

Modeling women's health during the menopausal transition: a longitudinal analysis

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ABSTRACT

Objective: There has been controversy about the relative effects on various health outcomes of hormonal, psychosocial, and lifestyle changes during the menopausal transition. In previous studies the risk factors for one particular health endpoint have been analyzed separately. Separate analyses do not provide an overall view of the relationships between all the variables or the relative importance of different factors. Thus, the objective of this study was to provide an overall analysis of the influence of hormonal changes during the menopausal transition on a range of health outcomes while simultaneously considering all the available predictors and all the endpoints and to test the hypothesis that prior health status predicts current health status.

Design: This was a 9-year prospective observational study of 438 Australian-born women, who at baseline were aged 45 to 55 years and had menstruated in the prior 3 months. Interviews were conducted and fasting blood and physical measurements were performed annually.

Results: Main outcome measures were hormone levels, sociodemographic variables, attitudes and lifestyle variables, self-rated health and well-being, bothersome symptoms, coronary heart disease risk, bone mineral density, and sexuality. Data from 336 women, 77% of the original sample, were analyzed. Statistical modeling using structural equations showed that for all health endpoints, the prior level of that variable was the most important predictor. Declining levels of estradiol during the menopausal transition affected certain health outcomes: bone mineral density, coronary heart disease risk, vasomotor symptoms, vaginal dryness, and sexual response. Well-being is negatively affected by symptoms, hassles, and stress. Exercise has beneficial effects on hot flushes, well-being, body mass index, and coronary heart disease risk. Relationship factors and mood affect sexual response.

Conclusions: This observational study provides a conceptual data-based framework for understanding changes in women's health during the natural menopausal transition.

Key Words: Symptoms – Menopause – Estradiol – Well-being – Sexuality – Bone density – Coronary heart disease risk.

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The Melbourne Women's Midlife Health Project is a prospective, population-based study of Australian-born women assessed annually over 9 years as they passed through the menopausal transition. This study provided the database for analyses of change in various health endpoints during the menopausal transition, including symptoms,¹⁻⁴ self-rated health,^{5,6} mood,^{7,8} well-being,^{9,10} sexual function,¹¹⁻¹⁴ menstrual patterns,^{15,16} cardiovascular risk,¹⁷ body composition,^{18,19} and bone mineral density (BMD).^{20,21} Various predictors were identified from baseline and annually recorded variables.²² These included hormone levels, socio-demographic and psychosocial variables (such as paid work status, years of education, stress, and relationship factors), as well as lifestyle variables, such as smoking habits or physical exercise. In all the above studies, the risk factors for one particular health endpoint were analyzed separately. These studies were essential to find out the relevant predictors of each endpoint. However, separate analyses do not provide an overall view of the relationships between all the variables. Nor do separate analyses account for the fact that in practice, health outcomes and determining variables are not separated but occur concurrently. One predictor or endpoint can be a valid predictor for another endpoint. For example, symptoms, such as hot flushes, considered as an endpoint influenced by a change in hormone levels, may themselves affect another endpoint, such as mood. Thus, the two models estimated separately in previous studies are not independent, and they need to be simultaneously estimated.

In previous analyses we have used different statistical techniques, such as cross-sectional estimates, summary statistics, multivariate analysis of variance, or regression in time. The choice of the technique was based on the type of variables and/or to increase the power of the tests. However, results are not then totally comparable between studies. Because of missing data and use of subsets of the cohort for some variables, the analyses were carried out with different sample sizes. Although this did not involve a problem in the analysis itself, it is sometimes difficult to compare results between analyses when the sample subsets and power vary.

In addition, some of our prior analyses were based on the first 6 years of follow-up, when only 37% of the cohort had actually reached their final menstrual period. Further analysis of the data now

allows incorporation of 9 years of data, by which time 51% of women had reached their final menstrual period.

Our objectives in this study were to provide an overall analysis of the influence of hormonal changes during the menopausal transition on a range of health outcomes while simultaneously considering all the available predictors and all the endpoints and to test the hypothesis that prior health status predicts current health status.

METHODS

Design

The Melbourne Women's Midlife Health Project is a prospective, population-based study of Australian-born women assessed annually for 9 years as they passed through the menopausal transition.^{14,22} The study began in 1991 with a population sampling of 2001 Australian-born women aged 45 to 55 years.¹ All women who had experienced menses in the prior 3 months and who were not taking oral contraceptive pills or hormone therapy (HT) were invited to participate in a longitudinal study ($n = 779$). Of those eligible, 438 (56%) accepted, and all participants were white. They took part in annual interviews conducted in their homes by trained field workers. Fasting blood samples were taken while the women were between days 4 and 8 of the menstrual cycle if they were still menstruating or on any day after 3 months of amenorrhea.

The study was approved by the Human Research Ethics Committee of the University of Melbourne, and the procedures followed were in accordance with the ethical standards of the National Health and Medical Research Council. All women provided written informed consent for their participation in the study.

Sample

Four hundred thirty-eight women comprised the longitudinal study cohort. Of these, 37 experienced surgical menopause, 5 used oral contraceptive pills for at least 1 month during the study, and 51 dropped out for various unrelated reasons. Nine women were excluded because they refused to have blood taken for hormone assays. Thus, the analysis was performed on 336 women.

At baseline, comparing the 438 participants with 341 nonparticipants,²³ participants more often reported better self-rated health, current employment, more

than 12 years of education, exercising at least once a week, and having had a Papanicolaou smear. The retention rate by year 9 of follow-up was 88%. Women who dropped out were significantly less likely to be married/living with a partner or to exercise at least once per week.

Menopausal status

Reproductive and menopausal status was determined from a question about a change in menstrual status asked at each annual interview for those women who were not taking HT. Following the recommendations of the Stages of Reproductive Aging Workshop,²⁴ late reproductive status was assigned to women who reported regular menstrual cycles, early menopausal transition status was assigned to women who had menstruated in the prior 3 months but reported a change in menstrual frequency, and late menopausal transition status was assigned when women reported at least 3 months of amenorrhea but less than 12 months of amenorrhea. Women were deemed to be postmenopausal when there had been amenorrhea for at least 12 months. Reports of 3 or more months of amenorrhea were verified by fieldworkers from prospectively kept daily menstrual diaries. Women who experienced a hysterectomy with or without an oophorectomy or an endometrial ablation were classified as having a surgical (or induced) menopause. Women using HT were categorized separately as HT users for those observations during which they used hormones.

Data

The following variables were recorded at baseline: parity, level of education, attitudes toward aging and menopause,²⁵ and prior history of premenstrual complaints. Variables measured at baseline and at each follow-up visit included employment status, marital status, exercise behavior, smoking habits, alcohol intake, self-rated health,^{5,6} mood (positive, negative, and overall well-being),⁷⁻⁹ general somatic and menopausal symptoms,²⁶ interpersonal stress,⁹ and menopausal status. Variables measured during each year of follow-up included height and weight (body mass index [BMI], calculated as weight in kg/height in m²), hormone levels (follicle-stimulating hormone, estradiol [E₂], inhibin, sex hormone-binding globulin [SHBG], testosterone, and dehydroepiandrosterone sulfate), coronary heart disease (CHD) risk (calculated using the PROCAM scoring system¹⁷), the number of daily hassles,^{7,27} and sexual functioning

(using the Short Personal Experiences Questionnaire²⁸⁻³⁰). BMD of the lumbar spine (second to fourth lumbar vertebrae) and of the femoral neck was measured on three occasions.

Hormone measures

E₂ was measured using the double-antibody radioimmunoassay kit purchased from Diagnostic Products Corporation (Los Angeles, CA). Serum testosterone was measured by double-antibody radioimmunoassay, after sample extraction and polyethylene glycol-enhanced separation of bound from free ligand, using ¹²⁵I iodinated testosterone as tracer. SHBG and dehydroepiandrosterone sulfate were measured by an automated chemiluminescent enzyme immunoassay (Diagnostic Products) using the Immulite automated analyzer.^{17,23} The free testosterone index was calculated as the ratio of measured testosterone to measured SHBG × 100.

Symptoms

The most important menopause-specific symptoms described in our previous article were hot flushes, night sweats, sore breasts, dry vagina, and trouble sleeping.² However, the symptom of sore breasts was not included in the first 3 years of study. We therefore excluded this symptom from analysis. The four remaining symptoms, hot flushes, night sweats, dry vagina, and trouble sleeping, were analyzed separately, whereas all others were grouped into an "other symptom" category. The symptoms were documented as presence/absence, intensity (1 = minor, 2 = interfering with normal life, and 3 = debilitating), and frequency (number of days in the last 2 weeks). To describe the severity of the first four symptoms, we computed intensity (*I*) and frequency (*F*) as $[(I \times F)/4.2]$ to produce a scale between 0 and 10. For the category other symptoms, to keep values between 0 and 10, we used the calculation $(I \times F)/39.2$. The divisor of 39.2 was calculated by multiplying the maximum number of symptoms (28) by the possible number of days (14), divided by 10. With this scale, a value of 10 would be a continuous debilitating state caused by a symptom and 0 would mean total absence of the symptom.

BMD

BMD of both the lumbar spine (second to fourth lumbar vertebrae) and of the femoral neck was measured by dual-energy x-ray absorptiometry using a Hologic QDR-1000 W densitometer in the Bone Densitometry Unit at the Royal Melbourne Hospital, on three visits, but only for a subset of women

($n = 159$).²¹ The mean (SD) time interval was 22.8 (8.9) months between the first and second measurements and 23.8 (2.6) months between the second and third measurements. A smaller cohort was used for these studies because not all women were able to attend the Royal Melbourne Hospital for measurements, and women who were taking HT were excluded.

Statistical analysis

Our objective was to encompass several health-related endpoints (symptoms, CHD risk, BMD, etc) measured at several time points. Thus, several regressions had to be conducted between variables and between time periods, such that an independent variable in one model could be an outcome or determining factor in another model. Structural equation modeling must be used to manage together several regressions in time and between variables.³⁰ Structural equation modeling necessitates the baseline assumption of an a priori model, assesses the goodness of fit of this model with the data sample, and permits exploratory optimization of the model. We defined our a priori model in assuming all the significant effects detected from the existing literature. From earlier results,^{8,30,31} we demonstrated the existence of a strong autocorrelation (each variable at time t correlated with itself at $t - 1$) and, because of yearly examinations, the existence of effects of variables at the same time (effects of these variables as predictors at earlier times were absorbed in autocorrelation), and finally the constancy of the effects between any two periods (Markov model autocorrelated at level 1 and cross-correlated at level 0). Post hoc ameliorations to our model were made possible through modification indices with the condition that these modifications were clinically justified. Hormones were log transformed for normality purposes. Multivariate normality was tested, and missing data were considered as missing at random and were imputed throughout using the systematic full information maximum likelihood technique.³² Age was systematically considered in structural equation modeling for all the regressions constituting this model. In addition, "hassles" and "smoking" were considered together in the simultaneous regression models. Possible confounding was thus taken into account.

RESULTS

Baseline profile of participants

Table 1 shows the baseline characteristics of the 336 women who participated in this analysis.

Preliminary model and goodness of fit of the final model

Our initial assumption, based on important autocorrelations with previous time points and cross-correlations with other variables at the same time point, was overwhelmingly confirmed except for a few relationships, in particular the following:

- BMI was found to be influenced by smoking habits (SHs) not only at time t but also at time $t - 1$. Because the paths for SH_t and SH_{t-1} are similar but of opposite signs, the results confirm the clinical experience that a change in weight is affected by changes in SH and not final SHs only.
- Partner (absence/presence) had an effect on sex response both at time $t - 1$ and time t . The path coefficients were of the same magnitude but of opposite signs. This finding is in complete accordance with previous findings that change of partner (and not simply presence of a partner) has an effect on sex response.³⁰

Regarding hormones, in our prior published studies we found that E_2 was the only hormone studied that affected health outcomes.^{2,14,17,21} In the structural equation modeling, we included all hormones

TABLE 1. Baseline characteristics of the sample ($n = 336$), aged 45 to 55 years (mean age 48.6, SD 2.5 years)

Variable	%
Years of education completed	
<6	2
6-10	44
11-12	21
>12	34
Marital status	
Married/living with partner	81
Separated/divorced	12
Widowed	4
Single	3
Paid employment	
Full-time	36
Part-time	37
None	27
Parity	
Median	3
Range	0-9
Menopausal status	
Late reproductive	40
Early menopausal transition	60
Smoking	
Yes	19
No	81
Exercise	
>1 time per week	55
Alcohol	
Zero drinks in last week	38
8+ drinks in last week	20
Self-rated health	
Better than most	48

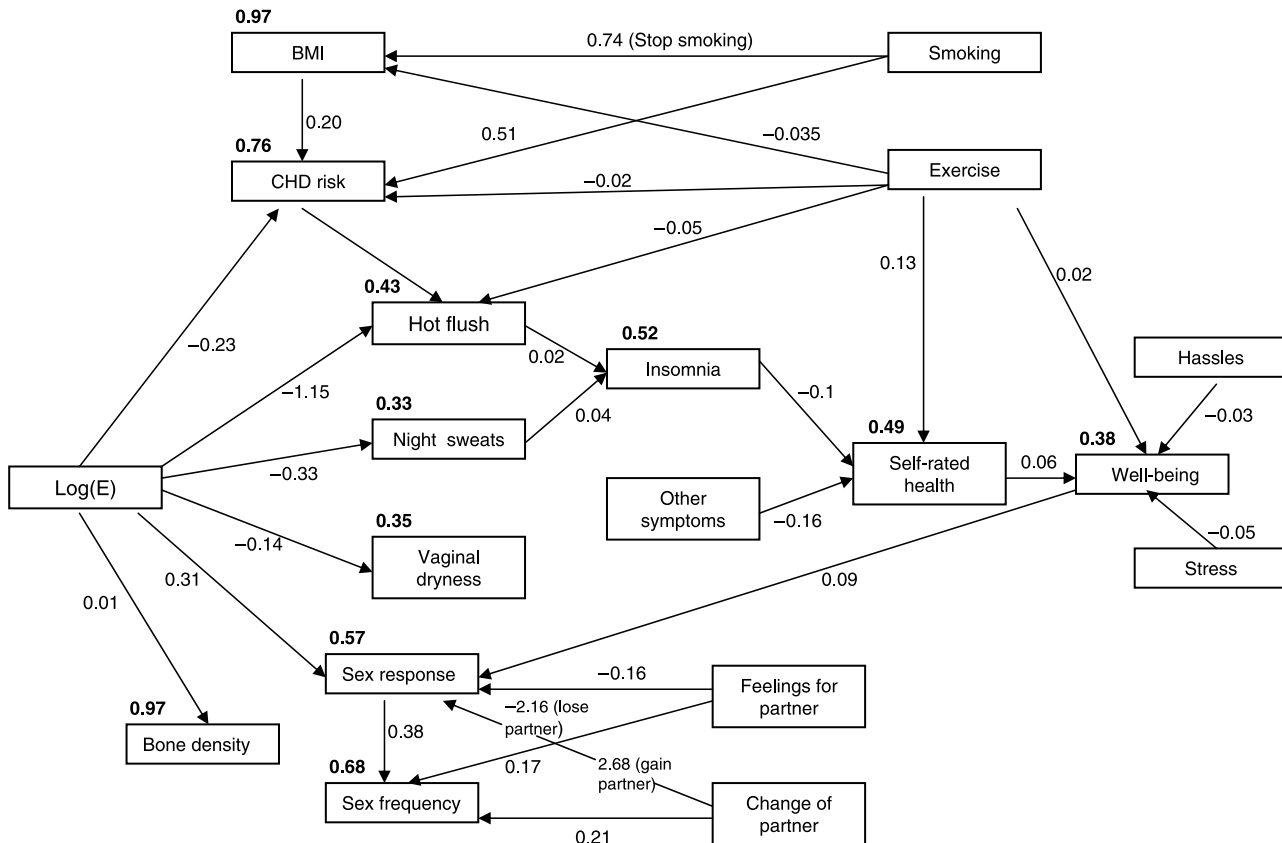


FIG. 1. Structural equation modeling of health outcomes and determinants during the menopausal transition. Boldface numbers indicate autocorrelation coefficients. Lightface numbers indicate β coefficients. Log(E) is the natural logarithm of estradiol. Insomnia represents a sleeping disorder. BMI, body mass index; CHD, coronary heart disease.

measured and confirmed the same structure as previously found for interrelationships among hormones.¹⁴ We therefore suppressed hormones other than E₂ in the diagram of the model and included in the text the few instances for which other hormones significantly affected variables.

A reasonable goodness of fit was found for the first model ($\chi^2/\text{degrees of freedom} = 1.68$, non-normed fit index = 0.88). We assessed the goodness of fit of the above model separately for each reproductive status group (late reproductive and early menopausal transition, late menopausal transition, postmenopause, and HT). Our model was found to be in conformity with a goodness of fit close to the undifferentiated model ($\chi^2/\text{degrees of freedom} = 1.35$, non-normed fit index = 0.88).

Figure 1 shows the results of the structural equation modeling and provides an overview of the relationships between determinants and health outcomes over time. The figure contains the correlation coefficients (both β coefficients and autocorrelation

coefficients) to illustrate the strength and direction of the relationships.

Final model

Symptoms

Baseline values of all symptoms were lower in women with higher education at baseline. Thus, baseline sociodemographic factors have an effect on baseline levels of symptoms, but changes in symptoms associated with the menopausal transition are not subsequently influenced by these sociodemographic variables. Thus, women with a higher educational level reported fewer symptoms at baseline while they were still menstruating, but subsequent changes in symptom levels during the menopausal transition are not affected by educational level.

Hot flushes

As a simple descriptive analysis we calculated the mean hot flush compound index for each menopausal

TABLE 2. Mean (SD) compound index (frequency and severity) for symptoms by menopausal status group

Menopausal status	Hot flushes	Night sweats	Vaginal dryness	Sleep problems	Other symptoms
Late reproductive	1.37 (2.17)	0.31 (1.05)	0.64 (0.83)	0.49 (0.63)	2.42 (1.98)
Early menopausal transition	1.29 (2.23)	0.30 (1.22)	0.86 (0.98)	0.58 (0.69)	2.75 (2.04)
Late menopausal transition	3.32 (3.18)	0.92 (1.96)	0.85 (1.01)	0.70 (0.74)	2.86 (2.02)
Postmenopausal	2.96 (3.06)	0.89 (1.89)	1.12 (1.11)	0.71 (0.74)	2.84 (1.94)
Using hormone therapy	1.12 (2.07)	0.28 (1.07)	0.97 (1.07)	0.66 (0.74)	2.75 (1.97)

status group (Table 2). The hot flush index varied from more than 1 for late reproductive, early menopausal transition, or HT to approximately 3 for late menopausal transition and postmenopause. Because this index was calculated to be relevant for clinical practice, a value of 3 represents either 30% of the time with hot flushes of mild severity or 10% of the time with hot flushes of debilitating severity. Thus, this value can be considered as a clinically relevant threshold of hot flushes. Table 2 shows that the late menopausal transition is the time when women are most bothered by hot flushes.

Some women reported hot flushes while they were still menstruating regularly. These women are more likely to be at risk for hot flushes during late menopausal transition and postmenopause. The hot flush index score in the late reproductive phase at baseline was not explained by the presence of premenstrual complaints. Level of education had an effect on hot flushes at baseline, but not on the change in hot flushes during the menopausal transition (regression coefficient $-0.34/\text{education level}$, $P < 0.001$). Hot flush reporting decreased with increasing exercise levels. Figure 1 shows that falling E_2 had a significant effect on hot flushes.

Night sweats

Similar results were found when a compound index was calculated for night sweats, as shown in Table 2, but the night sweats mean compound index was much smaller than that found for hot flushes across menopausal status groups.

The night sweats index peaked in the late menopausal transition. Women who experienced night sweats before the menopausal transition had night sweats of greater severity during the menopausal transition. There was no correlation of baseline night sweats index with premenstrual complaints at baseline. A lower night sweats index at baseline was associated with a higher level of education. Baseline educational level did not affect a subsequent change in the night sweats index. Figure 1 shows that falling E_2 has a significant effect on night sweats.

Vaginal dryness

The mean vaginal dryness index scores for menopausal status groups are shown in Table 2. Although a highly significant difference was found ($P < 0.001$), the results are not similar to the model seen for previous symptoms because a continuous increase was found from late menopausal transition to postmenopause. For vasomotor symptoms, there was a maximum around late menopausal transition. A multiple comparison of means test showed late reproductive scores to be significantly less than those for early menopausal transition and late menopausal transition. Late menopausal transition vaginal dryness scores were found to be significantly less than postmenopausal scores. Women using HT had mean values similar to those reported in the menopausal transition (early menopausal transition + late menopausal transition). At baseline, vaginal dryness was significantly associated with premenstrual complaints, whereas education level had a less significant association with vaginal dryness. Figure 1 shows that falling E_2 has a significant effect on vaginal dryness.

Sleeping problems

Index scores for this symptom are shown in Table 2. They were of similar magnitude to those for vaginal dryness and much smaller than those for hot flushes.

An increase was observed from late reproductive to early menopausal transition to postmenopausal status. A multiple comparison of means detected a significant difference between late reproductive + early menopausal transition combined against the other menopausal status groups. The data also suggest an apparent lack of efficacy of HT on this symptom. The main prognostic factor for this symptom was its earlier prevalence. Other explanatory factors for a change in this symptom are the vasomotor symptoms (hot flushes and night sweats).

Other symptoms

The other reported symptoms (respiratory, somatic, etc) were regrouped into one group. The mean value of the compound index for these symptoms by

menopausal status is shown in Table 2. The mean value remained less than 3; thus, the cumulative compound index for all these symptoms together remained reasonably small and slightly increased in time (expected with age), but without reaching a significant difference. There was no difference among menopausal status groups, and this index was found to be mostly influenced by baseline values ($r = 0.52$), which were associated with educational level. Thus, other symptoms are determined by their level before the menopausal transition with small variations. Although this nonspecific symptom group did not show specificity to the menopausal transition, it was kept in the subsequent analysis as a potential predictor of well-being and of self-perception of health.

Self-rated health

This scale measures subjective perception of health. Originally 0 to 2, it was multiplied to range within (0 to 10) to be more easily interpretable in the regression analyses.

Self-rated health at baseline was slightly negatively associated with other symptoms (-0.16 /unit score) and parity (-0.11 /children) and positively associated with exercise ($+0.13$ for exercise against no exercise). Thus, the prior value has a considerable effect on the current value for self-rated health ($r = 0.49$), and after adjusting for this influence, only sleeping problems and other symptoms were seen to negatively affect self-rated health. Symptoms specifically affected by the menopausal transition (vasomotor symptoms and vaginal dryness) have no effect on self-rated health.

Well-being

In this study we measured well-being as the difference between positive and negative mood scores. Well-being (mood) was seen to vary according to several predictors with an exceptionally good coefficient of determination ($r^2 = 0.5$).

First, a strong autocorrelation was found (0.38). Thus, women's well-being is first determined by their prior level of well-being. After this effect of baseline mood, subsequent mood was negatively affected by problems with sleeping, interpersonal stress, and the number and severity of daily hassles. Well-being was positively affected by positive feelings for partner, rating one's health as better than that of one's peers, and exercising frequently. Thus, a change in well-being is related to health symptoms (sleeping problems and self-rated health), external problems (daily hassles and interpersonal stress), feelings for partner, and exercise. There is no signi-

ficant direct association with hormonal status or change in hormonal status.

Sexual response and frequency of sexual activities

The causal structure reported previously^{14,30} was confirmed, with some additional findings taking into account all the variables. Sexual response was determined by the following decreasing variables: previous value (considerable value of 0.57), change in partner (losing partner or gaining a partner), feelings for partner, E_2 level, and well-being. Sexual response, changes in partner status, and feelings for partner were the only significant factors associated with frequency of sexual activities. An exceptionally high coefficient of determination was found for sexual response ($r^2 = 0.63$) and an even larger coefficient for frequency of sexual activities ($r^2 = 0.7$).

BMI

BMI increased when women stopped smoking. Ceasing smoking generated a weight gain of between 1 and 8 kg. Exercise has a small additional decreasing effect (change in $[\Delta]$ BMI = -0.035 /days of exercise). Increases in BMI were significantly associated with decreasing levels of SHBG.

CHD and BMD

The risk of CHD was shown to have a high autocorrelation ($r = 0.76$), and its change is affected by E_2 ($-0.23/\Delta E_2$), BMI ($0.20/\Delta$ BMI), exercise (-0.02), free testosterone index ($0.22/\Delta$ free testosterone index), and smoking (0.51 /smoking, yes = 1/no = 0). Exercise has a combined positive effect because it also reduces BMI, which in turn influences CHD.

BMD is extremely stable in time ($r = 0.97$), and a change in BMD is influenced only by E_2 . Baseline BMD is dependent on BMI.

DISCUSSION

Our objective was to study changes with menopausal and hormonal status, taking advantage of the longitudinal data. The model yielded a general structure consistent with the relationships found in prior studies. Our Melbourne study had previously, in single endpoint analyses, identified the health changes significantly associated with declining E_2 . These included an increase in vasomotor symptoms, vaginal dryness, and dyspareunia; a decline in BMD of the spine and femoral neck regions²⁰; an increase in CHD risk calculated using the PROCAM score¹⁷; and a decline in sexual function.¹⁴ Other factors have also contributed significantly to the results. A higher

than average BMI and an increase in BMI had a strong influence on CHD risk and abdominal fat, whereas aging and partner factors affected sexual function. Mood and self-rated health were not directly related to E_2 decline. Psychosocial and lifestyle factors had a significant effect on these outcomes. The menopausal transition did have an indirect effect on mood by increasing symptoms affecting health perception.⁷ Thus, the statistical overall model retained the key relationships.

Changing E_2 levels have a significant effect on the symptoms of hot flushes, night sweats, vaginal dryness, and (indirectly) sleep problems, with severity of these symptoms peaking in the late menopausal/postmenopausal periods. Reporting of other bothersome symptoms does not change during the menopausal transition. The path coefficients on the subgroups of late reproductive + early menopausal transition, late menopausal transition, and postmenopause are invariant. Thus, when the analysis is repeated at fixed stages of the menopausal transition, the model holds. This provides evidence that the effects of changing menopause status are entirely accounted for by changes in E_2 .

These results are similar to those reported previously.^{2,4} Sleep complaints increase from the early to late menopausal transition, and in our study hot flushes were an explanatory factor for a change in sleep problems. Other researchers^{33,34} have suggested that hot flushes do not cause sleep disturbances even though women often have a flush after waking. Further research is needed to clarify the mechanisms responsible.

The analysis highlights the importance of autocorrelation, the prior level of a specific variable. This particularly applies to self-rated health, well-being, and other symptoms, outcomes that have no significant association with menopause status or change in menopause status. In the current analysis attitudes toward aging and menopause did not significantly affect any of the endpoints measured. The effects of changing menopause status are entirely accounted for by changes in the hormonal system. We confirmed that changes in BMI were not directly associated with the menopausal transition.¹⁸

We carried out the analyses with the same sample size, using the same power for all health outcomes except BMD, for which only a subset of participants underwent scanning. We provide the results under a statistical scheme, facilitating an overall understanding of all the changes and pointing out the relative effects of hormonal changes on those of other variables. We present an overall model, not restrained to one separate

analysis of each endpoint but encompassing all the relations among the variables and endpoints within and between them. Thus, the overlapping aspects of separate analyses are now accounted for. Age was included in the figure since results were adjusted for age, but age did not influence the relationships displayed.

As far as possible we attempted to determine a direction for each relationship. When this direction was uncertain, we carried out simple alternative models to select the best direction, but when the results were not significantly different, we limited the model to a simple correlation, assuming evidence of relationships of unknown direction.

We previously reported on a structural equation modeling model using pooled data from the first 6 years of this study.³⁶ This earlier model showed no direct effects of hormonal variables on sexual response or frequency of sexual activities, whereas in the current analysis E_2 had a direct effect on sexual response (and on vaginal dryness). The difference in outcomes can be partly explained by the fact that a greater proportion of the cohort have passed through the menopausal transition and experienced the consequent decline of E_2 . Thirty-seven percent of women had experienced the menopausal transition after 6 years of follow-up, compared with 51% after 9 years.³⁷ In addition, by using longitudinal analysis we are now able to adjust for the prior level of each variable (using autocorrelation coefficients).

We did find a direction of effects for certain endpoints and relationships between variables. Well-being is affected by some symptoms and, in turn, affects sexual response. Physical exercise affects CHD risk and has a combined positive effect because it also reduces BMI, which in turn influences CHD risk. However, we have been unable to determine whether women with low CHD risk have a natural propensity to exercise more.

Limitations of this study include the fact that measurement of hormones was carried out only annually, attrition of the sample, and the fact that the results relate only to Australian-born white women. During reproductive aging there is a high degree of individual variability. The limited annual tracking of levels of individual hormones means that the interpretation of isolated hormonal measurements for women cannot be used reliably to define their reproductive status. The dropout rate was very low, 12% after 8 years of follow-up. The women who remained in the study were more likely to exercise and to be married or living with a partner. Thus, the attrition may have contributed to a healthy bias of the

sample. However, there was a wide range of lifestyle and sociodemographic characteristics, and the range is representative of an Australian-born population. Several studies of non-Western women suggest cultural differences in the reporting of menopausal symptoms.³⁸⁻⁴¹ The cultural mix of the Australian population is such that by limiting our cohort to Australian-born women, the odds of them all being white in this mid-age range are very high. Because our population was white, we were unable to do any comparisons with cross-cultural data.

Measurement error is also a limitation in cohort studies. We used validated questionnaires and repeated questions annually to eliminate this possibility. Because we used a $P < 0.05$ level of significance for all the relationships evident in the model, the model is not expected to take into account all the potential links among all the variables. This study has an observational design and provides a data-driven description of the natural history of a range of health outcomes and behaviors of women during the menopausal transition. We identify associations that can then be tested further in other studies.

Data from other published longitudinal studies of the menopausal transition, including the Massachusetts Women's Health Study,⁴² the Healthy Women study,⁴³ Manitoba Project on Women and Their Health in the Middle Years,⁴⁴ Norwegian Menopause Project,⁴⁵ Seattle Midlife Women's Health Study,⁴⁶ and the Study of Women's Health Across the Nation,⁴⁷ indicate that midlife women report many different types of symptoms, not all specific to menopause. However, these studies lack a conceptual framework to link symptoms and health experience to biological dimensions of menopause as well as the social and lifestyle environments in which women go through the menopausal transition. In the current article we have attempted to provide an empirical data-driven basis for conceptual framework development.

CONCLUSIONS

Using statistical modeling we found that declining levels of E_2 during the menopausal transition affect certain health outcomes: BMD, CHD risk, vasomotor symptoms, vaginal dryness, and sexual response (sexual interest, arousal, enjoyment, and orgasm). Well-being is negatively affected by a range of symptoms and by hassles and stress. Exercise has beneficial effects on hot flushes, well-being, BMI, and CHD risk. Relationship factors affect sexual response and frequency of sexual activities. The most

important factor affecting any health variable after the final menstrual period is prior health.

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