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Subfertility and risk of later life maternal cardiovascular disease

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BACKGROUND: Subfertility shares common pathways with cardiovascular disease (CVD), including polycystic ovarian syndrome, obesity and thyroid disorders. Women with prior 0–1 pregnancies are at an increased risk of incident CVD when compared with women with two pregnancies. It is uncertain whether history of subfertility among women eventually giving birth is a risk factor for CVD.

METHODS: Among Swedish women with self-reported data on subfertility in the Swedish Medical Birth Register ($n = 863\,324$), we used Cox proportional hazards models to relate a history of subfertility to CVD risk after adjustment for age, birth year, highest income, education, birth country, hypertension, diabetes, preterm birth, small for gestational age (SGA), smoking and for BMI in separate models. In additional analyses, we excluded women with: (i) pregnancy-related or non-pregnancy-related hypertension and/or diabetes; and (ii) preterm births and/or SGA babies.

RESULTS: Among nulliparous women eventually having a childbirth (between 1983 and 2005, the median follow-up time 11.9; 0–23 years and 9 906 621 person-years of follow-up), there was an increased risk of CVD among women reporting ≥5 years of subfertility versus 0 years (hazard ratio 1.19, 95% confidence interval 1.02–1.39). There were not significantly elevated CVD risks for women with 1–2 or 3–4 years of subfertility versus 0 years. Accounting for BMI did not change results. Excluding women with hypertension and/or diabetes attenuated associations, whereas exclusion of women with preterm and/or SGA births did not change findings.

CONCLUSIONS: Subfertility among women eventually having a childbirth is a risk factor for CVD even upon accounting for cardiovascular risk factors and adverse pregnancy outcomes. Future studies should explore the mechanisms underlying this association.

Key words: subfertility / cardiovascular disease / polycystic ovarian syndrome / pregnancy

Introduction

There are an estimated 70 million couples worldwide who are infertile and more than half of these persons seek medical treatment for infertility (Boivin *et al.*, 2007). Long-term clinical outcomes associated with subfertility (or a history of infertility for at least 1 year prior to conceiving) are not certain. A prior prospective investigation demonstrated that menstrual irregularity, a known correlate of subfertility (Kok *et al.*, 2003), is related to increased risks for women of cardiovascular disease (CVD) in later life (Solomon *et al.*, 2002). Nulliparous and primiparous women have an increased risk of CVD when compared with women having two pregnancies (Lawlor *et al.*, 2003; Parikh *et al.*, 2010) and subfertility is inversely related to parity (Kok *et al.*, 2003; Azziz *et al.*, 2009). Subfertility shares some common mechanistic pathways with CVD, including polycystic ovarian syndrome, thyroid dysfunction and excess adiposity. However, it is uncertain whether subfertility itself is a risk factor for incident CVD among women.

Therefore, we aimed to determine whether subfertility, an important public health issue, was itself related to incident CVD among women who eventually have a childbirth. We hypothesized that a history of subfertility among women eventually having a childbirth would be associated with excess risk of CVD and that the excess risk may not be fully explained by known CVD risk factors, including hypertension, smoking, diabetes and obesity. The Swedish Medical Birth Register and Population registers allowed us to test our hypothesis in a large and relatively unselected study sample using prospectively collected information on exposures and outcomes.

Materials and Methods

Data sources

We accessed data from population-based registers maintained at the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se/en/) and Statistics Sweden (http://www.scb.se). Individual records were linked across the registers using the unique personal identity number assigned to all Swedish residents, i.e. individuals either born in Sweden or immigrating to Sweden.

The Medical Birth Register was initiated in 1973 as a means to compile information on maternal, pregnancy and infant factors (National Board of Health and Welfare). The three primary foci of data collection are: (i) the basic record of antenatal care of the mother; (ii) the delivery record and (iii) the record for the pediatric examination of the newborn infant. From 1983 onwards, there is information of previous involuntary childlessness. Up to 1998, >98% of all births in Sweden were registered in the Medical Birth Register.

The Swedish Hospital Discharge Register started to collect data on in-patients treated at public hospitals beginning in the 1960s. From 1978, it covered a geographical area corresponding to 85% of the Swedish population, and from 1987, the coverage is nation-wide (Nyr'n *et al.*, 1998). The registry contains information about dates of admission and discharge, hospital and clinic codes and up to eight discharge diagnosis codes, the first representing the principal cause of hospitalization. The Swedish Cause of Death Register includes information about date, underlying and contributing causes of death. The Swedish Medical Birth Register, Hospital Discharge Register and Cause of Death Register utilize the International Classification of Diseases (ICD), edition 8 (ICD-8) until 1986, edition 9 (ICD-9) from 1987 to 1996 and edition 10 (ICD-10) from 1997 onwards.

In addition, we collected information from the Swedish Censuses of 1970 and 1990, the Educational Register (year 1995, 2000 and 2005), the Income Register (year 1973, 1980, 1985, 1990, 1995, 2000 and 2005) and the Register of Emigrations and Immigrations (1961 onwards).

Study population

All women who were registered in the Medical Birth Register having a first-time delivery between 1983 and 2005 were eligible for the present study ($n = 942\,842$). After exclusion of immigrating women (since we could not be sure that we ascertained data from their first delivery; $n = 994$), women with missing data on covariates ($n = 69\,366$) or missing information about involuntary childlessness ($n = 9158$), the full study sample consisted of 863 324 women. Data on BMI were available only in a smaller subset of the study sample ($n = 646\,609$). The study was approved by the Ethics Committee of Uppsala University, Uppsala, Sweden.

Assessment of subfertility and covariates

When registering for antenatal care in Sweden, the woman spends ~1 h with a midwife for an interview and examination. During this visit, the woman is asked whether she had tried to conceive without success for an extended period. If so, the number of unsuccessful years is recorded as duration of involuntary childlessness in the Medical Birth Registry. A duration of 1 year or more of involuntary childlessness is considered a period of subfertility.

Information on concurrent maternal smoking is also recorded at the first antenatal care visit, and coded as no smoking, 1–9 cigarettes per day and 10 or more cigarettes per day. Height has been registered in ~80% of the women since 1983. Pre-pregnancy weight (i.e. weight at this first antenatal care visit) has been registered since 1992, but can be accurately calculated from weight gain during pregnancy and weight at delivery for most women between 1983 and 1991. Overall, reliable calculations of pre-pregnancy BMI (weight in kg divided by the square of the height in meters) could be done in 75% of the full study sample.

Information about maternal diseases was retrieved from both self-reports to the midwife at registration to antenatal care (using check-boxes) and from ICD-codes provided by the physician when the women were discharged from hospital after birth. Hypertension (pre-gestational hypertension or gestational hypertension, with or without proteinuria) was defined by self-reported hypertension at first antenatal visit or by ICD-codes (ICD-8 codes 400-404 and 637; ICD-9 codes 401-405 and 642; ICD-10 codes I10-15, O10-O11 and O13-O16). Diabetes (type 1, type 2 or gestational diabetes) was defined by self-reported diabetes at first antenatal visit or by ICD-codes (ICD-8 code 250; ICD-9 codes 250, 648A and 648W and ICD-10 codes E10-E11 and O24). If either the self-reported or ICD-codes reflected the presence of hypertension or diabetes, a woman was considered to have the disease. Preterm birth was defined as occurring earlier than 37 completed weeks of pregnancy. Small for gestational age (SGA) was defined as birthweight >2 SDs below the mean birthweight for the gestational age according to the Swedish reference curve for fetal growth (Marsal *et al.*, 1996). Information about gestational age was based on ultrasound examination when available; otherwise we used information from the last menstrual period. In Sweden, early second-trimester ultrasonography to estimate gestational age has been routinely offered since 1990, with 95% of women undergoing the test (Hogberg and Larsson, 1997).

The highest total income (from employment, capital, real estate and business activities) before the first delivery (i.e. start of follow-up) was collected from the Income Register. Educational level according to the Swedish Educational Nomenclature was collected from the Swedish Censuses of 1970 and 1990 and the Educational Register in year 1995, 2000 and 2005. The highest registered educational level before the first delivery was used, and divided into four groups: 9 years or less of primary and secondary school, 2 years of high school (usually programs for manual, clerical or assistance work), 3 years of high school (theoretical programs) and college or university studies. Mothers' country of birth was defined from the Multi-Generation Register, and was divided into four groups: Sweden, other Nordic countries (i.e. Denmark, Finland, Iceland and Norway), other European countries and non-European countries.

Follow-up and outcomes

Follow-up started at the time of the first delivery. End of the follow-up was 31 December 2005 or the date of first occurrence of the following: first CVD event (as defined later), emigration from Sweden, or death.

Incidence of CVD was defined as the first hospitalization (assessed from the Hospital Discharge Register) or death (assessed from the Cause of Death Register), caused by coronary heart disease, stroke or heart failure. Coronary heart disease was defined as unstable angina (ICD-8 code 411, ICD-9 code 411B, ICD-10 code I20.0), or acute myocardial infarction (ICD-8 and ICD-9 code 410, ICD-10 codes I21-I22). Stroke was defined as cerebral infarction (ICD-8 codes 432-434, ICD-9 codes 433-434, ICD-10 code I63), cerebral hemorrhage (ICD-8 code 431, ICD-9 codes 431-432, ICD-10 codes I61-I62), subarachnoidal hemorrhage (ICD-8 and ICD-9 code 430, ICD-10 code I60), transient ischemic attack (ICD-8 and ICD-9 code 435, ICD-10 code G45) or other acute stroke (ICD-8 and ICD-9 code 436, ICD-10 code I64). Heart failure was defined by ICD-8 codes 427.00 and 427.10, ICD-9 code 428, ICD-10 code I50. We considered only hospitalizations or deaths with the earlier-mentioned diagnoses as primary diagnosis of the hospitalization or underlying cause of death. The positive predictive values (i.e. validity) of the myocardial infarction (Lindblad *et al.*, 1993; Hammar *et al.*, 2001), stroke (Lindblad *et al.*, 1993; Hammar *et al.*, 2001) and heart failure

(Ingelsson et al., 2005) diagnoses in the Swedish hospital discharge register have been demonstrated to be around 95% when only primary diagnoses are considered.

Statistical methods

Subfertility was analyzed as a categorical variable with four levels: 0, 1–2, 3–4 and 5 or more years of involuntary childlessness and as a dichotomous variable (≥1 years of involuntary childlessness versus 0). The highest income before the first delivery and BMI were analyzed as continuous variables, whereas birth year (≤1959; 1960–1969; ≥1970), educational level, country of birth, hypertension, diabetes, preterm birth, SGA and smoking were analyzed as categorical variables. We examined associations between subfertility and the first occurrence of CVD (hospitalization or death with coronary heart disease, stroke or heart failure as primary diagnosis) by unadjusted and multivariable-adjusted Cox proportional hazards regressions with maternal age as the underlying time variable. The proportionality of hazards was confirmed by plotting smoothed scaled Schoenfeld's residuals against time. The associations between subfertility and CVD were investigated in age-adjusted models and multivariable-adjusted models, adjusting for age, birth year, highest income before first delivery, education level, country of birth, hypertension, diabetes, preterm birth, SGA, smoking and attained parity. Attained parity was adjusted for by introducing subsequent deliveries as time-dependent covariates, splitting the risk time according to parities 1–4 or more. All other covariates were collected at the first pregnancy, i.e. baseline of the study. In a smaller subset of women with available information on BMI (n = 646 609), we reiterated the multivariable models with the addition of BMI as a covariate. Since BMI has a well-documented association with subfertility (Grodstein et al., 1994) and with incident CVD (Gregg et al., 2005), we studied the association between subfertility and CVD among well-established BMI categories (Obesity 2000) of underweight (BMI <18.5 kg/m^2), normal weight (18.5 ≤ BMI <2 5 kg/m^2) and overweight or greater (BMI ≥25 kg/m^2). We tested for effect modification of BMI (continuous) on the association between subfertility (categories) and CVD.

Secondary analyses

In order to study the association between subfertility and CVD in subgroups of women without factors that we believed could be involved in or could reflect markers within the mechanistic pathway between exposure and outcome, we analyzed the fully adjusted models (i.e. adjusted for all covariates including BMI) in two sub-samples, after exclusion of: (i) women with hypertension (pregnancy-induced or non-pregnancy-induced, with or without proteinuria) and/or diabetes (gestational or non-gestational) (sample size n = 605 145); and (ii) women having pre-term deliveries and/or SGA infants (sample size n = 588 872). We tested for cohort effect by stratifying our main analysis by year of birth (≤1959, 1960–1969 and ≥1970). We additionally tested for the effect modification by participant birth time period (≤1959, 1960–1969 and ≥1970).

Two-tailed 95% confidence intervals and P-values are given, with P < 0.05 regarded as significant. The statistical software package STATA 10.0 MP (Stata Corporation, College Station, TX, USA) was used for all analyses.

Results

The baseline characteristics of the study sample of women having their first delivery from 1983 to 2005 are given in Table I. The median follow-up time was 11.9 years (range 0–23.0; 25–75th percentile, 5.7–16.9) contributing to 9 906 621 person-years at risk. During this period, 3337 women developed a first CVD event (coronary heart disease, n = 878; stroke, n = 2217; heart failure, n = 242). The unadjusted incidence rates were 0.54 cases/1000 person-years at risk for women reporting at least 1 year of subfertility, compared with 0.32 cases/1000 person-years at risk for women without such history.

Subfertility for either 1–2 or 3–4 years when compared with 0 years was not related to incident CVD. Subfertility for at least 5 years when compared with 0 years was associated with an increased risk of CVD [multivariable-adjusted hazard ratio (HR) = 1.19 (1.02, 1.39), P = 0.02, Table II]. There was an association between subfertility ≥1 year and CVD that did not reach statistical significance HR = 1.10 (0.99–1.21), P = 0.07. A plot of age-adjusted CVD rates per year of subfertility demonstrates a positive association between years of reported subfertility and incident CVD (Fig. 1).

Models accounting for BMI

Upon adding BMI to fully adjusted models, the association of subfertility with CVD was not materially different (Table III). Among normal weight women (n = 465 458), there was an association between 5 or more years of subfertility and incident CVD [HR, 1.31; 95% confidence interval (CI) 1.05–1.63; P = 0.017]. Subfertility ≥1 year was not related to CVD upon adjustment for BMI HR = 1.10 (0.98, 1.24; P = 0.11). Among overweight women (n = 150 917), 5 or more years of subfertility was associated with an elevated risk of CVD that was not statistically significant (HR, 1.20; 95% CI 0.87–1.65; P = 0.27). Among underweight women (n = 30 234), there were no significant associations between subfertility and CVD. However, there was no evidence of a statistically significant effect modification of BMI on the association between subfertility for ≥5 years and CVD (P-value for interaction = 0.7).

Secondary analyses

Upon excluding women with hypertension (pregnancy-induced or non-pregnancy-induced with or without proteinuria) and/or diabetes (gestational or non-gestational), results were similar in terms of magnitude of association, though no longer statistically significant (HR, 1.20; 95% CI, 0.98–1.47; P = 0.08 for having 5 or more years of self-reported subfertility when compared with no history of subfertility). Upon excluding women with SGA babies and/or preterm deliveries, our results were similar to those of the main analyses (HR, 1.25; 95% CI 1.01–1.53; P = 0.037) for having 5 or more years of subfertility when compared with no subfertility).

In age-adjusted and multivariable models stratified by mother's birth year (≤1959, 1960–1969 and ≥1970), we found that women experiencing 5 or mores years of subfertility had increased risks of CVD that were statistically significant for the oldest group of women (Table IV). There was no evidence for the effect modification by birth time period (multivariable-adjusted P-value = 0.51).

Discussion

Principal findings

Among 863 324 women with self-reported fertility data at the time of their first delivery in the Swedish Medical Birth Register, we found that women reporting subfertility for ≥5 years had a 20% increased risk of incident CVD compared with women reporting no history of

Table I Baseline characteristics of the study sample[a].

	Number of years of subfertility			
	0 ($n = 781\,657$)	1–2 ($n = 43\,767$)	3–4 ($n = 20\,073$)	5 or more ($n = 17\,827$)
Birth year (%)				
1932–1959	15.1	22.8	27.8	45.8
1960–1969	48.6	46.3	47.2	42.7
1970	36.3	30.9	25.0	11.4
Highest mean (±SD) income before the first delivery (USD/year)[a]	37 999 ± 51 352	40 629 ± 76 002	40 616 ± 30 822	4062 ± 36 819
Educational level (%)				
0–9 years of primary and secondary school	9.0	7.3	7.2	11.2
2 years of high school	27.6	28.0	29.8	35.2
3 years of high school	23.1	21.9	19.8	17.0
College or university studies	40.3	42.7	43.2	36.5
Country of birth (%)				
Sweden	87.3	89.4	88.2	86.6
Other Nordic countries[b]	2.7	2.9	3.3	4.2
Other European countries	3.9	3.4	4.0	4.9
Countries from rest of the world	6.0	4.3	4.5	4.3
Hypertension (%)	5.4	6.6	7.0	8.3
Diabetes (%)	0.9	1.2	1.7	2.0
Preterm birth (%)	6.3	7.5	9.6	12.0
SGA (%)	3.4	3.6	4.1	5.2
Smoking (%)				
No smoking	80.8	83.5	83.0	77.8
1–9 cigarettes/day	13.0	11.4	11.4	14.3
10 or more cigarettes/day	6.3	5.1	5.6	7.9
BMI (kg/m^2)[c] mean (±SD)	23.1 ± 3.7	23.6 ± 4.1	23.9 ± 4.2	24.1 ± 4.4
Parity (%)				
1	27.0	31.2	39.2	50.8
2	49.9	49.7	44.7	37.7
3	18.1	15.6	13.4	9.6
4	3.9	2.7	2.2	1.5
≥5	1.1	0.7	0.5	0.4

USD, US dollar; SGA, small for gestational age.
[a]Originally recorded in Swedish crowns (1 SEK = 0.1622 USD, as of 11 June 2008).
[b]Finland, Norway, Denmark and Iceland.
[c]Available in a sub-sample of 646 609 women.

subfertility. Results were similar after accounting for BMI in a subset of women with available data on BMI. The association of subfertility with maternal CVD was only observed among women in the normal BMI range; however, a borderline significant association was seen also in overweight women. This difference across BMI categories is likely to be due to statistical power differences in the BMI strata—a notion supported by the lack of statistical significance of the interaction term.

Prior literature

To our knowledge, our study represents the first published report relating subfertility with incident maternal CVD. Menstrual irregularity is commonly reported among subfertile women (Kok *et al.*, 2003) and has been studied previously in relation to incident CVD (Solomon *et al.*, 2002). Our findings were consistent in direction though slightly lesser in magnitude of association when compared with that of 82 439 female nurses (Nurses' Health Study); study investigators reported a 50% increased risk of incident nonfatal myocardial infarction or fatal coronary heart disease among women reporting very irregular menstrual cycles when compared with normal cycles during ages 20–35 years (Solomon *et al.*, 2002). A study among women in Kaiser Permanente did not show an association between menstrual irregularity and CVD mortality upon adjustment for BMI (Wang *et al.*, 2011).

Table II CVD incidence by years of subfertility in Swedish women having their first delivery from 1983 to 2005 (n = 863 324)[a].

n	Age-adjusted		Multivariable-adjusted	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
0 years (781 657)	Referent	—	Referent	—
1–2 years (43 767)	1.04 (0.90, 1.20)	0.61	1.07 (0.92, 1.23)	0.38
3–4 years (20 073)	1.01 (0.83, 1.23)	0.93	1.01 (0.83, 1.23)	0.94
At least 5 years (17 827)	1.35 (1.16, 1.57)	<0.0001	1.19 (1.02, 1.39)	0.02

HR, hazard ratio; CI, confidence interval.
[a]Values are Cox proportional hazards ratios (95% confidence intervals) for subfertility with no subfertility used as a reference level. *P*-values are from likelihood ratio tests per year of subfertility or for differences across categories. The HRs are age-adjusted (adjusting for birth year and age at first delivery), or multivariable-adjusted (adjusting for birth year, age at first delivery, highest income before first delivery, education level, country of birth, hypertension, diabetes, preterm birth, SGA, smoking and parity).

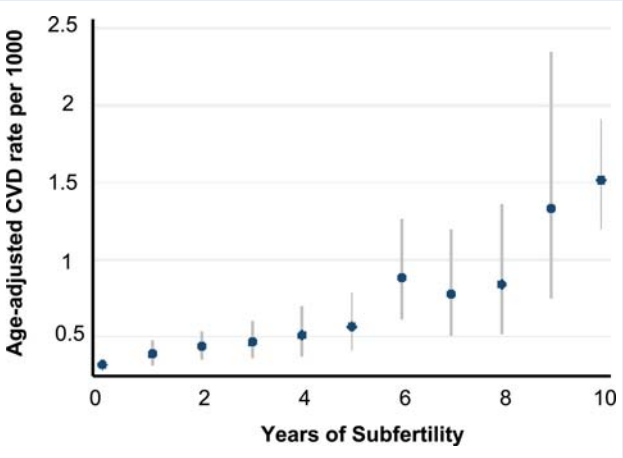

Figure 1 Age-adjusted CVD-rates by years of reported subfertility among Swedish women having their first delivery from 1983 to 2005 (n = 863 324).

Possible mechanisms

Subfertility and CVD may have some mechanistic pathways in common. We explored some of these potential pathways within our analysis**.** Excess adiposity as measured by BMI is related to subfertility (Grodstein *et al*., 1994), to menstrual cycle irregularity (Solomon *et al*., 2002) and to incident CVD (Gregg *et al*., 2005). However, adjustment for BMI neither nullified nor attenuated our CVD risk estimates, suggesting that factors other than BMI underlie the association between subfertility and CVD. We also sought to test whether BMI acted synergistically with subfertility to predict incident CVD. However, we found that associations between subfertility and CVD persisted among normal weight women, and that the interaction term for BMI was non-significant.

Upon excluding hypertension (pregnancy-induced or non-pregnancy-induced, with or without proteinuria) and/or diabetes (gestational or non-gestational), the association between subfertility and CVD was attenuated, suggesting that these conditions may be partial mediators of the association between exposure and outcome.

Adverse pregnancy outcomes such as preterm birth and having a SGA baby are associated with CVD (Smith *et al*., 2001). In models excluding mothers with SGA babies and pre-term deliveries, the association between subfertility and CVD was essentially unaltered, suggesting other underlying factors of the observed association.

Early miscarriages, a potential unrecognized cause of involuntary childlessness, can be due to hypercoaguable states/thrombophilia (Reindollar, 2000; Sotiriadis *et al*., 2007). Hypercoaguable states are associated with excess CVD risk and are also related to pregnancy-related complications such as pre-eclampsia (Hvas *et al*., 2009), which is a risk factor for incident maternal CVD (Irgens *et al*., 2001). Another possible mechanistic link between subfertility and CVD is hypothyroidism, which is linked to both infertility (Redmond, 2004) and incident CVD (Flynn *et al*., 2006).

Polycystic ovarian syndrome, prevalent in 6–8% of reproductive aged women (Azziz *et al*., 2009), accounts for up to 15% of female infertility and is associated with subclinical atherosclerosis as measured by carotid intima-media thickness (Talbott *et al*., 2000). However, the lack of adequate prospective data makes it uncertain whether polycystic ovarian syndrome leads to incident CVD independent of classic CVD risk factors. Upon excluding women with diabetes and/or hypertension (both features of polycystic ovarian syndrome) and controlling for BMI, subfertility was still associated with incident CVD with a similar degree of magnitude (albeit with borderline statistical significance). Thus, it is uncertain whether the association between subfertility and CVD was mediated through polycystic ovarian syndrome. The lack of data on the presence of polycystic ovarian syndrome in our study population did not allow us to examine this question fully in our data set.

Women who experience subfertility have high levels of psychologic stress manifesting as both depression and anxiety (Andrews *et al*., 1991) and psychosocial stressors in turn are linked to CVD (Yusuf *et al*., 2004). This is potentially through mechanisms related to altered immunomodulation (Loftis *et al*., 2010) or vascular dysfunction. Thus, psychosocial stress may contribute our findings of increased risk of incident CVD among women with prolonged periods of subfertility.

Fertility treatment for subfertility in our data set would not have been present in the form of IVF, as most pregnancies in this cohort took place in the 1980s. Thus, it is unlikely that IVF accounted for

Table III CVD incidence by years of subfertility in Swedish women giving their first delivery from 1983 to 2005 with additional adjustment for BMI and among BMI categories[a].

	All BMI categories (n = 646 609)		Underweight BMI <18.5 kg/m^2 (n = 30 234)		Normal weight 18.5 <BMI <25 kg/m^2 (n = 465 458)		Overweight or obese BMI ≥25 kg/m^2 (n = 150 917)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
0 years (n = 582 285)	Referent	—	Referent	—	Referent	—	Referent	—
1–2 years (n = 34 535)	1.07 (0.90–1.27)	0.43	1.28 (0.69–2.39)	0.43	1.16 (0.95–1.43)	0.14	0.79 (0.54–1.16)	0.23
3–4 years (n = 15 970)	0.95 (0.75–1.22)	0.70	0.55 (0.13–2.23)	0.40	0.87 (0.63–1.20)	0.41	1.17 (0.78–1.74)	0.45
At least 5 years (n = 13 819)	1.24 (1.04–1.49)	0.02	0.48 (0.12–1.98)	0.31	1.31 (1.05–1.63)	0.02	1.20 (0.87–1.65)	0.27

HR, hazard ratio; CI, confidence interval.
[a]Values are Cox proportional HRs (95% confidence intervals) for subfertility with no subfertility used as a reference level. *P*-values are from likelihood ratio tests per year of subfertility or for differences across categories. The HRs are multivariable-adjusted (adjusting for birth year, age at first delivery, highest income before first delivery, education level, country of birth, hypertension, diabetes, preterm birth, SGA, smoking, parity and BMI).

Table IV CVD incidence by years of subfertility in Swedish women having their first delivery from 1983 to 2005 among mother's birth year category[a].

Years of subfertility	Calendar year ≤1959 (n = 141 745)		Calendar year 1960–1969 (n = 417 579)		Calendar year ≥1970 (n = 304 000)	
	Age adjusted [HR (95% CI; *P*-value)]	MV adjusted [HR (95% CI; *P*-value)]	Age adjusted [HR(95% CI; *P*-value)]	MV adjusted [HR(95% CI; *P*-value)]	Age adjusted [HR(95% CI; *P*-value)]	MV adjusted [HR (95% CI; *P*-value)]
0	Referent					
1–2	1.06 (0.87, 1.30); $P = 0.54$	1.07 (0.88, 1.31); $P = 0.49$	1.16 (0.94, 1.45); $P = 0.17$	1.12 (0.90, 1.39); $P = 0.31$	0.59 (0.28, 1.25); $P = 0.17$	0.59 (0.28, 1.25); $P = 0.17$
3–4	1.13 (0.89, 1.45); $P = 0.32$	1.10 (0.86, 1.40); $P = 0.45$	0.92 (0.63, 1.34); $P = 0.67$	0.85 (0.59, 1.24); $P = 0.40$	0.94 (0.35, 2.51); $P = 0.89$	0.89 (0.33, 2.39); $P = 0.82$
≥5	1.41 (1.19, 1.68); $P < 0.01$	1.22, (1.03, 1.46); $P = 0.02$	1.49 (1.07, 2.07); $P = 0.02$	1.21 (0.87, 1.69); $P = 0.27$	2.37 (0.88, 6.37); $P = 0.09$	1.90 (0.70, 5.14); ($P = 0.21$)

HR, hazard ratio; CI, confidence interval.
[a]Values are Cox proportional HRs (95% confidence intervals) for subfertility with no subfertility used as a reference level. *P*-values are from likelihood ratio tests per year of subfertility or for differences across categories. The HRs are adjusted for birth year and age at first delivery only or multivariable (MV)-adjusted (adjusting for birth year, age at first delivery, highest income before first delivery, education level, country of birth, hypertension, diabetes, preterm birth, SGA, smoking and parity).

the association we found between subfertility and CVD, given that the effect was present in the oldest women in our study population. Whether or not fertility treatment present during the 1980s, such as ovulation stimulation therapy (i.e. clomiphene), accounted for the association between 5 or more years of subfertility, and CVD would be an important area of further study.

It is possible that unaccounted for confounding variables not captured in our study framework could, at least partly account for the increased risk of CVD found among women reporting 5 or more years of subfertility.

Strengths and limitations

Strengths of our study include a very large study sample that is unselected for CVD and for subfertility. We utilized detailed covariate data that allowed us to account for both socioeconomic factors and classic CVD risk factors. Data on these covariates also allowed us to do some exploration of potential mediators of the association. For ease of interpretation, we considered only a history of subfertility prior to a woman's first delivery. It is possible that subfertility experienced between pregnancies or after a woman's final pregnancy may also be associated with increased CVD risks not accounted for by our present study. Furthermore, our estimate of subfertility may lack precision in that we cannot verify that study participants with subfertility uniformly attempted to conceive during each fertile phase of each of her menstrual cycles for 12 months (Gnoth *et al.*, 2005). However, any exposure misclassification is most likely random and thus would have biased our estimates towards the null value. We were unable to assess the cause of subfertility, as this information is not recorded in the Swedish Medical Birth Register. Further, due to the fact that subfertility information was gleaned from the Swedish Maternal Birth Register in which only women eventually giving birth are registered, we were unable to assess CVD risk among nulliparous women with a history of subfertility/involuntary childlessness. The definition and diagnostic criteria of gestational diabetes mellitus changed during the study period, and we were not able to account for this change in definition within our study framework. Any misclassification of this

covariate would have resulted in random misclassification thus biasing estimated towards the null. Our study was of a Northern European population of white ancestry and thus these findings may not be generalizable to other ethnic groups or geographic regions. The CVD risk factors were available at the time of pregnancy, but risk factors that developed during the follow-up period were not assessed or accounted for within our analysis. We could not account for lipids abnormalities. We did not have measures of depressive symptoms that have been related to both subfertility (Lechner *et al*., 2007) and to recurrent CVD (Whooley *et al*., 2008; Whang *et al*., 2009) and thus could have either confounded or mediated associations demonstrated in our study.

Implications

Our results indicate that subfertility, for an extended period, although likely varied in its underlying etiologies, may be a marker for increased CVD risk among women. Future mechanistic studies investigating CVD pathways, including inflammation, adipokines, oxidative stress, endothelial dysfunction and measures of subclinical CVD among women and men with and without subfertility, may provide useful information. Prospective studies of women with infertility by cause and specifically the subset who receive infertility treatment are important and would be of public health interest, given the increased worldwide demand for fertility treatment.

Conclusions

Women reporting at least 5 years of subfertility prior to having their first child had modestly increased risks of incident CVD when compared with women reporting no history of subfertility prior to their first child.

Authors' roles

N.I.P., S.C., M.A.M. and J.F.L. were involved in study design, execution, manuscript drafting and critical discussion. E.I. participated in study design, analysis, execution, manuscript drafting and critical discussion.

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Conflict of interest

None declared.

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