

# Age at Natural Menopause and Risk of Cardiovascular Disease

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**Background:** Early natural menopause has been postulated to increase the risk of cardiovascular disease.

**Objective:** To examine the relation of age at natural menopause with risk of coronary heart disease (CHD) and stroke in the Nurses' Health Study.

**Methods:** Analysis was restricted to 35 616 naturally postmenopausal women who never used estrogen replacement therapy and with no diagnosed cardiovascular disease at baseline, followed up from 1976 to 1994. Information on menopausal status, age at menopause, and other risk factors was obtained in 1976 and updated every 2 years by mailed questionnaires.

**Results:** During 354 326 person-years of follow-up, we documented 757 incident cases of CHD and 350 incident cases of stroke. After adjusting for age, smoking status, and other cardiovascular risk factors, the relative risks (RRs) across categories of age at natural menopause (<40, 40-44, 45-49, 50-54, and  $\geq 55$  years) were 1.53, 1.42, 1.10, 1.00 (reference), and 0.95, respectively; the RR for each

1-year decrease in age at natural menopause was 1.03 (95% confidence interval, 1.01-1.05). Elevated risk with younger age at menopause was observed among current smokers (RR, 1.04 [95% CI, 1.01-1.07] for each 1-year decrease in age at natural menopause) but not among never smokers (RR, 1.00; 95% CI, 0.96-1.04). Age at natural menopause was not significantly associated with ischemic stroke (RR, 1.01; 95% CI, 0.97-1.04) or hemorrhagic stroke (RR, 1.03; 95% CI, 0.97-1.10).

**Conclusions:** We observed an overall significant association between younger age at menopause and higher risk of CHD among women who experienced natural menopause and never used hormone therapy. This increased risk was observed among current smokers but not among never smokers. The apparent elevated risk of CHD with decreased age at natural menopause among smokers might reflect residual confounding by smoking.

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**E**XOGENOUS estrogen use among postmenopausal women has consistently been associated with reduced risk of coronary heart disease (CHD),<sup>1</sup> and surgical menopause in young women approximately doubles the risk of CHD if exogenous hormones are not taken.<sup>2</sup> These observations suggest that early natural menopause might also increase CHD risk; however, few epidemiological studies have examined the relation of a broad range of ages at menopause with risk of cardiovascular disease. van der Schouw et al<sup>3</sup> found a nonsignificant decreased risk of cardiovascular mortality among women with later age at natural menopause. Results of 2 other relatively small studies<sup>4,5</sup> show a nonsignificant increase in risk of coronary death among women who had natural menopause before age 40 years. One limitation

of these studies is that none examined the association among never smokers. Because smoking is a strong risk factor for early menopause<sup>6</sup> and a strong independent risk factor for CHD, it may be such an important confounder that the issue may be best addressed among never smokers. In addition, few studies have adequately controlled for age. Rates of CHD approximately double between the ages of 50 and 55 years, and because age is so closely linked to menopause, adjustment by 5-year age categories—as done in some studies—may not adequately control for age.

The present study, with 18 years of follow-up, examines the relation of a broad range of ages at natural menopause with incidence of CHD and stroke, stratified by smoking status; this extends the previous report<sup>2</sup> on menopausal status and risk of CHD by 12 years of follow-up.

## PARTICIPANTS AND METHODS

### PARTICIPANTS

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses aged 30 to 55 years completed a mailed questionnaire about their medical history and lifestyle. Every 2 years, follow-up questionnaires are sent to obtain updated information on risk factors and to identify newly diagnosed diseases. We restricted our analyses to women who experienced natural menopause because conditions that lead to other types (eg, radiotherapy, surgery, and chemotherapy) may be associated with cardiovascular disease risk. We also restricted our analyses to women who never used postmenopausal hormones because use during the perimenopausal interval may artificially prolong cyclic menstrual bleeding and thus make it difficult to accurately assess the age at menopause.<sup>7</sup> We excluded women who reported having a diagnosis of CHD at baseline. Our final population (including women at baseline and those who later became menopausal) for analysis included 35 616 women who underwent natural menopause and never received hormone therapy.

### ASSESSMENT OF AGE AT NATURAL MENOPAUSE AND COVARIATES

On the 1976 and subsequent questionnaires, menopausal status was determined by asking whether the participants' menstrual periods had ceased permanently and, if so, at what age and for what reason (occurring naturally or after radiation treatment or surgery). Self-reported menopause status and age at menopause were highly reproducible in our cohort. In a validation study in a subsample of the Nurses' Health Study participants,<sup>8</sup> 82% of naturally postmenopausal women reported the same age at menopause (within 1 year) on 2 questionnaires mailed 2 years apart.

Information on other potential CHD risk factors, including participants' age; smoking status (never, past, number of cigarettes smoked currently); weight; use of postmenopausal hormones; and history of diabetes, hypertension, or hypercholesterolemia was assessed at baseline and updated every 2 years. Height, parental history of myocardial infarction (MI) before age 60 years, and age at menarche were assessed at baseline.

### ASCERTAINMENT OF END POINTS

The primary end points for this study were incident CHD (defined as nonfatal MI or fatal CHD) and stroke that occurred after the return of the 1976 questionnaire but before June 1, 1994. We requested permission to review medical records from women who reported having a nonfatal MI or stroke on a follow-up questionnaire. Study physicians with no knowledge of risk factor status reviewed the medical records. Nonfatal MI was confirmed if it met the criteria of the World Health Organization for symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzyme levels.<sup>9</sup> Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable (17%). We included all confirmed and probable cases in the analyses because, after excluding probable cases, results were

virtually the same. Stroke was confirmed by medical records according to the criteria of the National Survey of Stroke<sup>10</sup> and required a constellation of neurologic deficits, sudden or rapid in onset, lasting 24 hours or longer; strokes were further subclassified as hemorrhagic (subarachnoid or intraparenchymal), ischemic (thrombotic or embolic), or of unknown cause.

Deaths were reported by next of kin and the postal system or were ascertained through the National Death Index. Using all sources combined, we estimate that follow-up for the deaths was more than 98% complete.<sup>11</sup> Fatal CHD was confirmed by hospital records or autopsy results or by having CHD listed as the cause of death on the death certificate and evidence of previous CHD available. We designated as presumed CHD those cases in which CHD was the underlying cause on the death certificate but for which no records were available. Such cases constituted 14.7% of all fatal CHD cases. Analyses limited to confirmed cases yielded similar results, although with less precision. We also included sudden death within 1 hour of onset of symptoms in women with no other plausible cause (other than coronary disease) (12.3% of fatal CHD). Fatal strokes were coded using the same criteria as nonfatal cases, but we accepted autopsy evidence and the death certificate listing of cause.

### STATISTICAL ANALYSIS

Menopausal status was updated every 2 years. Once a participant was classified as postmenopausal, her age at natural menopause was determined and her status was not subsequently changed. Based on previous studies in the literature,<sup>4</sup> we categorized age at menopause into 5 groups (ie, <40, 40-44, 45-49, 50-54, and  $\geq 55$  years). For each eligible participant (ie, naturally menopausal women who never used hormone therapy), person-months were allocated according to the categories of age at natural menopause defined on the earliest questionnaire after menopause occurred; months of follow-up were calculated as the interval between the return of the last questionnaire and the end point, death, or June 1, 1994.

Person-time for each exposure category was accumulated, and incidence rates were calculated by dividing the number of events by person-time of follow-up in each category. Relative risk (RR) was computed as the rate in a specific category of age at menopause divided by that in the reference category (50-54 years old), with adjustment for age in single years to avoid any residual confounding by age. In multivariate analyses, we simultaneously included age (continuous), age at menarche (<13, 13, or >13 years), parity (nulliparous or 1-2, 3-4, or  $\geq 5$  children), smoking status (never, past, or current smoking of 1-14, 15-24, or  $\geq 25$  cigarettes per day), parental history of premature MI before age 60 years, history of diabetes, history of hypertension, and history of hypercholesterolemia in a pooled logistic regression.<sup>12</sup> As in previous studies,<sup>3</sup> we also considered age at natural menopause as a continuous variable in the logistic models and estimated the RR of CHD or stroke for each 1-year decrease in age at natural menopause. To address potential residual confounding by smoking, we conducted separate analyses according to smoking status (never, past, and current smokers). We also conducted separate analyses for past smokers who had quit smoking in the past 10 years and those who had quit smoking more than 10 years earlier.

**Table 1. Relative Risks (RRs) and 95% Confidence Intervals (CIs) of Coronary Heart Disease According to Age at Natural Menopause Among Women Who Never Used Postmenopausal Hormones: the Nurses' Health Study, 1976-1994\***

	Age at Natural Menopause, y					RR†
	<40	40-44	45-49	50-54	≥55	
<b>All women</b>						
Cases, No.‡	18	67	261	375	36	...
Person-years	6320	25 830	123 997	179 893	18 286	...
Incidence rate per 100 000 person-years	285 (153-416)	259 (197-321)	211 (185-236)	208 (187-230)	197 (132-261)	...
Age-adjusted RR	1.95 (1.21-3.13)	1.67 (1.28-2.17)	1.23 (1.05-1.44)	1.0 (ref)	0.82 (0.58-1.15)	1.05 (1.04-1.07)
Age- and smoking-adjusted RR	1.66 (1.03-2.68)	1.36 (1.05-1.78)	1.06 (0.90-1.25)	1.0	0.93 (0.66-1.31)	1.03 (1.01-1.05)
Multivariate RR§	1.53 (0.94-2.47)	1.42 (1.08-1.86)	1.10 (0.93-1.29)	1.0	0.95 (0.67-1.34)	1.03 (1.01-1.05)
<b>Never smokers</b>						
Cases, No.	2	7	50	105	19	...
Person-years	2172	8321	45 018	81 347	9855	...
Incidence rate per 100 000 person-years	92 (0-220)	84 (22-146)	111 (80-142)	129 (104-154)	193 (106-279)	...
Age-adjusted RR	1.07 (0.26-4.34)	0.94 (0.44-2.03)	1.11 (0.79-1.56)	1.0	1.23 (0.75-2.01)	1.00 (0.96-1.04)
Multivariate RR	0.92 (0.22-3.79)	1.08 (0.50-2.35)	1.12 (0.79-1.59)	1.0	1.33 (0.81-2.18)	1.00 (0.96-1.04)
<b>Past smokers</b>						
Cases, No.	4	17	54	104	8	...
Person-years	1790	7093	36 421	57 949	6158	...
Incidence rate per 100 000 person-years	223 (4-442)	240 (126-354)	148 (109-188)	179 (145-214)	130 (40-220)	...
Age-adjusted RR	1.74 (0.64-4.74)	1.77 (1.05-2.96)	1.02 (0.74-1.43)	1.0	0.61 (0.30-1.26)	1.06 (1.02-1.09)
Multivariate RR	1.23 (0.45-3.41)	1.79 (1.06-3.01)	1.02 (0.73-1.43)	1.0	0.64 (0.31-1.33)	1.05 (1.01-1.09)
<b>Current smokers  </b>						
Cases, No.	12	43	154	166	9	...
Person-years	2359	10 418	42 551	40 595	2273	...
Incidence rate per 100 000 person-years	509 (221-797)	413 (289-536)	369 (311-427)	409 (347-471)	396 (137-654)	...
Age-adjusted RR	1.72 (0.95-3.11)	1.29 (0.92-1.82)	1.03 (0.82-1.29)	1.0	0.84 (0.42-1.65)	1.03 (1.01-1.06)
Multivariate RR	1.76 (0.97-3.22)	1.36 (0.96-1.92)	1.08 (0.86-1.36)	1.0	0.80 (0.40-1.57)	1.04 (1.01-1.07)

\*95% CIs are given in parentheses; ellipses indicate data not applicable.

†For each 1-y decrease in age at natural menopause.

‡The number of cases in the smoking categories do not add up to the total number of cases because of missing smoking status for some participants.

§Adjusted for time periods; age (continuous); body mass index (quintiles); parental history of myocardial infarction; history of high blood pressure, hypercholesterolemia, or diabetes; smoking (never, past, or current 1-14, 15-24, or ≥25 cigarettes/day); and parity (null or 1-2, 3-4, or ≥5 children).

||Also adjusted for current smoking categories (1-14, 15-24, and ≥25 cigarettes/day).

## RESULTS

During 354 326 person-years of follow-up, we documented 757 incident cases of CHD (270 fatal CHD and 487 nonfatal MI cases) and 350 incident cases of stroke (205 cases of ischemic stroke, 77 cases of hemorrhagic stroke, and 68 cases of unclassified type).

Median age at natural menopause for the population was 50 years, and 65% of the women had natural menopause between ages 48 and 53 years. When stratified by cigarette smoking, median age at natural menopause was 50 years for past smokers, 49 years for current smokers, and 51 years for never smokers. Obese women (body mass index ≥29, calculated as weight in kilograms divided by the square of the height in meters) tended to have a later menopause (median, 51 years) than nonobese women (median, 50 years). Age at natural menopause did not vary with parity, age at menarche, past oral contraceptive use, or family history of MI. Women with diabetes, hypercholesterolemia, and hypertension tended to have a later menopause (median, 51 years for each), probably because of the associations between these conditions and obesity. The results remained unchanged when we restricted these analyses to women who were 65 years or older in the beginning of the last period

(1992) to avoid the potential bias caused by truncated age distribution.

After adjustment for age, there was a trend toward increased risk of CHD with decreasing age at natural menopause (**Table 1**). Age-adjusted RRs across categories of age at menopause (<40, 40-44, 45-49, 50-54, and ≥55 years) were 1.95, 1.67, 1.23, 1.00 (reference), and 0.82, respectively. The RR for each 1-year decrease in age at menopause was 1.05 (95% confidence interval [CI], 1.04-1.07). Adjustment for smoking somewhat attenuated the RRs (RR, 1.66 for age at menopause <40 years and RR, 1.03 [95% CI, 1.01-1.05] for each 1-year decrease in age at menopause). Additional adjustment for other covariates, including body mass index; parental history of MI; history of diabetes, hypercholesterolemia, and hypertension; parity; age at menarche; and past oral contraceptive use did not substantially change the results. Because relatively few CHD cases (n = 18) occurred in the lowest category of age at menopause (<40 years), we conducted additional analyses using an alternative categorization of the exposure variable (<45, 45-48, 49-51, 52-54, and ≥55 years); the results remained essentially unchanged (data not shown).

Because cigarette smoking is a powerful CHD risk factor and is strongly related to age at menopause, we

**Table 2. Relative Risks (RRs) and 95% Confidence Intervals (CIs) of Stroke According to Age at Natural Menopause Among Women Who Never Used Postmenopausal Hormones: the Nurses' Health Study, 1976-1994\***

	Age at Natural Menopause, y					RR†
	<40	40-44	45-49	50-54	≥55	
<b>Total stroke‡</b>						
Cases, No.	4	21	124	182	19	...
Person-years	6348	26217	125615	182125	18449	...
Incidence rate per 100 000 person-years	63 (1-125)	80 (46-114)	99 (81-116)	100 (85-114)	103 (57-149)	...
Age-adjusted RR	0.90 (0.33-2.44)	1.11 (0.70-1.75)	1.23 (0.98-1.55)	1.0	0.88 (0.55-1.41)	1.03 (1.00-1.05)
Multivariate RR§	0.74 (0.27-2.00)	0.95 (0.60-1.51)	1.13 (0.89-1.43)	1.0	0.98 (0.61-1.58)	1.01 (0.98-1.04)
<b>Ischemic stroke</b>						
Cases, No.	0	12	71	114	8	...
Incidence rate per 100 000 person-years	37 (16-58)	57 (43-70)	63 (51-74)	43 (13-73)	...	...
Age-adjusted RR	0.86 (0.48-1.57)	1.18 (0.87-1.59)	1.0	0.56 (0.27-1.15)	1.02 (0.98-1.06)	...
Multivariate RR	0.76 (0.42-1.39)	1.10 (0.81-1.49)	1.0	0.62 (0.30-1.28)	1.01 (0.97-1.04)	...
<b>Hemorrhagic stroke</b>						
Cases, No.	1	7	29	33	7	...
Incidence rate per 100 000 person-years	25 (8-42)	23 (15-31)	18 (12-24)	38 (10-66)	...	...
Age-adjusted RR	1.66 (0.76-3.64)	1.44 (0.87-2.40)	1.0	1.98 (0.87-4.50)	1.04 (0.99-1.10)	...
Multivariate RR	1.50 (0.68-3.33)	1.33 (0.80-2.23)	1.0	2.17 (0.95-4.96)	1.03 (0.97-1.10)	...

\*95% CIs are given in parentheses; ellipses indicate data not applicable.

†For each 1-y decrease in age at natural menopause.

‡Strokes of unclassified type (68 cases) were included in total stroke but not analyzed separately.

§Adjusting for the same variables in Table 1.

were concerned about potential residual confounding by smoking; therefore, we conducted separate analyses according to smoking status (Table 1). Multivariate RR for each 1-year decrease in age at menopause was 1.04 (95% CI, 1.01-1.07) for current smokers, 1.05 for past smokers (95% CI, 1.01-1.09), and 1.00 among never smokers (95% CI, 0.96-1.04). There was no evidence that these associations differed substantially for fatal and nonfatal diseases; among never smokers, the multivariate RR of fatal CHD for each 1-year decrease in age at menopause was 1.01 (95% CI, 0.96-1.06); the RR of nonfatal MI was 0.99 (95% CI, 0.92-1.06).

Among past smokers, time since quitting may further confound the association between age at natural menopause and coronary risk. Therefore, we examined the association separately among women who had quit smoking in the past 10 years and those who had quit more than 10 years earlier. Elevation in coronary risk with earlier age at menopause among past smokers was limited to women who recently stopped smoking (multivariate RR, 1.07 [95% CI, 1.03-1.10] for each 1-year decrease in age at menopause). Risk did not seem to increase among women who had quit smoking more than 10 years earlier (multivariate RR, 1.00; 95% CI, 0.93-1.07).

Age at natural menopause was not significantly associated with risk of total stroke (Table 2). The multivariate RR for each 1-year decrease in age at menopause was 1.01 (95% CI, 0.98-1.04). For ischemic stroke, there was a suggestion of a nonsignificant decrease in risk among women who had menopause at age 55 years or older (RR, 0.62; 95% CI, 0.30-1.28). However, there were only 8 cases in this category, and the RR for each 1-year decrease in age at menopause was 1.01 (95% CI, 0.97-1.04). For hemorrhagic stroke,

the risk seemed to increase in both lower and higher categories of age at menopause, but the number of cases was small in both groups. The multivariate RR of hemorrhagic stroke for age at menopause in single-year intervals was 1.03 (95% CI, 0.97-1.10).

#### COMMENT

In this prospective cohort study, we observed an overall significant association between younger age at menopause and higher risk of CHD among women who had natural menopause and never used hormone therapy. However, this increased risk was not observed among never or past smokers who had stopped smoking more than 10 years earlier. The apparent elevated risk of CHD with decreased age at natural menopause among current and past smokers who stopped smoking more recently might, therefore, be caused by residual confounding by smoking. In addition, we observed no significant association between age at natural menopause and risk of total, ischemic, or hemorrhagic stroke.

Smoking is a powerful risk factor for CHD; in this study, current smoking decreased the age of natural menopause by about 2 years and past smoking decreased it by 1 year. Thus, incomplete adjustment for smoking might artifactually increase the risk of CHD associated with early age of natural menopause. Therefore, it is critical to examine the association among never smokers. However, we cannot exclude the possibility that the null association of age at menopause with risk of CHD observed among the subgroup of never smokers was caused by chance. Also, because of the small number of cases among nonsmoking women with early menopause, CIs around the RRs were wide, indicating a broad range of possible effects.



The accuracy of self-reported menopausal status and age at menopause may be a potential concern. The prospective design, however, greatly reduced the probability of biased reporting of menopausal status and age at menopause, which can be a serious problem in case-control studies. To further reduce such misclassifications, we excluded women who had used postmenopausal hormone therapy because the use of hormones during the perimenopausal interval may artifactually prolong cyclic menstrual bleeding.<sup>7</sup> To examine the reliability of women's reports of natural menopause, we analyzed the responses of 4265 women who first reported the permanent cessation of menstrual periods in 1978 and compared these responses with those given to the same question on the 1980 follow-up questionnaire. Of these women, 4212 (98.8%) still reported being postmenopausal after an additional 2 years, substantiating the accuracy of their original report.<sup>2</sup> Also, among women who reported undergoing natural menopause between 1976 and 1978, 82% reported their age at menopause to within 1 year on 2 subsequent follow-up questionnaires.<sup>8</sup>

Persuasive evidence demonstrates that bilateral oophorectomy in premenopausal women increases the risk of CHD unless exogenous hormones are given.<sup>2</sup> However, there is no convincing evidence to support the hypothesis that natural menopause itself is a risk factor for CHD. In the Framingham Heart Study,<sup>13</sup> natural menopause was associated with a 4.1-fold increase in the 10-year incidence of CHD compared with rates in premenopausal women aged 50 to 59 years, but no adjustment was made for age or cigarette smoking. In a previous report from the Nurses' Health Study,<sup>2</sup> after adjustment for age in 5-year categories, the rate of CHD was significantly elevated in postmenopausal women, with an RR of 1.7 (95% CI, 1.1-2.8). However, when age was adjusted in single years, the RR reduced to 1.2 (95% CI, 0.8-1.9). Further adjustment for cigarette smoking diminished the RR to 1.0 (95% CI, 0.8-1.3). This demonstrates the need for close control of age and smoking.

Three prospective studies report the relation of age at natural menopause with risk of cardiovascular disease. In a 6-year study of 3334 California Adventists, Snowdon et al<sup>4</sup> found a nonsignificant increased risk of death caused by CHD and stroke among women with earlier natural menopause (RR, 1.59 [95% CI, 0.58-4.40] for CHD and age at menopause <40 years vs 50-54 years, RR, 1.87 [95% CI, 0.51-6.92] for stroke); however, the CI was wide because only 8 CHD cases and 8 stroke cases occurred among women with age at menopause younger than 40 years. In a 4-year follow-up of 3191 women from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study,<sup>5</sup> the RRs of CHD death across categories of age at natural menopause (<40, 40-44, 45-49, and ≥50 years) were 1.50, 0.61, 1.06, and 1.00 (reference), respectively. The corresponding RRs for death from cerebrovascular disease were 0.80, 0.95, 0.18, and 1.00. Both studies<sup>4,5</sup> were limited by small size and short follow-up. Neither study examined the associations by smoking status. The largest previous study was

conducted by van der Schouw et al,<sup>3</sup> who examined the relation of age at menopause with total cardiovascular mortality in a cohort of 12 115 Dutch women with 20 years of follow-up. When naturally and surgically and medically menopausal women were analyzed together, there was a significant increased risk with decreased age at menopause (RR, 1.02 [95% CI, 1.00-1.03] for each 1-year decrease in age at menopause), but this inverse association was not statistically significant among women with natural menopause. The authors found that the inverse association was limited to non-current smokers, but they did not examine the association specifically among never smokers. Taken together, these studies do not provide convincing evidence that early natural menopause increases the risk of cardiovascular disease.

Because exogenous estrogen use is consistently associated with reduced risk of CHD among postmenopausal women,<sup>14</sup> one would suspect that an early natural menopause, which could reduce lifetime exposure to endogenous estrogen, might be associated with an increased risk of CHD. However, natural menopause causes a gradual rather than an abrupt decline in estrogen production.<sup>15</sup> In an autopsy study,<sup>16</sup> the degree of atherosclerosis rose steadily, from about 5% with severe stenosis among 30- to 40-year-old women, to about 60% among those 70 to 80 years old. However, there was no suggestion of a sharp increase to coincide with the average age of menopause. In the general population, the rates of coronary mortality rise sharply with age among men and women. The largest increase in women occurs at about age 50 years—approximately the mean age at menopause. However, if the rates of increase are evaluated on a log scale, the rate of increase is smooth for women<sup>17,18</sup> and without any shift in the rate of increase at time of menopause, as has been observed for breast cancer.<sup>17</sup> Furthermore, the decreasing disparity of coronary mortality rates between men and women at older ages does not seem to be caused by a shift in women's rates at menopause but rather a slowed rate of increase in men.<sup>19</sup>

In summary, we observed an overall significant association between younger age at menopause and higher risk of CHD among women who had natural menopause and never used hormone therapy. However, this increased risk was not observed among never or past smokers who had stopped smoking more than 10 years earlier. The apparent elevated risk of CHD with decreased age at natural menopause among current and past smokers who stopped more recently might reflect residual confounding by smoking.

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