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Longitudinal Genetic Analysis of Menstrual Flow, Pain, and Limitation in a Sample of Australian Twins

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Genetically informative longitudinal data about menstrual disorders allow us to address the extent to which the same genetic risk mechanisms are operating throughout the reproductive life cycle. We investigate the relative contributions of genes and environment to individual differences in menstrual symptomatology reported at two waves, 8 years apart, of a longitudinal Australian twin study. Twins were questioned in 1980–1982 and 1988–1990 about levels of menstrual pain, flow, and perceived limitation by menses. Longitudinal genetic analysis was based on 728 pairs (466 MZ and 262 DZ) who were regularly menstruating at both survey waves. A bivariate Cholesky model was fitted to the two-wave data separately for flow, pain, and limitation variables. The baseline model comprised common genetic and environmental factors influencing responses at both waves and specific effects influencing only the second-wave response. We also included age as a covariate in the model. Proportions of the longitudinally stable variance in menstrual flow, pain, and limitation attributable to genetic and individual environmental effects were calculated for the best-fitting models. Genetic factors accounted for 39% of the longitudinally stable variation in menstrual flow, 55% for pain, and 77% for limitation. The remaining stable variance was due to individual environmental factors (61, 45, and 23%, respectively). Therefore the stable variance over the 8-year interval was largely environmentally influenced for menstrual flow, was approximately equally determined by genetic and by nonshared environmental influences in the case of pain, and was due almost entirely to genetic influences for limitation by periods. We demonstrate for the first time that the same genetic influences are operative throughout the reproductive life span.

KEY WORDS: Twins; menstruation; dysmenorrhea; menorrhagia; longitudinal genetic influences.

INTRODUCTION

The impact of women's menstrual disorders on women's quality of life, health, and work, paid and unpaid, and on the community is substantial. Menstrual dysfunction can begin in adolescence and persist for many years throughout the entire reproductive span (Bates and Boone, 1991). Sixty percent of 17 to 19 year olds in a college cohort reported at least one episode of severe menstrual pain (dysmenorrhea), and 13% reported severe pain more than half the time in a 1-year prospective study (Harlow and Park, 1996). Significant disabling symptoms related to the menstrual cycle have been estimated for approximately 5% of women in Western cultures during the reproductive years (O'Brien, 1985; Roughan, 1991). U.S. statistics indicate that one-fifth of all visits for diseases

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of the female genital tract (4 million office visits in 1977–1978) have been made annually for disorders of menstruation (National Center for Health Statistics, 1982). The 1989–1990 Australian National Health Survey identified substantial self-reported recent disorders of menstruation (experienced in the 2 weeks prior to survey) (Australian Bureau of Statistics, 1991, p. 16). Treatments for dysfunctional menstrual bleeding include surgical, medical and pharmaceutical therapies (Apgar, 1997).

Primary spasmodic dysmenorrhea has been attributed largely to excessive production and release of prostaglandins by the endometrium, causing abnormal hypercontractility of the uterus associated with uterine ischemia and hypoxia, although other factors such as ovarian steroids, cervical obstruction, and pituitary hormones may also affect menstrual pain (Dawood and Ramos, 1990). The mechanism causing uterine hypercontractility is unresolved. Excessive menstrual bleeding (menorrhagia) may be caused by noniatrogenic conditions including polyps, fibroids, adenomyosis, endometriosis, ovarian disease, endometrial prostaglandin concentration, and bleeding disorders (Wood, 1996). Menorrhagia may be a presentation of acquired or congenital deficiencies of coagulation factors or of the regulators of the fibrinolytic system (Ewenstein, 1996). Other associated factors have included parity, obesity, depression, heavy smoking, and excessive alcohol intake (Wood, 1996). The etiology and pathophysiology of menstrually related disorders such as dysmenorrhea are not well understood, however, and indeed have sometimes been "fiercely" debated (Halbreich *et al.*, 1993).

Environmental influences undoubtedly affect heterogeneity of menstrual patterns (Treloar *et al.*, 1967), and menstrual cycle hormonal profiles have been reported as varying between cultures (Wilson *et al.*, 1992). Not only are cross-sectional cross-cultural differences in premenstrual experience and attitudes to menstruation relevant (Chandra and Chaturvedi, 1989, 1992), but long-term evolutionary and cultural effects have been postulated (Dennis, 1992). Certainly these influences are important. But to what extent do they explain individual differences between women?

The tools of genetic epidemiology, until very recently, have not been widely applied to the reproductive health problems of women. Heritabilities of age at menarche (Chern *et al.*, 1980; Kantero and Widholm, 1971; Martin and Treloar, 1991; Meyer *et al.*, 1991; Treloar and Martin, 1990; Van den Akker *et al.*, 1987), length of cycle (Chern *et al.*, 1980; Kantero and Widholm, 1971; Van Den Akker *et al.*, 1987), duration of menses (Chern *et al.*, 1980; Kantero and Widholm, 1971), premenstrual tension (Kantero and Widholm, 1971; Kendler *et al.*, 1992; Van Den Akker *et al.*, 1987), psychiatric side effects of the oral contraceptive pill (OC) (Kendler *et al.*, 1988), and even liability to hysterectomy (Treloar *et al.*, 1992) have been investigated more extensively than the heritability of the two most salient features of menstruation, pain and flow, the extreme clinical presentations of which are diagnosed respectively as dysmenorrhea and menorrhagia. Kantero and Widholm (1971) reported only mother–daughter correlation coefficients of 0.15 ($p \leq .001$) and 0.19 ($p \leq .001$) for self-reported dysmenorrhea, although genetic and environmental influences cannot be distinguished using these data alone.

Menstrual and premenstrual symptoms have been investigated in the United States in a cross-sectional genetic design (Kendler *et al.*, 1992). Their heritability estimates were 0.34, 0.41, and 0.40, respectively, for flow, pain, and menstrual limitation. Earlier, genetic influences on menstrual flow, pain, and limitation had been reported from a multivariate analysis (Silberg *et al.*, 1987) in the initial assessment of the Australian female twin cohort of which twins in the present longitudinal analysis comprise part. Genetic factors were reported in that analysis to contribute to the report of menstrual flow, pain, and limitation with 22, 38, and 36%, respectively, of the total variance being additive genetic. The twins from that study have now been followed up 8 years later and in this paper we explore the stability over time of genetic influences on these menstrual characteristics.

Scientific knowledge of the natural history of menstrual disorders such as primary dysmenorrhea is still limited (Kennedy, 1997), having been the focus of only one major study (Sundell *et al.*, 1990). More was known over three decades ago about changes in menstrual periodicity over time (Treloar *et al.*, 1967) than is currently known about the natural history of changes in flow, pain, and women's perceptions of limitation by menstruation. Here we present the first genetically informative longitudinal data about menstrual disorders, data

which allow us to address the extent to which the same genetic risk mechanisms are operating throughout the reproductive life cycle.

SAMPLE AND METHODS

Sample

The 1981 Survey. In 1980–1982, as part of a health survey by mailed questionnaire, information was obtained from 1232 monozygotic (MZ) female and 747 dizygotic (DZ) female (1979 female pairs) twin pairs in a larger sample of 3808 adult twin pairs from the Australian NHMRC Twin Register (''1981 survey'') (Eaves *et al.*, 1989; Jardine *et al.*, 1984; Martin and Jardine, 1986). From 1980 to 1982 questionnaires were mailed to 5967 male, female, and opposite-sex twin pairs aged 18 years or greater. After one or two reminders to nonrespondents, completed questionnaires were returned by both members of 3808 twin pairs (an overall 64% pairwise response rate).

Three months prior to the 1980 survey a pilot questionnaire was sent to a subsample of 100 twin pairs. Replies to both the pilot and the main questionnaire were received from 67 female twins and these have been used to assess short-term repeatability.

In 1981 a two-item zygosity questionnaire was used to determine zygosity for same-sex pairs (Jardine *et al.*, 1984). Such questionnaires have been shown to give at least 95% agreement with diagnosis based on extensive blood typing (Martin and Martin, 1975). If there were any inconsistencies with unequivocal zygosity assignment in the responses of the twins, they were contacted for further information and frequently supplied photographs which assisted in making the decision.

Ages of the 3958 responding twins from female like-sex pairs in 1981 ranged from 18 to 88 years. All female twins answered questions on age at menarche, age at first pregnancy, pregnancy and childbirth history, and complications. Twins menstruating regularly at time of survey were asked about cycle length, duration of menstrual periods, menstrual symptoms, oral contraceptive use, and side effects. Twins who had stopped menstruating were asked whether this was due to hysterectomy, menopause, or some other cause and at what age these occurred.

The 1989 Survey. The same twins were followed up 8 years later, between 1988 and 1990, when the minimum age of respondents was 25 years. Most questionnaires were mailed exactly 8 years to the day from the chief mailout for the 1980–1982 study to standardise any time of year effects. Up to five attempts were made to follow up nonrespondents.

A 2-year follow-up to measure medium-term stability of reports over time was carried out following the 1989 wave 2 survey. Identical questionnaires were mailed in 1990 to the first 500 female and 500 male individual twins who responded to wave 2.

Sample for Longitudinal Analysis. Inclusion criteria for the longitudinal genetic analysis were that, at the 1981 survey, the twin had not stopped menstruating, was not pregnant, and was under 60 years old and that, at the 1989 wave, she was still menstruating (i.e., had not had menopause or a hysterectomy in the intervening years). Of the responding twins who satisfied the inclusion criteria, 728 pairs (466 MZ and 262 DZ pairs) provided information on all variables of interest.

Assessment

At both waves twins were asked, ''Are your periods ... 1. heavy, 2. moderate, 3. light'' (FLOW); ''... 1. very painful, 2. moderately painful; 3. no trouble'' (PAIN); and ''... 1. very limiting, 2. moderately limiting; 3. not limiting'' (LIMitation). Before analysis, responses were recoded so that the higher number corresponded to greater severity.

Fundamental to the twin method is the assumption that the environments of MZ cotwins are no more similar than those of DZ cotwins—or, if they are, that this does not influence intrapair similarity in the variable being analysed. Our study tried to measure environmental similarity in two ways. At both waves, twins were asked how much they see and contact each other on a 7-point scale, and in 1989 we also asked about four aspects of childhood ''environmental'' similarity (sharing the same room, being dressed alike, sharing the same playmates, and being in the same class), scored on a 4-point scale. Absolute differences in cotwins' menstrual symptoms were analysed by degree of contact and seeing each other (7-point scales) and

childhood environmental similarity (4-point scale), controlling for the effects of age and zygosity.

Statistical Methods

Six × six matrices of polychoric correlations and asymptotic covariances were estimated using the DOS Extender version of PRELIS 2.12a (Jöreskog and Sörbom, 1993a). Models were fitted separately for each twin group by weighted least squares in LISREL 8 (Jöreskog and Sörbom, 1993b) using standard genetic model-fitting methods (Neale and Cardon, 1992). A bivariate Cholesky model was fitted to the two-wave data separately for FLOW, PAIN, and LIM variables. The baseline model comprised common genetic and environmental factors influencing the responses at both waves and specific effects influencing only the second-wave response. We also included age as a covariate in the model. The likelihood-ratio chi-square and Akaike information criterion (AIC) (χ^2 − 2 df) were used to determine best-fitting models (Neale and Cardon, 1992).

RESULTS

Ages of eligible women in 1981 ranged from 18 to 46 years (mean 1981 age for this two-wave sample was 27 ± 6 years) and there was no difference in age distribution of MZ and DZ twins. The 1981 current oral contraceptive (OC) pill usage was 30% in MZ twins and 31% in DZ twins; 47% of MZ twins and 49% of DZ twins had ever been pregnant at the time of completing the questionnaire. There were no significant mean differences in menstrual function or oral contraceptive use between MZ and DZ twins at either the 1981 or the 1989 wave.

The distribution of menstrual flow, pain, and limitation was similar to that previously reported for the whole sample (1981 data) (Silberg *et al.*, 1987). In our two-wave sample of twins (N = 1456), from most severe to least severe, responses for 1981 menstrual flow were 13, 69, and 18%; for 1981 pain, 7, 47, and 46%; and for 1981 limitation, 3, 34, and 63%, respectively. Also, in the two-wave responding sample, responses for 1989 flow were 17, 64, and 19%; those for 1989 pain were 5, 48, and 47%; and those for 1989 limitation were 2, 31, and 67%, respectively. The two-wave 1989 figures were very similar to those for all 2036 still-menstruating individual twins at the 1989 survey, which were as follows (from most to least severe): flow, 18, 64, and 18%; pain, 6, 48, and 46%; and limitation, 3, 33, and 64%.

Contingency chi-square results showed significant differences in whether twins were menstruating or not in 1989 according to their level of menstrual limitation reported in 1981 (χ^2_2 = 24.57, 23.5, 24.6; all p's = .00), with higher than expected numbers of twins reporting severe limitation in 1981 not menstruating in 1989.

Effects of Environmental Similarity

The 1981 twin pair correlations for menstrual flow, pain, and limitation were homogeneous across all levels of contact, including cohabitation. None of the measures showed a significant effect of childhood environmental similarity on twin pair concordance for reporting of symptoms (within pair variance). Amount of current contact was associated with concordance for reported menstrual pain (F = 2.16, df = 6, p = .05), and the extent to which twins actually "saw" each other (as opposed to contact) was associated with concordance for reporting of menstrual flow (F = 2.61, df = 6, p = .02). However, in both cases the percentage of total sums of squares accounted for was trivial (1.89 and 2.12%, respectively). Correlations between absolute within-pair differences in menstrual variables and either contacting or seeing each other were not significant in either zygosity group.

Phase of Cycle

The possibility of response bias due to respondents being in the menstrual phase of their cycles was investigated using 1989 data. Neither more nor fewer respondents than expected were in the menstrual phases of their cycle at the time of completing the questionnaire in 1989 (complete data not shown). Phase was calculated, for women not using the oral contraceptive pill and with a usual cycle of ≤30 days (N = 614), by number of days since last menstrual period. Although there was a significant difference between observed and expected frequencies over the five phases (menstrual, preovulatory, ovulatory, postovulatory, premenstrual) (χ^2_4 = 13.74, p < .01), there were neither more nor fewer respondents than expected in the menstrual phase of their cycle at the time of

Table I. Stability of Menstrual Symptoms Over 2 and 8 Years: Polychoric Correlations (±SE)

	3 months[a] (N=67)	2 years[b] (N=223)	8 years[c] (N=1884)
Flow	0.80 ± .11	0.72 ± .07	0.48 ± .03
Pain	0.62 ± .15	0.74 ± .07	0.54 ± .03
Limitation	0.74 ± .15	0.64 ± .07	0.43 ± .03

[a] Before the 1981 survey, as reported by Silberg *et al.* (1997, p. 371).
[b] Following the 1989 survey.
[c] Between the 1981 and the 1989 survey waves.

completing their questionnaire in 1989. Results support a positive effect on "volunteering" related to the ovulation, with a postovulatory (but not premenstrual or menstrual) negative effect. This finding affirmed the conclusion of Doty and Silverthorne (1975), who also reported an excess of volunteers in the ovulatory and a deficit in the postovulatory phase.

Repeatability and Stability

Three-month repeatability and 2- and 8-year estimates of stability for menstrual symptoms are shown in Table I. The 8-year stabilities range from 0.43 for limitation to 0.54 for pain. We now wish to know the relative contributions of genes and environment to this stability.

1989 Twin Pair Correlations for Menstrual Flow, Pain, and Limitation

In the two-wave sample, genetic nonadditivity was still apparent for menstrual pain in 1989 (r_{MZ} = .36, r_{DZ} = .14), as it had been in 1981 (see correlations in boldface in Table II). The MZ-to-DZ ratio of twin pair correlations for menstrual flow (r_{MZ} = .25, r_{DZ} = .12) suggested additive genetic effects, as reported previously for 1981 full sample data (Silberg *et al.*, 1987). MZ-to-DZ ratios for limitation suggested a greater influence of shared environment at the 1989 survey (r_{MZ} = .31, r_{DZ} = .23) than was the case in 1981. However, MZ and DZ twin pair correlations for 1981 flow differed from expectations. They were both r = .15 in the two-wave sample, suggesting no genetic influence, compared with reported correlations in the full 1981 sample of r_{MZ} = .22 and r_{DZ} = .09 (Silberg *et al.*, 1987), an issue that is addressed further under Discussion.

Results of Longitudinal Genetic Model Fitting

Model-fitting results are presented separately for flow, pain, and limitation (Table III). Model 1 allows for additive genetic (A), shared environment (C), and individual environment (E) effects, common to both waves and specific only to wave 2. In each case, shared environment (or nonadditive genetic effects in the case of pain) can be eliminated from the model (model 2). We then test whether there are any wave specific genetic effects by eliminating the wave 2 genetic effect (model 3). In no case does this produce a significant worsening of fit, from which we conclude that the same genetic effects are influencing the menstrual symptoms on both occasions. Parameter estimates for the reduced model are shown in Fig. 1. Although response to 1989 survey and eligibility for consideration at both waves were influenced by age, age regressions for those who responded and were menstruating at 1989 survey were in all cases negligible. Cross-sectional heritabilities under the best-fitting model are 0.19, 0.26, and 0.39 for 1981 flow, pain, and limitation and 0.20, 0.35, and 0.29 for 1989 data, respectively.

Longitudinal Genetic and Environmental Correlations

Genetic correlations between the two waves for model 3 (see Table III) are unity, by definition. Individual environmental correlations across time were modest (flow r_e = .38, pain r_e = .36, limitation r_e = .16). Proportions of the longitudinally stable variance in menstrual flow, pain, and limitation attributable to genetic and individual environmental effects were calculated for the best-fitting models. Genetic factors accounted for 39% of the longitudinally stable variation in menstrual flow, 55% for pain, and 77% for limitation. The remaining stable variance was due to individual environmental factors (61, 45, and 23%, respectively). Therefore the stable variance over the 8-year interval was largely environmentally influenced for menstrual flow, was approximately equally determined by genetic and by nonshared environmental influences in the case of pain, and

Table II. MZ and DZ Polychoric Correlation Matrices for Menstrual Flow, Pain, and Limitation in 1981 and 1989

		Dizygotic pairs (N = 262)												
		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
I.	Twin 1—1981 FLOW	—	0.40	0.43	*0.60*[a]	0.24	0.37	**0.15**[b]	0.04	−0.02	***0.08***[c]	−0.02	0.00	0.04
II.	Twin 1—1981 PAIN	0.36	—	0.58	0.24	*0.43*	0.33	−0.04	**0.11**	−0.01	0.02	***0.14***	0.01	−0.15
III.	Twin 1—1981 LIM	0.29	0.56	—	0.29	0.28	*0.40*	−0.01	0.07	**0.16**	0.08	0.09	***0.07***	−0.15
IV.	Twin 1—1989 FLOW	*0.35*	0.21	0.22	—	0.41	0.42	***0.06***	−0.05	0.09	**0.12**	−0.13	0.01	0.15
V.	Twin 1—1989 PAIN	0.21	*0.60*	0.30	0.42	—	0.74	0.02	***0.10***	0.03	0.13	**0.14**	0.14	−0.09
VI.	Twin 1—1989 LIM	0.19	0.43	*0.43*	0.47	0.59	—	0.08	0.03	***0.08***	0.20	0.14	**0.23**	−0.01
VII.	Twin 2—1981 FLOW	**0.15**	0.12	0.04	***0.22***	0.15	0.14	—	0.40	0.29	*0.50*	0.19	0.13	0.00
VIII.	Twin 2—1981 PAIN	0.09	**0.32**	0.24	0.06	***0.30***	0.26	0.44	—	0.58	0.25	*0.51*	0.30	−0.12
IX.	Twin 2—1981 LIM	0.13	0.28	**0.41**	0.18	0.16	***0.30***	0.35	0.58	—	0.15	0.37	*0.39*	0.00
X.	Twin 2—1989 FLOW	***0.09***	0.10	0.15	**0.25**	0.11	0.20	*0.48*	0.23	0.31	—	0.44	0.62	0.16
XI.	Twin 2—1989 PAIN	−0.03	***0.33***	0.22	0.10	**0.36**	0.29	0.25	*0.60*	0.40	0.42	—	0.60	−0.02
XII.	Twin 2—1989 LIM	0.22	0.16	***0.36***	0.32	0.20	**0.31**	0.11	0.40	*0.48*	0.38	0.61	—	0.11
XIII.	Age	0.08	−0.18	−0.08	0.20	0.01	0.09	0.01	−0.23	−0.01	0.17	−0.08	0.19	—
		Monozygotic pairs (N = 466)												

[a] Within-person longitudinal correlations are in *italics* for Twin 1 (I with IV, II with V, III with VI) and for Twin 2 (VII with X, VIII with XI, IX with XII).

[b] Cross-sectional twin pair correlations are in **boldface** for 1981 data (I with VII, II with VIII, III with IX) and for 1989 data (IV with X, V with XI, VI with XII).

[c] Cross-occasion twin correlations are in ***boldface italics*** (I with X, II with XI, III with XII, IV with VII, V with VIII, VI with IX).

Table III. Results of Fitting Longitudinal Genetic Model and Submodels to 1981 and 1989 Data

Model	df	χ^2	p	AIC[a]
Flow				
1. Full ACE model	11	18.28	0.07	−3.72
2. No effects of shared environment (c)[b]	14	18.78	0.17	−9.22
3. Model 2 with no occasion-specific genetic effects	15	**20.03**	**0.17**	**−9.97**
4. Model 2 with no genetic effects[b]	17	51.47	0.00	17.47
Pain				
1. Full ADE model	11	10.26	0.50	−11.74
2. No effects of genetic nonadditivity (d)[b]	14	10.37	0.73	−17.63
3. Model 2 with no occasion-specific genetic effects	15	**10.45**	**0.79**	**−19.55**
4. Model 2 with no genetic effects[b]	17	78.67	0.00	44.67
Limitation				
1. Full ACE model	11	9.15	0.60	−12.85
2. No effects of shared environment (c)[b]	14	9.74	0.78	−18.26
3. Model 2 with no occasion-specific genetic effects	15	**10.46**	**0.79**	**−19.54**
4. Model 2 with no genetic effects[b]	17	92.85	0.00	58.85

[a] Akaike information criterion (χ^2 − 2 df).

[b] Either common to both occasions or specific to 1989.

for limitation by periods was due almost entirely to genetic influences.

DISCUSSION

Our study showed strong repeatability of short-term reports and strong stability of medium-term reports of menstrual symptoms. This suggests a consistency in women's experience of their periods in the short to medium term. Over a short period such as 3 months, menstruation is most likely to be influenced by factors such as initiation, cessation, and change in method of contraception. Over a period of 2 years, intervening events might

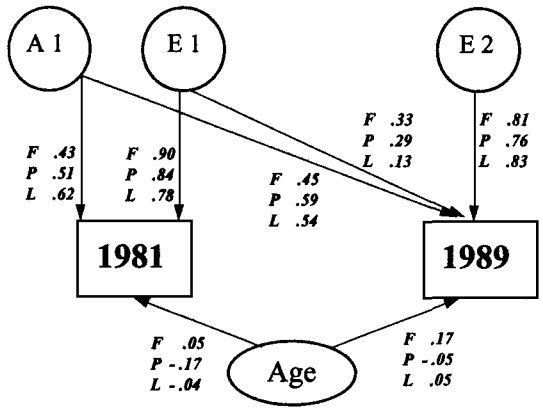

Fig. 1. Path diagram with parameter estimates for best-fitting longitudinal model for menstrual flow, pain, and limitation. A 1, genetic influences, time 1; E 1, environmental influences, time 1; E 2, environmental influences, time 2. F, flow; P, pain; L, limitation.

also include a maximum of two full-term pregnancies and breastfeeding, and these events might be greater in number over a period of 8 years. Age effects were negligible for flow and limitation in 1981 data, but at that time age showed a stronger negative phenotypic influence on menstrual pain. When the twins were 8 years older, the effect of age on reducing menstrual pain was less notable. Again, 8 years later, age was positively influencing increased menstrual flow. Risk factors for menorrhagia—higher parity, obesity, and anovulation approaching menopause (Wood, 1996)—are positively correlated with age. Also OC use, higher in younger women, is associated with decreased menstrual flow. So the finding of moderately high long-term stability of reported menstrual symptoms over an 8-year period is striking, given the number and variety of potential intervening effects.

Our findings replicated the 1981 univariate results of Silberg *et al.* (1987), where heritabilities of 0.22, 0.38, and 0.36 for flow, pain, and limitation, and no detectable influence of shared environment, were reported. There was evidence in this sample for nonadditive genetic influences on pain at both the 1981 and the 1989 surveys.

Longitudinal additive genetic stability was found for menstrual flow, pain, and limitation between the 1981 and the 1989 surveys. The stable component of variance for the limiting nature of menstrual periods over the 8-year period between 1981 and 1989 was largely genetically influenced, however, less of the stable variation was genetic in origin for pain, and even less for flow. This longitudinal genetic analysis provides new insight into what influences the stability of menstrual symptoms over a substantial period (about 20%) of an average woman's potential reproductive life. Implications of these findings can be tested in further analyses. For example, genetic influences on menstrual limitation may covary genetically with factors such as relatively stable personality traits, those on pain may covary with genetic factors influencing longer-term and less effectively treated conditions such as endometriosis, and genetic influences on flow may relate to more tractable conditions such as uterine fibroids.

Twins participating in this study have completed two long questionnaires 8 years apart and, hence, might be characterized by cooperativeness. Recruitment bias and response bias are potential problems in twin research, but less threatening when cooperativeness is uncorrelated with the trait being analysed. The women's health questions used in the 1989 twin study formed part of a 20-page health and lifestyle survey, so respondents would have been most unlikely to have any particular interest, for example, in menstrual function given the large number of different items in the questionnaire. Proportions experiencing "very heavy" and/or "very painful" periods were small, and although neither dysmenorrhea nor menorrhagia was clinically validated, the percentages were not inconsistent with those expected given the age of the twin sample on both survey occasions (dysmenorrhea being more prevalent among adolescents) (Abraham, 1984; Izzo and Labriola, 1991; Neinstein, 1990).

Potential limitations of our study require acknowledgment. First, menstrual symptoms were not reported in the context of any pelvic pathology, treatment, or medication regimen which may have influenced them. The reported menstrual pain symptom may have included both cramps or spasm (primary) and congestion or continuous abdominal pain (secondary). Dysmenorrhea was assumed by Silberg *et al.* (1987) to be primary, as data on possible organic pathology were not collected, and hence to be spasmodic rather than congestive, the latter commonly associated with chronic pelvic inflammatory disease or endometriosis. Twins were not asked to indicate whether they had been diagnosed as having any pelvic pathology, such as en-

dometriosis, leiomyoma, adenomyosis, or recurrent pelvic inflammatory disease, so it was questionable whether "dysmenorrhea" assumed from the question on painful periods could be classified as primary or secondary. Estimates of prevalence of these conditions vary, with estimates for endometriosis, for example, varying from 2% of women to 10% of women in their childbearing years. Nevertheless, primary and secondary cases were not distinguishable in these data.

Although associations were noted between, for example, oral contraceptive (OC) use and decreased menstrual flow, we did not exclude OC users from our analyses because we found no evidence of OC use affecting the expression of genetic influences on menstrual pain, flow, or limitation (data not shown). In all cases, using OC use as the dichotomous environmental factor, no G × E model fitted significantly better than a constrained *AE* model, so no G × E interaction was indicated. Nevertheless, the specific type of OC being taken was not ascertained, so menstrual function relative to potency of the oestrogen *vs.* progestogen component of OCs could not be assessed. Variability in estrogen content of available OCs at the time of the first data collection (1980–1982) was reported to be relatively low, as it was said to precede the widespread prescription of low-estrogen OC pills (Kendler *et al.*, 1988). Recent clinical studies offer conflicting conclusions concerning clinically ascertained response of dysmenorrhea to type of OC (Milsom *et al.*, 1990; Nabrink *et al.*, 1990). Consistency of OC use has also been reported as a relevant factor in reduction of dysmenorrhea (Robinson *et al.*, 1992).

Heaviness of flow, or perceived extent of blood loss, was reported by female twins outside the context of uterine, endocrine, or other pathology which may cause menorrhagia. There was no indication as to whether twins were using the intrauterine contraceptive device (IUCD), which, more so in 1980–1982 than in 1988–1990, was a commonly used method of contraception, the side effects of which were commonly increased menstrual pain and/or flow. Moreover, twins had no objective reference points by which they could judge their pain and flow. Their reports were their own perceptions. It is recognized that women seeking treatment for menorrhagia often do not have greater blood loss than average (Wood, 1996).

Comparison was made with U.S. twin data on menstrual symptoms (Kendler *et al.*, 1992) which were self-reported using the same questions on flow, pain, and limitation as in our Australian studies. The mean age of the responding pairs from the Virginia Twin Register sample in 1987–1988 was 30 ± 8 years (Kendler *et al.*, 1992), younger than the 1989 mean age of this Australian sample, menstruating at both survey waves, of 35 ± 6 years. OC users were excluded from the Virginia sample, however, which, in addition to the age factor, may well have explained their higher prevalence of moderate and severe menstrual pain. Prevalences in 1989 of moderate and severe pain in our two-wave sample for current OC users were 41.1 and 3.4% respectively, compared with 51.1 and 6.3% for menstruating women not taking the OC pill.

The distribution of other menstrual symptoms was similar in both studies. In the Virginia sample, models comprising only additive genetic and individual environmental influences explained the data for menstrual pain and limitation, while nonadditive genetic influences contributed to the best fitting model for flow. The estimated cross-sectional heritabilities for flow, pain, and limitation from the Virginia study were 0.34, 0.41, and 0.40, respectively, higher than the 1981 cross-sectional heritabilities for flow and pain from the two-wave Australian twin sample (0.19, 0.26), but almost-identical to our estimate for menstrual limitation (0.39).

As noted, however, the ratios of MZ-to-DZ polychoric correlations in the 1989 Australian twin data suggested that, for limitation, genetic influences were no longer influential. Analysis of hysterectomies performed in twins between 1981 and 1989 studies showed that limitation by menstruation in 1981 was one of the strongest correlates of subsequent hysterectomy (Treloar *et al.*, 1992). Those with the most severe limitation (LIM) in 1981 were less likely to have been menstruating in 1989, and since LIM was strongly associated with pain, the aging of the sample would have contributed also to a reduction in the genetic variance for limitation.

Our findings reinforce the view that there are substantial genetic effects on individual differences in menstrual symptoms but demonstrate for the first time that the same genetic influences are operative throughout the reproductive life span. A challenge

for the future is to identify by molecular means the loci responsible for this genetic variance.

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