Predictive factors of age at menopause in a large Australian twin study.

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Various studies have investigated potential predictors of age at natural menopause but have produced inconsistent results. The relationship between age at natural menopause and socioeconomic, reproductive, and health behavioral factors was evaluated using longitudinal data from 5961 Australian female twins, aged 17 to 88 years at the time of study. The sample consisted of women voluntarily enrolled in the Australian Twin Registry. Failure-time analysis was the principal statistical method used to handle censored observations. Kaplan-Meier estimates showed the overall median age at natural menopause to be 51 years (95% confidence interval, 50-51). Median age at menopause was earlier for women with earlier birth year, women with late age of menarche, women who had no children, or women who were smokers. Differences in age at menopause between social, occupational, and educational groups were statistically significant (Mantel-Cox test, p [less than] 0.001) for education, major occupational classification, combined income, and self-rated social class, with higher age at menopause for higher levels of each variable. A Cox proportional hazards model was used to estimate the odds ratio of the occurrence of natural menopause among different subgroups, adjusted to reflect simultaneous effects of all other significant covariates. This large study provided clear trends of association in predictors relating to age at menopause. These trends may help to resolve uncertainties and conflicting results identified in studies of comparable white samples. The nature of the twin data also sets a solid background for future analyses of genetic and environmental variance components using statistical modeling or related methods.

KEY WORDS: AGE; LONGITUDINAL STUDY, MENOPAUSE, RISK FACTORS, TWINS

Menopause is the permanent cessation of menstruation resulting from loss of ovarian follicular activity (World Health Organization Scientific Group 1981). By convention, the attribution of menopause is made retrospectively after twelve months of amenorrhea not resulting from pregnancy, lactation, or other factors (Sowers and La Pietra 1995). The final menstrual cycle marks not only the ending of the reproductive phase of life but also the beginning of a phase of permanently lowered estrogen secretion, which leads to somatic and metabolic changes. A great deal of hormonal, cytological, and experimental evidence shows that the ovary at menopause reaches a stage at which it fails to produce follicles fully capable of secretion and ovulation (Gosden and Faddy 1995).

Menopause occurs at approximately 50 years of age and usually ranges between 45 and 54 years in healthy, well-nourished populations worldwide (Treloar 1981; Gosden and Faddy 1995; Faddy and Gosden 1996; Gosden 1987). A cross-sectional study of 865 Australian women estimated the mean age at menopause to be 50.4 years for 341 women who had completed natural menopause (Walsh 1978).

It is generally agreed that contemporary industrialized populations demonstrate a later median age at menopause than populations that are nonindustrialized or poorly nourished (Gray 1976; Gosden 1985; Wood 1994; Leidy 1996). Almost all women living beyond 55 years will have experienced menopause. Menopause may interact with or accelerate events of normal aging. Early menopause may be a risk factor for earlier mortality from diseases related to decreased estrogen levels and may promote increased incidence of osteoporosis, heart disease, diabetes, hypertension, breast cancer, osteoarthritis, and autoimmune disease (Matthews et al. 1989, 1994; Holm and Penckofer 1992; Sowers and La Pietra 1995; Van der Schouw et al. 1996).

At present, it is not possible to predict with any confidence when natural menopause will occur in a given woman. Recent studies have shown that variation in age at menopause is associated with several factors, such as genetic, reproductive, sociodemographic, and certain behavioral influences (Boldsen and Jeune 1990; Luoto et al. 1994; Garrido-Latorre et al. 1996; Bromberger et al. 1997). In particular, current smokers experience significantly earlier menopause than past smokers or those who have never smoked. Among smokers, low relative weight is also predictive, with lean smokers having the highest risk of early menopause (Willett et al. 1983). Other common factors associated with earlier menopausal age include lower education or occupation (Stanford et al. 1987; Luoto et al. 1994), having no or few children (Willett et al. 1983; Whelan et al. 1990; Stanford et al. 1987), late age at menarche (Sherman et al. 1981), and never using oral contraceptives (Stanford et al. 1987). Recent results

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also suggest that irregular menstrual cycles, dieting, and stress (especially in African American women) are also predictive of earlier median age at menopause (Bromberger et al. 1997).

In this study we aim to assess the association between hypothesized covariates and age at menopause using phenotypic data from a large cohort from the Australian Twin Registry. Our study is the first large-scale investigation of the effect of birth year on menopausal age. We also aim to determine whether recall bias is a serious issue in reporting age at menopause. The main strengths of our study derive from increased power gained from a large sample and from the longitudinal nature of the data collection. Our longer-term goal, to investigate genetic factors in age at menopause, will be the focus of a subsequent paper.

Materials and Methods

Sample and Design. The study subjects were 6498 women, from different parts of Australia, enrolled with the Australian Twin Registry. The Australian Twin Registry, supported by the National Health and Medical Research Council (NHMRC), is a volunteer registry with more than 27,000 twin pairs enrolled, about 10-20% of the estimated number of twin pairs in the population. During 1980-1996, six longitudinal surveys of Australian twins were carried out by mailed questionnaires. The surveys obtained information about health history and behaviors, lifestyle factors, family structure, and personality.

The nature of follow-up is shown in Figure 1. Data were collected in six waves. Wave I was conducted in 1980-1982 and was part of a health survey (mailed questionnaires) funded by the NHMRC. Information was obtained from 4870 individual female twins [1231 monozygotic (MZ) and 748 dizygotic (DZ) female-female twin pairs; 912 females from DZ opposite-sex twin pairs]. The ages of the female respondents in 1980 ranged from 17 to 88 years (Silberg et al. 1987; Heath and Martin 1988; Kendler et al. 1988). Female twins answered questions on menstrual and reproductive history, including age at menarche, age at first pregnancy, childbirth history, hysterectomy, and natural menopause.

For wave 2 the same twins were followed up eight years later, between 1988 and 1990. A total of 4476 individual female twins responded, and their ages ranged from 25 to 87 years. This survey was supported by the NHMRC as a study of persistence of and changes in drinking habits. Women answered questions on menstrual, gynecological, and obstetric factors, including premenstrual symptoms, pregnancy and childbirth histories, menopause, and hysterectomy (Treloar et al. 1992; Heath and Martin 1994, Heath et al. 1995).

In 1990 a small repeat survey was conducted to obtain two-year test-retest reliability for information provided by respondents in wave 2. This survey is wave 3. The questionnaire from wave 2 was sent again to the first 500 wave 2 female respondents.

Wave 4 was a gynecological health study begun in August 1993. Questionnaires were sent to members of 1570 female twin pairs and 158 individual female twins (3297 individuals) who responded to the questionnaire in wave 2. Individual twins in incomplete pairs were included to validate hysterectomy and endometriosis, although their co-twins were no longer available for twin studies. The response rate was 94% (3096 individuals).

For wave 5 (1993-1995) a survey was commenced to study the health of twins aged over 50 years. The surveyed twins included a subset from wave 2 in addition to a new set of 1628 twins from which 1342 responded. The age range of these additional twins was 50 to 95 years. This survey elicited information on age of menarche, age at menopause and age at hysterectomy.

Last, to clarify inconsistencies in reported menopausal age and complicating factors such as hysterectomy, hormone replacement therapy (HRT), pregnancy, or breast feeding, a small telephone study was conducted in 1996 on 146 female twins followed up to 1995 (wave 6).

Thus overall there were two main cohorts: the original cohort of 4870 female twins recruited between 1980 and 1982 (aged 17 to 88 years), followed up until 1996; and a new cohort of 1628 women (aged over 50 years) recruited between 1993 and 1995.

A smaller number (n = 5961) from the two cohorts provided sufficient information on menstruation to enable their inclusion in these analyses. Women who commenced HRT before menopause (116 cases) and those with unresolved inconsistencies (18 cases) were excluded from the analysis. A total of 5593 women had a valid endpoint age for analyses and provided data on covariates.

Measures. Particular reproductive, lifestyle, and sociodemographic variables were hypothesized as covariates of age at menopause, along with zygosity and year of birth. The hypothesized covariates were birth year, education, social class, occupation, annual income, smoking habits, alcohol use, body mass index (BMI), age at menarche, and age at first full-term pregnancy. Selection of these variables was based on previous studies of determinants of menopausal age. Where information was collected in more than one survey, the

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value provided at the time closest to age at menopause was used, except for age at menarche, which was taken from the earliest survey, and quantities of smoking and drinking, which were accumulated over the woman's life span until age at menopause.

Birth year was treated as a continuous variable but was divided into two groups for computing Kaplan-Meier statistics.

Education data, collected in four surveys (waves 1-3 and 5), were categorized as (1) high school or less (including apprenticeship and diploma), (2) technical or teachers college, or (3) university or postgraduate degree.

Two surveys (waves 2 and 3) asked participants to classify their social class. Two levels, working or middle class, were used for analyses. The few classifying themselves as upper class were included in the middle class category.

Information on occupation was asked in four surveys (waves 1-3 and 5). The taxonomy of occupational classes based on the Australian Bureau of Statistics (ASCO) coding system (Australian Bureau of Statistics 1992), consisting of nine standard classifications, was used. We regrouped these into four major classes: (1) upper white-collar workers, (2) lower white-collar workers, (3) trade and sales service workers, and (4) blue-collar factory workers. Women who described their major lifetime occupation as homemakers, all married, were assigned their husband's occupation status.

Average annual income of twins and their spouses was calculated from two surveys (waves 2 and 3) and classified into (1) income less than Aus$10,000, (2) $10,000 to less than $30,000, (3) $30,000 to less than $50,000, or (4) $50,000 and more.

Smoking habits (current smoking, number of cigarettes smoked per day, age when subject began smoking, and periods when smoking was stopped) were investigated in four surveys. A smoker had reported smoking in any survey and started before menopause. A nonsmoker had reported that she had never smoked in all surveys, started smoking after menopause, or smoked only once or twice in her lifetime before menopause. Length of time smoked was calculated from age when smoking started to the age when smoking stopped or age at menopause, whichever occurred first, minus the total non-smoking periods in between. Pack years were calculated by multiplying the average number of cigarettes smoked per day by length of smoking time, divided by 20. Smokers were then classified into three groups: light smokers (less than 10 pack years), medium smokers (10-29 pack years), and heavy smokers (more than 29 pack years).

Alcohol use was assessed by questions on typical intake in the past 12 months, number of drinks in a typical week, and number of specific drinks (beer, wine, spirits, sherry, other) consumed each day of the past week. In wave 5 number of drinks consumed during different life periods (teenage, twenties, thirties, and forties) was added. Average daily consumption, presented in grams, was average number of drinks per day multiplied by 10. The final value, representing lifetime daily consumption, was obtained by averaging over the length of time a woman drank before menopause. Drinkers were classed as light (less than 10 g per day), moderate (10-19 g per day), or heavy (20 g or more per day).

Body mass index was computed separately for each of the four surveys where height and weight data were collected using the formula BMI = weight (kg)/[[height (m)].sup.2]. Average BMI was calculated by averaging BMI measures over surveys before menopause. Three groups of BMI were used: less than 21, 21-24, and greater than 24.

Age at menarche was reported in waves 1-3, 5, and 6. We used the age reported at earliest survey where possible. Age at menarche was then categorized into three groups: early ([less than or equal to]10 years), normal (11-14 years), and late ([greater than] 14 years). Four surveys (waves 1-3 and 5) asked about number of children and their dates of birth. Adopted and stepchildren were not included in these analyses.

Age at first full-term pregnancy was calculated from a woman's year of birth and her first child's date of birth. Parity was calculated by counting the number of live-born children reported in the latest survey where possible. Three groups were formed: (1) nulliparous (no children), (2) women with one or two children, and (3) women with more than two children.

For survival analysis the endpoint age was defined as one of the following: (1) age at natural menopause, (2) age at surgical menopause (i.e., hysterectomy or bilateral oophorectomy before natural menopause), (3) age when bleeding stopped because of other reasons, or (4) age at the last follow-up if the respondent was still menstruating and had never received HRT. All but age at natural menopause were considered censored observations.

Statistical Analyses. For univariate analyses all key independent variables [birth year, zygosity, smoking, BMI, age at menarche, age at first full-term pregnancy, level of alcohol intake, parity, and all socioeconomic indicators (self-rated social class, education, and income)] were first investigated for association with age at natural menopause. For multivariate analyses, to retain a large sample size, we did not use social class and income in

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simultaneous adjustments because they had substantial missing observations. Spearman rank correlations were also calculated for pairs of key independent variables in the final multivariate model. Failure-time analysis was the principal statistical method used.

Analyses were performed using SAS 6.09 (SAS Institute 1997). The Kaplan-Meier method was used to estimate the mean and median ages at natural menopause for different classes of each covariate. The Mantel-Cox (log rank) test was used to test for differences in menopausal age across the different classes of each variable. Cox proportional hazards regression models were used to calculate effects of the independent variables of interest and to obtain relevant relative risk for early menopause, estimated using the exponential of the parameter estimates, that is, the hazard ratios.

Results

Before investigating predictive factors, in order to test the representativeness of the sample with respect to age at menopause, we compared the distribution of menopausal age in the twins with the distribution in a control sample of nontwins (n = 855) collected for a population-based case-control study of ovarian cancer (Purdie et al. 1995). Control subjects were selected at random from the electoral roll, for which registration in Australia is compulsory and over 90% complete. Five thousand nine hundred sixty-one twin and 837 control women reporting information on menstruation patterns were classified into one of the following statuses: (0) still menstruating at last date of contact, (1) true postmenopausal, (2) hysterectomy or bilateral oophorectomy before menopause, (3) HRT before hysterectomy or menopause, (4) bleeding stopped because of other reasons, (5) unresolved inconsistencies (see Table 1).

None of the control women had a bilateral oophorectomy. Age at menopause was defined as age at the last menstrual period, determined retrospectively, after a woman had stopped menstruating for 12 months not as a result of pregnancy, lactation, or ill health [ILLUSTRATION FOR FIGURE 2 OMITTED]. The mean and median ages at natural menopause for twins (mean = 50.3, median = 51) were very close to the mean and median ages in the control group (mean = 50.7, median = 51). [TABULAR DATA FOR TABLE 1 OMITTED] Kaplan-Meier curves for age at menopause did not significantly differ between control subjects and twins (log rank p = 0.63) [ILLUSTRATION FOR FIGURE 3 OMITTED]. The proportion of women aged less than 40 years was lower in the control group (14%) than in the twin sample (40%). Consequently, the proportion of postmenopausal women was higher in the control sample.

Kaplan-Meier Estimate of Age at Menopause. Results of univariate analyses relating age at menopause to birth year, zygosity, and reproductive factors are presented in Table 2. The median age at menopause for all women was 51 years. Years of birth ranged from 1912 to 1964. Ten percent of the sample was born before 1925, 16% between 1925 and 1934, 25% between 1935 and 1944, 22% between 1945 and 1954, and 27% after 1954. We divided the sample into four birth cohorts (1915 or earlier, 1916-1925, 1926-1935, 1936 or later) with approximately equal proportions of postmenopausal women over 45 years of age. Incorporating a discrete birth-year effect revealed that the cohort born after 1935 had a 2-year later median age of natural menopause (52 years) than those with birth years before 1935 (p [less than] 0.0001) (Figure 4).

Compared with women with menarche at normal ages, women with late menarche had earlier menopause by 1 year (p [less than] 0.005), whereas the early menarche group was not significantly different. Median age at natural menopause was one year earlier for nulliparous than parous women (p [less than] 0.0006). Mean menopausal age was observed to increase with parity: 49.5, 50.5, and 50.7 for women with no children, those having 1 or 2 children, and those having more than 2 children, respectively. No significant variation in median age at menopause was found with respect to age at first full-term pregnancy, BMI, or zygosity.

Table 3 summarizes results of univariate analysis relating age at menopause to lifestyle and socioeconomic factors. The median age at natural menopause was one year earlier for smokers compared with nonsmokers (p [less than] 0.018). Similarly, women who drank alcohol had a median age at menopause one year later than abstainers (p [less than] 0.001). Among the smokers and drinkers no significant difference was observed between levels of consumption. Women with university degrees had a median age at menopause two years later than those with a high school education or less (p [less than] 0.0001). Significant differences in median age at menopause with respect to self-rated social class and occupation grouping were also observed. Specifically, women rating themselves as middle class had a later median age at menopause than their working class counterparts (51 vs. 50 years), and there was a monotonic decrease in median age at menopause with respect to the following occupational classes: upper white collar, lower white collar, blue collar, and others. The proportion of missing data for key variables varied from 0% to 8% of all responses, except for occupation, social class, and income, which had 16%, 37%, and 46% of observations missing, respectively. There was no indication of nonrandom patterns with respect to any missing variables.

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Cox Proportional Hazards Model. The Cox proportional hazards model is defined in terms of the hazard function, also known as the instantaneous failure rate or the age-specific failure rate. The hazard function is a measure of how likely an individual is to experience menopause as a function of the age of the individual. Univariate Cox models were first fitted to the age at natural menopause for all the covariates singly. Birth year, age at menarche, parity, smoking, drinking, education, occupation, social class, and income were found to be significant covariates (p [less than] 0.05), whereas zygosity, age at first full-term pregnancy, and BMI were not significant.

Birth year leads to the largest reduction in -2(log-likelihood) compared with other variables, with a parameter estimate of [Beta] = -0.02 (relative risk = 0.98, p [less than] 0.0001). Assuming that there is no recall bias with respect to age, this result can be interpreted as a 2% decrease in the hazard function for menopause for each increase in birth year; that is, more recent birth cohorts have later menopause.

Only those variables that appeared significant in the univariate models were considered for multivariate analyses using backward elimination. Statistical significance for retaining or removing a variable from the model was assessed by a likelihood ratio chi-square test. Despite significant results from univariate analysis for social class and income, these covariates could not be included in the multivariate model because of large proportions with missing responses.

First-order interaction effects between age and the other covariates were also investigated. The results of adding each interaction to the main-effects [TABULAR DATA FOR TABLE 2 OMITTED] model did not demonstrate any moderate level of statistical significance (p values for interactions were all greater than 0.2) and did not produce significant reductions in log-likelihood ratios. Thus the final Cox regression model included only main effects for birth year, age at menarche, parity, smoking, education, and occupation.

To obtain risk ratios and confidence intervals for the variables retained in the final model, only those observations with complete information for the variables birth year, age at menarche, parity, smoking, education, and occupation were included (n = 871) (Table 4). Spearman correlation coefficients were calculated for pairs of independent key variables in the final multivariate model. Mild correlations existed between birth year and parity ([Rho] = - 0.38), birth year and drinking ([Rho] = 0.31), and education and occupation ([Rho] = -0.48), with the highest category of occupation having the lowest level (see Table 3). All other correlations were much less than 0.3.

To assess the consistency of reporting over time, we estimated a two-year test-retest correlation of 0.92 [+ or -] 0.04 for 86 women who reported age at natural menopause in 1988 and again in 1990 (waves 2 and 3). In an overlapping sample of 413 women (waves 2 and 5) the 5-year consistency correlation was 0.83 [+ or -] 0.03, whereas the 8-year consistency measurement was 0.80 [+ or -] 0.03 in a common subset of 357 women (waves 1 and 2).

Inconsistencies in reporting age at menopause required resolution when the same women responded to different studies. To resolve these inconsistencies, we adopted the following rules. (1) If a woman reported different ages at menopause in different surveys, we accepted the age at menopause reported in the earliest survey as the true one (assuming that the reported value was more reliable when the age of reporting was closer to the age at menopause), provided that there were no other inconsistencies in subsequent surveys. (2) However, some women reported natural menopause in an earlier study but in later studies reported that they were still menstruating. Such discrepancies were mainly related to HRT. If a woman reported an age when she began HRT that was older than the reported age at menopause, then she was classified as postmenopausal with age at menopause as first reported. If she reported receiving HRT before menopause, then she was classified into the group with a status of 3. If no information on HRT or other reasons was given, then the subject was considered an unresolved case. If age at menopause was reported consistently in at least two surveys but the woman reported that she was still menstruating at a later survey, we assumed that she had started HRT after natural menopause, and she was classified as postmenopausal. (3) Occasionally "periods stopped" was reported in one survey but breast feeding and contraceptive use was reported in a later survey. If no subsequent information on menopause was reported, then such women were considered to be still menstruating at the time they reported breast feeding or use of contraceptives. Last, (4) when reported ages of menopause and hysterectomy were equal, then women were classified as having had a hysterectomy before natural menopause.

The longitudinal nature of our study, with self-reports of age at menopause available for multiple waves, allowed us to test the hypothesis that reporting bias increased with longer time since menopause. Regression analyses [TABULAR DATA FOR TABLE 4 OMITTED] were conducted to determine the difference in all possible pairs of reports in any two surveys against age of women at baseline. As the time since menopause increased, the

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slope of the regression reflected a downward trend, in support of the hypothesis, but was not significant (p [greater than] 0.4), suggesting that recall bias was not a severe problem in our study.

Discussion

This large longitudinal study on a large cohort of Australian twins evaluated the effect of reproductive, lifestyle, and socioeconomic factors, measured over a woman's life span, on age at natural menopause. The main advantages of this study are (1) it is the first large-scale prospective study of age at menopause conducted in Australia to test the influence of a wide range of predictive factors based on previous studies of menopause; (2) it includes a long follow-up period, approximately 16 years; and (3) it uses survival analyses and multivariate techniques to evaluate independent effects and to adjust for potential confounders.

Age at natural menopause has increased steadily over the past century in Australia. Our estimate compared closely with estimates from recent studies in other developed countries (Stanford et al. 1987; Luoto et al. 1994; Bromberger et al. 1997), although different age groupings did not allow comparison with the four-year age groupings of Kono et al. (1990).

Although it was difficult to evaluate the validity of self-reported age at menopause, because of the longitudinal nature of the twin study, consistency of reports could be assessed over study waves and was strong. Women tend to understate the age at which their last menstrual period occurred as the time lapse increases (McKinlay et al. 1972), and reproducibility of self-reported age at menopause has shown increasing within-person variance with increasing time since menopause (Colditz et al. 1987). This might explain the median age at menopause of women born before 1915 in our sample. However, analyses showed that recall bias was unlikely to be a substantial problem.

Previous studies have indicated that age at menarche either is not associated with age at menopause (Walsh 1978; Whelan et al. 1990; Purdie et al. 1995) or is confounded with smoking (Brambilla and McKinlay 1989). Benjamin (1969) suggested that the relationship between age at menarche and age at menopause is more likely to exist at the extremes of the distribution of age at menarche. In partial agreement with this, our study showed that women with late menarche ([greater than] 14 years) had a significantly earlier median age at menopause compared with women with normal age at menarche (10-14 years), even after adjusting for birth year, parity, smoking, education, and occupation. Parity was positively related to age at menopause, consistent with results from some studies (Soberon et al. 1966; Stanford et al. 1987), although other studies found no association (McKinlay et al. 1985; Purdie et al. 1995). Consistent with the results of Stanford et al. (1987), Brambilla and McKinlay (1989), and Luoto et al. (1994), BMI and age at first full-term pregnancy were not significant covariates. Smoking was significantly associated with age at menopause, although smoking quantity did not appear to be significantly associated with the median age at menopause, as found by McKinlay et al. (1985). However, a trend of decreasing mean age at menopause was observed with increasing amount smoked. Our results from multivariate analyses, with simultaneous adjustments for all covariates in the model, suggest that the predictive factors for age at menopause are birth year, age at menarche, parity, smoking, education and occupation.

The present study had several limitations. Although our study was longitudinal in design, women were not followed on a regular monthly basis, as in some prospective studies (Bromberger et al. 1997). Therefore estimated age at menopause was based on integer values reported retrospectively and hence may suffer from digit bias similar to that reported by Luoto et al. (1994). In addition, potential effects that result in partial unit-year differences in age at menopause would not be detected in this study. Whether age at menopause could be measured as precisely is questionable.

Our sample consisted of twins, which introduced correlated observations. If genetic influences are operating on age at menopause or on any covariates, the expected twin-pair correlation would be higher between members of MZ twin pairs than between members of DZ pairs, assuming equal environments. Repeat multivariate analyses using only one twin selected at random from each pair resulted in similar estimates for covariates, and the patterns of significance were the same for the full sample. To investigate whether age of menopause is genetic, more sophisticated statistical analytic methods using variance components modeling combined with Cox proportional hazards and related methods, such as estimating equations in the setting of correlated observations, should be used to obtain parameter estimates and tighter confidence intervals. This is a separate issue under investigation for a future paper.

Because the twins are a volunteer sample, it is possible that they are atypical of the population as a whole with respect to age at menopause. We showed, however, that the mean and median ages at natural menopause for twins were almost identical to those in the community control group. Differences between twin and control samples (e.g.,

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regarding proportions who had a hysterectomy or who were using HRT before menopause) arose because of the difference in age range of the samples and because longitudinal data were being compared with cross-sectional data. Discrepancies are unlikely to represent genuine biological differences. The sample was representative of the Australian female population with the highest level of educational attainment (Baker et al. 1996). Prevalence of recalled age at menarche has been shown to be comparable to the general Australian female population (Treloar and Martin 1990).

The physiological and endocrinological mechanisms through which the significant predictors influence age at menopause require identification. The debate between the relative contributions to menopausal age of compromised ovarian function and the hypothalamic-pituitary unit has been pursued and has been found wanting; the levels of complexity of the progressive changes in menstrual cycle functioning occurring with age are likely to be much greater than indicated by either of these explanations (Wise et al. 1996). Yet other factors, such as viral illness, have been hypothesized to affect oocyte depletion (Cramer et al. 1983). Most likely, highly complex interactions and multiple functions are in play among the molecular, cellular, neural, and hormonal factors affecting the menstrual cycle.

We have identified phenotypic associations between age at menopause and year of birth, age at menarche, parity, smoking, education, and occupation. To our knowledge, this is the first study that has investigated so rigorously the impact of birth year and recall bias on self-reported age at menopause. The cohort effect cannot be easily disentangled from associated effects of depression and poverty that are indirectly connected with education, occupation, and social class in earlier birth cohorts. Ascertainment bias cannot be the explanation for the cohort effect identified here because women who were born before 1926 and who died before 1980 (early deaths) were more likely to have had earlier menopause than those who were still alive in 1980. Therefore, if total ascertainment were possible, the effect of birth year would be magnified.

If age at menopause is found to be genetically influenced, as is age at menarche (Treloar and Martin 1990; Meyer et al. 1991; Loesch et al. 1995), future multivariate genetic analyses could decompose not only the genetic and environmental sources of variation but also the sources of covariation with the pertinent factors from the present analysis.

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