Reproductive factors and its association with peripheral arterial disease in women aged 52–81 years: The KORA F4 study

Doris Stöckl [a,b,*], Angela Döring [c], Barbara Thorand [a], Margit Heier [a,d], Annette Peters [a], Claudia Lamina [e], Florian Kronenberg [e], Christa Meisinger [a,d]

[a] Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[b] Department of Obstetrics and Gynaecology, Campus Grosshadern, Ludwig-Maximilians-University, Munich, Germany
[c] Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[d] Central Hospital of Augsburg, MONICA/KORA Myocardial Infarction Registry, Augsburg, Germany
[e] Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria

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A B S T R A C T

Objective: Sex differences in the onset of cardiovascular disease disappear in the postmenopause, suggesting that reproductive factors could be influential. The aim of the present study was to examine the possible association between reproductive parameters and peripheral arterial disease (PAD) in a female population-based sample.

Methods: In this cross-sectional study data of 887 women aged 52–81 years participating in the population-based KORA F4 study (conducted in 2006–2008) was analyzed. Reproductive parameters were obtained by standardized interviews. PAD was assessed by measuring noninvasively the ankle-brachial index and using a cut-off value of 0.9 and by assessing the presence of claudication by the Edinburgh questionnaire.

Results: In multivariable logistic regression analyses later age at menarche (>15 years) compared to age at menarche between 12 and 15 years was significantly associated with about half the probability for PAD (OR = 0.48; 95%CI 0.24–0.98). The presence of hot flashes was positively associated with PAD (OR = 2.09; 95%CI 1.11–3.92). Further reproductive parameters, such as parity, age at menopause, time since menopause, duration of fertility, ever use or current use of hormone replacement therapy, ever use of oral contraceptives, history of hysterectomy, bilateral oophorectomy and depressive mood in relation to menopausal transition showed no significant association with PAD.

Conclusions: Later age at menarche was inversely related to PAD and the presence of hot flashes was associated with an increased presence of PAD. Prospective population-based studies in women are needed to assess the impact of reproductive parameters on the development of PAD and subsequently cardiovascular disease.

1. Introduction

While younger women have a lower prevalence of cardiovascular disease and atherosclerosis than younger men [1], sex differences disappear in the postmenopause [2], suggesting a protective effect of the premenopausal hormone status in females. A recently published statement from the American Heart Association recognizes the lack of adequate research evaluating gender-based differences with respect to peripheral artery disease (PAD) [3].

Reproductive events during the life-span are associated with a variety of hormonal and metabolic changes in the female body and have been shown to be associated with chronic diseases. In prior studies lower age at menarche (AAM) was associated with diabetes [4], metabolic syndrome [5], cardiovascular disease (CVD) [6] and even mortality [6]. Parity was shown to be negatively associated with CVD [7] and the metabolic syndrome [8,9]. The menopausal transition was positively associated with CVD [10] and the presence of hot flashes was related to cardiovascular risk factors [11,12]. These associations are widely believed to be due to an effect of endogenous sex hormones during the premenopausal period. Factors influencing the hormone levels and therefore the lifetime

* Corresponding author. Institute of Epidemiology II, Helmholtz Zentrum München, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany. Tel.: +49 89 3187 4153; fax: +49 89 3187 3667.
E-mail address: doris.stoeckl@helmholtz-muenchen.de (D. Stöckl).

cumulative estrogen exposure are suggested to influence CVD risk [13]. Length of fertile period and age at menopause have been shown to be related to PAD in a case–control study of 269 post-menopausal women with amputation due to lower extremity arterial occlusive disease compared to 224 women with joint replacement due to osteoarthritis and 88 healthy women [13]. So far, to the best of our knowledge, population-based studies on this issue are missing and some reproductive factors, like the presence of hot flashes have not been previously studied.

The aim of this study was to investigate whether there is an association between a variety of reproductive parameters and PAD in women aged 52–81 years from the general population.

2. Methods

2.1. Subjects

The KORA F4 (2006–2008) study is the 7-year follow-up study of the KORA S4 (1999–2001) study, a population-based health survey performed in the city of Augsburg in Southern Germany and the two surrounding counties. The study design, sampling method and data collection have been described in detail elsewhere [14,15].

Assessment of PAD was performed in participants aged 52–81 years, therefore 943 women were eligible for analysis. From this sample, we excluded all women for whom no or incomplete information on ankle-brachial index (ABI) or any of the confounding covariables was available ($n = 56$). The analysis finally included 887 study participants.

The investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent of all study participants. The study was approved by the Ethics Committee of the Bavarian Medical Association.

2.2. Data collection

Trained medical staff obtained information on socio-demographic variables, physical activity level, medication use, medical history, alcohol consumption and smoking habits during a standardized face-to-face interview. In addition, all study participants underwent a standardized medical examination. All measurement procedures have been described in detail elsewhere [5,15]. Anthropometric measurements were performed after the probands had removed their shoes, heavy clothing and belts. Body height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. BMI was calculated as weight [kg] divided by height^2 [m^2].

Participants were classified as active during leisure time if they regularly participated in sports in the summer and winter and if they were active for >1 h/wk in either season. Women who consumed more than 20 g alcohol per day were regarded as heavy alcohol drinkers. The study participants provided information on their smoking behavior (never, past, current).

2.3. Assessment of reproductive parameters

Reproductive parameters were obtained by a personal interview in the KORA S4 and F4 survey [16]. Women were asked in S4 for AAM in years, in S4 and F4 to recall their age at their last menstruation, number of pregnancies, live-born children, if they ever used oral contraceptives (OC) or hormone replacement therapy (HRT). Women were defined as postmenopausal at the absence of menses for 12 consecutive months, if they had bilateral oophorectomy (either alone or in combination with hysterectomy) or had hysterectomy without bilateral oophorectomy and were aged above 50 years. Parity was defined as the number of reported deliveries. All participants were asked to bring to the interview all medications taken in the 7 days preceding the examination. The medications were categorized according to the Anatomical Therapeutical Chemical (ATC) classification index. From these data the variable "current use of HRT" was constructed. Ever use of OC or HRT was assessed in the interviews. Furthermore, the women were asked about the presence of two symptoms of the menopausal transition: hot flashes and depressive mood. Age at menopause was assessed in both surveys and was available for 641 women. From the variable age at menopause the variable 'time since menopause' (current age minus age at menopause) in years and 'duration of the fertile period' (age at menopause minus age at menarche) in years were constructed.

2.4. Assessment of PAD

The ABI was measured according to a standardized protocol by trained and certified examiners as described recently [17]. After the probands were lying in dorsal position for at least 15 min, systolic blood pressure (BP) was obtained with a stethoscope and a BP cuff on the right arm, and with a Doppler device (HNE Healthcare, Mini Doppler Modell Nr. D 900) on both ankles (posterior tibial artery).

Generally two measurements were performed and the mean of the two measurements was used for further calculations. If a difference of 10 mmHg or more between the two measurements was observed, a third measurement was performed and the mean of the two measurements which were closest to each other was calculated.

The ABI was calculated as mean systolic BP of that ankle side which was lowest divided by the mean of the two brachial systolic BP of the right arm. Claudication was assessed through the Edinburgh questionnaire [18]. The Edinburgh Claudication Questionnaire was first validated in 1992. This patient-administered questionnaire was tested in a predominantly European population and was found to have a sensitivity of 91.3% and a specificity of 99.3% specific for claudication in comparison to a medical diagnosis [18].

PAD in our study was defined as asymptomatic or symptomatic PAD with an ABI below 0.9 and/or claudication, assessed by the Edinburgh questionnaire. The cutpoint of 0.9 has a sensitivity of 95% for the presence of PAD documented by angiography [19].

2.5. Statistical analyses

Basic characteristics of the study population were described, stratified for the presence of PAD. For continuous variables the mean and standard deviation and for categorical variables percentages were calculated.

Logistic regression analyses were performed to analyze the association between different reproductive factors and PAD. Two models were fitted: a model controlling for age and a second model adjusting for age, BMI, education, family status, physical activity, smoking and alcohol consumption. Multivariable analyses were performed only for those reproductive parameters which were statistically significant associated in the age-adjusted model. For the selection of the confounders a literature research was performed, which showed that age, BMI, smoking, social status (in our study considered as education and family status) were used in similar studies [1,11,12,20,21]. In the multivariable model for the parameter 'hot flashes' 'current use of HRT' was additionally used as confounder. The variables age at menopause, time since menopause and duration of fertility were categorized in tertiles with the highest tertile used as the reference category. AAM was stratified in three groups. The mean age at menarche was 13.52 with a standard deviation of 1.57. Therefore, for the categorized model, the reference category was chosen to be 12–15 years, as previously described [5]. After a literature search we found that many authors regarding this issue tended to choose similar categories [6,22]. Thus we also chose this categorization to achieve better comparability