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Original article

Effect of menopause and age on vascular impairment

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ABSTRACT

Aims: The prevalence of cardiovascular diseases increases in women after menopause. The aim of the study was to determine the impact of conventional cardiovascular risk factors such as age, blood pressure, smoking, cholesterol, obesity, and glucose balance, but also menopausal state and sleep-disordered breathing on vascular impairment during menopausal transition.

Methods: 89 women initiated the study and 74 of them participated in the 10-year follow-up. Cardiovascular disease risk factor assessments, ultrasound measurements of brachial artery function, including nitroglycerin-mediated vasodilatation and flow-mediated endothelium-dependent vasodilation, and sleep studies were repeated at baseline and at 5-year and 10-year follow-ups.

Results: Over the study period, all the cardiovascular disease risk estimates increased. Both flow-mediated endothelium-dependent vasodilatation (decline 55 %) and nitroglycerin-mediated vasodilatation (decline 18 %) worsened over the 10 years ($p < 0.001$). Vascular function was not associated with menopausal state (determined with follicle stimulating hormone). Systolic blood pressure ($p = 0.009$) and smoking ($p = 0.006$) at baseline were negatively associated with nitroglycerin-mediated vasodilatation at 5-year follow-up and the use of hormonal therapy at 5-year follow-up was positively associated with concurrent nitroglycerin-mediated vasodilatation ($p = 0.041$). Intermittent nocturnal hypoxemia at baseline was associated with flow-mediated endothelium-dependent vasodilatation at 10-year follow-up ($p = 0.043$). High body mass index and impaired glucose balance at 5-year follow-up were associated with nitroglycerin-mediated vasodilatation decline at 10-year follow-up ($p = 0.022$ and $p = 0.037$, respectively).

Conclusions: We demonstrate how cardiovascular risk factors and vascular function evolve during menopausal transition. Although menopause was not associated with vascular impairment, short-term improvement in vascular function was observed in those using menopausal hormonal therapy. Intermittent nocturnal hypoxemia, obesity and impaired glucose control are early predictors of vascular decline during postmenopause.

1. Introduction

Despite of declining mortality rates, cardiovascular diseases (CVD) are still a leading cause of death in aged population [1]. The prevalence of CVD increases with age both in men and women [2], but CVD risk in women accelerates after menopause and even exceeds that of men [3–5]. This is thought to be due to the change in female hormone production at menopause, especially estrogen deficiency [6]. Moreover,

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hormone therapy (HT) is shown to be cardioprotective at the time of the menopause [7].

Endothelial dysfunction of the arteries is a marker of vascular impairment and predicts emerging CVD [8]. Decline in endothelial function accelerates in women across the state of menopause as the prevalence of CVD increases [9]. Despite numerous studies, our understanding of the interplay of female sex hormones, aging and endothelial function is not unanimous [5,10,11]. In some studies, flow mediated endothelium-dependent vasodilatation (FMD) has been inversely associated with age in menopausal women [5,10]. However, a marked immediate decrease of FMD after ovariectomy suggests also an important role of estrogen for endothelial function [11]. Therefore, during menopausal transition, both aging and coexistent hormonal deficiencies are likely to affect endothelial function, making it difficult to separate the effects.

In the present study, we have a unique cohort of women, whose 10 year follow-up covers the period of menopausal transition. We have assessed known risk factors for CVD at the age of 46 years (baseline) and after 5 (5Y, perimenopause) and 10 years (10Y, postmenopause) in the same individuals together with measurements of the endothelial function and sleep-disordered breathing (SDB). The aim was to investigate the evolution of CVD risk factors during menopausal transition. We hypothesized that early SDB might have an effect on CVD progression even in healthy women.

2. Methods

2.1. Subjects

Altogether 114 healthy women aged 46 years were recruited for the follow-up study through a newspaper announcement. This was a part of the larger long-term prospective study “Woman 46” designed to investigate sleep and cardiovascular risk factors in middle-aged women. At entry, all the women were premenopausal and free of known coronary heart disease, medication for hypercholesterolemia, diabetes, respiratory insufficiency or SDB. Twenty-five women were excluded from the study because of their peri- or postmenopausal hormonal status at the age of 46 (follicle stimulating hormone, FSH over 15 IU/L) or due to the missing ultrasound or laboratory measurements. All the included women had been invited to repeated investigations at three time points: at the age of 46, 51 and 56 years. From the original baseline cohort of 89 women, the tests were repeated in 77 women at 5Y and 74 women at 10Y. The FSH threshold of 15 IU/L at baseline was chosen to ensure the possibility to study the effects of hormonal cessation at menopause. Generally, FSH varies between 1.5 and 12.4 IU/mL in a premenopausal woman, but during the ovulation peak the values can be slightly higher. After menopause, however, FSH ranges from 25.8 to 134.8 IU/mL. With the FSH threshold 15 IU/L, we ensured that none of the women were already menopausal at the beginning of the study. During the follow-up period, some of the women initiated HT under the guidance of their own physician; 21 out of 77 were on HT at 5Y and 15 out of 74 women at 10Y.

The women with regular menstruation were tested during the follicular phase of the menstrual cycle (between days 3 and 10). Body mass index (BMI), waist circumference and blood pressure (BP) were measured. The following laboratory assays were taken after an overnight fast: serum FSH, total cholesterol, low-density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) and glycosylated haemoglobin A1C (HbA1C). A conventional in-lab polygraphic sleep recording (Embla®/Somnologica system, Medcare Flaga hf, Reykjavik, Iceland) included continuous overnight recordings of electroencephalogram, nasal pressure, thoracoabdominal movements and arterial oxyhaemoglobin saturation (SaO_2). The oxyhaemoglobin desaturation index (ODI_4), which is the number of SaO_2 dips of a minimum of 4 % units, was determined with an inbuilt Somnologica tool. Sleep stages and apnea-hypopnea-index (AHI) were manually scored according to the international criteria [12,13]. Apnea was defined as reduction in airflow amplitude of at least 90 % for a minimum duration of 10 s [13]. An episode of hypopnea was defined as a temporary reduction of airflow amplitude of at least 30 % but <90 % for a minimum duration of 10 s accompanied by a 4 % unit reduction in SaO_2 [13]. SDB was defined as an AHI $\geq$5 events/h [13]. Questionnaires were used to collect data on personal medical history and smoking.

2.2. Ultrasound imaging of brachial artery

Ultrasound imaging of the brachial artery were made in the morning after the overnight sleep recordings. The ultrasound measurements were made using an Acuson Sequoia 512 (Acuson Inc., Mountain View, CA, USA) ultrasonography with 13 MHz linear array transducer. Ultrasound scans were performed by an investigator or an experienced study nurse. Endothelial function was assessed with FMD and endothelium-independent vasodilatation with nitroglycerin-mediated vasodilatation (NMD) according to a standardized protocol [14]. The diameter of the brachial artery was measured in three states: at rest, after reactive hyperaemia (FMD) and after sublingual nitroglycerine (2.5 mg isosorbide dinitrate spray, NMD). The results are presented as change of the diameter relative to the resting diameter. The measurements were made at end-diastole. The averages of four to eight measurements in each state were entered in the analyses.

2.3. Statistical methods

After validation of the database, the data was transformed to SAS® System for Windows version 9.4, (SAS Institute, Cary, NC) for statistical analyses. The changes in continuous patient characteristic variables between baseline, 5-year follow-up and 10-year follow-up were analyzed with repeated measures analysis of variance (ANOVA). If assumptions for parametric models were not met, Friedman’s tests were substituted for ANOVA. Logistic regression with generalized estimating equations was used to test the changes in categorical patient characteristic variables. Multivariable linear models were used to investigate whether different cardiovascular risk factors had effect on vascular impairment. Some patient characteristics were excluded from the linear models due to their high correlation with other variables to avoid collinearity problems; BMI was chosen over waist circumference, LDL-cholesterol over HDL- and total cholesterol, systolic BP (SBP) over diastolic BP and ODI_4 over AHI. The dependent variable was either FMD or NMD, and independent variables included BMI, LDL, GHbA1C, SBP, ODI_4, smoking, HT and FSH, each in different time-points. Pairwise comparisons between smoking groups were done with Tukey’s method. All tests were two-sided and a significance level of 0.05 was used.

2.4. Ethical aspects

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland, and the work has been carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

3. Results

3.1. Characteristics of the patients at the 10-year follow-up

The study population consisted same individuals followed for 10 years. From the 89 women who participated in the study, 62 attended the baseline and both two follow-ups, 77 attended the baseline and 5Y and 74 attended the baseline and 10Y. Mean age at baseline was 46.0 years (SD 0.9), at 5Y 52.0 years (SD 1.2) and at 10Y 56.8 years (SD 1.0). In the beginning of the study all the women were premenopausal (inclusion criteria). At the 5Y 23 women were still premenopausal and the other 54 women were peri- or postmenopausal (FSH over 15 IU/L). At 10Y majority of the women had FSH >15 IU/L (95.9 %). Menopause was defined if the FSH values were over the 25.8 IU/mL, or a menopausal HT had been initiated by the woman's own physician. None of the women used hormonal therapy (HT) at baseline. At baseline, 9 women had undergone hysterectomy (without ovariectomy). During follow-up, estrogen therapy (ET) used by 19 women at 5Y decreased to 4 users at 10Y. Combination (estrogen + progesterone) therapy increased from 3 to 11 users during the same period. Seven out of 9 smokers at 5Y had stopped smoking by 10Y (Table 1).

In line with developing menopause during the follow-up period, FSH increased from 7.7 IU/L (SD 3.4) at baseline to 65.3 IU/L (SD 31.0) at 10Y. Higher BMI (p < 001) and larger waist circumference ($p < 0.001$) indicated change in body composition. At the same time there was an unfavorable evolution of serum lipids ($p <$ 001) and GHbA1C ($p =$ 0.001). The systolic BP increased from 125.8 mmHg (SD 14.2) to 133.8 mmHg (SD 18.4) ($p < 0.001$), whereas the diastolic BP tended to increase (from 84.0 mmHg to 85.9 mmHg, $p = 0.065$). Both ODI_4 and AHI increased during 10 years from 4.7/h to 7.8/h ($p = 0.009$) and from 3.3/h to 11.1/h ($p < 0.001$), respectively. At the baseline, 20.2 % of the patients had SDB, 37.7 % at 5Y and 45.9 % at 10Y. The FMD of brachial artery declined over time from 10.3 % to 4.6 % ($p < 0.001$) and NMD declined from 31.4 % to 25.6 % (p < 0.001, Fig. 1). FMD values at baseline and follow-ups were in accordance with reported reference measures [15] (Table 1).

Table 1
Patient characteristics over 10 years.

Characteristics	n	Baseline	n	5Y	n	10Y	p
Age, years	89	46.0 (0.9)	77	52.0 (1.2)	74	56.8 (1.0)	<0.001
FSH, IU/L	89	7.7 (3.4)	77	43.6 (33.5)	74	65.3 (31.0)	<0.001
FSH > 15, n (%)		0 (0)		54 (70.1)		71 (95.9)	
BMI, kg/m^2	89	26.4 (5.6)	70	28.2 (6.2)	74	28.5 (6.6)	<0.001
BMI > 30 kg/m^2, n (%)		17 (19.1)		19 (27.1)		23 (31.1)	
Waist circumference, cm	89	86.3 (14.3)	70	92.9 (15.5)	74	95.4 (14.5)	<0.001
Total cholesterol, mmol/L	89	5.2 (0.8)	76	5.5 (0.8)	74	5.7 (0.9)	<0.001
LDL, mmol/L	89	3.0 (0.8)	75	3.0 (0.8)	70	3.3 (0.8)	<0.001
HDL, mmol/L	89	1.7 (0.4)	76	1.9 (0.5)	74	1.8 (0.5)	<0.001
GHbA1C, % median (IQR)	89	5.4 (0.4)	75	5.6 (0.5)	74	5.3 (0.5)	0.001
SBP, mmHg	89	125.8 (14.2)	69	130.2 (17.8)	74	133.8 (18.4)	<0.001
DBP, mmHg	89	84.0 (9.5)	69	85.6 (9.3)	74	85.9 (9.6)	0.064
ODI_4, events/h, median (IQR)	81	2.5 (3.7)	65	2.3 (8.3)	72	3.9 (7.1)	0.009
AHI, events/h, median (IQR)	84	2.6 (3.7)	65	2.8 (10.5)	72	4.6 (9.7)	<0.001
Smoking, n (%)	89	9 (10.1)	75	8 (10.7)	74	2 (2.7)	<0.001
Estrogen therapy, n (%)	89	0 (0)	76	19 (25.0)	66	4 (6.1)	0.003[a]
Combination HT, n (%)	89	0 (0)	76	3 (3.9)	66	11 (16.7)	0.017[a]
FMD, %	89	10.3 (6.4)	73	7.4 (4.9)	74	4.6 (4.5)	<0.001
NMD, %	88	31.4 (9.8)	73	30.8 (9.0)	61	25.6 (6.9)	<0.001

Numbers are expressed as mean (SD) unless otherwise stated. 5Y; 5-year follow-up, 10Y; 10-year follow-up, FSH; follicle stimulating hormone, BMI; body mass index, LDL; low-density lipoprotein; HDL; high-density lipoprotein; GHbA1C; glycosylated haemoglobin A1C, SBP; systolic blood pressure, DBP; diastolic blood pressure, ODI_4; arterial oxyhaemoglobin desaturation of 4 % units or more, AHI; apnoea/hypopnea index, HT; hormone therapy, FMD; flow-mediated dilatation of brachial artery, NMD; nitroglycerin-mediated dilatation of brachial artery.

[a] Between 5-year and 10-year follow-ups.

3.2. *Multivariable linear models*

In the multivariable linear models, the baseline systolic BP and smoking were negatively associated with baseline NMD ($p = 0.009$ and $p = 0.006$, respectively), but not with FMD (Table 2). In a pairwise comparison between the groups of current smokers and never-smokers, the current smoking worsened NMD ($p = 0.013$).

In 5Y only the use of HT was positively associated with concurrent NMD at 5-years ($p = 0.041$, Table 3). However, in a pairwise comparison between the groups of no-HT, ET and combination HT there was no statistical difference on the association with NMD. (See Table 4.)

After menopause at 10Y, the baseline and 5Y values had a greater impact than the measurements during that particular visit. ODI_4 at baseline was associated with FMD at 10Y ($p = 0.043$), as well as BMI and GHbA1C at 5Y were associated with NMD at 10Y ($p = 0.022$ and $p =$ 0.037, respectively). The conventional CVD risk factors were no longer associated with the FMD or NMD at 10Y.

4. Discussion

Our results demonstrate how the CVD risk factors change over a 10 years study period in women during the menopausal transition. Of note, women's menopausal status had only little or no effect on CVD risk factors during the follow-up. At baseline all the women were approximately 46 years old and premenopausal. At the 5-year follow-up 29.8 % of the women were still premenopausal, and the other were either peri- or postmenopausal. At the end of the follow-up, all the women had reached postmenopause. Over the study period, vascular impairment (demonstrated by impaired vasodilative response assessed by FMD and NMD of brachial artery) occurred in all the women, but we found no association between vascular parameters and FSH concentrations. However, at 5-year follow-up, where most of the women were perimenopausal, the usage of HT was directly associated with NMD values. This effect was not seen any more at the end of the study, when all the women were postmenopausal.

All the conventional CVD risk factors chosen for the study aggravated during 10 years. Also, the prevalence of SDB increased over the years, although AHI and ODI_4 remained relatively low in this population of originally healthy women and symptomatic obstructive sleep apnea syndrome was not diagnosed during the follow-up. Even so, ODI_4 at the beginning of the study was associated with impaired endothelial function after 10 years. This finding further supports the importance of SDB either as a pathophysiologic mechanism [16–18], or more likely, as a marker of ongoing deterioration of vascular function. Even mild intermittent nocturnal hypoxemia has been associated with far-reaching cardiovascular effects [18–20]. In the recent study of Bouloukaki et al., it was shown that also very mild obstructive sleep apnea increases the risk of hypertension in otherwise healthy adults [20]. Deterioration of endothelial function, in turn, is an early stage change in the development of hypertension [21]. In our study, in healthy women with relatively low ODI_4, only slight intermittent hypoxemia predicted a decline in endothelial function after 10 years. Perhaps due to the sparsity of ODI_4 events, it only achieved marginal significance in association with vascular function in the 5- and 10 year follow-ups. Despite this, the finding further strengthens the interest of using SDB as a risk factor for CVD.

The number of smokers declined markedly from 9 to only 2 smokers at the end of the study. The small number of smokers prevented us to take it into the regression models at 10-year follow-up, but at baseline it's unfavorable effect on vascular function was evident and in line with several previous studies [22,23]. The association in our study, however, was only seen in NMD values. NMD represents vascular smooth muscle

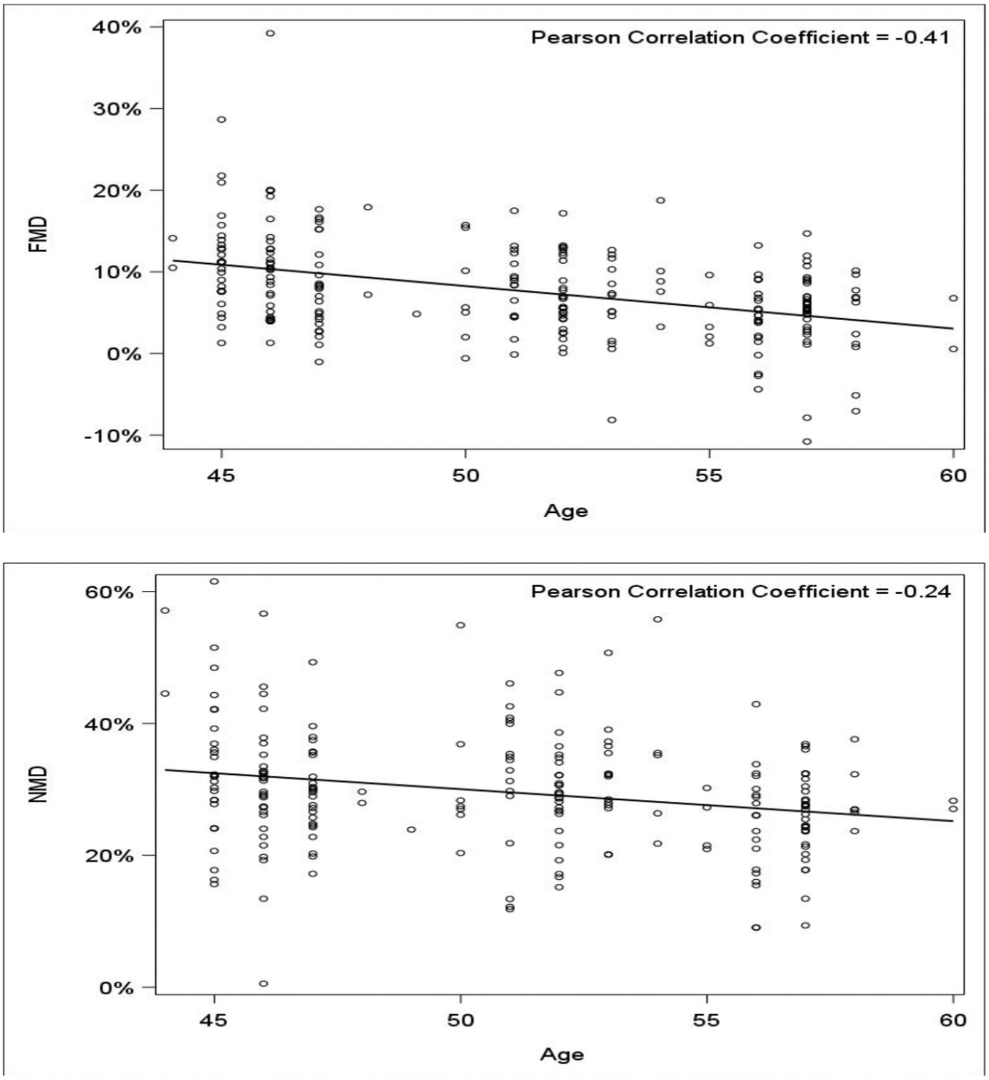

Fig. 1. Vascular function decline during the 10-year study period as measured with FMD and NMD.

FMD; flow-mediated dilatation of brachial artery, NMD; nitroglycerin-mediated dilatation of brachial artery. Dilatation of the brachial artery is represented as percentage (%) after shear stress method (FMD) and after sublingual nitroglycerine (NMD). The same subjects are measured two or three times during the study period ($p < 0.001$).

dilatation capacity, whereas FMD depends on the internal nitric oxide released from endothelium response to shear stress. These both measurements have earlier been associated with CVD risk factors [24,25]. Our lack of association between smoking and FMD is most probably only due to the small set of smokers.

Our results corroborate that high SBP, overweight and impaired glucose control increase the risk for developing CVD. SBP was associated with impaired NMD at baseline. Moreover, high BMI and GHbA1C at the timepoint of the 5-year follow-up were associated with impaired NMD values at the 10-year follow-up. Interestingly, none of the CVD risk factors measured at the 10-year follow-up were associated with concurrent FMD or NMD. Based on these results, it seems that the CVD risk profile of a woman at the menopausal transition can predict her future health condition, even after several years. The risk factors at menopausal transition seem to predict postmenopausal health better than the postmenopausal concurrent risk profile. Indeed, it is previously shown that the state of health at the time of the menopause has a significant association with the future development of CVD [26]. Healthy behavior in midlife can affect positively on women's health and well-being until early old age [26].

The production of female hormones declines rapidly at menopause [27]. Previous studies have shown an important role of estrogen on vascular function [27–29]. It is thought that the loss of vasodilatory effects of estrogen impair endothelial function at menopause. In our study, however, at the 5-year follow-up when FSH values varied greatly, it was not associated with FMD or NMD. This finding is also in line with our previous results [25]. Based on these results, it seems that the vascular response to estrogen declines with age, even if the estrogen production is still normal. This is also suggested by the finding that HT improved slightly vasodilatation at the 5-year follow-up but not anymore at the 10-year follow-up. In addition, Vitale et al. have recently showed that the effect of ET on FMD was decreased in women who had reached menopause over five years ago compared to women who had been postmenopausal less than five years [30].

Our study design offers unique information of the same individuals followed for 10 years. Menopausal status was confirmed at each of the three timepoint by measurement of FSH. This setting allows us to separate the effects of hormonal decline, HT and aging. At baseline, the measurements were performed at the follicular phase of menstrual cycle, expect the patients with hysterectomy, to avoid the hormonal fluctuation as a confounding factor. It is known that brachial artery diameter can vary during the menstrual cycle, being on its largest in follicular phase [31]. However, it was not always possible to get the subjects into the laboratory assays exactly at the right menstrual phase, which may have affected the baseline ultrasound measurements. Besides, in the study of Kawano et al. they found no difference in the percentage of increase in blood flow during reactive hyperemia in different phases of menstrual cycle, which suggests that the hormonal state effect on our

Table 2

Effect of baseline cardiovascular risk factors on vascular function over 10 years.

Baseline risk factors	Baseline						5-year follow-up						10-year follow-up					
	FMD			NMD			FMD			NMD			FMD			NMD		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p
BMI	0.06	0.17	0.720	0.04	0.26	0.864	−0.07	0.15	0.668	−0.43	0.26	0.102	−0.07	0.12	0.559	−0.17	0.22	0.43
LDL	0.66	0.97	0.497	1.27	1.50	0.402	−0.45	0.90	0.623	−2.17	1.51	0.155	0.03	0.75	0.971	0.89	1.39	0.525
GHbA1c	−0.33	2.18	0.882	1.38	3.35	0.683	1.14	1.96	0.561	−0.03	3.31	0.336	0.63	1.75	0.722	2.68	3.43	0.439
SBP	−0.08	0.05	0.129	−0.22	0.08	0.009	−0.02	0.05	0.739	0.00	0.08	0.97	−0.07	0.04	0.132	−0.06	0.08	0.468
ODI_4	−0.11	0.13	0.374	−0.03	0.20	0.878	−0.02	0.12	0.898	0.05	0.19	0.79	−0.22	0.11	0.043	−0.26	0.18	0.165
Smoking[a]			0.169			0.006			0.815			0.174			0.423			0.542
Current	9.51	0.73		30.59[b]	1.12		7.44	0.69		30.49	1.13		4.86	0.54		25.71	0.96	
Never	11.08	3.93		48.54[b]	6.04		8.23	3.40		37.16	5.66		7.55	3.34		33.83	7.43	
Before	14.53	2.56		38.17	4.30		5.81	2.69		22.58	5.19		3.01	1.74		24.7	4.22	
FSH	−0.11	0.21	0.601	−0.08	0.33	0.803	0.05	0.20	0.803	0.02	0.33	0.954	−0.04	0.16	0.820	−0.27	0.30	0.369

FMD; flow-mediated dilatation of brachial artery, NMD; nitroglycerin-mediated dilatation of brachial artery, BMI; body mass index, LDL; low density lipoprotein cholesterol, GHbA1C; glycosylated haemoglobin A1C, SBP; systolic blood pressure, ODI_4; arterial oxyhaemoglobin desaturation of 4 % units or more.

[a] Smoking is presented as adjusted mean with standard error (SE), while all the other values are adjusted regression coefficient β with standard error (SE).

[b] Between the groups of never and current smokers there was a difference in the association with NMD (p = 0.013), indicating markedly higher NMD on never smokers.

results is probably minimal [31]. However, since the follow-up in our study was every five years, we cannot evaluate the effect of rapid hormonal changes on the blood vessels at the exact moment of menopause.

In addition to the female hormonal variety, a potential weakness of the study is recruiting method; recruiting healthy individuals to a follow-up study via a newspaper announcement can bias the population with individuals who are more interested in their own health than women on average. Moreover, we cannot exclude that lifestyle changes beyond cessation of smoking may have occurred during the study period. However, other possible life style changes were ineffective to dilute our observed associations between risk factors and vascular function. The power of the study would be increased by a larger number of the subjects, but unfortunately, with such a long follow-up, some of the participants are always left out of the follow-ups for one reason or another. Data is also missing from some of the subjects due to a technical or human error, or because the study could not be conducted.

5. Conclusions

The present study demonstrates how CVD risk factors change over 10 years at the menopausal transition. Marked vascular impairment occurs during the study period. Menopause, defined by FSH, was not associated with vascular impairment. However, the use of HT during the transition phase of menopause had a short-term positive effect on blood vessel function, which was no longer observed later in the 10-year follow-up. Early sings of SDB verified as intermittent nocturnal hypoxemia, obesity and impaired glucose control in middle age contribute to vascular decline in women even after several years.

Contributors

Jenni Aittokallio contributed to study design, data collection, interpreting the results, and writing the manuscript.

Tarja Saaresranta contributed to study design, data collection, interpreting the results, and writing the manuscript.

Markus Riskumäki contributed to statistical analysis, figure formatting, and manuscript content approval.

Tiina Hautajärvi contributed to statistical analysis and manuscript content approval.

Tero Vahlberg contributed to statistical analysis and writing the manuscript.

Olli Polo contributed to study design, data collection, and manuscript content approval.

Olli Heinonen contributed to study design, data collection, and manuscript content approval.

Olli Raitakari contributed to study design, data collection, and manuscript content approval.

Nea Kalleinen contributed to study design, data collection, interpreting the results, and writing the manuscript.

All authors approved the final version submitted.

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Ethical approval

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from all participants.

Table 3
Effect of 5-year follow-up cardiovascular risk factors on vascular function over 5 years.

5-year follow-up risk factors	5-year follow-up						10-year follow-up					
	FMD			NMD			FMD			NMD		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
BMI	−0.12	0.14	0.397	−0.20	0.24	0.416	−0.19	0.19	0.316	−0.51	0.21	0.022
LDL	−0.41	0.92	0.661	−0.92	1.53	0.553	0.14	1.21	0.907	−0.96	1.36	0.488
GHbA1c	3.10	2.29	0.184	−3.22	3.85	0.408	0.77	3.06	0.803	8.21	3.71	0.037
SBP	−0.01	0.05	0.862	−0.11	0.08	0.195	−0.05	0.06	0.490	0.04	0.08	0.610
ODI$_4$	−0.03	0.07	0.709	0.00	0.11	0.969	−0.04	0.08	0.645	−0.25	0.14	0.084
Smoking[a]			0.624			0.347			0.844			0.056
Current	8.91	1.33		36.37	2.97		3.18	1.60		23.82	2.25	
Never	6.80	3.00		35.38	5.31		1.83	3.71		11.06	5.42	
Before	4.98	5.59		18.62	10.43		6.52	6.57		33.42	7.70	
HT[a]			0.314			0.041			0.874			0.528
No HT	4.78	2.35		22.74	4.54		4.64	2.81		25.2	3.75	
ET	6.88	2.52		28.87	4.77		4.53	3.01		24.86	3.65	
Combination HT	9.03	3.22		38.76	6.44		2.37	3.84		18.23	4.80	
FSH	−0.02	0.02	0.480	−0.02	0.04	0.607	0.01	0.03	0.821	−0.01	0.04	0.815

FMD; flow-mediated dilatation of brachial artery, NMD; nitroglycerin-mediated dilatation of brachial artery, BMI; body mass index, LDL; low density lipoprotein cholesterol, GHbA1C; glycosylated haemoglobin A1C, SBP; systolic blood pressure, ODI$_4$; arterial oxyhaemoglobin desaturation of 4 % units or more.HT; hormone therapy, FSH; follicle stimulating hormone.

[a] HT and smoking are presented as adjusted mean with standard error (SE), while all the other values are adjusted regression coefficient β with standard error (SE).

Table 4
Effect of cardiovascular risk factors on vascular function at the 10-year follow-up.

10 year follow-up risk factors	10 year follow-up					
	FMD			NMD		
	β	SE	p	β	SE	p
BMI	−0.09	0.10	0.333	−0.22	0.16	0.185
LDL	−0.56	0.62	0.367	−1.40	1.12	0.218
GHbA1c	0.00	0.08	0.970	−0.09	0.16	0.596
SBP	−0.04	0.03	0.136	−0.07	0.05	0.173
ODI$_4$	0.04	0.05	0.409	0.16	0.08	0.054
Smoking[a]			N/A			N/A
HT[b]			0.161			0.882
No HT	5.19	0.55		26.17	1.02	
ET	1.63	1.89		28.00	3.52	
Combination HT	5.95	1.34		26.62	2.21	
FSH	−0.03	0.02	0.097	0.00	0.03	0.988

FMD; flow-mediated dilatation of brachial artery, NMD; nitroglycerin-mediated dilatation of brachial artery, BMI; body mass index, LDL; low density lipoprotein cholesterol, GHbA1C; glycosylated haemoglobin A1C, SBP; systolic blood pressure, ODI$_4$; arterial oxyhaemoglobin desaturation of 4 % units or more.HT; hormone therapy, FSH; follicle stimulating hormone.

[a] Too few smokers ($n = 2$) for linear model.

[b] HT is presented as adjusted mean with standard error (SE), while all the other values are adjusted regression coefficient β with standard error (SE).

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Research data (data sharing and collaboration)

There are no linked data sets for this paper. Data will be made available upon reasonable request.

Declaration of competing interest

The authors declare that they have no competing interest.

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