HHS Public Access

Author manuscript

Circulation. Author manuscript; available in PMC 2017 May 31.

Published in final edited form as:

Circulation. 2016 May 31; 133(22): 2149–2158. doi:10.1161/CIRCULATIONAHA.115.017854.

Reproductive Risk Factors and Coronary Heart Disease in the Women's Health Initiative Observational Study

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Journal Subject Terms: Women; Epidemiology; Pregnancy

Author Contributions: All authors contributed to each of the following aspects of the study: 1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, 2) Drafting the work or revising it critically for important intellectual content, 3) Final approval of the version to be published, 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Drs. Parikh and Howard take responsibility for the accuracy and integrity of the data analysis.

Disclosures: None.

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Abstract

Background—Reproductive factors provide an early window into a woman's coronary heart disease (CHD) risk, however their contribution to CHD risk stratification is uncertain.

Methods and Results—In the Women's Health Initiative Observational Study, we constructed Cox proportional hazards models for CHD including age, pregnancy status, number of live births, age at menarche, menstrual irregularity, age at first birth, stillbirths, miscarriages, infertility ≥ 1 year, infertility cause, and breastfeeding. We next added each candidate reproductive factor to an established CHD risk factor model. A final model was then constructed with significant reproductive factors added to established CHD risk factors. Improvement in C-statistic, net reclassification index (or NRI with risk categories of <5%, 5–<10%, and ≥10% 10-year risk of CHD) and integrated discriminatory index (IDI) were assessed. Among 72,982 women [n=4607 CHD events, median follow-up=12.0 (IQR=8.3–13.7) years, mean (SD) age 63.2 (7.2) years], an age-adjusted reproductive risk factor model had a C-statistic of 0.675 for CHD. In a model adjusted for established CHD risk factors, younger age at first birth, number of still births, number of miscarriages and lack of breastfeeding were positively associated with CHD. Reproductive factors modestly improved model discrimination (C-statistic increased from 0.726 to 0.730; IDI=0.0013, p-value < 0.0001). Net reclassification for women with events was not improved (NRI events=0.007, p-value=0.18); and for women without events was marginally improved (NRI non-events=0.002, p-value=0.04)

Conclusions—Key reproductive factors are associated with CHD independently of established CHD risk factors, very modestly improve model discrimination and do not materially improve net reclassification.

Keywords

Women; Coronary heart disease; Reproductive Factors; Risk stratification; Risk factors

Introduction

Heart disease is the leading cause of mortality among women in the United States.[1] The importance of knowing whether a woman's risk of CHD is low, medium or high is important when considering when and how aggressively to modify her CHD risk factors. If we had an earlier "window" of detection into a woman's level of CHD risk, we would be better able to institute earlier lifestyle change counseling and when appropriate, pharmacotherapy to change risk factors such as hypertension or dyslipidemia.

There are several reproductive history factors in women that have been individually associated with CHD, including number of pregnancies,[2, 3] a lack of breast feeding,[4] menstrual cycle irregularities,[5] pregnancy loss (i.e., stillbirth and miscarriage),[6, 7] and a history of infertility/difficulty conceiving.[8] These reproductive history factors can be

ascertained prior to the onset of traditional CHD risk factors and could potentially be used for earlier and more aggressive risk factor modification. However, it is uncertain which of these reproductive factors are significantly associated with CHD when considered together and whether they are independently related to CHD over and beyond established CHD risk factors.

Methods

Study Sample: Women's Health Initiative (WHI) Observational Study

The WHI recruitment began in 1991 and consisted of a set of clinical trials and an observational study of hormone therapy, dietary modification and calcium/vitamin D supplementation on cardiovascular disease, cancer and fractures. We considered all women who participated in the WHI observational study but not in the clinical trials in order to avoid effects of interventions on outcomes. Among all women in the WHI observational study (n=93,676) we excluded those with missing reproductive (n=13,155) and/or CHD risk factor information (n=4,101), women without follow-up (n=476), and women with prevalent or unknown history of CHD (n=5,902). After exclusions our final sample size was n=72,982.

Ascertainment of Reproductive Exposures

Information on reproductive factors was collected via a questionnaire at the second screening visit in the WHI (between 1993–1998). Candidate reproductive risk factors for CHD included: pregnancy status (ever/never had a pregnancy lasting at least 6 months), number of live births, age at menarche, menstrual irregularity [no (referent), yes, sometimes regular and sometimes irregular], age at first birth (referent group= women giving birth at age > 25 years), number of stillbirths, number of miscarriages, any reported history of infertility ≥ 1 year (defined as trying to conceive unsuccessfully for ≥ 1 year whether or not this led to eventually becoming pregnant), the specific cause of the infertility (among women reporting this), having breastfed one's baby for at least 1 month (reporting ≥ 1 months of lifetime exposure of breastfeeding).

Ascertainment of Established CHD Risk Factors Values

Body mass index (BMI) was calculated using height and weight (kg/m^2) measured by study staff at baseline. Systolic blood pressure was measured at the baseline examination and antihypertensive medications were recorded. Diabetes was identified by self-reported use of anti-diabetic medications and hyperlipidemia by self-reported use of cholesterol lowering medications. Medication use was validated on enrollment by nurse examination of medication bottles. Physical activity was assessed by questionnaire as was self-reported family history of premature CHD (age less than 60 in any first degree relative).

Ascertainment of Coronary Heart Disease (CHD) Outcomes

The primary outcome for our study was physician-adjudicated fatal and non-fatal CHD (including clinical myocardial infarction, CHD death, or coronary artery revascularization in the form of coronary artery bypass surgery or percutaneous coronary intervention). As of September 30^{th}, 2010 there were 4,607 CHD events in our sample.

Statistical Analysis Plan

In our methodologic approach, we employed several of American Heart Association consensus recommended metrics to evaluate the utility of reproductive factors on CHD risk stratification.[9] Briefly, these metrics were recommended as a means to assess the utility of novel biomarkers in CVD risk stratification. Specific metrics include assessing the independence of the risk markers over and beyond established risk factors, assessing the ability of the diagnostic test (or in this case a risk model) to increase the C-statistic (which in this analysis we estimated based on survival times), and assessing the ability of the risk marker to accurately reclassify patients into higher or lower risk categories by taking into account observed versus expected events. Descriptive characteristics including n's, means and standard deviations are presented. We performed Kendall's Tau correlations between the reproductive factors and established risk factors in order to anticipate potential model collinearity. We employed multivariable Cox proportional hazards regression analysis for CHD outcomes. Follow up time began at WHI Study enrollment. In order to assess the utility of a reproductive history as a "standalone test" in women, assuming that in many cases, it would be available in younger women before the onset of established risk factors, we first constructed a model with age and the candidate reproductive risk factors. Next, we assessed each reproductive factor in models with established CHD risk factors. In this step, we began with established CHD risk factors including age, diabetes, systolic blood pressure, hypertension medications, dyslipidemia, and smoking status and added each reproductive factor in separate models to determine if the reproductive factor was independently related to CHD. If a reproductive factor was significantly related to CHD when considered with established CHD risk factors at an alpha of ≥ 0.1 then it was added to a final model with other significant reproductive factors plus established risk factors. The C-statistic and its change, together with 95% confidence intervals for these models were calculated.

The net-reclassification approach using a survival approach[10] was employed in order to determine whether knowledge of the reproductive factors more accurately stratified women into CHD risk categories.[11] We constructed two different sets of CHD risk classes. First we chose <5%, 5–<10%, and ≥10% 10-year risk of CHD given that most women have relatively lower 10-year predicted CHD risks than males[12] and do generally fall in the <5 or < 10% 10-year risk categories.[12, 13] Secondly, based on the recent CVD prevention guidelines,[14] we assessed dichotomous risk categories with the cut-point of estimated CHD risk at 7.5%. We additionally calculated an integrated discriminatory index (or IDI) which measures the improvement in the slope of model discrimination with the new marker (the IDI is useful when risk cut-points are not available).[11]

In secondary models adjusting for established CHD risk factors, we explored dose response relationships between the following reproductive factors and CHD: number of live births, number of stillbirths, number of miscarriages and number of tubal pregnancies. In a secondary analysis aimed at assessing confounding of reproductive factor and CHD associations by socioeconomic status (or SES), we added income, education and a neighborhood/zipcode-based SES indicator[15] to age-adjusted reproductive factor CHD models. We explored models that contained BMI, physical activity index and a family history of premature CHD (age < 60 years of age)[16] in addition to reproductive and

established risk factors given that these are common clinically measured risk factors that have traditionally aided clinicians in CHD risk stratification of patients. All analyses were conducted in SAS version 9.3 and R version 2.15. The study was approved by an institutional review committee at the University of California San Francisco and the subjects gave informed consent.

Results

Table 1 summarizes the characteristics of study participants at the first study visit. Women were an average (SD) of 63.2 (7.3) years of age. Of participants, 85.6% were White, 6.9% Black, 3.1% Hispanic, and 2.9% Asian/Pacific Islander. There were 4,607 CHD events, median follow-up=12.0 years (interquartile range: 8.3–13.7 years) with an annualized event rate of 0.57%. The most highly correlated reproductive factors were pregnancy status and stillbirths (Kendall's Tau correlation=0.87, $p< 0.0001$), pregnancy status and number of live births (Kendall's Tau correlation=0.61, $p< 0.0001$) and pregnancy status and number of miscarriages (Kendall's Tau correlation=0.58, $p< 0.0001$). Several of the other reproductive factors were all statistically significant but much less strongly correlated with one another (data not shown). The established CHD risk factors were not strongly correlated with reproductive factors (all Kendall's Tau correlation <0.1).

Reproductive Risk Factors AND CHD

Upon age-adjusted Cox proportional hazards analysis, age at first birth < 20 years [HR=1.65 (95% CI, 1.49–1.82)] or 20 to 24 years of age [HR =1.25 (95% CI, 1.17–1.35)] (referent= age at first birth > 25 years), having one stillbirth [HR=1.24 (95% CI, 1.07–1.44)], and having one miscarriage [HR=1.13 (95% CI, 1.05–1.22), 2–4 miscarriages [HR=1.28 (95% 1.16–1.41) or having ≥ 5 miscarriages [HR=1.55 (95% CI,1.15–2.09), always having irregular menses [HR=1.13 (95% CI, 1.01–1.26)] or sometimes having irregular menses [HR=1.12(1.02–1.24)] were positively associated with CHD whereas having breastfed one's baby for at least 1 month [HR=0.88 (95% CI, 0.83–0.94)] was protective for CHD. Number of live births, pregnancy status, age at menarche, number of tubal pregnancies, history of infertility or cause of infertility were not independently associated with CHD in this model (data not shown).

Models of Reproductive Risk Factors added to Established Risk Factors

Supplemental Table 1 summarizes the models of each reproductive factor added to established CHD risk factors. From these models the following reproductive variables were related to CHD (at a p value of ≤ 0.1) and thus considered in the next model: menstrual irregularity, ever pregnant, number of live births, age at first birth, stillbirths, miscarriages, and having breastfed one's baby for at least 1 month. When considered together with established CHD risk factors, the following reproductive factors remained significantly related to CHD (at a p value of < 0.05): age at first birth, stillbirths, miscarriages and having breastfed one's baby for at least 1 month (protective for CHD) (Table 2).

Model Discrimination

The age-adjusted reproductive risk model had a C-statistic of 0.675 while the established CHD risk factor model had a C-statistic of 0.726 (Table 3). Table 3 demonstrates the change in CHD discrimination/C-statistic for the established CHD risk factor model with the addition of each individual reproductive risk factor. When significant reproductive risk factors (age at first birth, number of stillbirths, number of miscarriages, breastfed one's baby for at least 1 month) were all added to the established CHD risk factor model, the C statistic changed from 0.726 to 0.730, [mean increase 0.0033, (Bootstrap 95% CI: 0.0022, 0.0051)] (Table 3).

Net Reclassification of CHD

Table 4a demonstrates the net reclassification of women with low (<5%), medium (5 to ≤10%), and high (>10%) risk of CHD as predicted by the established risk factor model alone and with the addition of the pregnancy factors. Thirty one percent of women that developed CHD events were in the low risk, 39% in the intermediate and 30% in the high risk group (as classified by the established CHD plus significant reproductive risk factors model). Of women who experienced CHD events, 6.8% were correctly reclassified to a higher risk category as compared to 6.1% of women incorrectly reclassified to a lower risk category (NRI events= 0.007, p=0.18). Sixty one percent of women not experiencing events were in a low risk, 27% in a medium and 12% in a high risk group among women not experiencing events (as classified by the established CHD plus significant reproductive risk factors model). Among women not experiencing a CHD event, 4.3% were correctly reclassified to a lower risk group as compared to 4.5% of women incorrectly reclassified to a higher risk group (NRI non-events=0.002, p=0.04).

Next, we analyzed net reclassification utilizing dichotomous categories of <7.5% and ≥ 7.5%. Fifty three percent of women who experienced a CHD event were classified as low risk, and 47% as high risk using this cut-point (as classified by the established CHD plus significant reproductive risk factors model). Among women experiencing a CHD event, 3.9% were correctly reclassified from low to high risk versus 3.0% were incorrectly reclassified from high to low risk (NRI events=0.009, p= 0.02). Seventy nine percent of women not experiencing an event were classified as low risk and 21% as high risk (as classified by the established CHD plus significant reproductive risk factors model). Among women who did not experience a CHD event, 2.0% of women were correctly reclassified from high to low risk and 2.2% of women were incorrectly reclassified from low to high risk (NRI non-events=0.002, p=0.02).

Integrated Discrimination Improvement

The integrated discrimination improvement of reproductive factors added to established CHD risk factors model yielded an IDI of 0.0013 with a p-value < 0.0001.

Secondary Analyses

Assessment of Dose Response Relationships of Selected Reproductive Factors and CHD—When considered in separate models adjusting for established CHD

risk factors, number of live birth categories was positively associated with CHD in a dose response relationship (HR=1.03, 95% CI:1.01–1.06, p trend=0.02). Increasing number of stillbirths were associated with CHD (HR=1.14, 95% CI: 1.06–1.22, p trend =0.0003). Similarly number of miscarriages and CHD demonstrated a dose response relationship (HR: 1.10, 95% CI: 1.07–1.14, p trend <0.0001). Additionally, number of tubal pregnancies was associated with CHD in a dose response fashion (HR=1.09, 95% CI: 1.004–1.18, p trend=0.04).

Exploration of SES on Relationship between Reproductive Factors and CHD— After adding income, education and a census tract/zipcode-based neighborhood SES indicator variable to the reproductive risk factor model, the hazard ratios between age at first birth (referent= age > 25 years) and CHD was slightly attenuated but was still statistically significant [no pregnancy lasting at least 6 months 1.00 (0.89–1.12), age < 20 years; HR 1.27 (1.14–1.42), age 20–24 years; HR 1.14 (1.06–1.23), p value<0.001]. The association between breastfeeding and CHD was attenuated but remained statistically significant(HR 0.93 (0.87–1.00), p value 0.04). Other reproductive factors and CHD were not materially different upon accounting for SES variables.

Accounting for Other CHD Clinical Risk Predictors—After addition of BMI, physical activity index and family history of premature CHD to models containing reproductive risk factors and established risk factors, results were not materially changed (Supplemental Table 2).

Discussion

Summary of Main Findings

Among post-menopausal women the following reproductive factors were related to CHD in age-adjusted models: early at first birth, stillbirths, miscarriages, irregular menses, and breastfeeding for ≥ 1 month. An age-adjusted model including these reproductive factors yielded CHD model discrimination of 0.675. In models of reproductive factors added to established CHD risk factors all of the same reproductive factors except irregular menses were independently associated with CHD risk and very modestly increased model discrimination over and beyond established CHD risk factors (C-statistic increased from 0.726 to 7.30). Further adjustment for SES attenuated but did not fully account for the associations between reproductive factors and CHD. Reproductive factors did not materially improve overall CHD net reclassification over and beyond established CHD risk factors.

Potential Mechanisms and Prior Studies Linking Reproductive Risk Factors and CHD—In an earlier investigation of reproductive effects and CHD in the Nurse's Health Study, investigators did not demonstrate significant associations between parity, age at first birth or age at menarche and coronary heart disease.[17] Though the sample size in this study was larger than in our current study (n= 119,963 versus 72,982), the follow up time and number of events was substantially smaller (number of events in prior study=308 versus 4607)[17] which likely accounted for similar event sizes but lack of statistical significance in the prior analysis. Consistent with our findings, a prior investigation in the WHI has also

demonstrated that a longer duration of infant breastfeeding is associated with decreased development of maternal hypertension, diabetes, hyperlipidemia, and CVD.[18] Breastfeeding practices are modifiable and thus may represent a potential target for intervention to reduce later CHD risk in women.

Pregnancy in adolescence can disrupt a still growing female's cardiometabolic health and in turn can lead to greater postpartum maternal weight retention as compared with having a pregnancy in adulthood.[19] Having a history of a prior term pregnancy at an age < 20 years is associated with adverse effects on cardiometabolic profile in women[20] including lipid profile[21], increased blood pressure,[20] and greater adiposity.[19] Consistent with these prior investigations, we demonstrate that early pregnancy is related to CHD upon accounting for both established CHD risk factors and other reproductive factors in WHI. Our secondary analysis suggests that SES does not fully account for the association between age at first birth and later CHD in women. However, a prior investigation from the United Kingdom did suggest that social and behavioral factors accounted for the association between an early age at first pregnancy and most cardiometabolic risk factors (with the exception of high blood pressure) in adulthood in both men and women.[20] Therefore, it is still possible that income, education and neighborhood/zipcode-based SES do not fully account for socioeconomic differences in WHI.

In WHI, pregnancy loss has been previously related to increased cardiovascular events.[7] It is estimated that 10% of stillbirths are due to maternal factors including hypertension, diabetes, smoking, and obesity.[22, 23] Indeed our findings demonstrated that history of stillbirth and miscarriages[24] were associated with incident CHD, independent of established risk factors, other reproductive/pregnancy risk factors and SES.

Early age at menarche is more common among girls with a high BMI and is in turn associated with a higher BMI later in life.[25, 26] Early menarche has been reported to be associated with later life increases in insulin resistance[27], metabolic syndrome[27], systolic blood pressure[25] and dyslipidemia,[25] and recently age at menarche was found to have a U-shaped relationship with CVD in a large UK cohort.[28] However, we did not demonstrate that age at menarche is independently associated with increased CHD, after accounting for other reproductive factors and established risk factors.

Menstrual irregularity, a proxy for polycystic ovarian syndrome, has been associated with incident CVD[29] and CVD mortality[5] (though in the latter study, not independent of body mass index)[5]. In our study, we found that the association between menstrual irregularity and CHD was likely mediated through established CHD risk factors. The difference between our study and a prior investigation[29] may be due to the fact that our study accounted both for other reproductive factors as well as hypertension, hypercholesterolemia, and diabetes.

Utilizing Reproductive Risk Factors in CHD Risk Stratification—Taken as a whole, our analyses indicate that key reproductive risk factors are independently associated with CHD but do not materially add to traditional risk prediction in post-menopausal women. In terms of comparison with traditional risk scores such as the 10-year Framingham Risk Score for CHD[30] (risk factors= age, gender, total cholesterol, HDL cholesterol, systolic

blood pressure, hypertension medications, smoking), we did not account for serum levels of total or HDL cholesterol. We did include use of cholesterol medications and diabetes mellitus. Diabetes is indeed included in the more recent 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (or ASCVD risk score).[14]

Our data suggest that reproductive information may be the most useful in premenopausal women, and possibly prior to the development of traditional risk factors such as hypertension, diabetes, dyslipidemia. In particular, the model discrimination of 0.675 for the age-reproductive factor model demonstrated in our study, though lower than major CHD risk prediction scores (that have C-statistics in the range of 0.75–0.80[16, 31, 32]), is very similar to that of other widely used clinical risk scores such as the CHADS2-VASC[33] for stroke risk stratification and anticoagulation decision making in atrial fibrillation.[34] Among younger women, reproductive factors often precede the onset of established CHD risk factors and could thus guide risk factor modification. Furthermore, the reproductive risk factors are based solely on a medical history or upon medical chart review, and therefore constitute a simple, non-invasive, and inexpensive risk stratification tool. Thus, their use in CHD risk stratification, either alone or in concert with established factors, may enhance our ability to risk stratify young women in a simple and cost-effective way.

It is important highlight that our study only ascertained post-menopausal CHD events and that we did not have adjudicated premenopausal events which may be even more strongly related to reproductive factors than post-menopausal CHD. Future studies should focus on better elucidating the association between reproductive factors and premenopausal or early CHD and the ability of reproductive factors to add to risk stratification in women at younger ages.

Strengths and Limitations—The WHI represents a unique and rare source of longitudinal data on reproductive/pregnancy factors, CHD risk factors and CHD. Measures were carefully standardized and CHD outcomes were rigorously assessed. Although one of the primary aims of the WHI study was to assess the effects of hormone replacement therapy on CVD outcomes, we performed our analysis in the observational study and not in the hormone therapy clinical trial. There are several limitations which should be emphasized. Our findings demonstrating associations between reproductive factors and incident CHD were modest in effect size. Also, information on preeclampsia/pregnancy-induced hypertension, gestational diabetes, gestational age and infant birth weight and size, which have been related to CHD in prior studies[35–38], and which would have been relevant to include in the current study, were unfortunately not available in WHI. Due to the constraints of enrollment in WHI we considered the start of follow up time at study enrollment/ perimenopause and not at the time of pregnancy which would have been the most desirable approach. Thus, premenopausal CHD events were not adjudicated so we could not assess the association between reproductive factors and premenopausal CHD. We could not account for pre-pregnancy risk factors in this study. Further, we did not account for hormone therapy because this is not routinely done in most CVD risk stratification models. Systolic blood pressure was directly measured however dyslipidemia and diabetes were assessed by self-report and use of medications. We did not perform validation of our model on a separate

cohort. Selection of variables was performed, and therefore our effect sizes are likely over-estimated.

Conclusions

When considered together, early age at first birth, number of stillbirths and miscarriages, and lack of breastfeeding for ≥ 1 month are independently associated with post-menopausal CHD and very modestly improve post-menopausal CHD event discrimination over and beyond established risk factors. Net reclassification of CHD is not materially improved by the addition of reproductive factors to established risk factors. Our findings highlight the need for future studies relating reproductive factors to early/pre-menopausal CHD in women and a need for studies inclusive of additional validated pregnancy complications such as gestational diabetes, preeclampsia, gestational age, and infant size that have even stronger demonstrated associations with maternal CHD than reproductive factors, and therefore may also serve as useful primordial and primary CHD prevention risk markers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to acknowledge the late Dr. David Curb who made this study possible with his guidance and support of Dr. Nisha Parikh. We would like to also acknowledge the WHI Program Office.

Funding Sources: This work was supported by American Heart Association Grant 13CRP17350002 (Nisha I. Parikh), NIH Grant Support provided by NIH grants 7R21HL115398 (Nisha I. Parikh), KL2TR000160 (Molly E. Waring) and U01HL105268 (Molly E. Waring). The WHI programs is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts, HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C.

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Clinical Perspectives

When considered together, the following reproductive factors are independently associated with post-menopausal coronary heart disease in women: early age at first birth, number of stillbirths and miscarriages, irregular menses and lack of breastfeeding for ≥ 1 month. When considered along with established risk factors these reproductive factors do not improve our ability to risk stratify coronary heart disease in post-menopausal women. However, our study suggests that a reproductive history may be useful as an “early window”, before the onset of established CHD risk factors, to predict which women are most likely to experience a future coronary heart disease event.

Table 1

Baseline characteristics of women, Women's Health Initiative Observational Study.

	(N=72,982)	
	N	**Mean (SD) or %**
Mean age screening, y	72982	63.2 (7.3)
Race/ethnicity		
White	62462	85.6
Black	5030	6.9
Hispanic	2251	3.1
Native American	256	0.4
Asian/Pacific Islander	2093	2.9
Unknown	890	1.2
Education		
0–8 years	816	1.1
Some high school	2097	2.9
High school diploma/GED	11146	15.4
School after high school	26019	35.9
College degree or higher	32367	44.7
Family income		
< $10,000	2430	3.6
$10,000–$19,999	7031	10.3
$20,000–$34,999	15391	22.6
$35,000–$49,999	13921	20.5
$50,000–$74,999	14344	21.1
$75,000 +	14908	21.9
Smoking status		
Never	37117	50.9
Past	31421	43.1
Current	4444	6.1
Body-mass index, kg/m^2	72207	27.1 (5.8)
Systolic BP, mm Hg	72982	126.2 (17.8)
Diastolic BP, mm Hg	72946	74.7 (9.2)
History of diabetes requiring medications	3444	4.7
History of high cholesterol requiring medications	9623	13.2
On antihypertensive medications	17609	24.1
Age at menarche, y		
≤11	16216	22.2

	(N=72,982)	
	N	**Mean (SD) or %**
12	19160	26.3
13	21369	29.3
≥14	16237	22.2
Number of pregnancies		
None	8273	11.3
1	4899	6.7
2–4	43539	59.7
5+	16271	22.3
Number of live births±		
None	10555	14.5
1	6216	8.5
2–4	47608	65.2
5+	8603	11.8
Age at first birth±		
No term pregnancy	10462	14.3
<20	8780	12.0
20–24	29803	40.8
25–29	17834	24.4
30–34	4638	6.4
35–39	1242	1.7
40–44	211	0.3
45+	12	<0.1
Number of still births±		
None	70218	96.2
1	2375	3.3
2–4	365	0.5
5+	24	<0.1
Number of miscarriages±		
None	51279	70.3
1	14536	19.9
2–4	6691	9.2
5+	476	0.7
Number of tubal pregnancies±		
None	71407	97.8
1	1444	2.0
2–4	123	0.2
5+	8	<0.1
Irregular periods		

	(N=72,982)	
	N	**Mean (SD) or %**
Yes	5672	7.8
No	60169	82.4
Sometimes regular, sometimes irregular	7141	9.8
Tried becoming pregnant for more than 1 year	12346	16.9
Saw doctor because you didn't conceive	9823	67.1
Reason found for non-pregnancy	5729	62.8
Reason–hormones or ovulation	977	1.4
Reason–tubes or uterus	1818	2.6
Reason—endometriosis	1007	1.4
Reason–other problem with you	1006	1.4
Reason–problem with partner	1907	2.7
Reason–don't know reason	4264	6.1
Breastfed for at least one month	36884	50.5
Hysterectomy at randomization	30011	41.1
Estrogen + progesterone use		
Never	51160	70.1
Past	6536	9.0
Current	15257	20.9
Unopposed estrogen use		
Never	45712	62.7
Past	8683	11.9
Current	18542	25.4

Circulation. Author manuscript; available in PMC 2017 May 31.

Table 2

Reproductive factors and CHD adjusted for established CHD risk factors among WHI OS participants.

	Established Risk Factors + Independently significant reproductive variables (p≤0.10)			Established Risk Factors + Reproductive variables: Final Model		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age at enrollment	1.07	1.07, 1.08	<.0001	1.07	1.07, 1.08	<.0001
History of high cholesterol requiring pills			<.0001			<.0001
No	1.00			1.00		
Yes	1.37	1.28, 1.48		1.37	1.28, 1.48	
Current hypertension			<.0001			<.0001
No	1.00			1.00		
Yes	1.49	1.40, 1.59		1.49	1.39, 1.58	
Log Systolic BP	6.01	4.80, 7.51	<.0001	5.99	4.80, 7.49	<.0001
Current smoker			<.0001			<.0001
No	1.00			1.00		
Yes	1.82	1.64, 2.03		1.83	1.64, 2.03	
Diabetes ever			<.0001			<.0001
No	1.00			1.00		
Yes	2.62	2.39, 2.86		2.62	2.40, 2.87	
Irregular menstrual cycle			0.08			
Yes	1.09	0.98, 1.21				
No						
Sometimes regular, sometimes irregular	1.09	0.99, 1.20				
Ever pregnant			0.44			
No	1.00					
Yes	0.92	0.75, 1.13				
Number of live births			0.65			

	Established Risk Factors + Independently significant reproductive variables (p≤0.10)			Established Risk Factors + Reproductive variables: Final Model		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
None	1.00					
1–4	1.29	0.57, 2.90				
≥5	1.25	0.55, 2.82				
Age at first birth			<.0001			<.0001
No pregnancy lasting at least 6 months	1.23	0.53, 2.82		1.02	0.92, 1.13	
<20	1.43	1.29, 1.57		1.42	1.29, 1.56	
20–24	1.21	1.13, 1.30		1.21	1.13, 1.30	
≥25	1.00			1.00		
Number of still births			0.03			0.04
None	1.00			1.00		
1	1.18	1.03, 1.37		1.18	1.02, 1.35	
>1	1.24	0.90, 1.72		1.24	0.89, 1.71	
Number of miscarriages			<.0001			<.0001
None	1.00			1.00		
1	1.12	1.04, 1.20		1.11	1.03, 1.20	
2–4	1.25	1.14, 1.37		1.24	1.13, 1.36	
5+	1.39	1.04, 1.86		1.39	1.04, 1.86	
Breastfed for ≥ 1 month			0.001			0.001
No	1.00			1.00		
Yes	0.90	0.85, 0.96		0.90	0.85, 0.96	

Table 3

CHD discrimination among WHI women who have ever been pregnant for established CHD risk factors, reproductive factors and combined models.

Model	C-statistic (n=72,982)	C Difference from Established Risk Factor Model	Bootstrap 95% CI for difference from Established Risk Factor Model (n=72,982)
Age + reproductive risk factors *	0.675		
Established risk factors †	0.726		
Established risk factors + age at first birth	0.728	0.0019	(0.0010, 0.0032)
Established risk factors + number of stillbirths	0.727	0.0005	(0.0001, 0.0013)
Established risk factors + number of miscarriages	0.727	0.0010	(0.0004, 0.0020)
Established risk factors + breast feeding	0.726	0.0001	(−0.00002, 0.0005)
Established risk factors + significant reproductive factors ‡	0.730	0.0033	(0.0022, 0.0051)

* Reproductive risk factors include menstrual irregularity, age at first birth, still births, miscarriages, and breastfeeding ≥ 1 month.

† Established risk factors modeled include age, high cholesterol requiring pills, currently taking pills for hypertension, log of systolic blood pressure, current smoker, diabetes.

‡ Significant reproductive risk factors include age at first birth, still births, miscarriages, and breastfeeding ≥ 1 month.

Table 4a

Net-reclassification (NRI)* of 10-year risk of CHD among WHI OS participants with and without incident CHD after adding significant reproductive factors to the established CHD risk factor model.

Established CHD risk factors plus significant reproductive factors† model								
	Low risk (0–5%)		Intermediate risk (>5–10%)		High risk (>10%)		Total	
Established CHD risk factor model**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Participants with incident CHD								
0–5%	1281	89.02	158	10.98	0	0.00	1439	31.2
>5–10%	144	8.00	1501	83.34	156	8.66	1801	39.1
>10%	0	0.00	137	10.2	1230	89.98	1367	29.7
Total	1425	30.9	1796	39.0	1386	30.1	4607	–
Participants with no incident CHD								
0–5%	40040	95.25	1996	4.75	0	0.00	42036	61.5
>5–10%	1929	10.52	15306	83.45	1106	6.03	18341	26.8
>10%	0	0.00	1014	12.68	6984	87.32	7998	11.7
Total	41969	61.4	18316	26.79	8090	11.83	68375	–

NRI = 0.005, 95% CI: −0.006, 0.015; p-value = 0.37

NRI events = 0.007, 95% CI: −0.003, 0.018; p-value = 0.18

NRI for non-events = 0.002, 95% CI: 0.0001, 0.005; p-value = 0.04

Integrated discrimination improvement = 0.0013, 95% CI: 0.0008, 0.0017; p-value < 0.0001

*Survival measures were used to estimate reclassification statistics[10]

**Established risk factors modeled include age, high cholesterol requiring pills, hypertension medications, log of systolic blood pressure, current smoker, diabetes.

†Significant pregnancy risk factors include age at first birth, still births, miscarriages, and breastfeeding ≥ 1 month.

Table 4b

Net-reclassification (NRI) of 10-year risk of CHD among WHI OS participants with and without incident CHD after adding significant reproductive factors to the established CHD risk factor model.

Established CHD risk factors plus significant reproductive factors† model						
	Low risk (0–7.4%)		High risk (≥7.5%)		Total	
Established CHD risk factor model**	**N**	**%**	**N**	**%**	**N**	**%**
Participants with incident CHD						
0–7.4%	2324	92.89	178	7.11	2502	54.3
≥7.5%	136	6.46	1969	93.54	2105	45.7
Total	2460	53.40	2147	46.60	4607	–
Participants with no incident CHD						
0–7.4%	52622	97.18	1525	2.82	54147	79.2
≥7.5%	1399	9.83	12829	90.17	14228	20.8
Total	54021	79.01	14354	20.99	68375	–

NRI = 0.007, 95% CI: −0.0004, 0.015; p-value = 0.06

NRI for events = 0.009, 95% CI: 0.002, 0.017; p-value = 0.02

NRI for non-events = 0.002, 95% CI: 0.0003, 0.003; p-value = 0.02

Integrated discrimination improvement = 0.0013, 95% CI: 0.0008, 0.0017; p-value < 0.0001

*Survival measures were used to estimate reclassification statistics[10]

**Established risk factors modeled include age, high cholesterol requiring pills, hypertension medications, log of systolic blood pressure, current smoker, diabetes.

†Significant pregnancy risk factors include age at first birth, still births, miscarriages, and breastfeeding ≥ 1 month.