Effect of age, sex hormones and aldosterone on SCORE in perimenopausal women

Ganna S. Isayeva[1], Alexander V. Martynenko[2], Olga A. Beloded[3] , Tat'yana A. Struk[3], Marina V. Vovchenko[1], Tat'yana N. Bondar[1]

[1] Government Institution «National Institute of Therapy named after L.T. Malaya of National Academy of Medical Science of Ukraine», prospect of Postishev 2A, 61039, Harkov, Ukraine, GU «National Institute of therapy ufter L.T.Maloy»
[2] V. N. Karazin Kharkiv National University
[3] Kharkiv Medical Academy of Post-graduate Education

Abstract. The paper investigates the effect of age and sex hormones level on cardiovascular risk in women during their natural perimenopause. Methods and results. Cross-sectional study with participation of 160 perimenopausal women was conducted. All patients underwent cardiovascular risk assessment using SCORE and relative SCORE system. Follicle-stimulating hormone, prolactin, estradiol, progesterone, testosterone and aldosterone serum content was assessed in the serum. Principle Component Analysis was applied for assessment of effects of age and hormone levels on SCORE. It was found out that, besides age, SCORE in perimenopausal women may be considerably affected by follicle-stimulating hormone, aldosterone and progesterone levels. Conclusion. Aldosterone, follicle-stimulating hormone and progesterone levels influence on cardiovascular risk in perimenopausal women.
[Isayeva G.S., Martynenko A.V., Beloded O.A., Struk T.A., Vovchenko M. V., Bondar T. N. **Effect of age, sex hormones and aldosterone on SCORE in perimenopausal women.** *Life Sci J* 2015;12(1s):44-49] (ISSN:1097-8135). http://www.lifesciencesite.com. 11

Keywords: cardiovascular risk factors, women, sex hormones

Introduction

The risk of cardiovascular events is known to be greatly increased in postmenopausal women [1, 2, 3]. At the same time, both reproductive ageing and cardiovascular risk are age-related. Isolation of individual effects of the latter and assessment of the effects of sex hormones homeostasis changes on processes occurring in cardiovascular system is rather complicated. Thus, SWAN study devoted to investigation of changes in risk factors during menopause has allowed establishing that only total cholesterol, low-density lipoprotein cholesterol (LDLC) and apolipoprotein B showed reliable changes in a year and during 1 year after the last menstruation. Such cardiovascular risk factors as blood pressure, glucose, insulin, C reactive protein and fibrinogen levels were predominantly related with age and not with hormonal changes [4]. In this study, only follicle-stimulating hormone level as the main marker of woman's reproductive ageing was studied. Menopause effect on lipid levels is also confirmed in the paper by Reddy Kilim S [5].

Results of studies investigating the relation between endogenous sex hormone levels and cardiovascular pathology, first of all coronary heart disease, are rather contradictory. Thus, no relation between estrone levels and the risk of coronary heart disease was found [6]. Besides, another study has shown the trend to higher mortality rate from coronary heart disease in women with lower estrone level. Besides, patients with higher estrone level had lower body weight, essential hypertension and diabetes mellitus were less frequent in them, and triglyceride level was lower as well [7]. The study by Jeon G.H. has proven lower coronary calcium level (coronary artery calcium score) in patients with higher estradiol level; this relation was independent of age and other risk factors [8]. At the same time, it was shown that higher estradiol level in elderly women is a coronary heart disease risk factor [9]. The study by He H. has established that low estradiol/progesterone and estradiol/testosterone ratios in women are coronary atherosclerosis predictors in them [10]. Positive relation between free endogenous testosterone levels and coronary heart disease was shown [11, 12]. The study by Haring R., et al. has shown positive relation between prolactin level and cardiovascular mortality [13]. In female patients aged 70 years old, relation between cardiovascular pathology and low pregnenolone, 17-hydroxypregnenolone, and dihydroepiandrosterone levels has been found [14]. Lower progesterone levels were detected in young women after myocardial infarction, leading sedentary lifestyle and suffering from obesity [15]. The above papers, as well as other studies investigating the role of sex steroids in cardiovascular pathology development, rarely describe essentiality of age-dependent changes data. Effects of one or other hormones may greatly vary in different age groups.

The goal of this work was establishing the effect of age, sex hormones and aldosterone on cardiovascular risk in perimenopausal women.

Materials and methods

Cross-sectional study with participation of 160 perimenopausal women was conducted. All patients were examined by gynecologist for exclusion of genital diseases and confirmation of natural perimenopause nature.

Patients with coronary heart disease, cardiac failure, severe arterial hypertension (arterial pressure 180/110 *mm Hg*), thyroidal hormone producing function disorders, gastric and duodenal ulcerative disease, diseases limiting the life span to 1 year, menopause duration exceeding 5 years, and surgical menopause were excluded from the study. Patients received no therapy prior to exclusion to the study.

Total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured by enzymatic method using a photometer-analyzer Humareader N 2106-1709.

Follicle-stimulating hormone (FSH) serum content was tested by enzyme-linked immunoassay using a set of reagents Gonadotropin IFA-FSH from Alkor Bio Company LLC. PROGESTERONE-IFA from KHEMA LLC was used for progesterone test, PROLACTIN-IFA from KHEMA LLC was used for prolactin test, and TESTOSTERONE-IFA from KHEMA LLC was used for testosterone test. Estradiol was tested using Estradiol ELISA kit from DRG Instruments GmbH. Plasma aldosterone content was tested using a set of reagents Aldosteron ELISA from DRG International Inc. Semi-automatic immunoenzyme analyzer Immunochem-2100 was used for the test.

Cardiovascular risk was calculated for all patients using SCORE and relative SCORE system.

The study protocol was approved by local ethics commission of L.T. Malaya National Institute of Therapy of Ukraine. The aim of the study was explained to all patients and informed consent was signed before any study related procedures.

SPSS 21 for Windows PC software was used for statistical data processing. Principle component factor analysis was used to identify hormonal and age influence on SCORE. Variables with the strongest loadings on the most significant principal component were selected.

Results

Table 1 shows characteristics of examined population of women.

Table 1. Baseline characteristics of studied population

Characteristic	
Age, years, Median [25%-75%]	51,5 [47,0 – 59,0]
Body mass index, kg/m^2, Median [25%-75%]	28,0 [25,8 – 31,6]
Age of menopause, years, Median [25%-75%]	50,0 [47,5 – 52,7]
Systolic blood pressure, mm Hg, Median [25%-75%]	72,0 [62,5 – 80,5]
Diastolic blood pressure, mm Hg, Median [25%-75%]	130,0 [110,0 – 142,0]
Heart rate, beats per minutes, Median [25%-75%]	80 [70,0 – 90,0]
Ejection fraction, %, Median [25%-75%]	63,0 [58,7 – 66,0]
Total Cholesterol, mmol/l, Median [25%-75%]	5,23[4,52-5,81]
Triglycerides, mmol/l, Median [25%-75%]	1,21[0,89-1,71]
LDL Cholesterol, mmol/l, Median [25%-75%]	3,16[2,45-3,64]
HDL Cholesterol, mmol/l, Median [25%-75%]	1,26[1,07-1,52]
Prolactin, mmol/l, Median [25%-75%]	208,03[160,65-286,76]
Testosterone, mmol/l, Median [25%-75%]	0,48 [0,33-0,69]
Progesterone, nmol/l, Median [25%-75%]	3,46 [2,52-4,37]
Estradiol, pg/ml, Median [25%-75%]	50,85 [33,84-123,66]
FSH IU/l, Median [25%-75%]	33,15 [10,03 – 62,9]
Aldosterone, pg/ml, Median [25%-75%]	171,1[142,65-343,62]
Smoking, n (%)	35 (21,9%)
Diabetes mellitus, n (%)	35 (21,9%)
Hypertension, n (%)	104,9 (65,6%)
Heart failure, I functional class, NYHA, n (%) II functional class, NYHA, n (%) III functional class, NYHA, n (%)	 33 (20,6%) 51 (31,87%) 12 (7,5%)
Hot flashes, n (%)	94 (58,8%)

Majority of the women in the study has low to moderate cardiovascular risk. Median SCORE was 1%; the minimal value for the whole group was 0 points, and the maximal one was 5 points. Besides, relative SCORE parameter was calculated; its median for the whole group was 2%, the minimal value was 0 points, and the maximal value was 7 points (Fig. 1 a, b).

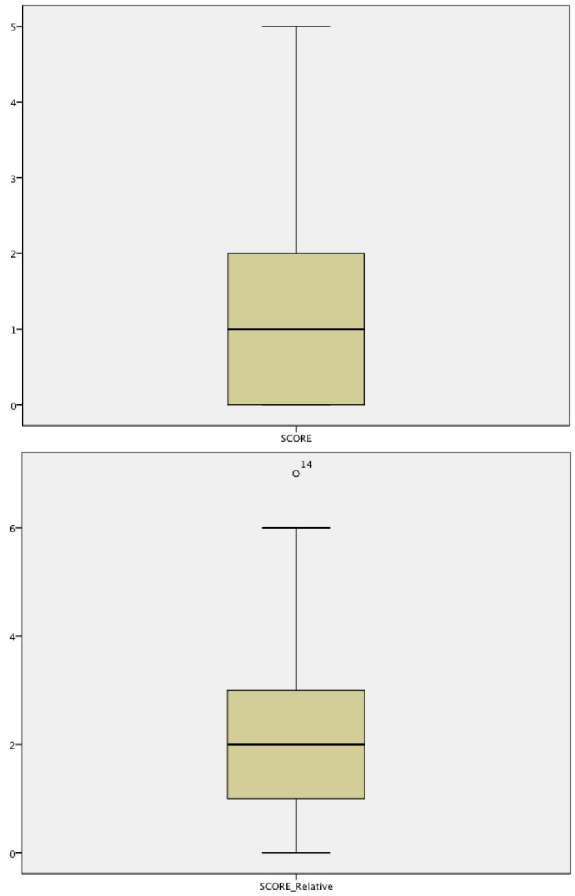

Fig 1. SCORE (a) and relative SCORE values (б) in studied population.

The following necessary steps were performed in order to test the power and statistical value of relations between the experimental variables "Age", "Hormones", and dependent variables "Absolute SCORE" and "Relative SCORE":

1. Pearson correlation matrices were plotted for groups of variables enabling to reduce "Age" group of variables and age group classification "Age group" to one most significant variable "Age group", and keep using only this variable in the future. Analysis of correlation matrices for other variable groups does not allow drawing similar conclusions (Table 2).

2. In order to separate significant variables in "Hormones" group Principal Component Analysis (PCA) was applied. We shall consequently build PCA models of effects of "Hormones" group on variables of "SCORE" groups with reduction of non-significant variables from "Hormones" group:

a. all 6 variables from "Hormones" group are used, and hormonal contribution into PCA model factors is tabulated (Tab. 3);

Table 2. Correlation matrix of variables included in factor analysis (n=160 females)

	Age	Age group	Relative SCORE	SCORE
Age	---	0.885884*	0.191014	0.739587*
Age group	0.885884*	---	0.244792*	0.768892*
Relative SCORE	0.191014	0.244792*	---	0.520596*
SCORE	0.739587*	0.768892*	0.520596*	---

*p < 0,05

Table 3. Coefficient and variables of factors

Variables	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Prolactin	-0.236946	-0.310241	0.485705	-0.591788	0.553816	-0.10297
Aldosterone	0.155687	0.289879	**0.726811**	-0.145646	-0.610336	0.10597
Progesterone	-0.258948	0.322005	-0.399634	**-0.719134**	-0.359408	-0.32646
Estradiol	-0.454271	-0.234862	0.146829	0.414443	-0.392855	-0.83709
Testosterone	-0.058322	**0.624432**	0.148667	0.236005	**0.589165**	-0.58820
FSH	**0.517071**	-0.204094	-0.050636	-0.196745	-0.021124	**-1.04436**

Factors loading in bold type are > 0,5

The most significant factors are recognized, and we can reduce "Hormones" group on the account of prolactin and estradiol.

b. reduced group of 4 hormones is used, and hormonal contribution into PCA model factors is tabulated.

Table 4. Coefficient and variables of factors after reduction of prolactin and estradiol

Hormones	Factor 1	Factor 2	Factor 3	Factor 4
Aldosterone	-0.008688	**0.766621**	-0.517023	-0.427596
Progesterone	0.473132	-0.250562	**-0.796908**	0.390828
Testosterone	0.432270	0.469416	0.502633	0.653250
FSH	**-0.554382**	0.140164	-0.280091	**0.849611**

Factors loading in bold type are > 0,5

The most significant factors are recognized, and we can reduce "Hormones" group on the account of testosterone.

c. reduced group of 3 hormones is used, and hormonal contribution into PCA model factors is tabulated.

Table 5. Coefficients and variables of factors after reduction of testosterone

Hormones	Factor 1	Factor 2	Factor 3
Aldosterone	-0.271528	**0.963726**	-0.067736
Progesterone	**0.588427**	0.263048	**0.809859**
FSH	**-0.598387**	-0.178636	**0.827115**

Factors loading in bold type are > 0,5

Further reduction of the group is impossible, and we keep aldosterone, progesterone, and FSH for further analysis.

3. Finally, in order to evaluate the power of the remaining factors, we plot a joint 3-factor PCA model with age consideration:

Table 6. Coefficients and variables of 3-factores model including age group

	Factor 1	Factor 2	Factor 3
Aldosterone	-0.438747	**0.805223**	0.181882
Progesterone	**0.627581**	0.435327	**-0.644391**
FSH	**-0.673157**	-0.339277	**-0.512215**
Age group	**-0.721478**	0.205551	-0.193223

Factors loading in bold type are > 0,5

It can be seen that Factor 1 is mostly represented by "age group" parameter and hormones progesterone, FSH; Factor 2 is greatly formed due to hormone aldosterone; Factor 3 is represented by hormones progesterone and FSH.

The rate of influence of individual hormones may be clearly seen from the example of SCORE dependency from "age group" and progesterone.

It can be clearly seen that high progesterone level exerts much higher effect on SCORE than affiliation to one or another age group. At the same time, relation, unlike the effect of "age group" variable, has pronounced non-linear nature, which becomes more and more apparent with age increase. Moreover, for older age group, optimal progesterone level may be specified, deviation from which may significantly increase SCORE value.

Thus, the factors were detected, which, besides age, may have significant impact on cardiovascular risk level in perimenopausal women. Such parameters include follicle-stimulating hormone, aldosterone and progesterone levels.

FSH effect on cardiovascular risk factors was previously shown in some experimental works. Thus, in women with maintained menstrual function, higher FSH was associated with formation of unfavorable lipid profile. In patients with FSH level exceeding 7 IU/l, total cholesterol (TC) and low-density lipoprotein cholesterol (LDLC) levels on menstrual cycle day 3 were reliably higher than those in patients with FSH not exceeding 7 IU/l [16]. Positive relation was detected between FSH level and intima media thickness (IMT) in perimenopausal patients; at the same time, no relation between IMT and estradiol and testosterone levels was established [17]. Relation between FSH level and adventitia diameter was found in a large-scale SWAN study, which was maintained after data normalizing by estradiol level [**18**].

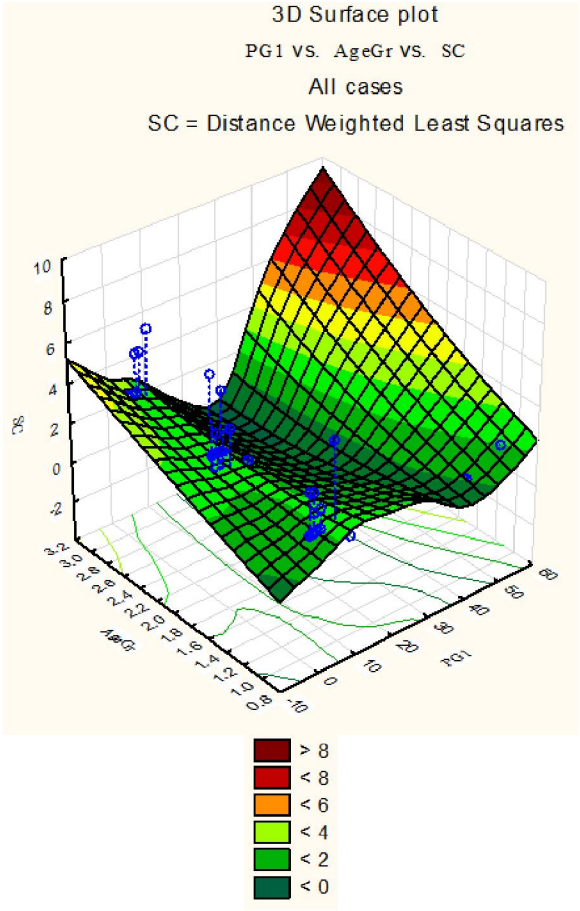

Fig. 2 Age and progesterone level effect on SCORE parameter (PG - progesteron)

Negative aldosterone effect on cardiovascular system is well described in literature [19, 20].

Information about progesterone cardiovascular effects are rather limited compared to the data on endogenous estrogens effects. Available studies mostly describe the effects of various exogenous progestins within the formulation of hormonal replacement therapy. Nevertheless, paranephric synthesis of this hormone, besides the ovarian one, is known to exist; this one can theoretically be activated in the conditions of FSH relative hyperproduction. Besides, great similarity between progesterone receptors and mineral corticoidal and glucocorticoidal receptors has been established [21]. Progesterone has been known to

possess both glucocorticoidal activity and anti-mineral corticoidal activity [22, 23]. It should be mentioned that progesterone anti-mineral corticoidal activity is manifested only provided its level conforms to the cycle luteal phase or its level during pregnancy [23]. In our study, progesterone levels are quite low, conforming either to postmenopausal state or cycle follicular phase.

Conclusion

Aldosterone, follicle-stimulating hormone and progesterone levels affect SCORE level in perimenopausal women.

Corresponding Author:
Dr.Isayeva Ganna S.
Government Institution «National Institute of Therapy named after L.T. Malaya of National Academy of Medical Science of Ukraine», prospect of Postishev 2A, 61039, Harkov, Ukraine, GU «National Institute of therapy ufter L.T.Maloy»

References

1. Ablewska, U., K. Jankowski, E. Rzewuska, D. Liszewska-Pfejfer, T.A. Hryniewiecki, 2011. levels of endogenous gonadal hormones and their relationship with selected coronary artery disease risk factors among young women post myocardial infarction. Acta Biochim Pol, 58(3): 385-389.
2. Braunstein, G.D., B.D. Johnson, F.Z. Stanczyk, V. Bittner, S.L. Berga, L. Shaw, T.K. Hodgson , M. Paul-Labrador, R. Azziz and C.N. Merz, 2008. Relations between endogenous androgens and estrogens in postmenopausal women with suspected ischemic heart disease. J Clin Endocrinol Metab , Nov 93(11): 4268-75.
3. Brown, J.M., P.C. Underwood,C. Ferri, P.N. Hopkins, G.H. Williams, G.K. Adler and A. Vaidya , 2014. Aldosterone dysregulation with aging predicts renal vascular function and cardiovascular risk. Hypertension, Jun;63(6): 1205-1211.
4. Cauley, J.A., J.P. Gutai, N.W. Glynn, M. Paternostro-Bayles, E. Cottington, and L.H. Kuller, 1994. Serum estrone concentrations and coronary artery disease in postmenopausal women. Arterioscler Thromb, Jan 14(1): 14-18.
5. Celestino Catão Da Silva, D., A. Nogueira De Almeida Vasconcelos, J. Cleto Maria Cerqueira, D. De Oliveira Cipriano Torres, F.C. Oliveira Dos Santos, H. De Lima Ferreira Fernandes Costa and L.O. Bregieiro Fernandes Costa, 2013. Endogenous sex hormones are not associated with subclinical atherosclerosis in menopausal women. Minerva Ginecol, Jun 65(3): 297-302.
6. Chu, M.C., M. RathK, J. Huie, H.S. Taylor, 2003. Elevated basal FSH in normal cycling women is associated with unfavourable lipid levels and increased cardiovascular risk. Hum. Reprod, 18 (8): 1570-1573.
7. Dosi, R., N. Bhatt, P. Shah and R. Patell, 2014. Cardiovascular disease and menopause. J Clin Diagn Res, Feb 8(2): 62-64.
8. El Khoudary, S.R., R.P. Wildman, K. Matthews, R.C. Thurston, J.T. Bromberger, K. Sutton-Tyrrell, 2012. Endogenous Sex Hormones Impact the Progression of Subclinical Atherosclerosis in Women during the Menopausal Transition. Atherosclerosis, Nov 225(1): 180–186.
9. Haring R., N. Friedrich, H. Völzke, R.S. Vasan, S.B. Felix, M. Dörr, H.E. Meyer zu Schwabedissen, M. Nauck, H. Wallaschofski, 2014. Positive association of serum prolactin concentrations with all-cause and cardiovascular mortality. Eur Heart J, May 35(18): 1215-1221.
10. He, H., F. Yang, X. Liu, X. Zeng, Q. Hu, Q. Zhu and B.Tu, 2007. Sex hormone ratio changes in men and postmenopausal women with coronary artery disease. Menopause, May-Jun 14(3 Pt 1): 385-390.
11. Jeon, G.H., S.H. Kim, S.D. Yun, H.D. Chae, C.H. Kim, B.M. Kang, 2010. Association between serum estradiol level and coronary artery calcification in postmenopausal women. Menopause, Sep-Oct 17(5): 902-907.
12. Kattoula, S.R., M.E. Baker, 2014. Structural and evolutionary analysis of the co-activator binding domain in vertebrate progesterone receptors. J Steroid Biochem Mol Biol, May 141: 7-15.
13. Leuzzi, C.,R. Marzullo and M.G. Modena, 2012. Is menopause a risk factor for ischemic heart disease in women? G Ital Cardiol (Rome), Jun 13(6): 401-406.
14. Matthews, K.A., S.L. Crawford, C.U. Chae, S.A. Everson-Rose, M.F. Sowers, B. Sternfeld and K. Sutton-Tyrrell, 2009. Are changes in cardiovascular diseaserisk factors in midlifewomen due to chronological aging or to the menopausal transition? J Am Coll Cardiol, Vol. 54, No. 25: 2367-2773.
15. Naessen, T., U. Sjogren, J. Bergquist, M. Larsson, L. Lind, M.M. Kushnir, 2010. Endogenous steroids measured by high-specificity liquid chromatography-tandem mass spectrometry and prevalent cardiovascular disease in 70-year-old men and women. J Clin Endocrinol Metab, Apr 95(4): 1889-1997.

16. Phillips, G.B., B.H. Pinkernell, T.Y. Jing, 1997. Relationship between serum sex hormones and coronary artery disease in postmenopausal women. Arterioscler Thromb Vasc Biol, Apr 17(4): 695-701.
17. Quinkler, M., B. Meyer, C. Bumke-Vogt, C. Grossmann, U. Gruber, W. Oelkers, S. Diederich and V. Bahr, 2002. Agonistic and antagonistic properties of progesterone metabolites at the human mineralocorticoid receptor. Eur J Endocrinol, Jun 146(6): 789-99.
18. Reddy, Kilim. S. and S.R. Chandala, 2013. A comparative study of lipid profile and oestradiol in pre- and post-menopausal women. J Clin Diagn Res, Aug 7(8): 1596-1598.
19. Scarabin-Carré, V., M. Canonico, S. Brailly-Tabard, S. Trabado, P. Ducimetière, M. Giroud, J. Ryan, C. Helmer, G. Plu-Bureau, A. Guiochon-Mantel and P.Y. Scarabin, 2012. High level of plasma estradiol as a new predictor of ischemic arterial disease in older postmenopausal women: the three-city cohort study. J Am Heart Assoc, Jun 1(3):1 (3):e001388. doi: 10.1161/JAHA.112.001388. Epub 2012 Jun 22. (Last Accessed: 14 July, 2014).
20. Schindler, A.E., C. Campagnoli, R. Druckmann, J. Huber,J.R. Pasqualini, K.W. Schweppe and J.H. Thijssen, 2013. Classification and pharmacology of progestins. Maturitas, Dec 10; 46 Suppl 1: S7-S16.
21. Silva, T.C., E. Barrett-Connor, J.A. Ramires and A.P. Mansur, 2008. Obesity, estrone, and coronary artery disease in postmenopausal women. Maturitas, Mar 20;59(3): 242-248.
22. Verdugo, F.J., F.A. Montellano, J.E. Carreño, E.T. Marusic, 2014. Mineralocorticoid receptor antagonists and therapeutic strategies of cardiovascular damage. Rev Med Chil, Jan 142(1): 61-71.
23. Wellons, M., P. Ouyang, P.J. Schreiner, D.M. Herrington and D. Vaidya, 2012. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. Menopause, Oct 19(10): 1081-1087.

9/19/2014