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Murugappan, Gayathree
Leonard, Stephanie A
Farland, Leslie V
et al.

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Association of Infertility with Atherosclerotic Cardiovascular Disease among Post-Menopausal Participants in the Women's Health Initiative

Gayathree Murugappan, MD[1], **Stephanie A. Leonard, PhD**[1], **Leslie V. Farland, ScD**[2,3], **Emily S. Lau, MD, MPH**[4], **Aladdin H. Shadyab, PhD**[5], **Robert A Wild, MD,MPH,PHD**[6], **Peter Schnatz, DO**[7], **Suzan L. Carmichael, PhD**[1,8], **Marcia L. Stefanick, PhD**[1,9], **Nisha I. Parikh, MD, MPH**[10]

[1]Department of Obstetrics and Gynecology, Stanford University Medical Center, Stanford, CA.

[2]Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ

[3]Department of Obstetrics and Gynecology, College of Medicine-Tucson, University of Arizona, Tucson, AZ

[4]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston, MA

[5]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA

[6]Departments of Ob/Gyn, Biostatistics and Epidemiology University of Oklahoma Health Sciences Center Oklahoma City, Oklahoma 3104

[7]Department of Obstetrics and Gynecology and Internal Medicine, Reading Hospital, Reading, PA

[8]Department of Pediatrics, Stanford University Medical Center, Stanford, CA

[9]Department of Medicine, Stanford Prevention Research Center

[10]Division of Cardiovascular Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA.

Abstract

Objective: To investigate the association of infertility with atherosclerotic cardiovascular disease (ASCVD) in the Women's Health Initiative. We hypothesized that nulliparity and pregnancy loss may reveal more extreme phenotypes of infertility, allowing further understanding of the association of infertility with ASCVD.

Corresponding author: Gayathree Murugappan, MD, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Stanford University, 1195 W Fremont Avenue Sunnyvale, California; gm807@stanford.edu; phone: 650-498-7911.

Design: Prospective cohort study

Setting: U.S.

Patients: Women's Health Initiative Cohort

Exposures: Infertility, parity, pregnancy loss

Main Outcome Measures: Primary outcome was risk of ASCVD among women with and without a history of infertility, stratified by history of live birth and pregnancy loss. Cox proportional hazards models were adjusted for demographics and ASCVD risk factors.

Results: Among 158,787 women, 25,933 (16.3%) reported a history of infertility, among whom 20,427 (80%) had at least one live birth and 9,062 (35%) experienced at least one pregnancy loss. There was a modest overall association between infertility and ASCVD (aHR 1.02, 95% CI 0.99–1.06) over 19 years of follow up. Among nulliparous women, infertility was associated with a 13% higher risk of ASCVD (95% CI 1.04–1.23). Among nulliparous women who experienced a pregnancy loss, infertility was associated with a 36% higher risk of ASCVD (95% CI 1.09–1.71).

Conclusions: Women with a history of infertility overall experienced a modestly higher risk of ASCVD compared to women without a history of infertility. ASCVD risk was much higher among nulliparous infertile women and among nulliparous infertile women who also experienced a pregnancy loss, suggesting that in these more extreme phenotypes, infertility may be associated with ASCVD risk.

Capsule:

Infertility is associated with increased risk of cardiovascular disease among nulliparous women in the Women's Health Initiative.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death among women in the U.S. (1). Compared with men, women generally present with different symptoms of ASCVD, are more likely to be mis-diagnosed, and experience worse outcomes, including a higher risk of death after a major cardiovascular event (2–4). Innovative strategies are needed to improve ASCVD prevention and treatment among women.

Infertility, defined as the inability to conceive after attempting for more than a year, affects 15% of reproductive-age women in the U.S. (5). The consequences of an infertility diagnosis extend beyond the pursuit of family building, because women with infertility also face increased risks for severe maternal morbidity, cancer, chronic disease, and death (6–9). Underlying mechanisms remain unclear, including whether infertility itself or underlying conditions drive the increased morbidity risk. Several studies have reported an association between infertility and ASCVD, primarily in pre-menopausal women of reproductive age (7, 10, 11). Studies that determine later-life ASCVD risk among infertile women are needed.

Current studies also consider infertility as a single homogenous exposure, when in fact there is significant variation in cause and duration of infertility with varied biologic pathways to ASCVD (10–13). The inability to achieve live birth, manifested either as pregnancy loss or nulliparity, can reveal more extreme phenotypes of infertility. Nulliparity, defined as a state of not having given birth to a child, is more frequent among women with a history of infertility(14) and women with infertility who never achieve live birth may represent a more severe form of the underlying disease process leading to infertility. While pregnancy loss is distinct from infertility (15), infertile women who conceive have a 2.6-fold higher risk of pregnancy loss compared to fertile women (16). Infertility and pregnancy loss have shared risk factors, the most significant of which is female age, and are both common events of reproductive failure (17). The objective of this study is to explore the association of infertility with ASCVD among 158,787 postmenopausal participants in the Women's Health Initiative (WHI) Cohort. We hypothesized that nulliparity and pregnancy loss may reveal more extreme phenotypes of infertility, allowing further understanding of the association of infertility with ASCVD.

Methods

Study Cohort

The WHI enrolled 161,808 postmenopausal women, aged 50–79 years at baseline (1993–1998), as described previously (18, 19). WHI participants were included in the present study if they responded to questions regarding their reproductive history at the time of enrollment in the WHI; those with missing information on infertility status (N=1,644) or number of live births or pregnancy losses (N=1,377) were excluded. The current analysis includes outcomes through September 2020. The WHI was reviewed and approved by the IRB of the Fred Hutchinson Cancer Research Center in accordance with U.S. Department of Health and Human Services regulations at 45 CFR 46 (approval number: 3467-EXT).

Definition of Study Exposures

Infertility was self-reported at the time of enrollment in the WHI. Participants were asked: "Have you ever tried to become pregnant for more than 1 year without becoming pregnant?". Those who marked "yes" were designated as infertile. Number of live births and spontaneous pregnancy losses, defined in the questionnaire as occurring before 6 months gestation, were also self-reported at enrollment. Women with no live births were considered nulliparous and women with at least one live birth were considered parous. Pregnancy loss was considered as both a binary outcome for the primary analysis and categorical variable (0,1,2,3+) for a subgroup analysis. Additional pregnancy outcomes collected in WHI including stillbirth (defined in the questionnaire as loss of pregnancy after 6 months gestation), pregnancy termination, and ectopic pregnancy were not included in this study due to small sample sizes of these outcomes.

Definition of Study Outcome

The primary outcome was any first-time ASCVD event, as defined by the American Heart Association, including any one of the following phenotypes: clinical myocardial infarction, coronary revascularization, ischemic stroke, peripheral arterial disease, carotid

artery disease, and CVD death (due to definite coronary heart disease, cerebrovascular disease, pulmonary embolism, or other or unknown cardiovascular cause) (20). ASCVD events were prospectively ascertained by review of medical records between study entry and 2020, and adjudicated using standard criteria (21). ASCVD was considered as both a composite outcome as well as individual disease phenotypes.

Covariates

We analyzed baseline characteristics from the data collected at enrollment into the WHI. Data on age, race, ethnicity, education level, and family income were recorded at study entry. We additionally examined ASCVD risk factors identified from the 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease (20). The ASCVD risk factors included age at menopause, hyperlipidemia (defined as self-reported use of cholesterol-lowering drugs), hypertension (defined as self-reported treated or untreated hypertension), diabetes (self-reported and not pregnancy related), body mass index (BMI) as kg/m^2 (based on clinical measures at baseline of weight and height), and self-reported smoking status (smokers defined as ever having smoked 100 cigarettes over their lifetime) and were also recorded at study entry.

Statistical Analyses

We first compared baseline characteristics, including ASCVD risk factors and pregnancy histories, between women with and without a history of infertility using Student's T-test for continuous outcomes and Chi-square test for categorical outcomes. We then calculated the distribution of ASCVD outcomes (composite, defined as having at least one of the CVD phenotypes, as well as individual phenotypes) among women with and without a history of infertility. We additionally stratified the prevalence of ASCVD outcomes by parity and pregnancy loss based on differences hypothesized *a priori* that infertile women who are also nulliparous or experience a pregnancy loss have a more severe infertility phenotype. We then conducted multivariable time-to-event analyses for the composite ASCVD outcome using Cox proportional hazards models to compare women with and without a history of infertility. We additionally stratified infertility-ASCVD regression models by parity and pregnancy loss based on differences hypothesized *a priori*. For each subgroup analysis, the reference group was restricted to women with the pregnancy-related exposure (parity or pregnancy loss) and without a history of infertility. All regression models were adjusted for age at enrollment, income, education, smoking status and race/ethnicity as potential confounders. The model was then adjusted for ASCVD clinical risk factors including age at menopause, hyperlipidemia, hypertension, diabetes and BMI (linear and quadratic). Sequential adjustment was performed because ASCVD risk factors were collected at the time of enrollment in WHI, therefore the temporality in relation in infertility diagnosis cannot be ascertained. Person-months at risk were calculated from entry into the analytic cohort at study baseline until independently confirmed death, loss to follow-up, or ASCVD diagnosis. Multiple imputation using 10 imputations by fully conditional specification methods was used in all multivariable models to account for missing values of the following covariates: family income, education level, smoking history, race/ethnicity, age at menopause, hypertension, diabetes, and hyperlipidemia. Missingness of imputed covariates for the models ranged from 0–7%. Multiple imputation was used for covariates,

but not for exposures (infertility, pregnancy loss, and parity) due to controversy in imputing values for the exposure based on the covariates and outcome, and then using those values to estimate the effect of the exposure on the outcome (22). A sensitivity analysis was performed excluding women with ASCVD risk factors to determine their influence on effect estimates. Statistical analyses were conducted in SAS version 9.4. A two-sided P-value less than 0.05 was considered statistically significant.

Results

Of the 161,808 women enrolled in the WHI, 158,787 were eligible for this analysis (Figure 1). Among these participants, 25,933 (16.3%) reported a history of infertility. On average, women were 63 years of age at the time of enrollment and subsequently followed for an average of 19 years (Table 1), with no differences by history of infertility. Average age at primary ASCVD event was 81.4 years in both groups. Compared to women with no history of infertility, women with history of infertility were more likely to be White (Hispanic and Non-Hispanic), to have received a college degree or higher level of education, and have an annual family income over $75,000. Women with a history of infertility were also more likely to report hyperlipidemia and smoking history, while age at menopause and the prevalence of hypertension and diabetes were similar between the groups. 1.9% of WHI participants (N=3,021) were excluded from the analysis because they did not respond to questions about infertility or prior pregnancy history. These participants were more likely to be Black or Hispanic and had lower SES indicators than included participants, but did not differ in prevalence of ASCVD (Supplementary Tables 7 and 8).

Number of pregnancies, pregnancy losses and live birth differed between groups. Among women with a history of infertility, 21,867 (84.3%) became pregnant at least once, 20,455 (79.9%) had at least one live birth, and 9,091 (35.0%) experienced at least one pregnancy loss. Among women with no history of infertility, 122,140 (91.9%) became pregnant at least once, 119,164 (89.7%) had at least one live birth and 39,230 (29.5%) experienced at least one pregnancy loss.

The prevalence of any ASCVD outcome was 15.4% among all women with a history of infertility, and 14.9% among all women without a history of infertility (Table 2). The prevalence of peripheral arterial disease (1.2 vs 1.0%, respectively) and carotid artery disease (1.2 vs 1.0%, respectively) was higher among women with a history of infertility compared to women without a history of infertility. We replicated the comparisons by infertility status after stratifying by parity and pregnancy loss history (Supplementary Tables 1–6). Among all nulliparous women and nulliparous women with at least one pregnancy loss, a history of infertility was associated with a higher prevalence of any ASCVD outcome and higher prevalence of several individual ASCVD phenotypes.

Using time-to-event analysis, infertility was associated with a modest risk of ASCVD overall (aHR 1.02, 95% CI 0.99–1.06, Table 3). Based on *a priori* hypotheses, we modeled the association between infertility and ASCVD stratified by the other reproductive factors (Table 3). Among all nulliparous women, women with a history of infertility had a 21% higher risk of ASCVD in the crude model (HR 1.21, 95% CI 1.11–1.31), which attenuated

to 13% higher risk after adjustment for covariates (HR 1.13, 95% CI 1.04–1.23). Among nulliparous women who also experienced a pregnancy loss, women with a history of infertility had a 33% higher risk of ASCVD in the crude model (HR 1.33, 95% CI 1.07–1.65) and 36% higher risk after adjustment for covariates (HR 1.36, 95% CI 1.09–1.71). Among nulliparous women without a history of pregnancy loss, infertility was weakly associated with ASCVD risk after covariate adjustment (HR 1.09, 95% CI 0.99–1.20).

Among all parous women, a history of infertility was not associated with ASCVD risk before or after covariate adjustment (aHR 1.01, 95% CI 0.97–1.05). Similarly, a history of infertility was not associated with ASCVD risk among parous women with a history of pregnancy loss (aHR 0.98, 95% CI 0.92–1.04) or parous women without a history of pregnancy loss (aHR 1.03, 95% CI 0.98–1.08).

In a subgroup analysis among nulliparous women with a history of infertility, the association of number of pregnancy losses and ASCVD was ascertained using time-to-event analysis. While the results are limited by small sample size, ASCVD risk was non-significant but higher after 2 pregnancy losses (aHR 1.28, 95% CI 0.92–1.77) and significantly higher after 3 or more pregnancy losses (aHR 1.51, 95% CI 1.10–2.06) but not increased after a single pregnancy loss (aHR 1.12, 95% CI 0.90–1.39) compared to women with no pregnancy loss (Supplementary Table 9).

Finally, we performed a sensitivity analysis excluding women with ASCVD risk factors, including age at menopause < 40 years, hyperlipidemia, hypertension, diabetes, and BMI > 30 kg/m^2 with similar results to the overall analysis (Supplementary Table 10).

Discussion

In this large, multiracial cohort of postmenopausal women followed for up to 26 years, women with infertility experienced a modestly higher risk of ASCVD compared to women without a history of infertility. Among nulliparous women, particularly those with a history of pregnancy loss, the risk of ASCVD associated with infertility was much higher. These findings suggest that in these more extreme phenotypes, infertility may be associated with ASCVD risk. Our findings were robust to adjustment for sociodemographic characteristics and ASCVD risk factors. The exploration of nulliparity and pregnancy loss as more extreme infertility phenotypes and their relation to ASCVD risk among infertile women is a novel aspect of our study. We have previously reported among 64,000 infertile women (median age 34 years during 2003–2016) a 14% higher risk of cardiovascular disease compared to fertile women (7). These findings are complementary to a small study using the National Health and Nutrition Examination Survey data, which identified an 83% increased risk of cardiovascular disease among 111 women with a history of infertility (median age 40 years) (11) as well as a Swedish cohort of 80,000 women (median age 50 years), among whom infertility was associated with 20% increased risk of incident CVD compared to women without a history of infertility (10). Among older cohorts of women, however, infertility has not been consistently associated with increased risk of ASCVD (23, 24), suggesting that as women age, they may develop risk factors for cardiovascular disease that are stronger than infertility, such as metabolic syndrome.

Population studies of infertility are currently limited by considering infertility as a binary exposure, and not accounting for variation in severity or heterogenous underlying causes. The results of our study suggest significant associations of infertility and ASCVD among women who experience infertility and do not achieve live birth. This group may represent a more severe form of infertility. Alternative explanations for increased risk of ASCVD among nulliparous women include biological or social risk factors not captured by the current study design (25). For example, breastfeeding has a protective effect on ASCVD risk among women in the WHI, suggesting that hormonal exposures which are also affected by parity may play a significant role in ASCVD risk (24).

The highest risk group for ASCVD in our study was nulliparous women with a history of infertility who also experienced a pregnancy loss. Pregnancy loss is more common among women with a history of infertility and may be a more extreme phenotype of infertility, linked by common risk factors, including female age (26). Pregnancy loss has also been independently associated with an 11% higher ASCVD risk later in life among women in the WHI (27). In a subgroup analysis among nulliparous women with a history of infertility, we found non-significant but higher ASCVD risk among women with 2 or more pregnancy losses, but no increase in risk among with a single pregnancy loss. Our findings suggest that both infertility and pregnancy loss may be associated with ASCVD risk, and further investigation of these exposures is warranted in other cohorts.

Among women who become pregnant and achieve live birth, evidence is accumulating that pregnancy outcomes can be used to improve cardiovascular disease risk prediction. The physiologic demands of pregnancy exacerbate subclinical metabolic and vascular susceptibilities, such that pregnancy is viewed as a maternal stress test that can unmask future risk of cardiovascular disease(13). As over 80% of women with infertility eventually become pregnant (28), further studies are needed to understand the relation between infertility and adverse pregnancy outcomes, which are independently associated with ASCVD risk (29).

The biological mechanisms underlying the association of infertility and later life ASCVD are not addressed by our study and warrant evaluation. Perturbations at any level of the female reproductive system, ranging from hypothalamic/pituitary regulation and ovarian function to anatomic reproductive tract differences, can also cause female infertility (30). Infertility may be a cause or consequence of chronic inflammation, which has been strongly associated with ASCVD risk (31, 32). Reproductive disorders including ovulatory dysfunction, menstrual irregularity, polycystic ovarian syndrome (33, 34), and endometriosis(35) can cause infertility and also have been associated with increased risk of ASCVD (36).

Study Strengths

The WHI is a rare and unique source of longitudinal data on reproductive factors including infertility. A significant advantage of our study is that participants were followed for an average of 19 years after study enrollment (average age at enrollment=63 years). The median age for onset of ASCVD in women is 73 years (37) and prior studies of infertility (30) and ASCVD risk are primarily in younger cohorts of women (median age 34–40 years)

(7, 11). Additional strengths of our study include the size of our cohort and utilization of adjudicated ASCVD outcomes.

An additional advantage of this study is our ability to study the natural history of infertility as it relates to ASCVD risk. Due to the age of WHI participants at time of enrollment (50–79 years between 1993–1998), very few participants would have had access to IVF. The first successful birth from IVF took place in 1981 in the U.S. (38), and access to IVF was not widely available until 1990 (39) when the youngest WHI participants were beyond their reproductive years and approaching menopause. Future studies are warranted in contemporaneous cohorts to compare ASCVD risk among women receiving infertility treatment from women with an infertility history.

Study Limitations

There are several limitations to our study design and analysis. Infertility, pregnancy loss and conditions associated with infertility including menstrual cycle irregularity have all been associated with premature mortality including premature cardiovascular mortality (40–43). Women with earlier onset or more severe ASCVD, as well as women with reproductive exposures that increase risk of premature mortality, may have been excluded from enrollment in the WHI. This possibility of selection bias may limit the conclusions of our study, and potentially result in underestimating the association of infertility with ASCVD. In addition, it is possible that the study included women with a history of cardiovascular disease and thus events that occurred prior to study entry were not captured. While we did adjust for cardiovascular disease risk factors in our analysis, we did not adjust for history of cardiovascular disease in accordance with the principles put forth by Howards et al(44).

While infertility is a heterogenous disease process and individual causes of infertility may have varied biologic pathways to ASCVD (45), a limitation of our work is that underlying causes of infertility are not investigated. For example, women with male factors as the only cause of infertility would not be expected to face an increased risk of ASCVD. By including heterogenous causes of infertility as a single exposure, we may be under or over-estimating associations with ASCVD risk. Duration of infertility has also been associated with ASCVD risk (10, 46), which we were unable to account for using the WHI.

Infertility is a highly memorable experience for women and self-report has been validated in studies compared to medical records (47) and the prevalence of infertility among WHI participants is similar to the prevalence of infertility in the US (30). Nevertheless, a potential for recall bias resulting in misclassification of infertility could have attenuated associations. The characteristics of women with infertility in the WHI also differ from previous findings from ethnically diverse cohorts of US women (48) including a lower proportion of infertile women who identify as Black, low income and with a lower prevalence of ASCVD risk factors including hypertension, obesity and hyperlipidemia. Because these characteristics are also independently associated with ASCVD risk (20, 49–51), their under-representation in the WHI may limit generalizability of our results. Furthermore, it is not possible to ascertain whether ASCVD risk factors developed before or after a woman's reproductive years (at the time of her infertility diagnosis), as these data were collected at the time of enrollment

into the WHI cohort. Because of this concern, we conducted two adjusted models, with the second containing covariates that could have preceded infertility including hypertension, BMI, dyslipidemia. A sensitivity analysis was also performed excluding women with ASCVD risk factors, with similar results to the overall analysis.

Conclusion

In conclusion, in this large, diverse cohort of women followed for nearly two decades, we report that infertility overall was modestly associated with risk of ASCVD; however, more extreme phenotypes of infertility among women provide significant insight into a woman's cardiovascular health. Infertile women who did not achieve live birth or who also experienced a pregnancy loss faced a significantly higher ASCVD risk compared to women without a history of infertility. Given that infertility and pregnancy loss occur during a woman's reproductive years, our findings suggest this period may present a unique opportunity for early identification and modification of ASCVD risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

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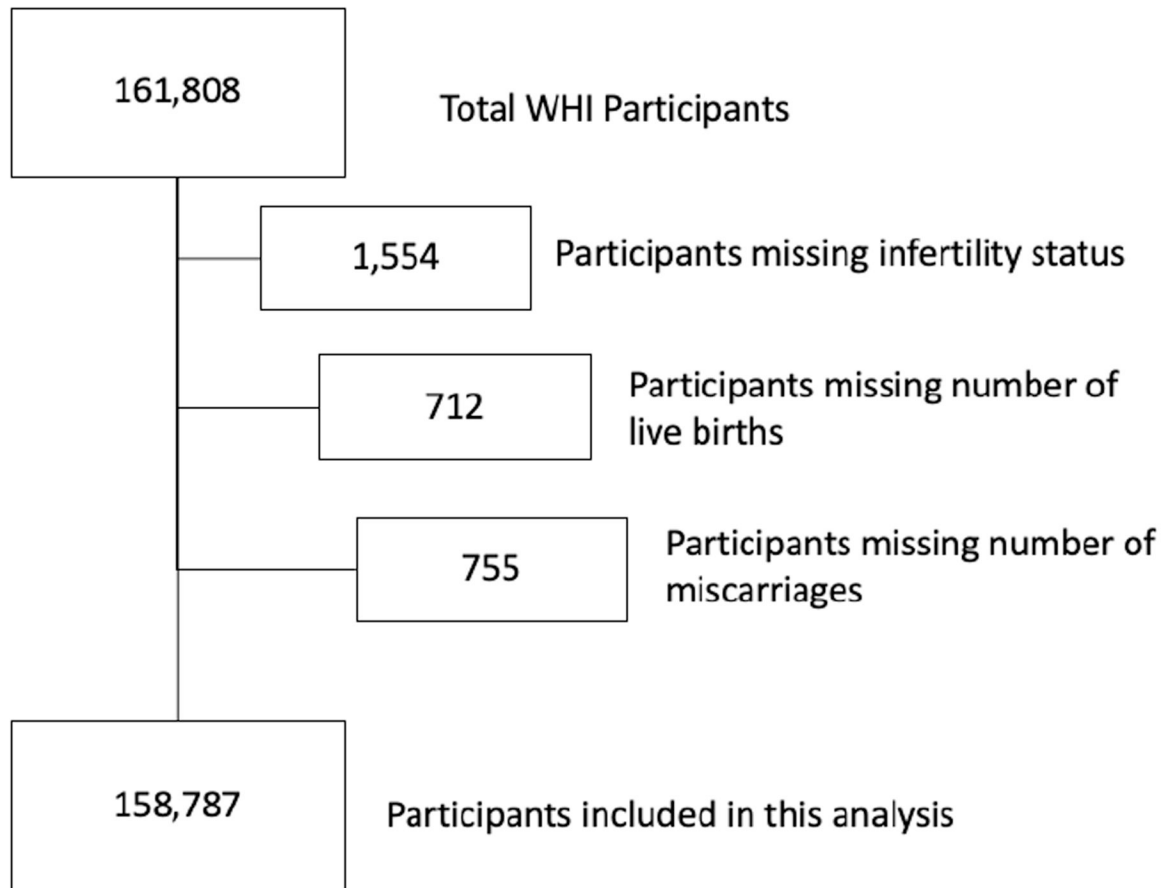
Figure 1.
Flow Diagram for the Selection of Study Participants from the Women's Health Initiative (WHI)

Table 1.

Baseline Characteristics of Study Population from the Women's Health Initiative

Variable[*]	History of Infertility N=25,933 (16.3%)	No History of Infertility N=132,854 (83.7%)	P-value[**]
Age at enrollment, mean (SD), yrs	63.2 (7.4)	63.2 (7.2)	0.88
Duration of follow up, mean (SD), yrs	19.3 (5.1)	19.3 (5.2)	0.43
Race, N (%)			<0.01
Asian	573 (2.2)	2,585 (1.9)	
Black	1,773 (6.8)	11,904 (9.0)	
Native American/Alaska Native	56 (0.2)	231 (0.2)	
Pacific Islander	19 (0.1)	97 (0.1)	
White	22,047 (85.0)	109,217 (82.2)	
>1 Race	277 (1.1)	1,352 (1.0)	
Ethnicity, N (%)			<0.01
Hispanic	928 (3.6)	6,067 (4.6)	
Non-Hispanic	25,005 (96.4)	126,787 (95.4)	
Highest Level of Education			<0.01
High school degree or less	5,243 (20.4)	30,103 (22.8)	
Vocational or training school	2,559 (9.9)	13,548 (10.3)	
College or higher level education	17,945 (69.7)	88,220 (66.9)	
Annual Family income (USD)			<0.01
<20,000	3,374 (14.0)	21,343 (17.2)	
20,000–75,000	15,617 (64.6)	80,328 (64.7)	
>75,000	5,191 (21.5)	22,404 (18.1)	
Atherosclerotic Cardiovascular Disease Risk Factors			
Age at menopause, mean (SD), yrs	47.4 (6.8)	48.2 (6.4)	<0.01
BMI (kg/m^2)			<0.01
<18.5	222 (0.86)	1,132 (0.86)	
18.5–24.9	9,222 (35.9)	44,736 (34.0)	
25.0–29.9	8,963 (34.9)	45,688 (34.7)	
30.0–34.9	4,524 (17.6)	24,631 (18.7)	
>35	2,785 (10.8)	15,387 (11.7)	
Hypertension, N (%)	8,270 (33.6)	42,815 (34.0)	0.28
Diabetes, N (%)	1,525 (5.9)	7,844 (5.9)	0.89
Ever smoker, N (%)	13,197 (51.3)	64,545 (48.9)	<0.01
Hyperlipidemia, N (%)	3,623 (14.8)	17,455 (13.9)	<0.01

Variable[*]	History of Infertility N=25,933 (16.3%)	No History of Infertility N=132,854 (83.7%)	P-value[**]
Age at primary atherosclerotic cardiovascular disease event, mean (SD), yrs	81.4 (7.6)	81.4 (7.5)	0.97
Number of pregnancies, N (%)			<0.01
0	4,066 (15.7)	10,714 (8.1)	
1	3,419 (13.2)	7,658 (5.8)	
2	5,540 (21.4)	25,002 (18.9)	
3	2,192 (20.1)	30,230 (22.8)	
4	3,462 (13.4)	24,003 (181)	
5+	4,206 (16.3)	35,021 (26.4)	
Number of live births, N (%)			<0.01
0	5,478 (21.1)	13,690 (10.3)	
1	4,492 (17.3)	9,905 (7.5)	
2	7,249 (28.0)	33,407 (25.2)	
3	4,965 (19.2)	33,690 (25.4)	
4	2,283 (8.8)	21,562 (16.2)	
5+	1,466 (5.7)	20,600 (15.5)	
Number of pregnancy losses, N (%)			<0.01
0	16,842 (65.0)	93,624 (70.5)	
1	5,596 (21.6)	26,100 (19.7)	
2	2,051 (7.9)	8,601 (6.5)	
3+	1,444 (5.6)	4,529 (3.4)	

[*] Percentage is column percentage. The percentage of missing observations for each covariate was as follows: 0% for age at screening, 1% for race and ethnicity, 0.7% for education, 6.6% for income, 5.7% for age at menopause, 0.9% for BMI, 5.2% for hypertenstion, 0.1% for diabetes, 0.7% for smoking status and 5.7% for hyperlipidemia.

[**] Student's T-test for continuous outcomes and Chi-square test for categorical outcomes.

Table 2.

Prevalence of Atherosclerotic Cardiovascular Disease inclusive of individual clinical phenotypes, stratified by fertility status.

	History of Infertility N=25,933	No History of Infertility N=132,854
	N (%)	N (%)
Atherosclerotic Cardiovascular Disease (composite)[ψ]	4,000 (15.4)	19,860 (14.9)
Clinical myocardial infarction	1,084 (4.2)	5,330 (4.0)
Cardiac procedure (i.e., stent)	1,523 (5.9)	7,507 (5.7)
Percutaneous transluminal coronary angioplasty	1,132 (4.4)	5,471 (4.1)
Ischemic stroke	863 (3.3)	4,420 (3.3)
Peripheral arterial disease	305 (1.2)	1,335 (1.0)
Carotid artery disease	297 (1.2)	1,309 (1.0)
Death due to Cardiovascular Disease	1,629 (6.3)	8,181 (6.2)

[ψ]Includes any one of the following phenotypes: clinical myocardial infarction, coronary revascularization, ischemic stroke, peripheral arterial disease, carotid artery disease, or cardiovascular disease death.

Table 3.

Association of Fertility Status with Atherosclerotic Cardiovascular Disease using Cox proportional hazards models, stratified by pregnancy -related exposures.

	N	Composite Atherosclerotic Cardiovascular Disease Prevalence, N (%)	Crude HR (95% CI)	Adjusted HR[1] (95% CI)	Adjusted HR[2] (95% CI)
All women, No History of Infertility	132,854	19,814 (14.9)	-- (Ref)		
All women, History of Infertility	25,933	3,992 (15.4)	1.03 (0.99–1.07)	1.04 (1.00–1.07)	1.02 (0.99–1.06)
Stratified by history of livebirth and pregnancy loss					
Among all nulliparous					
No History of Infertility	13,690	1,742 (12.7)	-- (Ref)		
History of Infertility	5,478	831 (15.2)	1.21 (1.11–1.31)	1.17 (1.08–1.27)	1.13 (1.04–1.23)
Among nulliparous with 1 pregnancy loss					
No History of Infertility	1,152	150 (13.1)	-- (Ref)		
History of Infertility	986	171 (17.5)	1.33 (1.07–1.65)	1.47 (1.18–1.84)	1.36 (1.09–1.71)
Among nulliparous without pregnancy loss					
No History of Infertility	12,538	1,593 (12.7)			
History of Infertility	4,492	661 (14.7)	1.17 (1.07–1.28)	1.12 (1.02–1.23)	1.09 (0.99–1.20)
Among all parous					
No History of Infertility	119,164	18,072 (15.2)	-- (Ref)		
History of Infertility	20,455	3,161 (15.5)	1.02 (0.98–1.05)	1.03 (0.99–1.07)	1.01 (0.97–1.05)
Among parous with 1 pregnancy loss					
No History of Infertility	38,078	6,329 (16.6)	-- (Ref)		
History of Infertility	8,105	1,310 (16.2)	0.96 (0.91–1.02)	0.99 (0.94–1.06)	0.98 (0.92–1.04)
Among parous without pregnancy loss					
No History of Infertility	81,086	11,785 (14.5)			
History of Infertility	12,350	1,856 (15.0)	1.03 (0.98–1.08)	1.04 (0.99–1.09)	1.03 (0.98–1.08)

[1] Adjusted for age at enrollment, family income, highest level of education attained, smoking status, race, and ethnicity.

[2] Additionally adjusted for Atherosclerotic Cardiovascular Disease risk factors assessed at enrollment including age at menopause, hyperlipidemia (defined as use of cholesterol-lowering drugs), hypertension (including use of antihypertensive drugs), and diabetes (not pregnancy related), and BMI