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James A. McCubbin
Clemson University, Jmccubb@clemson.edu

Suzanne G. Helfer
Clemson University

Fred S. Switzer III
Clemson University

Thomas M. Price
Clemson University

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Blood Pressure Control and Hormone Replacement Therapy in in Postmenopausal Women at Risk for Coronary Heart Disease

James A. McCubbin, Ph.D., Suzanne G. Helfer, Ph.D., Fred S. Switzer III, Ph.D., and Thomas M. Price, M.D.

Departments of Psychology and Biological Sciences, Clemson University

Clemson, SC

Abstract

Background

Coronary Heart Disease (CHD) in women is strongly associated with estrogen deprivation. For example, risk for CHD increases dramatically after menopause, however the role of hormone replacement therapy in CHD prevention is currently unresolved. In order to better understand CHD in women, the precise mechanisms by which estrogen affects circulatory function require clarification. Evidence suggests that exogenous estrogen may affect blood pressure control, but its interaction with other CHD risk factors has not been systematically characterized. The present study examines the role of mildly elevated resting blood pressure, family history of CHD and hormone replacement on blood pressure responses to stress in postmenopausal women.

Methods and Results

Postmenopausal women taking chronic hormone replacement therapy were recruited along with a control group of postmenopausal women not taking hormone replacement. These women were divided into higher versus lower risk for CHD based on level of resting blood pressure and family history of CHD. Blood pressure control mechanisms were assessed by measurement before, during and after a computer-controlled laboratory stressor. Results indicate that women with elevated resting blood pressure and positive family history of CHD have exaggerated blood pressure reactivity to stress, and hormone replacement therapy inhibits this effect of risk on blood pressure reactivity.

Conclusions

This study suggests that unmedicated postmenopausal women with mildly elevated resting blood pressure and positive family history of CHD have altered blood pressure control as indicated by exaggerated blood pressure responses to stress. Hormone replacement therapy eliminates the cumulative effect of resting blood pressure and family history on blood pressure reactivity, suggesting that the circulatory effects of estrogen replacement may operate, at least in part, through normalization of blood pressure reactivity in higher risk postmenopausal women.

Menopause is a major risk factor for coronary heart disease (CHD) in women. For example, throughout their reproductive years, women have greatly reduced risk for CHD when compared to men of the same age. However, around the age of natural menopause, the incidence of CHD in women rises rapidly (1). Although atherogenic mechanisms in women are not well understood, the systemic effects of estrogen deprivation are believed to be of great importance to postmenopausal increases in CHD (2). In many epidemiological studies, hormone replacement therapy is associated with reduced CHD in postmenopausal women (3-9). However, recent clinical trials complicate interpretation of these findings (10-13). For example, Herrington and co-workers (13) found no benefit of estrogen or estrogen plus medroxyprogesterone acetate in women with angiographically verified coronary disease. In part, these conflicting results may reflect differences in the way that estrogen affects the initial atherogenic process versus progression of established atherosclerosis. Clearly, more studies are needed to resolve this clinically important issue.

There are several mechanisms that may contribute to the role of estrogen deprivation in atherogenesis. For example, postmenopausal estrogen deprivation increases low-density lipoproteins, and hormone replacement reverses this trend (14, 15). There are vascular effects of estrogen at both endothelial and smooth muscle levels, including both genomic and nongenomic pathways (16). Finally, there are neuroendocrine and neurocirculatory pathways for estrogen-associated risk reduction, including estrogenic influences on autonomic function (17) and blood pressure control (18).

Exaggerated blood pressure reactivity associated with stress may contribute to the atherogenic process in both men and women. Multiple studies have shown that reactivity to stress is greater in persons at risk for CHD and in persons with established disease (19-22). In a prospective study, Keys and co-workers showed that blood pressure reactivity to cold pressor stress predicted later CHD (23). Moreover, increased circulatory stress reactivity in monkeys is associated with greater coronary artery intimal area (24, 25), and chronic treatment with propranolol inhibits this association (17).

There are several well-established risk factors for CHD. For example, both family history of CHD and elevated resting blood pressure levels independently increase risk (26, 27). Nevertheless, there have been few studies of the cumulative effect of these risk factors on potential atherogenic circulatory mechanisms in postmenopausal women. Therefore, the present study was designed to determine the effects of hormone replacement on blood pressure responses to stress in postmenopausal women with mildly elevated resting blood pressure and positive family history of CHD.

Method

Participants

Study participants were 79 postmenopausal women with either natural or surgical menopause. They were confirmed postmenopausal by history (cessation of menses for at least 6 months) and by plasma FSH levels (40 mIu/ml or greater). Thirty-nine had been taking hormone replacement therapy for at least three months prior to participation. Of these 39 women, 20 were taking estrogen and progesterone and 19 were taking estrogen alone. Forty participants had not taken hormone replacement therapy for at least 6 months. There were no differences between estrogen, estrogen plus progesterone, and

non-hormone replacement therapy groups in age, height, weight, or proportion with a positive family history of CHD. Women on estrogen alone had a greater number of years since menopause compared to estrogen plus progesterone and non-hormone replacement groups ($p<.05$).

Regardless of hormone replacement status, participants had no history of reproductive cancers or other contraindication for hormone replacement therapy. They were in good health and were taking no medications with psychoactive or cardiovascular effects. All participants were non-smokers. Those with hypercholesterolemia, frank hypertension, and diabetes were excluded from participation. Participants ranged in age from 43 to 70 ($M=57.35$, $sd=6.61$).

Participants were divided into high normal and low normal resting blood pressure groups using a median split of resting mean arterial pressure. The lower resting blood pressure group had a mean systolic pressure of 112.81 (sd 9.83) and a mean diastolic pressure of 64.84 (sd 6.63). The higher resting blood pressure group had a mean systolic pressure of 138.7 (sd 12.26) and a mean diastolic pressure of 75 (sd 8.69). To conduct analyses based on family history of CHD, participants were further divided into positive family history and negative family history groups. Positive family history is defined as one or both parents with CHD, obtained by self-report. Parental history of hypertension and CHD have been shown to be self reported with reasonable accuracy (31, 32). Seventeen women who were on hormone replacement therapy and 14 women who were not on hormone replacement therapy had a positive family history of heart disease. Table I shows participant characteristics for blood pressure, family history, and hormone replacement groups.

Apparatus

The testing environment for each experimental session was a quiet, temperature controlled room. A Critikon Dinamap Model 8100 Vital Signs Monitor (Johnson and Johnson, Tampa) was used to measure heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure. This device has a high degree of reliability and accuracy, especially for repeated determinations. In a pilot study, a random sample of stethoscopic and Dinamap readings from 25 participants showed mean stethoscopic SBP=122.2, sd=8.4, and mean Dinamap SBP=125.6, sd=12.6. Mean stethoscopic DBP=77.7, sd=7.78, and mean Dinamap DBP=81, sd=6.7. In the present study, the research nurse routinely verified comparability of Dinamap and stethoscopic values at the beginning of each experimental session.

Procedure

Participants were recruited using newspaper ads and fliers. Volunteers were first scheduled for a screening exam. Upon arrival for the screening, exclusion criteria were explained and participants gave informed consent. Because of a related interest in the effects of opioid antagonists, participants were scheduled for two separate sessions of laboratory testing one week apart, for drug and placebo studies.

Participants were asked to refrain from caffeine consumption for 24 hours prior to their laboratory visits. Upon arrival, participants were given a brief physical exam followed by an instrumentation and adaptation period. Then they rested quietly for a 10 minute baseline blood pressure measurement. Next, participants were given either 0.7 mg/kg naltrexone (ReVia, DuPont) or placebo. Order of administration was

counterbalanced and participants were blind to medication. Placebo data were used for the current analysis. Results from naltrexone studies are to be reported elsewhere.

During the subsequent 50 minutes, participants rested quietly and answered study questionnaires. This was followed by another ten minute resting baseline blood pressure measurement. Next, participants completed a ten-minute math task. The math task was a computerized mental arithmetic test that adjusted speed and problem difficulty according to the performance level of the participant. As an incentive, participants started the task with $5.00 and $0.25 was awarded for each correct answer and $0.25 was subtracted for each incorrect answer. Variations of this task have been successfully used in various populations, including college students, Pima Native Americans, Zimbabwean medical students, and pregnant women (28-30). Following the math task, there was another ten minute resting baseline. Finally, participants were asked to complete an orthostatic stressor. Participants stood for two minutes while their blood pressure was measured. During each baseline and the task periods, systolic blood pressure, diastolic blood pressure, mean arterial pressure (each in mmHg), and heart rate (bpm) were measured every two minutes. They were paid $100 upon completion of the experiment. This study was approved by the institutional review boards of Clemson University and the Greenville Hospital Systems.

Data Analysis

Systolic, diastolic and mean arterial blood pressures and heart rate were averaged across each ten-minute rest period, the ten-minute math stressor and the two-minute orthostatic stressor. Reactivity to each task was derived by subtracting the pre-stress average from the task average for each measure.

Power analyses were conducted using the Power and Precision program (33). Between 7 and 15 participants per group are required for power of .75, assuming a medium to large effect size for the three-way interaction.

Results

Women taking estrogen did not differ from women taking estrogen plus progesterones in blood pressure reactivity analyses, so these women have been combined into a single hormone replacement therapy group. Table II shows the means and standard deviations of blood pressures and heart rate for women with and without hormone replacement therapy. Multivariate analyses of variance revealed significant main effects for the experimental conditions for all blood pressures and heart rate (p's$<.001$), indicating that the arithmetic stressor raised circulatory parameters significantly above resting levels.

Analyses of Variance (ANOVA's) were conducted to examine the effect of hormone replacement therapy, resting blood pressure level, and family history of CHD on circulatory responses to the mental arithmetic task. Analyses indicated that the three-way interaction was significant for MAP ($p<.05$). The interaction for SBP was similar, but not significant at the .05 level, ($p=.07$). In women not taking hormone replacement, planned comparisons showed the largest blood pressure responses to stress were observed in women with both a positive family history and higher resting blood pressure levels ($p<.05$). In women on hormone replacement, there were no effects of risk on blood pressure responses. For example, women not taking hormone replacement who also had a positive family history and higher resting blood pressure levels had a stress-induced increase three times larger than women who had the same risk factors but who were

taking hormone replacement therapy (MAP response of 18.4 vs.5.4 mmHg, SBP response of 22.8 vs. 6.4 mmHg, see Figure 1).

Significant two-way interactions and main effects were also found. Interactions between resting blood pressure and HRT were found for SBP ($p<.01$) and MAP ($p<.01$). In the higher resting blood pressure group, those women not on HRT had a larger blood pressure reaction to the mental arithmetic task than those on HRT. In the lower resting blood pressure group, there were no reactivity differences based on HRT status. Interactions of family history and HRT were found for MAP ($p<.05$) and DBP ($p<.05$). In the positive family history group, those women not on HRT had larger blood pressure reactions to the mental arithmetic task than women on HRT. Among those women who did not have a family history of CHD, there were no differences in blood pressure reactivity between the women taking HRT and those not. Main effects of resting blood pressure were found for SBP ($p<.01$), MAP ($p<.05$), and DBP ($p<.01$), indicating that those participants with mildly elevated resting blood pressure also had higher reactivity to the task.

ANOVAs were also conducted on the response to the orthostatic stressor to explore the effects of HRT, family history of CHD and resting blood pressure. These three variables did not interact to affect circulatory responses to the orthostatic stressor.

Discussion

The relative protection from CHD enjoyed by women during their reproductive years is firmly established (1,2), although the precise mechanisms that mediate this phenomenon are poorly understood. Many factors related to lifestyle, including diet, smoking, physical activity and social support may contribute to delayed atherogenesis in

women (34, 35), however the vascular and/or other systemic effects of estrogen and other gonadal hormones may have primary responsibility for gender differences in CHD incidence. Many epidemiological studies have suggested that hormone replacement therapy inhibits the postmenopausal surge in CHD incidence (6-9), but the recent emergence of conflicting findings suggests that there may be other factors involved. For example, recent clinical trials report either no effect or a transient increase in CHD risk following hormone replacement in women with prexisting disease (10-13). As a result, recommendation of hormone replacement to reduce CHD incidence in postmenopausal women requires further clarification, especially since initial etiologic mechanisms may differ significantly from factors promoting disease progression. In order to better assess the role of hormone replacement in CHD development, there is need for systematic investigation of the interactive effects of risk factors and estrogen on circulatory control mechanisms. We now report that asymptomatic postmenopausal women with mildly elevated resting blood pressure and positive family history of CHD show exaggerated circulatory responses to behavioral stress. Moreover, this hemodynamic effect is eliminated in women on hormone replacement. These data suggest that hormone replacement may be most beneficial in prevention of circulatory atherogenic processes in women at highest risk.

The circulatory response to behavioral stress is a sensitive index of the integrity of underlying blood pressure control mechanisms. Exaggeration of the hemodynamic response to stress may be involved in the etiology of CHD. For example, a series of studies in cynomolgus monkeys by Manuck, Kaplan and co-workers (24, 25) describes the interaction of chronic psychosocial stress, gonadal hormones, and circulatory control

mechanisms in monkeys fed an atherogenic diet. Regardless of gender, monkeys with highest levels of behaviorally induced heart rate reactivity showed the greatest atherosclerosis by histological examination at necropsy. The causal role of this neurocirculatory reactivity is supported by the prevention of histopathology by chronic treatment with propranolol (17). There are several potential mechanisms by which estrogen may affect the relationship between hemodynamic reactivity and atherogenesis. For example, Williams, et al. (36-38) have shown that estrogen modulates the effects of acetylcholine on circumflex arterial vasomotion in ovariectomized monkeys.

There are numerous studies of hemodynamic reactivity and circulatory disease in humans (for a review, see 39). Prospective studies in humans indicate that the magnitude of blood pressure response to stress is predictive of both CHD (23, 40) and essential hypertension (41). Bairey-Merz and colleagues (42) have shown larger cardiovascular responses to stress in postmenopausal women relative to both men and premenopausal women, suggesting that estrogen deficiency may produce altered blood pressure control. Moreover, estrogen appears to blunt blood pressure responses in postmenopausal women (43). The present results confirm and extend these findings. We observed that blood pressure responses to stress are exaggerated in postmenopausal women with the multiple risk combination of positive family history of CHD and mildly elevated resting blood pressure. Interestingly, women with the same cluster of risk factors who had been receiving hormone replacement therapy show blood pressure responses comparable with their lower-risk counterparts. This suggests that postmenopausal estrogen deprivation is necessary, but not sufficient to engender circulatory dysfunction. Only the combination

of estrogen deprivation, elevated resting blood pressure, and positive family history of CHD produced significantly larger blood pressure reactions to stress.

These findings suggest a partial explanation for the differences in the published effects of hormone replacement on CHD risk in postmenopausal women. For example, results from epidemiological studies of CHD and hormone replacement in postmenopausal women may reflect variations in the distribution of familial and other risk factors in their study populations. The greater representation of higher risk women would be associated with a greater likelihood of positive hormone replacement effects. This view, however, does not explain the discrepancies in studies of women with pre-existing CHD. In these populations, greater degrees of existing disease could preclude or override the cardiovascular effects of estrogen. The present study suggests that postmenopausal risk factors interact with estrogen status to produce a significant effect on blood pressure reactivity to stress. Elevated resting blood pressure and positive family history of CHD in the absence of hormone replacement therapy produced a three-fold increase in blood pressure reactivity. The magnitude of this effect is sufficient to suggest that the resulting altered hemodynamic milieu could be associated with significant pathophysiological changes.

The observed effects of hormone replacement may represent central and/or nonvascular mechanisms of action. Although the vascular effects of estrogen are well-established and probably play a role in the current results (16), there are some findings that cannot be easily explained by a peripheral site of estrogenic action. For example, there were no significant interactions of risk factors and hormone replacement on blood pressure responses to the orthostatic challenge. If the observed effects on behavioral

stress reactivity were mediated via vascular phenomena, then similar results would have been expected during orthostasis. The orthostatic challenge stimulates sympathetic vascoconstrictor mechanisms via baroreflex circuits while the arithmetic stressor stimulates sympathetic neuronal activity via higher central sympathetic control structures. Peripheral vascular effects of estrogen would be equally engaged during both orthostatic and arithmetic stress, whereas higher central control mechanisms would be more likely engaged by the arithmetic stressor. There is a significant neuroanatomical substrate for estrogenic influence on central control of autonomic responsivity. For example, ovarian hormones interact with both diencephalic and brainstem serotonergic neurons associated with central autonomic control (44). These collective results suggest further examination of the potential central nervous system effects of estrogen.

There are important limitations in the interpretation of data from cross sectional research designs. Self-selection bias of intact groups always limits strong causal interpretation of results, and the present study is no exception. However, a randomized longitudinal estrogen trial has been conducted in our lab and confirms the current findings. For example, women randomized to either estrogen or combined estrogen/progestin therapy for three months show reduced systolic blood pressure reactivity (45) consistent with the present study. Combined results from the current cross sectional study and the randomized estrogen trial suggest that the present findings represent the effects of estrogen *per se,* and are not simply an effect of self-selection bias.

There are additional methodological limitations that should be considered in interpretation of the present findings. The observed interactions of estrogen with family history and elevated blood pressure may not necessarily apply to other CHD risk factors.

For example, we excluded smokers and women with frank hypertension, diabetes and hypercholesterolemia from the current study. Analysis of lipoprotein levels in our study showed no correlation with blood pressure reactivity, suggesting that our observed findings are independent of cholesterol effects. In addition, the present methodology did not assess age of onset of familial CHD. While there are reasons to suspect that both stress and ovarian function interact in premenopausal atherogenesis (46), additional research is necessary to adequately address this important issue.

In summary, the present results suggest that postmenopausal women with mildly elevated resting blood pressure and positive family history of CHD show dysregulation of blood pressure control during stress. Hormone replacement therapy reinstates normal blood pressure reactivity to stress in higher risk postmenopausal women. The precise mechanisms of estrogenic influence on autonomic reactivity remain to be fully specified. Nevertheless, the present results suggest that the circulatory effects of estrogen may operate via blood pressure control mechanisms in postmenopausal women.

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Table I. Mean (standard deviation) participant characteristics by Family History of Coronary Heart Disease (FH), Hormone Replacement Therapy (HRT), and Resting Blood Pressure Grouping[1.]

	Positive FH Non-HRT	Positive FH HRT	Negative FH Non-HRT	Negative FH HRT
Lower Blood Pressure				
Age	57 (4)	56 (8)	56 (7)	58 (6)
Systolic Blood Pressure	115 (18)	117 (8)	115 (13)	114 (12)
Diastolic Blood Pressure	66 (5)	62 (7)	68 (7)	64 (6)
Body Mass Index	25.4 (1.6)	25.4 (3.6)	27 (4.2)	24 (4.0)
Activity Level[2]	2.60 (1.14)	2.61 (1.11)	3.17 (.94)	2.62 (1.04)
Higher Blood Pressure				
Age	60 (4)	58 (8)	59 (7)	55 (8)
Systolic Blood Pressure	148 (15)	146 (9)	141 (14)	134 (9)
Diastolic Blood Pressure	77 (10)	80 (11)	79 (13)	71 (8)
Body Mass Index	26.2 (6.1)	23.6 (3.1)	28.0 (4.4)	26.5 (5.9)
Activity Level[2]	2.67 (1.00)	2.50 (3.1)	2.86 (.66)	2.62 (.92)

1. Smoking, hypertension, hyperlipidemia, and diabetes were exclusion criteria and therefore were not present in this sample.

2. Self-report of regular aerobic activities on a 4-point scale where higher numbers denote higher activity levels.

Table II. Means (standard deviations) of SBP, DBP, MAP and HR during resting and arithmetic stress for HRT and Non-HRT groups

		HRT	Non-HRT
SBP	Pre-stress	124.3 (17.80)	129.0 (16.91)
	Math	133.1 (19.42)	140.6 (22.59)
	Recovery	125.2 (17.62)	129.6 (17.29)
MAP	Pre-stress	90.4 (11.86)	95.1 (11.93)
	Math	98.6 (11.56)	104.2 (14.14)
	Recovery	90.8 (12.33)	96.1 (12.33)
DBP	Pre-stress	69.1 (10.44)	73.4 (9.13)
	Math	75.4 (9.08)	81.4 (11.81)
	Recovery	68.1 (10.84)	72.8 (10.11)
HR	Pre-stress	69.4 (8.26)	68.6 (6.74)
	Math	74.9 (9.15)	74.2 (7.59)
	Recovery	69.5 (7.94)	68.7 (5.79)

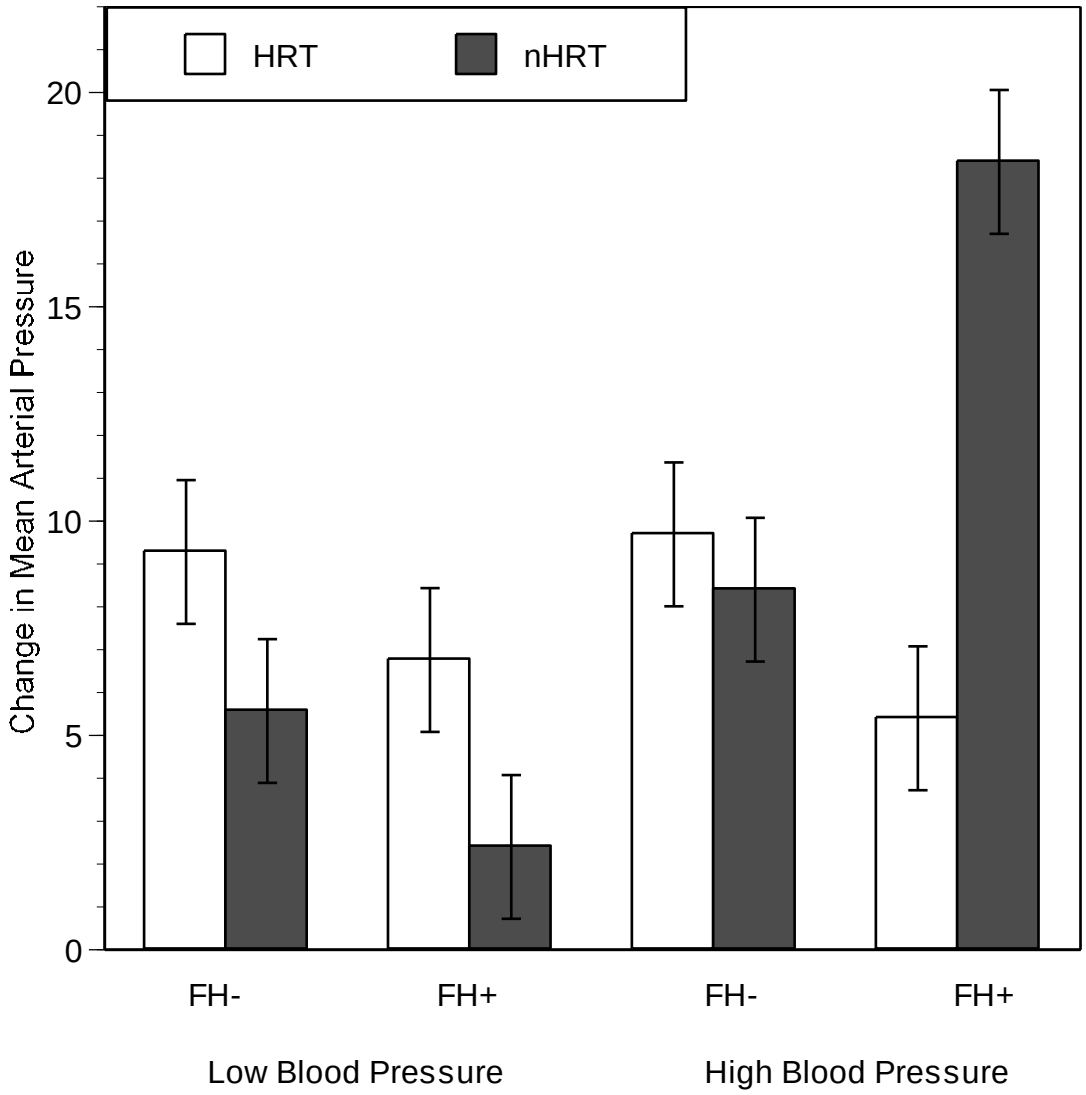

Figure 1: Effects of mildly elevated resting blood pressure, family history of coronary heart disease, and hormone replacement on mean arterial blood pressure reactivity to stress (mean ± standard error) in postmenopausal women. FH+ positive family history of CHD, FH- negative family history of CHD.