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The Association of Reproductive History with All-cause and Cardiovascular Mortality in Older Women: the Rancho Bernardo Study

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Abstract

Objective—To examine associations of gravidity and parity with all-cause, CVD and CHD mortality in postmenopausal women.

Design—Prospective cohort study.

Setting—Rancho Bernardo, a southern California community.

Patients—1,294 postmenopausal women aged 50–96 who attended a 1984–87 research clinic visit when reproductive and medical histories were obtained, and were followed through 2007.

Interventions—None.

Main Outcome Measures—All-cause, CVD, CHD, and non-CHD CVD mortality, determined by nosologist-coded death certificates.

Results—Average baseline age was 70.6±9.2. Numbers of pregnancies ranged from 0–13 (median=2); births ranged from 0–11 (median=2). During a median of 19.3 years follow-up, 707 women (54.6%) died with 46.5% attributed to CVD, 20.5% to CHD, and 26.0% to non-CHD CVD. Trend analyses showed inverse associations of gravidity with CVD mortality ($p=0.05$) and non-CHD CVD mortality ($p=0.05$). Women with ≥ 4 pregnancies were less likely than nulligravid to have fatal CVD (HR=0.63, 95% CI=0.40–0.99) and non-CHD CVD (HR=0.48, 95% CI=0.26–0.91) independent of age, years post-menopause, obesity, and HDL. Associations increased after the first decade of follow-up. Parity and gravidity were not associated with overall or CHD mortality.

Conclusions—High gravidity was associated with reduced CVD and non-CHD CVD mortality in postmenopausal women. Protective associations could reflect biological mechanisms occurring

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with repeated pregnancy or greater social support related to family size among multiparous women.

Keywords

cardiovascular disease; childbearing; pregnancy history; reproductive history; mortality

Introduction

Heart disease is the leading cause of death among women in the United States, accounting for approximately 316,000 deaths each year (1). Unfortunately, many women do not perceive themselves to be at risk for cardiovascular disease (2), and almost two-thirds who die suddenly from heart disease had no previous symptoms (3). Thus, a better understanding of CVD and CHD risk factors unique to women is imperative.

Numerous studies have examined the association of childbearing history with morbidity in postmenopausal women. Although not always consistent, these studies suggest a positive association of parity and gravidity with cardiovascular risk factors including plasma glucose and insulin resistance (4–7), obesity (6, 8), and cholesterol levels (6–8). Risk of diabetes (5, 9), coronary artery plaque (6, 10), heart disease (8, 11, 12), and myocardial infarction (13, 14) were also reported to increase with parity, although elevated risk may not be apparent with less than four or five pregnancies (10–12).

The reported associations of parity (number of live-births) or gravidity (number of pregnancies) with heart disease and its risk factors would be expected to predict an increased risk of mortality. However, few studies examine the association of pregnancy history with all-cause or cardiovascular disease (CVD) mortality. In the largest study consisting of over one million British women aged 45–74, Beral and colleagues reported higher coronary heart disease (CHD) mortality rates among parous than nulliparous women (15). Another study of over 100,000 women aged 26–69, reported a non-significant trend of increasing risk of CVD death with increasing parity (16). In contrast, others either report no association of parity with CHD mortality (17) or that parous women are at lower risk of sudden cardiac death (18).

Most previous studies did not adjust for potentially confounding behavioral, lifestyle or clinical CVD risk factors (15, 16), and most examined live-births rather than number of pregnancies (15–18). In addition, no previous studies specifically focused on older women who were past their reproductive years (15–17), and the only study that reported a cardioprotective effect for parity found the strongest effect among women over age 50 (18).

We report here the association of gravidity and parity with all-cause and CVD mortality in older community-dwelling postmenopausal women in the context of potentially confounding behavioral and biological covariates.

Materials and Methods

Participants

In 1972–74, 82% of all residents of the middle class, Southern California community of Rancho Bernardo were surveyed to assess heart disease risk factors. In 1984–87, 1,364 (~80%) surviving, local community-dwelling women aged 50 and older participated in a follow-up research clinic visit. After excluding women not yet postmenopausal (n=56) and those missing information on number of pregnancies or live-births (n=14), there remained 1,294 women for these analyses.

Participants were followed with periodic clinic visits and annual mailed questionnaires; death certificates were requested for all decedents. Vital status information was collected through 2007. This study was approved by the University of California, San Diego Human Subjects Protections Program; all participants gave written informed consent.

Procedures

At the 1984–87 visit, a standard interview was used to obtain information on reproductive history, including numbers of pregnancies lasting three months or more, live-births, and menopausal history, including age at menopause and use of estrogen therapy. History of heart surgery and physician diagnosis of diabetes, myocardial infarction, angina, stroke, transient ischemic attack (TIA), or intermittent claudication was obtained, and the Rose Cardiovascular Questionnaire (19) was administered. Information on behaviors, including cigarette smoking (never/past/current), alcohol use (drinks of beer, wine, liquors or hard alcohol consumed in the past week), and exercise ≥ 3 times/week (no/yes) was obtained during the interview. Current medication use, including use of postmenopausal estrogen therapy, was validated with pills and prescriptions brought to the clinic for that purpose.

During the clinic visit, height and weight were measured with the participants wearing light clothing and no shoes; body mass index (BMI; kg/m^2) was calculated as an estimate of obesity. Waist and hip circumferences were measured in centimeters, and their ratio was used as an estimate of adiposity. Blood pressure was measured by a nurse trained in the Hypertension Detection and Follow-up Program (HDFP) (20) after the participant had been seated for at least 5 minutes; two readings were recorded. Fasting venous blood was drawn for later measurement of glucose, lipids and lipoproteins, followed by an oral glucose tolerance test (75-g glucose load) administered in the morning after a 12–16 hour overnight fast. Blood was also obtained two hours after the glucose load.

Cholesterol and triglyceride levels were analyzed by enzymatic techniques using the ABA-200 biochromatic analyzer (Abbot Laboratories, Irving, TX), high-performance cholesterol reagent (no. 23669 1; Boehringer Mannheim Diagnostics, Indianapolis, IN), and triglyceride agent (no. 6097; Abbott Laboratories). High-density lipoprotein (HDL) levels were measured after precipitation of other lipoproteins with heparin and manganese chloride, according to the standardized procedures of the Lipid Research Clinical Manual. Low-density lipoprotein (LDL) levels were estimated using the Friedewald formula. All measures were performed in a Center for Disease Control Certified Lipid Research Clinical laboratory. Fasting plasma glucose (FPG) and 2-hr glucose were measured in a diabetes research laboratory using a glucose-oxidase method.

Death certificates, available for 89% of decedents, were coded for causes of death by a certified nosologist using the *International Classification of Diseases, Ninth Revision* (ICD9). CVD deaths included codes 401–414, 426–438, and 440–448, CHD death included codes 410–414, and non-CHD CVD death (defined as CVD death not due to heart disease, for example, stroke, atherosclerosis, and hypertensive diseases) included codes 401–405, 426–438, and 440–448.

Statistical Analysis

Gravidity and parity were grouped into five categories (0, 1, 2, 3, 4+ pregnancies/live-births); zero was used as the reference group based on published studies and preliminary analyses of our data. Age at menopause was defined as age at last menses for women who had a natural menopause or hysterectomy with bilateral oophorectomy. For women with a hysterectomy with ovarian conservation, age at menopause was defined as the age when use of hormone therapy began, (or for the 24 women who did not use hormones, the mean age of

natural menopause (age 49) in this cohort was used as age at menopause). Number of years post-menopause was calculated as the difference between current age and reported age at menopause. Prevalent cardiovascular disease (CVD) was defined by a physician-diagnosis of myocardial infarction, stroke, TIA or intermittent claudication, heart surgery, or diagnosis of angina pectoris based on response to the Rose Cardiovascular Questionnaire (19). Prevalent coronary heart disease (CHD) was defined as reported physician diagnosis of myocardial infarction or heart surgery, or response to the Rose Cardiovascular Questionnaire.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of anti-hypertensive medication. Diabetes was classified in accordance with the 1999 World Health Organization (WHO) criteria (21); specifically, individuals were considered to have Type 2 diabetes if either FPG ≥ 7.0 mmol/l or 2-hour postload plasma glucose ≥ 11.1 mmol/l during a 75-g OGTT, or if they reported use of diabetes medication (oral or insulin). Nine women who were missing glucose measures or information on diabetes medication use were classified as having diabetes only if they reported a history of physician-diagnosed diabetes.

Univariate analyses were used for descriptive statistics of all exposures, outcomes, and potential covariates. Differences in means and proportions of potential covariates and outcomes across exposure categories after adjusting for age were examined using analysis of covariance (ANCOVA) for all continuous variables and Pearson's chi-square for all categorical variables. Chi-square tests for trend across exposure groups were done using linear regression for continuous variables and logistic regression for categorical variables. Covariates having a significant trend with either gravidity or parity after adjusting for age were retained for inclusion in multivariate regression models. All statistical tests were 2-tailed; $p < 0.05$ was considered statistically significant.

Cox proportional hazard models were used to examine the association of gravidity and parity with CVD, CHD, and non-CHD CVD mortality and all-cause mortality after adjusting for covariates. Graphical and statistical tests were done to test proportional hazard assumptions for all outcomes. Models for all cause and CHD mortality met the proportional hazard assumption, but models for CVD and non-CHD CVD mortality did not. Statistical testing indicated CVD and non-CHD CVD mortality risk varied over time for one pregnancy compared with no pregnancies, in violation of the proportional hazard assumption; therefore a time-dependent covariate for this group was included in all models of CVD and non-CHD CVD mortality to account for the non-proportionality. Analyses were also stratified by length of follow-up to further assess the non-proportionality of these models. Model 1 adjusted for covariates that were most significantly associated with gravidity and parity ($p < 0.01$; age, age at menopause, number of years post-menopause), and Model 2 adjusted for all covariates that were significantly associated with gravidity and parity ($p < 0.05$; BMI and HDL cholesterol, in addition to Model 1 covariates), to assess whether inclusion of these additional variables modified the estimates obtained in Model 1. Due to the high degree of collinearity between age at menopause and number of years post-menopause, only number of years post-menopause was included in multivariate models; results were similar after adjusting for age at menopause. Time to event was calculated from the time the participant entered the study until the occurrence of the event of interest (CVD, CHD, non-CHD CVD, or all-cause mortality). Hazard ratios and 95% confidence intervals are reported; 95% confidence intervals not including 1.0 are considered statistically significant. All analyses were conducted using SAS 9.2 statistical programming software for PC.

Results

Baseline age of the participants ranged from 50–96 years, with an average age of 70.6 (SD=9.2) and a median age of 72 years. Number of pregnancies (gravidity) ranged from 0–13, with a median of 2, and number of live births (parity) ranged from 0–11, with a median of 2. 978 (76%) reported at least one pregnancy (gravid), and, and 888 (68.6%) reported at least one live-birth (parous). 240 (19%) reported 4+ pregnancies, and 131 (10%) reported 4+ live-births. The average age at menopause was 46.5 years (SD=7.2) with a median of 48; women had been postmenopausal an average of 23.7 years (SD=11.1, median=24). Follow-up ranged from 0.6 to 23.9 years, with a median of 19.3 years; more than half (54.6%) died during follow-up. Among the 707 who died, 46.5% (n=329) of deaths were attributed to CVD overall, 20.5% (n=145) to CHD, and 26.0% (n=184) to non-CHD CVD.

Age-adjusted comparisons of baseline characteristics by gravidity are shown in Table 1. Trend analyses indicated significant positive associations of gravidity with age at menopause ($p=0.005$) and BMI ($p=0.02$), and significant inverse associations with age at the baseline visit (unadjusted, $p<0.0001$), number of years post-menopause ($p=0.003$), and HDL cholesterol ($p=0.03$). No other significant trends were seen. Results comparing these characteristics by parity were similar (data not shown).

Figure 1 shows age-adjusted comparisons of all-cause, overall CVD, CHD and non-CHD CVD mortality by gravidity. Trend analyses indicated an inverse association of gravidity with CVD mortality overall ($p=0.05$) and with non-CHD CVD mortality ($p=0.05$). Although a significant difference between women with 4+ and 3 pregnancies was found for overall mortality, no other significant trends were seen. Analyses comparing mortality by varying levels of parity were similar but weaker with no significant trends (data not shown).

Results of multivariate models are shown in Table 2. After adjustment for age and years post-menopause, women with four or more pregnancies had a significantly lower risk of CVD mortality (HR=0.61, 95% CI 0.38–0.96) and non-CHD CVD mortality during follow-up (HR=0.48, 95% CI 0.26–0.90) than women with no pregnancies. Results were similar after further adjustment for BMI and HDL cholesterol (HR=0.63, 95% CI 0.40–0.99 and HR=0.48, 95% CI 0.26–0.91 respectively). No associations were observed for women with fewer pregnancies. Trend analyses adjusted for all covariates in Model 2, indicated trends for decreasing risk of overall CVD mortality ($p=0.06$) and non-CHD CVD mortality ($p=0.03$) with increasing gravidity. Associations of live births with CVD and non-CHD CVD mortality were similar, although not significant (HR=0.92, 95% CI=0.55–1.54 and HR=0.51, 95% CI=0.22–1.19 respectively, results not shown). No significant associations were seen between numbers of pregnancies or births and overall or CHD mortality. A fully saturated model that also included all classic risk factors for CVD (smoking history, estrogen therapy, alcohol use, exercise, and use of medications for high blood pressure, high cholesterol, and hyperglycemia) did not materially change these estimates (results not shown).

Because risk for CVD and non-CHD CVD mortality varied over time for women with a single pregnancy as compared to those with no pregnancies (the reference category), Kaplan-Meier survival curves comparing survival by pregnancy were examined. These survival curves showed that early in follow-up (<10 years), women with one pregnancy had a higher risk of CVD mortality compared to women with no pregnancies; however, later in follow-up (10+ years), women with one pregnancy had a decreased risk of CVD mortality as compared to women with no pregnancies. To remove the effect of the non-proportionality among this group, analyses were repeated for CVD mortality and non-CHD CVD mortality, stratifying by decade of follow-up (Table 3). Results indicate that after adjusting for age,

number of years post-menopause, BMI, and HDL cholesterol, the association of gravidity with CVD and non-CHD CVD mortality was strongest after the first decade of follow-up, as women with four or more pregnancies were significantly less likely than women with no pregnancies to experience CVD and non-CHD CVD mortality more than 10 years into follow-up (HR=0.52, 95% CI 0.29–0.94 and HR=0.42, 95% CI 0.19–0.90 respectively), although the direction of association was similar within the two time periods. Results were similar for live births (HR=0.80, 95% CI=0.41–1.57 and HR=0.45, 95% CI=0.16–1.27 respectively) although not statistically significant.

Multivariate analyses repeated among gravid women only, using one pregnancy as the reference category yielded similar results; those with four pregnancies or more had a non-significant decreased risk of all-cause, CVD, CHD and non-CHD CVD mortality as compared to women with one pregnancy (data not shown). No associations were observed for pregnancy losses (difference between number of live-births and number of pregnancies), or for the number of years between last pregnancy and onset of menopause (difference between reported age at last pregnancy and age at menopause), with all-cause, CVD, CHD, or non-CHD CVD mortality was observed (data not shown). In order to determine the effect of baseline age on these associations, a sensitivity analysis was performed repeating the analyses for CVD and non-CHD CVD mortality stratified by mean age at baseline (70), with no material change in the hazard ratios. Because this greatly reduced the sample size, the p-values were no longer statistically significant (data not shown).

Discussion

In this cohort of older women, those with four or more pregnancies had a significantly lower risk of death attributable to CVD, especially non-CHD CVD, than women who had not been pregnant. This decreased risk was observed before and after controlling for other risk factors associated with gravidity, including age, number of years post-menopause, BMI, and HDL cholesterol. Analyses examining number of live-births as the predictor yielded similar, weaker results, likely due to fewer women reporting 4+ live-births as compared to pregnancies.

Results of the present study are in accord with Colditz and colleagues who also found a slightly increased, non-significant risk of CHD among nulliparous women compared to women with three pregnancies (reference category) (17). However, in that study, CHD included both mortality and non-fatal MI, without distinguishing between these outcomes. Similarly, a case-control study by Talbott et al. reported that women over the age of 50 who experienced sudden cardiac death were more likely to be childless than controls, even after adjustment for age, history of hypertension or diabetes, cigarette intake, death of a significant other, or psychiatric disease (18).

Results of the present study are in contrast to other studies reporting an increasing risk of CVD mortality with increasing parity (15, 16). These differences in results between the present study and others may be partially due to variations in study design and sample characteristics. For example, Beral et al. and Green et al. were unable to adjust for potentially confounding behavioral and lifestyle factors or clinically assessed covariates (15, 16). In the present study, more than 90% of the women were classified as Hollingshead index I–III (22), and multiparity may exert more negative effects in lower SES groups. Factors such as education and socioeconomic status may explain the inconsistency of results between studies (23); results of the present study are independent of SES, and SES is often a confounder for number of pregnancies.

Differences between studies may also be due to variation in the CVD outcomes investigated. We investigated CVD, CHD, and non-CHD CVD mortality; others examined specific, more limited outcomes, such as sudden cardiac death, degenerative heart disease, and hypertensive disease (15, 16, 18), in addition to CHD mortality (15, 17), which is only a subset of CVD mortality. This is also important as the strongest associations in the present study were observed for non-CHD CVD, which shares most of the same risk factors as CHD, but has different etiology. Variation in results may also reflect age differences; the present study focused on women aged 50–94, more than half of whom were at least 20 years since last possible pregnancy, and who would be at greater risk for mortality, while others included women still in their childbearing years.

Prior to menopause, rates of cardiovascular disease (CVD) and particularly CHD are much lower among women compared to men of the same age (14). These sex differences decrease with age (14). One theory regarding the loss of female cardioprotection is diminishing levels of endogenous estrogen after menopause. The greater the number of pregnancies, the longer the duration of exposure to high levels of estrogen and progesterone. It is also possible that higher fertility may reflect women who are healthier in general and therefore, at lower risk of CVD and non-CHD CVD mortality, as compared to women who are not as fertile. Additional analyses, such as limiting models to gravid women only and looking at number of pregnancy losses, were undertaken to investigate this possibility, and suggested that increased number of pregnancies rather than fertility is driving the observed association. It is also conceivable that larger families offer higher levels of social support which may also exert a cardioprotective effect against CVD and non-CHD CVD mortality.

One of the most surprising findings of the present study was the association of number of pregnancies with reduction of non-CHD CVD mortality specifically, rather than mortality due to CHD. Consistent with these findings, Yang et al. reported decreased risk of stroke and hemorrhagic stroke specifically among parous compared to nulliparous women, after adjustment for established stroke risk factors (24).

The protective effect of pregnancy for non-CHD CVD specifically may reflect the increased endothelial function observed during normal pregnancy, which results in greater bioavailable nitric oxide. Previous studies also show enhanced endothelial function during pregnancy despite concurrent hyperlipidemia and metabolic changes (25), an effect which may carry over postpartum. Endothelial dysfunction is a hallmark of vascular diseases and hypertension, and is predictive of future cardiovascular events (26). The improved endothelial function experienced during repeated periods of pregnancy may mediate CVD risk factors and reduce the risk of future CVD mortality.

Several limitations and strengths of this study should be noted. The Rancho Bernardo cohort has exceptional longevity, was relatively healthy in 1972–74, had relatively high SES, and had good access to health care. Therefore generalizability may be limited. However, this homogeneity also reduces confounding due to socioeconomic stressors. Women in Rancho Bernardo tend to be relatively lean, exercise more, and include few current smokers, compared to other cohorts (27). Adjusting for these variables singly (BMI, exercise, and smoking history) did not materially alter the HRs, possibly reflecting the homogeneity of the study sample with regard to these measures, rather than their lack of association with the outcomes of interest. Thus, results of the present study may be conservative. In addition, analyses of the association of gravidity and mortality were adjusted for confounding due to estrogen therapy, but not due to specific dosage or preparation of estrogen used. Further, we were unable to quantify the effects of social support many years after childbearing, and it is unknown the extent to which social support from children could have affected mortality.

In conclusion, women in this study had less CVD mortality risk if they had more than 4 pregnancies, with the strongest association observed for non-CHD CVD mortality. The mechanism by which this decreased risk occurs is unknown, however, it may reflect higher fertility in healthier women, the effect of prolonged exposure to higher levels of circulating estrogen or other hormones during pregnancy, increased endothelial function during pregnancy, or the added social support from a larger family. Future studies should examine whether increased number of pregnancies decreases risk for specific types of non-CHD CVD, and whether pregnancy history is associated with postmenopausal estrogen levels or endothelial function to establish whether spikes in estrogen levels or increased endothelial function during the reproductive period carry over into menopause, providing further support for the biologically protective effect of pregnancy against cardiovascular death.

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Figure 1. Age-adjusted comparison of overall and cause-specific mortality^a in postmenopausal women by

^a Overall mortality percent represents percent of deaths within the study population; percent for CVD, CHD, and non-CHD CVD mortality is percent among those who died

Table 1

Baseline age-adjusted comparison of characteristics by gravidity in Rancho Bernardo, CA, from 1984–2007^a

	Gravidity					<i>p</i> trend
	0	1	2	3	4+	
N	316	225	305	208	240	
Age at Visit (average)	73.4	72.8	71.5	68.4	65.4	<0.0001
Age at Menopause (average)	45.8	45.5	46.7	47.4	47.2	0.005
Years Post-menopause (average)	24.3	24.7	23.5	22.8	22.9	0.003
BMI (average, kg/m²)	23.9	24.2	24.1	24.5	24.7	0.02
Waist/Hip Ratio (average)	0.80	0.79	0.79	0.80	0.80	0.62
Systolic Blood Pressure (average)	140.6	140.6	138.9	140.3	139.8	0.58
Diastolic Blood Pressure (average)	75.6	74.7	75.2	75.8	75.0	0.82
Total Cholesterol (average, mg/dl)	230.9	229.7	230.5	229.6	224.4	0.10
HDL (average, mg/dl)	70.6	68.3	69.0	68.4	65.8	0.03
LDL (average, mg/dl)	138.2	138.6	139.4	136.5	135.3	0.34
Triglycerides (average, mg/dl)	114.8	117.5	114.3	127.5	118.2	0.52
FPG (average, mg/dl)	97.5	99.7	96.0	100.1	98.7	0.38
Alcohol Use (average, grams/week)	76.4	56.5	61.7	74.4	56.3	0.19
Current Smoking (%)	12.9	16.0	14.4	15.5	11.3	0.68
Current Estrogen Therapy (%)	29.7	27.3	29.9	22.7	24.3	0.09
Blood Pressure Medication (%)	33.9	28.0	29.5	31.4	31.4	0.66
Blood Sugar Medication (%)	1.5	1.9	3.2	4.6	3.2	0.09
Cholesterol Medication (%)	1.3	0.9	1.7	0.5	0.3	0.28
Exercise 3 times/week (%)	80.5	77.9	78.0	76.3	77.3	0.31
Hypertension (%)	33.9	28.0	29.5	31.4	31.4	0.66
Diabetes (%)	11.3	14.5	11.2	15.6	13.4	0.46
Stroke (%)	1.2	3.0	3.4	3.5	3.0	0.21
Prevalent CHD (%)	14.7	24.4	16.2	22.9	21.5	0.20
Prevalent CVD (%)	18.0	27.1	19.4	24.7	23.6	0.72

^aResults of ANCOVA and Pearson's chi-square, and chi-square test for trend

Table 2

Associations of gravidity with risks of all-cause, CVD, CHD, and non-CHD CVD mortality; results of Cox proportional hazard modeling

	N (Deaths)	Model 1 ^a		Model 2 ^b		p-trend ^c
		HR	95% CI	HR	95% CI	
Overall Mortality	707					
Gravidity						0.52
0	198	1.00	Ref.	1.00	Ref.	
1	138	1.03	0.82–1.30	1.04	0.82–1.31	
2	179	1.13	0.91–1.41	1.12	0.90–1.40	
3	109	1.25	0.97–1.60	1.29	1.00–1.66	
4+	83	0.88	0.67–1.15	0.87	0.66–1.14	
CVD Mortality	329					
Gravidity						0.06
0	100	1.00	Ref.	1.00	Ref.	
1	74	1.95	0.96–4.00	1.96	0.96–4.00	
2	81	1.06	0.77–1.44	1.06	0.77–1.44	
3	50	1.23	0.86–1.78	1.27	0.87–1.85	
4+	24	0.61	0.38–0.96	0.63	0.40–0.99	
CHD Mortality	145					
Gravidity						0.88
0	41	1.00	Ref.	1.00	Ref.	
1	33	1.23	0.75–2.01	1.30	0.76–2.16	
2	39	1.34	0.84–2.14	1.44	0.89–2.34	
3	20	1.23	0.69–2.19	1.42	0.79–2.55	
4+	12	0.81	0.42–1.57	0.87	0.45–1.71	
Non-CHD CVD Mortality	184					
Gravidity						0.03
0	59	1.00	Ref.	1.00	Ref.	
1	41	2.53	0.84–7.66	2.78	0.85–9.15	
2	42	0.87	0.57–1.33	0.83	0.54–1.28	
3	30	1.23	0.77–1.97	1.18	0.72–1.93	

	N (Deaths)	Model 1 ^a		Model 2 ^b		p-trend ^c
		HR	95% CI	HR	95% CI	
4+	12	0.48	0.26-0.90	0.48	0.26-0.91	

^aModel 1 adjusted for: age and years post-menopause

^bModel 2 adjusted for: age, years post-menopause, BMI, an HDL cholesterol

^cTrend analyses adjusted for all variables in Model 2; chi-square test for trend

Sample size by gravidity: 0 n=316; 1 n=225; 2 n=305; 3 n=208; 4+ n=240

Associations of gravidity with risks of CVD and non-CHD CVD mortality after stratification by years of follow-up; Cox proportional hazard modeling^a

Table 3

Gravidity	≤10 years follow-up ^b		>10 years follow-up ^b	
	N (Deaths)	HR 95% CI	N (Deaths)	HR 95% CI
<u>CVD Mortality</u>				
	144		185	
0	39	1.00 Ref.	61	1.00 Ref.
1	32	1.50 0.90–2.51	42	0.96 0.63–1.48
2	39	1.12 0.67–1.89	42	1.01 0.67–1.53
3	24	1.28 0.71–2.29	26	1.11 0.68–1.83
4+	10	0.91 0.43–1.92	14	0.52 0.29–0.94
<u>Non-CHD CVD Mortality</u>				
	67		117	
0	19	1.00 Ref.	40	1.00 Ref.
1	16	1.53 0.75–3.16	25	0.79 0.46–1.36
2	17	0.82 0.38–1.76	25	0.82 0.48–1.39
3	11	0.98 0.39–2.44	19	1.18 0.66–2.13
4+	4	0.79 0.25–2.47	8	0.42 0.19–0.90

^a Adjusted for: age, years post-menopause, BMI, and HDL cholesterol

^b Mean follow-up time: ≤10 years follow-up=6.0 years; >10 years follow-up=19.5 years

Sample size by gravidity (≤10 years): 0 n=81; 1 n=58; 2 n=82; 3 n=46; 4+ n=32

Sample size by gravidity (>10 years): 0 n=235; 1 n=167; 2 n=223; 3 n=162; 4+ n=208