

# **SUPPLEMENTAL MATERIAL**

**Table S1. Hazard ratios (95% confidence intervals) for the risk of coronary heart disease (CHD) according to history of infertility, stratified by body mass index (BMI) at age 18, current BMI, cigarette smoking status, parity, and hypertensive disorders of pregnancy (NHSII, 1993-2017).**

Stratifying factors	Ever Reported Infertility	
		Yes*
<b>BMI at age 18</b>		
<25 kg/m <sup>2</sup> (n=1,223 cases)		1.14 (1.00, 1.28)
≥25 kg/m <sup>2</sup> (n=277 cases)		1.19 (0.91, 1.55)
P-value, test for multiplicative interaction†	0.74	
<b>Current BMI</b>		
<25 kg/m <sup>2</sup> (n=405 cases)		0.88 (0.70, 1.11)
≥25 kg/m <sup>2</sup> (n=1095 cases)		1.24 (1.09, 1.41)
P-value, test for multiplicative interaction†	0.005	
<b>Cigarette smoking status</b>		
Never (n=741 cases)		1.13 (0.96, 1.32)
Ever (past + current) (n=759 cases)		1.14 (0.98, 1.34)
P-value, test for multiplicative interaction†	0.99	
<b>Parous</b>		
No (n=173 cases)		1.06 (0.74, 1.52)
Yes (n=1,327 cases)		1.13 (1.01, 1.27)
P-value, test for multiplicative interaction†	0.66	
<b>History of Hypertensive disorders of pregnancy‡</b>		
No (n=1,098 cases)		1.05 (0.92, 1.20)
Yes (n=402 cases)		1.31 (1.06, 1.61)
P-value, test for multiplicative interaction†	0.14	

CHD includes fatal and non-fatal MI (ICD-8:410), fatal coronary heart disease (ICD-8: 412) and self-reported coronary artery bypass grafting (CABG)/angioplasty/stent

\* Models were jointly stratified by age (months) and calendar time (months) and adjusted for at menarche (<12, 12, 13, ≥14 years of age), White Non-Hispanic race/ethnicity (yes, no), marital status (ever married, never), daily aspirin use (yes, no), oral contraceptive use (never, past, current), gravidity (≤1, 2, 3, or ≥4 pregnancies), body mass index (BMI) at age 18 years (<19, 20.5-21.9, 22-24.9, 25-29.9, or ≥30 kg/m<sup>2</sup>), breastfeeding duration (<3, 3-12, or >12 months), current BMI (<24.9, 25-29.9, 30-34.9, or ≥35 kg/m<sup>2</sup>), cigarette smoking status and current dose (never, past, current 1-34 cigarettes/day, current ≥35 cigarettes/day), physical activity (0, 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles).

† Likelihood ratio test for interaction compared model with an interaction term between the covariate and the exposure to a model without an interaction term

‡ Restricted to parous women

**Table S2. Hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of coronary heart disease (CHD) according to infertility in relation to pregnancy history among 103,729 women (NHSII, 1989-2017).**

	No infertility	Secondary Infertility	Primary Infertility
<b>Coronary Heart Disease (CHD)</b>			
Events, No.	966	270	264
Person-years	1,676,149	364,537	365,796
Age-adjusted model*	1.00 [Referent]	1.19 (1.04, 1.37)	1.14 (0.99, 1.30)
Multivariable model 1†	1.00 [Referent]	1.18 (1.03, 1.35)	1.19 (1.02, 1.37)
Multivariable model 2‡	1.00 [Referent]	1.13 (0.98, 1.30)	1.13 (0.97, 1.30)

CHD includes fatal and non-fatal MI (ICD-8:410), fatal coronary heart disease (ICD-8: 412) and self-reported coronary artery bypass grafting (CABG)/angioplasty/stent

\* Models were jointly stratified by age (months) and calendar time (months)

† Model 2 additionally adjusted for age at menarche (<12, 12, 13, ≥14 years of age), White Non-Hispanic race/ethnicity (yes, no), marital status (ever married, never), daily aspirin use (yes, no), oral contraceptive use (never, past, current), gravidity (≤1, 2, 3, or ≥4 pregnancies), body mass index (BMI) at age 18 years (<19, 20.5-21.9, 22-24.9, 25-29.9, or ≥30 kg/m<sup>2</sup>), and breastfeeding duration (<3, 3-12, or >12 months).

‡ Model 3 is additionally adjusted for time-varying BMI (<24.9, 25-29.9, 30-34.9, or ≥35 kg/m<sup>2</sup>), cigarette smoking status and current dose (never, past, current 1-34 cigarettes/day, current ≥35 cigarettes/day), physical activity (0, 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles).

**Table S3. Sensitivity analysis for the association of infertility history with the risk of coronary heart disease (CHD) (NHS II, 1989-2017).**

	<b>Coronary Heart Disease (CHD)</b>	
	<b>No infertility</b>	<b>With infertility</b>
<b>Updating infertility status until participants reached 37 years of age</b>		
Events, No.	1,005	495
HRs for age-adjusted model*	1.00 [Reference]	1.22 (1.10, 1.36)
HRs for multivariable model 1 <sup>†</sup>	1.00 [Reference]	1.24 (1.11, 1.39)
HRs for multivariable model 2 <sup>‡</sup>	1.00 [Reference]	1.17 (1.05, 1.31)
<b>Excluding women reporting infertility only due to spouse or partner factors</b>		
Events, No.	971	490
HRs for age-adjusted model*	1.00 [Reference]	1.16 (1.04, 1.30)
HRs for multivariable model 1 <sup>†</sup>	1.00 [Reference]	1.17 (1.05, 1.31)
HRs for multivariable model 2 <sup>‡</sup>	1.00 [Reference]	1.12 (1.00, 1.25)

\* Models were jointly stratified by age (months) and calendar time (months)

<sup>†</sup> Based on age-adjusted models with further adjustment for age at menarche (<12, 12, 13, ≥14 years of age), White race/ethnicity (yes, no), marriage status (ever/currently married or never), and time-varying daily aspirin use (yes or no), oral contraceptive use (never, past, or current), gravidity (≤1, 2, 3, or ≥4), BMI at age 18 years (<19, 20.5-21.9, 22-24.9, 25-29.9, or ≥30 kg/m<sup>2</sup>), and breastfeeding duration (<3, 3-12, or >12 months).

<sup>‡</sup> Based on multivariable model 1 with further adjustment for time-varying BMI (<24.9, 25-29.9, 30-34.9, or ≥35 kg/m<sup>2</sup>), 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 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles).

**Table S4. Hazard ratios (HR) and 95% confidence intervals (CI) for the risk of stroke according to conditions that were reported to be the cause of infertility (NHSII, 1989-2017).**

Attributed causes of infertility	Ever Reported Infertility Diagnosis	
	No <sup>§</sup>	Yes <sup>#</sup>
<b>Ovulatory disorder</b>		
Events, No.	531	68
Age-adjusted model*	1.00 [Referent]	1.00 (0.78, 1.29)
Multivariable model 1 <sup>†</sup>	1.00 [Referent]	0.98 (0.76, 1.27)
Multivariable model 2 <sup>‡</sup>	1.00 [Referent]	0.90 (0.66, 1.21)
<b>Endometriosis</b>		
Events, No.	531	46
Age-adjusted model*	1.00 [Referent]	1.23 (0.91, 1.66)
Multivariable model 1 <sup>†</sup>	1.00 [Referent]	1.28 (0.93, 1.74)
Multivariable model 2 <sup>‡</sup>	1.00 [Referent]	1.27 (0.87, 1.84)
<b>Cervical mucus disorder</b>		
Events, No.	531	12
Age-adjusted model*	1.00 [Referent]	0.89 (0.50, 1.57)
Multivariable model 1 <sup>†</sup>	1.00 [Referent]	0.92 (0.51, 1.63)
Multivariable model 2 <sup>‡</sup>	1.00 [Referent]	0.79 (0.41, 1.52)
<b>Tubal blockage</b>		
Events, No.	531	24
Age-adjusted model*	1.00 [Referent]	0.90 (0.59, 1.35)
Multivariable model 1 <sup>†</sup>	1.00 [Referent]	0.90 (0.59, 1.36)
Multivariable model 2 <sup>‡</sup>	1.00 [Referent]	0.79 (0.49, 1.25)
<b>Spouse or partner factors</b>		
Events, No.	531	40
Age-adjusted model*	1.00 [Referent]	0.88 (0.63, 1.21)
Multivariable model 1 <sup>†</sup>	1.00 [Referent]	0.88 (0.63, 1.23)
Multivariable model 2 <sup>‡</sup>	1.00 [Referent]	0.79 (0.54, 1.16)
<b>Other cause</b>		
Events, No.	531	39
Age-adjusted model*	1.00 [Referent]	1.05 (0.76, 1.45)
Multivariable model 1 <sup>†</sup>	1.00 [Referent]	1.05 (0.75, 1.46)
Multivariable model 2 <sup>‡</sup>	1.00 [Referent]	0.97 (0.67, 1.40)
<b>Cause not found</b>		
Events, No.	531	47
Age-adjusted model*	1.00 [Referent]	0.87 (0.65, 1.18)
Multivariable model 1 <sup>†</sup>	1.00 [Referent]	0.89 (0.66, 1.21)
Multivariable model 2 <sup>‡</sup>	1.00 [Referent]	0.88 (0.64, 1.21)
<b>Cause not investigated</b>		
Events, No.	531	55
Age-adjusted model*	1.00 [Referent]	0.84 (0.64, 1.11)
Multivariable model 1 <sup>†</sup>	1.00 [Referent]	0.84 (0.63, 1.11)
Multivariable model 2 <sup>‡</sup>	1.00 [Referent]	0.80 (0.59, 1.06)

CHD includes fatal and non-fatal MI (ICD-8:410), fatal coronary heart disease (ICD-8: 412) and self-reported coronary artery bypass grafting (CABG)/angioplasty/stent \*Models were jointly stratified by age (months) and calendar time (months). <sup>†</sup>Model 2 additionally adjusted for age at menarche (<12, 12, 13, ≥14 years of age), White Non-Hispanic race/ethnicity (yes, no), marital status (ever married, never), daily aspirin use (yes, no), oral contraceptive use (never, past, current), gravidity (≤1, 2, 3, or ≥4 pregnancies), body mass index (BMI) at age 18 years (<19, 20.5-21.9, 22-24.9, 25-29.9, or ≥30 kg/m<sup>2</sup>), and breastfeeding duration (<3, 3-12, or >12 months). <sup>‡</sup>Model 3 is additionally adjusted for current BMI (<24.9, 25-29.9, 30-34.9, or ≥35 kg/m<sup>2</sup>), cigarette smoking status and current dose (never, past, current 1-34 cigarettes/day, current ≥35 cigarettes/day), physical activity (0, 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 h/week), Alternative Healthy Eating Index 2010 diet quality score (quintiles) and mutually adjusted for other infertility diagnoses. <sup>§</sup>Comparison group is gravid women without a history of any kind of infertility. <sup>#</sup>Attributed causes of infertility are not mutually exclusive.

**Table S5. Association of infertility due to ovulatory disorders and risk of coronary heart disease (CHD), stratified by Polycystic ovary syndrome symptoms.\***

	No infertility	Infertility due to ovulatory disorders compared to no infertility
<b>Menstrual cycle length in adulthood</b>		
<32 days (n=1311 cases)	1.00 [Referent]	1.28 (1.03, 1.60)
≥32 days (n=189 cases)	1.00 [Referent]	1.21 (0.78, 1.88)
<b>Menstrual cycle length in adulthood</b>		
Very regular or regular (n=1143 cases)	1.00 [Referent]	1.30 (1.03, 1.65)
Irregular or no period (n=357 cases)	1.00 [Referent]	1.19 (0.83, 1.71)
<b>Hirsutism</b>		
No (n=1421 cases)	1.00 [Referent]	1.23 (1.00, 1.52)
Yes (n=79 cases)	1.00 [Referent]	1.24 (0.59, 2.62)

\*Models were jointly stratified by age (months) and calendar time (months) and adjusted for age at menarche (<12, 12, 13, ≥14 years of age), White race/ethnicity (yes, no), marriage status (ever/currently married or never), daily aspirin use (yes or no), oral contraceptive use (never, past, or current), gravidity (≤1, 2, 3, or ≥4), breastfeeding duration (<3, 3-12, or >12 months), current BMI (<24.9, 25-29.9, 30-34.9, or ≥35 kg/m<sup>2</sup>), 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 h/week), and Alternative Healthy Eating Index 2010 diet quality score (quintiles).