International Journal of Epidemiology

Vol. 19, No. 2
Printed in Great Britain

Relationship of Menopausal Status and Sex Hormones to Serum Lipids and Blood Pressure

ZUNYOU WU, XIKE WU AND YANWEN ZHANG

Wu Z (Department of Epidemiology, Anhui Medical University, Meishan Road, Hefei, Anhui Province, P.R. of China), Wu X and Zhang Y. Relationship of menopausal status and sex hormones to serum lipids and blood pressure. *International Journal of Epidemiology* 1990, **19**: 297–302.

Arterial blood pressure and serum lipids were measured in 598 Chinese women aged 40–54 years. Menopausal or post-menopausal women had higher means of serum cholesterol, triglyceride and HDL-cholesterol, and had higher prevalence of hypertension, hypotension, hypercholesterolaemia and hypertriglyceridaemia than premenopausal counterparts. There were no differences in means of systolic and diastolic pressures among pre-menopausal, menopausal and postmenopausal women. Fat Synergic Index was first used in this study instead of Quetelex Index, and it was found that Fat Synergic Index is the strongest factor which affects serum cholesterol, triglyceride, HDL-cholesterol and systolic and diastolic blood pressure in multiple linear regression analyses. The role of oestradiol, progesterone and testosterone in three serum-lipid multiple regression models are different, but they are similar in systolic and diastolic blood pressure regression models. Conditional logistic regression analysis found that progesterone is a protective factor only and testosterone is one of the risk factors for hypertension.

Great attention has been given to the association between menopause and cardiovascular disease in recent years. Assessment of the frequency of clinical cardiovascular disease in developed countries has shown that the ratio of males to females is high, and that is several times higher before the age of menopause than after.[1] It is unclear whether menopause is a risk factor for cardiovascular disease. Some cross-sectional and longitudinal data demonstrated that post-menopausal women had higher serum cholesterol and triglyceride than premenopausal women.[2-11] Many reports have showed differing conclusions on the relationship between menopause and blood pressure.[3-5,7,9,11-14] Shibata *et al*[10] suggested a strong relationship between menopause and blood pressure, or serum lipid metabolism. This warrants further investigation involving direct measurements of female hormones among natural menopausal women who have not been taking exogenous sex hormones. This paper deals with the relationship of menopausal status and sex hormones to serum lipids and blood pressure.

Department of Epidemiology, Anhui Medical University, Meishan Road, Hefei, Anhui Province, P. R. of China.
Reprint requests to: Zunyou Wu, Department of Anti-Epidemic, Anhui Anti-Epidemic Station, 125 Wuhu Road, Hefei, Anhui Province, P. R. of China.

METHODS

The present survey was carried out between April and July 1987. The study subjects comprised 603 women between the age of 40 and 54 years. It included workers, executives, teachers, researchers and retired women, drawn from thirteen units, in all 682 women aged 40–54 years from the urban area of Hefei city (population 830 000). The women were categorized into three groups: premenopausal—women who still regularly menstruated; menopausal—women who had menstruated irregularly for at least six months or not menstruated for 11 months and were not pregnant and postmenopausal—women who had ceased menstruating 12 months or more before, had not had hysterectomy and were not pregnant.

Arterial blood pressure was measured on the arm by the auscultation method using a standard mercury sphygmomanometer. A cuff was selected that was at least 20% wider than the diameter of the arm. An adult cuff ($14 \times 23\ cm^2$) was available to examiners. Measurements were taken after resting for not less than five minutes. The systolic blood pressure (SBP) was read at the first pulse sound while diastolic pressure (DBP) was taken at the fifth Korotkoff sound. The blood pressure of each subject was measured twice by two physicians at same time during the course of the

TABLE 1 *Mean and standard deviation of blood pressure and serum lipids distributions in Chinese women aged 40–54 years by age and menopausal status*

Age		No.	SBP, mmHg	DBP, mmHg	Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL-cholesterol (mg/dl)	Cholesterol/ HDL-cholesterol
40	Premenopause	75	117.6±15.3	75.2±10.3	154 5±33.5	141.1±134.7	44.3±10.7	3.6±0.9
	Menopause	48	116 8±17.7	73.3±10.2	184.4±32.5†	148.3±89.9	48.9±11.8*	3.9±1.0
	Postmenopausal	12	119.5±18.9	76.8±11.3	176.9±32.5*	192.5±225.2	53.3±9.9*	3.4±0.6
45	Premenopause	91	119.1±16 3	75.2±9 5	155.9±32.7	127.2±73.2	47.6±10.8	3.4±1.0
	Menopause	124	122.7±22.1	75.9±12.7	171.9±36.6†	141.6±127.1	48.3±13.9	3.8±1.0*
	Postmenopausal	93	121.9±19.8	75.9±11.6	176.2±40.5†	157.8±78.2†	50.5±20.5	3.8±1.2*
50	Premenopause	10	121.5±7.7	77.2±7.2	159.0±36.1	180.7±86.1	45.0±10.3	3.7±1.1
	Menopause	21	131.8±19.9	80.5±12.9	152.1±26.8	145.7±79.0	44.1±11.5	3.6±0.9
	Postmenopausal	124	125.5±20.6	75.9±10.6	170.5±41.7‡	192.8±155 0‡	54.5±23.1†‡	3.5±1.2
Total		598	121.7±19.3	75.7±11.0	167.9±36.1	154.8±121.4	49.3±17.9	3.6±1.0

*$p<0.05$, †$p<0.01$ when compared with corresponding premenopausal value
‡$p<0.05$ when compared with corresponding menopausal value.

examination. The average of the eight readings was used for analysing and estimating the prevalence of elevated and decreased blood pressure. For this article, hypertension is defined as SBP equal to or more than 160 mmHg or DBP equal to or more than 95 mmHg or both; borderline hypertension as SBP equal to or more than 140 mmHg and less than 160 mmHg, or DBP equal to or more than 90 mmHg and less than 95 mmHg, or both; hypotension as SBP less than 90 mmHg or DBP less than 60 mmHg or both. Someone who had been diagnosed as hypertensive and was taking anti-hypertensives during the period of examination was defined as hypertensive whether or not her arterial pressure was lower than the above limits.

Height, waist circumference and weight were measured without shoes and with light clothing. Fat Synergic Index was used in this study instead of Quetelet Index and it was calculated as weight × waist circumference/height (kg). Presence or absence of contraception and method and sex hormone replacement were determined and other information obtained by questionnaire during the examination.

Blood samples were taken from the cubital vein 12 hours after eating. Total serum cholesterol and HDL-cholesterol were measured by the enzymic method[15,16] and triglyceride by acetylacetone colorimetric method.[17] Oestradiol, progesterone and testosterone were measured with parallel tubes for each blood sample by the radioimmunoassay method[18,19] and the mean of the two measures was used for analysis. Students t-test was used for mean of blood pressure and serum lipids by menopausal status in each age group and expanding Mantel-Haenszel trend chi-squared test was used for rate of hypertension, hypotension, hypercholesterolaemia and hypertriglyceridaemia after age had been adjusted. Covariate analysis was used for testing difference in sex hormones by menopausal status after adjusting for age.

Multiple linear regression was used for serum lipids and blood pressure. For serum lipids, the three dependent variables were total serum cholesterol, HDL-cholesterol and triglyceride and the independent variables were age, Fat Synergic Index, oestradiol, progesterone and testosterone. For blood pressure, the two dependent variables were systolic and diastolic pressure, and the independent variables were age, Fat Synergic Index, heart rate, ratio of cholesterol to HDL-cholesterol, triglyceride, oestradiol, progesterone and testosterone.

Sixty-one cases of hypertension and an age-matched (± 2 years) control were selected randomly from this data. For these 61 matched pairs conditional logistic regression was carried out. The dependent variables were hypertensive or not and independent variables were history of hypertension in pregnancy, Fat Synergic Index, heart rate, ratio of cholesterol to HDL-cholesterol, triglyceride, oestradiol, progesterone and testosterone. Each independent variable entered into the fomula at the level of $\alpha = 0.05$.

RESULTS

Five women who were surgically postmenopausal were excluded from the sample, because this group was too small for comparative purposes, so all the postmenopausal group were naturally postmenopausal. Female hormone replacement has not been used by menopausal or postmenopausal women and intrauterine devices have been used by premenopausal women instead of oral contraceptives in this population.

TABLE 2 *Distributions of hypertension, hypotension, hypercholesterolaemia and hypertriglyceridaemia in Chinese women aged 40–54 years by age and menopausal status (%)*

Age group (years)		No.	Hypertension	Hypertension + borderline hypertension	Hypotension	Cholesterol ≥ 220 mg/dl	Triglyceride ≥ 200mg/dl
40	Premenopause	75	13.33	21.33	2.67	1.33	16.00
	Menopause	48	12.5	16.67	4.17	12.5	16.67
	Postmenopause	12	8.33	16.67	—	—	16.67
45	Premenopause	91	10.99	14.29	—	2.20	7.69
	Menopause	124	19.35	23.39	6.45*	4.84	12.10
	Postmenopause	93	18.28	26.88*	5.83*	12 90†‡	25.81†‡
50	Premenopause	10	10.00	20.00	—	10.00	40.00
	Menopause	21	23.81	42.86	9.52	—	14.29
	Postmenopause	124	25.00	32.26	3.23	11.29	33.06
Total		598	17.56	24.08	3.85	7.02	19.40
Relative risk and Mantel-Haenszel trend chi-squared test for all age group			CRRmo=2.18 CRRpm=2.74 SRRmo=1.95 SRRpm=1.53 x^2=3.05 p>0 05	CRRmo=1.89 CRRpm=2.60 SRRmo=1.67 SRRpm=1.72 x^2=4.50 p>0.05	CRRmo=1.92 CRRpm=1.21 SRRmo=2.38 SRRpm=0.71 x^2=2 59 p>0.05	CRRmo=1 38 CRRpm=2.32 SRRmo=2.15 SRRpm=1.29 x^2=5.97 p>0.05	CRRmo=1.58 CRRpm=2.76 SRRmo=1.70 SRRpm=1.78 x^2=9.70 p>0.05

*p<0.05, †p<0.01 compared with premenopausal and ‡p<0 05 compared with menopausal values. CRRmo and CRRpm are crude relative risks for menopausal and postmenopausal women respectively compared to premenopausal women. SRRmo and SRRpm are standard relative risks for menopausal and postmenopausal women respectively compared to premenopausal women when age had been adjusted x^2 is the value of expanding Mantel-Haenszel test when age had been adjusted.

Table 1 presents the distribution of the mean and standard deviation of systolic and diastolic blood pressure, total serum cholesterol, HDL-cholesterol and triglyceride for premenopausal, menopausal and postmenopausal women in each of the three five-year age groups. There were no significant differences between the three different menopausal groups in systolic and diastolic pressure. Menopausal or postmenopausal women had higher means of serum cholesterol, HDL-cholesterol, triglyceride, ratio of cholesterol to HDL-cholesterol and higher prevalence of hypertension, hypotension, hypercholesterolaemia and hypertriglyceridaemia than premenopausal counterparts in the same age group (Table 1, 2). Though not the case in every age group, the differences amongst them could have been due to the fact that the number of postmenopausal women in the 40 year-old group and premenopausal women in the 50 year-old group were too small. It was also found that the prevalence of hypertriglyceridaemia increased gradually from premenopausal to postmenopausal status when age adjusted (Table 2).

Figures for plasma sex hormones are presented in Table 3. The mean of sex hormones have been adjusted by age. Premenopausal and menopausal women had higher means of oestradiol level than postmenopausal counterparts, and premenopausal women had higher progesterone concentrations than postmenopausal counterparts. There were no significant differences between the three menopausal groups in testosterone levels.

The results from the multiple linear regression analyses are given in Tables 4 and 5. Fat Synergic Index had the strongest association and was positively associated

TABLE 3 *Distributions of the mean and standard deviation of sex hormones according to menopausal status in Chinese women aged 40–54 years when age-adjusted*

Variable	Premenopause 1 (No.=176)	Menopause 2 (No.=193)	Postmenopause 3 (No.=229)	p-value 1 versus 2	1 versus 3	2 versus 3
Oestradiol (pg/ml)	4.57±0.66	4.74±0.64	3.92±1.30	NS	<0.01	<0.01
Progesterone (ng/ml)	−0.376±1.41	−0.737±1.80	−1.23±1.38	NS	<0.05	NS
Testosterone (ng/100ml)	70.8±43.1	65.7±44.4	59.2±43.7	NS	NS	NS

Oestradiol and progesterone are natural logarithm value and testosterone is the value of direct measures. p-value is the value of covariate analysis while age-adjusted. NS=no significant difference.

TABLE 4 *Association between known affective factors and sex hormones and serum lipids (mg%) in Chinese women aged 40–54 years based on multiple linear regression models*

Variable	Cholesterol		HDL-cholesterol		Triglyceride	
	BI	SBI	BI	SBI	BI	SBI
Age	−0.2738	−0.0326	−0.0626	−0.0178	3.9747	0 1516
Fat Synergic Index	0.8039	0 1815	−0.493	−0.2665	2.4788	0.1794
Oestradiol	−0.0756	−0.1735	0.0034	0.0187	0.553	0.0407
Progesterone	−1.1007	−0.0562	−0.1998	−0.0244	−6.3259	−0.1035
Testosterone	−0.0135	−0.0162	0.0336	0.0964	−0.1692	−0.0649
	Multiple r=0.2614 F=2.2834 p<0.05		Multiple r=0.2839 F=2.4893 p<0.05		Multiple r=0.2609 F=2.2743 p<0.05	

BI and SBI are regression coefficient and standard regression coefficient respectively. F is the value of F test.

with serum cholesterol and triglyceride level and systolic and diastolic blood pressure and inversely associated with HDL-cholesterol concentration. Table 4 gives the results for serum lipids. The strongest associations with sex hormones in this study were the negative association with oestradiol for cholesterol, the positive association with testosterone for HDL-cholesterol and the negative association with progesterone for triglyceride. In the multiple linear regression analysis of systolic and diastolic blood pressure, the strongest association with sex hormones were the positive association with testosterone and the negative association with progesterone.

Table 6 shows the results from the multiple conditional logistic regression analysis. Of five independent variables (hypertension in pregnancy, Fat Synergic Index, heart rate, progesterone, and testosteone) entered into the logistic regression model only progesterone was a protective factor for hypertension.

DISCUSSION

Several previous studies have disagreed about the relationship between early menopause and arterial pressure, or serum lipids.[2-14] Our findings of no difference in systolic and diastolic pressure among premenopausal, menopausal and postmenopausal Chinese women of the same age group agrees with the views of Hjortland *et al*[4] and Shibata *et al*[5] and Eferakeya and Imasuen.[9,12,13] The finding of a higher prevalence of hypertension in the postmenopausal group than in premenopausal women agrees with the views of Weiss[3], Eferakeya and Imasuen[12,13] and Colditz *et al.*[14] However, in the latter study the patient group was heavily weighted with women who had had surgical menopause (179 out of 200), and there was no standardization of measurement techniques between the case and control groups.

The prevalence of hypotension is also described in this paper. Higher prevalence of hypertension and hypotension in menopausal or postmenopausal women than in premenopausal women suggests that menopausal status might elevate or lower arterial pressure in some women so that the variation about the mean of systolic or diastolic pressure might be higher or lower in menopausal or postmenopausal women than in premenopausal women, or but give no difference among different menopausal groups.

Blood pressure alters during the normal menstrual cycle[20,21] suggesting that female hormones may affect blood pressure. Since hypertension is less common in women before menopause than in men, it has been suggested that oestrogens in premenopausal women might act as a protective factor for hypertension.[3] This view was confirmed by findings that menopausal women using oestrogens had lower blood pressure than controls.[22,23] However, oral contraceptives (containing exogenous oestrogens) are known to increase blood pressure.[24,25] It may be because oestrogens used

TABLE 5 *Association between known affective factors and sex hormones and blood pressure (mmHg) in Chinese women aged 40–54 years based on multiple linear regression models*

Variable	Systolic pressure		Diastolic pressure	
	BI	SBI	BI	SBI
Age	0 9138	0.1596	0 4285	0.1297
Fat Synergic Index	0.8937	0.2962	0.6689	0 3842
Heart rate	0.5063	0.2033	0 3960	0.2755
Cholesterol/ HDL-cholesterol	2.3067	0.0898	1.2908	0.0871
Triglyceride	−0.0134	−0.0615	−0.0063	−0.0498
Oestradiol	−0.0163	−0.0549	−0.0171	−0.0999
Progesterone	−0.9403	−0.1454	−0.9330	−0.1212
Testosterone	0.0878	0.1543	0.0508	0.1546
	Multiple r=0 4628 F=4.7371 p<0.01		Multiple r=0.5591 F=7.9026 p<0.01	

BI and SBI are regression coefficient and standard regression coefficient respectively. F is the value of F test.

TABLE 6 *Relative risk estimates of hypertension in Chinese women aged 40–54 years for known risk factors and sex hormones based on a multiple conditional logistic regression mode*

Variable	B	SB	Standard error (B)	Relative risk	95% CI
Hypertention in pregnancy	2.0026	2.1630	0.7124	7.41	1.78–30.79
Fat Synergic Index	1.7462	2.2807	0.3670	5.73	2.75–11.94
Heart rate	0.904	1.3814	0.4488	2.49	1.01– 6.06
Progesterone	−6.726	−0.9436	1.0216	1.2E-03	1.55E-04–9.25E-0
Testosterone	1.2687	1.1346	0.3972	3.56	1.61– 7.87

B and SB are regression coefficient and standard regression coefficient respectively.

in oral contraceptives are synthetic agents, prescribed at relatively high doses, and given with a synthetic progestin, while oestrogens most often used for menopausal therapy are natural agents, given in relatively low doses and prescribed cyclically.[26] Stern *et al*[27] and Wilson *et al*[28] confirmed that pure oestrogen or progestogen oral contraceptives did not elevate blood pressure, and Rylance *et al*[29] found that natural progesterone has anti-hypertensive action. These are similar to the results of this study in which progesterone was negatively associated with systolic and diastolic pressure and is a protective factor for hypertension.

Our survey confirmed the results of many previous studies,[2-11] which showed that menopause might give rise to increases in serum cholesterol and triglyceride levels. Further analyses show that sex hormones play some role in the course of menopausal status affecting serum lipids.

Fat Synergic Index (weight × waist circumference/height) was first used in this survey instead of Quetelet Index. We think that it is a better measure of obesity than Quetelet Index because waist circumference is one of the major fat signs is considered in this index. If a very strong man is as tall and heavy as a fat man, their Quetelet Indexes are equal, but their Fat Synergic Indexes would be different. The Fat Synergic Index of the fat man is bigger than that of the strong man, because it considers weight, waist circumference and height. In this survey, it is found that Fat Synergic Index is the strongest factor which affects serum cholesterol, triglyceride, HDL-cholesterol and systolic and diastolic pressure in multiple linear regression analyses.

ACKNOWLEDGEMENTS

The authors are grateful for the help of the staff in Department of Epidemiology, Anhui Medical University, and the staff in Hefei Maternal and Child Health Station.

REFERENCES

[1] Report of a WHO Scientific Group. Research on menopause. WHO, Geneva 1981.

[2] Hallberg L, Svanborg A. Cholesterol, phospolipids and triglycerides in plasma in 50-year-old women. *Acta Med Scand* 1967; **181:** 185–94.

[3] Weiss N S Relationship of menopause to serum cholesterol and arterial blood pressure: The United States' Health Examination Survey of adults. *Am J Epidemiol* 1972; **96:** 237–41.

[4] Hjortland M C, McNamara P M, Kannel W B. Some atherogenic concomitments of menopause: the Framingham Study. *Am J Epidemiol* 1976; **103:** 304–11.

[5] Shibata H, Matsuzaki T, Hatano S. Relationship of relevant factors of atherosclerosis to menopause in Japanese women. *Am J Epidemiol* 1979; **109:** 420–4.

[6] Heiss G, Haskell W, Mowery R, *et al.* Lipoprotein cholesterol distribution in selected North American population: the lipid research clinics program prevalence study. *Circulation* 1980; **61:** 302–14.

[7] Lindquist O, Bengtsson C, Lapidus L. Relationship between the menopause and risk factor for ischaemic heart disease. *Acta Obstet Gynaecol Scand* 1985; **Suppl 130:** 43–47.

[8] Baird D D, Tyroler H A, Heiss G, Chambless L E, Hames C G. Menopausal change in serum cholesterol: black/white differences in Evans County, Georgia. *Am J Epidemiol* 1985; **122:** 982–93.

[9] Eferakeya A E, Imasuen E J. Relationship of menopause to serum cholesterol and arterial blood pressure in some Nigerian women. *Publ Hlth* 1986; **100:** 28–32.

[10] Shibata H, Haga H, Suyama Y, *et al.* Serum total and HDL cholesterol according to reproductive status in Japanese females. *J Chron Dis* 1987; **40:** 209–13.

[11] Colditz G A, Willett W C, Stampfer M J, *et al.* Menopause and risk of coronary heart disease in women. *N Engl J Med* 1987; **316:** 1105–10.

[12] Eferakeya A E, Imasuen E J. Menopausal hypertension in the Nigerian female: role of psychosocial stress. *Publ Hlth* 1985; **99:** 235–8.

[13] Eferakeya A E, Imasuen E J. Role of socioeconomic factor on menopausal hypertension. *Publ Hlth* 1986; **100:** 100–4.

[14] Taylor R D, Corcoran A C, Page I H. Menopausal hypertension: a critical study. *Am J Med Sci* 1947; **213:** 475–6.

[15] Liu Zemin, Zhao Qiongrui, Fang Guoting, *et al.* Methodological studies of direct enzymatic determination of total cholesterol in serum. *Chinese J Med Lab Tech* 1984; **7:** 69–71.

[16] Li Peiying, Li Jianzhai. Selection of methods for determination of serum high density lipoprotein cholesterol. *Chinese J Med Lab Tech* 1984; **7:** 132–6.

[17] Li Peiying, Li Jianzhai, Wang Shu. Acetylacetone colorimetric determination of serum triglyceride: A summary of 12-year clinical application. *Chinese J of Med Lab Tech* 1987; **10:** 193–7.

[18] Research Laboratory of Endocrinology, Second Shanghai Medical College. Radioimmunoassay of plasma testosterone. *Chinese J Med Lab Tech* 1978; **1:** 19–24.

[19] Ding Ting, Zhu Zhongyi, Jin Jingfen, Zhang Meiyun. Radioimmunoassay of plasma estradiol. *Chinese J Med Lab Tech* 1981; **4:** 135–9.

[20] Greenberg G, Imeson J D, Thompson S G, Meade T W. Blood pressure and the menstrual cycle. *Br J Obstet Gynecol* 1985; **92:** 1010–4.

[21] Casslen B. Blood pressure alter during the normal menstrual cycle. *Br J Obstet Gynaecol* 1986; **93:** 523–6.

[22] Lind T, Cameron E C, Hunter W M, *et al.* A prospective controlled trial of six forms hormone replacement therapy given to postmenopausal women. *Br J Obstet Gynaecol* 1979; **86 (suppl 3):** 1–29.

[23] Barrett-Connor E, Brown W V, Turner J, *et al.* Heart disease risk factors and hormone use in postmenopausal women. *JAMA* 1979; **241:** 2167–9.

[24] Spellay W N, Birk S A. The effect of intrauterine devices, oral contraceptive, estrogen and progestogens on blood pressure. *Am J Obstet Gynaecol* 1972; **112:** 912–9.

[25] Weir R J, Briggs E, Mack A, *et al.* Blood pressure in women taking oral contraceptives. *Br Med J* 1974; **1:** 533–5.

[26] Bush T L, Barrett-Connor E. Non-contraceptive estrogen use and cardiovascular disease. *Epidemiologic Reviews* 1985; **7:** 80–1.

[27] Stern M P, Brown B W, Haskell W L, *et al.* Cardiovascular risk and use of estrogens or estrogen-progestagen combinations, stanfors three community study. *JAMA* 1976; **235:** 811–5.

[28] Willson E S B, Cruickshank J, McMaster M, Weir R J. A prospective controlled study of the effect on blood pressure of contraceptive preparations containing different types and dosages of progestogen. *Obstetrical and Gynecological Survey* 1985; **40:** 598–9.

[29] Rylance P B, Brincat M, Lafferty K, *et al.* Natural Progesteron and antihypertensive action. *Br Med J* 1985; **290:** 13–4.

(Revised version received August 1989)