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Longitudinal Study of Risk Factors for Coronary Heart Disease Across the Menopausal Transition

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The patterns of change in blood lipids, diastolic blood pressure, body mass index, smoking and drinking behaviors, and exercise were examined in an ongoing longitudinal study from 1991 to 1995 of 150 middle-aged Melbourne, Australia, women as they passed through menopause. Changes in risk factors over time were examined with reference to time of the final menstrual period (FMP). Random effects models were fitted with adjustments for repeated measures and other covariates, including age. There were overall net increases between 3 years before and the 3 years after menopause of 0.25 mmol/liter for low density lipoprotein cholesterol, 0.05 mmol/liter for high density lipoprotein cholesterol (HDL cholesterol), 0.34 mmol/liter for triglycerides, 0.12 kg/m^2 for body mass index, and 0.48 mmHg for diastolic pressure. The proportion of drinkers decreased by 13%, that of smokers increased by 17%, and that of women who exercised at least once a week increased by 6%. The only change dependent on the FMP was a significant decrease in HDL cholesterol (counterbalanced by a similar rise in HDL cholesterol in the year before the FMP), and the rate of decrease was maximal around 9 months after menses ceased, with an instantaneous estimate of slope of 0.55 mmol/liter per year. *Am J Epidemiol* 2000;151:584–93.

coronary disease; longitudinal studies; menopause; random effects model; risk factors

The risk of coronary heart disease in women rises with increasing age, increasing body weight, high blood pressure, increased cigarette smoking, decreased exercise, and low alcohol intake (1–7). Elevated serum lipids and lipoproteins are often associated with these factors and also indicate elevated risk of coronary heart disease. Coronary heart disease is rare before menopause, but incidence increases significantly in the postmenopausal years (8). Several studies have reported adverse effects of menopause on serum concentrations of triglycerides, low density lipoprotein cholesterol (LDL cholesterol), diastolic blood pressure, and body mass index (9), although it is difficult to disentangle the impact of menopause from that of age effects on cardiovascular risk factors. Many reports have not been able to adjust for this adequately.

The pattern of change in high density lipoprotein cholesterol (HDL cholesterol) around the time of menopause remains controversial. Some early cross-sectional studies that compared premenopausal with postmenopausal women reported no differences in HDL cholesterol levels as a consequence of menopause (9, 10), while another (11) described a decrease in HDL cholesterol that occurred gradually over the 2 years preceding menopause. A recent, large study based on more than a thousand women (12) showed that HDL cholesterol was not correlated with age and did not change significantly as a consequence of menopause. Many, if not most, of these previous studies have been limited by their cross-sectional nature. While in one study (11) attempts were made to investigate the time-course of the menopausal changes in hormones and lipids based on 170 women who completed a longitudinal study, only 10 premenopausal women made the transition to postmenopausal status during follow-up over 2 to 3 years.

The methodology used in analyzing previous longitudinal studies of lipids has usually been classical repeated measures analyses (13). These assume "fixed effects," that is, that every woman has the same pattern of change over time, but this is unlikely to reflect the complexity of actual patterns over time. For example, higher rates of change are positively correlated with higher initial blood pressure measurements (14, 15). In this study, we have addressed both of these problems.

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Abbreviations: BMI, body mass index; FMP, final menstrual period; HDL cholesterol, high density lipid cholesterol; LDL cholesterol, low density lipid cholesterol.

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With longitudinal data collected annually over 5 years from 150 women aged 45–55 years at baseline, we have examined the patterns of change in various major risk factors for cardiovascular disease, including changes in lipids, during the menopausal transition. Specifically, we can study the overall net changes in risk factors from pre- to postmenopause, changes with respect to the last menstrual period, and other interrelations causing independent changes over time. In addition, analyses have been based on random-effects models to disentangle menopausal effects from the interrelations among independently changing risk factors and, thus, more accurately reflect the variable changes in a woman's risk factors over time.

MATERIALS AND METHODS

Study population

The cohort of women in this study is participating in a large, ongoing longitudinal study, the Melbourne Women's Midlife Health Project (16–19). Study subjects were initially identified during a cross-sectional survey of a random sample of 2,001 women from the population of Melbourne who were Australian-born and between ages 45 and 55 years inclusive in May 1991. To be eligible for the longitudinal study, women had to have menstruated in the previous 3 months, to have an intact uterus and at least one ovary, and to not be taking hormones or oral contraceptives. There were 779 eligible women who completed the baseline questionnaire, of whom 438 (56 percent) were recruited. In December 1997, there were 150 women with known date of the final menstrual period (FMP).

Data collection

The first round of yearly, face-to-face follow-up interviews (L1) began in September 1991, and four rounds of face-to-face interviews were conducted annually between September and December every year from 1992 to 1994 (L2–L4). The distribution of time (months) in relation to FMP is given in figure 1. In addition to updating menstrual and contraceptive histories, information about various cardiovascular risk factors was obtained on each occasion. Smoking status was self-reported as never smoked, ex-smoker, current smoker (1–10 ,11–20, and ≥21 cigarettes per day), and alcohol consumption was ordered according to the number of drinks consumed in the previous 7 days (none, ≤2, 3–6, or ≥7). The amount of recreational exercise was assessed according to frequency in response to the question, "How often, if at all, do you participate in physical activities or sports for fitness or recreational purposes?" with answers recorded as every day, 4–6 times a week, 2 to 3 times a week, once a week, a few times a month, less than once a month, or never.

Menopausal status and FMP

At baseline (May 1991) and at L1–L5 (September to December 1991–1995), respondents were classified as

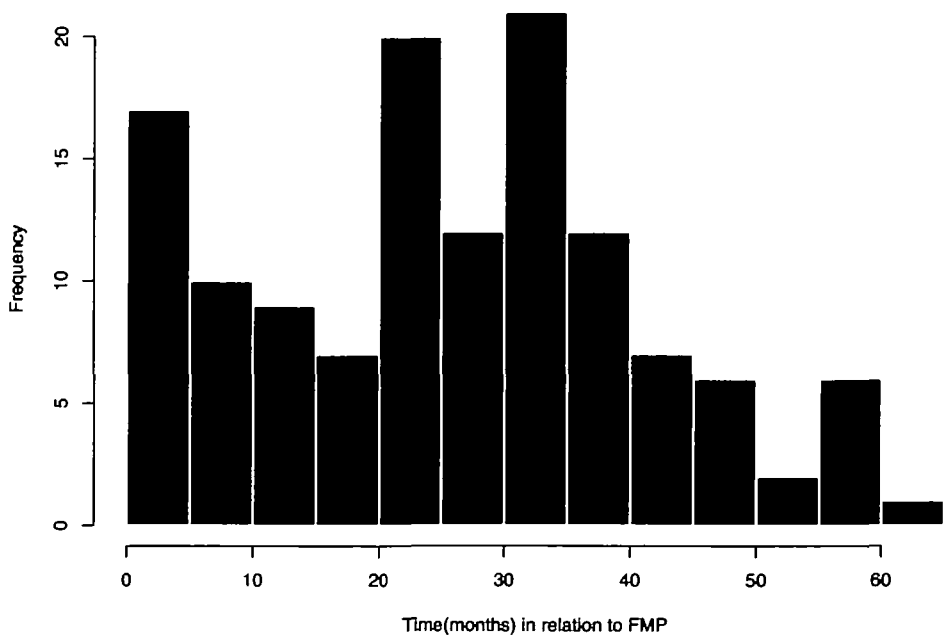

FIGURE 1. Distribution of times since FMP for the 150 Melbourne, Australia, women at the end of 5 years follow-up, Melbourne, Australia, 1991–1995.

premenopausal if they reported no change in menstrual frequency in the previous 12 months, perimenopausal if menses had been reported in the last 12 months but with changes in frequency, or naturally postmenopausal if no menses had occurred in the last 12 months and the woman had a uterus and at least one ovary intact (20). Women who had undergone surgical menopause and those taking hormone therapy were excluded. The exact date of the FMP was rescaled to take the value 0 on the time scale, and the interview dates in 1991–1995 were transformed to take values $X_1,\ldots,X_5$ on the continuous time scale (in months) relative to the FMP, with negative and positive values representing the amount of time before and after the FMP, respectively. In this study, analyses concern 150 women who had reported the exact date of their FMP during the follow-up period. Of these 150 women, five were lost to follow-up after the first 2 years, and 131 remained in the study at the end of 5 years.

Laboratory assays and measurements

A fasting, morning blood sample was taken for measurements of HDL cholesterol, LDL cholesterol, and triglycerides according to standard enzymatic methods and using an American Monitor Corporation "Perspective" Selective Chemical Analyzer (AMC, Indianapolis, Indiana). Diastolic pressure was measured twice, 5 minutes apart, with the subject seated, and the mean of the two measurements was calculated. Body mass index (BMI) was calculated as weight (kg)/height (m^2). For quality control, a random subset of 25 women was chosen from which reassays of frozen blood samples at each time point were performed. The results indicated that the consistency of laboratory measures over the study period was well within two standard deviations from the original measures.

Statistical analysis

Because of skewed distributions, the triglyceride values were log-transformed before analysis. Our longitudinal data have been defined as repeated measures data ordered by time; that is, observations within individuals have not been randomly assigned to the different time points, and hence, serial correlation exists (21). Linear and nonlinear mixed-effects analyses were used to model the repeated measurements of lipids and blood pressure (the response variables) as a function of time (number of months) from the FMP. Inspection of the data and some preliminary fits indicated that linear models were well suited to model LDL cholesterol, triglycerides, and diastolic pressure in relation to menopausal time. However, a double logistic model was found to be more appropriate for the relation of HDL cholesterol with FMP over time. For each time point X_i ($i = 1,\ldots,5$), let Y_i be the dependent variable representing one of the following measurements: HDL cholesterol, LDL cholesterol, or diastolic pressure and $X_{1i},\ldots,X_{qi}$ be measured covariates. Let μ_i be the mean, conditional on the observed values of the covariate(s). To model mean response as a function of $X_{11},\ldots,X_{15}$ = time (from FMP) alone, let μ be the double logistic function

$$\mu_i(\text{time from FMP}) = h_1 - 2(h_1 - h_\theta)/ \quad (1)$$

$$\{\exp[\lambda_0(\text{time} - \theta)] + \exp[\lambda_1(\text{time} - \theta)]\},$$

where θ is the approximate time of maximum change rate, h_1 is the maximum or minimum mean, h_θ is the mean at maximum change, and λ_0 and λ_1 are parameters representing rates of change (22–24). This particular family of functions allows flexibility in the fitted curves without a possibly artificial symmetry of time to FMP (as would occur with quadratic fits). To model a dependent variable as a function of time to FMP and other covariates, let

$$\mu_i^Y = \mu_i(\text{time from FMP}) + a_1x_{1i} + \quad (2)$$

$$a_2x_{2i} + \ldots + a_qx_{qi}.$$

The parameter vector can vary from individual to individual, allowing for random-effects fitting. Models were fitted by restricted maximum likelihood using an iterative procedure in which the assumption of normal errors is tenable (21). Analyses were performed using SAS with the main model fittings implemented by PROC MIXED and PROC NLINMIX (25). Selection between a linear or a double logistic model was guided by the Akaike's information criterion. Comparison between a number of possible models, which need not necessarily be nested, is made on the basis of the statistic

$$\text{Akaike's information criterion} = -2\log(\text{likelihood}) +$$

$$2(\text{number of unknown parameters}).$$

The smaller the value of this statistic, the better the model. In general, the value of Akaike's information criterion will tend to increase when unnecessary terms are added to the model.

In the interpretation of longitudinal analyses, the main stumbling block is the conventional thinking of changes over time as the differences between two time points. In the present context of 5 time points, one should think in terms of a continuous framework; in particular, one needs to look at change in the rate of

change. The longitudinal analysis proposed here is based on *smoothed changes* in the covariates, typically fitting a smooth curve to the profile of HDL cholesterol, for instance, for each subject, allowing for different coefficients that determine the curve to vary between individuals. The effect of changes in covariates is smoothed out to avoid excessive influence of "*noisy*" one-off changes, e.g., stopping smoking for a year. To judge whether HDL cholesterol is affected by menopause, one needs to look at the smoothed fitted curve and see if there are any changes in the curve around FMP. When the best-fitting curves are *straight lines*, indicating that their rates of change (slopes) do not change over the entire length of 5-year observation, this is equivalent to a constant aging effect, and there is no indication of change of rate of change around FMP.

RESULTS

Preliminary cross-sectional analyses of baseline data have been reported elsewhere (26, 27). To gain an initial insight into the changes over time with reference to the last menstrual period, we first calculated sample means and standard errors for HDL cholesterol; LDL cholesterol; triglycerides; BMI; diastolic pressure; and group proportions of alcohol consumption, smoking, and exercise levels in seven intervals: within 1 month of FMP, 1 month to 1 year before or after FMP, 1–3 years before or after FMP, and more than 3 years before or after FMP (tables 1 and 2). The overall net changes between 3 years before and after menopause were 0.25 mmol/liter for LDL cholesterol, 0.05 mmol/liter for HDL cholesterol, 0.34 mmol/liter for triglycerides, 0.12 kg/m^2 for BMI, and 0.48 mmHg for diastolic pressure. Over the same observation interval, the proportion of drinkers decreased by 13 percent, the proportion of smokers increased by 17 percent, and the proportion of women who exercised at least once a week increased by 6 percent. Inspection of the tables did not reveal any obvious trends with time for diastolic pressure or BMI. However, mean triglycerides and LDL cholesterol exhibited a steady increase with time, while HDL cholesterol exhibited a slight nonlinear trend, starting out at 1.50 mmol/liter, mean HDL cholesterol increased steadily to around FMP, peaked at 1.71 mmol/liter right around FMP, and gradually decreased again to 1.55 mmol/liter at 3 years after FMP. To confirm these observations, we modeled each continuous risk factor against time to FMP by using both a linear and a double logistic function with random effects. Model-fitting results showed that a flat parabolic curve was the best fit to HDL cholesterol (figure 2), exhibiting a peak right around FMP. In addition, mean HDL cholesterol decreased maximally about 9 months after menses ceased (approximate time from FMP at maximum change rate θ(months) = 9.1 (0.03 standard error); mean at maximum change time, h_θ = 1.71 mmol/liter (0.031 standard error). The estimate of the instantaneous slope 9 months or more after FMP was 0.55 mmol/liter per year.

TABLE 1. Sample distribution of lipids, measured at different intervals from the final menstrual period, for 150 Australian women, Melbourne Women's Midlife Health Project, 1991

	>3 years before FMP*	1–3 years before FMP	1 month to 1 year before FMP	Within 1 month of FMP	1 month to 1 year after FMP	1–3 years after FMP	>3 years after FMP
Triglycerides							
1st quartile	0.70	0.70	0.70	0.77	0.70	0.80	0.80
Median	0.90	1.00	0.96	1.10	0.91	1.00	1.25
3rd quartile	1.23	1.14	1.40	1.40	1.40	1.40	1.75
Mean	1.08	1.07	1.11	1.17	1.17	1.19	1.42
SE*	0.09	0.08	0.06	0.10	0.06	0.04	0.12
HDL cholesterol*							
1st quartile	1.26	1.27	1.35	1.39	1.36	1.36	1.21
Median	1.49	1.59	1.63	1.76	1.70	1.63	1.49
3rd quartile	1.65	1.91	1.95	1.99	2.04	1.96	1.77
Mean	1.50	1.61	1.66	1.71	1.71	1.68	1.55
SE	0.07	0.03	0.04	0.08	0.04	0.03	0.06
LDL cholesterol*							
1st quartile	3.13	3.10	3.00	3.20	3.10	3.10	3.15
Median	3.70	3.60	3.62	3.70	3.80	3.87	3.90
3rd quartile	4.20	4.22	4.40	4.29	4.40	4.50	4.70
Mean	3.67	3.69	3.72	3.81	3.84	3.87	3.92
SE	0.16	0.08	0.10	0.20	0.09	0.07	0.15

* FMP, final menstrual period; SE, standard error; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol.

TABLE 2. Sample distribution of nonlipid risk factors, including body mass index and diastolic blood pressure, measured at different intervals from the final menstrual period, for 150 Australian women, Melbourne Women's Midlife Health Project, 1991

	>3 years before FMP*	1–3 years before FMP	1 month to 1 year before FMP	Within 1 month of FMP	1 month to 1 year after FMP	1–3 years after FMP	>3 years after FMP
Body mass index							
1st quartile	23.13	22.80	22.98	23.56	22.57	22.61	23.11
Median	25.90	25.18	25.76	25.61	25.30	25.49	26.09
3rd quartile	28.76	28.27	28.28	28.06	27.79	27.95	28.60
Mean	26.46	26.42	26.54	26.95	26.33	26.14	26.58
SE*	0.84	0.42	0.50	0.65	0.51	0.36	0.69
Diastolic blood pressure							
1st quartile	70.00	70.00	70.00	70.00	70.00	70.00	70.00
Median	75.00	75.00	76.00	77.50	77.25	75.00	77.25
3rd quartile	80.00	80.00	82.25	80.00	80.00	80.00	80.25
Mean	76.40	75.55	77.21	76.57	76.58	76.23	76.88
SE	1.86	0.82	0.94	1.71	0.84	0.68	1.24
Alcohol (drinks/week) (%)							
None	47.22	37.09	42.10	48.15	46.09	47.98	60.42
1–2	22.22	15.23	16.67	18.52	17.19	16.16	8.33
3–7	22.22	28.48	31.58	22.22	25.78	23.23	27.08
≥8	8.33	19.20	9.65	11.11	10.94	12.63	4.17
Smoke (cigarettes/day) (%)							
None	75.00	67.33	69.91	62.96	69.29	60.51	58.33
Ex-smoker	13.89	16.67	17.70	14.82	18.90	21.03	25.00
1–10	2.78	6.67	3.54	3.70	3.15	4.10	6.25
11–20	5.55	4.00	4.43	11.11	3.94	9.23	10.42
≥21	2.78	5.33	4.42	7.41	4.72	5.13	0.00
Exercise (times/week) (%)							
Never	25.00	25.17	26.32	22.22	23.44	23.35	18.75
Once	19.45	13.24	19.30	25.93	13.28	12.69	10.42
2–3	19.44	23.84	23.68	22.22	25.78	22.84	27.08
4–6	25.00	17.22	14.03	18.52	17.19	17.26	20.83
Every day	11.11	20.53	16.67	11.11	20.31	23.86	22.92

* FMP, final menstrual period; SE, standard error.

Figure 3 shows the mean of log(triglycerides), LDL cholesterol, diastolic pressure, and BMI modeled by random-effects linear regression on time from FMP. This was the best model to fit log(triglycerides), triglycerides/HDL cholesterol, LDL cholesterol, and diastolic pressure against time to FMP. Letting (*) and (NS) denote significance ($p < 0.05$) and nonsignificance, respectively, when compared with models that fit only a constant, we have the resulting linear regression models of the form:

$$\text{Dependent variable} = \text{Intercept (SE)} + \text{Slope (SE)}$$

$$\log(\text{triglycerides}) = 0.013(0.014) + 0.0036\,(0.0005) \times (\text{months from FMP})(*)$$

$$\log(\text{triglycerides/HDL cholesterol}) = 0.545\,(0.011) + 0.0009\,(0.0003) \times (\text{months from FMP})(*)$$

$$\text{LDL cholesterol} = 3.78\,(0.07) + 0.004\,(0.0017) \times (\text{months from FMP})(*)$$

$$\text{Diastolic pressure} = 76.3\,(0.369) + 0.014\,(0.016) \times (\text{months from FMP})(\text{NS})$$

$$\text{BMI} = 26.3\,(0.42) + 0.016\,(0.003) \times (\text{months from FMP})(*).$$

A significant slope in the above linear regression equations may be interpreted as significant changes of the response variable with time at a constant rate and does not indicate any influence of menopause transition.

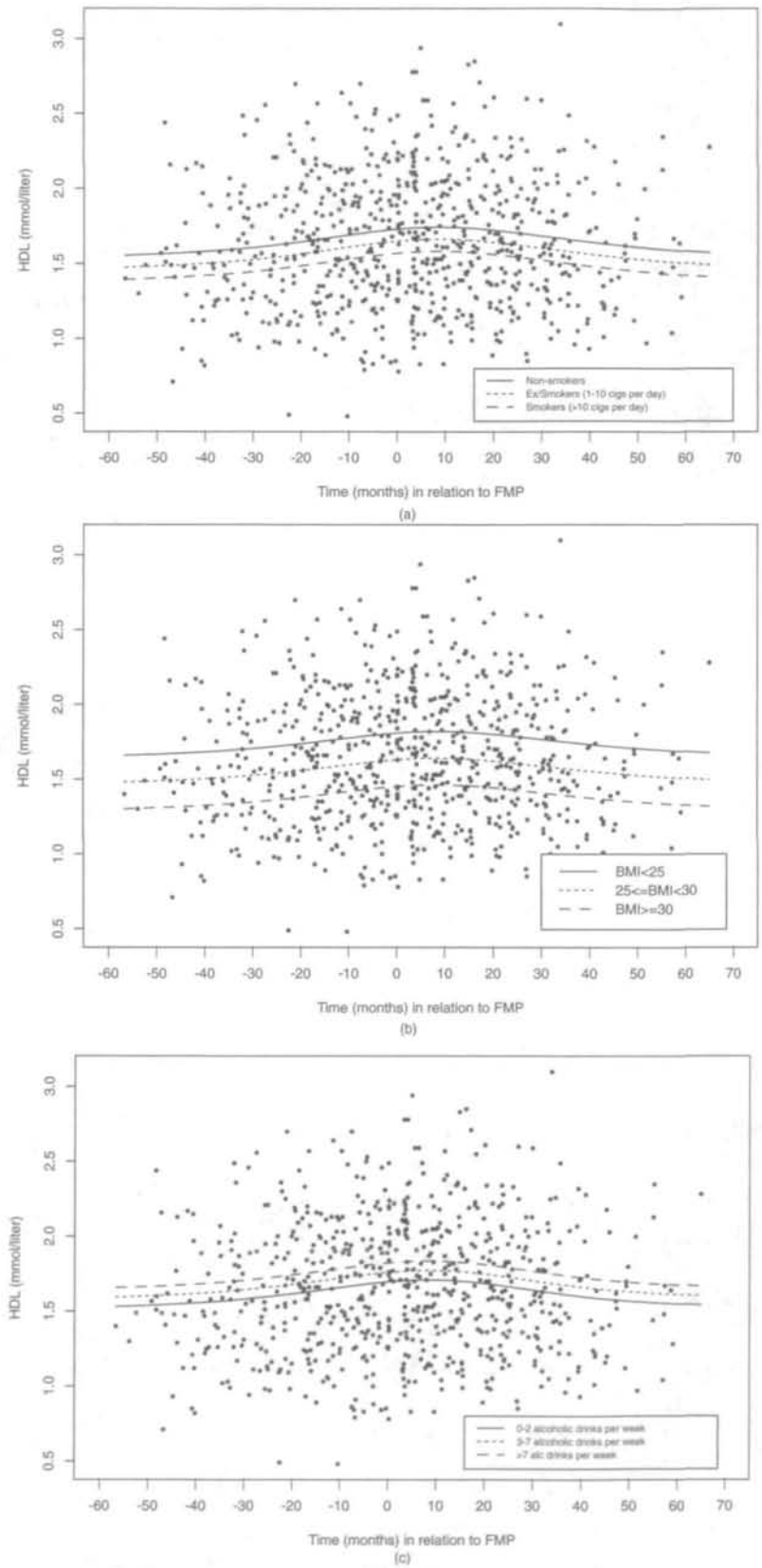

FIGURE 2. Changes in HDL cholesterol across the menopausal transition for 150 Melbourne, Australia, women from 1991–1995, stratified by (a) smoking status, (b) BMI groups, and (c) alcohol status. The horizontal axis represents time with respect to FMP (0). Negative and positive numbers indicate time before or after FMP, respectively.

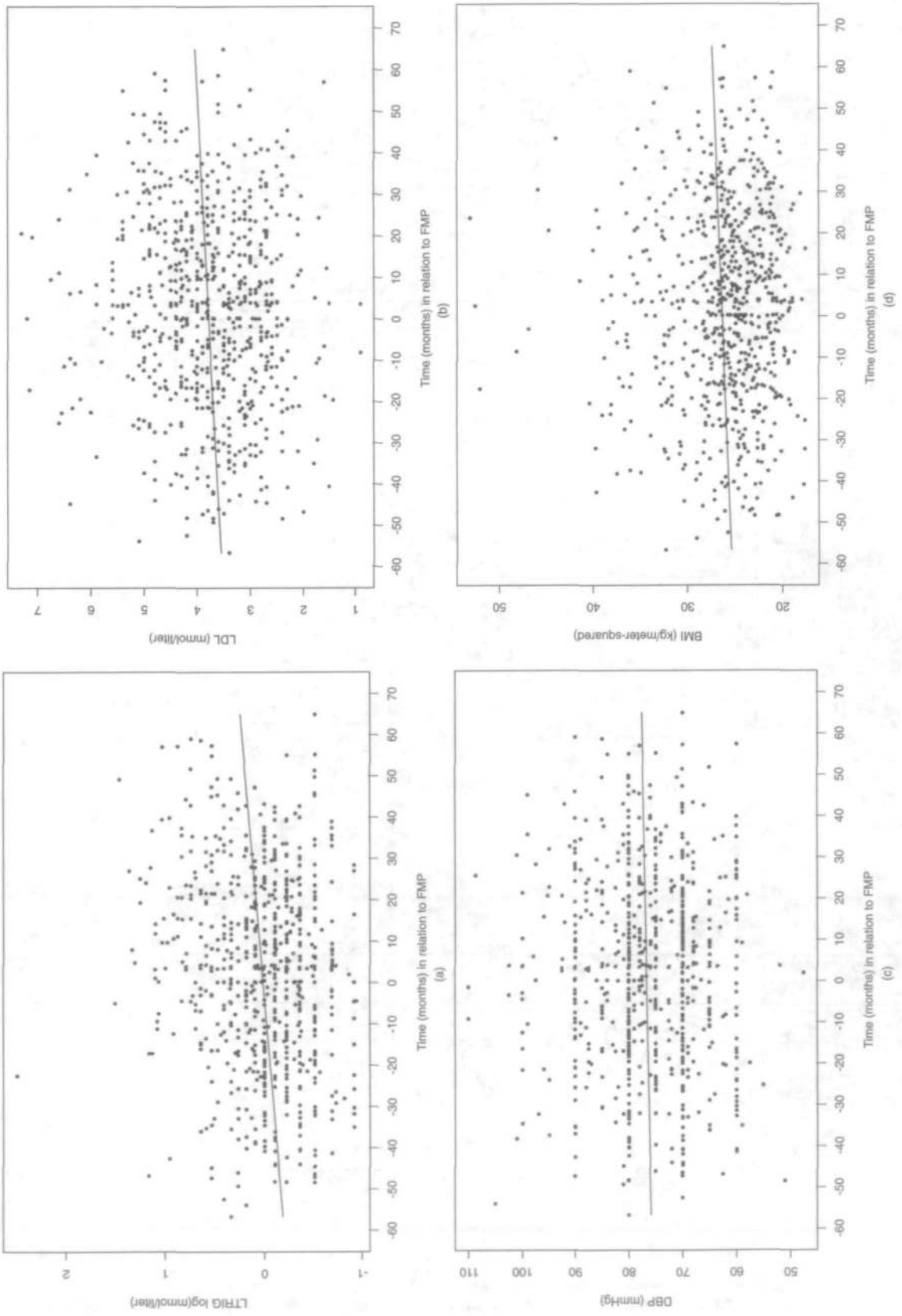

FIGURE 3. Changes in (a) triglycerides, (b) LDL cholesterol, (c) diastolic pressure, and (d) BMI across the menopausal transition for 150 Melbourne, Australia, women from 1991–1995. The horizontal axis represents time with respect to FMP (0). Negative and positive numbers indicate time before or after FMP, respectively.

To gain an insight into the relations among risk factors, we calculated pairwise Spearman correlations. The largest correlation was –0.53 between HDL cholesterol and triglycerides. HDL cholesterol was also inversely correlated with LDL cholesterol (r = –0.22), BMI (r = –0.36), diastolic pressure (r = –0.22), and smoking (r = –0.13) and was positively correlated with alcohol consumption (r = 0.21). BMI was positively correlated with LDL cholesterol (r = 0.12), with triglycerides (r = 0.32), and with diastolic pressure (r = 0.41), but was inversely correlated with exercise (r = –0.16). Diastolic pressure was also inversely correlated with exercise (r = –0.16) but was positively correlated with LDL cholesterol (r = 0.15) and triglycerides (r = 0.22). Smoking was correlated with triglycerides (r = 0.20) and alcohol consumption (r = –0.24), but was negatively correlated with exercise levels (r = –0.11). All other correlations were smaller than 0.10 or were negligible.

To investigate changes in one risk factor while accounting for simultaneous changes in another, we fitted multivariate linear or nonlinear random-effects models by adding other covariates to the above models. Statistically significant covariates for each of the risk factors investigated are presented in table 3. The results indicate that the rate of change in HDL cholesterol did not vary in women with different baseline ages. The same patterns of change in HDL cholesterol during menopause transition were observed in all women, although the absolute levels of mean HDL cholesterol were systematically and significantly lower in the presence of other cardiovascular risk factors. For example, a nonsmoker who started smoking more than 10 cigarettes per day would, on average, lower her HDL cholesterol level by 0.13 mmol/liter, while excessive smokers who ceased might increase their HDL cholesterol levels by an estimated amount of 0.17 mmol/liter. Conversely, the significant effect of exercise starts to be apparent only when inactive women exercise at least 2 or 3 times a week, thereby decreasing their LDL cholesterol levels by, on average, at least 0.2 mmol/liter. Similarly, a nondrinker who started drinking at least 3 times a week might increase her HDL cholesterol level by about 0.14 mmol/liter. Thus, mean HDL cholesterol levels were lowest over the transition period in women with the highest BMI and in those currently smoking. Women with the highest alcohol intake had the highest mean HDL cholesterol levels. Exercise was not associated with HDL cholesterol levels through menopause. The older the women were at baseline, the higher their triglycerides were relative to HDL cholesterol. For example, a 1-year increase in age induced an increase of 1.02 in the ratio triglycerides/HDL cholesterol. The mean ratio triglyceride/HDL cholesterol levels were also highest in women with the highest BMI and in those currently smoking. Analyses of triglycerides alone indicated that triglyceride levels were highest in women with the highest BMI and in those currently smoking. On the other hand, changes in triglycerides alone were independent of the age of women at baseline and of exercise and alcohol levels. Mean LDL cholesterol increased with age, although the actual rate of increase did not vary among women with different baseline ages or smoking levels. Mean LDL cholesterol was significantly higher for women with high alcohol consumption and high BMI. LDL cholesterol was inversely associated with exercise. Through the menopausal transition, diastolic pressure increased with age at a constant rate. Diastolic pressure was higher among older women at baseline and among women with higher BMIs. It decreased as the frequency of exercise increased. Changes in diastolic pressure were independent of changes in smoking and of alcohol intake patterns. BMI increased with age, and women who were younger at baseline had higher absolute mean BMIs. BMI also increased with decreased levels of exercise and was independent of changes in smoking and of alcohol patterns.

TABLE 3. Results of model fitting*, Melbourne Women's Midlife Health Project, 1991

Dependent variable	Independent variables									
	Age (month)		BMI†		Smoking		Alcohol		Exercise	
	Beta	(SE†)	Beta	(SE)	Beta	(SE)	Beta	(SE)	Beta	(SE)
HDL cholesterol†			–0.026	(0.0030)	–0.076	(0.0139)	0.140	(0.0200)		
LDL cholesterol†	0.030	(0.0150)	0.014	(0.0075)					–0.049	(0.0182)
Triglyceride			0.020	(0.0048)	0.060	(0.0220)				
Triglyceride/HDL cholesterol	0.019	(0.0086)	0.014	(0.0029)	0.037	(0.0133)				
DBP†	0.620	(0.2380)	0.811	(0.0945)					–0.503	(0.1601)
BMI	–0.218	(0.0856)							–0.443	(0.0902)

* The beta coefficients are for significant linear factors ($p < 0.05$).

† BMI, body mass index; SE, standard error; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; DBP, diastolic blood pressure.

DISCUSSION

Through the course of follow-up, only one of the factors associated with risk of cardiovascular disease, HDL cholesterol, showed a statistically significant pattern of change suggesting an association with menopause itself. HDL cholesterol levels decreased gradually after menopause, and the greatest rate of decrease occurred toward the end of the first year after menses ceased. However, there was a similar upward slope for HDL cholesterol around 1 year before menopause, and thus, the decelerating slope in the first year after the FMP counterbalanced this, resulting in little net change in HDL cholesterol in this cohort across the menopausal transition. None of the other risk factors for cardiovascular disease changed because women experienced menopause; the observed changes in the other blood lipids and in diastolic pressure and BMI during menopause were related either to the women's increasing age or to simultaneous changes in one of the other risk factors.

All changes related to increased age were deleterious: Serum triglycerides, diastolic pressure, weight (BMI), and LDL cholesterol showed significant increases. The older the women were premenopausally, the greater the increase in serum triglycerides adjusted for HDL cholesterol levels and the greater their rise in blood pressure; the younger the women, the greater their increase in relative weight.

The factor that had the most far-reaching adverse influence on cardiovascular risk in this menopausal cohort was excessive relative weight (high BMI). Overweight women had lower levels of HDL cholesterol, higher levels of LDL cholesterol, and higher diastolic pressure. BMI itself was determined by level of exercise as well as by premenopausal age, such that women of any given height who exercised most often had the lowest weights after the menopausal transition. The adverse effects of smoking on serum lipids and the beneficial effects of alcohol consumption and exercise that are well-established for groups elsewhere (7, 12, 28, 29) were observed as well in these Australian women around the time of menopause. Increasing cigarette consumption lowered HDL cholesterol levels, and increasing alcohol consumption and exercise had the opposite effect on both HDL cholesterol and LDL cholesterol.

This study suffered from a relatively small sample size and short follow-up. Specifically, the sample of women who changed their smoking/drinking/exercise profiles over the follow-up period was quite small; thus, the impact of, for example, change in smoking pattern on LDL cholesterol could not be addressed. This difficulty is shared with other studies (7, 11). One interesting feature we noted was that the group with the highest LDL cholesterol levels at any one time consisted of women who did not report smoking levels (n = 3–7). The nonsignificant inverse association of LDL cholesterol and smoking status reported here may be due to underreporting of excessive smoking.

Our results differ from those of Jensen et al. (11), who found that LDL cholesterol and triglycerides increased significantly as a consequence of menopause and that all increases occurred within 6 months of cessation of menstrual periods. They also found that HDL cholesterol decreased significantly as a consequence of menopause, but the decline occurred gradually over the 2 years preceding cessation of menses. Bergmann et al. (12) concluded that HDL cholesterol was not correlated with age and did not change significantly as a consequence of menopause. In addition, they found that cigarette smoking decreased HDL cholesterol and that alcohol intake and physical activity did not influence HDL cholesterol, but that physical activity in the workplace lowered triglycerides/HDL cholesterol ratios. Most compatible with our study was that by Burnette et al. (7), who reported that HDL cholesterol increased among women who stopped smoking (although not significantly) and that LDL cholesterol increased for all groups, but there was no difference in the size of the increase between smoking groups. In our study, we cannot explain the nonsignificant positive slope of HDL cholesterol with time before menopause. However, the change from a positive to a negative slope around the FMP suggests that menopause per se does have a negative effect on HDL cholesterol; this effect may be borne out more clearly with additional follow-up data.

In summary, based on these data, HDL cholesterol appears to be the only biological risk factor for cardiovascular disease that changes as a direct consequence of menopause. The results indicate that levels of all risk factors (including HDL cholesterol) are amenable to change, given the observed inverse associations of BMI and smoking with HDL cholesterol. Thus, risk factor modification would not only be beneficial in general (as stated), but would also help to offset the observed initial decrease in HDL cholesterol if it continues. It may be particularly important for perimenopausal women to engage in healthy behaviors that are possibly associated with elevated HDL cholesterol in order to minimize or counteract a potential menopausal decline.

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