

Genes Control the Cessation of a Woman's Reproductive Life: A Twin Study of Hysterectomy and Age at Menopause*

HAROLD SNIEDER, ALEX J. MACGREGOR, AND TIM D. SPECTOR

Twin Research Unit, St. Thomas' Hospital, London, United Kingdom SE1 7EH

ABSTRACT

A classical twin study was performed to assess the extent to which genetic factors explain individual differences in age at menopause and (indications for) hysterectomy. It was further examined whether a genetic effect on the timing of the menopause was mediated through a genetic effect on age at menarche. The subjects were 275 monozygotic and 353 dizygotic female twin pairs. Maximum likelihood model fitting was used to estimate genetic and environmental variance components, Kaplan-Meier survival analysis was used to account for censored data, and the Cox proportional hazards model was used to adjust for potential confounders. A model specifying additive genetic and unique environmental factors showed the best fit to the data, yielding a heritability (h^2) for age at menopause of 63%. The significance of the genetic effect was confirmed by the survival analysis and

was not affected by adjustment for confounders. Both early and late menopause were found to be significantly influenced by genetic factors. Hysterectomy also showed considerable heritability ($h^2 = 59\%$), as did its two main indications: fibroids ($h^2 = 69\%$) and menorrhagia ($h^2 = 55\%$). The genetic contribution to the variance in age at menarche was estimated to be 45%, with the majority (37%) being due to dominant genetic effects. No correlation was found between age at menopause and age at menarche, suggesting different genetic mechanisms. This study provides convincing evidence for the importance of genetic factors in determining natural and surgical menopause. Understanding how genes control the timing of menopause and exploring whether these genes are indirectly associated with disease are important areas for future study. (*J Clin Endocrinol Metab* **83**: 1875–1880, 1998)

THE IRREVERSIBLE end of a woman's reproductive life is reached with the cessation of menstruation at the age of menopause. Humans are the only primates to experience menopause, and its origins and purpose are unclear, although it has been suggested that long postmenopausal lifespans (the grandmother effect) may have had survival value in human evolution (1). In contrast to the timing of the onset of the menstrual cycle, the age at menarche, for which a considerable genetic influence has been shown (2–4), there is little information on possible genetic influences on the timing of menopause. Knowledge of the influencing factors may have important clinical implications. Early menopause is associated with a higher risk of cardiovascular disease (5, 6), osteoporosis (7), and ovarian cancer (8), whereas delayed menopause may increase the risk of endometrial and breast cancer (9). A range of behavioral, reproductive, and anthropometric factors have been reported to be associated with age at menopause (10–15). However, with the exception of tobacco smoking, which advances menopause by 1.5–2.0 yr, these factors have failed to show a consistent and replicable influence (11, 16, 17). A possible explanation for the failure to detect important predictors of age at menopause may be that most of the variation in menopausal age is indepen-

dently determined by the influence of genes. Genetic factors have been implicated in two recent studies. One showed family history to be a predictor of early menopause (18), and the other found a strong relationship between mothers' and daughters' menopausal ages (19). However, preferential recall of family history by women with early menopause may have contributed to these results. Also, the studies did not provide information on the extent to which the timing of menopause was determined by genetic or environmental factors.

The reproductive life of one in five women ends prematurely in developed countries because they have a hysterectomy before they reach their natural menopause (20). Rates of surgical menopause are increasing in these countries, and it is unclear whether genetic factors are involved in the etiology of its two main indications: menorrhagia and fibroids.

These latter questions can be addressed by the analysis of data on genetically informative subjects, of which twins are the most useful. To date, no twin studies on age at menopause have been performed.

The main aim of this study was to estimate the relative importance of genetic and environmental influences on the timing of the natural menopause and on hysterectomy and its principal clinical indications by using quantitative genetic modeling of data from a large cross-sectional sample of unselected female twins. We further examined whether a genetic effect on age at natural menopause may have been mediated by a genetic effect on age at menarche. By using survival analysis approaches, we focused on potential sources of bias arising from censored observations from premenopausal twins and the possible influence of confounding

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Address all correspondence and requests for reprints to: Dr. Harold Snieder, Twin Research Unit, St. Thomas' Hospital, Lambeth Palace Road, London, United Kingdom SE1 7EH. E-mail: h.snieder@umds.ac.uk.

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by smoking, alcohol use, social class, body mass index (BMI), or use of the contraceptive pill.

Subjects and Methods

Subjects

The subjects were 628 twin pairs (age range, 19–76 yr) ascertained from the general population through a national media campaign in the United Kingdom (21). Table 1 shows the composition of the sample with respect to menopausal status (pre/pre, pre/post, and post/post twin pairs) and the age range of the three subgroups. Zygosity was determined by standardized questionnaire, and DNA fingerprinting was used for confirmation (21). Demographic and gynecological information, including information on operations and indications for surgery, was obtained by a standardized nurse-administered questionnaire.

Two hundred and fifty-six monozygotic (MZ) and 269 dizygotic (DZ) pairs in which at least 1 twin of each pair was postmenopausal were used for the analysis of age at menopause (post/pre and post/post pairs; see Table 1). Menopausal age was assessed as 1) the recalled age at the last regular period in 699 individuals and as 2) the age of starting hormone replacement therapy (HRT) to treat menopausal symptoms in 16 subjects with a history of hysterectomy. It was not possible to determine menopausal age with precision in an additional 282 postmenopausal subjects, of whom 242 had had a hysterectomy before becoming menopausal, 38 had started HRT before their last regular period, and 2 had missing data for other reasons.

Background to twin analysis

Twin methodology makes use of the fact that MZ twins share identical genotypes, whereas DZ twins are no more alike genetically than siblings, sharing, on the average, 50% of their segregating genes. A higher MZ than DZ intraclass correlation (r) provides a first impression of the magnitude of genetic influence, which is based on the classic formula to estimate heritability: $h^2 = 2(r_{MZ} - r_{DZ})$ (22). Model-fitting analysis of twin data, however, has some major advantages over the classic twin methodology (23, 24). It allows a more extensive separation of the observed phenotypic variance into its genetic and environmental components: additive genetic variance (A), dominance genetic variance (D), shared (or common) environmental variance (C), and specific (or unique) environmental variance (E), which also contains measurement error. A general univariate genetic model can be represented by the following linear structural equations: $P_i = hA_i + dD_i + cC_i + eE_i$ (Eq I) and $V_p = h^2 + d^2 + c^2 + e^2 = V_A + V_D + V_C + V_E$ (Eq II), where P is the phenotype of the i th individual, scaled as a deviation from zero; A , D , C , and E can be conceived of as uncorrelated latent factors with zero mean and unit variance; h , d , c , and e are regression coefficients of the observed variable on the latent factors; and V_p is the phenotypic variance. The squared regression coefficients are equal to the (unstandard-

ized) variance components. Dividing each of these components by the total variance, V_p , yields the different standardized components of variance, e.g. the heritability ($h^2 = V_A/V_p$). In twin studies, the effects of D and C are confounded, which means that they cannot both be included in the same univariate model. Estimates of the genetic variation in the quantitative genetic model as applied here represent the influence of the sum of several genes on the trait (*i.e.* polygenic). Monogenic (or major gene) inheritance cannot be evaluated in the present twin design, even if it is present.

Analytical approach

Model-fitting procedure. Estimates of variance components and their confidence intervals were obtained by quantitative genetic model fitting. The significance of A , C , and D was tested by removing them sequentially in specific submodels, eventually leading to a model that gives the most parsimonious fit to the data, *i.e.* a model in which the pattern of variances and covariance is explained by as few parameters as possible. Submodels were compared with the full model by hierarchic χ^2 tests. The difference between minus twice the log-likelihood ($-2\ln L$) for a submodel and that of the full model is approximately distributed as χ^2 , with degrees of freedom equal to the difference of the number of estimated parameters in the full model and the number of estimated parameters in the submodel.

As stated, menopausal age could not be determined with precision in a considerable number of people (see Table 1). Standard methods of maximum likelihood model fitting, which require complete information on all individuals, could thus not be applied to this dataset. To derive quantitative estimates of genetic and environmental variance components of the age at menopause, we therefore fitted models to the raw data using normal theory maximum likelihood (25, 26). This method allowed us to use the information provided by unpaired observations. Besides the complete data (post/post pairs in Table 1), data from the 185 single individuals for whom menopausal age was known precisely for themselves but not for their cotwin [post/pre, post/?, and post/hysterectomized (hyst) pairs in Table 1] could be incorporated in the model fitting.

To estimate the genetic and environmental influences on hysterectomy and on its main indications, menorrhagia and fibroids, we used survival analysis and genetic modelling of dichotomous (yes/no) data as described by Neale and Cardon (23) using data from all 628 twin pairs, *i.e.* regardless of their menopausal status. Akaike's information criterion ($AIC = \chi^2 - 2 \text{ df}$) was used to evaluate the fit of the genetic models. The model with the lowest AIC reflects the best balance between goodness of fit and parsimony.

Censorship. Some inherent aspects of the data could potentially have biased the modelling results for age at menopause and hysterectomy. The age at ascertainment for MZ twins was higher than that for DZ twins (Table 2). Therefore, cotwins of menopausal MZ twins had greater opportunity to have become menopausal or have undergone a hysterectomy themselves at the time of ascertainment than cotwins of menopausal DZ twins. This characteristic of the data, which for age at menopause was confirmed by the significant 1-yr difference in MZ compared to DZ pairs ($\chi^2[1] = 6.62; P < 0.025$) and the higher number of DZ pairs discordant for menopausal status (post/pre pairs; Table 1), could theoretically introduce a spurious genetic effect.

To account for this potential source of bias, we used a nonparametric survival analysis approach (Kaplan-Meier) that allowed us to include censored observations and compare the probability of undergoing the menopause or a hysterectomy for MZ and DZ twins in the interval after their respective cotwins had become menopausal or had undergone a hysterectomy. If this analysis shows a higher risk in MZ compared to DZ twins, a genetic effect is implicated. The difference between the MZ and DZ survival curves was evaluated using the Wilcoxon test. It should be noted that although the survival analysis can show whether there is an indication of a genetic effect, it cannot confirm or refute the size of the heritability as estimated in the model-fitting approach.

For the analysis of age at menopause, censored observations from two types of twin pairs were included in addition to the complete data (post/post pairs; Table 1). In these pairs the menopausal age was known with precision in the postmenopausal twin, but the cotwin was either still premenopausal (post/pre pairs; Table 1) or had a hysterectomy before reaching menopause (post/hyst pairs; Table 1). The actual age

TABLE 1. Composition of the available twin sample and range of age at ascertainment of the three subgroups

Pair type	N_{MZ}	N_{DZ}	N_{total}	Age range (yr)
Pre/pre	19	84	103	19–53
Post/pre				
?/pre	3	13	16	
Post/pre	5	32	37	
Subtotal	8	45	53	33–54
Post/post				
?/?	34	25	59	
Post/?	60	70	130	
Post/hyst	3	15	18	
Post/post	151	114	265	
Subtotal	248	224	472	41–76
Overall total	275	353	628	19–76

N , Number of pairs; pre, premenopausal; ?, postmenopausal but age at menopause could not be precisely determined; post, postmenopausal and precise estimate of age at menopause available; hyst, hysterectomy before reaching menopause.

TABLE 2. Characteristics of MZ (N = 256) and DZ (N = 269) twin pairs of which at least one was postmenopausal

	MZ	DZ
Age at ascertainment (yr)	58.4 (5.6)	55.4 (7.2)
Menopause (yr) ^a	49.0 (4.5)	48.0 (4.8)
Median	50	49
Menarche (yr) ^b	13.3 (1.6)	13.2 (1.6)
Median	13	13
Hysterectomy (%)	27.3	27.2
Due to menorrhagia (%)	21.4	19.2
Due to fibroids (%)	39.3	40.4
Ever used HRT (%)	35.5	43.1
Ever used oral contraceptives (%)	45.8	55.9
Social class I-II (%)	60.0	54.0
Ht (m)	1.61 (0.06)	1.62 (0.06)
Wt (kg)	63.2 (9.6)	64.7 (10.4)
Body mass index (kg/m ²)	24.4 (3.6)	24.7 (4.0)
Current smoking (%)	15.7	15.6
Alcohol use	1.76 (1.25)	1.86 (1.31)

The mean (SD) is shown, unless stated otherwise.

^a For menopause, complete data were available for 370 MZ and 345 DZ individuals.

^b For menarche, complete data were available for 266 MZ and 352 DZ twin pairs.

and the age at hysterectomy were used as censored observations for premenopausal and hysterectomy twins, respectively.

For the analysis of hysterectomy, pairs were included if at least one twin of each pair had undergone a hysterectomy and the age at hysterectomy was known (98 MZ and 125 DZ pairs). Observations were censored in case a cotwin of a twin with hysterectomy had remained without hysterectomy until the age at ascertainment.

To investigate whether a genetic effect on age at menopause may have been restricted to either early or late menopause, menopausal cotwins were classified into early and late menopausal groups using the median age of 49 yr as a cut-off. The excess risk of becoming menopausal for MZ compared with DZ twins was subsequently compared for the younger and older menopausal groups by means of a Cox proportional hazards model.

Confounding. A possible genetic influence on age at menopause could be due to a genetic effect on age at menarche, which was measured as the recalled age at the first period. To assess the potential confounding effect of age at menarche, we used standard maximum likelihood modelling to first determine whether age at menarche was influenced by genetic factors itself.

A Cox proportional hazards model was used to further explore confounding in the data. The following covariates were included in the model: current smoking (yes/no), alcohol use (measured on a seven-point scale), age at menarche, body mass index (weight/height²), social class (I–II), and use of contraceptives (ever/never) (10–15).

Statistical software. All model fitting was carried out with Mx (25), a software package specifically designed for the analysis of genetically informative data. The Kaplan-Meier survival analysis and Cox proportional hazards model were performed using STATA (27).

Results

Table 2 shows general characteristics of twin pairs of which at least one of the pair was postmenopausal. The MZ pairs were, on the average, 3 yr older than the DZ pairs at the time of ascertainment. The median and mean ages at menopause were 1 yr greater in MZ compared to DZ twins. Age at menarche was similar for MZ and DZ twins (median of 13 yr), as were most of the other characteristics.

Intraclass correlations for menopausal age in the 151 MZ and 114 DZ twin pairs for which we had complete data were 0.58 and 0.39, respectively, suggesting an important genetic

influence. This was confirmed by the results of model fitting, which included the 185 unpaired observations (Table 3). Shared environmental and dominance genetic effects did not contribute significantly to the explanation of the data; they could be dropped from the model without a significant worsening of fit. A model specifying additive genetic (A) and unique environmental (E) variance components gave the most parsimonious explanation of the data, yielding a heritability estimate of 63% [95% confidence interval (CI), 0.53–0.71; Table 5].

The Kaplan-Meier survival analysis showed that the probability of undergoing the menopause in the interval after their respective cotwins had become menopausal was consistently greater in MZ than in DZ twins (Fig. 1; by Wilcoxon's test: $\chi^2[1] = 34.56$; $P < 0.0001$). Five years after their cotwins had undergone the menopause, 86% of MZ twins, compared with only 55% of DZ twins, had become menopausal themselves.

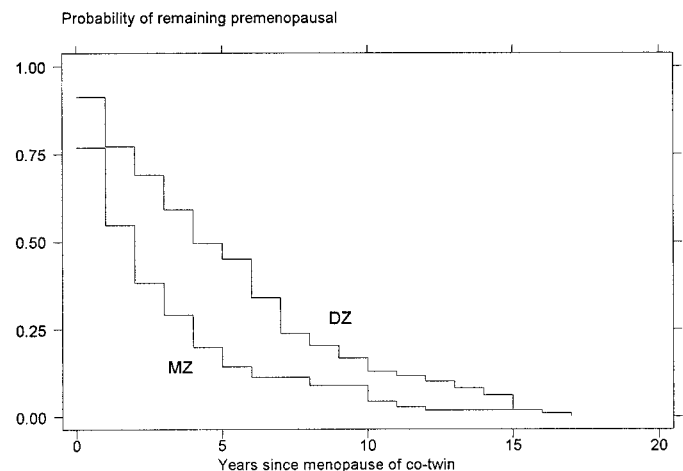
The excess risk of becoming menopausal for MZ compared with DZ twins was significant in both the early and the late menopausal group; MZ vs. DZ hazard ratios were 1.61 (95% CI, 1.16–2.23; $P = 0.004$) and 1.65 (95% CI, 1.10–2.48; $P = 0.016$), respectively. Thus, the genetic influence was not restricted to either early or late menopause.

Intraclass correlations for age at menarche were 0.61 and 0.18 for MZ and DZ twin pairs, respectively. The MZ correlation is more than twice the DZ correlation, which is an indication of dominance genetic effects. This was confirmed by the quantitative genetic modelling, which showed that a

TABLE 3. Results of model fitting to (raw) age at menopause data

Model	-2lnL	df	Δdf	χ^2	P
ACE	4148.643	710			
ADE	4149.417	710			
AE	4149.417	711	1	0.774	NS
CE	4156.864	711	1	8.221	<.005

-2lnL, Minus twice the log-likelihood; Δdf, (number of estimated parameters, full model) - (number of estimated parameters, submodel), $\chi^2 = (2\ln L_{\text{submodel}}) - (2\ln L_{\text{full model}})$. See text for other abbreviations. The most parsimonious solution is printed in *boldface*.

**FIG. 1.** Probability of developing menopause for MZ and DZ twins after their respective cotwins had gone through menopause.

model that included A, D, and E showed the best fit to the data. The total contribution of genetic factors to age at menarche was estimated to be 45%, 37% due to dominance and 8% due to additive genetic effects. No correlation was observed between age at menarche and age at menopause ($r = 0.032$).

The results of the Cox proportional hazards model showed that the genetic effect on age at menopause remained highly significant after adjustment for a range of covariates, the MZ vs. DZ hazard ratio decreased only minimally from 1.85 (95% CI, 1.45–2.36; $P < 0.001$) to 1.84 (95% CI, 1.34–2.51; $P < 0.001$) after adjusting for current smoking, alcohol use, age at menarche, BMI, social class, and use of contraceptives in the second twin. Current smoking was the only variable that had an independent effect, bringing forward age at menopause by 1.6 yr ($P < 0.001$).

Genetic modelling of dichotomous data showed that hysterectomy was also under genetic influence, with a heritability of 0.59 (95% CI, 0.43–0.72; Tables 4 and 5). The genetic effect was confirmed by survival analysis (Fig. 2; by Wilcoxon test: $\chi^2[1] = 5.17$; $P = 0.023$). Our data showed that estimates for the two main indications for hysterectomy, fibroids and menorrhagia, were similar, with heritabilities of 0.69 (95% CI, 0.49–0.83) and 0.55 (95% CI, 0.24–0.78) for fibroids and menorrhagia, respectively (Tables 4 and 5).

Discussion

This study investigated the extent to which genetic factors contribute to etiology of natural and surgical menopause in

TABLE 4. Results of model fitting to (dichotomous) data of hysterectomy and its two main indications: fibroids and menorrhagia

Model	χ^2	df	P	AIC
Hysterectomy				
ACE	7.45	3	0.06	1.45
ADE	7.83	3	0.05	1.83
AE	7.83	4	0.10	-0.17
CE	10.61	4	0.03	2.61
Fibroids				
ACE	1.60	3	0.66	-4.40
ADE	2.48	3	0.48	-3.52
AE	2.48	4	0.65	-5.53
CE	3.19	4	0.53	-4.81
Menorrhagia				
ACE	4.41	3	0.22	-1.59
ADE	4.02	3	0.26	-1.98
AE	4.41	4	0.35	-3.59
CE	6.61	4	0.16	-1.39

χ^2 , χ^2 goodness of fit statistic; AIC, Akaike's information criterion. See text for other abbreviations. The most parsimonious solution is printed in *boldface*.

TABLE 5. Parameter estimates and 95% confidence intervals of the most parsimonious models are shown for age at menopause, hysterectomy, fibroids, and menorrhagia

	h^2	95% CI	e^2	95% CI
Age at menopause	0.63	0.53–0.71	0.37	0.30–0.47
Hysterectomy	0.59	0.43–0.72	0.41	0.28–0.57
Fibroids	0.69	0.49–0.83	0.31	0.17–0.51
Menorrhagia	0.55	0.24–0.78	0.45	0.22–0.76

h^2 , Heritability; e^2 , unique environmental variance component.

women. Our data showed that the timing of the natural menopause is largely under genetic control. Quantitative genetic model fitting showed that 63% of the variation in age at menopause could be explained by genetic factors. Survival analysis confirmed a significant genetic effect that was not affected by adjustment for confounders. Hysterectomy and its two main indications were under genetic influence as well, with heritabilities between 55–69%.

A major difficulty in this cross-sectional study was the high prevalence of hysterectomy and HRT use, which compromised obtaining precise estimates of the menopausal age. In our study a precise age at menopause was only available in 68% of the total of 1050 subjects. By fitting a model to the raw data we made optimal use of the available information, because unpaired observations could be included. The best-fitting model yielded the above-mentioned heritability estimate of 63%. Age at menopause was obtained by self-report of the age at the last regular period. Although self-report can introduce error, the alternative would have been to perform a highly impractical longitudinal twin study. Random measurement errors due to inaccuracies in this recalled age enlarge the estimate of e^2 in the genetic model fitting. It can thus be argued that if recall errors had any effect on our results, it would have resulted in an underestimation of the genetic effect.

Some other characteristics of the data may still have biased the model-fitting results. The higher age at ascertainment in MZ compared to DZ twins may have given cotwins of menopausal MZ twins or cotwins of MZ twins with hysterectomy a greater opportunity to have undergone the menopause or hysterectomy themselves. This could have caused a higher concordance among MZ twins, thereby introducing a spurious genetic effect. Application of survival analysis allowed us to include censored data and thus account for the effect of imbalances in their distribution between the zygosity. Survival analysis demonstrated a genetic effect on both age at menopause and hysterectomy, thereby making a large effect of bias on the model-fitting results unlikely. The genetic effect on age at menopause was not restricted to early menopause alone, because the increased risk in MZ com-

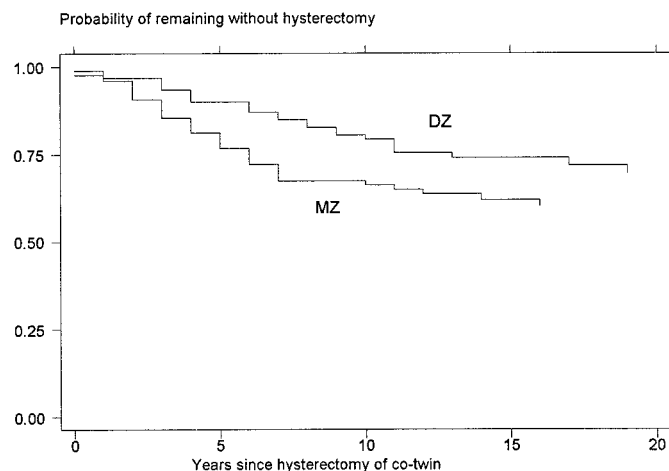


FIG. 2. Probability of undergoing hysterectomy for MZ and DZ twins after their respective cotwins had had a hysterectomy.

pared with DZ twins was significant for those with an early and a late menopause.

The exclusion from the analysis due to hysterectomy of 23% of the total number of twins could in principle have led to biased results if an association between determinants of hysterectomy and menopause had existed. However, two previous studies on determinants of age at menopause imply that individuals undergoing hysterectomy would otherwise have had a normal age at natural menopause (11, 28). Had there been an association between (the genetic effect on) hysterectomy and age at menopause, exclusion of people with hysterectomy in our analysis could only have underestimated the genetic influence on age at menopause.

Although indications for surgery are of a heterogeneous nature, the finding that hysterectomy shows a major genetic component is unlikely to be an artifact, as the genetic influences on the two main indications of hysterectomy, menorrhagia and fibroids, were of similar sizes. Both indications are of unclear etiology, but are likely to have hormonal imbalance as part of the pathogenesis (29). Although the diagnoses were based on recall, it is unlikely that this resulted in systematic bias. Confirmation of these results in a larger study with more validated clinical and pathological information could be of great interest in understanding these processes.

An early age at menarche might imply a faster depletion of the follicle reserve and thus an earlier age at menopause (12). The genetic influence on age at menopause could, therefore, have simply been the result of a genetic effect on age at menarche. The total heritability of age at menarche was estimated to be 45%. The greater part of the genetic variance was due to dominance, confirming findings from large (*i.e.* sufficiently powered) Australian and Finnish twin studies (2, 4). Directional dominance effects are often found for fitness traits. This explanation also has an intuitive appeal, as the age at which a female begins to menstruate will certainly affect her reproductive fitness (3). Although both onset and cessation of menstruation were under genetic control, no correlation between age at menarche and age at menopause was observed. This lack of relationship and the influence of dominance on age at menarche, but not on age at menopause, indicate that there is no overlap between the genetic and environmental mechanisms determining the two events.

In an earlier study of the same twin pairs we have shown that, besides age at menarche, other possible confounders, such as BMI, smoking, alcohol use, and social class, may show higher MZ than DZ correlations as well (30). The possibility that a genetic effect on age at menopause was due to these confounders seems unlikely, as adjustment had no influence on the excess risk to develop menopause in MZ compared to DZ twins. Only smoking had a significant independent effect. The observed advance in age at menopause of 1.6 yr was in accordance with the literature (11, 16, 17).

To our knowledge our study is the first to show that individual differences in the timing of the menopause are largely due to genetic factors. Earlier studies suggested a link between premature ovarian failure and the gene that causes galactosemia (31), and there is considerable support for X-chromosomal errors as a factor in early menopause (18, 32). Recent studies by Cramer *et al.* (18) and Torgerson *et al.* (19)

showed family history to be a predictor of menopausal age, but recall bias could have affected the results.

An extensive body of literature is devoted to the question of which processes govern the onset and aging of the reproductive system. The start of menstruation has been linked to the accumulation of a critical amount of body fat (33). Findings by Kaprio *et al.* (4), who observed that BMI (a measure of obesity) and age at menarche had a substantial proportion of their genetic effects in common, support the idea that the genetic regulation of the onset of menarche is related to the accumulation of body fat. A recent study by Chebab *et al.* (34) in which prepubertal female mice were injected with leptin suggests that this hormone, secreted from adipose tissue, acts as the signal that triggers female puberty. Aging of the reproductive system, determined by the rate at which the reserve of follicles depletes, has not only been linked to factors within the ovary itself, but also to alterations in neuroendocrine activity (35–37). In a recent review of the evidence, Wise *et al.* (38) conclude that both the ovary and the brain are key pacemakers in determining the age at menopause. Our results suggest that these pacemakers are largely under genetic control.

From an evolutionary perspective, the genetic influence on the current distribution of menopausal ages in the population may be the result of a slow directional selection favoring earlier menopause and longer postmenopausal lifespans [the concept of the helpful grandmother (1)] and stabilizing selection against a menopause so early that it would have resulted in a reduction in the total number of offspring. Similar examples of stabilizing selection for quantitative traits resulting in high levels of genetic variability were described by Weiss (39).

The combined evidence of both the genetic model fitting and the survival analysis provided convincing evidence for the importance of genetic factors in determining the timing of age at menopause. Genes that predispose to early or late menopause may induce metabolic and endocrine changes that lead to an enhanced risk of cardiovascular disease, osteoporosis, and a number of reproductive cancers (40). Genes affecting the age of menopause may through this intermediary effect be partly responsible for the genetic effect on these diseases, which has to be considered in future studies of their genetic origins. From a practical point of view, information on early menopause in other family members may have implications in clinical decisions relating to family planning, hysterectomy, and institution of HRT.

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