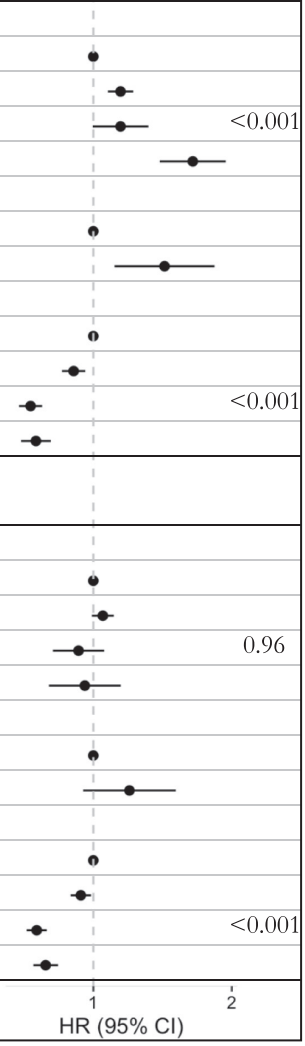

Figure 2. Pregnancy History and Risk of Later Stroke in Women and Male Partners. HR indicates hazard ratio. *Incidence rate per 10 000 person-years. †Estimated using a Cox proportional hazards model. Analyses adjusted for number of live births, stillbirths, parental history of stroke, calendar period, and age. ‡Pregnancy loss defined as the spontaneous demise of fetus before gestational week 28 until 2004, and before gestational week 22 after 2004.

significantly elevated after their partner had experienced pregnancy loss.

All-Cause Mortality

The cohorts assessing the outcome of all-cause mortality were similar in size to those investigating the outcomes of stroke and myocardial infarction, as seen in Figure 3. During follow-up, 15 644 women died, compared with 29 051 in the male partner cohort. The median age of death for women was 44.3 years (IQR, 36.4–50.5 years), and for men, 44.2 years (IQR, 35.9–50.8 years). The adjusted HR of all-cause mortality after pregnancy loss or stillbirth was not significantly elevated in either cohort. One or more live births showed a large protective effect against all-cause mortality in both cohorts.

Secondary Analyses

The prevalence of risk factors for cardiovascular disease at the age of 40 years was assessed, by number of prior pregnancy losses, as seen in Table 1. As the number of prior pregnancy losses increased for women, so did the proportion with depression, diabetes, parental history of myocardial infarction, and

Covariate	Events	Person-years	Incidence rate*	Crude HR (95% CI)	Adjusted HR (95% CI)†	p for trend
All-cause mortality						
Female cohort n = 1,112,563						
Pregnancy losses‡						
0	13,530	18,431,436	7.3	1	1	
1	1,670	2,090,396	8.0	0.84 (0.80-0.89)	1.04 (0.99-1.09)	
2	284	338,806	8.4	0.81 (0.72-0.91)	1.01 (0.90-1.14)	0.06
≥3	160	160,303	10.0	0.95 (0.81-1.11)	1.14 (0.98-1.34)	
Stillbirths						
0	15,563	20,938,117	7.4	1	1	
≥1	81	82,823	9.8	1.08 (0.87-1.35)	1.24 (0.997-1.54)	
Live births						
0	6,548	8,119,753	8.1	1	1	
1	3,896	4,933,411	7.9	0.68 (0.65-0.70)	0.75 (0.72-0.79)	
2	3,713	5,884,948	6.3	0.43 (0.42-0.45)	0.50 (0.48-0.53)	<0.001
≥3	1,487	2,082,828	7.1	0.44 (0.42-0.47)	0.52 (0.49-0.55)	
Male partner cohort n = 1,120,352						
Partner pregnancy losses‡						
0	25,171	18,029,124	14.0	1	1	
1	3,151	2,079,363	15.2	0.86 (0.83-0.89)	1.00 (0.97-1.04)	
2	508	333,760	15.2	0.79 (0.73-0.87)	0.96 (0.88-1.05)	0.10
≥3	221	157,177	14.1	0.73 (0.64-0.83)	0.85 (0.74-0.97)	
Partner stillbirths						
0	28,912	20,517,329	14.1	1	1	
≥1	139	82,094	16.9	0.99 (0.83-1.16)	1.08 (0.91-1.28)	
Partner live births						
0	11,310	7,845,459	14.4	1	1	
1	7,780	5,002,299	15.6	0.75 (0.73-0.77)	0.75 (0.73-0.77)	
2	6,975	5,619,793	12.4	0.48 (0.46-0.49)	0.51 (0.49-0.52)	<0.001
≥3	2,986	2,131,872	14.0	0.47 (0.45-0.49)	0.50 (0.48-0.52)	

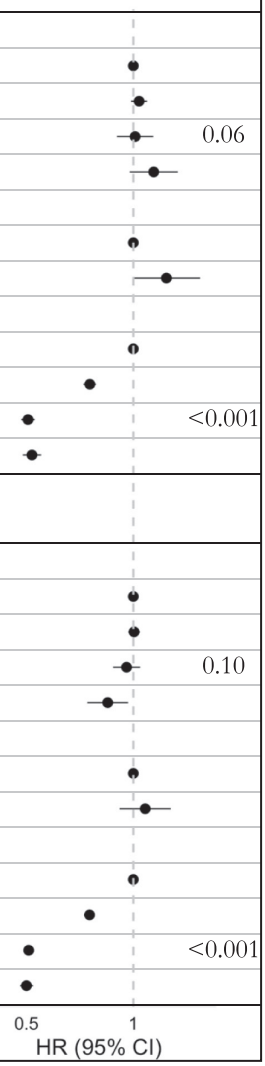

Figure 3. Pregnancy History and Risk of All-Cause Mortality in Women and Male Partners. HR indicates hazard ratio. *Incidence rate per 10 000 person-years. †Estimated using a Cox proportional hazards model. Analyses adjusted for number of live births, stillbirths, calendar period, and age. ‡Pregnancy loss defined as the spontaneous demise of fetus before gestational week 28 until 2004, and before gestational week 22 after 2004.

obesity, and those who were tobacco smokers. The corresponding trends were not observed in the male cohort. As seen in Table S2, further adjusting for these lifestyle factors (pregestational body mass index and smoking status) or mediating variables (depression, diabetes, dyslipidemia, and hypertension) did not change the significance of the results. Two or three consecutive pregnancy losses were not significantly associated with outcomes, compared with nonconsecutive losses, except for the outcome of stroke. Three consecutive pregnancy losses increased the hazard of stroke significantly compared with 3 nonconsecutive losses, as seen in Table 2. First pregnancy loss at ≤23 years of age, compared with no pregnancy loss, was significantly associated with outcomes of myocardial infarction, stroke, and all-cause mortality in both women and their male partners (Table S3).

DISCUSSION

In this nationwide partner comparison study with >40 million years of time at risk, women displayed a significantly increased risk of myocardial infarction and stroke after pregnancy loss or stillbirth, as opposed

Table 1. Prevalence of Risk Factors for Myocardial Infarction at the Age of 40 Years, by Number of Prior Pregnancy Losses

Pregnancy losses	0	1	2	≥3	*P* value*
Female cohort (n=642 623)					
Total No.	526 117	91 872	16 611	8023	
Depression†	11 718 (2.2)	2157 (2.3)	437 (2.6)	227 (2.8)	<0.001
Hypertension†	1879 (0.4)	334 (0.4)	76 (0.5)	30 (0.4)	0.21
Dyslipidemia†	1359 (0.3)	246 (0.3)	57 (0.3)	27 (0.3)	0.10
Diabetes†	1778 (0.3)	316 (0.3)	81 (0.5)	49 (0.6)	<0.001
Parental history of MI					<0.001
No	430 000 (81.7)	75 968 (82.7)	13 565 (81.7)	6480 (80.8)	
Yes	67 297 (12.8)	11 348 (12.4)	2112 (12.7)	1076 (13.4)	
Unknown	28 820 (5.5)	4556 (5.0)	934 (5.6)	467 (5.8)	
Bachelor's degree					<0.001
No	350 442 (66.6)	59 481 (64.7)	10 880 (65.5)‡	5160 (64.4)‡	
Yes	175 025 (33.3)	32 380 (35.2)	5730 (34.5)‡	2860 (35.6)‡	
Unknown	650 (0.1)	11 (<0.1)	<5‡	<5‡	
High BMI§					<0.001
No	109 262 (20.8)	26 330 (28.7)	5122 (30.8)	2606 (32.5)	
Yes	15 039 (2.9)	3765 (4.1)	807 (4.9)	471 (5.9)	
Unknown	401 816 (76.4)	61 777 (67.2)	10 682 (64.3)	4946 (61.6)	
Smoking status§					<0.001
No	274 610 (52.2)	60 607 (66.0)	11 187 (67.3)	5188 (64.7)	
Yes	78 769 (15.0)	17 179 (18.7)	3320 (20.0)	1544 (19.2)	
Unknown	172 738 (32.8)	14 086 (15.3)	2104 (12.7)	1291 (16.1)	
Male cohort (n=694 900)					
Total No.	576 408	94 349	16 364	7779	
Antidepressant use†	6569 (1.1)	1072 (1.1)	187 (1.1)	83 (1.1)	0.95
Hypertension†	1930 (0.3)	306 (0.3)	57 (0.3)	21 (0.3)	0.73
Dyslipidemia†	2283 (0.4)	347 (0.4)	56 (0.3)	23 (0.3)	0.21
Diabetes†	1657 (0.3)	212 (0.2)	34 (0.2)	18 (0.2)	0.002
Parental history of MI					<0.001
No	469 080 (81.4)	77 460 (82.1)	13 265 (81.1)	6349 (81.6)	
Yes	76 411 (13.3)	12 089 (12.8)	2230 (13.6)	1000 (12.9)	
Unknown	30 917 (5.4)	4800 (5.1)	869 (5.3)	430 (5.5)	
Bachelor's degree					<0.001
No	444 786 (77.2)	71 477 (75.8)	12 365 (75.6)	5835 (75.0)	
Yes	129 240 (22.4)	22 661 (24.0)	3963 (24.2)	1927 (24.8)	
Unknown	2382 (5.4)	211 (0.2)	36 (0.2)	17 (0.2)	

Data are given as number (percentage). BMI indicates body mass index; and MI, myocardial infarction.
*Calculated using χ^2 test.
†Identified by fulfilling a prescription for relevant medication; data available since January 1, 1995.
‡Rounded to nearest 10, or assigned <5, to comply with Danish regulations.
§High pregestational BMI (defined as ≥30 kg/m^2) and smoking status were only available for women with a delivery after 1997 and 2004, respectively.

to their male partners, where no significant effect was found. Consecutive pregnancy losses did generally not contribute significant excess risk of outcomes, compared with nonconsecutive pregnancy losses, except for the outcome of stroke, which was significantly increased after 3 consecutive pregnancy losses. However, exposure to pregnancy loss before the age of 24 years was associated with both myocardial infarction and all-cause mortality in both women and male partners. The study did not provide evidence of a common mechanism in both men and women, such as changes in lifestyle after pregnancy loss, explaining the association. Despite the excess risk of stroke and myocardial infarction after pregnancy loss in women, the hazard of mortality before end of follow-up at the age of 60 years was not significantly elevated. The incidence rate of myocardial infarction in women, irrespective of the number of prior pregnancy losses, was lower than in men.

Table 2. Association of Consecutive Pregnancy Losses With Myocardial Infarction, Stroke, and All-Cause Mortality in Female Cohort

Covariate	Events	Person-years	Incidence rate *	Crude HR (95% CI)	Adjusted HR (95% CI)†
Myocardial infarction, female cohort					
≥2 Pregnancy losses	n=34 062				
Nonconsecutive	64	167 171	3.8	1	1
Consecutive‡	132	298 504	4.4	1.16 (0.86–1.57)	1.15 (0.85–1.57)
≥3 Pregnancy losses	n=11 556				
Nonconsecutive	20	33 356	6.0	1	1
Consecutive‡	47	115 815	4.1	0.83 (0.57–1.21)	0.80 (0.55–1.17)
Stroke, female cohort					
≥2 Pregnancy losses	n=34 030				
Nonconsecutive	120	166 590	7.2	1	1
Consecutive	200	297 827	6.7	0.94 (0.75–1.17)	0.92 (0.73–1.16)
≥3 Pregnancy losses	n=11 546				
Nonconsecutive	32	33 145	9.7	1	1
Consecutive‡	101	115 396	8.8	1.35 (1.05–1.74)	1.32 (1.02–1.70)
All-cause mortality, female cohort					
≥2 Pregnancy losses	n=34 072				
Nonconsecutive	120	167 510	7.2	1	1
Consecutive	264	299 383	8.8	1.22 (0.99–1.52)	1.11 (0.88–1.38)
≥3 Pregnancy losses	n=11 563				
Nonconsecutive	65	54 926	11.8	1	1
Consecutive‡	73	94 673	7.7	0.96 (0.75–1.24)	0.91 (0.7–1.18)

HR indicates hazard ratio.
*Incidence rate per 10 000 person-years.
†Estimated using a Cox proportional hazards model. Analyses in the female cohort were adjusted for parity, obtained bachelor's degree, calendar period, and age. Outcome of myocardial infarction also adjusted for parental history of myocardial infarction. Outcome of stroke also adjusted for parental history of stroke.
‡Either 3 consecutive registered pregnancy losses or a specific diagnosis of recurrent pregnancy loss.

Prior studies have focused on women's risk of cardiovascular disease after pregnancy loss and stillbirth, and none have, to our knowledge, investigated the corresponding risk in men. A study using data from the NHS (Nurses' Health Study) included 95 465 women and found that exposure to 1 or ≥2 pregnancy losses was associated with later coronary heart disease by adjusted HRs of 1.14 (95% CI, 1.01–1.29) and 1.52 (95% CI, 1.25–1.87), compared with women with no pregnancy losses.[2] Our study supports these findings. A study also using data from the NHS included 101 681 women, and found exposure to 1, 2, or ≥3 pregnancy losses was associated with premature mortality (defined as age <70 years at death), by adjusted HRs of 1.17 (95% CI, 1.05–1.28), 1.23 (95% CI, 1.00–1.50), and 1.59 (95% CI, 1.17–2.15), respectively, compared with women with no losses.[8] The highest attained age during follow-up in the current study was 60 years, and the results may therefore not be directly comparable; however, our results did not support these findings. A study also using Danish register data until 2004 found women with pregnancy loss had a significantly increased risk of all-cause mortality.[9] The study population was notably younger than in the current investigation (mean age at outcome of death, 27.4 years; SD, 7.30 years), which may explain the difference in findings.

The current study further found live births to be associated with a significant decrease in risk of cardiovascular disease in both women and men, with the lowest risk estimates generally seen after 2 live births. The finding that having 2 children confers the least risk of later cardiovascular disease is supported by findings by Lawlor et al, who studied 3828 women and 4252 men between the ages of 60 and 79 years in Britain.[24] Furthermore, the study by Lawlor et al found that each additional child after 2 increased the risk of coronary heart disease linearly. This contrasts findings from the current study, which generally finds high parity (≥3 live born children) to be a protective factor against later cardiovascular disease in both sexes. The differences in findings could be explained by differences in lifestyle among people with high parity in Britain and Denmark, and further by differences in study size, calendar period of study, and age distributions of the cohort.

Limitations

This study has several limitations. First, exposure misclassification could potentially influence the results. Assuming nondifferential misclassification, this would likely bias the results toward the null. However, presence

of a diagnosis of pregnancy loss was likely accurate, as a study found presence of such a diagnosis in the National Patient Register could be confirmed in 114 out of 117 records (97.4%).[32] After the year 2000, some pregnancy losses in Denmark were only treated in private gynecology practices, and therefore not included in hospital registers. However, a study found only a minor decrease in the number of pregnancy losses registered in the Danish hospital registers after this date.[33] Exposure to pregnancy loss in the male cohort was based on correct partnering. Three sources were used to establish the male partner at each pregnancy loss during follow-up: cohabitation, marriage, and paternity at delivery. To further ascertain correct partnering, a secondary analysis censored men if changes in partnering occurred (Table S4). The results were materially unchanged. A male partner could be identified for most (85.1%), but not all, pregnancies. The remaining pregnancies are expected to include pregnancies after fertility treatment of women without a male partner or women who have never lived with the father of the child.

Second, the current study adjusted for lifestyle factors and risk factors for cardiovascular disease in secondary analyses to minimize residual confounding and to assess whether pregnancy loss was an individual risk factor despite presence of traditional risk factors for atherosclerosis. The adjustments did not change the significance of the results. We acknowledge that registration of lifestyle factors was limited and only known for women with live or stillbirths after specific dates and therefore not necessarily transferable to other women. We encourage researchers with recurring lifestyle data to examine possible changes following pregnancy loss. Third, outcome misclassification could also potentially bias results. However, a diagnosis of myocardial infarction has been shown to have a positive predictive value of 93.6%[34] in the Danish hospital registers and the Civil Registration System, considering information on the outcome of death is assumed to be virtually complete.[35] Fourth, the Danish population during the study period was predominantly of White race. The findings may therefore not necessarily be extrapolated to other groups.

The mechanisms accountable for the association between pregnancy loss and myocardial infarction in women remain elusive. Possibly, preceding maternal factors, such as endothelial dysfunction, immunological disease, or genetic disposition, explain some of the association. In addition, women may make adverse lifestyle changes because of the stress of losing multiple pregnancies. Likely, the cause is multifactorial and complex, and further studies should aim to assess the additional benefit of using pregnancy history in addition to traditional risk factors for cardiovascular disease when predicting future cardiovascular morbidity and mortality.

CONCLUSIONS

This nationwide cohort study found that pregnancy loss or stillbirth was significantly associated with incident myocardial infarction and stroke, but not all-cause mortality, in women. Pregnancy loss or stillbirth was not significantly associated with any of the examined outcomes in male partners.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Tables S1–S4
Figure S1

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SUPPLEMENTAL MATERIAL

Data S1. Restriction periods between pregnancies

As pregnancies could lead to multiple hospital contacts during clinical contact, a set of restriction periods were used to ascertain each pregnancy was only counted once. In case two pregnancies were overlapping, the first was kept.

- At least 90 days between two complications of early pregnancy (i.e. pregnancy loss, induced abortion, extrauterine pregnancy, or molar pregnancy).
- At least 154 days between a complication of early pregnancy and a succeeding live or stillbirth.
- At least 60 days between a live or stillbirth and a succeeding complication of early pregnancy.
- At least 154 days between a live or stillbirth and a succeeding live or stillbirth.

Table S1. Registers and definitions used

Variable	Register	Codes	Note	Missing *, %
Outcome				
Myocardial infarction	NPR	ICD-8: 410, ICD-10: I21, I22.	Incident primary or secondary diagnosis code	0
Stroke	NPR	ICD-8 433, 434, 436, ICD-10: I63, I64	Incident primary or secondary diagnosis code	0
All-cause mortality	CRS		Date of death	0
Exposure				
Pregnancy loss	NPR, MBR	ICD-8: 6346, 6438, 6439, 6451, ICD-10: O020, O021, O03		0
Stillbirth	MBR		Individual variable	0
Live birth	MBR		Individual variable	0
Two consecutive pregnancy losses	NPR		Two consecutive registered pregnancy losses	0
Three consecutive pregnancy losses	NPR	ICD-8: Y6439,6430, ICD-10: N96, O262	Specific diagnosis or three consecutive registered pregnancy losses	0
Other				
Registered partner	CRS, DST, MBR		Time-dependent variable updated as the newest registered partner through cohabitation, marriage or at a delivery	0
Date of birth, death, immigration, emigration, and first-degree relatives	CRS		Individual variables	0
Obtained bachelor's degree or higher educational degree	DST		Individual variable. Only available for females	0.3
Parental history of myocardial infarction	NPR	ICD-8: 410, ICD-10: I21, I22.	Incident primary or secondary diagnosis	4.6
Depression	LMDB	ATC: N06A	First prescription	0
Diabetes	LMDB	ATC: A10	First prescription	0
Dyslipidemia	LMDB	ATC: C10A	First prescription	
Hypertension	LMDB	Two or more classes of antihypertensive drugs (Classes: i. Adrenergic antagonist, ii. Diuretic, iii. Vasodilator, iv. Beta blocker, v. Calcium Antagonist, vi. Renin–Angiotensin–Aldosterone System Inhibitors).		0
Body mass index	MBR		Registered for women giving birth after 2003	45.1
Smoking status	MBR		Registered for women giving birth after 1996	10.0

Abbreviations: ATC: Anatomical Therapeutic Chemical Code, CRS: Danish Civil Registration System; DST: Demographic Registers of Statistics Denmark; ICD-8: International Classification of Disease and Health Related Problems, 8th revision; ICD-10: 10th revision; LMDB, Danish Prescription Register; MBR: Danish Medical Birth Register; MSR: Danish Multiple Sclerosis Register; NPR: Danish National Patient Register

* Percent of total female cohort with missing data.

Table S2. Estimated increase in hazard ratio of outcomes per pregnancy loss, adjusted for available risk factors

	n *	Increase in adjusted HR per pregnancy loss (95% CI)	n *	Increase in adjusted HR per pregnancy loss (95% CI)
		Outcome: Myocardial infarction		
		Female cohort		**Male cohort**
Crude hazard ratio	1,112,507	1.09 (1.04-1.15)	1,120,029	1.00 (0.96-1.03)
Primary adjusted model †	1,112,507	1.12 (1.06-1.18)	1,120,029	1.01 (0.98-1.04)
Primary model further adjusted for lifestyle factors ‡	410,623	1.24 (1.09-1.40)	-	-
Primary model further adjusted for mediators §	1,050,827	1.14 (1.08-1.2)	1,057,133	1.02 (0.99-1.06)
		Outcome: Stroke		
		Female cohort		**Male cohort**
Crude hazard ratio	1,112,048	1.11 (1.07-1.16)	1,119,936	0.97 (0.94-1.01)
Primary adjusted model †	1,112,048	1.14 (1.10-1.18)	1,119,936	1.00 (0.97-1.04)
Primary model further adjusted for lifestyle factors ‡	410,222	1.17 (1.07-1.28)	-	-
Primary model further adjusted for mediators §	1,050,534	1.13 (1.09-1.18)	1,057,345	1.00 (0.96 – 1.04)
		Outcome: All-cause mortality		
		Female cohort		**Male cohort**
Crude hazard ratio	1,112,563	0.90 (0.87-0.93)	1,120,352	0.88 (0.86-0.90)
Primary adjusted model †	1,112,563	1.03 (0.998-1.07)	1,120,352	0.98 (0.96-1.00)
Primary model further adjusted for lifestyle factors ‡	410,692	0.95 (0.86-1.05)	-	-
Primary model further adjusted for mediators §	1,050,933	1.00 (0.97-1.04)	1,057,655	0.98 (0.95-1.00)

Abbreviations: BMI, Body mass index; CI, Confidence interval; HR, Hazard ratio

* Number of persons included in analysis.

† Primary analysis adjusted for age, calendar year, and parental history of myocardial infarction/stroke.

‡ Complete-case analysis further adjusting for pregestational BMI above 30kg/m^2 and smoking status which was available for women with a delivery after 1997 and 2004, respectively.

§ Complete-case analysis further adjusting for hypertension, dyslipidemia, depression, and diabetes. Data about these variables was available for since January 1, 1995.

Table S3. Association of age at first pregnancy loss with myocardial infarction, stroke, and all-cause mortality

Outcome	Events	Person-years	Incidence rate *	Crude HR (95% CI) †	Adjusted HR (95% CI) †,‡
		Female cohort			
Myocardial infarction, n = 1,112,507					
Age at first pregnancy loss §					
None	3,655	17,163,612	2.1	1	1
≥30 years	344	1,844,229	1.9	0.79 (0.70-0.88)	0.84 (0.75-0.93)
24-29 years	305	1,504,861	2.0	1.04 (0.93-1.17)	1.08 (0.96-1.21)
≤23 years	159	479,048	3.3	2.30 (1.96-2.70)	2.06 (1.75-2.42)
Stroke, n = 1,112,048					
Age at first pregnancy loss §					
None	6,998	17,132,330	4.1	1	1
≥30 years	636	1,839,598	3.5	0.77 (0.71-0.84)	0.81 (0.74-0.88)
24-29 years	617	1,501,510	4.1	1.07 (0.99-1.16)	1.11 (1.02-1.21)
≤23 years	249	477,693	5.2	1.69 (1.49-1.92)	1.59 (1.40-1.81)
All-cause mortality, n = 1,112,563					
Age at first pregnancy loss §					
None	13,530	17,187,344	7.9	1	1
≥30 years	902	1,847,156	4.9	0.57 (0.53-0.61)	0.68 (0.64-0.73)
24-29 years	841	1,506,762	5.6	0.77 (0.72-0.82)	0.93 (0.87-1.00)
≤23 years	371	479,987	7.7	1.32 (1.19-1.47)	1.49 (1.34-1.65)
		Male cohort			
Myocardial infarction, n = 1,120,029					
Age at first pregnancy loss §					
None	11,479	16,727,444	6.9	1	1
≥30 years	1,408	2,292,676	6.1	0.80 (0.76-0.85)	0.84 (0.79-0.89)
24-29 years	789	1,258,192	6.3	1.03 (0.95-1.10)	1.02 (0.95-1.10)
≤23 years	162	220,854	7.3	1.69 (1.44-1.97)	1.55 (1.32-1.81)
Stroke, n = 1,119,936					
Age at first pregnancy loss §					
None	9,397	16,746,383	5.6	1	1
≥30 years	1,124	2,295,617	4.9	0.79 (0.74-0.84)	0.83 (0.78-0.88)
24-29 years	623	1,259,568	5.0	0.99 (0.92-1.08)	1.02 (0.94-1.11)
≤23 years	132	221,339	6.0	1.68 (1.41-1.99)	1.60 (1.35-1.90)
All-cause mortality, n = 1,120,352					
Age at first pregnancy loss §					
None	25,171	16,807,948	15.0	1	1
≥30 years	2,111	2,305,268	9.2	0.57 (0.55-0.60)	0.65 (0.62-0.68)
24-29 years	1,388	1,263,995	11.0	0.80 (0.75-0.84)	0.90 (0.85-0.95)
≤23 years	381	222,212	17.1	1.52 (1.37-1.68)	1.65 (1.49-1.83)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Incidence rate per 10,000 person-years.

† Estimated using a Cox proportional hazards model.

‡ Analyses adjusted for number of live births, stillbirths, parental history of myocardial infarction/stroke, calendar period, and age.

§ Pregnancy loss defined as the spontaneous demise of fetus prior to gestational week 28 before until 2004, and before gestational week 22 after.

Table S4. Association of pregnancy loss with myocardial infarction, stroke, and all-cause mortality in male partner cohort, censored at partner change

Covariate	Events	Person-years	Incidence rate *	Crude HR (95% CI) †	Adjusted HR (95% CI) †‡
Male cohort					
Outcome: myocardial infarction n = 1,120,015					
Partner pregnancy losses §					
0	7,046	12,935,068	5.4	1	1
1	989	1,271,671	7.8	0.96 (0.90-1.02)	1.01 (0.94-1.08)
2	178	194,439	9.2	0.99 (0.86-1.15)	1.06 (0.91-1.23)
≥3	79	91,841	8.6	0.92 (0.74-1.15)	0.97 (0.77-1.21)
Partner stillbirths					
0	8,259	14,440,762	5.7	1	1
≥1	33	52,257	6.3	0.78 (0.55-1.09)	0.77 (0.55-1.09)
Outcome: stroke n = 1,119,922					
Partner pregnancy losses §					
0	5,668	12,947,112	4.4	1	1
1	782	1,273,705	6.1	0.96 (0.89-1.04)	1.05 (0.97-1.13)
2	115	194,976	5.9	0.82 (0.68-0.98)	0.90 (0.75-1.09)
≥3	56	92,017	6.1	0.84 (0.64-1.09)	0.90 (0.69-1.17)
Partner stillbirths					
0	6,584	14,455,493	4.6	1	1
≥1	37	52,317	7.1	1.12 (0.81-1.55)	1.15 (0.83-1.59)
Outcome: all-cause mortality n = 1,120,338					
Partner pregnancy losses §					
0	16,510	12,985,292	12.7	1	1
1	1,658	1,278,762	13.0	0.80 (0.76-0.84)	0.97 (0.92-1.02)
2	237	195,766	12.1	0.68 (0.60-0.77)	0.86 (0.76-0.98)
≥3	110	92,367	11.9	0.67 (0.55-0.80)	0.80 (0.66-0.97)
Partner stillbirths					
0	18,440	14,499,690	12.7	1	1
≥1	75	52,498	14.3	0.91 (0.72-1.14)	1.04 (0.83-1.31)

Abbreviations: CI, confidence interval; HR, hazard ratio

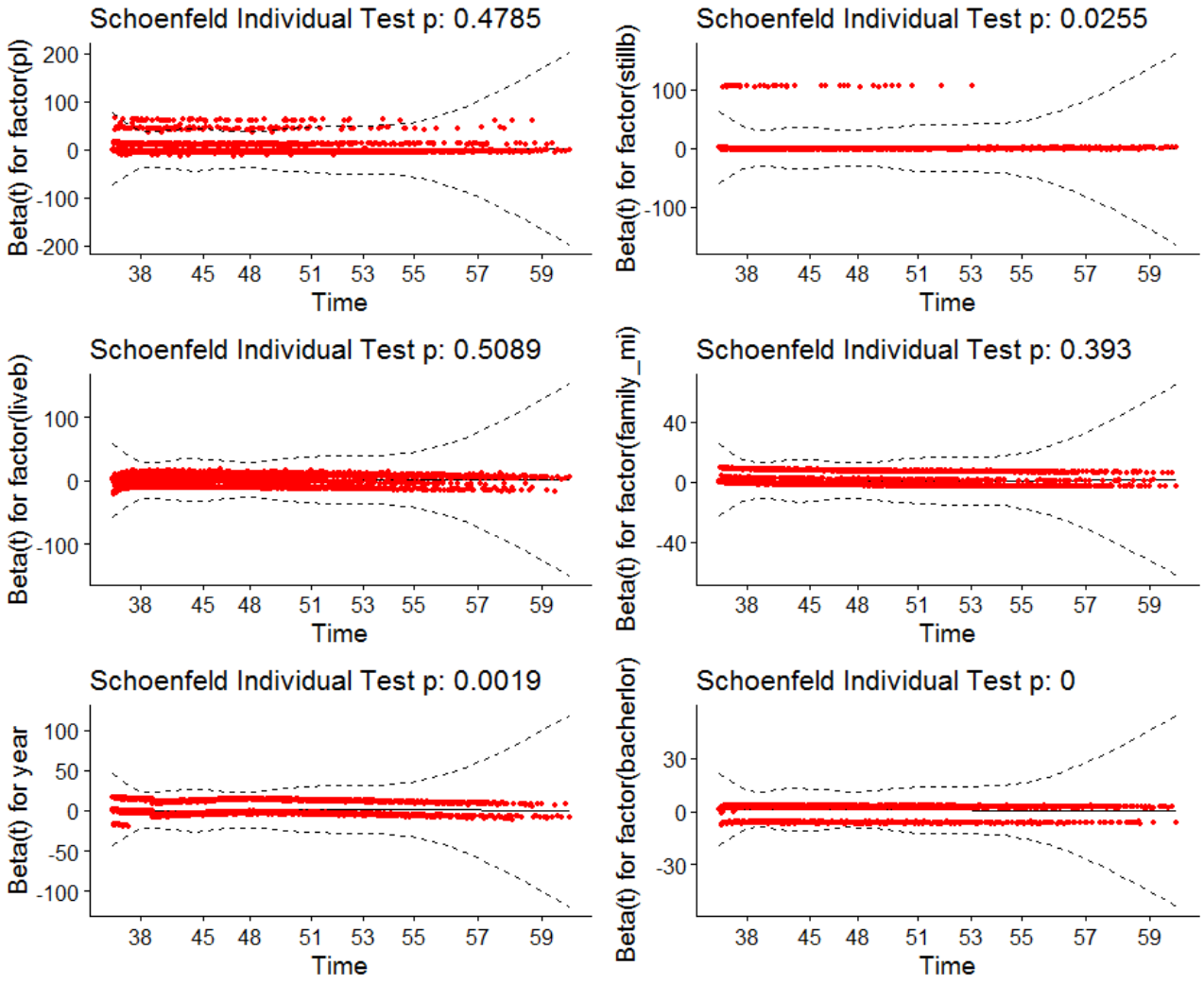
* Incidence rate per 10,000 person-years.

† Estimated using a Cox proportional hazards model.

‡ Analyses adjusted for number of live births, stillbirths, parental history of myocardial infarction/stroke, calendar period, and age.

§ Pregnancy loss defined as the spontaneous demise of fetus prior to gestational week 28 before until 2004, and before gestational week 22 after.

Figure S1. Schoenfeld residuals



Scaled Schoenfeld residuals for parameters of model estimating adjusted hazard ratio of exposure to pregnancy loss and outcome of myocardial infarction in the female cohort. Linearity and zero-slope indicated non-violation of proportional hazards assumption.