Is Early Natural Menopause a Biologic Marker of Health and Aging?

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Abstract: The relation between age at natural menopause and all-cause mortality was investigated in a sample of 5,287 White women, ages 55 to 100 years, naturally-postmenopausal, Seventh-day Adventists who had completed mailed questionnaires in 1976. The age-adjusted odds ratio of death during 1976–82 in women with natural menopause before age 40 was 1.95 (95% confidence interval = 1.24, 3.07), compared to the reference group of women reporting natural menopause at ages 50 to 54. Corresponding odds ratios of death were 1.39 (95% CI = 1.06, 1.81) for natural menopause at ages 40 to 44, and 1.03 (95% CI = 0.84, 1.25) for natural menopause at ages 45 to 49. Among 3,166 White, 55- to 100-year-old, surgically-postmenopausal, Adventist women, there was no relation between age at surgical menopause and mortality. Logistic regression analyses indicated that findings from this study were apparently not due to confounding by smoking, over- or underweight, reproductive history, or replacement estrogen use. (*Am J Public Health* 1989; 79: 709–714.)

Introduction

Advancing age is associated with substantial adverse changes in many physiologic characteristics,[1–10] increases in morbidity,[11] decreases in the capacity for self care at older ages,[12] and increases in mortality.[13] Reproductive functions also show a strong and predictable change with advancing adult age. As age increases between age 30 and menopause, women experience more anovulatory cycles, infertility, chromosomal abnormalities related to oogenesis, and spontaneous abortions.[14] While other organs and physiologic systems usually decline in performance yet continue to function with advancing age, the ovaries decline and essentially cease functioning at menopause.

Several animal species, such as some salmon, mollusk, spiders, and octupus die within a predictable time after mating or reproducing.[15] While these may be extreme examples, they suggest that neural and endocrine mechanisms play a role in determining length of life in some animals. Furthermore, environmental factors that affect the health and aging of reproductive organs also might simultaneously affect other organs and tissues. For example, cigarette smoking adversely affects the function of the reproductive system[16–18] as well as the function of the cardiovascular system, in addition to reducing life expectancy.[18,19]

Based on these considerations, we hypothesized that age at natural menopause would be a biologic marker of the general health and aging state of the individual. Because mortality is an indicator of health and aging, we tested the hypothesis that age at natural menopause is negatively associated with all-cause mortality.

Methods

Study Population and Questionnaires

In 1974, Seventh-day Adventist households in California were identified from church records and a Census Questionnaire mailed to virtually every household. A total of 25,186 White Adventist women 25 to 100 years of age, not of Hispanic origin, were identified by the census. In 1976, Adventists identified in the previous census were mailed another questionnaire called the Lifestyle Questionnaire. Of the 25,186 women originally identified in the census, 19,586 (78 percent) completed the Lifestyle Questionnaire. Variables from the Lifestyle Questionnaire used in the multivariate analysis and our method of coding are described in the Appendix.

Of the 19,586 women 25 to 100 years of age who completed the Lifestyle Questionnaire, 10,198 were 55 to 100 years of age. Of these women, 5,287 (51.8 percent) reported they were naturally-postmenopausal, 3,166 (31.0 percent) surgically-postmenopausal, 75 (0.7 percent) pre-menopausal, and 1,670 (16.4 percent) were either unknown for type or age at menopause or had an implausible age at menopause (i.e., age at menopause was greater than 64 or greater than the subject's age). While there is no generally accepted normal range for age at menopause,[20] age 64 was used in this study as the last acceptable year. Thus, the study population for this report was the 5,287 naturally- and 3,166 surgically-postmenopausal women who were 55 to 100 years of age at the start of the study (i.e., restricted to those ages where virtually all women were postmenopausal).

Mortality Surveillance

Mortality data in this report cover the time between the completion of the Lifestyle Questionnaire in 1976 and the end of the follow-up on December 31, 1982. Of the 19,586 women who completed the Lifestyle Questionnaire, 17,447 (89.1 percent) were known to be alive when the follow-up ended because they completed a mailed questionnaire in 1983, a death certificate indicated they died after 1982, or a personal contact by phone indicated they were alive in 1983. A total of 1,439 (7.3 percent) of the 19,586 women died during the 1976–82 time period. All deaths were confirmed by death certificates. Vital status at the end of follow-up in 1982 could not be determined for 700 (3.6 percent) of the 19,586 women. Data for these 700 women were compared to data on the computerized California state death certificate files for 1976–82 and the National Death Index for 1979–83 but no positive matches with an accompanying death certificate were located. Thus, these 700 women were treated as "alive" in the data analyses.

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*Dr. Phillips, Professor of Epidemiology at Loma Linda University, died March 8, 1987.

Editor's Note: See related editorial p 687 this issue.

Statistical Analyses

Prior to analyses, age at menopause was categorized into five groups (i.e., less than 40 years, 40 to 44, 45 to 49, 50 to 54, and 55 to 64) with those having menopause at ages 50 to 54 as the reference category (for all odds ratios). Age-specific odds ratios and their confidence intervals were estimated by methods described by Mantel and Haenszel.[21] Age-adjusted odds ratios and their precision-based confidence intervals were estimated by methods for stratified data described by Woolf and Haldane.[22,23] Odds ratios adjusted for other variables were estimated by a maximum likelihood logistic regression model.[24]

Results

Age at Natural Menopause

These analyses were based on 5,287 naturally-postmenopausal women who were 55 to 100 years of age at the start of the study in 1976. The mean age at natural menopause in these women was 49.21 (SE = 9.70); mode = 50, median = 50, 25th percentile = 46, and 75th percentile = 52.

Of these 5,287 women, 772 died during the study (i.e., 1976–82), 4,356 survived to the end of the study, and 159 were presumed to be alive at the end of the study (i.e., we lost contact with these subjects sometime during the study). However, there was no difference in the age at natural menopause between the 4,356 women known to have survived and the 159 presumed to have survived to the end of the study. Age-specific Spearman rank correlations ranged from −0.01 to 0.07 for the association between age at natural menopause and "living status" (i.e., 0 = presumed alive; 1 = known alive).

Age-specific results (Table 1) indicated that the odds ratio of death decreased with increasing age at natural menopause until age 55. This negative association between age at natural menopause and death was evident within each age group except women 85 years of age and older in 1976. Other age-specific results (Figure 1) also indicated similar negative associations between age at natural menopause and the probability of death (denominator based on counts of people) and the rate of death (denominator based on person-years of observation). Because of these findings, all other analyses were limited to odds ratios (based on counts of people).

To control for potential confounders, logistic regression analyses were done using four models which adjusted for (I)

TABLE 1—Age at Natural Menopause and the Age-specific and Age-adjusted Odds Ratios of Death in 5,287 California Seventh-day Adventists, 1976–82

Age in 1976	Age at Natural Menopause (years)	Odds Ratio of Death[a] (95% CI)	Number At-Risk (1976)	Number Deaths (1976–82)	Number Person-Years[b] (1976–82)
55–64	<40	2.03 (0.46, 8.91)	31	2	195
	40–44	1.55 (0.70, 3.45)	160	8	1006
	45–49	1.50 (0.86, 2.59)	497	24	3126
	50–54	1.00	914	30	5749
	55+	1.57 (0.85, 2.92)	316	16	1988
		trend p = 0.51[p = 0.10][c]			
65–74	<40	2.54 (1.21, 5.30)	48	10	302
	40–44	1.55 (0.96, 2.50)	188	26	1183
	45–49	1.00 (0.68, 1.45)	534	50	3359
	50–54	1.00	777	73	4887
	55+	0.81 (0.49, 1.34)	283	22	1780
		trend p = 0.006[p = 0.01]			
75–84	<40	1.67 (0.75, 3.71)	28	10	176
	40–44	1.26 (0.83, 1.91)	139	41	874
	45–49	1.05 (0.77, 1.44)	373	97	2346
	50–54	1.00	476	119	2994
	55+	0.91 (0.58, 1.44)	129	30	811
		trend p = 0.11[p = 0.16]			
85+	<40	1.52 (0.57, 4.07)	19	12	120
	40–44	1.33 (0.69, 2.55)	50	30	315
	45–49	0.76 (0.47, 1.22)	128	59	805
	50–54	1.00	147	78	925
	55+	2.06 (1.04, 4.10)	50	35	315
		trend p = 0.45[p = 0.41]			
Age-Adjusted[d] (Ages 55+)	<40	1.95 (1.24, 3.07)	126	34	793
	40–44	1.39 (1.06, 1.81)	537	105	3378
	45–49	1.03 (0.84, 1.25)	1532	230	9636
	50–54	1.00	2314	300	14555
	55+	1.11 (0.85, 1.46)	778	103	4894
		trend p = 0.02[p = 0.002]			

[a]The reference category for the odds ratio was the group of women that became naturally-postmenopausal at ages 50 to 54.
[b]Women who survived to the end of the study had 6.29 person-years of observation (i.e., the years that elapsed between the beginning of the study on September 15, 1976 and the end of the study on December 31, 1982). For women who died during the study, person-years corresponded to the years that elapsed between the beginning of the study and the date of death.
[c]Trend p refers to the two-tailed p-value for the test of the linear trend in odds ratios across all "age at menopause" groups. The value in brackets refers to the trend p-value across all "age at menopause" groups except the "55+ age at menopause" group.
[d]Age-adjusted by stratification.

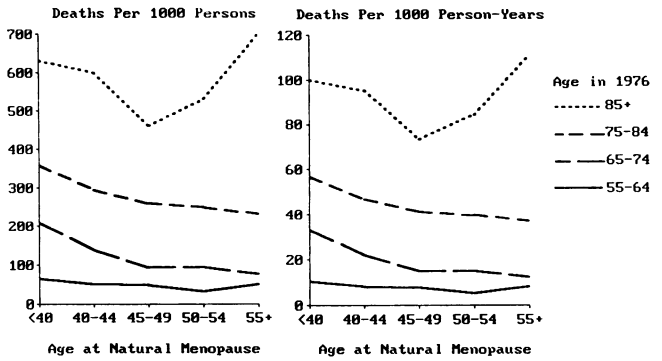

FIGURE 1—Age at Natural Menopause and the Probability and Rate of Death for 5,287 California Seventh-day Adventists, 1976–82

age in 1976, (II) age in 1976 and lifestyle-related factors (III) age in 1976, lifestyle-related factors, and reproductive-related factors, and (IV) age in 1976, lifestyle- and reproductive-related factors, and replacement estrogen use. Variables included in these models and our method of coding are described in the Appendix. Odds ratios of death for different age at natural menopause groups were essentially identical when these four types of analyses were done separately (Table 2). Since the type of model used in the regression analyses did not materially affect these and other odds ratios, all subsequent multivariate-adjusted findings refer to the results from Model IV. Model IV results indicated that women with natural menopause before age 40 had a multivariate-adjusted odds ratio of death of 3.03 (95% CI = 1.62, 5.65), compared to women with natural menopause at ages 50 to 54. The odds ratio of death also decreased in a stepwise fashion with increasing age at natural menopause until age 55.

These odds ratios (Table 2) were larger than those from the age-adjusted stratified analyses (Table 1) because the regression was limited to 3,334 women who had known values for all the variables included in the logistic model rather than the 5,287 women who only had known values for age in 1976 and menopausal status. This increase in the odds ratios appeared to be due, in part, to a selective loss of older subjects: 74 percent (1415/1918) of the 55 to 64 year-old age group were in both analyses, compared to 60 percent (1096/1830) in the 65 to 74 year-old age group, 52 percent (596/1145) in the 75 to 84 year-old age group, and 58 percent (227/394) in the group that was 85 years of age and older. Within each of these age groups, however, women with natural menopause before age 40 had the highest multivariate-adjusted odds ratio of death (ranging from 1.56 among women who were 75 to 84 years of age in 1976 to 8.49 among women who were 85 years of age and older).

In separate analyses to estimate possible effects of replacement estrogens, the odds ratio of death for women who were naturally-postmenopausal before age 40 was 3.33 (95% CI = 1.14, 9.72) within the group that ever used replacement estrogens and 2.91 (95% CI = 1.33, 6.36) within the group that never used replacement estrogens (compared to the reference group who were naturally-postmenopausal at age 50 to 54). Among all naturally-postmenopausal women, the multivariate-adjusted odds ratio of death was 1.13 (95% CI = 0.88, 1.45) for those who ever used replacement estrogens compared to those who never used replacement

TABLE 2—Age at Natural Menopause and the Age-adjusted and Multivariate-adjusted Odds Ratio of Death in 3,334 California Seventh-day Adventists, 1976–82[a]

Model	Factors Adjusted for in Logistic Regression Analyses	Age at Natural Menopause (years)	Multivariate-Adjusted Odds Ratio of Death (95% CI)
I	Age in 1976[b]	<40	3.06 (1.67, 5.62)
		40–44	1.54 (1.06, 2.23)
		45–49	1.10 (0.83, 1.44)
		50–54	1.00
		55+	1.41 (1.00, 1.97)
II	Age in 1976; Lifestyle Factors[c]	<40	2.97 (1.60, 5.50)
		40–44	1.50 (1.04, 2.18)
		45–49	1.07 (0.81, 1.41)
		50–54	1.00
		55+	1.42 (1.01, 2.01)
III	Age in 1976; Lifestyle Factors; Reproductive Factors[c]	<40	3.02 (1.62, 5.62)
		40–44	1.51 (1.04, 2.19)
		45–49	1.07 (0.81, 1.42)
		50–54	1.00
		55+	1.41 (1.00, 1.99)
IV	Age in 1976; Lifestyle Factors; Reproductive Factors; Replacement Estrogens	<40	3.03 (1.62, 5.65)
		40–44	1.51 (1.04, 2.20)
		45–49	1.07 (0.81, 1.42)
		50–54	1.00
		55+	1.40 (0.99, 1.97)

[a]There were 5,287 women with known responses to the menstrual-related questions on the questionnaire. Of these women, 3,334 had known responses to all the lifestyle- and reproductive-related variables included in the multivariate-adjusted analyses (i.e., logistic regression).

[b]For the 3,334 women (known for all the variables included in the multivariate analyses), the age-adjusted (by stratification) odds ratio of death was 3.34 (95% CI = 1.79, 6.21) for natural menopause before age 40, 1.58 (95% CI = 1.08, 2.30) for menopause at ages 40 to 44, 1.12 (95% CI = 0.86, 1.47) for menopause at ages 45 to 49, 1.00 for menopause at ages 50 to 54, and 1.41 (95% CI = 0.99, 2.02) for natural menopause at ages 55 and older.

[c]Lifestyle and reproductive variables are described in the Appendix.

estrogens. Within each age at natural menopause group, ever use of replacement estrogens was associated with only a slight elevation of the odds ratio. Thus, replacement estrogen use did not weaken the association between age at natural menopause and mortality.

Age-adjusted and multivariate-adjusted cause-specific analyses were done in order to determine which of the major causes of death might be responsible for the relationship between age at natural menopause and all-cause mortality (e.g., the multivariate-adjusted analyses on heart disease had the dependent variable equal to "1" if the person died of coronary heart disease and "0" if the person was alive at the end of the study or died of some other cause). Coronary heart disease and stroke mortality each had elevated age- and multivariate-adjusted odds ratios associated with early natural menopause, while the multivariate-adjusted odds of cancer mortality was slightly lower in women with early natural menopause (Tables 3 and 4). Early natural menopause was associated with an excess mortality due to all other causes of death combined. Separate analyses on injuries and other specific causes of death were not performed because there were not enough deaths due to these causes.

Age at Surgical Menopause

Age at surgical menopause was weakly and inconsistently positively associated with all-cause mortality in the age-adjusted analysis on 3,166 women, and the multivariate-adjusted analyses on 2,096 women (who had known responses to all the variables included in the multivariate analyses). The multivariate-adjusted odds ratio of death was 0.75 (95% CI = 0.47, 1.20) in women who were surgically-postmenopausal before age 40, 0.84 (95% CI = 0.52, 1.35) in those surgically-postmenopausal at ages 40 to 44, 0.77 (95% CI = 0.47, 1.28) in those postmenopausal at ages 45 to 49, and 0.89 (95% CI = 0.32, 2.43) in those postmenopausal at age 55 and older, when compared to those surgically-postmenopausal at ages 50 to 54. Age at surgical menopause was unrelated to mortality due to coronary heart disease, stroke, cancer, and all other causes combined.

Replacement estrogen use was associated with a slight decrease in the risk of all-cause mortality in the surgically-postmenopausal women. Among all surgically-postmenopausal women, the multivariate-adjusted odds ratio of death was 0.80 (95% CI = 0.56, 1.14) for those who ever used replacement estrogens compared to those who never used replacement estrogens. These odds ratios for ever use of replacement estrogens were lowest among women with early surgical menopause. For example, within the group that were surgically-postmenopausal before age 40, the multivariate-adjusted odds ratio of death for ever use of replacement estrogens was 0.57 (95% CI = 0.29, 1.10), compared to never use of replacement estrogens.

Discussion

Findings from this study suggest that early age at natural menopause is associated with a substantial excess mortality. In addition, women who report natural menopause at ages 55

TABLE 3—Age at Natural Menopause and the Age-adjusted Odds Ratio of Death due to Selected Causes in 5,287 California Seventh-day Adventists, 1976–82[a]

Cause of Death[b]	Age at Natural Menopause (years)	Age-Adjusted Odds Ratio of Death[c] (95% CI)	Number of Deaths
Coronary Heart Disease	<40	1.29 (0.61, 2.74)	8
	40–44	1.43 (0.95, 2.16)	36
	45–49	1.06 (0.76, 1.46)	74
	50–54	1.00	91
	55+	1.17 (0.76, 1.81)	33
		trend p = 0.42[p = 0.18][d]	
Stroke	<40	3.07 (1.34, 7.03)	8
	40–44	1.39 (0.76, 2.53)	16
	45–49	0.92 (0.56, 1.51)	30
	50–54	1.00	41
	55+	1.32 (0.72, 2.44)	16
		trend p = 0.27[p = 0.06]	
Cancer	<40	1.83 (0.73, 4.59)	4
	40–44	1.20 (0.71, 2.05)	19
	45–49	1.09 (0.74, 1.60)	50
	50–54	1.00	66
	55+	1.07 (0.66, 1.74)	23
		trend p = 0.67[p = 0.60]	
All Other Causes of Death	<40	2.14 (1.15, 3.99)	14
	40–44	1.22 (0.81, 1.84)	34
	45–49	0.99 (0.72, 1.36)	76
	50–54	1.00	102
	55+	0.97 (0.63, 1.50)	31
		trend p = 0.08[p = 0.07]	

[a]See Table 2 for explanation.
[b]Cause of death is the underlying cause of death from the death certificate that was coded by the California State nosologist. Cause-of-death codes from the International Classification of Disease, version nine, were used to classify deaths by major cause; coronary heart disease = codes 410–414, stroke = 430–438, cancer = 140–239, and all other causes of death combined = all other codes.
[c]All results in this table have been age-adjusted by stratification. The reference category for the odds ratio was the group of women that became naturally-postmenopausal at ages 50 to 54.
[d]See footnote "c" in Table 1.

TABLE 4—Age at Natural Menopause and the Multivariate-adjusted Odds Ratio of Death due to Selected Causes in 3,334 California Seventh-day Adventists, 1976–82[a]

Cause of Death[b]	Age at Natural Menopause (years)	Multivariate-Adjusted[c] Odds Ratio of Death (95% CI)
Coronary Heart Disease	<40	1.59 (0.58, 4.40)
	40–44	1.68 (0.96, 2.94)
	45–49	1.02 (0.65, 1.60)
	50–54	1.00
	55+	1.17 (0.67, 2.06)
Stroke	<40	1.87 (0.51, 6.92)
	40–44	1.41 (0.65, 3.07)
	45–49	0.79 (0.42, 1.50)
	50–54	1.00
	55+	1.09 (0.47, 2.50)
Cancer	<40	0.93 (0.22, 4.01)
	40–44	0.83 (0.37, 1.89)
	45–49	1.18 (0.72, 1.94)
	50–54	1.00
	55+	1.35 (0.75, 2.45)
All Other Causes	<40	4.58 (2.10, 9.99)
	40–44	1.56 (0.87, 2.80)
	45–49	1.14 (0.73, 1.79)
	50–54	1.00
	55+	1.43 (0.83, 2.48)

[a]See Table 2 for explanation.
[b]See Table 3 for explanation.
[c]These logistic regression analyses adjusted for age in 1976, replacement estrogen use, and the lifestyle- and reproductive-related variables described in the Appendix.

and older may have a slightly higher risk of death than women with natural menopause at ages 50 to 54. While we have no data to test the hypothesis directly, some of the women who reported menstrual periods at such a late age may have mistaken disease-related vaginal or uterine bleeding for normal menstrual bleeding. If this occurred, it could explain the slightly higher risk of death in these women.

Our study used self-reports of type of menopause and age at menopause from a mailed questionnaire. No studies have investigated the validity of self-reported age at natural menopause. However, a study of 6,591, 30- to 55-year-old nurses found that for questionnaires mailed two years apart, 95 percent of the surgically-postmenopausal women and 82 percent of the naturally-postmenopausal women reported their age at menopause within one year on both questionnaires.[25]

The possibility that our findings were due to confounding by potential correlates of age at menopause was investigated by logistic regression analyses. Controlling for self-reported cigarette smoking, over- and underweight, reproductive history, and replacement estrogen use did not materially alter our findings. Moreover, cigarette smoking is not an important issue in this study population because at the beginning of our study only 1.5 percent of the women were current smokers and 13.2 percent former smokers.

While our findings seem solid, it would be reassuring to find evidence of these associations in other populations. Other studies have investigated only the relationships between age at menopause and the risk of specific diseases. Age at natural or surgical menopause was positively associated with the risk of breast cancer in several studies.[26] Age at menopause (both surgical and natural combined), however, has been negatively associated with osteoporosis.[27,28] Results from two small Swedish studies also suggest that age at menopause is negatively associated with the risk of developing myocardial infarction.[29,30] Among 45- to 54-year-old women in the Framingham Study, naturally- and surgically-postmenopausal women both had 2.7 times the incidence of coronary heart disease (including angina pectoris) compared to pre-menopausal women of the same age.[31]

We found no evidence that estrogen depletion was related to mortality. Replacement estrogen use was not associated with a reduction in mortality in women with early or late age at natural menopause. In spite of the "estrogen depletion" in the group of surgically-postmenopausal women in our study, age at menopause was unrelated to mortality in these women.

Premature natural menopause may be related to mortality because of aging-related physiologic processes that are associated with early natural menopause. The function of the ovaries throughout life and the start and permanent cessation of menstruation are highly dependent on age. The average number of ovarian germ cells or oocytes present in human females appears to be greatest around the fifth or sixth month of fetal development.[32] Thereafter, the number of surviving oocytes regularly declines pre- and post-natally until menopause is apparently precipitated by an insufficient number of surviving oocytes and follicles.[14] This involution of the ovaries would appear to be a natural consequence of aging (as opposed to disease), particularly since the average age at menopause appears to have been remarkably consistent in western countries throughout the last three decades.[33]

Ovarian aging, as reflected by age at natural menopause, may be highly correlated to the aging of other tissues and to the mortality produced by aging (i.e., the increase in mortality with age that would probably inevitably occur even in the absence of disease). Further investigation is needed to pinpoint whether age at natural menopause is only related to a few diseases, or whether it is a marker of multiple aspects of health and aging.

APPENDIX

Variables from the Lifestyle Questionnaire

The Lifestyle Questionnaire contained questions on food and beverage consumption, physical activity, smoking, occupation, psychosocial characteristics, and medical history. The questionnaire also contained questions on whether the subject's menstrual periods had permanently stopped, why they stopped, and the age of the subject when they stopped. Each participant's responses to six questions on the Lifestyle Questionnaire also were used to create a summary index of participation in church activities (e.g., attending church services, holding church office, and attending church social events). Variables used in the regression models (and our method of coding) are described below:

Age in 1976

1. chronologic age (as one continuous term).

Lifestyle Factors

1. cigarette smoking status in 1976 (as a dummy, binary, term indicating whether they currently smoked),
2. pack-years of cigarettes smoked in the past (as one continuous term),
3. Quetelets Index (using dummy terms for each of the top three quartiles of the "weight in kilograms/height in meters squared" distribution with the bottom quartile as the reference),
4. education (as one ordinal term),
5. marital status (as one binary term indicated whether the women had ever married),
6. age at joining the Adventist Church (as one ordinal term), and

7. index of participation in church activities (as one ordinal term).

Reproductive Factors

1. age at first live birth (using dummy terms for less than 25 years of age, 25 to 30, and 31 or older, with the group of women with no live births serving as the reference),
2. number of live births (as one continuous term),
3. combined number of miscarriages and stillbirths (as one continuous term),
4. age at menopause (using dummy terms for less than 40 years of age, 40 to 44, 45 to 49, and 55 and older, with the group of women with menopause at ages 50 to 54 serving as the reference).

Replacement Estrogens

1. replacement estrogen use (as a binary term indicating whether the subject had ever or never used replacement estrogens).

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