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The association between high sensitivity C-reactive protein and hypertension in women of the CARDIA study:

C-reactive protein and hypertension

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Abstract

Objective—The aim of this study was to determine the prevalence of hypertension in mid-life women, characterize the association between high sensitivity C-reactive protein (hs-CRP) and hypertension in women, and describe differences in hypertension prevalence by menopausal stage.

Methods—We included 1625 women, aged 43-55 years, with measurements of hs-CRP and detailed reproductive histories in the Coronary Artery Risk Development in Young Adults Study at follow up year 25. Prevalent hypertension was defined as a systolic blood pressure of 140 mm hg, or diastolic blood pressure of 90 mm hg, or greater or use of antihypertensive medications. Logistic regression was used for analysis.

Results—The prevalence of hypertension was 25.8 %, 37.8 %, and 39.0 % in premenopausal, perimenopausal and postmenopausal women respectively. The median (25^{th}, 75^{th} percentiles) of hs-CRP was 3.08 (1.12, 7.98) μg/ml and 1.18 (0.48, 3.15) μg/ml in women with and without hypertension respectively. After adjusting for confounders, metabolic factors and body mass index (BMI), a doubling (100% increment) in hs-CRP levels was significantly associated with hypertension in premenopausal (1.27 [1.01 - 1.59]) but not in perimenopausal (1.12 [0.99 - 1.27]) or postmenopausal (1.09 [0.95 - 1.26]) women.

Conclusions—Hypertension was common in mid-life women. The association of hs-CRP and hypertension was consistent across menopausal stages. The association of hs-CRP with hypertension was independent of BMI in premenopausal but not in perimenopausal or postmenopausal women.

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Disclosures. None

Keywords

C-reactive protein; menopause; hypertension

Introduction

Blood pressure (BP) increases after menopause in most women[1]. In the United States, more than 75% of women aged 60 years and older have hypertension[2, 3]. The prevalence of hypertension is greater in men than women before 45 years of age but becomes similar in both sexes between the ages of 45 to 64 years[4]. After 64 years of age, the prevalence of hypertension becomes greater in women than men[4]. The increases that occur in BP are greater after menopause when compared to the perimenopausal period[5]. Menopause has been implicated as a unique cardiovascular disease (CVD) risk factor in women,[6] therefore, it is important to determine if changes in the predominance of risk factors such as inflammation that occur during the menopausal transition could affect the prevalence of hypertension.

Inflammatory markers such as C-reactive protein (CRP) have been associated with an increased risk of developing hypertension[7-9]. CRP was a predictor of future hypertension in the Women's Health Study even in the absence of traditional CVD risk factors[9]. Inflammation has been implicated in postmenopausal hypertension[10] but the influence of menopausal stage on the relationship between inflammation and hypertension has not been previously investigated.

Our objective was to investigate whether menopausal stage modifies the relationship between high sensitivity CRP (hs-CRP) and the prevalence of hypertension in women of the Coronary Artery Risk Development in Young Adults Study (CARDIA) at follow up year 25 (2010 - 2011). We hypothesized that hs-CRP will be associated with prevalent hypertension after controlling for known risk factors but the association will be greater in postmenopausal and perimenopausal women when compared to premenopausal women. In postmenopausal women, we also hypothesized that hs-CRP will be associated with prevalent hypertension in women with early menopause (when menopause occurs before 45 years of age) but not in those without early menopause.

Methods

Study Population

CARDIA is a population-based, prospective cohort of 5115 black and white participants (including 2787 women), aged 18-30 years at baseline (1985 -1986) and recruited from 4 regions in the United States; Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota and Oakland, California. The aim of CARDIA was to examine the development and determinants of clinical and subclinical CVD and its risk factors in young adults. The retention rate was 72% of the surviving cohort at the year 25 exam. The design, recruitment methodology and cohort characteristics of CARDIA have been previously reported[11]. The number of eligible participants (and percentage completing the baseline exam) were 3252

(65.2%), 2205 (51.6%), 2473 (81.7%) and 2213 (70.2%) at the Birmingham, Chicago, Minneapolis and Oakland study centers respectively[11]. The protocol was approved by institutional review boards of participating institutions and informed consent was obtained from participants.

Sample Selection

Out of 1981 CARDIA women available for the year 25 exam, we sequentially excluded women who were missing measurements of hs-CRP (n=17), always on oral contraceptive pills (OCP), pregnant or lactating (n=35), unsure of changes in the regularity of their menstrual cycles (n=41) or length of their menstrual periods (n=12), missing information on type of menopause (n= 112) or ovarian surgery (n=25). Because serum levels of sex steroids were not obtained, we were unable to determine the menopausal stage of women who had one or both ovaries preserved but also self-reported that their periods had stopped due to surgery. Consequently, we further excluded 115 women to obtain our analytical sample of 1625 women.

Data Collection

Standardized protocols were used to collect data across study centers at the year 25 exam. Participants were asked to fast for at least 12 hours and to avoid smoking or intensive physical activity for at least 2 hours before their clinic visit. All staff were trained and certified to collect study data according to the protocol.

Menopause status

Questionnaires were used to collect self-reported information on menopause, menstrual cycle characteristics (regularity, length, duration and flow), use of OCP and menopausal hormone therapy (MHT), pregnancy, lactation, presence of hot flashes or night sweats and surgeries relating to hysterectomy or oophorectomy. Women who reported that they had gone through menopause were asked how their periods had stopped and the age at which this occurred. We classified women as postmenopausal if they reported that they had gone through menopause or “change of life” or had no periods in more than 12 months. Using CARDIA methods based on menstrual cycle changes and derived from the SWAN classification, we classified women as perimenopausal if they reported that they had no periods in the past 3 months or were experiencing menstrual cycle irregularities (their periods had become further apart, closer together, stopped completely or occurred at more variable intervals) within the last 12 months[12]. Women who reported that they had experienced a period in the past 3 months and had no changes in menstrual cycle regularity were classified as premenopausal[12]. Postmenopausal women included women with natural menopause or surgical menopause with bilateral oophorectomy.

Blood pressure measurement

Three measurements of seated BP were taken from the right arm of each participant after resting for 5 minutes with an Omron HEM907XL automated BP monitor using an appropriately sized cuff. The average of the second and third readings was used for analyses. Information on antihypertensive medication use was obtained by self-report and examination

of medication bottles during the clinic visit. Prevalent hypertension was defined as a systolic BP of 140 mm hg, or diastolic BP of 90 mm hg or greater or use of antihypertensive medications[8].

High sensitivity C-reactive protein (hs-CRP)

At year 25, hs-CRP was measured using fasting plasma samples with a Roche latex-particle enhanced immunoturbidimetric assay kit and read on the Roche Modular P Chemistry analyzer. The assay range for hs-CRP was 0.175 to 1100 μg/ml. Thirty-seven participants had hs-CRP levels below the lower limits of detection. The intra-pair coefficient of variation of hs-CRP was 3.7% in quality control studies.

Covariates at year 25

Information on age, race, years of education, pregnancies, births, medical history and medication use was obtained using questionnaires. Participants were required to bring their medication bottles to the clinic visit. Cigarette smoking and alcohol use was assessed through interviewer-administered questionnaires. Participants who reported a history of alcohol use within the last one year were classified as current drinkers. Participants were categorized as current cigarette smokers if the reported that they were still smoking at least 5 cigarettes per week almost every week. Parity was defined as the total number of pregnancies that resulted in delivery of a live infant > 20 weeks of gestation[13]. A woman was considered grand multiparous if she had given birth 5 or more times. The CARDIA physical activity history interviewer-administered questionnaire was used to record self-reported participation in 13 different categories of exercise over the past year and was scored in exercise-units[14]. Details on components of the total physical activity summary score is available on the CARDIA website at www.cardia.dopm.uab.edu[14]. Weight was measured with a balance-beam scale and rounded to the lower 0.2 kg while standing height was measured with a vertical ruler and rounded to the nearest 0.5 cm with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Women were categorized as having normal weight (BMI <25 kg/m^2), being overweight (BMI: 25-29.9 kg/m^2) or obese (BMI> 30 kg/m^2). Waist circumference (WC) was measured with a tape and rounded to the nearest 0.5 cm at the point of minimal abdominal girth[15]. Central obesity was present if WC was greater than 88 cm. Fasting blood samples were obtained and processed in a central laboratory. Glucose was measured using hexokinase coupled to glucose-6-phosphate dehydrogenase at collaborative studies clinical laboratory (Minneapolis, MN) while glycated hemoglobin A_{1c} was measured using Tosoh G7 high performance liquid chromatography method (Tosoh Bioscience)[15]. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dl or use of antidiabetic medications or a 2-hour postprandial glucose load ≥ 200 mg/dl or a glycated HbA1C ≥ 6.5[15]. Total cholesterol and high density lipoprotein-cholesterol (HDL-C) was assayed by the trinder-type method and determined enzymatically on the Abbot spectrum. Details of quality control activities that were conducted at CARDIA field centers, coordinating centers, laboratories, and reading centers are available on the CARDIA website at www.cardia.dopm.uab.edu.

Statistical Analysis

Data are presented according to menopausal stage using mean (SD) for continuous variables and percentages for categorical variables. Comparisons were made between groups using Chi-square test (categorical variables) and one way ANOVA (continuous variables). We also compared women according to their hypertension status. Binary log-transformations were performed for hs-CRP due to skewness. The total physical activity score was divided into quartiles.

Unadjusted and multivariable adjusted logistic regression analyses were used to model associations of hs-CRP with prevalent hypertension by menopausal stage We adopted a sequential adjustment process, model 1: unadjusted analysis; model 2: adjusted for age and race; model 3: model 2 plus years of schooling, smoking, physical activity, alcohol use and center; and model 4: model 3 plus total cholesterol, HDL-C, diabetes, cholesterol lowering-medicine use and parity. The relationship between CRP and incident hypertension is attenuated[7] or nullified[8] after adjusting for BMI, therefore, we also adjusted for BMI in model 5. Central obesity is strongly related to hypertension[16] so we performed a sensitivity analysis in our final model in which we replaced BMI, a measure of generalized obesity with WC, a measure of central obesity. We also performed analyses that additionally adjusted for OCP and MHT use at each menopausal stage. We tested for the presence of interactions between hs-CRP and menopausal stage, and between hs-CRP and BMI.

Using logistic regression analysis and a similar model building pattern, we performed exploratory analyses in postmenopausal women where we modeled the associations of hs-CRP and hypertension by early menopause status. The predictive ability of each model was estimated with C-statistics. The percentage of missing values was <3% for all variables. Therefore, sample sizes may have varied slightly between the models. Two-sided *P* values < 0.05 were considered statistically significant. Statistical analysis was performed using SAS enterprise guide version 5.1 (SAS Institute, Inc, Cary NC).

Results

Our total sample size of 1625 consisted of 295 premenopausal, 712 perimenopausal and 618 postmenopausal women. The overall prevalence of hypertension was 36.1% with prevalences of 25.8%, 37.8%, and 39.0% in premenopausal, perimenopausal, and postmenopausal women respectively. Characteristics of study participants are presented according to menopausal stage in table 1. The mean (SD) age was 47.0 (2.9), 49.4 (3.4) and 52.6 (2.5) years in premenopausal, perimenopausal, and postmenopausal women respectively. Hypertension, diabetes and use of cholesterol lowering medicine were more common in perimenopausal and postmenopausal when compared to premenopausal women. Total cholesterol levels were greater in perimenopausal and postmenopausal when compared to premenopausal women. Hs-CRP levels were lower in premenopausal when compared to perimenopausal women. Characteristics of study participants are also presented according to hypertension status (see table, supplemental digital content 1). Women who had hypertension at year 25 were more likely to be older, black, diabetic, current smokers, non drinkers of alcohol and less educated but less likely to be premenopausal. BMI, WC, and hs-CRP levels were higher while HDL-C was lower in women with hypertension. OCP only

use was reported in 6 premenopausal and 14 perimenopausal women. MHT only use was reported in 36 perimenopausal and 73 postmenopausal women. Combined use of OCP and MHT was reported in 1 premenopausal and 2 perimenopausal women. No postmenopausal woman was using OCP.

Hs-CRP was positively associated with a greater prevalence of hypertension in all mid-life women (see table, supplemental digital content 2). The interaction term between hs-CRP and menopausal stage was not statistically significant ($P_{interaction}$ = 0.98) but we presented our results according to menopausal stage in concordance with our study hypothesis (table 2). The interaction term between hs-CRP and BMI was also not statistically significant ($P_{interaction}$ = 0.71). The association between hs-CRP and hypertension prevalence was significant across all three menopausal stages in unadjusted models. These associations were gradually attenuated but remained significant in models that adjusted for age, race, years of schooling, smoking, physical activity, alcohol use, center, total cholesterol, HDL-C, diabetes, cholesterol lowering medicine use and parity. The association was no longer statistically significant in perimenopausal and postmenopausal women after we adjusted for BMI. When BMI was replaced with WC, the associations became non significant in all menopausal groups with odd ratios of 1.16 (0.92 - 1.45), 1.12 (0.99 - 1.27), and 1.03 (0.89 - 1.19) for premenopausal, perimenopausal, and postmenopausal women respectively. When OCP and MHT use were also accounted for, the odd ratios were 1.30 (1.02 - 1.65), 1.12 (0.99 - 1.27), and 1.09 (0.95 - 1.26) in premenopausal, perimenopausal and postmenopausal women respectively. The predictive ability of our final model for prevalent hypertension was 0.79, 0.82, and 0.81 for premenopausal, perimenopausal, and postmenopausal women respectively. We had proposed to examine our associations according to type of menopause (natural or surgical) and ovarian status but only 80 postmenopausal women had surgical menopause with bilateral oophorectomy and we had insufficient power to perform this subgroup analysis.

In analysis involving postmenopausal women only, the interaction term between hs-CRP and early menopause was also not statistically significant ($P_{interaction}$ = 0.27) but we presented our results by early menopause status in concordance with our exploratory hypothesis (table 3). The prevalence of hypertension was 47.1 % and 37.1 % in women with and without early menopause respectively. In unadjusted analyses, hs-CRP was significantly associated with prevalent hypertension in both women with and without early menopause. After adjusting for confounders, metabolic factors and BMI, the association between hs-CRP and hypertension prevalence was not statistically significant in both women with and without early menopause. However, we were limited by a small sample size (n = 119) in the early menopause group.

Discussion

In this cross-sectional study, we have shown that hs-CRP is positively associated with the prevalence of hypertension in mid-life women as has been reported in previous epidemiological studies[7-9, 17-20]. Although menopause has been associated with increases in CRP[10], menopausal stage did not modify the relationship between hs-crp and hypertension. BMI attenuated the association between hs-CRP and hypertension which remained

significant in premenopausal but not in perimenopausal and postmenopausal women. When BMI was replaced by WC, the associations also became non significant in premenopausal women. Central obesity is more strongly associated with metabolic derangements[21] and may better indicate an inflammatory state than generalized obesity in premenopausal women.

Weight gain particularly abdominal fat deposition increases during the menopausal transition and persists into the postmenopausal period[3, 22-24]. Obesity was common amongst women in our study particularly among perimenopausal and postmenopausal women. Obesity is a strong independent risk factor for hypertension[7, 8, 16, 19] and is also associated with elevated CRP levels[7, 8, 19]. The role of obesity in the relationship between CRP and hypertension is likely complex[7]. Weight gain especially abdominal obesity not only causes inflammation but could also be preceded by inflammation[9]. Prior studies have so far produced conflicting results. In some studies, the relationship between CRP and hypertension was mostly explained by BMI[7, 8, 20, 25] as we demonstrated in perimenopausal and postmenopausal women. However, other studies have shown independent associations between CRP and hypertension[17-19] like we did in premenopausal women. Our findings appear different to those reported by Chen et al. in which obesity (both BMI and WC) was shown to have greater effects on the risk of hypertension in premenopausal Taiwanese women[26].

The postmenopausal state has been identified as an independent risk factor for hypertension[27], but it is difficult to determine the specific effects of menopause on blood pressure in the perimenopausal and postmenopausal periods due to the concurrent existence of other risk factors for hypertension[5]. The association of hs-CRP with prevalent hypertension was attenuated by BMI in both women with and without early menopause. In women without early menopause this association was almost completely nullified. Early menopause and a longer postmenopausal period are associated with higher blood pressure levels[2] and possibly a longer duration of obesity. We speculated that other unmeasured risk factors such as endogenous sex steroids could be contributory to the increased prevalence of hypertension in women with early menopause. Endogenous sex steroids such as estrogens, testosterone and dehydroepiandrosterone have been associated with hypertension[28]. Serum levels of sex steroids were not included in this study and their role in our associations should be explored in future studies.

Inflammation, obesity and loss of endogenous estrogens are some of the mechanisms that have been implicated in the development of postmenopausal hypertension[1-3, 10]. CRP contributes to development of hypertension by decreasing the production of nitric oxide from endothelial cells which results in vaso-dysregulation and endothelial dysfunction[18, 19], upregulating angiotensin II subtype 1 (AT1) receptors which leads to activation of the renin-angiotensin-aldosterone systems (RAAS) and proliferation of vascular smooth muscle cells[9, 18] and induction of plasminogen activator inhibitor 1 activity[18]. Obesity not only confounds the association between CRP and hypertension but also shares a common pathway that incorporates endothelial dysfunction and RAAS[7, 29]. Greater hs-CRP levels shown in perimenopausal women in our study have been linked to increases in central obesity[10].

Estrogen loss suppresses estrogen-receptor dependent mechanisms that regulate vascular tone through processes like endothelium-independent vasodilation, increases in nitric oxide production, inhibition of vascular smooth muscle cell growth and proliferation after injury, inhibition of RAAS and the endothelin system and inhibition of the sympathetic nervous system[2, 3, 10, 30]. The loss of the vasoprotective effects mediated by estrogens would likely enhance BP rise. Collectively, there appears to be interplay and overlap between the effects of inflammation, obesity and estrogen loss in the development of hypertension in the perimenopausal and postmenopausal periods.

Our study has strengths. To the best of our knowledge this is the first study to explore the role of menopausal stage on the associations between hs-CRP and hypertension. Data collection methods in CARDIA are highly standardized and the availability of detailed reproductive histories in our biracial population allowed us to appropriately classify menopausal stage. There is comprehensive data on CVD risk factors in CARDIA. We also acknowledge limitations. Due to our cross-sectional design, we were unable to establish causality or temporality in our associations. We were unable to classify participants as having premenopausal, perimenopausal or postmenopausal hypertension because if a woman developed hypertension and a change in menopausal stage within the same follow up interval, we could not definitively determine which change occurred first. Menopausal stage was determined by self-report and serum levels of sex steroids were not measured. There is a possibility of residual confounding from measured and unmeasured risk factors including endogenous sex steroids. We had inadequate power to perform subgroup analyses according to type of menopause. We had limited power for our exploratory analysis in postmenopausal women because few women experienced early menopause. Thus, caution must be applied to findings from our exploratory analyses.

Conclusion

Irrespective of menopausal stage, hypertension is common in mid-life women. The association of hs-CRP and hypertension is consistent across menopausal stages. The association of hs-CRP and prevalent hypertension is independent of BMI in premenopausal but not in perimenopausal or postmenopausal women, whereas, WC attenuated the association in all menopausal groups. Interventions aimed at decreasing hypertension should begin early and should target both generalized and central obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hage FG, Mansur SJ, Xing D, Oparil S. Hypertension in women. Kidney Int Suppl. 2013; 3:352–356.
2. Barton M, Meyer MR. Postmenopausal Hypertension: Mechanisms and Therapy. Hypertension. 2009; 54:11–18. [PubMed: 19470884]
3. Lima R, Wofford M, Reckelhoff J. Hypertension in Postmenopausal Women. Curr Hypertens Rep. 2012; 14:254–260. [PubMed: 22427070]
4. Go AS, Mozaffarian D, Roger VL, et al. Heart Disease and Stroke Statistics--2014 Update: A Report From the American Heart Associstion. Circulation. 2014; 129:e28–e292. [PubMed: 24352519]
5. Chae CU, Derby CA. The Menopausal Transition and Cardiovascular Risk. Obstet Gynecol Clin N Am. 2011; 38:477–488.
6. He L, Tang X, Li N, et al. Menopause with cardiovascular disease and its risk factors among rural Chinese women in Beijing: A population-based study. Maturitas. 2012; 72:132–138. [PubMed: 22445219]
7. Lakoski SG, Cushman M, Siscovick DS, et al. The relationship between inflammation, obesity and risk for hypertension in the Muti-Ethnic Study of Atherosclerosis (MESA). J Hum Hypertens. 2011; 25:73–79. [PubMed: 20944659]
8. Lakoski SG, Herrington DM, Siscovick DM, Hulley SB. C-Reactive Protein Concentration and Incident Hypertension in Young Adults. Arch Intern Med. 2006; 166:345–349. [PubMed: 16476876]
9. Niskanen L, Laaksonen DE, Nyyssonen K, et al. Inflammation, Abdominal Obesity, and Smoking as Predictors of Hypertension. Hypertension. 2004; 44:859–865. [PubMed: 15492131]
10. Yanes LL, Reckelhoff JF. Postmenopausal Hypertension. Am J Hypertens. 2011; 24:740–749. [PubMed: 21509049]
11. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: Study Design, Recruitment, And Some Characteristics Of The Examined Subjects. J Clin Epidemiol. 1988; 41(11):1105–1116. [PubMed: 3204420]
12. Whitham HK, MacLehose RF, Harlow BL, Wellons MF, Schreiner PJ. Assessing the Utility of Methods for Menopausal Transition Classification in a Population-Based Cohort: The CARDIA Study. Maturitas. 2013; 75:289–293. [PubMed: 23707105]
13. Gunderson EP, Chiang V, Pletcher MJ, et al. History of Gestational Diabetes Mellitus and Future Risk of Atherosclerosis in Mid-life: The Coronary Artery Risk Development in Young Adults Study. J Am Heart Asoc. 2014; 3:e000490.
14. Gabriel KP, Sidney S, Jacobs DR, et al. Convergent Validity of a Brief Self-Reported Physical Activity Questionnaire. Med Sci Sports Exerc. 2014; 46:1570–1577. [PubMed: 24496119]
15. Reis JP, Hankinson AL, Loria CM, et al. Duration of Abdominal Obesity Beginning in Young Adulthood and Incident Diabetes Through Middle Age. Diabetes Care. 2013; 36:1241–1247. [PubMed: 23248193]
16. Soltani Z, Washco V, Morse S, Reisin E. The Impacts of Obesity on the Cardiovascular and Renal Systems: Cascade of Events and Therapeutic Approaches. Curr Hypertens Rep. 2015; 17:520.
17. Lakoski SG, Cushman M, Palmas W, Blumenthal R, D'Agostino RB, Herrington DM. The Relationship Between Blood Pressure and C-Reactive Protein in the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol. 2005; 46:1867–1874.
18. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-Reactive Protein and the Risk of Developing Hypertension. JAMA. 2003; 290:2945–2951. [PubMed: 14665655]
19. Sesso HD, Wang L, Buring JE, Ridker PM, Gaziano JM. Comparison of Interleukin-6 and C-Reactive Protein for the Risk of Developing Hypertension in Women. Hypertension. 2007; 49:304–310. [PubMed: 17159088]
20. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-α) and essential hypertension. J Hum Hypertens. 2005; 19:149–154. [PubMed: 15361891]

21. Loehr LR, Rosamond WD, Poole C, et al. Association of Multiple Anthropometrics of Overweight and Obesity With Incident Heart Failure: The Atherosclerosis Risk in Communities Study. Circ Heart Fail. 2009; 2:18–24. [PubMed: 19808311]

22. Davis SR, Castelo-Branco C, Chedraui P, et al. Understanding weight gain at menopause. Climateric. 2012; 15:419–429.

23. Dasgupta S, Salman M, Lokesh S, et al. Menopause versus aging: The predictor of obesity and metabolic aberrations among menopausal women of Karnataka, South India. J Midlife Health. 2012; 3:24–30. [PubMed: 22923976]

24. Abdulnour J, Doucet E, Brochu M, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa new emerging team group study. Menpause. 2012; 19:760–767.

25. Wang L, Manson JE, Gaziano JM, et al. Circulating Inflammatory and Endothelial Markers and Risk of Hypertension in White and Black Postmenopausal Women. Clin Chem. 2011; 57:729–736. [PubMed: 21398601]

26. Chen SC, Lo TC, Chang JH, Kuo HW. Variations in Aging Gender Menopause, and Obesity and Their Effects on Hypertension in Taiwan. Int J Hypertens. 2014; 515297

27. Zhou Y, Zhou X, Guo X, et al. Prevalence and risk factors of hypertension among pre- and post-menopausal women: A cross-sectional study in a rural area of NorthEast China. Maturitas. 2015; 80:282–287. [PubMed: 25563399]

28. Wang L, Szklo M, Folsom AR, Cook NR, Gapstur SM, Ouyang P. Endogenous Sex Hormones, Blood Pressure Change, And Risk Of Hypertension in Postmenopausal Women: The Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2012; 224:228–234. [PubMed: 22862963]

29. Ebong IA, Goff DC Jr, Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. Obes Res Clin Pract. 2014; 8:e540–e548. [PubMed: 25434909]

30. Yanes LL, Romero DG, Lliescu R, Reckelhoff JF. A single pill to Treat Postmenopausal Hypertension? Not yet. Curr Top Med Chem. 2011; 11:1736–1741. [PubMed: 21463249]

Table 1

Characteristics of CARDIA women with detailed reproductive histories and measures of high sensitivity C-reactive protein at year 25 according to menopausal status

Characteristics	Premenopause n=295	Perimenopause n=712	Postmenopause n=618	p-value
Age, years	47.0 (2.9)	49.4 (3.4)	52.6 (2.5)	<0.01[a,b,c]
Black race, %	49.5	55.1	39.3	<0.01[b,c]
Years of schooling	15.3 (2.6)	15.1 (2.6)	15.3 (2.6)	0.35
Current cigarette smoking, %	10.9	15.5	15.7	0.12
Current alcohol use, %	77.6	74.3	78.5	0.18
Physical activity, %				0.10
≤ 100 exercise units	24.4	28.4	23.3	
100.1 - 222.0 exercise units	26.4	24.6	24.1	
222.1 - 414.0 exercise units	20.7	24.6	27.0	
>414.0 exercise units	28.5	22.5	25.6	
Grand multiparity (5 or more births), %	4.8	2.3	1.8	<0.05[a,b]
Cholesterol lowering-medicine use, %	7.5	13.8	17.5	<0.01[a,b]
Diabetes mellitus, %	5.8	11.8	11.5	0.01[a,b]
Hypertension, %	25.8	37.8	39.0	<0.01[a,b]
High density lipoprotein cholesterol, mg/dl	61.3 (18.8)	62.8 (17.7)	65.0 (18.5)	0.01[b]
Total cholesterol, mg/dl	184.6 (35.1)	191.9 (35.9)	199.9 (37.7)	<0.05[a,b,c]
Body mass index (BMI), kg/m^2	30.3 (7.8)	31.3 (8.2)	30.2 (8.0)	0.04[c]
Waist circumference, cm	90.1 (16.5)	91.9 (16.4)	90.9 (16.5)	0.25
Generalized obesity				<0.01[b,c]
Normal weight (BMI: < 25 kg/m^2)	27.1	24.4	33.2	
Overweight (BMI: 25 - 29.9 kg/m^2)	29.5	25.7	21.0	
Obese (BMI: ≥30 kg/m^2)	43.4	49.9	45.8	
Central obesity	49.5	55.5	50.3	0.09
High sensitivity C-reactive protein[*], µg/ml	1.4 (3.6)	1.9 (3.6)	1.6 (3.6)	<0.01[a]

Postmenopausal women included those with natural menopause and surgical menopause with bilateral oophorectomy. Central obesity was present if waist circumference was greater than 88 cm. Values are expressed as means (SD) unless otherwise indicated; *p*-values were determined using chi-squared test for categorical variables and one-way ANOVA for continuous variables. Adjustment for multiple comparisons was done using Tukey-Kramer's method for continuous variables. Significant *P*-values are comparisons of

[a] premenopausal vs perimenopausal;

[b] premenopausal vs postmenopausal;

[c] perimenopausal vs postmenopausal.

[*] Values are geometric means. Exercise units, refers to a weighted sum, based on the intensity of activity and the number of months of less frequent participation, plus three times the number the number of months of "frequent participation"[14].

Table 2

Odd ratios of hypertension associated with doubling (100% increment in) high sensitivity C-reactive protein levels according to menopausal status in CARDIA women at year 25

	No of sample (%)	Odd ratios	95% CI	p-value
Premenopause	295 (18.2)			
Model 1		1.44	1.24 - 1.68	<0.001
Model 2		1.38	1.17 - 1.63	<0.001
Model 3		1.38	1.16 - 1.64	<0.001
Model 4		1.35	1.12 - 163	0.002
Model 5		1.27	1.01 - 1.59	0.004
Perimenopause	712 (43.8)			
Model 1		1.43	1.31 - 1.56	<0.001
Model 2		1.32	1.21 - 1.46	<0.001
Model 3		1.27	1.15 - 1.40	<0.001
Model 4		1.24	1.11 - 1.38	<0.001
Model 5		1.12	0.99 - 1.27	0.065
Postmenopause	618 (38.0)			
Model 1		1.42	1.29 - 1.56	<0.001
Model 2		1.29	1.16 - 1.43	<0.001
Model 3		1.26	1.13 - 1.40	<0.001
Model 4		1.24	1.10 - 1.40	<0.001
Model 5		1.09	0.95 - 1.26	0.215

Model 1: Unadjusted analysis
Model 2: Model 1 adjusted for age and race
Model 3: Model 2 plus years of schooling, smoking, physical activity, alcohol use and center
Model 4: Model 3 plus total cholesterol, high density lipoprotein-cholesterol, diabetes, cholesterol lowering medication use and parity
Model 5: Model 4 plus for body mass index
Postmenopause women included those with natural menopause and surgical menopause with bilateral oophorectomy. Hs-CRP was measured in microgram/ml.

Table 3

Odd ratios of hypertension associated with doubling (100% increment in) high sensitivity C-reactive protein levels in postmenopausal CARDIA women at year 25 according to early menopause status

Category	No. of sample (%)	Odd ratios	95% CI	p-values
Early menopause present	119 (19.3)			
Model 1		1.64	1.28 - 2.09	<0.001
Model 2		1.55	1.18 - 2.03	0.002
Model 3		1.49	1.10 - 2.02	0.010
Model 4		1.52	1.07 - 2.17	0.020
Model 5		1.32	0.87 - 1.99	0.192
Model 6		1.32	0.86 - 2.01	0.225
Early menopause absent	499 (80.7)			
Model 1		1.37	1.24 - 1.52	<0.001
Model 2		1.25	1.11 - 1.39	<0.001
Model 3		1.22	1.08 - 1.37	0.001
Model 4		1.18	1.03 - 1.34	0.018
Model 5		1.04	0.89 - 1.22	0.633
Model 6		1.04	0.89 - 1.22	0.632

Model 1: Unadjusted analysis
Model 2: Model 1 adjusted for age and race
Model 3: Model 2 plus years of schooling, smoking, physical activity, alcohol use and center
Model 4: Model 3 plus total cholesterol, high density lipoprotein-cholesterol, diabetes, cholesterol lowering medication use and parity
Model 5: Model 4 plus body mass index
Model 6: Model 5 plus menopausal hormone therapy use and presence of hot flashes
This analysis included women with natural menopause and surgical menopause with bilateral oophorectomy. Early menopause was present if menopause occurred before 45 years of age. Hs-CRP was measured in microgram/ml.