Early signs of sleep-disordered breathing in healthy women predict carotid intima-media thickening after 10 years

Nea Kalleinen [a, b, *], Tarja Saaresranta [b, c], Olli Polo [d], Olli T. Raitakari [e, f, g], Markus Riskumäki [h], Tero Vahlberg [h], Jenni Aittokallio [b, i, j]

[a] Heart Center, Turku University Hospital and University of Turku, Turku, Finland
[b] Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Turku, Finland
[c] Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and University of Turku, Finland
[d] Bragée ME/CFS Center, Stockholm, Sweden
[e] Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland
[f] Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland
[g] Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland
[h] Biostatistics, Department of Clinical Medicine, University of Turku, Turku, Finland
[i] Department of Anesthesiology and Intensive Care, Turku University Hospital and University of Turku University of Turku, Turku, Finland
[j] Division of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, Turku, Finland

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of death in women. The risk of CVD increases in women after menopause. The aim was to study how sleep parameters and cardiovascular risk factors in 46-year-old women predict future carotid intima-media thickness (IMT) 10 years after.
Methods: Prospective study of 92 healthy women, aged 46 years, were studied at baseline and at 10-year follow-up. Polysomnography for sleep and breathing; blood samples for cholesterol, glucose and follicle stimulating hormone; blood pressure (BP), weight and height measurements; questionnaires for background variables and vasomotor symptoms were carried out at both time points. Carotid ultrasound was scanned for IMT at 10-year follow-up.
Results: After adjusting for conventional risk factors, apnea-hypopnea index (AHI) during rapid-eye-movement (REM) sleep was the only parameter at baseline that predicted IMT 10 years after (IMT mean: β 81.4 [95% CI, 14.0−148.8]; IMT max: β 104.7 [95% CI, 15.4−194.1]). At 10-year follow-up, higher arousal index (IMT mean: β 55.6 [95% CI, 19.5−91.8]; IMT max β 59.9 [95% CI, 11.4−108.4]) and lower vasomotor symptoms (IMT max: β −60.5 [95% CI, −119.0 to −2.0]) were associated with concurrent higher IMT. The conventional risk factors at baseline did not associate with future IMT but 10 years after higher concurrent HbA1c (IMT mean: β 11.0 [95% CI, 3.4−18.5]; IMT max β 14.0 [95% CI, 4.1−23.8]) and systolic BP (IMT mean: β 2.4 [95% CI, 1.1−3.7]; IMT max: β 2.7 [95% CI, 1.03 to 4.53]) were associated with higher IMT.
Conclusions: In healthy 46-year-old women, AHI during REM sleep predicted IMT 10 years after. The conventional risk factors (HbA1c and BP) only associated with the concurrent IMT at 10-year follow-up.

Clinical trial registration

This trial was not registered because enrollment began prior to July 1, 2005.

* Corresponding author. Heart Center, Turku University Hospital, P.O. Box 52, 20521, Turku, Finland.
E-mail address: nea.kalleinen@utu.fi (N. Kalleinen).

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in women, and there has been an alarming stagnation in the reduction of CVD burden in women during the past decade. According to the recent release from the Lancet women and cardiovascular disease Commission, cardiovascular disease in women remains under-studied, under-recognized, underdiagnosed and undertreated. The risk of CVD in women accelerates after menopause [1]. Menopause

is determined by permanent cessation of menstruation resulting from the loss of ovarian function. Estrogen deficiency is thought to be one of the causes for the increased risk of CVD in post-menopausal women [2].

Sleep-disordered breathing (SDB), especially obstructive sleep apnea (OSA), is associated with increased CVD risk [3]. The severity of SDB is determined by apnea-hypopnea index (AHI) but other measures such as nocturnal hypoxic burden [4] or AHI during REM sleep [5] might be critical in determining the risk of CVD in SDB patients. AHI and oxyhemoglobin desaturation index (ODI_4) in OSA patients as well as snoring in women are associated with carotid intima-media thickness (IMT) [6–9]. Increased carotid IMT, a marker of subclinical CVD, is a potent predictor of future vascular events, even if adjusted for other risk factors [10].

Premenopausal systolic blood pressure (SBP), low-density lipoprotein (LDL) cholesterol and body mass index (BMI) [11] as well as sleep duration and subjective sleep quality [12] have been shown to predict postmenopausal IMT. Moreover, menopausal vasomotor symptoms are linked to CVD risk factors, including higher IMT [13,14], and also to increased risk of later CVD events [15]. Less is known about the effect of premenopausal SDB or sleep architecture on future IMT. Therefore, we followed healthy 46 years old women for 10 years and studied their sleep and breathing with polysomnography (PSG) and cardiovascular (CV) risk factors with blood samples, BMI and blood pressure measurements. Examinations were performed at baseline and after 10 years of follow-up. The aim of the study was to investigate the association between early baseline sleep parameters and CV risk factors, and the IMT measured at 10-year follow-up. We hypothesized that early signs of SDB at baseline would predict higher IMT 10 years after.

2. Materials and methods

This was a part of a larger prospective study "Woman 46" investigating sleep and cardiovascular risk factors in middle-aged women. Altogether 147 healthy women of 46 years of age were recruited using newspaper announcements. Individuals with coronary heart disease, respiratory insufficiency, sleep apnea, neurological disease, liver disease, malignancies or alcohol abuse were excluded. The women were restudied 10 years later. This study included all 92 women who had all required measurements at both time points, at baseline and at 10-year follow-up. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland. All subjects signed a written informed consent.

At baseline, menstruating women were studied at the beginning of their follicular phase (days 1–7 of the menstrual cycle). The blood sample for S-FSH, HbA1c and cholesterol measurements were taken in the morning on the day of the sleep study. Height, weight and blood pressure were measured in the evening before sleep study. Other background variables were assessed with questionnaires. Vasomotor symptoms during the past 6 months were scored with two questions (night sweats and hot flashes). The frequency of the symptoms was determined on a four-point scale: one ("seldom or never"), two ("approx. once a month"), three ("approx. once a week"), and four ("almost every day"). The vasomotor symptom score was the sum of these two answers. The study protocol was repeated identically at the 10-year follow-up with the addition of an ultrasound study to measure IMT in the morning following the overnight recordings.

From the total of 92 women 4 women were categorized as late perimenopausal determined by FSH (30 IU/l $\geq$ FSH $\geq$25 IU/l) and 10 women postmenopausal (FSH $\geq$30 IU/l) at baseline [16]. The rest of the women were premenopausal or early perimenopausal. One of the women was using menopausal hormone therapy at baseline. At the 10-year follow-up all women were postmenopausal and 23 of

them were using menopausal hormone therapy. Four (4,3%) of the women at baseline, and 5 (5,4%) at the follow-up used sedatives, hypnotics or antidepressants regular basis.

2.1. Sleep studies

PSG recordings at baseline and at 10-year follow-up were carried out in the sleep laboratory of The Turku Sleep Research Centre. They consisted of continuous monitoring of electroencephalograms (EEG; C3/A2, C4/A1, O1/A2 and O2/A1), two electrooculograms and a mandibular electromyogram (Embla®, Medcare Flaga hf. Medical Devices, Reykjavik, Iceland). Nasal prongs connected to a pressure transducer were used to measure nasal inspiratory airflow. Arterial oxyhemoglobin saturation (SaO_2) was measured with a finger probe pulse oximeter (Nonin® oximeter built in with Embla®/Somnologica system; MedcareFlaga hf, Reykjavik, Iceland). The recordings were visually scored in 30 s epochs off-line by an experienced technician according to conventional R–K criteria [17]. Five sleep stages [stage 1 (S1), stage 2 (S2), stage 3 and 4 (S3 and S4, SWS) and REM sleep], as well as wake after sleep onset (WASO) were classified. Sleep stages were expressed as percentages of total sleep time and WASO as minutes. The American Academy of Sleep Medicine (AASM) criteria were not used since they were not published at the time of the study initiation [18]. Arousal index was the sum of awakenings and arousals per hour. An awakening was determined as entering a wake stage from sleep and the criteria of the American Sleep Disorders Association were used to score arousals [19].

AHI was scored visually. Reduction of at least 90% in airflow (amplitude of the nasal flow signal) for at least 10 s was classified as apnea and hypopneas were defined as a minimum reduction of 30% in airflow for at least 10 s accompanied by a 4% desaturation before the event. The mean and minimum SaO_2 levels, percentage of SaO_2 below 90% and the arterial oxyhemoglobin desaturation events of 4% units or more per hour (ODI_4) were calculated with the Embla®/Somnologica system after manual removing the possible artifacts.

2.2. Intima media thickness of carotid artery

Carotid ultrasound scans were performed during the 10-year follow-up in the morning following the overnight recordings. IMT was assessed of the left common carotid wall 1–2 cm proximal to the carotid bulb. The common carotid artery wall was scanned longitudinally, and IMT was measured at the site of the far wall. Measurements were taken four to eight times and the average values were used for the predictive modelling. The ultrasound equipment used was an Acuson Sequoia 512 (Acuson Inc., Mountain View, CA, USA) ultrasonography with 13 MHz linear array transducer. Ultrasound scans were performed by experienced operators unaware of the results of the overnight recordings.

2.3. Statistical methods

After manual curation of the database, the data was transformed to IBM SPSS® System for Mac version 27 (IBM Corp., Armonk, NY) for statistical analyses. The changes in continuous variables between baseline and 10-year follow-up were analyzed with paired-sample t-test for normally distributed variables and with Wilcoxon signed-rank test for non-normally distributed variables. For categorical variables McNemars test was used for testing the differences between baseline and 10-year follow-up.

Linear regression model was used to test the association between the sleep parameters and IMT. The regression model was adjusted for age, HbA1c, SBP, LDL cholesterol, BMI and smoking. If a variable was not normally distributed, logarithmic-transformed

Table 1
Patient characteristics at baseline and at 10-year follow-up.

Characteristics	Baseline n = 92	10-year FU n = 92	p
Age, mean (SD), years	46.0 (0.9)	56.9 (1.1)	
FSH, mean (SD), IU/l	14.1 (16.5)	66.5 (28.4)	<0.001
HbA1C, mean (SD), %	36 (2.0)	34 (2.0)	0.071
Total Chol, mean (SD), mmol/l	5.3 (0.8)	5.6 (0.9)	<0.001
LDL Chol, mean (SD), mmol/l	3.0 (0.7)	3.2 (0.8)	0.028
BMI, mean (SD), kg/m^2	26.4 (5.3)	29.1 (6.5)	<0.001
Waist, mean (SD), cm	85.8 (13.0)	96.4 (15.1)	<0.001
SBP, mean (SD), mmHg	125.7 (14.0)	135.2 (18.1)	<0.001
Smoking, n (%)	15 (16.3)	7 (7.6)	0.005
Menopausal hormone therapy, n (%)	1 (1.1)	7 (7.6)	0.034
Total sleep time, median (IQR), min	390.0 (342.0–420.3)	363.0 (323.5–395.5)	0.006
WASO, median (IQR), min	43.9 (23.0–84.0)	69.0 (41.5–105.0)	0.003
REM, mean (SD), min	71.7 (29.6)	63.7 (24.3)	0.014
SWS, mean (SD), min	73.0 (50.7)	94.7 (29.6)	<0.001
AHI, median (IQR), 1/h	2.4 (0.9–4.9)	5.1 (2.3–16.2)	<0.001
ODI$_4$, median (IQR), 1/h	2.0 (0.6–4.3)	4.2 (1.2–10.5)	<0.001
REM AHI, median (IQR), 1/h	5.3 (1.5–15.1)	13.6 (2.2–35.0)	<0.001
Time SaO$_2$ < 90, median (IQR), %	0.0 (0.0–0.2)	0.1 (0.0–0.6)	0.001
Arousal index, median (IQR), 1/h	4.1 (2.0–6.2)	9.1 (6.1–14.3)	<0.001
Vasomotor symptom score, median (IQR)	2.0 (2.0–4.0)	2.0 (2.0–5.0)	0.003
IMT mean, mean (SD), μm		538.5 (126.5)	
IMT max, mean (SD), μm		631.4 (163.2)	

The numbers are means (SD, standard deviation) or median (IQR, interquartal range) and for categorical variables (Menopausal hormone therapy and Smoking), n (%). FU, follow-up; FSH, follicle stimulating hormone; HbA1C, hemoglobin A1C, Chol, cholesterol; LDL, low density lipoprotein; BMI, body mass index; SBP, systolic blood pressure; WASO, wake time after sleep onset; REM, rapid-eye-movement sleep; SWS, slow wave sleep; AHI, apnea-hypopnea index; ODI$_4$, oxyhemoglobin desaturation index; SaO$_2$, oxyhemoglobin saturation; IMT, intima-media thickness.

Table 2
Association of baseline sleep variables (at the age of 46) and carotid intima-media thickness (μm) after 10 years (at the age of 56).

Baseline Sleep Variables	IMT mean			IMT max		
	β	95% CI	P	β	95% CI	p
AHI (1/h)	52.27	−8.92–113.46	0.093	68.45	−10.22–147.12	0.087
REM AHI (1/h)	81.43	14.04–148.83	**0.019**	104.72	15.40–194.05	**0.022**
ODI$_4$ (1/h)	25.32	−45.88–96.52	0.480	35.23	−57.78–128.24	0.452
Time SaO$_2$ < 90% (%)	−21.05	−94.70–52.60	0.565	−19.13	−123.65–85.40	0.712
Total sleep time (min)	70.28	−175.3–315.85	0.571	87.93	−229.49–405.35	0.583
WASO (min)	−4.31	−65.02–56.41	0.888	−9.39	−87.85–69.06	0.812
SWS (min)	0.023	−0.52–0.57	0.932	0.011	−0.69–0.71	0.976
REM (min)	−0.211	−1.16–0.74	0.659	−0.125	−1.35–1.10	0.840
Arousal index (1/h)	45.10	−31.05–121.24	0.242	52.64	−37.58–142.86	0.249
Vasomotor symptom score	49.13	−113.49–211.74	0.550	61.11	−149.10–271.31	0.565

Adjusted for Age, HbA1C, SBP, LDL cholesterol, BMI and Smoking at baseline. Betas are reported per 1-unit increase in sleep variable. Logaritmic-transformed variables: AHI, REM AHI, ODI$_4$, SaO$_2$ < 90%, Total sleep time, WASO, Arousal index and Vasomotor symptom score. IMT, intima-media thickness; AHI, apnea-hypopnea index; REM, rapid-eye-movement sleep; ODI$_4$, oxyhemoglobin desaturation index; SaO$_2$, oxyhemoglobin saturation; WASO, wake time after sleep onset; SWS, slow wave sleep.

variable transformation was used in regression model. All statistical tests were two-sided and a significance level of 0.05 was used.

3. Results

During the 10 years of follow-up, serum concentrations of FSH, total cholesterol and LDL cholesterol as well as BMI, waist circumference and SBP increased and the use of menopausal hormone therapy became more common. The low number of smokers at the baseline decreased further in 10 years. There was no change in HbA1c. The sleep parameters and breathing during sleep also altered during the 10-years of follow-up: total sleep time and REM sleep decreased, while WASO, SWS, AHI, ODI4, REM AHI, time in SaO$_2$ < 90% and arousal index as well as vasomotor symptom score increased (Table 1). At baseline, eight individuals were treated for hypertension medication but none for hypercholesterolemia. At 10-year follow-up seven individuals were treated for hypertension and seven for hypercholesterolemia.

According to the linear regression model, higher REM AHI values at baseline were associated with higher IMT values (both mean and

max) 10 years after. No other overnight variable or vasomotor symptom score at baseline was associated with the IMT values at 10-year follow-up (Table 2). At 10-year follow-up, the concurrent higher arousal index was associated with higher IMT mean and maximum values. In addition, higher vasomotor symptom score was associated to lower IMT maximum values (Table 3). Adjusting the model for FSH did not alter the results.

Linear regression was also used to test if any of the conventional CVD risk factors (the parameters used to adjust the original linear regression model) were associated with IMT of the follow-up either at baseline or at 10-year follow-up. At baseline, no association between the traditional risk factors and future IMT mean of maximum values was found. At 10-year follow-up, higher HbA1c and SBP were associated with higher concurrent mean IMT and higher concurrent IMT maximum values (Table 4).

4. Discussion

Our study on women showed that after controlling for the conventional CV risk factors (age, diabetes, SBP, cholesterol, BMI

Table 3
Association of sleep variables and intima-media thickness (µm) in women at 10-year follow-up (at the age of 56).

Follow-up Sleep Variables	IMT mean			IMT max		
	β	95% CI	p	β	95% CI	p
AHI (1/h)	28.80	−2.17–59.76	0.068	38.33	−2.46–79.11	0.065
REM AHI (1/h)	13.58	−6.85–43.01	0.190	14.71	−12.31–41.73	0.282
ODI_4 (1/h)	11.65	−15.99–39.29	0.404	14.51	−21.94–50.95	0.431
Time SaO_2 < 90% (%)	15.78	−24.71–56.27	0.441	22.31	−31.02–75.63	0.408
Total sleep time (min)	−43.11	−158.17–71.94	0.458	−42.42	−194.25–109.41	0.580
WASO (min)	26.99	−9.70–63.68	0.147	28.46	−20.10–77.03	0.247
SWS (min)	−0.77	−1.58–0.05	0.064	−0.77	−1.84–0.31	0.160
REM (min)	−2.06	−6.40–2.30	0.349	−3.38	−9.53–1.87	0.185
Arousal index (1/h)	55.65	19.50–91.79	**0.003**	59.92	11.42–108.42	**0.016**
Vasomotor symptom score	−37.47	−82.01–7.08	0.098	−60.51	−119.00–−2.02	**0.043**

Adjusted for Age, GHbA1C, SBP, LDL cholesterol, BMI and Smoking at 10-year follow-up. Betas are reported per 1-unit increase in sleep variable. Logaritmic-transformed variables: AHI, REM AHI, ODI_4, SaO_2 < 90%, Total sleep time, WASO, Arousal index and Vasomotor symptom score. IMT, intima-media thickness; AHI, apnea-hypopnea index; REM, rapid-eye-movement sleep; ODI_4, oxyhemoglobin desaturation index; SaO_2, oxyhemoglobin saturation; WASO, wake time after sleep onset; SWS, slow wave sleep.

Table 4
Association of cardiovascular risk factors with IMT (µm) at 10-year follow-up.

Baseline (age 46 years)	IMT mean			IMT max		
	β	95% CI	p	β	95% CI	p
HbA1C	−1.42	−9.71–6.86	0.733	−2.28	−12.97–8.41	0.672
LDL cholesterol	15.92	−23.47–55.44	0.423	11.55	−39.36–62.46	0.653
BMI	1.49	−3.91–6.88	0.585	4.13	−2.83–11.09	0.242
SBP	0.58	−1.54–2.71	0.585	0.66	−2.08–3.39	0.634
Smoking	39.22	−34.63–113.07	0.294	35.17	−60.12–130.46	0.465
Follow-up (age 56 years)						
HbA1C	10.96	3.44–18.47	**0.005**	13.96	4.10–23.83	**0.006**
LDL cholesterol	−7.10	−36.65–22.45	0.634	−8.45	−47.27–30.36	0.666
BMI	−1.04	−4.99–2.90	0.600	−0.26	−5.45–4.93	0.920
SBP	2.44	1.11–3.77	**<0.001**	2.78	1.03–4.53	**0.002**
Smoking	41.75	−0.48–83.98	0.053	44.82	−10.66–100.29	0.112

IMT, intima media thickness; HbA1C, haemoglobin A1C; LDL, low density lipoprotein; BMI, body mass index; SBP, systolic blood pressure.

and smoking), SDB during REM sleep in 46-year-old women predicted higher carotid IMT 10 years later. Meanwhile, the conventional CV risk factors at baseline were not able to predict future IMT. At the 10-year follow-up, higher concurrent HbA1c and SBP as well as higher arousal index and lower vasomotor symptom score were associated with higher IMT. The results suggest that breathing during sleep is related to the future CV health even in healthy women.

CVD is the leading cause of death in men and women in developed countries but in contrast to the continuously decreasing mortality rates seen in men, the decline in women seems to be slowing down or even stagnating during the past decade [1]. The fact that women tend to get CVD 10 years later than men explains some part of the difference but not all. Possible causes for worse prognosis in women include delays in recognizing symptoms, underutilization of diagnostic tests and treatments, as well as anatomic, physiological, and genetic factors [20]. As the recent article from the Lancet women and cardiovascular disease Commission emphasized, further research is urgently needed on CVD in women to better elucidate underlying sex-specific pathophysiology and biological differences [1]. Coronary heart disease symptoms also tend to be atypical in women, emphasizing the importance of primary prevention for reducing morbidity.

Previous studies on women have shown that premenopausal systolic and pulse pressure, LDL and HDL cholesterol, triglycerides, and BMI predict higher carotid IMT and atherosclerotic plaque later in postmenopause [11]. In addition to these conventional CVD risk factors, SDB is linked to higher IMT both in men and women [7,8]. SDB during REM sleep is more common in women but it is shown to decrease with age as NREM SDB increases [21]. In our study, REM-AHI seemed to be the only predictor of later risk of higher IMT, thus

reflecting higher risk of CVD, in healthy premenopausal or early postmenopausal women. The conventional risk markers, such as LDL cholesterol, HbA1c and SBP at baseline did not have any association to later IMT. At the 10-year follow-up, there was no association of REM-AHI with concurrent IMT but concurrent higher HbA1c and SBP were linked to IMT. SBP increased from baseline to follow-up but HbA1c did not change, thus the differences in associations at baseline and follow-up cannot be completely explained by marked increases in the conventional risk factors. It must be underscored that the IMT values were relatively low in our study and no atherosclerotic plaques were detected, which could have been reflected in the lack of associations compared to previous studies [11]. It could also be argued that the conventional risk factors become more dominant after menopause with the loss of the protective effect of estrogen, whereas the premenopausal REM-AHI could be an early sign of a disease process leading to CVD later in life.

REM sleep accounts for approximately 20–25% of the sleep time and predominates in the morning hours. Unlike NREM sleep, REM sleep is associated with marked hemodynamic variability, an increase in sympathetic activity and an increased propensity for upper airway collapse [22,23]. SDB events during REM sleep tend to be longer, more frequent and associated with greater oxyhemoglobin desaturation as the respiratory effort in response to upper airway collapse is lower compared to those during NREM sleep [24,25]. CPAP therapy adherence covering also the morning hours of REM sleep is therefore of importance in treating symptomatic patients. SDB during REM sleep has been independently associated with hypertension and impairments in glucose metabolism [26]. Moreover, recent data show that REM-AHI > 30/h is associated with higher incidence of CV endpoints in people with prevalent CVD [5].

Cardiovascular events in general are more common in the morning hours. It is therefore possible that cardiovascular circadian rhythms [27] make the cardiovascular system more vulnerable to concurrent detrimental effects of REM sleep apneas and hypopneas in the morning hours. Even though AHI and REM-AHI increased during our follow-up, the frequency remained relatively low in our healthy population. Therefore, premenopausal REM-AHI is more likely a marker of an underlying disease process than the disease mechanism per se.

Previous data show sex differences in the upper airway, fat distribution, and respiratory stability in OSA. Female SDB is characterized by a lower AHI, shorter episodes of apnea, hypopnea or upper airway resistance that do not meet the criteria for apnea episodes [28]. Objectively measured snoring has also been linked to higher IMT in non-apneic women but not in men [8]. The clinical and prognostic relevance of AHI itself has been questioned lately both in men and women. Especially for the CVD risk or for the positive outcome of SDB treatment, hypoxemic burden [4], REM-AHI [5] and symptoms of sleepiness [29] are suggested to be more determining. In OSA patients, it is also shown that arousal index has an independent association with higher concurrent IMT [9]. We studied mainly healthy women with low AHI but we were able to demonstrate a link between higher concurrent arousal index and higher IMT at follow-up. AHI, arousal index and vasomotor symptom score can interfere with each other. In contrast to previous research showing linkage between vasomotor symptoms and CVD [14,15,30], we found an association between lower vasomotor symptom score and concurrent higher IMT at follow-up. However, this association was not strong in our sample of 92 women and could have emerged by chance or been interfered with the menopausal hormone therapy use of 23 individuals. It should be noted that even if AHI, arousal index and vasomotor score increased in follow-up, they remained at relative low level, most often without clinical significance. More importantly, their baseline values did not demonstrate any predictive importance for IMT 10 years after.

The main strength of the current study is the longitudinal setting with a follow-up of 10 years. However, there are also some limitations. First, the number of our study participants is lower than in some previous studies although also comparable to some others [7—9]. With a larger study population, the association between baseline AHI and later IMT might have reached significance but for other parameters the results would most likely have stayed unchanged, judging by the raw data. Second, the frequency of vasomotor symptoms was assessed with a questionnaire covering the past 6 months before the sleep study and vasomotor symptoms were not objectively measured. Third, the women were in slightly different phases of premenopause judging by FSH at baseline. Although limited usage, menopausal hormone therapy was not controlled. However, the use of menopausal hormone therapy, sedatives or antidepressants was rather limited. In addition, one major limitation of the study is the lack of baseline IMT measurements. Unfortunately, baseline IMT measurements could not be used in our study as they were not comparable with follow-up measurements due to the rapid technical development of ultrasonic transducers, as their accuracy have evolved remarkably. Finally, we included healthy women to see potential early phenomena of developing CVD. The observed associations could be different in patient populations with initially presenting risk factors of significant co-morbidity.

5. Conclusions

REM-AHI in healthy women before menopause predicts future IMT over conventional risk factors. Our findings further suggest that early changes in SDB uncover hidden disease processes that may later result in CVD. Early risk factor detection is of importance when targeting primary preventive measure of CVD in menopausal transition.

Credit author statement

NK contributed to the design of this study, took part in the acquisition and management of the data, conducted the literature search and the article screening, interpreted the data and drafted the manuscript. TA and OP designed the Nainen46 study and together with OTR provided administrative and material support. MR and TR provided support in statistical work and interpretation of the data. JA contributed to the design of this study, performed the statistical analyses, interpreted the data and contributed to the to the acquisition and management of the data. NK, TA, OP, OTR and JA contributed to discussion. All authors critically read the manuscript and approved it.

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