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Does the hormonal situation modify lipid effects by lifestyle factors in middle-aged women? Results from a population-based study of Swedish women: the Women's Health in the Lund Area study

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Abstract

The aim of the study was to outline whether the influence by lifestyle factors on serum lipids was modified by the hormonal situation in middle-aged women. Six thousand nine hundred eight women, aged 50 to 59 years, participated in a health assessment program, including a serum lipid profile evaluation. The women were grouped according to their hormonal status into premenopausal (PM) (n = 492), postmenopausal without hormone therapy (HT) (PM0) (n = 3600), and postmenopausal with HT (PMT) (n = 2816). From the PMT group, we analyzed oral (n = 901) and transdermal HT (n = 351) regimens, containing norethisterone acetate and 17β-estradiol. Serum lipids and lipoproteins were determined by conventional methods. Lifestyle factors included smoking and physical activity at leisure time and at work. Multivariate linear regression analysis controlling for age, education, and dietary habits showed that *current smoking* was positively associated with triglycerides in the PM, PM0, PMT, and oral HT groups. In the PM0, PMT, and oral HT groups, current smoking was positively associated with total cholesterol and low-density lipoprotein and negatively associated with high-density lipoprotein (HDL). *Low physical activity at leisure time* was positively associated with triglycerides in the PM and PMT groups and negatively associated with HDL in the PM0 and PMT groups. *High physical activity at work* was positively associated with triglycerides in the PMT group and with total cholesterol in the PM0 group, but negatively associated with HDL in the PMT and transdermal groups. Body mass index was positively associated with triglycerides and negatively with HDL in all the groups regardless of the hormonal situation. The serum lipid profile as influenced by lifestyle factors was modified by the hormonal situation. Compared with the postmenopausal women without HT use, the use of HT contributes to fewer "negative" effects by lifestyle factors on serum lipids.

1. Introduction

Coronary heart disease (CHD) is the most important cause of morbidity and mortality in the Western world. Perturbations of lipid metabolism are major contributors to atherosclerotic cardiovascular disease (CVD) in general and to CHD in particular [1,2].

Before menopause, endogenous estrogens exert favorable effects on serum lipids. After menopause, the lipid profile changes toward atherogenicity [3].

The atherogenic lipid profile is due not only to the loss of hormones, but also influenced by, for example, lifestyle factors. Advancing age and lifestyle factors like weight gain and smoking have been shown to induce an unfavorable low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio, and to raise triglycerides and total cholesterol levels [4-6].

Compelling evidence from both prospective and retrospective observational studies suggests that estrogen monotherapy as well as sequential hormone therapy (HT) could reduce the risk of CVD in healthy postmenopausal women [7,8]. The mechanisms by which estrogen could confer protection are multiple [9]. Over the last few years, however, findings from large randomized primary and

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secondary prevention controlled trials of HT suggested that overall health risks exceeded benefits [10,11] with no appreciable cardiovascular benefit.

Regular exercise reduces cardiovascular morbidity and mortality in the general population as well as in patients with CHD [12,13]. One contributing mechanism for this effect is the beneficial influence on plasma lipids. It is well documented that HDL-C is increased with exercise [14,15]. Prevention, not treatment, is the most feasible goal. Use of hormone replacement could be part of an overall strategy including lifestyle modification and other prevention measures, especially cessation of smoking [16].

To date, a possible modification by the hormonal status on effects induced by lifestyle factors has not been studied in detail.

The aim of the present study was to outline if the influence by lifestyle factors on serum lipids was modified by the hormonal situation in middle-aged women.

2. Materials and methods

This report is an analysis of the project Women's Health in the Lund Area (WHILA). The Lund area is located in southern Sweden and is composed of a university town with ~100 000 inhabitants and its surrounding rural areas are mainly farmland with a population of ~50 000 inhabitants.

The primary objectives of this project were to survey perimenopausal women in this area and to evaluate their health status, lifestyles, as well as social and medical risk factors for future disease. All women in the WHILA study were offered a health assessment program that included a mailed generic self-administered questionnaire tied to certain laboratory examinations performed at a screening center. Women who had findings indicative of disease received appropriate medical attention. The generic questionnaire contained 104 questions. Most of the questions had been used and validated previously [17-19]. After the subjects had filled out the questionnaire, a personal interview was carried out by a specially trained nurse-midwife to endorse and correct questionnaire replies. This resulted in 1 or more corrections in 19% of the questionnaires due mainly to thoughtless mistakes rather than to misunderstanding of the text.

Informed consent was obtained from participating subjects. The ethics committee at Lund University approved the study.

The WHILA project covered all women (n = 10 766) who were born between December 2, 1935, and December 1, 1945, and living in the Lund area by December 1, 1995. The women were identified through a population register comprising all inhabitants.

2.1. Participants

Of the total population of 10 766 women, 6908 (64.2%) women completed the generic questionnaire and underwent a physical and laboratory assessment. The main reasons for nonresponse were foreign nationality, having moved out of the community before the appointment given, refusal, and death.

According to the hormonal situation, participants (n = 6908 women) were divided into 3 groups, that is, 7.1% (n = 492) were classified into a premenopausal (PM) group, which included the subjects who still had regular menstruation, 52.1% (n = 3600) into a postmenopausal without HT (PM0) group, and 40.8% (n = 2816) into a postmenopausal with HT (PMT) group. *Menopause* was defined as a bleed-free interval of at least 12 months.

Among the PMT group, several regimens of HT were used. In the present analysis, we analyzed current users of the 2-combined oral regimen (continuous oral estradiol [E_2] 2 mg + norethisterone acetate [NETA] 1 mg) + (sequential oral E_2 2 mg + NETA 1 mg) (n = 901) and a transdermal patch (E_2 50 μg + NETA 250 μg) (n = 351) regimens [20], as by far these were the most commonly used regimens.

Apart from filling out the questionnaire, all women were also interviewed by a specially trained nurse-midwife about the questionnaire and the hormone use. For the interview, women were asked to bring packages of their current brand of HT and use of HT was as retained.

2.2. Laboratory variables

The baseline physical examination included measurements of body weight and body mass index (BMI) measured at the time of the screening. Serum levels of triglycerides, total cholesterol, HDL-C, and LDL-C were measured on random blood sample with a Cholestech LDX instrument (Cholestech Corporation, Hayward, CA).

2.3. Dietary habits

Food intake was described in 4 categories: fat, fruit and vegetable, fiber, and cakes and sweets. The consumption was subdivided into high, moderate, and low.

We divided the women into 3 groups using the sum of "less healthy diets," that is, high fat (especially animal fat, but relatively low vegetable oil, high-fat milk and meat, less fish, more sausages, bakeries, and whip cream), low fruit and vegetable, low fiber (less fiber-rich bread and whole grain cereals), and high sweet contents (using extra sugar, eating sweets, cookies, or other bakeries).

Healthy dietary habits	Women with healthy diet were defined as those with none or only 1 of the less healthy type of diet.
Unhealthy dietary habits	Women with unhealthy diet were defined as those with 3 or 4 less healthy diet types.
Intermediate dietary habits	Women that belonged to neither of the aforementioned categories.

2.4. Physical activity

The women answered questions about leisure physical activity, divided into low physical activity up to 2 to 4 h/wk

Table 1
Baseline characteristics of groups with different hormonal status (PM, PM0, and PMT) and in different groups concerning mode of administration of HT (transdermal and oral groups)

	PM (n = 492)	PM0 (n = 3600)	PMT (n = 2816)	Transdermal HT (n = 351)	Oral HT (n = 901)
Age (y); mean (SD)	53.2 (1.6)	56.9 (2.9)	56.2 (2.8)	55.7 (2.5)	56.6 (2.8)
Education (%)					
Comprehensive education	9.7	22.5	14.0	14.0	12.2
Secondary education	40.5	47.1	48.2	43.9	50.5
University education	49.8	30.4	37.8	42.2	37.4
Physical activity at work (%)					
Sedentary work	42.4	33.0	37.9	39.0	36.9
Light activity work	36.3	38.2	39.2	39.6	39.6
Heavy activity work	21.3	28.8	23.0	21.4	23.5
Smoking habit (%)					
Never smokers	66.1	64.8	64.0	62.1	62.9
Past smokers	19.7	16.8	21.3	21.1	21.0
Current smokers	14.2	18.4	14.7	16.8	16.1
High physical activity at leisure time(%)	47.8	41.0	43.1	46.3	44.2
Dietary habit (%)					
Healthy	41.5	39.6	42.4	48.7	39.5
Unhealthy	21.8	26.9	25.2	25.1	25.5
Intermediate	36.7	33.4	32.4	26.3	35.0

of light exercise (eg, walking, dancing) and more intensive activity, that is, regular physical exercise of 1 to 2 h/wk including vigorous training (eg, running, swimming).

Physical activity at work during the last year was categorized into low, moderate, and high physical intensity at work. Low referred to sedentary (white collar) work, moderate to mostly walking but not lifting heavily, and high to work with high degree of walking and lifting. Those without work during the last year were asked to categorize their work at home.

2.5. Smoking

Smoking was categorized by the lifetime consumption of pack-years. One pack-year corresponded to a consumption of 20 cigarettes per day for 1 year. Subjects were divided into 3 categories: never smokers (<1 pack-year), past smokers, and current smokers (=1 pack-year for both). Past smokers were those who had stopped smoking 1 month or more before the study.

2.6. Statistical approach

For continuous variables judged as normally distributed, Student *t* test and 1-way analysis of variance were used for determination of differences between groups. When not normally distributed, continuous variables were analyzed using Mann-Whitney test and Kruskal-Wallis test. Bonferroni correction for multiple comparisons was applied with *P* values of less than .017 regarded as significant. Pearson and, when applicable, Spearman correlation coefficients were calculated regarding BMI and lipid values. Multiple linear regression analyses controlling for age, educational level, and dietary habits were performed to evaluate the influence of lifestyle factors (smoking, physical activity at leisure time and at work as well as BMI) on each of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels.

Dummy variables were constructed to show risk estimates related to unfavorable conditions. These dummy variables were smoking (current vs never and past vs never), leisure time physical activity (low vs high), and physical activity at work (high vs low and moderate vs low). *P* values of .05 or less were regarded as statistically significant. Calculations were performed using the statistical program SPSS version 11.5 (SPSS Inc, Chicago, IL).

3. Results

Baseline characteristics of each group are shown in Table 1.

As described before [21], levels of serum triglycerides, total cholesterol, and LDL-C were significantly higher in the PM0 than in the PMT and PM groups. High-density lipoprotein cholesterol level was significantly lower in the PMT group than in PM0 and PM groups (data not shown). Data were not shown for bivariate analysis.

3.1. Smoking habits

Total cholesterol, LDL, and triglycerides were higher and HDL was lower among current smokers than among past and never smokers in the PM0 group. These differences were the same in the PMT group except there was no different in total cholesterol. In addition, serum triglycerides were higher in current and past smokers than in never smokers in the PM group. High-density lipoprotein was lower and LDL was higher in current smokers than in past and never smokers in the oral HT group.

3.2. Physical activity at leisure time

Serum triglycerides were lower and HDL was higher in women with high physical activity at leisure time in all 5 groups. Women in the PM group with high physical activity also had lower total cholesterol and LDL.

Table 2A
Triglycerides

Linear regression	PM group (n = 453)			PM0 group (n = 2822)			PMT group (n = 2350)			Transdermal HT (n = 288)			Oral HT (n = 754)		
Predictors	B coefficient	95% Confidence interval for B	*P*	B coefficient	95% Confidence interval for B	*P*	B coefficient	95% Confidence interval for B	*P*	B coefficient	95% Confidence interval for B	*P*	B coefficient	95% Confidence interval for B	*P*
Smoking habits															
Current vs never	.1	.004-.2	.04	.1	.1-.2	<.001	.07	.02-.1	.002			NS	.09	.02-.2	.015
Past vs never	.2	.05-.4	.01			NS			NS			NS	.15	.02-.3	.02
Physical activity at leisure time (low vs high)	.2	.08-.4	.002			NS	.1	.07-.2	<.001			NS			NS
Physical activity at work															
High vs low			NS			NS	.1	.02-.2	.01			NS			NS
Moderate vs low			NS			NS			NS	.2	.05-.4	.01			NS
BMI	.05	.03-.06	<.001	.05	.05-.06	<.001	.06	.05-.07	<.001	.07	.05-.1	<.001	.04	.03-.06	<.001

The association of lifestyle factors (smoking, physical activity at leisure time and at work, and BMI) with triglycerides in different hormonal status groups (PM, PM0, and PMT) and in different groups concerning mode of administration of current HT (transdermal and oral groups). Multiple linear regression analysis controlled for age, education, and dietary habits. NS indicates nonsignificant.

3.3. Physical activity at work

Total cholesterol was higher in women with high vs low physical activity at work in the PM0 group. The same was found regarding triglycerides in the PM0, PMT, and transdermal HT groups. High-density lipoprotein was lower in women with high vs low physical activity at work in the transdermal HT group as well as was lower in high vs moderate in the PM0 and PMT groups.

3.4. Body mass index

Body mass index was positively correlated with LDL and triglycerides in all 5 groups. The same was true for total cholesterol with exception of the transdermal HT group. Body mass index was negatively correlated with HDL in all groups.

3.5. Multiple linear regressions

Multivariate linear regression analyses, controlling for age, education, and dietary habits, showed that current smoking was positively associated with triglycerides in the PM, PM0, PMT, and oral groups, whereas the same association for past smoking in the PM and oral HT group was found. In the PM0, PMT, and oral HT groups, current smoking was positively associated with total cholesterol and LDL and negatively associated with HDL (Tables 2A–2D).

Low physical activity at leisure time was positively associated with triglycerides in the PM and PMT groups and negatively associated with HDL in the PM0 and PMT groups.

High physical activity at work was positively associated with triglycerides in the PMT group and with total cholesterol in the PM0 group. It was negatively associated with HDL in the PMT and transdermal groups.

Body mass index was positively associated with triglycerides and negatively with HDL in all the groups regardless of the hormonal situation.

4. Discussion

Serum lipids are influenced by several factors. Apart from sex steroids and BMI, lifestyle factors such as smoking and physical activity at leisure time and at work have an impact.

As lipids are influenced by several other lifestyle factors, a stepwise linear regression was introduced to test the hypothesis if lifestyle factors could be modified by the hormonal situation.

Table 2B
High-density lipoprotein

Predictors	PM group (n = 453)			PM0 group (n = 2821)			PMT group (n = 2351)			Transdermal HT (n = 288)			Oral HT (n = 755)		
	B coefficient	95% Confidence interval for B	*P*	B coefficient	95% Confidence interval for B	*P*	B coefficient	95% Confidence interval for B	*P*	B coefficient	95% Confidence interval for B	*P*	B coefficient	95% Confidence interval for B	*P*
Smoking habits															
Current vs never			NS	-.07	−.1 to −.05	<.001	−.06	−.09 to −.04	<.001			NS	−.1	−.1 to −.06	<. 001
Past vs never			NS			NS			NS			NS			NS
Physical activity at leisure time (low vs high)			NS	-.05	−.08 to −.02	.002	−.06	−.09 to −.02	<.001			NS			NS
Physical activity at work															
High vs low			NS			NS	−.05	−.09 to −.02	.01	−.1	−.04 to −.009	.002			NS
Moderate vs low			NS			NS			NS			NS			NS
BMI	−.03	−.04 to −.02	<.001	−.03	−.03 to −.025	<.001	−.02	−.03 to −.02	<.001	−.02	−.04 to −.002	.04	−.01	−.02 to −.008	<.001

The association of lifestyle factors (smoking, physical activity at leisure time and at work, and BMI) with HDL in different hormonal status groups (PM, PM0, and PMT) and in different groups concerning mode of administration of current HT (transdermal and oral groups). Multiple linear regression analysis controlled for age, education and dietary habits.

Table 2C
Total cholesterol

Predictors	PM group (n = 453)			PM0 group (n = 2822)			PMT group (n = 2351)			Transdermal HT (n = 288)			Oral HT (n = 755)		
	B coefficient	95% Confidence interval for B	P	B coefficient	95% Confidence interval for B	P	B coefficient	95% Confidence interval for B	P	B coefficient	95% Confidence interval for B	P	B coefficient	95% Confidence interval for B	P
Smoking habits															
Current vs never			NS	.07	.02-.1	.008	.07	.009-.1	.02			NS	.1	.02-.2	.02
Past vs never			NS						NS			NS			NS
Physical activity at leisure time (low vs high)			NS	−.08	−.1 to .000	.05			NS			NS			NS
Physical activity at work															
High vs low			NS	.09	.003-.2	.04			NS			NS			NS
Moderate vs low			NS						NS			NS			NS
BMI			NS	.01	.002-.02	.02	.03	.02-.04	<.001			NS	.03	.01-.05	.003

The association of lifestyle factors (smoking, physical activity at leisure time and at work, and BMI) with total cholesterol in different hormonal status groups (PM, PM0, and PMT) and in different groups concerning mode of administration of current HT (transdermal and oral groups). Multiple linear regression analysis controlled for age, education, and dietary habits.

4.1. Smoking habits

Among PM0 women the major effect by smoking seemed to be in lipids. This implies that loss of endogenously produced estrogens and progesterone exerts an influence on cholesterol and triglycerides metabolism, which is seemingly different in current smokers and nonsmokers. In essence, HDL particles are produced by the liver, and the effect by smoking is therefore tentatively suggested to be mainly a hepatic process. The effect on LDL could be either indirect, that is, secondary to low HDL-C or direct via an effect on LDL receptors. Cholesterol levels were minimally influenced by smoking in the PM group. Tentatively endogenous hormones neutralize the negative influence by smoking on cholesterol. The differences in plasma lipids between current smokers and nonsmokers were most abundant in the PM0 group.

Recently, Mueck and Seeger [22] demonstrated that the reduction or loss of therapeutic efficacy is mainly caused by dose-dependent elevated hepatic clearance, partially in conjunction with lower estrogen levels, but this has been demonstrated only for oral estrogen applications. Furthermore, smokers have less estrogenic influence than nonsmokers, one reason being a shift in the metabolism so that more E_2 is metabolized via 2 and 4 hydroxylation pathways of the A ring, which give rise to a number of metabolites often referred to as catechol estrogens with almost no estrogenic activity compared with metabolites produced by the 16-hydroxy pathway [22].

The higher triglycerides in the PM0 group of women could be a result either of increased triglycerides synthesis or decreased triglycerides removal. Low level of endogenous E_2 seems to decrease triglycerides, whereas higher levels, such as in pregnancy, clearly augment triglycerides. The loss of fairly low doses from the premenopausal to the postmenopausal status could explain the triglyceride increase. The mechanism behind this increase remains unknown, but it is tentatively suggested that this is due to a lower peripheral lipoprotein lipase activity, which would be in line with a higher insulin resistance, which has been described before. Oral, but not transdermal, estrogens are known to increase triglycerides, but the concomitant administration of a progestogen, especially of the 19-norethisterone derivatives, such as norethisterone, could result in unchanged or lowered triglycerides even in oral HT. It is also known that E_2 may increase insulin sensitivity and reduce insulin resistance. Smoking has been shown to have an opposite effect, that is, to increase insulin resistance. Smoking cessation, at least in men, is associated with a decrease in insulin resistance [23].

Godsland [24] reviewed studies on HT and lipids. Oral estrogens raised triglycerides, but transdermal 17β-estradiol lowered triglycerides. However, transdermal E_2 has less an impact on cholesterol metabolism, leaving HDL almost

Table 2D
Low-density lipoprotein

Predictors	PM group (n = 453)			PM0 group (n = 2822)			PMT group (n = 2351)			Transdermal HT (n = 288)			Oral HT (n = 755)		
	B coefficient	95% Confidence interval for B	P	B coefficient	95% Confidence interval for B	P	B coefficient	95% Confidence interval for B	P	B coefficient	95% Confidence interval for B	P	B coefficient	95% Confidence interval for B	P
Smoking habits															
Current vs never			NS	.08	.04-.1	<.001	.01	.04-.1	<.001			NS	.2	.08-.3	<.001
Past vs never			NS			NS			NS			NS			NS
Physical activity at leisure time (low vs high)			NS			NS			NS			NS			NS
Physical activity at work															
High vs low			NS			NS			NS			NS			NS
Moderate vs low			NS			NS			NS			NS			NS
BMI	.03	.008-.05	.009	.01	.007-.02	<.001	.02	.01-.03	<.001			NS	.03	.009-.05	.005

The association of lifestyle factors (smoking, physical activity at leisure time and at work, and BMI) with LDL in different hormonal status groups (PM, PM0, and PMT) and in different groups concerning mode of administration of HT (transdermal and oral groups). Multiple linear regression analysis controlled for age, education, and dietary habits.

unchanged, and less pronounced reduction of total and LDL-C than oral therapy [24].

Indeed, one of our recent reports suggested that there is less an impact on the oral glucose tolerance test by transdermal compared with oral HT administration in women with feature of the metabolic syndrome [20].

High triglycerides are often linked to disturbances in carbohydrate metabolism. Again, this is probably a liver effect, which could be further underlined by the fact that the positive association between current smokers and total cholesterol, LDL, and triglycerides and a negative one with HDL were seen in the oral HT users, but not in transdermal HT users. The differences in various lipid fractions are consistent also with findings for bone mineral density [25].

4.2. Physical activity at leisure time and at work

Exercise is considered to be an effective way to lose weight as it promotes energy expenditure as well as metabolic rate and also alters body composition [26,27] and reduces insulin resistance. One study [28] reported that even small increases in physical activity at menopause might help to prevent adverse lipid changes and weight gain.

After controlling for confounding variables, multiple linear regression analysis showed that low physical activity at leisure time mainly had a negative impact on triglyceride level in the PM and PMT groups and on HDL level in the PM0 and PMT groups. This in contrast to the physical activity at work showing that high activity had a negative impact on HDL in the PMT and transdermal HT groups and much less an influence on triglycerides as triglycerides tend to increase with physical activity at work at least in the PMT group. This increase is probably due to a concomitant increased intake of fat and other high-energy diets with high physical activity at work as high activity at work could tentatively be accompanied by a more stressful situation. To some extent this could also explain why blue-collar workers have a higher incidence of CVD than academics [29]. Low-density lipoprotein cholesterol remains virtually unaltered with physical activity at work and leisure time in all 5 groups.

4.3. Body mass index

Excessive body fat is a problem faced by many postmenopausal women, and a common problem with obesity is inactivity.

Body mass index seemed to be associated with higher triglycerides and lower HDL in all 5 groups of women (PM, PM0, PMT, oral, and transdermal HT), and hence independent of the hormonal situation and mode of administration. Levels of lipoprotein lipase in adipose tissue are directly proportional to BMI; they affect the maintenance of fat, cell size, body weight, and obesity [30]. Insulin resistance may also be the cause of high triglycerides, which lead to decreased HDL.

In randomized control trials, all participants receive very similar medical attention, which is not the case in observational studies. It is suggested that women who are prone to use HT had a healthier lifestyle than the nonusers [31], which in turn may contribute to many of the discrepancies between observational data and randomized control trial.

The present data demonstrate that the effects on the serum lipid profile by lifestyle factors depend on the hormonal situation. This suggests interactions between female hormone and lifestyle factors.

In general, lifestyle factors seem to be most important for the PM0 group and least important for the PM group with the PMT in between. Ideally, the PMT group should be similar to the PM group, but this seems not to be the case. Hence, there is room for improvement of HT regimens.

5. Conclusions

The serum lipid profile as influenced by lifestyle factors seems to be modified by the hormonal situation.

Compared with the postmenopausal women not using HT, the use of HT contributes to fewer “negative” effects by lifestyle factors on serum lipids. Effects were still different between premenopausal and postmenopausal women using HT. Hence, existing HT regimens are still far from ideal.

High physical activity at leisure time lowered triglycerides and increased HDL-C in the postmenopausal women using HT, but the reverse was true in physical activity at work. There was a positive impact of a high physical activity at leisure time on HDL among the postmenopausal women without HT and on triglycerides among premenopausal women. For transdermal HT users, high physical activity at work decreased HDL-C, which was not a case for the oral group.

Transdermal route of HT seems to induce a different pattern compared with the oral group.

Further studies including biologic markers are needed to further clarify these associations.

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