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Heart Disease Risk Determines Menopausal Age Rather Than the Reverse

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OBJECTIVES The purpose of this study was to investigate whether a harmful cardiovascular risk profile accelerates menopause.

BACKGROUND Women with an early menopause are at an increased risk of cardiovascular disease. Although increased cardiovascular risk has been proposed as consequence of menopause, the alternative hypothesis, that increased premenopausal cardiovascular risk promotes early menopause, needs to be examined.

METHODS We used data from the Framingham Heart Study cohort. This study started in 1948 and has followed up participants biennially since then. Women who were premenopausal at study entry and who reached natural menopause after at least two examination rounds were included in the study (n = 695). Premenopausal age-independent levels of serum total cholesterol, relative weight, blood pressure, and Framingham risk score were determined, as well as premenopausal changes in cholesterol, body weight, and blood pressure.

RESULTS A higher premenopausal serum total cholesterol level was statistically significantly associated with an earlier age at menopause, as were increases in total serum cholesterol, relative weight, and blood pressure in the premenopausal period. A decrease in total serum cholesterol during premenopause was statistically significantly associated with later age at menopause. Decreasing blood pressure was associated with a later menopausal age, but this association was not statistically significant. A decrease in relative weight was associated with a significant earlier age at menopause. Each 1% higher premenopausal Framingham risk score was associated with a decrease in menopausal age of 1.8 years (95% confidence interval −2.72 to −0.92).

CONCLUSIONS The findings support the view that heart disease risk determines age at menopause. This offers a novel explanation for the inconsistent findings on cardiovascular disease rate and its relationship to menopausal age and effects of hormone replacement therapy. (J Am Coll Cardiol 2006;47:1976–83) © 2006 by the American College of Cardiology Foundation

Women with an early menopause are at an increased risk of cardiovascular disease (1,2). Cardiovascular risk factor changes occurring with menopause have been considered the biological mechanism (3). There is evidence to show that menopause is accompanied by unfavorable levels of several cardiovascular risk factors (4,5). Deprivation of endogenous estrogen is assumed to be a crucial factor in the explanation of this change to a less favorable risk profile, but conflicting results have been published, leaving the role of (sudden) estrogen deprivation under debate (6,7). Observational studies have consistently reported beneficial effects of estrogen intake after menopause on cardiovascular disease risk (8). However, large-scale primary (Women's Health Initiative) and secondary (Heart and Estrogen-Progestin Replacement Study) prevention trials assessing the effect of hormonal replacement therapy on cardiovascular events could not show a positive effect (9,10). These findings not only cast doubt on the benefits of postmenopausal estrogen repletion therapy, but also question the supposed causality of the association between menopause and increased risk for cardiovascular disease, forcing consideration of other hypotheses.

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Ovaries are highly vascularized organs, and subsequent ischemic damage to the ovaries may induce early menopause. In more general terms, although atherosclerosis progression has been proposed to be a consequence of menopause, the alternative scenario that atherosclerosis promotes early menopause merits further investigation. We set out to investigate the role of premenopausal cardiovascular risk factors on early ovarian failure, characterized by early age at menopause.

METHODS

Study population. The Framingham Heart Study is a long-term prospective study of cardiovascular disease. The sampling procedure, design, and methods of the study have been amply described (11,12). The participants eligible for this study consisted of 2,873 women age 29 to 62 years at the beginning of the study in 1948, and participants have been examined biennially since then.

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Abbreviations and Acronyms
CI = confidence interval
HDL = high-density lipoprotein

To allow investigation of the premenopausal change in the variables, data from at least two examinations are required. Data on menopausal status and type of menopause were first reported in examination 2, and then at each subsequent examination. At each examination, the date of the last menstrual period was recorded. To be classified as having had a natural menopause at a given examination, a woman must have had complete cessation of menses for at least one year before that examination.

Women classified as menopausal at examination 2 (n = 1,653) were excluded because of insufficient premenopausal data on cardiovascular risk factors. Women were excluded from the sample if they experienced an artificial menopause, i.e., surgical, chemical, or radiological (n = 258), or were lost to follow-up before reaching menopause (n = 230). For the remaining women the age at menopause was determined at the time of clinical visits, and an unknown age at menopause resulted in exclusion (n = 37). From examination 2 through 13, a total of 695 (57% of those eligible) women reached natural menopause.

Determinants. Cardiovascular risk factors examined in this study are: 1) premenopausal total serum cholesterol level, 2) premenopausal change in total serum cholesterol, 3) premenopausal relative weight, 4) premenopausal change in relative weight, 5) premenopausal blood pressure, 6) premenopausal change in blood pressure, and 7) premenopausal Framingham risk score, representing a 10-year probability of coronary heart disease.

Total serum cholesterol was measured by the Abell-Kendall method in mg/dl (13). The Framingham relative weight is the ratio of each individual's body weight to the smoothed median weight for a person in that sex and height group multiplied by 100 (4). The risk score represents the estimate of total coronary heart disease risk (%) over the course of 10 years for persons without known heart disease and was determined by using the equations that are given in the Appendix (14).

Data analysis. Because of differences in age at enrollment in the study and at natural menopause, the number of examinations and corresponding age differed among participants. This caused variation in the number of available measurements of cholesterol, relative weight, and systolic and diastolic blood pressure per woman. A three-step method was used to make optimal use of the abundance of longitudinal data, to correct for age at the measurements, and to assess the effects of both premenopausal risk factors and change in risk factors on age at menopause.

First, a linear regression analysis was conducted separately for each woman relating cholesterol levels to chronological age. For this purpose, we used cholesterol levels determined at 2-year intervals preceding menopause with a maximum of 20 years. Consequently, the regression equations are based on 2 to 10 measurements. The resulting regression-coefficient (b) represents the individual change in cholesterol level with advancing age. From the individual regression function, premenopausal cholesterol levels were estimated at age 43 years, which represents the mean age of cholesterol measurements for all women. Using the mean age prevents the need for extensive estimation of values by extrapolation. Women who reached menopause before the age of 43 years were not excluded from the analyses (n = 23).

The second step involved linear regression analyses with age at menopause as the dependent variable and the age-adjusted estimated cholesterol level (at age 43 years) as the independent variable. Finally, to assess the effect of cholesterol change during the premenopausal period, three categories were created: 1) women with decreasing levels of cholesterol with advancing age ($b \leq -0.5$); 2) women with stable cholesterol levels with advancing age ($-0.5 < b < 0.5$); and 3) women with increasing cholesterol levels with advancing age ($b \geq 0.5$). To determine the size of the effect of increasing and decreasing levels within a category, linear regression analysis was conducted using b as a continuous, independent variable. The same three-step procedure was followed for relative weight, systolic blood pressure, and diastolic blood pressure.

To control for potential confounding in these analyses, adjustments were made for smoking status. Smoking status (yes or no) was preferably determined at the examination as close to menopause as possible.

In all analyses for total serum cholesterol level, women were excluded if they reported use of cholesterol-lowering drugs. Similarly, women who reported using antihypertensive drugs were excluded from all analyses of systolic and diastolic blood pressure.

The Framingham risk score includes age, total serum cholesterol, high-density lipoprotein (HDL) cholesterol, smoking status, diabetes, and blood pressure, and interactions between these factors. In the equations for calculating the score a quadratic term for age is incorporated, and therefore no linear relation between the Framingham risk score and age can be assumed. Thus, the effect of premenopausal change in heart disease risk reflected in the Framingham risk score cannot be assessed. The actual premenopausal 10-year cardiovascular risk according to the Framingham risk score can, however, be determined validly and was computed at age 35 years. About half of the women in the study population (n = 310) were included at or before 35 years of age. The HDL cholesterol level was not available because this was not included in the earliest examinations. To determine the individual scores, all women were assigned a normal HDL cholesterol value that corresponds with 0 points for this factor. The equations estimate coronary heart disease risk over 10 years. Linear regression analysis was conducted with risk as an independent variable

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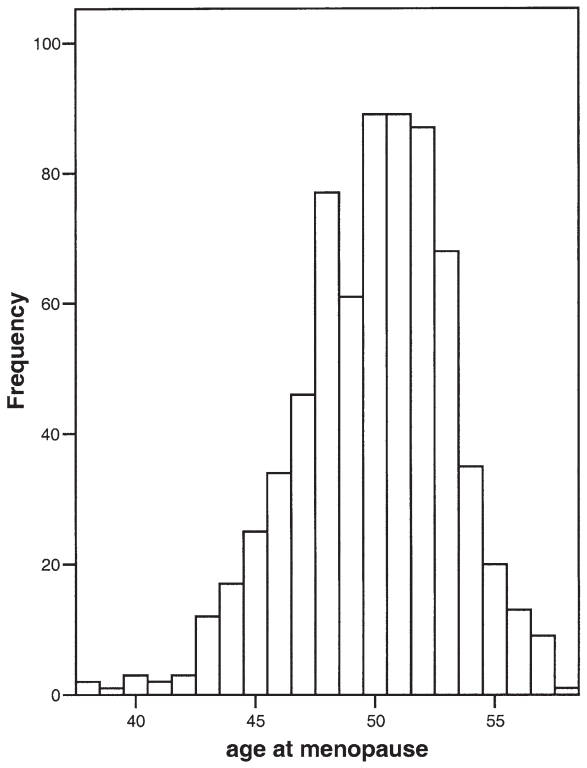

Figure 1. Distribution of age at menopause.

and age at menopause as a dependent variable. All analyses were performed using SPSS 11 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

For our study population (n = 695), the age at study entry ranged from 34 to 55 years (mean 45.5 years, standard deviation 3.3 years). Age at menopause ranged from 38 to 58 years (mean 49.9 years, standard deviation 3.2 years) (Fig. 1). Cardiovascular risk factors at the time of menopause are shown in Table 1.

Smoking. Forty-two percent of the women reported smoking during the period preceding menopause, and the smokers experienced menopause on average 1.6 years earlier than nonsmokers (95% CI 1.1 to 2.1).

Cholesterol. Five women used cholesterol-lowering drugs in the premenopausal period and were excluded from the analyses. Of the remaining 690 women, 648 women had data on cholesterol level from at least two examinations. The range of total serum cholesterol level of all premenopausal cholesterol measurements was 119 to 490 mg/dl (3.1 to 12.7 mmol/l). In six women, the age-adjusted estimated cholesterol level at age 43 years fell out of the range of original cholesterol levels, and they were excluded from further analyses. The mean number of examinations for the remaining 642 women was 4.9 (standard deviation 1.7). The mean estimated cholesterol level was 220.6 mg/dl (standard deviation 38.6 mg/dl) (5.7 mmol/l, standard deviation 1.0 mmol/l).

Table 1. Mean Values of Cardiovascular Risk Factors at the Time of Menopause

Risk Factor	Mean	SD
Cholesterol (mg/dl)	248.5	45.2
Diastolic blood pressure (mm Hg)	83.6	14.4
Systolic blood pressure (mm Hg)	127.3	22.0
Framingham relative weight	101.4	15.8

Adjusted for smoking, each 20-mg/dl (0.52-mmol/l) higher estimated premenopausal cholesterol level was associated with a 0.14-year earlier occurrence of menopause (95% CI −0.26 to −0.00) (Table 2). Within the subgroup of women with increasing levels of cholesterol, adjusted for smoking, each 20-mg/dl increase in total serum cholesterol was associated with a 2.60-year earlier occurrence of menopause (95% CI −0.06 to −1.14). Within the subgroup of women with decreasing levels of cholesterol, adjusted for smoking, each 20-mg/dl decrease in total serum cholesterol was associated with a 4.16-year later age at menopause (95% CI 0.08 to 8.24) (Table 3).

Relative weight. For 656 women at least two premenopausal relative weight measures were available, and premenopausal age-independent estimated relative weight was computed at 43 years of age. The mean number of examinations available per woman was 5.9 (standard deviation 2.1). The mean estimated relative weight was 99.1% (standard deviation 15.7%). Adjusted for smoking status, a 5% higher premenopausal relative weight was associated with a 0.07-year (95% CI −0.02 to 0.17) higher age at menopause, although this was not statistically significant (Table 2). Within the group of women who gained weight, menopause occurred 7.15 years earlier per 5% increase in relative weight (95% CI −12.00 to −2.33) after adjustment for smoking. In the group of women who became leaner, adjusted for smoking, each 5% decrease in relative weight was associated with a 3.54-year earlier age at menopause (95% CI −6.20 to −0.88) (Table 3).

Blood pressure. After exclusion of women who used antihypertensive drugs (n = 92), 561 women had two or more blood pressure measurements, and premenopausal age-independent systolic and diastolic blood pressure was computed at age 43 years. Five women were excluded because the estimated values fell out of the range of original blood pressure values, leaving 556 women for the analyses. The mean number of examinations available per woman was 5.4 (standard deviation 2.0). The mean estimated systolic blood pressure was 121.4 mm Hg (standard deviation 14.1 mm Hg), and the mean diastolic blood pressure was 77.9 mm Hg (standard deviation 10.0 mm Hg).

Systolic blood pressure. Adjusted for smoking, estimated systolic blood pressure level was not statistically significantly associated with age at menopause (Table 2). In the group of women with increasing levels of systolic blood pressure during the premenopausal period, each 10-mm Hg increase is associated with a 3.45-year earlier menopause (95% CI −5.42 to −1.49) when adjusted for smoking. Among the

Table 2. Relationship Between Premenopausal Cardiovascular Risk and Age at Menopause by Linear Regression Analysis

Determinant	n	Crude Change in Age at Menopause (yrs)	95% CI	Adjusted for Smoking Change in Age at Menopause (yrs)	95% CI
Premenopausal cholesterol level (per 20 mg/dl* higher level)	642	−0.20	−0.32 to −0.06	−0.14	−0.26 to −0.00
Premenopausal relative weight (per 5% higher relative weight)	656	0.09	0.02 to 0.15	0.07	−0.02 to 0.17
Premenopausal systolic blood pressure (per 10 mm Hg higher level)	556	0.14	−0.04 to 0.32	0.12	−0.05 to 0.31
Premenopausal diastolic blood pressure (per 10 mm Hg higher level)	560	−0.09	−0.37 to 0.19	−0.11	−0.38 to 0.15

*20 mg/dl = 0.5 mmol/l.
CI = confidence interval.

women with decreasing levels of systolic blood pressure, each 10-mm Hg decrease is associated with a 1.53-year later age at menopause (95% CI −0.00 to 3.06) after adjustment for smoking (Table 3).

Diastolic blood pressure. Adjusted for smoking, estimated diastolic blood pressure level was not statistically significantly associated with age at menopause (Table 2). Women with increasing levels of diastolic blood pressure had a 7.38-year earlier occurrence of menopause with each 10-mm Hg increase (95% CI −10.78 to −3.98) after adjusting for smoking. In the group of women with decreasing levels of diastolic blood pressure, menopause was reached 2.48 years (95% CI −0.53 to 5.48) later for each 10-mm Hg increase when adjusted for smoking (Table 3).

Framingham risk score. The Framingham risk score was determined at age 35 years. For 248 women of the 310 women eligible for this analysis, all variables (except HDL cholesterol) were available to determine a Framingham risk score. The risk ranged from 0.43% to 2.80% with a mean of 1.1% (standard deviation 0.46%). A 1% higher 10-year risk for coronary heart disease was associated with a significantly lower age at menopause, a mean reduction in menopausal age of 1.8 years (95% CI −2.72 to −0.92). Considering the risk range in this population, the effect on menopausal age could amount to more than four years in women with the highest risk.

DISCUSSION

The results of this analysis from data on female participants in the Framingham Heart Study show that levels of premenopausal risk factors for cardiovascular disease affect the age at menopause. This offers an alternative explanation for the seemingly adverse effect of early menopausal transition on cardiovascular disease risk. Current views on the relationship between menopause and cardiovascular risk assume estrogen depletion to be a causal factor in the increase in cardiovascular risk. Conversely, however, menopause may not induce a change in cardiovascular risk profile, but a woman's atherosclerotic status may influence age at onset of menopause. Consequently, the observation that women with an early age at menopause are at a higher risk for cardiovascular disease might, in part, reflect an unfavorable risk profile present before menopause. These results are not necessarily in conflict with the possibility that estrogen depletion during and after menopause has a role in the change in cardiovascular risk; both hypotheses are not mutually exclusive.

Table 3. Effect of Premenopausal Increasing or Decreasing Cholesterol Level, Relative Weight, and Blood Pressure

Subgroup	n	Crude Change in Age at Menopause (yrs)	95% CI	Adjusted for Smoking Change in Age at Menopause (yrs)	95% CI
Cholesterol					
Increasing cholesterol level	514	−2.48 yrs per 20 mg/dl* increase	−3.88 to −1.08	−2.60 yrs per 20 mg/dl increase	−4.06 to −1.14
Decreasing cholesterol level	94	3.44 yrs per 20 mg/dl* decrease	−0.14 to 7.02	4.16 yrs per 20 mg/dl decrease	0.08 to 8.24
Relative weight					
Increasing relative weight	274	−6.60 yrs per 5% increase	−11.25 to −1.90	−7.15 yrs per 5% decrease	−12.00 to −2.33
Decreasing relative weight	90	−3.36 yrs per 5% decrease	−6.10 to −0.60	−3.54 yrs per 5% increase	−6.20 to −0.88
Systolic blood pressure					
Increase in systolic blood pressure	273	−3.00 yrs per 10 mm Hg increase	−5.06 to −0.96	−3.45 yrs per 10 mm Hg increase	−5.42 to −1.49
Decrease in systolic blood pressure	135	1.74 yrs per 10 mm Hg decrease	0.19 to 3.30	1.53 yrs per 10 mm Hg decrease	−0.00 to 3.06
Diastolic blood pressure					
Increase in diastolic blood pressure	229	−7.01 yrs per 10 mm Hg increase	−10.49 to −3.54	−7.38 yrs per 10 mm Hg increase	−10.78 to −3.98
Decrease in diastolic blood pressure	117	2.98 yrs per 10 mm Hg decrease	−0.11 to 6.06	2.48 yrs per 10 mm Hg decrease	−0.53 to 5.48

*20 mg/dl = 0.5 mmol/l.
CI = confidence interval.

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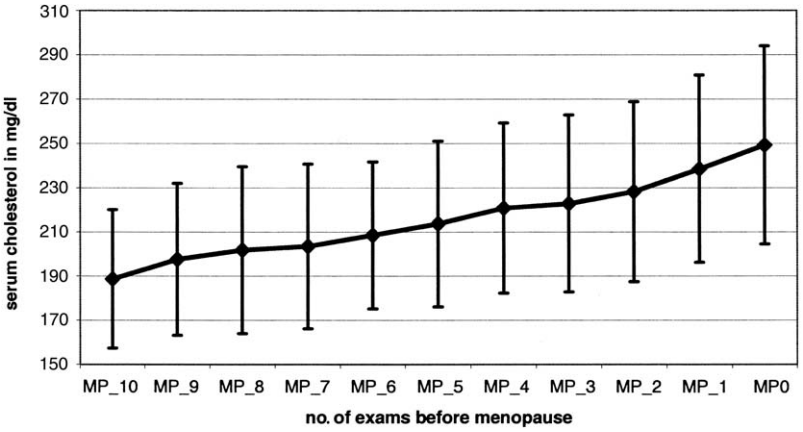

Figure 2. Association of years before menopause (MP0 = menopause; MP_1 = one examination before menopause; MP_2 = two examinations before menopause, and so on) and mean cholesterol level in mg/dl.

It should be emphasized that premenopausal cholesterol level as well as premenopausal relative weight are age-independent estimated values computed from all available premenopausal measurements for an individual. An assumption of the linearity of the relationships between age and cholesterol level and age and relative weight, respectively, was made. Based on Figures 2 and 3, this seems justified, for both associations the R^2 value for the linear relationship was 97%, and the linear terms were significantly different from zero ($p < 0.001$). Moreover, these results are in line with those reported in Figure 1 by van Beresteijn et al. (15).

The strength of the methods used for analysis relates to the issue of confounding by chronological age while using all data available for each woman. When cholesterol level, relative weight, and blood pressure were determined at a fixed number of years before menopause for all women, differences in chronological age at time of measurement might have confounded the results.

A potential drawback of the method as applied is the need for extrapolation of the regression line for age and cholesterol and for age and relative weight for part of the women to determine their estimated value at age 43 years. No selection of age could fully prevent extrapolation, but the choice of this age resulted in the least extrapolations necessary, i.e., 8.7% for cholesterol, 2.1% for relative weight, and 5.8% for blood pressure. In our opinion, these limitations are easily outweighed by the advantage of separating the effects of level and change without confounding by age.

Concerns have been expressed regarding the reliability of reported age at menopause, especially after a long follow-up (16,17). In the current study, as a result of the frequent examinations, the time interval is always small, making errors in reported menopausal ages unlikely. A point of concern, however, is to what extent menopause can really be seen as a distinct event at a discrete point in time. Natural menopause does not ordinarily occur abruptly, and the changes in hormonal status associated with it could involve

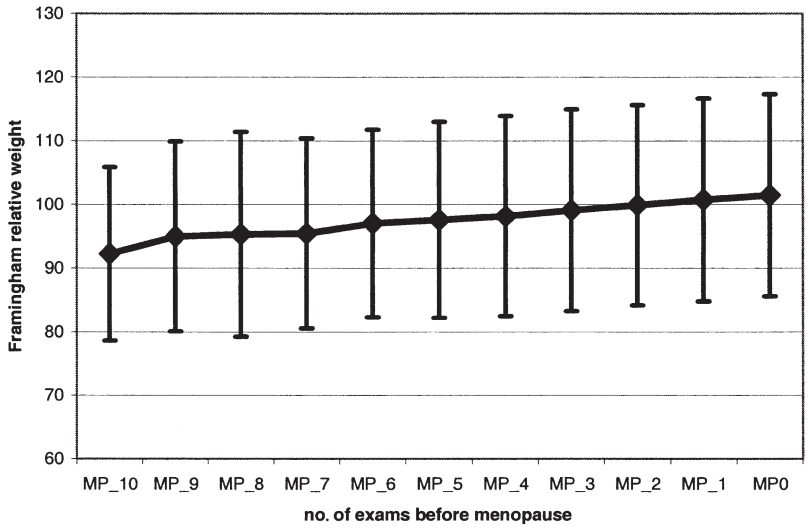

Figure 3. Association of years before menopause (MP0 = menopause; MP_1 = one examination before menopause; MP_2 = two examinations before menopause, and so on) and mean relative weight.

a dynamic process of progressive decline in ovarian function. Therefore, the data included in the analyses that were obtained during the years directly before the reported cessation of menses may not be completely independent of the effect of the gradual hormonal changes preceding the last menstruation. Several studies have shown that the perimenopause, characterized by an irregular menstrual cycle pattern, lasts on average four years (18–20). Furthermore, it has been shown that estradiol levels remain relatively unchanged until the onset of the menopausal transition and are usually well preserved until the late perimenopause, presumably in response to elevated follicle-stimulating hormone levels (21,22). Burger et al. (23) reported that estradiol levels begin to decline about two years before the last menstrual period, decrease most rapidly around that time, and plateau two years later. Because our results are based on a mean premenopausal period of approximately 10 years for each woman, we argue that our results are likely to be unaffected by menopause itself. To confirm this assumption, we reanalyzed the data while excluding the examination preceding menopause, thus evaluating data until two years before menopause. These analyses yielded similar results as those presented using all data. However, most of the studies that look at premenopausal and peri-menopausal hormonal levels have evaluated estradiol levels at certain fixed time points in the cycle, a design that does not capture dynamic changes in levels. Premenopausally, hormonal levels can fluctuate strikingly within the cycle and from cycle to cycle with intermittent estrogen surges. Therefore, we cannot fully exclude the possibility that the worsening of risk factors that seems to relate to menopausal age is not a consequence of changes in the hormonal environment before cessation of menstruation.

Although there are several studies suggesting that overweight decelerates menopause, there are also studies indicating no effect of body weight on timing of menopause (24–26). These conflicting results might be a result of residual confounding for example by age. In the one article that was particularly able to exclude confounding by age (27) by selection of women born in one week in 1946, no effect of body weight was found on the timing of menopause.

It is well known that overweight increases cardiovascular disease risk, moreover, several observational as well as intervention studies have shown that cardiovascular risk factors rapidly improve when weight is reduced (28,29). Weight loss would therefore be expected to result in decreased excess mortality associated with overweight; however, the opposite has been found in several large epidemiologic studies (30–33). In particular cardiovascular disease remains the main cause of mortality in people losing weight. The biological mechanism behind this phenomenon is not known; apparently weight loss is not only associated with beneficial effects, such as improved cardiovascular risk factor profile, but also with some harmful effects, of which loss of fat-free mass has been suggested to be one factor (34). Maybe these harmful effects also accelerate menopause, but this is still theoretical.

Smoking is known to affect menopausal age, and menopause occurs 0.8 to 2 years earlier in smoking women (35,36). Explanations have been sought in an antiestrogenic effect of nicotine and a toxic effect on the follicles (37). However, theoretically, smoking could promote atherosclerosis of the ovarian arteries and ischemia. In that case, smoking might have been better captured by adjusting for lifetime smoking exposure, or in this case, by smoking exposure at enrollment in the Framingham study. However, we recently found that only smoking at or around the onset of menopause affects the timing of menopause (38). Previous smoking does not affect the onset of menopause; therefore, it is justified to study smoking behavior only at the last examination before menopause.

Blood vessel stiffness increases over time, whereas diastolic blood pressure tends to decrease. The women with decreasing diastolic pressure levels probably consist at least in part of those with "hardening of the arteries." This is a likely explanation for the fact that "beneficial" changes in diastolic blood pressure did not result in a statistically significant increase in menopausal age.

Cohort studies investigating menopause or menopausal age and cardiovascular disease risk have compared premenopausal levels or premenopausal trends of risk factors, such as cholesterol or body weight, with postmenopausal levels or trends. Alternatively, risk factor levels of fertile women were compared with levels of postmenopausal women (4,15,39). Still, doubt remains regarding whether menopause worsens the cardiovascular risk patterns (40).

The inevitable consequence of cross-sectional studies on age-matched premenopausal and postmenopausal women is that women with a later age at menopause are compared with women with an earlier age at menopause. In view of our hypothesis, the observation that the postmenopausal group has a less favorable risk profile may simply reflect that these are women with an earlier menopause as a consequence of a worse cardiovascular risk profile.

Recently, we have shown that the factor V Leiden mutation is associated with an earlier age at menopause, supporting the idea of a vascular mechanism involved in determining age at menopause (41).

Although the cardiovascular risk profile appears to be a strong determinant of age at menopause, the mechanism is not apparent. Atherosclerosis is a generalized process (42). However, the idea that atherosclerotic changes in the microvascularization of the ovaries accelerate ovarian aging through decreased perfusion may be too simplistic. Body weight, cholesterol level, diabetes mellitus, blood pressure, and smoking have negative vascular effects, but may also affect the endocrine system, which in turn could have an impact on menopausal age. Because several of the factors mentioned earlier are included in definitions of the metabolic syndrome (43), it is possible that insulin resistance partly determines when menopause occurs. Hyperinsulin-

emia is associated with an increase in the ratio of androgens to estrogens in plasma, and this process might play a role (44,45). No insulin or gonadal hormone levels are available for Framingham women before the time of menopause, but studies of insulin resistance and sensitivity in premenopausal women are possible in future investigations.

In an alternative hypothesis, early natural menopause may be interpreted as a sign of accelerated general aging. Cardiovascular risk is known to increase with age. A relatively accelerated biologic aging would then be reflected by both early menopause and an increased risk for cardiovascular disease.

In conclusion, our results provide evidence for the view that atherosclerosis risk determines age at menopause rather than the reverse. This provides a novel explanation for the inconsistent findings of cardiovascular disease rate and its relationship to menopausal age and the effects of hormonal replacement therapy.

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APPENDIX

For the calculation of the Framingham risk score, please see the online version of this article.