FERTILITY AND STERILITY®
VOL. 82, NO. 5, NOVEMBER 2004

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

Heritability of menopausal age in mothers and daughters

Kristel M. van Asselt, M.D., Ph.D.,[a,b,c] *Helen S. Kok, M.D., Ph.D.,*[a,b,c] *Peter L. Pearson, M.D., Ph.D.,*[c] *Judith S. Dubas, Ph.D.,*[d] *Petra H. M. Peeters, M.D., Ph.D.,*[a] *Egbert R. te Velde, M.D., Ph.D.,*[b] *and Paulus A. H. van Noord M.D., Ph.D.*[a]

University Medical Center Utrecht, and Utrecht University, Utrecht, The Netherlands

Objective: To determine the heritability of age at natural menopause from mother-daughter pairs.

Design: Two-generation families were selected to study heritability of menopausal age.

Setting: Subjects were drawn from a population-based study.

Patient(s): One hundred sixty-four mother-daughter pairs with a natural menopausal age.

Intervention(s): None.

Main Outcome Measure(s): The heritability of age at natural menopause estimated by a random-effects model.

Result(s): A heritability of 44% (95% confidence interval, 36%, 50%) was estimated.

Conclusion(s): This study confirms that heritable components largely determine the natural age at menopause. Reasons for the differences between heritability estimates based on sibling pairs and parent-child comparisons are discussed. (Fertil Steril® 2004;82:1348–51. ©2004 by American Society for Reproductive Medicine.)

Key Words: Menopause; heritability; genetics

Received December 4, 2003; revised and accepted April 5, 2004.

Reprint requests: Petra H. M. Peeters, University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, Heidelberglaan Room D01.335, Box 85500, Utrecht 3508, The Netherlands (FAX: 31-30-250-5485; E-mail: P.H.M.Peeters@jc.azu.nl).

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht.

[b] Department of Reproductive Medicine, University Medical Center Utrecht.

[c] Department of Medical Genetics, University Medical Center Utrecht.

[d] Department of Developmental Psychology, Utrecht University.

0015-0282/04/$30.00
doi:10.1016/j.fertnstert.2004.04.047

Population studies indicate that fecundity in women begins its steep decrease around age 35 (1), which is about 15 years before the average age of menopause, which is around 50 years. This interval, from the onset of the decline in fertility to menopause, as derived from population averages, appears to apply also to individual women (2). This start of the decrease in fertility cannot (yet) be measured directly. The genetic factors underlying menopausal age may be the same genetic factors influencing the end of fertility.

The heritability of age at natural menopause, which is defined as the proportion of the population variation attributable to genetic variation, has previously been estimated at 70% in sisters and twins from an open Dutch population (3). In this study, we carried out a mother-daughter comparison to estimate the heritability of menopausal age using essentially the same open Dutch population used previously in a sister-sister comparison.

MATERIALS AND METHODS

Female participants were volunteers in the Diagnostisch Onderzoek Mammacarcinoom [Diagnostic Investigation Mamma Cancer] (DOM) breast cancer screening project that started in 1974 in the open population of the province of Utrecht, The Netherlands (4). Mothers were selected among the women of the oldest birth cohorts screened, that is, those born between 1911 and 1926. Daughters were selected from the younger birth cohorts and were born between 1932 and 1946. All women gave informed consent to use their data and urine for future scientific research. The Institutional Review Board of the University Medical Center Utrecht, The Netherlands, approved the study.

Probabilistic linkage was used to trace mother-daughter pairs based on information provided by the participants: date of birth of the mother, date of birth of the children, birth order, and part of the (maiden) name, similar to the way in which this information was documented and successfully applied before (3).

Natural menopause was defined as at least 1 year of amenorrhea not due to surgery or other obvious cause. Women had provided information on whether their last menstruation was natural or due to medical interventions. Most

women in the oldest cohorts were already postmenopausal upon first screening. Members of the younger cohorts were either menopausal upon first screening or their natural menopause was assessed in one of the following ways: in subsequent screening rounds, during participation in the Prospect-EPIC study between 1993 and 1997 (5), or through follow-up by filling out menstruation calendars. Only mother-daughter sets, where both a mother and her daughter (the oldest in case of more than one daughter) had had a natural menopause were included in the analysis. To estimate heritability by intraclass correlation, a random-effects model using maximum likelihood was applied in SPLUS. Paired *t*-tests on mean differences in ages at menopause between the two mother-daughter groups were done.

RESULTS

Probabilistic linkage identification traced 164 actual mother-daughter pairs in which both mother and daughter had experienced a natural menopause. Actual mother-daughter comparisons showed a significant difference of 1 year in mean ages at menopause ($O = .022$). This is illustrated by Figure 1, which shows the distributions of menopausal age of the mother cohort and the daughter cohort.

The random-effects model resulted in an intraclass correlation of 0.22, and since mothers and daughters share half of their polymorphic alleles, the heritability was assumed to be 0.44 (95% confidence interval [CI], 0.36, 0.50). The shared variance was 3.8, and the nonshared variance was 13.8.

DISCUSSION

This study shows that the heritability of menopausal age based on mother-daughter pairs is 44% (95% CI, 36%, 50%) and confirms that age at natural menopause is also determined by "heritable" components. Both comparisons among sisters and twin-sisters as well as between mothers and daughters found indications for genetic components.

The existence of genetic variance in menopausal age was already suggested by a case-control study (6) and a cross-sectional study (7) in which early menopause tended to cluster in families. Former heritability studies of menopausal age of twins and siblings all showed substantial genetic variance (8–11).

Heritability estimates differ when estimates are based on studies including parent-offspring instead of siblings for several reasons. The shared variance is estimated by use of familial correlations. However, this shared variance consists of the genetic contribution and common environmental factors that may influence the trait. Since many of the environmental factors are unmeasured, or unknown, adjustments are not possible. The heritability is therefore overestimated if many shared environmental factors are present. This would occur especially in siblings because they share a relatively more homogeneous environment, prenatally as well as postnatally, than parents and offspring who belong to two different generations.

Furthermore, because heritability is expressed as a proportion of the total phenotypic variance, a substantially smaller environmental variance in the siblings compared with the mother-daughter comparison may also result in a lower heritability estimate in studies of parent-offspring (12). It is argued, however, that the influence of environmental factors on menopausal age is very limited; the explained variance by known environmental factors was only a few percent (13).

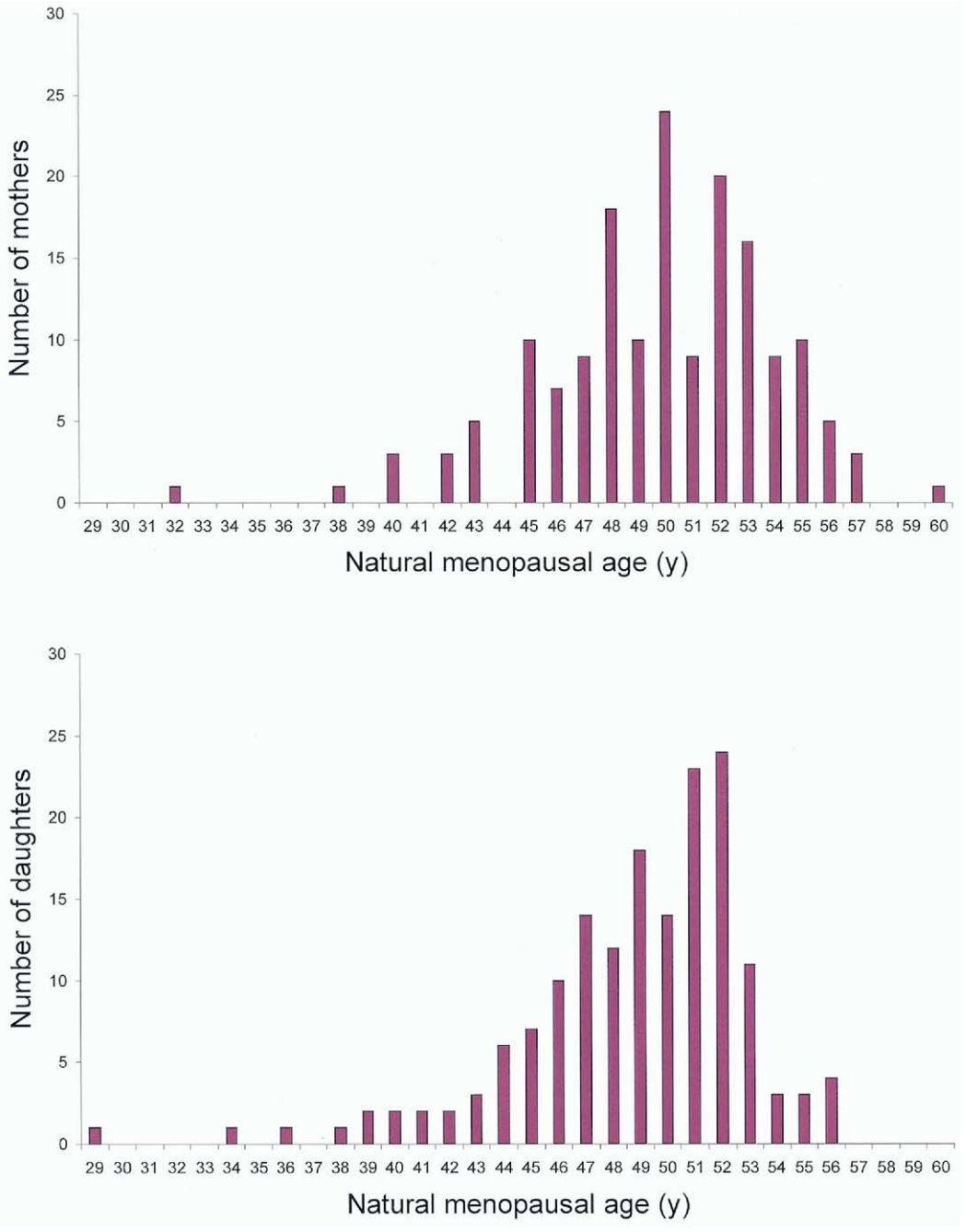
Moreover, studies among sister pairs cannot distinguish certain types of additive and nonadditive variances. Additive effects of loci (the effects of loci when they act independently) can be estimated in parent-offspring studies because parents and offspring always have half of their genes in common. However, siblings do not share exactly 50% of their genetic variance, but it is on average 50%. This implies that siblings can share both or neither of the parental alleles. The genetic variance in siblings therefore also includes dominance variance, which is the residual genetic variance when both alleles interact on the same locus. Parent-offspring variance has no dominance variance, and therefore the total genetic variance is lower compared with siblings.

On average, the daughters experienced menopause 1 year earlier than their mothers, which might be explained by several mechanisms. First, an incomplete follow-up of the daughter group may have resulted in a deficiency of daughters in the later menopausal age range. The histogram shows a stronger left skewing of the daughters compared with the mothers, indicating that this might be a cause of the lower mean menopausal age of the daughters. Second, left censoring may differ between mothers and daughters, that is, women with an extremely early menopause are less likely to give birth. Among mothers, women were included only if they had a daughter. Women with extremely early menopausal ages may be underrepresented in the group of mothers. This selection had not occurred for the daughters. Excluding mother-daughter pairs in which the daughter was nulliparous changes the mean menopausal age of the daughters from 48.8 to 49.2. Third, environmental factors that influence age at menopause may have changed over time and may have therefore affected the menopausal age between birth cohorts. Such factors may be smoking, the average number of births, being overweight, and the use of oral contraceptives. Secular trends in age at menopause have been investigated, but the results are not consistent. However, if there is a trend, it would be a later age at menopause instead of a decreasing age (14–16).

An underlying assumption of heritability estimates relates to the assumption that the genetic variation is inherited in a Mendelian fashion with half of the variation being paternally derived and the other half maternally. It

FIGURE 1

Distribution of menopausal age of mothers and daughters.



van Asselt. Heritability of menopausal age. Fertil Steril 2004.

is possible that variation in the mitochondrial genome, which is entirely maternally inherited, may also contribute. However, there are no examples of proven mitochondrial disorders that have premature female infertility as a feature, making it unlikely that the mitochondria play a significant role in familial transmission of reproductive features such as age at menopause.

However, mitochondria may play a role in fertility, as was suggested by Cohen et al., who found that ooplasm donation

with young donor-mother mtDNA was shown to revitalize less fit oocytes before conception (17).

Maternal chronological age determines the chance of becoming pregnant, of giving birth to a healthy child, and of miscarrying. However, studies demonstrate that there is a great variation in the rate of ovarian aging in women; therefore menopausal age may be a far better predictor of female reproductive performance than chronological age (2).

Unraveling the genetic determinants involved in menopausal age potentially opens the way to identify which women are at risk of premature ovarian aging and who can afford delaying having their families without fear of infertility. Since (genetic) tests are lacking to predict the age at menopause, an important indication may be family history on menopausal age.

Acknowledgments: The authors thank all the women who volunteered in the DOM project. Without their kind collaboration, this type of study would not have been possible. The contributions of I. den Tonkelaar, Ph.D, and S. Elias, M.Sc., in updating the menopausal status are greatly appreciated. We thank G. Haars, M.Sc., for the probabilistic linkage and H. Putter, Ph.D, for statistical advice.

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