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longitudinal twin research**

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Pathways to hysterectomy: Insights from longitudinal twin research

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OBJECTIVE: We hypothesized that genetic influences act on "liability" to hysterectomy, that secular influences might differentially affect relative importance of genetic and environmental influences, and that the sources of genetic influences could be identified from reported risk factors.

STUDY DESIGN: Hysterectomy data from an Australia-wide volunteer sample of female adult monozygotic and dizygotic twins are reported. In 1980 through 1982 a mailed questionnaire was completed by 1232 monozygotic female twin pairs and 751 dizygotic female twin pairs (3966 women) from the Australian Twin Register (wave 1). The same twins were surveyed by questionnaire 8 years later (wave 2).

RESULTS: A total of 366 had undergone hysterectomy by wave 1 and a further 198 at wave 2. The twin-pair correlations for liability to hysterectomy at wave 1 (0.61 ± 0.06 for monozygotic and 0.20 ± 0.11 for dizygotic) and wave 2 (0.65 ± 0.05 for monozygotic and 0.32 ± 0.09 for monozygotic) indicated a substantial genetic contribution. Reported risk factors accounted for only 15% of total variance.

CONCLUSION: Genetic influences on liability to hysterectomy were substantial and stable across birth cohorts, but the important sources of genetic influence on liability to hysterectomy are yet to be identified. (AM J OBSTET GYNECOL 1992;167:82-8.)

Key words: Hysterectomy, twins, genetic influences

Hysterectomy has been the subject of considerable recent investigation as a result of the need to distinguish "real" clinical indications for the procedure from service provision distortions arising from health financing systems. In Australia the incidence of hysterectomy peaked in 1978,¹ with an age-standardized rate of 460 per 10^5 ,² compared with the United States peak in 1975.³ The 1973 rate in the United States was 651 per 10^5 women, still significantly higher than the age-standardized Australian rate, which had declined to 376 per 10^5 by 1983. There is less variation in rate between Australian states than within the United States.²

Investigation of patient characteristics has found variance to be associated with factors such as race, education, and parity.⁴ The role of patient demand in influencing hysterectomy rates in Australia has been noted,⁵ and high pre-hysterectomy levels of psychiatric symptoms have been reported.^{6,7} To investigate further the causes of hysterectomy in Australian women, this

prospective two-wave study of twins sought to identify the relative roles of environmental and genetic factors on "liability" to hysterectomy and the extent to which these are modulated through known risk factors. Twins discordant for hysterectomy, particularly monozygotic pairs, offer the ultimate matched-pair design to detect the effect of independent variables measured before the operation, and we have taken advantage of the 106 discordant pairs in our study for this purpose. We also investigated whether genetic effects could be detected on the age at which hysterectomy was performed in pairs concordant for hysterectomy.

Methods

Wave 1 (1980 through 1982). In 1980 through 1982, as part of a health survey by mailed questionnaire, information about hysterectomy was obtained from 1983 female twin pairs in a large sample of 3808 adult twin pairs from the Australian National Health and Medical Research Council Twin Register.⁸⁻¹⁰ Questionnaires were mailed to 5967 twin pairs aged ≥ 18 years. Ages of respondents then ranged from 18 to 88 years. After one or two reminders to nonrespondents, completed questionnaires were returned by both members of 3808 twin pairs (64% pairwise response rate). A two-item zygosity questionnaire was used to determine zygosity for same-sex pairs.⁸ Such questionnaires have been shown to give at least 95% agreement with diagnosis on the basis of extensive blood typing.^{11,12}

Twins who were menstruating regularly at the time of survey were asked about cycle length, duration of

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menstrual periods, flow, pain, and limitation related to menstruation. Twins who had stopped menstruating were asked whether this was due to hysterectomy, menopause, or some other cause and at what age it occurred. Wave 1 variables tested for association with subsequent hysterectomy status were oral contraceptive use and duration of use, age at menarche, history of pregnancy, total pregnancies, age at first pregnancy, terminations of pregnancy, days of menstrual bleeding, self-ratings (three-point scales) of heaviness of menstrual flow, menstrual pain, and whether menstruation was limiting, average menstrual cycle length, and number of obstetric difficulties experienced, DSSI/sA (Delusions-Symptoms-States Inventory/States of Anxiety and Depression) anxiety and depression scores,¹³ Extraversion and Neuroticism scores,¹⁴ educational attainment, and history of smoking.

Wave 2 (1988 through 1990). Between 1988 and 1990, twin pairs who had responded to the wave 1 survey were traced and relocated for follow-up. The second questionnaire replicated many of the earlier questions, including that on hysterectomy, and included some new items on premenstrual syndrome and other potential risk factors. This two-wave design allowed us to consider wave 1 variables prospectively as possible "risk factors" for subsequent hysterectomy. Wave 2 variables tested for association with hysterectomy were premenstrual symptom interference in usual activities, self-diagnosis of "premenstrual syndrome or premenstrual tension," whether treatment had ever been sought for premenstrual problems, perception of own social class, total Parental Bonding Instrument (PBI) score¹⁵ and PBI factor scores on parental coldness, overprotection, and discouragement of child's autonomy, and total number of life events from a series of items including experience of rape or sexual assault and loss of a pregnancy or a child.

Twin pair correlations. We assume that hysterectomy is performed when a threshold is crossed on an underlying continuum of symptoms. These symptoms have many (multifactorial) causes; therefore it is reasonable to assume that the continuum is normally distributed. It is much more informative to consider the correlation between relatives for the continuous trait, or *liability*, than for the simple dichotomy of presence or absence of hysterectomy. The appropriate statistic that estimates this correlation in liability between twins is the *polychoric correlation*, of which the special case for two dichotomous variables is the tetrachoric correlation. These may be calculated with the PRELIS 1.12 software system.¹⁶

Results

Response. Responses to wave 1 were received from 1983 complete female pairs (1232 monozygotic and 751 dizygotic), and 1448 (921 monozygotic and 527 dizy-

gotic) also answered the hysterectomy question at wave 2 (76% of pairs where both twins were still alive). Of the 366 women reporting hysterectomy at wave 1, 339 also completed the wave 2 survey. A total of 564 hysterectomies was reported over the two waves (366 at wave 1 and a further 198 at wave 2), 475 being in responding pairs at wave 2 (319 monozygotic and 156 dizygotic pairs). Pairwise concordance for hysterectomy for twins born before 1947 in wave 1 was 34.1% for monozygotic twins and 15.7% for dizygotic twins. At wave 2, for twins born before 1955, pairwise concordance was 39.4% for monozygotic twins and 21.4% for dizygotic twins. At wave 1 only 17 hysterectomies were reported by women born after 1946, and at wave 2 only five were reported by women born after 1954.

Twins who had undergone hysterectomy were asked in both questionnaires how old they were when they had the operation and in the wave 2 questionnaire whether the hysterectomy was before, during, or after menopause and whether both ovaries were removed. The mean \pm SD for age at hysterectomy in wave 2 was 40.4 years \pm 7.9, with a range of 18 to 76 years. Most hysterectomies were performed between the ages of 34 and 43 years (53%), so most women (77%) underwent hysterectomy before menopause.

Survival analysis. Hysterectomy increases in incidence with age but, as previously discussed, prevalence has also varied for secular reasons including changes in surgical fashion and health financing. Both these temporal effects may differentially affect the importance of genetic and environmental influences on hysterectomy, and it is important to try to disentangle them. Fortunately, the two-wave design of our study gives some scope for this. It is also important to ensure that any such temporal effects are similar in the monozygotic and dizygotic subsamples.

Survival to age at hysterectomy was calculated for twins in the two study waves. The most powerful test of secular change in hysterectomy rates was comparison of women aged ≥ 40 in wave 1 (born before 1940) with those in the same age group at wave 2 (born before 1948). There was overlap in the two samples, because women born before 1940 who responded to wave 2 were also in the second sample. Nevertheless, we see a marked secular increase in hysterectomy rates (Fig. 1) in the wave 2 sample (Lee-Desu $\chi^2_1 = 9.49$, $p = 0.002$). There was no heterogeneity in survival to hysterectomy between older (>40 years) monozygotic and dizygotic twins at wave 1 ($\chi^2_1 = 2.76$, $p = 0.10$) or wave 2 ($\chi^2_1 = 0.89$, $p = 0.35$).

Twin correlations. Because hysterectomy incidence varies with age and also for secular reasons, we tabulated the tetrachoric correlations (and their asymptotic standard errors) for liability to hysterectomy in monozygotic and dizygotic twins for three age bands (34 to 40, 41 to 48, and >48 years) and for the total sample

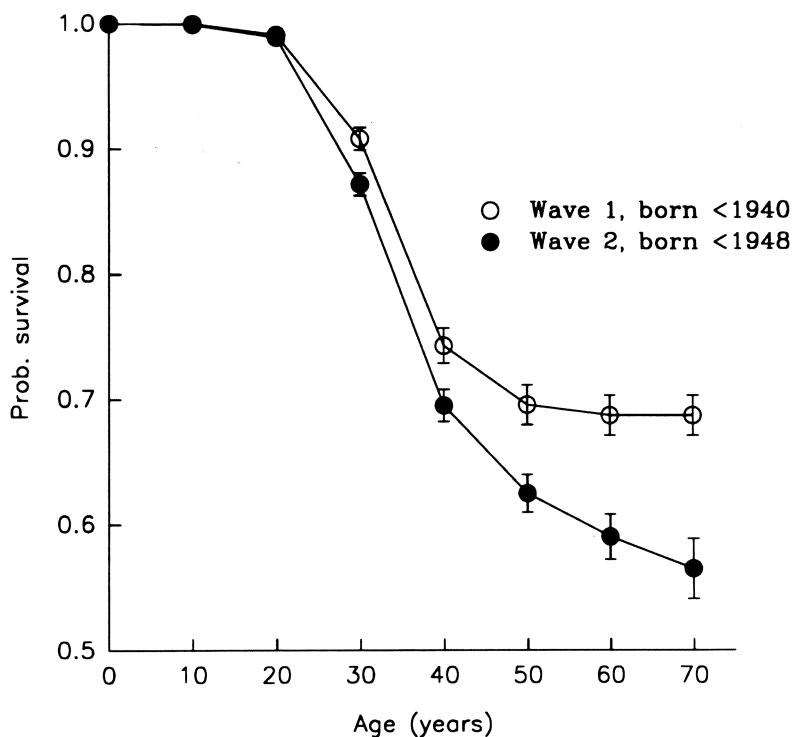


Fig. 1. Probability of reaching given age without hysterectomy in women aged >40 in waves 1 and 2.

Table I. Concordance for presence or absence of hysterectomy and twin pair correlations in liability by zygosity, age group, and study wave

Wave No.	Born	Monozygotic					Dizygotic				
		H^-H^-	H^+H^-	H^+H^+	Total	$r \pm SE$	H^-H^-	H^+H^-	H^+H^+	Total	$r \pm SE$
1	pre-1932	148	59	35	242	0.60 ± 0.08	79	57	9	145	-0.04 ± 0.15
2	pre-1940	126	79	65	270	0.58 ± 0.07	68	57	18	143	0.15 ± 0.14
1	1932-1939	77	34	18	129	0.54 ± 0.12	45	19	5	69	0.31 ± 0.22
2	1940-1947	111	30	14	155	0.62 ± 0.11	58	28	7	93	0.28 ± 0.19
1	1940-1946	144	17	4	165	0.57 ± 0.17	96	15	3	114	0.46 ± 0.21
2	1948-1954	170	28	10	208	0.62 ± 0.12	104	14	2	120	0.38 ± 0.24
TOTAL											
1	pre-1947	369	110	57	536	0.61 ± 0.06	220	91	17	328	0.20 ± 0.11
2	pre-1955	407	137	89	633	0.65 ± 0.05	230	99	27	356	0.32 ± 0.09

H^-H^- , Hysterectomy absent in both twins; H^+H^- , hysterectomy present in one twin and absent in the other; H^+H^+ , hysterectomy present in both twins.

(aged >33 years) in both waves of the study (Table I). The first point to notice is that correlations are remarkably consistent between waves for the same age band, and this gives us confidence that secular changes in incidence have little effect on twin correlations. Second, the monozygotic correlations are remarkably consistent (around 0.6) in all age bands. In contrast, the dizygotic correlations appear to increase from the oldest to the youngest age band, although the standard errors are large.

Pearson correlations for age at hysterectomy within pairs concordant for hysterectomy at wave 2 sug-

gested that genetic influence might be operating on the timing of hysterectomy ($r = 0.49 \pm 0.11$ for monozygotic and $r = 0.15 \pm 0.22$ for dizygotic), as well as on "liability" to hysterectomy. This was not apparent at wave 1, because monozygotic and dizygotic correlation coefficients were of equal magnitude ($r = 0.50 \pm 0.14$ for monozygotic and $r = 0.50 \pm 0.25$ for dizygotic), suggesting that variation might be due to environmental influences only. Note, however, that numbers are small (Table I) and that there were only 17 concordant dizygotic pairs at wave 1.

Model fitting to test for heterogeneity. The decline

in the dizygotic correlation for hysterectomy liability with increasing age suggests that the relative importance of genetic and environmental influences may also vary with age, genetic factors becoming more important in older women. To test this formally, we used LISREL 7.16¹⁷ software to fit models of variation simultaneously to monozygotic and dizygotic correlations for the three age bands. Variance disaggregates into three components: additive gene action (*h*), environmental influences specific to the individual (*e*), and either environmental effects common to both cotwins (*c*) or nonadditive gene action (*d*) (for example, dominance or epistasis).

Fitting the simplest model consistent with the observed correlations (comprising only *h* and *e*) to the three cohorts in wave 1 resulted in a very good fit ($\chi^2_5 = 5.47$). Adding shared environment ($\chi^2_4 = 5.47$) or nonadditivity ($\chi^2_4 = 4.41$) did not significantly improve fit, and dropping gene action from the model (*c* and *e*, no *h*) significantly worsened fit ($\chi^2_5 = 14.88$, $p = 0.011$). Also with wave 2, models fitted to the three birth cohorts simultaneously resulted in a best-fitting simple model comprising *h* and *e* ($\chi^2_5 = 1.35$). Again, fit significantly worsened when *h* was dropped (*ce* model $\chi^2_5 = 11.09$, $p = 0.05$). These results are not consistent with the existence of heterogeneity in genetic and environmental effects between older and younger twins. Estimates of heritability of liability were consistent across study waves ($h^2 = 0.56$ for wave 1 and $h^2 = 0.59$ for wave 2), affirming that genetic predisposition to hysterectomy was stable and not influenced by changing environmental influences. Any significant influence of shared environment was also rejected.

Covariates of hysterectomy. Polychoric correlations were computed between the potential risk factors in Methods and post-wave 1 hysterectomy. Wave 2 reports of whether premenstrual symptoms ever interfered “with work, daily activities, usual social events or . . . relationships with others” (retrospective) were the most highly correlated with hysterectomy. All significant covariates are presented in Table II. Hypotheses concerning preexisting psychologic morbidity and experiences of loss in women undergoing hysterectomy were not supported by our data.

Twins discordant for hysterectomy. Discordant twin pairs, especially monozygotic pairs, provide an ideal case-control design. Variables hypothesized as precursors of hysterectomy were tested for the 106 twin pairs discordant for “new” hysterectomy, where one twin had a hysterectomy after the wave 1 survey and her cotwin had not had a hysterectomy by wave 2 (see Table III). “New” hysterectomy was selected because the two-wave design allowed for characteristics reported at wave 1 to be reported independently of the subsequent operation. We performed *t* tests on continuous variables. Fisher’s exact test was used on contingency tables to

Table II. Significant wave 1 covariates* of subsequent hysterectomy in twins born before 1955

Covariate	<i>r</i>
1. Premenstrual syndrome symptoms interfered ever†	0.28
2. Limitation by menstruation	0.23
3. Menstrual flow	0.22
4. Average length of menses (days of bleeding)	0.19
5. Menstrual pain (dysmenorrhea)	0.17
6. No. of obstetric problems	0.15
7. Length of average menstrual cycle	-0.08
8. Neuroticism score	0.06
9. Education level	-0.05

*Sample size of 1530 to 2263. All correlations significant at $p < 0.001$ level except 7 and 8 ($p < 0.01$) and 9 ($p < 0.05$).

†Reported retrospectively at wave 2.

detect significant differences in rates of endorsement of extreme values of categoric variables (for example, “very painful” menses vs “moderately painful” or “no trouble”).

In discordant pairs, liability to hysterectomy was associated with the extreme category of “very painful” periods (odds ratio 9.99, 95% confidence interval 2.58 to 38.89). Also risk factors, but to a lesser extent, were the extreme categories of retrospectively reported interference of premenstrual symptoms in usual activities (“a lot”) (odds ratio 5.64, 95% confidence interval 1.70 to 18.68), having ever suffered from premenstrual syndrome (odds ratio, 2.04, 95% confidence interval 1.05 to 4.05), previous “heavy” menstrual flow (odds ratio 2.19, 95% confidence interval 1.04 to 4.58), and having ever sought treatment for premenstrual syndrome (odds ratio 2.08, 95% confidence interval 1.00 to 4.41). Reporting “very limiting” periods (odds ratio 3.24, 95% confidence interval 0.74 to 14.15) was not a significant risk factor.

Multivariate path analysis. To see how much of the variance in liability to hysterectomy could be explained by these covariates, a simple multivariate path model was fitted with LISREL software (Fig. 2). The influence of particular variables may appear inconsistent with the odds ratios reported previously because the highest odds ratios were found for the rarest events (i.e., those with least frequent endorsement) and in the path analysis the entire distributions are entered. Our path model had the advantage of specifying one-way effects from the possible risk factors to the underlying risk of hysterectomy and ipso facto of addressing the latent variable rather than only the observed event. We were unable to explain satisfactorily the basis of the genetic variance in liability to hysterectomy by identifying genetic and environmental influences on reported risk factors. The major covariates of hysterectomy measured in our study accounted for only 15% of the phenotypic variance in liability to hysterectomy. Cholesky

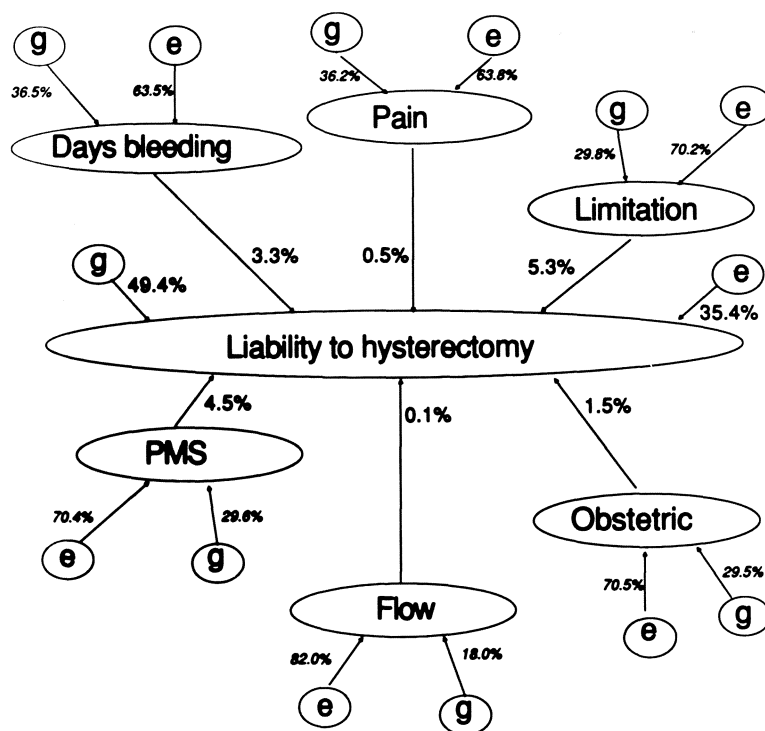


Fig. 2. Path model for causes of variation in liability in hysterectomy. Genetic and unique environmental sources of variation specific to each variable are denoted *g* and *e*. Paths between measured variables denote direct phenotypic influence. Percentages on paths indicate percent of variance in target variable contributed by each source.

saturation of the model to allow for all intercorrelations^{18,19} similarly revealed no notable genetic loading of hysterectomy on other risk factors but considerable environmental loading (data not shown). Thus genetic influences on liability to hysterectomy can be ascribed only in small part (perhaps 10%) to genetic influences on identified risk factors, so the major heritable factors are yet to be identified.

Comment

We have found clear evidence of genetic influences on liability to hysterectomy. These influences are stable across birth cohorts in which there are differences in incidence because of both aging and secular changes in surgical practice and health financing. Our analysis of reported risk factors has not revealed the basis of the largest part (85%) of the variance in liability to hysterectomy, and at least half of this is due to unidentified genetic factors. Extent of perceived interference of premenstrual problems, accounting for <5% of variance, was ahead of other menstrual dysfunction variables as risk factors for hysterectomy. The personality trait Neuroticism was barely a significant covariate and certainly played no notable role in explaining the variance. Measures of depression and anxiety proved to have no explanatory relevance. Our findings do not

support the important role of these psychological dimensions in risk for hysterectomy claimed by some authors.^{6,7}

Central to our interpretation of higher monozygotic than dizygotic twin correlations as evidence for genetic influence on hysterectomy liability is the assumption that monozygotic twins experience environmental treatments no more similarly than their dizygotic counterparts, at least insofar as these treatments pertain to the trait in question, in this case hysterectomy. This "equal environments assumption" has been challenged on the grounds that there is indeed a higher "environmental" correlation between monozygotic than dizygotic twin pairs. Evidence suggests, however, that any such effect arises because monozygotic twins, being genetically identical, create more similar environments for themselves.²⁰⁻²² If some monozygotic twins were becoming concordant for hysterectomy from frivolous reasons of imitation rather than genuine medical need, one might expect the prevalence to be higher in monozygotic than dizygotic twins; however, as our survival analysis shows, there is no significant difference in the rates of the two zygosity groups. This does not support the possibility either that physicians might have treated adult dizygotic twins (as individuals) differently from monozygotic twins or that monozygotic twin pairs were

Table III. Significant differences in pairs who became discordant for hysterectomy between wave 1 and wave 2

	Discordant pairs (H^+H^-)								
	Monozygotic (66 pairs)			Dizygotic (40 pairs)			Monozygotic plus dizygotic (106 pairs)		
	H^+	H^-	p	H^+	H^-	p	H^+	H^-	p
“Very painful” menses (%)	28.6	4.1	0.001	16.7	0.0	0.026	24.1	2.5	0.000
Days of bleeding	5.9	4.9	0.001	5.5	4.8	0.071	5.7	4.9	0.000
Premenstrual syndrome interfered “a lot” (%)	24.3	6.1	0.009	12.1	0.0	0.057	19.5	3.8	0.001
“Heavy” flow (%)	34.0	22.6	0.075	30.0	10.0	0.042	32.5	18.1	0.015
“Premenstrual syndrome” suffered (%)	72.9	62.5	0.096	72.7	48.5	0.027	72.8	56.8	0.014
Treatment for premenstrual syndrome (%)	34.7	24.5	0.096	28.1	9.4	0.042	32.1	19.8	0.020
Menses “very limiting” (%)	10.3	5.4	0.237	10.3	0.0	0.118	10.3	2.9	0.066
Years of using oral contraceptives	4.1	3.7	0.473	4.1	5.9	0.023	4.1	4.5	0.333

H^+ , Hysterectomy present; H^- , hysterectomy absent.

more likely to be referred to the same specialist as dizygotic twin pairs. Similarly, the argument that, if the increased dizygotic twinning in older mothers is genetically influenced, there might be selection against earlier hysterectomy in dizygotic twins compared with monozygotic twins is not supported by the similar age-at-hysterectomy distributions in the two zygosity groups.

Limitations of the study demanding acknowledgement are: (1) data censoring, (2) validity of self-reporting, and (3) representativeness of the sample. Using twin pairs discordant for recent hysterectomy increases the likelihood of the cotwin having a future (and yet-to-be-reported) hysterectomy after wave 2. Analysis of hysterectomy, like analysis of many procedures, events, or illnesses of importance to epidemiologists, is influenced by the problem of timing of onset, leading to data censoring.²³ Only if subjects were assessed at death could the exact lifetime prevalence of hysterectomy be known. The approach of Neale et al.²⁴ will be used in future analyses to deal with the problem, which has also arisen in analyses of appendectomy²⁵ and tonsillectomy²⁶ twin data.

All variables were measured by self-report; hysterectomy was not validated by the twin in person, her cotwin, or a medical practitioner. For most women, however, hysterectomy would be a noteworthy event requiring hospitalization and therefore would likely be more accurately reported than less well-defined medical conditions. The wave 1 questionnaire actually stated that hysterectomy was “removal of the womb.” In support, none of the twins who answered “no” to hysterectomy at wave 2 had said “yes” at wave 1. When age at hysterectomy was reported at both waves, the Pearson correlation for the two reports was $r = 0.94$

($p < 0.001$), suggesting acceptable consistency in reporting over an average of 8 years.

The twin sample has been shown to be representative of the Australian population on a number of variables, such as drinking behavior,²⁷ personality factors, and anxiety and depression.^{8,20} The wave 1 sample was unselected for anything except volunteering to enroll in the Australian National Health and Medical Research Council Twin Register and returning the questionnaire. On the basis of age-specific hysterectomy rates in the Australian State of New South Wales in 1983, the expected cumulated total proportion of women having lost a uterus was 29% (25% for a 65-year-old woman).² Our cumulated risk of hysterectomy in the wave 1 sample (1980 through 1982) was 31% at age 65, a higher but comparable proportion. At wave 2 the cumulated risk was 41% at age 60, reaching a maximum of 43%, which is higher than might be expected from 1983 projections, although the modal year of wave 2 data collection was 1989, for which we have no normative data and numbers were relatively small in these older age groups.

We intend to include medical and pathology records relating to hysterectomy in further analysis to help elucidate the sources of genetic influence. We need to compare the distribution of indications for the hysterectomies in monozygotic and dizygotic twins. Clinical symptoms presented to twins’ medical practitioners may have differed from the self-reported characteristics assessed in this study. Hysterectomy may have followed wave 1 reports by between 1 and 8 years; therefore there may be considerable heterogeneity in our sample in the relationship with antecedent “risk factors.” Lack of consensus concerning recognition and significance of medical indications may make retro-

spective interpretation difficult.³ Nevertheless, we plan to gather information on indications and the twins' reasons for hysterectomy in a new phase of the study. The power of our findings will be further tested by analysis of data being collected on hysterectomy from these twins' mothers, sisters, and adult daughters and from female relatives of male twins in the Australian Twin and Family Study.

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