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Original Article

Infertility and the Risk of Cardiovascular Disease: Findings From the Study of Women's Health Across the Nation (SWAN)

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of death in women globally. In recent years, attention has turned to infertility and pregnancy-related events as potential markers for early mortality and future CVD.

Methods: The Study of Women's Health Across the Nation (SWAN) is an ongoing longitudinal cohort study of women's health. Women aged 42-52 years with a uterus and $\leq$ 1 intact ovary, a menstrual period, and no hormone medications within 3 months before enrollment were eligible. Infertility was self-reported and defined as the inability to achieve pregnancy after 12 months of trying to conceive, or use of fertility medications for $>$ 1 month. Outcomes included development of metabolic syndrome over a 7-year follow-up, and any atherosclerotic CVD event (ie, stroke, angina, myocardial infarction) over a 10-year follow-up. Cox proportional hazards models were used to calculate hazard ratios (HRs) for metabolic syndrome and CVD events in participants with infertility, with adjustment for relevant covariates. Participants without infertility were used as the comparison group.

RÉSUMÉ

Introduction : Les maladies cardiovasculaires (MCV) sont la principale cause de décès chez les femmes dans le monde. Au cours de dernières années, l'infertilité et les complications de la grossesse ont retenu l'attention, à savoir qu'ils constituent des marqueurs potentiels de la mortalité précoce et des MCV futures.

Méthodes : La Study of Women's Health Across the Nation (l'étude SWAN) qui constitue une étude de cohorte longitudinale sur la santé des femmes est en cours. Les femmes âgées de 42 à 52 ans qui ont un utérus et $\leq$ 1 ovaire intact, une période menstruelle et qui ne prenaient aucun médicament hormonal 3 mois avant le recrutement étaient admissibles. L'infertilité était autodéclarée et définie comme l'incapacité à être enceinte après 12 mois de tentatives de conception ou l'utilisation de médicaments pour traiter l'infertilité durant $>$ 1 mois. L'issue était la suivante : la survenue du syndrome métabolique au cours du suivi de 7 ans ou de tout événement lié à la MCV athérosclérotique (c.-à-d. l'accident vasculaire cérébral, l'angine, l'infarctus du myocarde) au cours du suivi de 10 ans. Nous

Globally, cardiovascular disease (CVD) is the leading cause of death in women,[1] highlighting the need for examination of sex-specific risk factors. Although CVD rates have decreased globally, cardiovascular mortality has stagnated in women younger than 55 years of age.[2,3] Approximately 36% of women in the United States aged 20 and older live with CVD, which translates to a staggering 47 million people; non-Hispanic black women experience even higher risk of CVDs, with a prevalence of 47.7%.[4] Infertility affects approximately 15% of women in the United States and has recently been highlighted as a potential risk factor for CVD.[5,6] The potential relationship between infertility and future CVD might be specifically related to the underlying causes of infertility (eg, polycystic ovarian syndrome, endometriosis), risks incurred by treatment of fertility, and/or a lack of risk reduction from a healthy pregnancy.[6] To date, the body of evidence on infertility and CVD is inconclusive and lacking in longitudinal analyses with large sample sizes, especially those

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Ethics Statement: This research has adhered to all relevant guidelines. All participants signed informed consent and the institutional review board at each site approved the study protocol.

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See page 407 for disclosure information.

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Results: We included 2370 participants in the analysis of metabolic syndrome risk, and 2809 participants were included in the analysis of CVD event risk. Participants with self-reported infertility did not have a higher risk of developing metabolic syndrome (HR, 0.91; 95% confidence interval, 0.71-1.15) or experiencing CVD events (HR, 0.79; 95% confidence interval, 0.52-1.21) after adjusting for relevant covariates.
Conclusions: Infertility was not associated with development of metabolic syndrome or CVD events in women; further research is required to investigate the effects of specific causes of infertility and fertility treatments on CVD outcomes.

Résultats : Nous avons recruté 2 370 participantes pour l'analyse du risque de syndrome métabolique, et 2 809 participantes pour l'analyse du risque d'événements liés aux MCV. Les participantes qui avaient autodéclaré leur infertilité n'avaient pas de risque plus élevé de souffrir du syndrome métabolique (RR, 0,91 ; intervalle de confiance à 95 %, 0,71-1,15) ou de subir des événements liés aux MCV (RR, 0,79 ; intervalle de confiance à 95 %, 0,52-1,21) après l'ajustement des covariables pertinentes.
Conclusions : L'infertilité n'était pas associée à la survenue du syndrome métabolique ou des événements liés aux MCV chez les femmes. D'autres recherches qui porteront sur les effets des causes particulières de l'infertilité et des traitements favorisant la fertilité sur l'évolution des MCV sont nécessaires.

that follow women until ages at which cardiovascular events could be expected to happen.[7-13] The reproductive period provides an opportunity to identify early markers of CVD in women, with potential for low-cost and implementable screening and primary prevention strategies (eg, routine blood pressure, glucose, and cholesterol checks), as well as lifestyle modifications before and during subsequent pregnancies (eg, increased physical activity, healthy diet).[6]

Our objectives were to examine whether self-reported infertility in women was associated with the development of: (1) cardiovascular risk factors (metabolic syndrome, a validated marker of CVD risk[14]); and (2) CVD events (stroke, myocardial infarction, angina), using data from the **S**tudy of **W**omen's Health **A**cross the **N**ation (SWAN), a multisite, prospective, epidemiologic study on women's health.

Methods

Study design and data source

We performed a secondary analysis of a prospective cohort study using data from baseline through the 10th annual follow-up visit for women enrolled at all sites included in the publicly available SWAN study data set. SWAN is a multi-site, longitudinal, epidemiological study that collects data on the physical, biological, psychological, and social health of women in their middle years, with the goal of understanding how midlife experiences affect quality of life and health during aging.[15] Details of SWAN methodology have been published elsewhere.[15] Longitudinal data collection began in 1996 when 3302 premenopausal women were enrolled at 7 sites across the United States. Eligible participants were 42-52 years old at recruitment with a uterus and at least 1 intact ovary, a menstrual period within 3 months before enrollment, and had not taken oral contraceptives or postmenopausal hormone therapy in the previous 3 months. Participants self-identified from the following 5 options for racial/ethnic backgrounds: Caucasian/white non-Hispanic, black/African American, Japanese/Japanese American, Hispanic, and Chinese/Chinese American. Participants were assessed annually with interviewer- and self-administered questionnaires, physical examination measurements (ie, weight, height, blood pressure), and fasting morning blood tests.

Ethical approval

All participants signed informed consent and the institutional review board at each site approved the study protocol.

Exposures

Infertility, defined as the inability to achieve a clinical pregnancy for a period of $>$ 12 months of trying to conceive[16] or use of fertility medications for $>$ 1 month, was self-reported at baseline. Unexposed participants were those who did not self-report infertility. Participants were excluded from all analyses if they had missing data on infertility or pregnancy history, or if they reported no attempts to conceive.

Outcomes

The primary outcome was metabolic syndrome, a validated marker of CVD risk[14] that might be even more pronounced in women.[17] Metabolic syndrome is a well established cluster of inter-related risk factors that have been shown to be a precursor of CVD.[18] Participants were classified as having metabolic syndrome if they had 3 or more of the following 5 cardiovascular risk factors, as measured by study staff: elevated waist circumference ($\geq$ 80 cm if the participant identified as Chinese/Chinese American or Japanese/Japanese American; $\geq$ 88 cm if the participant identified as Caucasian/white non-Hispanic, Hispanic, or black/African American); elevated triglycerides ($\geq$ 1.7 mmol/L); reduced high-density lipoprotein cholesterol ($<$ 1.3 mmol/L); elevated blood pressure (systolic blood pressure $\geq$ 130 mm Hg, diastolic blood pressure $\geq$ 85 mm Hg, or use of antihypertensive medications); and elevated fasting glucose ($\geq$ 6.1 mmol/L and/or diabetes). This definition is based on harmonized guidelines for the identification and definition of metabolic syndrome[19] and has been used as a proxy for CVD risk in previous studies using SWAN data.[13,20-22] Participants were excluded from the analysis of metabolic syndrome risk if they had diabetes or metabolic

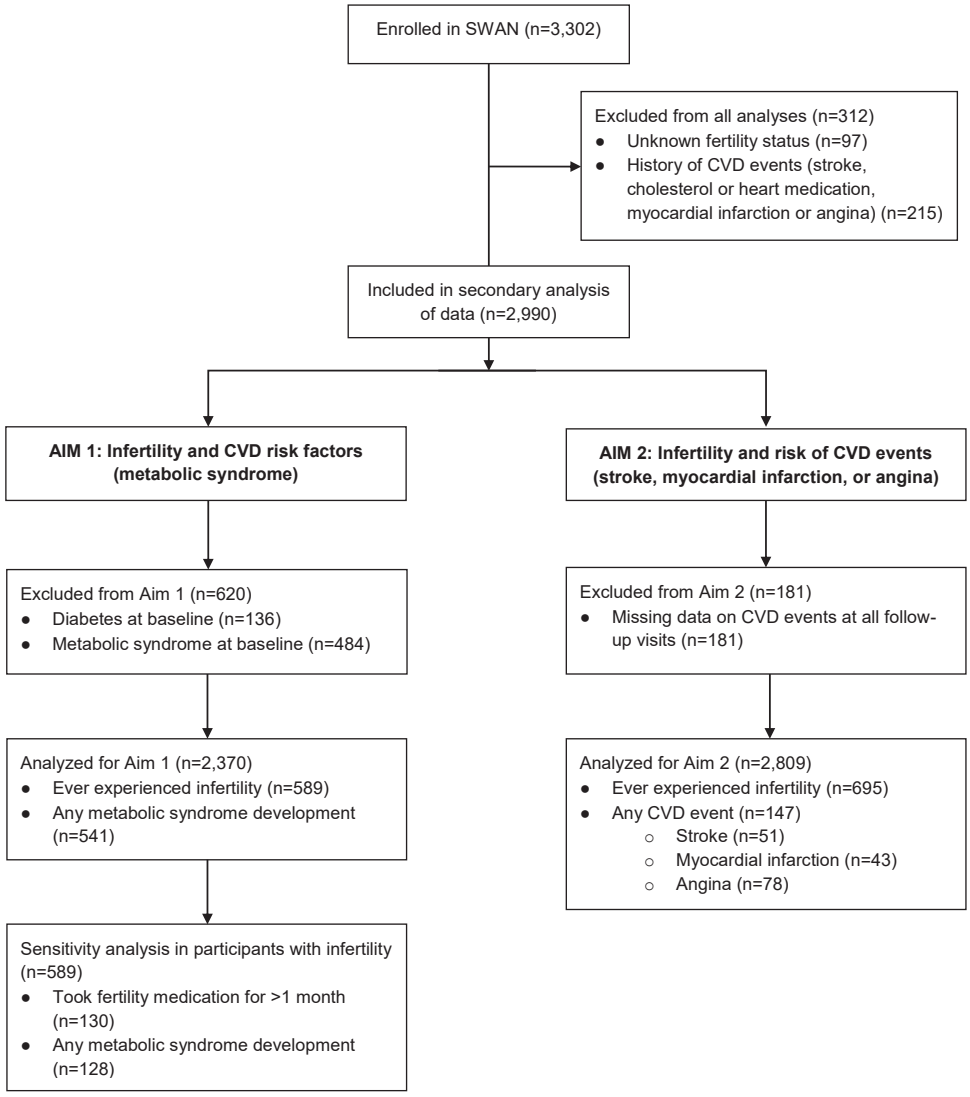

Figure 1. Flow diagram of sample selection. CVD, cardiovascular disease; SWAN, **S**tudy of **W**omen's Health **A**cross the **N**ation.

syndrome at baseline. Components of metabolic syndrome were measured in SWAN until the 7th annual follow-up visit.

CVD events self-reported in SWAN were stroke, myocardial infarction, and angina. Participants were excluded from analysis of CVD event risk if they had missing data on all CVD events at all follow-up visits. CVD events were measured at all visits for which data is publicly available (10 annual follow-up visits).

Participants were excluded from both analyses (metabolic syndrome and CVD) if they had previous stroke, myocardial infarction, angina, or reported taking any cholesterol-lowering or cardiac medication at baseline.

Covariates

Covariates included age, race/ethnicity, education, insurance, marital status, income, body mass index (BMI), birth control pills or other female hormones used continuously from age 25-35 years, family history of CVD events, hypertension, diabetes, menopausal status, any postmenopausal hormone use, smoking, and alcohol consumption. Income was categorized according to total family income before taxes ($\leq$ \$19,999; \$20,000-\$49,999; \$50,000-\$99,999; $\geq$ \$100,000). Marital status was determined by participants reporting being married or in a committed relationship at each follow-up visit. BMI was calculated from metric height and weight measures at each follow-up visit, and further categorized using race-specific cutoffs: Caucasian/white non-Hispanic, Hispanic, and black/African American participants were categorized as underweight or average weight (BMI $<$ 25), overweight (BMI 25-29.9), or obese (BMI $\geq$ 30); and Chinese/Chinese American or Japanese/Japanese American participants were categorized as underweight or average weight (BMI $<$ 23), overweight (BMI 23-24.9), or obese (BMI $\geq$ 25).[22,23] Participants were considered to have a family history of CVD events if any immediate family members had a history of stroke, myocardial infarction, or other heart disease. Menopausal status was categorized at each follow-up visit as premenopausal (pregnant, breastfeeding, or premenopausal), perimenopausal (early or late perimenopausal), or postmenopausal (natural or nonsurgical postmenopausal). Smoking was recorded at each follow-up visit as current, former, or never. Participants were considered to

Table 1. Baseline characteristics of SWAN participants with and without infertility (N = 2990)

Characteristic	Infertility (n = 738)	No infertility (n = 2252)
Mean age (SD), years	45.7 (2.7)	45.8 (2.7)
Race/ethnicity		
Black/African American	187 (25.3)	661 (29.4)
Chinese/Chinese American	51 (6.9)	191 (8.5)
Japanese/Japanese American	70 (9.5)	149 (6.6)
Caucasian/white non-Hispanic	375 (50.8)	1063 (47.2)
Hispanic	55 (7.5)	188 (8.4)
Education		
Less than high school	38 (5.2)	171 (7.6)
High school diploma	118 (16.0)	405 (18.0)
Some college/technical school	248 (33.6)	700 (31.1)
College degree	149 (20.2)	451 (20.0)
Postgraduate education	180 (24.4)	511 (22.7)
Missing	5 (0.7)	14 (0.6)
Insurance		
Private	655 (88.8)	1874 (83.2)
Government (Medicare, Medicaid, veteran)	25 (3.4)	96 (4.3)
Other	15 (2.0)	95 (4.2)
No insurance	41 (5.6)	174 (7.7)
Missing	2 (0.3)	13 (0.6)
Married or in a committed relationship		
Yes	626 (84.8)	1696 (75.3)
No	112 (15.2)	556 (24.7)
Income		
Less than $19,999	80 (10.8)	334 (14.8)
$20,000-$49,999	225 (30.5)	777 (34.5)
$50,000-$99,999	294 (39.8)	775 (34.4)
$100,000 or more	118 (16.0)	314 (13.9)
Missing	21 (2.9)	52 (2.3)
Body mass index		
Underweight or average weight	269 (36.5)	834 (37.0)
Overweight	200 (27.1)	595 (26.4)
Obese	258 (35.0)	784 (34.8)
Missing	11 (1.5)	39 (1.7)
Birth control or female hormones used continuously from 25-35 years		
Yes	51 (6.9)	193 (8.6)
No	686 (93.0)	2058 (91.4)
Missing	1 (0.1)	1 (0.04)
Family history of CVD events		
Yes	402 (54.5)	1251 (55.6)
No	233 (31.6)	681 (30.2)
Missing	103 (14.0)	320 (14.2)
Hypertension		
Yes	132 (17.9)	409 (18.2)
No	604 (81.8)	1841 (81.8)
Missing	2 (0.3)	2 (0.1)
Diabetes		
Yes	36 (4.9)	100 (4.4)
No	701 (95.0)	2150 (95.5)
Missing	1 (0.1)	2 (0.1)
Menopausal status		
Premenopausal	405 (54.9)	1189 (52.8)
Perimenopausal	330 (44.7)	1045 (46.4)
Missing	3 (0.4)	18 (0.8)
Postmenopausal hormone use		
Yes	181 (24.5)	504 (22.4)
No	557 (75.5)	1748 (77.6)
Smoking		
Current	110 (14.9)	395 (17.5)
Former	204 (27.6)	538 (23.9)
Never	421 (57.1)	1.300 (57.7)
Missing	3 (0.4)	19 (0.8)
Alcohol		
Yes	379 (51.4)	1057 (46.9)
No	333 (45.1)	1076 (47.8)
Missing	26(3.5)	119 (5.3)

Data are presented as n (%) except where otherwise noted.
CVD, cardiovascular disease.

consume alcohol if they had consumed any beer, wine, liquor, or mixed drinks since their previous follow-up visit.

Statistical methods

Categorical variables, stratified according to fertility status were described using frequencies and percentages. Modified Poisson regression was used to calculate risk ratios (RRs) for: (1) metabolic syndrome development; and (2) any CVD event in women who had infertility compared with women who never had infertility (the referent). Cox proportional hazards models were then used to calculate hazard ratios for: (1) time to development of metabolic syndrome; and (2) time to first CVD event in women who had infertility. These women were compared with women who never had infertility (the referent). A sensitivity analysis was conducted among participants who had infertility, comparing metabolic syndrome development in those who reported using fertility medications, compared with those who had never used fertility medications. A forwards modelling strategy was used to find the most parsimonious model, in which univariate analyses were used to identify candidates for the multivariate model using a liberal P value cutoff of < 0.25, including clinically or epidemiologically significant variables. A multivariable model was then fit including all covariates identified as potentially related. Variables with a $P > 0.05$ in this model were then removed and assessed for their change in β. If $> 10\%$ change in β occurred, the excluded variable was deemed important and included in the model. Potential covariates were continuous (age), categorical (race/ethnicity, education, insurance, family history of CVD events, birth control pills or other female hormones used continuously from age 25-35 years, postmenopausal hormone use), and time-varying (marital status, income, BMI, hypertension, diabetes, menopausal status, smoking, and alcohol consumption). Diabetes and hypertension development were only included as potential covariates in analysis for CVD event risk, because diabetes and hypertension are 2 of 5 variables included in the measurement of metabolic syndrome. The last observation carried forward was used to account for missing in time-varying covariates.[24,25] An α of 0.05 was used for all analyses. Analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Descriptive analyses

A total of 2990 participants were enrolled after excluding those with unknown fertility status (n = 97) and a history of CVD events at baseline (n = 215; Fig. 1). To assess the

Table 2. Univariate and adjusted HRs and 95% CIs for the development of metabolic syndrome (N = 2370)

	Univariate		Adjusted	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Infertility				
No	1.00 (Referent)	0.49	1.00 (Referent)	0.42
Yes	0.93 (0.76-1.14)		0.91 (0.71-1.15)	
Age	1.04 (1.01-1.07)	0.01	—	—
Race/Ethnicity				
Caucasian/white non-Hispanic	1.00 (Referent)	< 0.0001	—	—
Chinese/Chinese American	0.94 (0.67-1.33)			
Japanese/Japanese American	1.07 (0.76-1.50)			
Black/African American	1.63 (1.35-1.98)			
Hispanic	1.48 (1.08-2.03)			
Education				
High school diploma	1.00 (Referent)	0.0005	—	—
Less than high school	1.07 (0.75-1.53)			
Some college/technical school	0.91 (0.72-1.16)			
College degree	0.64 (0.49-0.85)			
Postgraduate education	0.66 (0.50-0.86)			
Insurance				
Private	1.00 (Referent)	0.009	—	—
Government	1.59 (1.07-2.36)			
Other	1.68 (1.15-2.46)			
No insurance	1.05 (0.75-1.48)			
Family history of CVD events				
No	1.00 (Referent)	0.002	1.00 (Referent)	0.27
Yes	1.36 (1.12-1.64)		1.13 (0.91-1.41)	
Birth control or female hormones used continuously from 25-35 years				
No	1.00 (Referent)	0.43	—	—
Yes	1.13 (0.84-1.51)			
Any postmenopausal hormone use				
No	1.00 (Referent)	0.15	1.00 (Referent)	0.02
Yes	1.15 (0.95-1.40)		1.32 (1.05-1.65)	
Married or in a committed relationship*	0.82 (0.68-1.00)	0.04	1.21 (0.94-1.56)	0.15
Income*	0.85 (0.77-0.93)	0.0003	0.86 (0.76-0.97)	0.02
Body mass index*	3.16 (2.80-3.57)	< 0.0001	3.18 (2.74-3.67)	< 0.0001
Menopausal status*	1.24 (1.06-1.45)	0.007	—	—
Smoking*	1.10 (0.99-1.23)	0.09	1.11 (0.97-1.27)	0.14
Alcohol*	0.80 (0.67-0.96)	0.02	0.79 (0.64-0.98)	0.03

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
*Included as a time-varying covariate.

development of metabolic syndrome, an additional 620 participants were excluded because of preexisting diabetes (n = 136) and metabolic syndrome (n = 484). Of the remaining 2370 participants, 24.9% (n = 589) self-reported infertility, and 22.8% (n = 541) developed metabolic syndrome over 7 years of available follow-up data. For the sensitivity analysis, 22% (n = 130) of the participants who had infertility reported using fertility medications for > 1 month. To assess CVD event risk, 181 participants were excluded because of missing data on CVD events at all follow-up visits. Of the remaining 2809 participants, 24.7% (n = 695) self-reported infertility and 5.2% (n = 147) experienced a CVD event over 10 years of available follow-up. Because of low event rates, a sensitivity analysis of fertility medications and CVD event risk could not be completed in this sample.

Baseline characteristics of the final study population are described in Table 1. Overall, 7.3% were Japanese/Japanese American, 8.1% were Chinese/Chinese American, 8.1% were Hispanic, 28.4% were black/African American, and 48.1% were Caucasian/white non-Hispanic. Approximately 25% of participants had a high school education or less. At baseline, 53% of participants were premenopausal, whereas the remaining 46% were in perimenopause.

Risk of development of metabolic syndrome

Results of univariate and adjusted analyses for hazard ratios of the development of metabolic syndrome are presented in Table 2. Covariates included in the final model for metabolic syndrome risk were family history of CVD events, any postmenopausal hormone use, marital status, income, BMI, smoking, and alcohol consumption. After adjustment for covariates, the hazard ratio for time to metabolic syndrome development in women with infertility, compared with those without infertility, was 0.91 (95% confidence interval [CI], 0.71-1.15). BMI, any postmenopausal hormone use, income, and alcohol consumption were most strongly associated with metabolic syndrome development.

There was no increase in relative risk of metabolic syndrome development over the entire follow-up period (RR, 0.93; 95% CI, 0.73-1.20) for participants who had infertility, compared with those who never had infertility, after adjusting for the same covariates included in the time-to-event model.

Table 3. Univariate and adjusted HRs and 95% CIs for any CVD event (stroke, myocardial infarction, or angina; N = 2809)

	Univariate		Adjusted	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Infertility				
No	1.00 (Referent)	0.27	1.00 (Referent)	0.27
Yes	0.80 (0.54-1.19)		0.79 (0.52-1.21)	
Age	1.07 (1.01-1.13)	0.03	—	—
Race/ethnicity				
Caucasian/white non-Hispanic	1.00 (Referent)	< 0.0001	1.00 (Referent)	0.006
Chinese/Chinese American	0.67 (0.31-1.48)		0.92 (0.39-2.18)	
Japanese/Japanese American	0.20 (0.05-0.83)		0.24 (0.06-0.97)	
Black/African American	2.16 (1.52-3.07)		1.63 (1.11-2.38)	
Hispanic	2.07 (1.11-3.87)		2.03 (1.02-4.03)	
Education				
High school diploma	1.00 (Referent)	0.02	—	—
Less than high school	1.69 (0.90-3.17)			
Some college/technical school	1.07 (0.67-1.69)			
College degree	0.61 (0.34-1.07)			
Postgraduate education	0.72 (0.43-1.21)			
Insurance				
Private	1.00 (Referent)	0.0002	—	—
Government	3.19 (1.83-5.57)			
Other	1.71 (0.80-3.67)			
No insurance	1.83 (1.03-3.26)			
Family history of CVD events				
No	1.00 (Referent)	0.0009	1.00 (Referent)	0.01
Yes	1.99 (1.33-2.99)		1.71 (1.12-2.61)	
Birth control or female hormones used continuously from 25-35				
No	1.00 (Referent)	0.21	1.00 (Referent)	0.08
Yes	0.64 (0.31-1.30)		0.51 (0.24-1.09)	
Any postmenopausal hormone use				
No	1.00 (Referent)	0.38	—	—
Yes	1.18 (0.82-1.68)			
Married or in a committed relationship*	0.59 (0.43-0.83)	0.002	—	—
Income*	0.66 (0.56-0.78)	< 0.0001	—	—
Body mass index*	1.85 (1.49-2.31)	< 0.0001	1.44 (1.12-1.84)	0.004
Hypertension*	2.65 (1.90-3.69)	< 0.0001	1.61 (1.10-2.35)	0.01
Menopausal status*	1.43 (1.05-1.95)	0.03	—	—
Smoking*	1.59 (1.30-1.94)	< 0.0001	1.48 (1.20-1.84)	0.0003
Alcohol*	0.67 (0.48-0.93)	0.02	—	—
Diabetes*	4.03 (2.72-5.98)	< 0.0001	2.50 (1.62-3.87)	< 0.0001

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
*Included as a time-varying covariate.

Risk of CVD events

Results of univariate and adjusted analyses for hazard ratios of CVD events are presented in Table 3. Covariates included in the final model for CVD event risk were race/ethnicity, family history of CVD events, birth control pills or other female hormones used continuously from age 25-35 years, hypertension, diabetes, BMI, and smoking. After adjustment for covariates, the hazard ratio for time to first CVD event was 0.79 (95% CI, 0.52-1.21). Similar to development of metabolic syndrome, hypertension, BMI, and smoking were strongly associated with CVD events, as was diabetes. Race/ethnicity, specifically black/African American and Hispanic races/ethnicities, was strongly associated with outcomes.

There was no increase in relative risk of any CVD event over the entire follow-up period (RR, 0.78; 95% CI, 0.51-1.21) for participants who had infertility, compared with those who never had infertility, after adjusting for the same covariates included in the time-to-event model.

Risk of metabolic syndrome in participants who used fertility medications

Results of the sensitivity analysis are presented in Table 4. Covariates included in the final model were income, BMI, and smoking. After adjustment for covariates, the hazard ratio for time to metabolic syndrome development in participants who reported using fertility medications was 0.80 (95% CI, 0.46-1.38), compared with those who reported never using fertility medications.

Discussion

In this 10-year nationally representative cohort study of 2990 middle-aged women, we examined the association between infertility and development of cardiovascular risk factors and events. Of almost 3000 participants, approximately one-quarter reported experiencing infertility, 23% developed metabolic syndrome, and 5% experienced CVD events. After

Table 4. Univariate and adjusted HRs and 95% CIs for the development of metabolic syndrome among women who experienced infertility and used fertility medications, compared with those who experienced infertility but did not use fertility medications (N =589)

	Univariate		Adjusted	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Fertility medication used > 1 month				
No	1.00 (Reference)	0.005	1.00 (Reference)	0.42
Yes	0.47 (0.28-0.80)		0.80 (0.46-1.38)	
Age	1.04 (0.97-1.10)	0.27	—	—
Race/ethnicity				
Caucasian/white non-Hispanic	1.00 (Reference)	0.01	—	—
Chinese/Chinese American	0.88 (0.42-1.85)			
Japanese/Japanese American	0.61 (0.29-1.27)			
Black/African American	1.76 (1.19-2.59)			
Hispanic	1.28 (0.63-2.59)			
Education				
High school diploma	1.00 (Reference)	0.06	—	—
Less than high school	1.75 (0.80-3.85)			
Some college/technical school	1.21 (0.72-2.03)			
College degree	0.87 (0.48-1.56)			
Postgraduate education	0.66 (0.36-1.21)			
Insurance				
Private	1.00 (Reference)	0.47	—	—
Government	1.85 (0.82-4.21)			
Other	1.46 (0.46-4.59)			
No insurance	1.02 (0.45-2.31)			
Family history of CVD events				
No	1.00 (Reference)	0.009	—	—
Yes	1.70 (1.14-2.53)			
Birth control or female hormones used continuously from 25-35 years				
No	1.00 (Reference)	0.71	—	—
Yes	1.13 (0.59-2.16)			
Any postmenopausal hormone use				
No	1.00 (Reference)	0.03	—	—
Yes	1.51 (1.05-2.19)			
Married or in a committed relationship*	0.70 (0.46-1.07)	0.10	—	—
Income*	0.72 (0.59-0.86)	0.0005	0.85 (0.68-1.07)	0.16
Body mass index*	3.56 (2.73-4.63)	< 0.0001	3.80 (2.79-5.17)	< 0.0001
Menopausal status*	1.17 (0.84-1.63)	0.34	—	—
Smoking*	1.34 (1.08-1.68)	0.009	1.44 (1.11-1.87)	0.007
Alcohol*	0.88 (0.60-1.28)	0.51	—	—

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

*Included as a time-varying covariate.

adjusting for relevant covariates, no association was observed between infertility and time-to-event of metabolic syndrome development or CVD event (stroke, myocardial infarction, or angina), nor was there an association between the use of fertility medications in participants with infertility and time-to-event of metabolic syndrome development.

Rates of infertility in SWAN were higher than the reported averages for the United States and North America,[5] whereas rates of metabolic syndrome[26] and CVD events were lower than rates reported in the literature.[4] Although SWAN was designed to be nationally representative in its selection of participants with varying racial, economic, and educational backgrounds, these results indicate potential for selection bias,[5] and should be used in caution with respect to generalizing the results to a broader population. Our results align with much of the existing literature on infertility and CVD risk, although several cross-sectional studies have reported higher rates of cardiovascular risk factors and events in women with infertility[7-9,12] as well as in women with diminished ovarian reserve.[11] However, a longitudinal study of 116,430 women followed > 18 years in the United States showed no increased risk of hypertension for women with self-reported infertility, except for in those with tubal disease infertility.[27] Likewise, in a nationwide cohort study of women in Denmark who received medically assisted reproduction, rates of hospitalization for CVD were no higher than in women not diagnosed with infertility.[13] Results of our study suggest that in a longitudinal rather than cross-sectional study, and after the inclusion of relevant covariates, there is no association between infertility and CVD risk.

Our study has several limitations. First, we were not able to ascertain the cause of infertility, which might be relevant to the underlying pathophysiology of CVD in women. For example, women with polycystic ovarian syndrome have been reported to be more likely to develop CVD than the general population,[28] and women with tubal disease infertility have been reported to have increased risk of hypertension.[27] Furthermore, male-factor infertility is solely responsible for approximately one-third of infertility and contributes to 50% of infertility.[29] We expect that up to half of the infertility reported in our study was related to male-factor infertility, which might bias the results toward the null. Because of small

sample size, we could not complete a sensitivity analysis in women who had infertility and did not go on to have any children, which might also be a relevant factor in the relationship between infertility and CVD risk; in a population-based study of 28,442 women who received fertility therapy, the rate of cardiovascular events or death was 21% higher in women who did not ultimately give birth compared with those who did.[10] We were also not able to measure the dose of fertility treatments that women underwent, or the type of treatment used, the guidelines for which might have changed over the course of this long-term prospective study. Moderate and severe ovarian hyperstimulation syndrome, a rare but serious condition associated with assisted reproductive technologies, has been identified as a potential connection between infertility and vascular health and was not measured in this study.[6,30] This association should be investigated in future studies on the topic.

This study also relies on several self-report measures. Outcome measurement in our study was not fully inclusive, because there are many CVD events not captured in SWAN (eg, transient ischemic attacks, heart failure, and peripheral artery disease), and further relies on self-reported outcomes not confirmed by medical records. Although data on life-threatening events (eg, myocardial infarction and stroke) are well identified through self-report, data on chronic cardiovascular disorders including angina are captured with less reliability.[31] Similarly, the use of self-reported infertility as an exposure measure likely overestimates the prevalence in the population. Together, these measurement errors might act to bias the results toward the null. Finally, SWAN presents a relatively small sample size, limiting statistical power.

In conclusion, in a longitudinal cohort study of women in their middle years, no association was observed between self-reported infertility and metabolic syndrome or cardiovascular events. Further studies should examine the specific causes of infertility and aim to select a sample broader than only those undergoing fertility treatment, because this reduces generalizability. Although infertility in general might not be associated with CVD, there might be specific groups at increased risk of CVD who might benefit from targeted CVD risk factor screening and prevention strategies.

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