

Measures of Menopausal Status in Relation to Demographic, Reproductive, and Behavioral Characteristics in a Population-based Study of Women Aged 35–49 Years

Glinda S. Cooper,¹ Donna D. Baird,¹ and F. Rebecca Darden²

The purpose of this cross-sectional analysis of women aged 35–49 years from the Third National Health and Nutrition Examination Survey, conducted between 1988 and 1994, was to assess associations with menopausal status based either on menstrual cycle patterns or on elevated (>20 IU/liter) follicle-stimulating hormone. Menstrual cycle-based menopausal status was defined for women who had not had surgical menopause by months since the last period (<2, 2–12, and >12 months for pre-, peri-, and postmenopause, respectively). Logistic regression was adjusted for age, smoking, and unilateral oophorectomy. Higher body mass index (≥ 30 kg/m² compared with < 25.0 kg/m²) was associated with a lower likelihood of elevated follicle-stimulating hormone (odds ratio (OR) = 0.6, 95% confidence interval (CI): 0.4, 0.9) but this association was not seen with the menstrual measure of menopause. Exercise (three or more times per week) was associated with a lower likelihood of being postmenopausal on the basis of menstrual (OR = 0.3, 95% CI: 0.2, 0.7) and hormonal (OR = 0.6, 95% CI: 0.4, 1.0) measures. Alcohol use also tended to be associated with postmenopausal status by either measure, but not significantly so. There was little evidence of associations with ethnicity, education, age at menarche, number of livebirths, and oral contraceptive use. Menstrual-based definitions of menopause can be misclassified for women with menstrual irregularity. This might explain why obese women were classified menstrually as menopausal while remaining hormonally premenopausal. *Am J Epidemiol* 2001;153:1159–65.

alcohol drinking; menarche; menopause; obesity; parity

Early natural menopause has been associated with an increased risk of all-cause (1, 2) and cardiovascular (3) mortality. Age at natural menopause has also been proposed as a marker of ovarian toxicity for factors that may directly or indirectly damage the follicular pool (4). Approximately 5–10 percent of women in the United States experience natural menopause by age 45 years, and the median age at menopause is approximately 51 years (5). Numerous studies (6–13), including a 1990 meta-analysis (6), reported an earlier age at natural menopause among current smokers compared with women who had never smoked. An early age at menopause in women with lower levels of education has been observed in univariate analyses in many studies, but this association was not seen when adjustment was made for smoking and other factors (8–11, 13, 14). Increasing parity was associated with a later age at menopause in most studies that examined this factor (11, 13–17). Relatively few

studies have examined other factors (e.g., alcohol use, age at menarche) in relation to age at natural menopause, and there are inconsistent results among the studies that are currently available.

Most studies that examine risk factors for menopause have used self-reported menstrual characteristics to define menopause. A few (18–20) have used the hormonal marker follicle-stimulating hormone (FSH). FSH concentrations may increase for up to several years before menstrual cycles cease (21, 22).

We examined the associations between lifestyle, demographic, and reproductive factors (specifically, body mass index, exercise, alcohol use, ethnicity, education, age at menarche, pregnancy history, and oral contraceptive use) and menopause in women of late reproductive age from a representative sample of the United States population. The use of both menstrual and hormonal measures of menopause allows us to determine consistencies and inconsistencies between them.

MATERIALS AND METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) was a national, cross-sectional, population-based study of 33,994 noninstitutionalized, civilian persons aged 2 months to 74 years conducted between 1988 and 1994 by the National Center for Health Statistics. NHANES III was designed to evaluate the nutri-

Received for publication April 6, 2000, and accepted for publication October 20, 2000.

Abbreviations: CI, confidence interval; FSH, follicle-stimulating hormone; NHANES, National Health and Nutrition Examination Survey; NHANES III, Third National Health and Nutrition Examination Survey; OR, odds ratio.

¹Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, NC.

²Westat, Inc., Research Triangle Park, NC.

Reprint requests to Dr. Glinda S. Cooper, Epidemiology Branch A3-05, National Institute of Environmental Health Sciences, Durham, NC 27709 (e-mail: cooper1@niehs.nih.gov).

tional and health statuses of the United States population and used a stratified, multistage sampling procedure to select the study sample. Data collection included a standardized in-person interview, blood sample, physical examination, and other clinical and laboratory procedures (23).

We selected NHANES III women aged 35–49 ($n = 2,205$) for study. This age restriction was chosen because we were interested in factors that affected early menopause. The reasons for exclusion varied somewhat between the analysis of menstrual patterns status and FSH (table 1), but 227 women were excluded from both analyses because of specific medical indications or medication use (bilateral oophorectomy, current oral contraceptive use, and menopause related to chemotherapy or radiation) that precluded assessment of current menstrual periods and FSH levels. For the analyses of menstrual patterns, 274 women who had had surgical menopause (hysterectomy) or had an

uncertain menopausal status were excluded. For the FSH analyses, women who had had a hysterectomy without bilateral oophorectomy were included, but 184 women who were currently pregnant or breastfeeding or who had missing hormone or oophorectomy data were excluded.

At the time of the blood draw, women were asked, "About how long ago was your last period," with response categories: having it now, less than 2, 2–3, 4–6, 7–9, and 10–12 months ago. Women who had not had a period in the previous 12 months were asked about their age at their last period. FSH concentrations in postmenopausal women far exceed those found at any time during the premenopausal menstrual cycle, but perimenopausal FSH can be similar in concentration to increases seen at time of ovulation for premenopausal women. Since the blood samples were not timed to a specific day of the cycle, some samples were taken around the time of ovulation and could not be used to assess menopausal status reliably. The rise in luteinizing hormone is greater than that in FSH around the time of ovulation, with luteinizing hormone-to-FSH ratios of 1.5–2.0 or higher (24). In contrast, FSH tends to rise before luteinizing hormone during the premenopausal years, resulting in a luteinizing hormone-to-FSH ratio of less than 1.0 (21). On the basis of this information, we excluded 65 women with a ratio of luteinizing hormone to FSH higher than 2.0 to reduce the potential influence of increases in FSH that occur around ovulation.

Use of hormone replacement therapy may present some difficulties in the classification of menopausal status based on either menstrual cycles or FSH because of withdrawal bleeding that can occur with progestins and because of a suppressive effect of estrogen on FSH. However, excluding users of hormone replacement therapy could introduce a selection bias into the study, and including hormone replacement therapy use in the logistic regression models could produce attenuated estimates due to overadjustment of an intermediary variable. We included 19 women who were currently using hormone replacement therapy in the analysis of menopause based on menstrual cycles. Twelve of the women were classified as postmenopausal (>12 months since the last menstrual period), and seven were classified as perimenopausal. We also examined the effect of hormone replacement therapy on FSH by using the NHANES III data. Among 129 women aged 35–49 years with a bilateral oophorectomy, 85 percent of the women who were currently using hormone replacement therapy pills had an FSH that exceeded 20 IU/liter compared with 86 percent of nonusers. However, the prevalence of very high (>40 IU/liter) levels was somewhat lower among hormone replacement therapy users (52 percent compared with 67 percent for nonusers; odds ratio (OR) = 0.5, 95 percent confidence interval (CI): 0.2, 1.3, $p = 0.13$). A cutpoint of 20 IU/liter differentiated between 50 premenopausal and 49 oophorectomized women in a study by Nordin et al. (25). For these reasons, we chose to define elevated FSH as above 20 IU/liter, and we included 59 current users of hormone replacement therapy in the FSH analysis.

After all exclusions, there were 1,555 premenopausal women (1,520 who had had a period in the previous 2 months, 19 currently pregnant, and 16 currently breastfeed-

TABLE 1. Sample size and exclusions in analyses of menopausal status based on menstrual cycle patterns and follicle-stimulating hormone in women aged 35–49 years, Third National Health and Nutrition Examination Survey, 1988–1994

	Menstrual cycle patterns analysis	FSH* analysis
Total potentially eligible	2,205	2,205
Reason for exclusion common to both analyses ($n = 227$)		
Bilateral oophorectomy	136	136
Currently using oral contraceptives	82	82
Menopause related to chemotherapy or radiation	9	9
Reason for exclusion from menstrual cycle analysis ($n = 274$)		
Surgical menopause (hysterectomy) without bilateral oophorectomy	266	
Missing or uncertain menopausal status	8	
Reason for exclusion from FSH analysis ($n = 249$)		
Currently pregnant		19
Currently breastfeeding		16
Surgical menopause (hysterectomy) but missing oophorectomy data		8
Missing FSH or luteinizing hormone data		141
Luteinizing hormone:FSH ratio greater than 2.0		65
Total available in sample	1,704	1,729
Total after excluding missing covariate data†	1,696	1,721

* FSH, follicle-stimulating hormone.

† Age, smoking status, oophorectomy, and (for FSH analysis) hysterectomy.

ing), 66 perimenopausal women (2–12 months since the last menstrual period), and 75 postmenopausal women (>12 months since the last menstrual period), for a total of 1,696 women in the menstrual-cycle analysis. There were 1,721 women in the FSH analysis (1,481 with FSH \leq 20 IU/liter and 240 with FSH >20 IU/liter).

The interview data collected in NHANES III included information on age, ethnicity, education, smoking history, menopausal status, use of birth control pills, use of hormone replacement therapy, number of pregnancies, and number of livebirths. Information on alcohol use was obtained from the food frequency questionnaire that included three questions about usual consumption over the previous month of beer and light beer, wine, wine coolers, sangria, champagne, and hard liquor. An additional question asked about frequency of binge drinking (nine or more drinks in a day) over the previous 12 months. Categorization of exercise was based on the summation of self-reported frequency of eight specific activities (running/jogging, bicycling, swimming, aerobics, other dancing, calisthenics, gardening, and lifting weights) during the previous month. Height and weight were measured as part of the physical examination and were used to calculate body mass index (kg/m^2). We divided body mass index based on cutpoints defining obesity that were used in a previous analysis of National Health and Nutrition Examination Survey (NHANES) data (26).

FSH was measured in NHANES III by using an immunoradiometric assay (FSH MAIAclone, Serono Diagnostics, East Walpole, Massachusetts). The coefficient of variation was 8.9 percent for low controls and 3.1 percent for high controls (27).

Logistic regression, fitting generalized logits to model a three-level, nominal (nonordered) outcome of menopausal status based on menstrual cycles (premenopause, perimenopause, and postmenopause), was used for the analysis. Age (as a continuous variable), current smoking (yes/no), and unilateral oophorectomy were included in all models because these were predictors of menopausal status in other studies (6, 17, 20, 28). Other factors (body mass index, exercise, alcohol use, ethnicity, education, age at menarche, parity, and oral contraceptive use) were added to the model one at a time. We then looked for evidence of confounding between these variables by examining the change in associations when combinations of variables that could be correlated (e.g., body mass index and exercise; education and ethnicity; and body mass index, ethnicity, and education) were added to the model. We stratified by smoking status to examine the possible interaction between smoking and body mass index. This interaction was reported in a previous study (7). Results are presented in terms of odds ratios and 95 percent confidence intervals.

We used logistic regression to analyze the prevalence of elevated FSH (>20 IU/liter). In addition to age, smoking, and unilateral oophorectomy, we adjusted for hysterectomy in this model (20). The analytic strategy was similar to the process described for the analysis of menstrually based menopausal status.

We examined the effect of some of our inclusion and exclusion decisions by comparing results with subsets of the data.

For example, we included 35 women who were currently pregnant or breastfeeding in the analysis of menopausal status based on menstrual cycles and classified them as premenopausal. There was little difference in the observed associations when we excluded these women. We also repeated the analyses, limiting both sets to the 1,487 women who had FSH and the menstrually defined measure of menopausal status, to determine whether any differences in the associations that we observed could be attributed to differences in the sample. Our results were similar when using this more limited sample. We present the results from the larger, more representative sample.

RESULTS

FSH was strongly correlated with the menstrually defined measure of menopause (figure 1). The proportions with FSH of at least 20 IU/liter were 6, 50, and 85 percent for the premenopausal, perimenopausal, and postmenopausal groups, respectively.

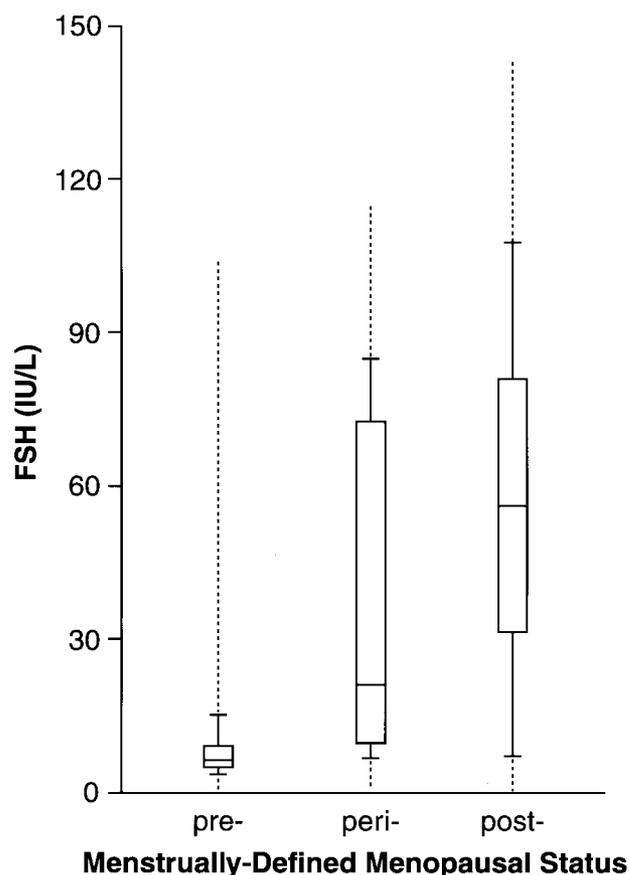


FIGURE 1. Follicle-stimulating hormone (FSH) level in relation to menstrually defined menopausal status in 1,487 women aged 35–49 years in the Third National Health and Nutrition Examination Survey (1988–1994): premenopause (<2 months since the last menstrual period, $n = 1,360$), perimenopause (2–12 months since the last menstrual period, $n = 62$), and postmenopause (>12 months since the last menstrual period, $n = 65$). The ends of the dashed lines represent the range; short, horizontal lines represent the 10th and 90th percentiles; and the boxes represent the 25th, 50th, and 75th percentiles of the distributions, respectively.

Higher body mass index was associated with lower FSH levels (adjusted OR = 0.6 for ≥ 30 kg/m² compared with < 25.0 kg/m²) (table 2). However, the direction of the associations with the measures based on menstrual cycle patterns were reversed. Higher body mass was associated with

an increased risk of being peri- or postmenopausal, although the confidence intervals around these estimates were wide and included 1.0. Results were similar when stratified by smoking status, so there was no evidence of effect modification.

TABLE 2. Associations with menopausal status (based on menstrual cycle patterns) and elevated follicle-stimulating hormone (follicle-stimulating hormone > 20 IU/liter) among women aged 35–49 years, Third National Health and Nutrition Examination Survey, 1988–1994

Demographic or lifestyle factor	Menopause status*						FSH > 20.0 IU/liter†			
	No.	%‡	Perimenopausal		Postmenopausal		No.	%¶	OR	95% CI
			OR§	95% CI§	OR	95% CI				
Body mass index (kg/m²)										
<25.0	587	35	1.0	Referent	1.0	Referent	587	34	1.0	Referent
25.0–29.9	503	30	0.8	0.4, 1.7	0.7	0.4, 1.4	509	30	0.9	0.6, 1.3
≥ 30.0	604	36	1.6	0.9, 2.8	1.2	0.7, 2.1	624	36	0.6	0.4, 0.9
Exercise (times per week)#										
0	644	38	1.0	Referent	1.0	Referent	643	37	1.0	Referent
<3	624	37	1.5	0.8, 2.7	0.6	0.4, 1.1	651	38	0.8	0.6, 1.2
≥ 3	425	25	1.1	0.6, 2.3	0.3	0.2, 0.7	425	25	0.6	0.4, 1.0
Alcohol (drinks per week)**										
None	963	57	1.0	Referent	1.0	Referent	976	57	1.0	Referent
<3	535	32	0.8	0.4, 1.4	0.5	0.3, 1.0	551	32	1.0	0.7, 1.4
≥ 3	197	12	0.9	0.4, 1.9	0.5	0.2, 1.1	193	11	0.8	0.5, 1.3
Ethnicity										
African American	548	33	1.2	0.6, 2.4	1.6	0.9, 2.9	567	33	1.3	0.9, 1.8
Hispanic	543	33	2.4	1.2, 4.8	1.3	0.6, 2.6	535	32	1.0	0.7, 1.7
White	576	35	1.0	Referent	1.0	Referent	594	35	1.0	Referent
Education (years)										
<12	518	31	1.0	Referent	1.0	Referent	523	30	1.0	Referent
12	560	33	0.9	0.5, 1.8	0.6	0.3, 1.2	605	35	0.8	0.5, 1.2
>12	610	36	1.2	0.6, 2.3	0.7	0.4, 1.4	588	34	0.8	0.5, 1.2
Age at menarche (years)										
8–10	135	8	0.9	0.3, 2.6	2.0	0.9, 4.3	147	9	1.5	0.9, 2.6
11–13	1,083	65	1.0	Referent	1.0	Referent	1,090	64	1.0	Referent
14–15	360	21	1.3	0.7, 2.3	0.7	0.3, 1.3	367	22	1.3	0.9, 2.0
16–19	101	6	0.7	0.2, 2.4	1.1	0.4, 2.8	102	6	1.3	0.7, 2.4
Livebirths										
0	212	13	1.0	Referent	1.0	Referent	196	11	1.0	Referent
1	236	14	1.7	0.6, 5.3	0.9	0.3, 2.3	247	14	1.3	0.7, 2.5
2	494	29	1.0	0.3, 2.8	0.8	0.3, 1.8	507	29	0.9	0.5, 1.5
3	355	21	1.4	0.5, 4.0	1.1	0.5, 2.6	360	21	1.2	0.7, 2.2
≥ 4	396	23	1.9	0.7, 5.2	0.6	0.2, 1.4	411	24	0.9	0.5, 1.6
Oral contraceptives (months)										
Never	404	24	1.0	Referent	1.0	Referent	400	2	1.0	Referent
1–12	409	24	1.1	0.6, 2.2	0.9	0.4, 1.8	436	26	1.0	0.6, 1.6
13–60	446	27	0.9	0.5, 1.9	1.0	0.5, 1.9	442	26	0.9	0.6, 1.4
>60	423	25	0.9	0.4, 1.8	0.9	0.4, 1.7	428	25	1.0	0.7, 1.6

* Categorical regression model analyzing menopausal status in relation to age (per year), smoking status (current, noncurrent), and unilateral oophorectomy. Women who had hysterectomies were excluded from the sample. The model with body mass index also adjusts for exercise, the model with exercise adjusts for body mass index, the model with ethnicity adjusts for education, and the model with education adjusts for ethnicity. Referent group is premenopausal status.

† Logistic regression model analyzing follicle-stimulating hormone (FSH) above 20.0 IU/liter as the outcome variable, adjusting for age (continuous), smoking status (current, noncurrent), unilateral oophorectomy, and hysterectomy. The model with body mass index also adjusts for exercise, the model with exercise adjusts for body mass index, the model with ethnicity adjusts for education, and the model with education adjusts for ethnicity. Women who had ratio of luteinizing hormone:FSH ratio greater than 2.0 were excluded from the sample. Women with hysterectomies who had at least one ovary were included.

‡ Percent refers to the prevalence within the total sample after exclusions for missing covariates. Total sample: $n = 1,696$; 1,555 premenopausal, 66 perimenopausal, and 75 post-natural menopausal. Missing data: body mass index ($n = 2$), exercise ($n = 43$), alcohol ($n = 1$), ethnicity ($n = 29$), education ($n = 8$), age at menarche (17 years), livebirths (3), and oral contraceptive use ($n = 14$).

§ OR, odds ratio; CI, confidence interval.

¶ Percent refers to the prevalence within the total sample after exclusions for missing covariates. Total sample: $n = 1,721$; 1,481 with FSH ≤ 20 IU/liter, 240 with FSH > 20 IU/liter. Missing data: body mass index ($n = 1$), exercise ($n = 2$), alcohol ($n = 1$), ethnicity ($n = 25$), education ($n = 5$), age at menarche (15 years), livebirths ($n = 0$), and oral contraceptive use ($n = 15$).

Based on summation of the reported frequency of eight specific activities (running/jogging, bicycling, swimming, aerobics, other dancing, calisthenics, gardening, and lifting weights) during the previous month.

** Based on reported frequency of consumption over the previous month of beer, wine, and hard liquor.

Exercise was associated with a lower likelihood of having an elevated FSH level or of being postmenopausal as defined by menstrual cycle patterns (table 2). Similar, but somewhat weaker, associations were seen with alcohol use. Little association was seen with perimenopausal status with either exposure. Binge drinking (nine or more drinks per day at least once during the previous year) was reported by only 5 percent of the study participants. The patterns of association with binge drinking (OR for being postmenopausal = 0.4, 95 percent CI: 0.1, 1.9; OR for elevated FSH = 0.8, 95 percent CI: 0.3, 1.7) were similar to the associations with the alcohol measure based on drinks per week, but, given the low frequency of this exposure, these are imprecise estimates.

On the basis of menstrually defined menopause, African Americans had a somewhat increased likelihood of being postmenopausal and Hispanics were more likely to be perimenopausal, but there was little association with the hormonally defined menopause measure in either group. There was little evidence of an association between FSH or menstrually defined menopausal status and education level, number of livebirths, or oral contraceptive use. Additional adjustment for body mass index had little effect on the associations with ethnicity or education (data not shown). Younger age at menarche (≤ 10 years) was somewhat associated with postmenopausal status and with increased FSH levels, but the estimates were not statistically significant. No association was seen with later age at menarche.

DISCUSSION

The purpose of this study was to identify factors that can influence the process of ovarian senescence, marked by missed menses and elevations in FSH. Ovarian senescence is caused by the final demise of the prenatally determined pool of follicles. Follicular atresia by apoptosis occurs throughout a woman's life, and variation in age of menopause is thought to reflect variation in rates of atresia. Little is known about the biologic factors controlling atresia.

The menstrual-based measures of menopause allowed us to identify perimenopause women as a separate group. However, it does not necessarily follow that factors that cause early menopause would also affect perimenopause. Perimenopause, defined by a time of irregular menstrual cycling before final amenorrhea, may or may not occur. It is possible for women to have regular cycles up to the time of their last period, thus skipping a menstrually defined perimenopausal interval. An exposure that extended the perimenopausal interval but did not result in earlier entry into menopause would be a risk factor for perimenopause but might actually reduce the likelihood of menopause. Therefore, we evaluated menstrually defined perimenopause and postmenopause separately rather than as a single ordinal outcome.

We observed an association between higher body mass index and reduced risk of being menopausal (OR = 0.6), as defined by a hormonal measure of elevated FSH. However, the associations with menopausal status based on menstrual cycle patterns were in the opposite direction (that is, odds ratios were greater than 1.0). Similar patterns with body

mass index were seen in smokers and nonsmokers. Data from the Nurses' Health Study suggested that heavier women had a reduced risk of becoming menstrually postmenopausal during 2 years of follow-up, but this association was seen only in smokers (7).

Because obesity is associated with menstrual irregularity (29, 30), obese premenopausal women may be misclassified as peri- or postmenopausal. Consistent with this interpretation, only 37 percent of very obese women (body mass index ≥ 30.0 kg/m²) who were classified as perimenopausal based on menstrual cycle patterns (2–12 months since the last menstrual period) had an FSH of more than 20 IU/liter compared with 63 percent of perimenopausal women with a lower body mass index (OR = 0.4, 95 percent CI: 0.1, 1.0). Comparable differences were seen with higher FSH values: 27 percent of the very obese perimenopausal women had FSH values of 40 IU/liter or more compared with 53 percent of thinner perimenopausal women (OR = 0.3, 95 percent CI: 0.1, 0.9). Postmenopausal estrogen levels may be higher in obese compared with nonobese women, but still are well below premenopausal levels (31). Whether such a small change in estrogen could account for the low FSH in obese women who reported peri- and postmenopausal status is doubtful.

There was an association between exercise frequency and reduced risk of both hormonal and menstrual menopause in the NHANES data. This association has not been reported previously. In our study, younger women (those aged 35–39 years) were somewhat more likely to exercise three or more times per week than were those aged 40–44 or 45–49 years, so we repeated the exercise analyses, excluding women aged 35–39. This exclusion did not appreciably change the associations we had observed, so we do not think our results are due to residual confounding by age. Because exercise is a modifiable behavior, it is important to examine the relation between it and menopause in additional studies, including prospective designs that would specifically address exercise habits antecedent to menopause.

Our analysis suggested an association between alcohol use and reduced risk of hormonally or menstrually defined menopause, but the relations were not statistically significant. Torgerson et al. (16) reported a reduced risk (OR = 0.5) of menopause with higher alcohol consumption in a population-based study of 2,073 women aged 45–49 years. A mechanism for an alcohol effect has not been proposed.

NHANES included a large proportion of African Americans and Hispanics. Although there was some evidence of increased risk of being postmenopausal based on menstrual-cycle patterns in African Americans compared with Whites, this association was not statistically significant, and there were no clear associations in Hispanics. Some other studies have reported an earlier age at menopause in African Americans (11, 14, 28), but this difference was statistically significant in only one of the studies (11). There was no association between education level and either measure of menopausal status in our analysis. This finding is similar to those of other studies that adjusted for smoking (8–11, 13, 14).

There was some evidence of an association between early menarche (age < 11 years) and earlier menopause in

our study. Data from other studies on this question have been inconsistent (13–15, 17). We did not observe any pattern with respect to menopausal risk and number of live-births. Several studies have reported an association between higher parity and later age at menopause (13–17) or perimenopause (32), but no association was seen in the prospective study by Brambilla et al. (9). None of these studies included analyses that adjusted for body mass index. Analyses of menopause in relation to oral contraceptive use (11, 14, 17), like those in our analysis, do not provide evidence for an association.

There are limitations to our study. In analyzing FSH, we could not control for day of cycle, since information about the exact date of the last menstrual period was not collected. However, our exclusion of participants with a ratio of luteinizing hormone to FSH higher than 2.0 should reduce the likelihood of misinterpreting an ovulation-related increase in FSH. There is an arbitrary element to any categorization of a continuous variable, such as we used with the dichotomous outcome of FSH greater than 20 IU/liter. Cutpoints of 20, 25, 40, and 70 IU/liter have been used in clinical and epidemiologic studies of ovarian function and menopause (18, 33–36). We chose 20 IU/liter because this cutpoint differentiated between 50 premenopausal and 49 oophorectomized women in a study by Nordin et al. (25) and best allows for inclusion of women using hormone replacement therapy. These are cross-sectional data, so some associations could be due to behavioral changes that might occur with menopause. For example, if women stopped exercising at menopause, that could explain data showing that exercise is protective of menopause.

A strength of our study is that it is a population-based, relatively large sample of the United States population, with a substantial number of African Americans and Hispanics included in the sample. A standardized protocol was used for the interview. Collection of menstrual cycle and FSH data allows for analysis of both measures. These parallel analyses can be very informative, even (or especially) when results are “discrepant,” such as are seen with the analyses of body mass index. Our analysis highlights potential problems with the classification of menopausal status based on menstrual cycle patterns in obese women or those with other characteristics or exposures that affect menstrual regularity.

Understanding of the extent to which ovarian senescence is influenced by weight, exercise, alcohol, and other behavioral or environmental factors can stimulate research into the mechanisms involved in follicular atresia as well as identify modifiable exposures that influence menopause.

ACKNOWLEDGMENTS

Supported by the Intramural Research Program of the National Institute of Environmental Health Sciences.

Drs. Allen Wilcox and Amy Sayle reviewed an earlier draft of the manuscript.

REFERENCES

1. Snowdon DA, Kane RL, Beeson WL, et al. Is early natural menopause a biologic marker of health and aging? *Am J Public Health* 1989;79:709–14.
2. Cooper GS, Sandler DP. Age at natural menopause and mortality. *Ann Epidemiol* 1998;8:229–35.
3. van der Schouw YT, van der Graaf Y, Steyerberg EW, et al. Age at menopause as a risk factor for cardiovascular mortality. *Lancet* 1996;347:714–18.
4. Mattison DR. Clinical manifestations of ovarian toxicity. In: Dixon RL, ed. *Reproductive toxicology*. New York, NY: Raven Press, 1985:109–30.
5. Cramer DW, Xu H. Predicting age at menopause. *Maturitas* 1996;23:319–26.
6. Midgette AS, Baron JA. Cigarette smoking and the risk of natural menopause. *Epidemiology* 1990;1:474–80.
7. Willett W, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. *Am J Epidemiol* 1983;117:651–8.
8. McKinlay SM, Bifano NL, McKinlay JB. Smoking and age at menopause in women. *Ann Intern Med* 1985;103:350–6.
9. Brambilla DJ, McKinlay SM. A prospective study of factors affecting age at menopause. *J Clin Epidemiol* 1989;42:1031–9.
10. Luoto R, Kaprio J, Uutela A. Ages at natural menopause and sociodemographic status in Finland. *Am J Epidemiol* 1994;139:64–76.
11. Bromberger JT, Mathews KA, Kuller LH, et al. Prospective study of the determinants of age at menopause. *Am J Epidemiol* 1997;145:124–33.
12. Cooper GS, Sandler DP, Bohlig M. Active and passive smoking and age at natural menopause. *Epidemiology* 1999;10:771–3.
13. Parazzini F, Negri E, La Vecchia C. Reproductive and general lifestyle determinants of age at menopause. *Maturitas* 1992;15:141–9.
14. Stanford JL, Hartge P, Brinton LA, et al. Factors influencing the age at natural menopause. *J Chronic Dis* 1987;40:995–1002.
15. Whelan EA, Sandler DP, McConaughy DR, et al. Menstrual and reproductive characteristics and age at natural menopause. *Am J Epidemiol* 1990;131:625–32.
16. Torgerson DJ, Avenell A, Russell IT, et al. Factors associated with onset of menopause in women aged 45–49. *Maturitas* 1994;19:83–92.
17. Cramer DW, Xu H, Harlow B. Does “incessant” ovulation increase risk for early menopause? *Am J Obstet Gynecol* 1995;172:568–73.
18. Cramer DW, Barbieri RL, Xu H, et al. Determinants of basal follicle-stimulating hormone levels in premenopausal women. *J Clin Endocrinol Metab* 1994;79:1105–9.
19. Cooper GS, Baird DD, Hulka BS, et al. Follicle-stimulating hormone concentrations in relation to active and passive smoking. *Obstet Gynecol* 1995;85:407–11.
20. Cooper GS, Thorp JM. FSH Levels in relation to hysterectomy and unilateral oophorectomy. *Obstet Gynecol* 1999;94:969–72.
21. Lenton EA, Sexton L, Lee S, et al. Progressive changes in LH and FSH and LH:FSH ratio in women throughout reproductive life. *Maturitas* 1988;10:35–43.
22. Metcalf MG, Donald RA, Livesey JH. Pituitary-ovarian function before, during and after the menopause: a longitudinal study. *Clin Endocrinol (Oxf)* 1982;17:489–94.
23. National Center for Health Statistics. 1995 Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–1994. Hyattsville, MD: National Center for Health Statistics, 1994. (Vital and health statistics, series 1: programs and procedures, no. 32) (DHHS publication no. (PHS) 94–1308) (GPO no. 017–022–01260–0).
24. Djahanbakhch O, McNeilly AS, Warner PM, et al. Changes in plasma levels of prolactin, in relation to those of FSH, oestradiol, androstenedione and progesterone around the preovulatory surge of LH in women. *Clin Endocrinol* 1984;20:463–72.
25. Nordin BEC, Crilly RG, Marshall D, et al. Oestrogens, the menopause and the adrenopause. *J Endocrinol* 1981;89:131–43.
26. Flegal KM, Carroll MD, Kuczmarski RJ, et al. Overweight and obesity in the United States: prevalence and trends, 1960–1994.

- Int J Obes 1998;22:39–47.
27. Gunter EW, Lewis BG, Koncikowski SM. Laboratory procedures used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. Atlanta, GA: Centers for Disease Control and Prevention, 1996.
 28. MacMahon B, Worcester J. Age at menopause—United States—1960–1962. *Vital Health Stat 1* 1966;11:1–20.
 29. Kato I, Toniolo P, Koenig KL, et al. Epidemiologic correlates with menstrual cycle length in middle aged women. *Eur J Epidemiol* 1999;15:809–14.
 30. Cooper GS, Sandler DP, Whelan EA, et al. Association of physical and behavioral characteristics with menstrual cycle patterns in women age 29 to 31. *Epidemiology* 1996;7:624–8.
 31. Potischman N, Swanson CA, Siiteri P, et al. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *J Natl Cancer Inst* 1996;88:756–8.
 32. Hardy R, Kuh D. Reproductive characteristics and the age at inception of the perimenopause in a British national cohort. *Am J Epidemiol* 1999;149:612–20.
 33. Menon RK, Okonofua FE, Agnew JE, et al. Endocrine and metabolic effects of simple hysterectomy. *Int J Gynaecol Obstet* 1987;25:459–63.
 34. Feeney DD, Moore DH, Look KY, et al. The fate of the ovaries after radical hysterectomy and ovarian transposition. *Gynecol Oncol* 1995;56:3–7.
 35. Lindsay MK, Usher DJ. Unrecognized ovarian failure after hysterectomy. *Br J Gen Pract* 1992;42:529–30.
 36. Scott RT, Toner JP, Muasher SJ, et al. Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome. *Fertil Steril* 1989;51:651–4.