Author(s): Hyvärinen, Matti; Karvanen, Juha; Juppi, Hanna-Kaarina; Karppinen, Jari E.; Tammelin, Tuija H.; Kovanen, Vuokko; Aukee, Pauliina; Sipilä, Sarianna; Rantalainen, Timo; Laakkonen, Eija K.

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Original article

Menopausal symptoms and cardiometabolic risk factors in middle-aged women: A cross-sectional and longitudinal study with 4-year follow-up

Matti Hyvärinen [a,*], Juha Karvanen [b], Hanna-Kaarina Juppi [a], Jari E. Karppinen [c], Tuija H. Tammelin [d], Vuokko Kovanen [c], Pauliina Aukee [e], Sarianna Sipilä [a], Timo Rantalainen [a], Eija K. Laakkonen [a]

[a] Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, P.O. Box 35, 40014, Finland
[b] Department of Mathematics and Statistics, University of Jyväskylä, P.O. Box 35, 40014, Finland
[c] Faculty of Sport and Health Sciences, University of Jyväskylä, P.O. Box 35, 40014, Finland
[d] LIKES, JAMK University of Applied Sciences, Piippukatu 2, 40100 Jyväskylä, Finland
[e] Department of Obstetrics and Gynecology, The Wellbeing Services County of Central Finland, 40620 Jyväskylä, Finland

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ABSTRACT

Objective: To study associations of menopausal symptoms with cardiometabolic risk factors.
Study design: A cross-sectional and longitudinal study of a representative population sample of 1393 women aged 47–55 years with a sub-sample of 298 followed for four years. The numbers of vasomotor, psychological, somatic or pain, and urogenital menopausal symptoms were ascertained at baseline through self-report. Their associations with cardiometabolic risk factors were studied using linear regression and linear mixed-effect models. Models were adjusted for age, menopausal status, body mass index, the use of hormonal preparations, education, smoking, and alcohol consumption.
Main outcome measures: Cardiometabolic risk factors included total cholesterol, low-density and high-density lipoprotein cholesterol, blood pressure, glucose, triglycerides, total and android fat mass, and physical activity.
Results: All cholesterol and fat mass measures had modest positive associations with menopausal symptoms. The number of vasomotor symptoms, in particular, was associated with total cholesterol (B = 0.13 mmol/l, 95 % CI [0.07, 0.20]; 0.15 mmol/l [0.02, 0.28]) and low-density lipoprotein cholesterol (0.08 mmol/l [0.03, 0.14]; 0.12 mmol/l [0.01, 0.09]) in cross-sectional and longitudinal analyses, respectively. However, these associations disappeared after adjusting for confounders. The number of symptoms was not associated with blood pressure, glucose, triglycerides, and physical activity. Menopausal symptoms at baseline did not predict the changes in the risk factors during the follow-up.
Conclusions: Menopausal symptoms may not be independently associated with cardiometabolic risk, and they do not seem to predict the changes in risk factors during the menopausal transition.

1. Introduction

The menopausal transition marks the time in women's life characterized by the hormonal changes including decrease in systemic estradiol (E2) and increase in follicle-stimulating hormone (FSH) levels, and it has been linked to adverse metabolic changes and a significant increase in the risk of cardiovascular disease [1]. During the menopausal transition, women experience various symptoms, such as sleep disturbances, depression, anxiety, sexual dysfunction, and vasomotor symptoms (VMS) including hot flushes and night sweats [2].

The incidence of cardiovascular disease and metabolic syndrome increases during the menopausal transition [3,4]. This is at least partially due to the unfavorable changes in cardiometabolic disease (CMD) risk factors that are independent of the effect of aging [5,6]. For instance, the menopausal transition has been associated with an increase in blood lipids, blood glucose, blood pressure, and total and abdominal

* Corresponding author at: Faculty of Sport and Health Sciences, University of Jyväskylä, P.O. Box 35 (LL232), 40014, Finland.
E-mail addresses: matti.v.hyvarinen@jyu.fi (M. Hyvärinen), juha.t.karvanen@jyu.fi (J. Karvanen), hanna.k.juppi@jyu.fi (H.-K. Juppi), jari.e.j.karppinen@jyu.fi (J.E. Karppinen), tuija.tammelin@jamk.fi (T.H. Tammelin), pauliina.aukee@hyvaks.fi (P. Aukee), sarianna.sipila@jyu.fi (S. Sipilä), timo.rantalainen@jyu.fi (T. Rantalainen), eija.k.laakkonen@jyu.fi (E.K. Laakkonen).

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fat mass [5,6]. As CMD is one of the leading causes of death in women [3], the early identification of individuals with highlighted risk of developing CMD after menopause could have significant clinical and public health implications.

Menopausal symptoms have been associated with increased CMD risk. This association may differ with age and is mainly explained by the unfavorable risk factor profile in symptomatic women [7–9]. However, it is still unclear whether menopausal symptoms are an independent risk factor for metabolic syndrome [10]. Furthermore, the link between menopausal symptoms and CMD risk is mostly derived from cross-sectional studies, highlighting the need for longitudinal studies on this topic [9–11]. Only one previous study with three different sub-studies has explored longitudinal changes in CMD risk factors during the menopausal transition based on the menopausal symptoms and the focus of those studies was only on the VMS [12–14].

The objective of this study was to investigate the associations of diverse menopausal symptoms with CMD risk factors in cross-sectional and longitudinal study designs. The risk factors of interest included several blood-based biomarkers, blood pressure, and measures of body composition and physical activity. The focus of the study was to explore if the prevalence of menopausal symptoms could be used to predict future cardiometabolic health in middle-aged women.

2. Materials and methods

2.1. Study design and population

This observational study was part of the Estrogenic regulation of Muscle Apoptosis (ERMA) and its follow-up the Estrogen MicroRNAs and the risk of Metabolic Dysfunction (EsmiRs) study (dataset: 10.17011/jyx/dataset/83491). The baseline measurements in ERMA were conducted in 2015–2016. The follow-up measurements in EsmiRs were initiated at the beginning of 2019, and they were discontinued on March 16, 2020 due to the pandemic. The studies were performed in accordance with the Declaration of Helsinki, and they were approved by the ethical committee of the Central Finland Health Care District. All participants provided written informed consent.

The participant selection procedures for both cross-sectional [15] and longitudinal [6] parts of the study have been described elsewhere. Briefly, 1393 women aged 47–55 years living in the Central Finland participated in the baseline ERMA measurements. The ERMA exclusion criteria included conditions affecting ovarian function, systemic hormone levels or inflammatory status, such as bilateral oophorectomy, pregnancy, lactating and severe obesity (self-reported body mass index (BMI) $\geq 35\ kg/m^2$). Additionally, participants using estrogen-containing medications and continuous cortisone or inflammatory drug treatment were excluded. The loss of participants during the study is illustrated in Fig. 1.

The cross-sectional analyses of the study were carried out using the data from the ERMA baseline measurement (n = 1393), and the longitudinal analyses utilize data from the ERMA baseline and EsmiRs 4-year follow-up measurements (n = 298). Menopausal symptoms were only assessed at baseline, but all other covariates of the study are assessed in both time points.

2.2. Menopausal symptoms

At baseline, participants were asked to report if they had experienced any of the symptoms related to menopause based on the list of 10 predetermined symptoms (Table 1) [15,16]. The questionnaire also included the option to describe a maximum of three additional symptoms [15]. Reported symptoms were classified into four categories (vasomotor, psychological, somatic or pain, and urogenital) [16]. To consider the quantity of the distinct symptoms as well as the prevalence

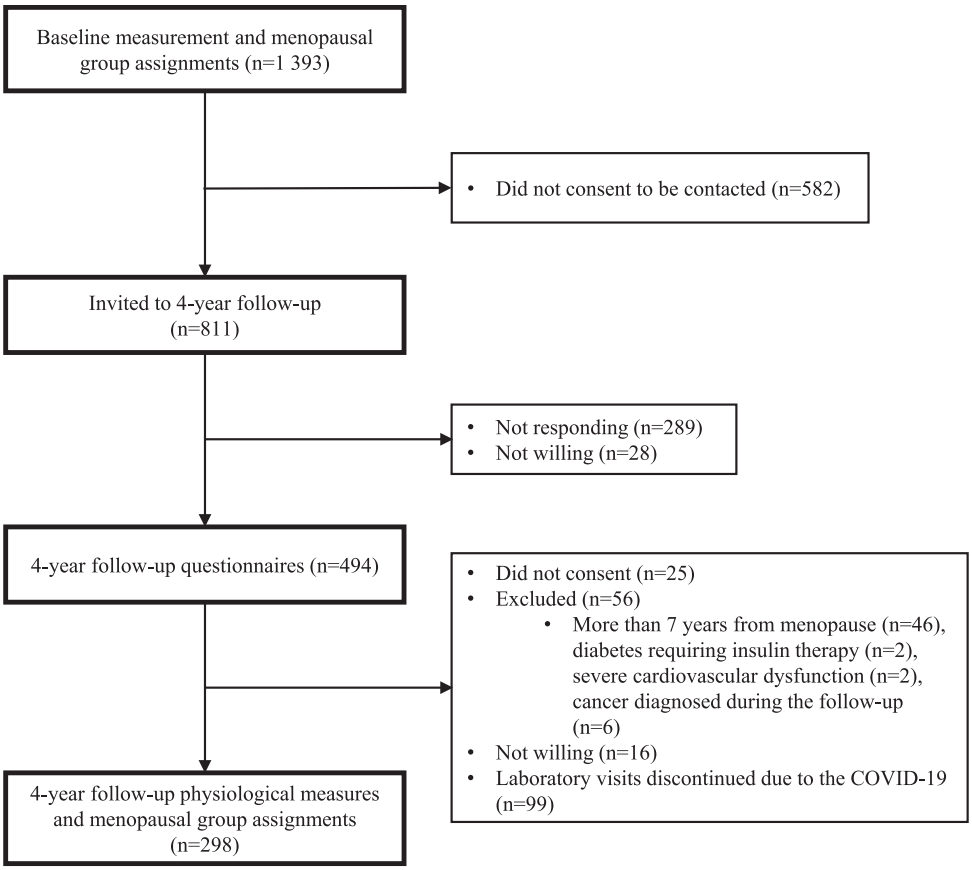

Fig. 1. The flow chart of the study.

Table 1
Classification of menopausal symptoms.

Symptom category (maximum number of symptoms[a])	Symptoms included in the questionnaire	Additional self-described symptoms
Vasomotor symptoms (3)	Sweating Hot flashes	Cold flashes Heart palpations Coldness
Psychological symptoms (4)	Sleeplessness Tiredness Mood swings	Memory problems Irritability Inability to concentrate Weepiness
Somatic or pain symptoms (3)	Headache Aching joints	Stomach pain Migraine Hip pain Muscle pain Breast pain Dizziness Swelling Weakness
Urogenital symptoms (4)	Vaginal symptoms Urinary tract symptoms Lack of sexual desire	Vaginal infection Urinary tract infection Vaginal dryness

[a] The number of symptoms was determined as the sum of all reported predetermined symptoms in each category with one additional symptom for participants who reported one or more additional self-described symptoms in that category.

of the symptoms, the number of reported symptoms in each category was determined.

2.3. Cardiometabolic risk factors

Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glucose, and triglycerides were measured from the serum samples using KONELAB 20XTi analyzer (Thermo Fischer Scientific, Vantaa, Finland). Blood pressure was measured in a sitting position after a 10-minute rest using Omron M6 Comfort (Omron Healthcare, Kioto, Japan) and the mean value of two measurements was used for systolic (SBP) and diastolic blood pressure (DBP). Total and android fat mass were assessed with dual energy X-ray absorptiometry (DXA; LUNAR, GE Healthcare, Chicago, IL, USA). All measurements were carried out after overnight fasting and during the first five days of the menstrual cycle for participants with a predictable menstrual cycle.

Physical activity was assessed with accelerometers using the mean amplitude deviation method (ACC-MAD). The detailed description of the procedure is described elsewhere [6]. Briefly, participants used hip-worn accelerometers (ActiGraph GT3X and wGT3X; Actigraph LLC, Pensacola, FL, USA) for seven consecutive days during waking hours, except for water-based activities. The data were collected at 60 Hz, and the Euclidian norm of the resultant acceleration was computed for each time point. Finally, mean amplitude deviation values were computed for non-overlapping five-second epochs, and ACC-MAD was computed as their mean value.

2.4. Covariates

Serum concentrations of E2 and FSH were measured using IMMULITE® 2000 XPi (Siemens Healthineers, Erlangen, Germany). Participants were categorized as pre-, peri-, or postmenopausal based on the FSH concentrations and self-reported menstrual bleeding diaries using the adapted Stages of Reproductive Aging Workshop (STRAW +10) guidelines [15]. BMI was calculated using body mass and height measured with standard procedures.

Structured questionnaires were used to assess education (primary or secondary/tertiary), smoking status (non-smoker/smoker) and alcohol consumption in portions per week. The use of hormonal preparations and medications was assessed based on self-reports. Regarding hormonal preparations, the participants were classified as non-user, only progestogen, only estrogen, and combined estrogen and progestogen users. All exogenous sex hormone preparations for contraceptive and hormone therapy use were included, except for the intravaginal local estrogen therapy. The regular prescription medication users were classified using the Anatomical Therapeutic Chemical (ATC) classification separately for participants using preparations affecting serum lipids (ATC C10) and blood pressure (ATC C02-C05 and C07-C09).

2.5. Missing data

The percentage of missing values across the variables varied from 0 to 44 at baseline (n = 1393) and from 0 to 7 at follow-up (n = 298) (Table 2). The missing data values were 7238 out of 43,869 (16 %). Missing data occurred due to invalid or missing measurements and unclear and incomplete questionnaire responses. Missing data were assumed to occur at random and multiple imputation was used to create 50 multiply imputed data sets. Multiple imputation was carried out recursively. That is, baseline values for each variable were imputed first, and the imputed baseline measurement values were then utilized for the imputation of follow-up measurement [17]. Variables measured at the same timepoint and the target variable measurement from the other timepoint were used for the imputation of each variable. The number of iterations for chained equations [18] was set to 50, and passive imputation was used for the derived variable BMI. The model parameters were estimated separately for each data set. Multiple imputation and pooling of the model estimates were carried out in R [19] using the standard settings of the "mice" package [18]. We also performed the complete case analysis and there were no notable differences in the results.

2.6. Statistical analyses

Linear regression models and linear mixed-effect models with random intercept were used for the cross-sectional and longitudinal analyses, respectively. Models were created separately for each CMD risk factor as the outcome variable (total cholesterol, LDL-C, HDL-C, glucose, triglycerides, SBP, DBP, total fat mass, android fat mass, and physical activity). We constructed models both with and without confounders (Model 1 and model 2, respectively). In linear mixed-effect models, the main effect of the menopausal symptoms at baseline, time (0 = baseline, 1 = follow-up), and their interaction was included in all models to study the changes in outcome variable over time based on the menopausal symptoms. The confounding factors in the model 2 were age, BMI, menopausal status, use of hormonal preparations, education, smoking status, and alcohol consumption. However, BMI was not included in the total fat mass and android fat mass models due to its strong association with the outcome variable. We also constructed models that were additionally adjusted with E2 and FSH. Furthermore, the confounding of symptoms from other categories was taken into account by including all symptom categories in the same models as predictors. Finally, we conducted sensitivity analyses for blood lipids and blood pressure by excluding the participants who used lipid modifying agents and antihypertensives, respectively. Residual plots, Q–Q plots, and correlation analysis were used for testing the model assumptions. The analyses were carried out using base R and the "nlme" package [20].

3. Results

3.1. Characteristics of the study population

The characteristics of the study population are shown in Table 2 and Fig. S1. At baseline, percentages of the participants in pre-, peri-, and postmenopausal groups were 28, 34, and 38, respectively. On average,

Table 2
Characteristics of the study population.

	Cross-sectional study	Longitudinal study		
	Baseline	Baseline	Follow-up	Change[a]
Menopausal symptoms[b]	1097	276		
Number of vasomotor symptoms[c]				
No symptoms	41 (454)	49 (135)		
2 or more symptoms	29 (313)	23 (64)		
Number of psychological symptoms[c]				
No symptoms	50 (549)	61 (167)		
2 or more symptoms	28 (305)	22 (61)		
Number of somatic or pain symptoms[c]				
No symptoms	76 (835)	79 (219)		
2 or more symptoms	5 (53)	4 (12)		
Number of urogenital symptoms[c]				
No symptoms	65 (713)	69 (191)		
2 or more symptoms	15 (167)	12 (33)		
Total number of symptoms[c]				
No symptoms	24 (260)	30 (82)		
2 or more symptoms	60 (657)	52 (143)		
Age & menopausal status (n)	1393	298	298	298
Age [years]	51.3 ± 2.1	51.3 ± 1.8	55.1 ± 1.8	3.8 ± 0.2
Menopausal status[c]				
Pre	28 (389)	34 (100)	5 (15)	
Peri	34 (474)	35 (105)	14 (42)	
Post	38 (530)	31 (93)	81 (241)	
Blood-based biomarkers (n)	1393	298	298	298
Estradiol [nmol/l]	0.34 ± 0.41	0.38 ± 0.57	0.26 ± 0.28	−0.12 ± 0.63
Follicle-stimulating hormone [IU/l]	44.0 ± 38.6	39.9 ± 37.1	69.5 ± 37.5	29.5 ± 40.5
Total cholesterol [mmol/l]	5.30 ± 0.91	5.24 ± 0.91	5.67 ± 1.00	0.43 ± 0.88
HDL-C [mmol/l]	1.72 ± 0.46	1.72 ± 0.47	1.91 ± 0.50	0.19 ± 0.39
LDL-C [mmol/l]	3.05 ± 0.80	3.05 ± 0.80	3.41 ± 0.88	0.37 ± 0.76
Glucose [mmol/l]	5.28 ± 0.84	5.15 ± 0.45	5.16 ± 0.62	0.02 ± 0.55
Triglycerides [mmol/l]	1.09 ± 0.72	1.08 ± 0.61	1.27 ± 0.73	0.19 ± 0.53
Dual-energy X-ray absorptiometry (n)	902	244	292	240
Fat mass [kg]	25.0 ± 8.5	24.2 ± 8.4	25.9 ± 9.1	2.0 ± 3.3
Android fat mass [kg]	2.24 ± 0.97	2.14 ± 0.91	2.39 ± 1.01	0.27 ± 0.42
Blood pressure & body mass index (n)	932	249	298	249
Systolic blood pressure [mm Hg]	132.5 ± 17.5	132.0 ± 16.3	133.2 ± 18.3	2.0 ± 13.4
Diastolic blood pressure [mm Hg]	84.5 ± 9.7	84.1 ± 9.2	81.9 ± 10.0	−2.1 ± 6.5
Body mass index [kg/m^2]	25.5 ± 3.7	25.3 ± 3.7	25.8 ± 4.1	0.7 ± 1.4
Accelerometer-measured PA (n)	784	235	283	222
ACC-MAD [mg]	29.2 ± 9.2	30.2 ± 10.0	28.3 ± 8.6	−1.9 ± 7.2
Lifestyle habits & medications (n)	1098	276	298	276
Alcohol consumption [portions/week]	3.82 ± 3.75	3.73 ± 3.92	3.24 ± 3.43	−0.53 ± 2.63
Smoking[c]				
Non-smoker	93 (1014)	95 (262)	94 (280)	
Smoker	7 (78)	5 (13)	6 (18)	
Education[c]				
Primary or secondary	59 (643)	55 (165)	55 (165)	
Tertiary	41 (455)	45 (133)	45 (133)	
Use of hormonal preparations[c]				
Non-user	61 (676)	62 (186)	60 (180)	
Progestogen	39 (426)	38 (112)	19 (56)	
Estrogen	0 (0)	0 (0)	3 (10)	
Progestogen + estrogen	0 (0)	0 (0)	18 (52)	

Data are mean ± standard deviation unless otherwise specified. HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, PA physical activity, ACC-MAD, accelerometer-measured physical activity mean amplitude deviation, mg milligravity (0.00981 m/s^2).
[a] For participants with baseline and follow-up measurement.
[b] Measured only at baseline.
[c] Data are % (n).

participants had slight overweight at baseline with a mean BMI of 25.5 kg/m^2 and had slightly elevated SBP (132.5 mm Hg), DBP (84.5 mm Hg), total cholesterol (5.23 mmol/l), and LDL-C (3.05 mmol/l). Vasomotor and psychological symptoms were the most frequently reported symptoms, with 59 % and 50 % of the participants reporting at least one symptom of those categories in the full sample, respectively. One or more somatic or pain symptoms and urogenital symptoms were reported by 24 % and 35 % of the participants, respectively. Consequently, 76 % of the participants reported at least one symptom from any category. At baseline, 4 % (n = 43) and 17 % (n = 192) of the participants reported using lipid modifying agents and antihypertensives.

3.2. Cross-sectional analyses

In simple linear regression models, the number symptoms in most categories were positively associated with cholesterol levels (Table 3). Especially, vasomotor, urogenital, and the total number of symptoms were associated with higher total cholesterol and LDL-C. Also, VMS associated with higher HDL-C. However, after adjusting the models with confounders, all associations between symptoms and cholesterol levels disappeared. In unadjusted models, a higher total number of symptoms associated positively with higher total (B = 0.31 kg, 95 % CI [0.03, 0.59]) and android fat mass (B = 0.04 kg, 95 % [0.01, 0.07]). Adjusting the models did not notably affect these results. Participants who reported more somatic or pain symptoms tended to have higher SBP in unadjusted (B = 1.95 mm Hg, 95 % CI [−0.18, 4.09]) and adjusted (B = 1.36 mm Hg, 95 % CI [−0.65, 3.37]) models. Including all symptom categories in the same models (Tables S1 and S2), adjusting the models with E2 and FSH (Table S3), and removing the participants using medications directly affecting the outcome variables (Table S4) did not change the results notably. No interactions between symptoms and other covariates were observed, and omitting BMI from the list of confounders did not significantly affect the results in adjusted models (data not shown). The full models shown in Tables S1 and S2 indicate that BMI was positively associated with most of the outcome variables, while age and menopausal status were positively associated with cholesterol levels.

3.3. Longitudinal analyses

The number of menopausal symptoms in each category tended to

Table 3
Associations of menopausal symptoms with cardiometabolic risk factors in cross-sectional study design (n = 1393).

	Total cholesterol [mmol/l]		LDL-C [mmol/l]		HDL-C [mmol/l]		Glucose [mmol/l]		Triglycerides [mmol/l]		Systolic blood pressure [mm Hg]		Diastolic blood pressure [mm Hg]		Total fat mass [kg][a]		Android fat mass [kg][a]		Physical activity[b] [mg]	
	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI
Vasomotor symptoms																				
Model 1	0.13***	[0.07, 0.20]	0.08**	[0.03, 0.14]	0.06***	[0.03, 0.09]	−0.04	[−0.10, 0.02]	0.03	[−0.02, 0.08]	0.21	[−1.07, 1.49]	0.16	[−0.55, 0.87]	0.44	[−0.33, 1.21]	0.06	[−0.03, 0.14]	−0.26	[−0.91, 0.40]
Model 2	0.00	[−0.08, 0.07]	−0.03	[−0.09, 0.03]	0.02	[−0.02, 0.06]	−0.04	[−0.10, 0.03]	0.01	[−0.05, 0.06]	−0.33	[−1.71, 1.05]	−0.23	[−0.98, 0.51]	0.55	[−0.35, 1.45]	0.05	[−0.05, 0.15]	−0.28	[−1.05, 0.49]
Psychological symptoms																				
Model 1	0.06*	[0.01, 0.11]	0.04	[0.00, 0.09]	0.01	[−0.02, 0.03]	−0.02	[−0.07, 0.02]	0.02	[−0.02, 0.06]	0.07	[−0.98, 1.13]	0.16	[−0.42, 0.74]	0.49	[−0.16, 1.14]	0.05	[−0.02, 0.13]	−0.13	[−0.71, 0.45]
Model 2	0.01	[−0.04, 0.06]	0.00	[−0.04, 0.05]	−0.01	[−0.03, 0.02]	−0.02	[−0.07, 0.02]	0.01	[−0.03, 0.05]	−0.23	[−1.26, 0.80]	−0.07	[−0.62, 0.48]	0.50	[−0.17, 1.16]	0.05	[−0.03, 0.12]	−0.10	[−0.70, 0.50]
Somatic or pain symptoms																				
Model 1	0.10	[−0.01, 0.20]	0.08	[−0.01, 0.17]	0.00	[−0.05, 0.05]	0.01	[−0.08, 0.10]	0.04	[−0.03, 0.12]	1.95	[−0.18, 4.09]	0.63	[−0.53, 1.79]	0.91	[−0.34, 2.16]	0.11	[−0.03, 0.24]	−0.21	[−1.17, 0.74]
Model 2	0.03	[−0.08, 0.13]	0.02	[−0.07, 0.12]	−0.01	[−0.06, 0.03]	0.01	[−0.09, 0.10]	0.03	[−0.05, 0.11]	1.36	[−0.65, 3.37]	0.17	[−0.87, 1.22]	0.83	[−0.46, 2.13]	0.09	[−0.05, 0.23]	−0.18	[−1.17, 0.80]
Urogenital symptoms																				
Model 1	0.09**	[0.02, 0.15]	0.09**	[0.03, 0.14]	0.01	[−0.02, 0.04]	−0.01	[−0.07, 0.05]	−0.01	[−0.05, 0.04]	0.13	[−1.19, 1.45]	0.32	[−0.41, 1.05]	0.60	[−0.23, 1.44]	0.08	[−0.01, 0.17]	−0.11	[−0.74, 0.51]
Model 2	0.01	[−0.06, 0.08]	0.03	[−0.03, 0.08]	−0.01	[−0.05, 0.02]	−0.02	[−0.08, 0.05]	−0.02	[−0.07, 0.03]	−0.41	[−1.77, 0.95]	−0.05	[−0.74, 0.65]	0.60	[−0.26, 1.47]	0.07	[−0.03, 0.17]	−0.08	[−0.74, 0.58]
Total number of symptoms																				
Model 1	0.05***	[0.03, 0.07]	0.04***	[0.02, 0.06]	0.01	[0.00, 0.02]	−0.01	[−0.03, 0.01]	0.01	[−0.01, 0.03]	0.18	[−0.33, 0.69]	0.14	[−0.14, 0.42]	0.31*	[0.03, 0.59]	0.04*	[0.01, 0.07]	−0.09	[−0.33, 0.15]
Model 2	0.01	[−0.02, 0.03]	0.00	[−0.02, 0.02]	0.00	[−0.02, 0.01]	−0.01	[−0.04, 0.01]	0.00	[−0.02, 0.02]	−0.07	[−0.58, 0.43]	−0.04	[−0.31, 0.22]	0.35*	[0.03, 0.67]	0.04	[0.00, 0.07]	−0.09	[−0.36, 0.19]

Model 1 is simple linear regression model. Model 2 is adjusted with age, body mass index, menopausal status, use of hormonal contraception, education, smoking status, and alcohol consumption unless otherwise specified. LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol. CI confidence interval, mg milligravity (0.00981 m/s^2).

[a] Model 2 is adjusted with age, menopausal status, use of hormonal contraception, education, smoking status, and alcohol consumption.

[b] Accelerometer-measured physical activity mean amplitude deviation.

* $p \leq 0.05$.

** $p \leq 0.01$.

*** $p \leq 0.001$.

associate positively with total cholesterol, LDL-C, total fat mass, and android fat mass (Tables 4 and 5). Notably, a higher number of VMS associated with higher total cholesterol (B = 0.15 mmol/l, 95 % CI [0.02, 0.28]) and LDL-C (B = 0.12 mmol/l, 95 % CI [0.01, 0.24]). However, adjusting the models with confounders diminished the associations, especially with total cholesterol and LDL-C. Participants reporting more psychological, somatic or pain, and urogenital symptoms tended to have higher SBP with an estimated increase per reported symptom varying from 0.96 to 2.83 mm Hg. Participants reporting more VMS tended to have lower SBP, with an estimated decrease per reported symptom varying from 0.91 to 1.71 mm Hg. A higher number of VMS was associated with a 0.09 mmol/l (95 % CI [0.01, 0.17]) greater increase in triglycerides during the follow-up. The results did not differ notably when including all symptoms in the same models (Tables S5 and S6), adjusting the models with E2 and FSH (Table S7), or removing participants using lipid modifying agents and antihypertensives (Table S8). The full models in Tables S5 and S6 show that all studied cholesterol levels increased and DBP decreased during the follow-up. Also, BMI associated positively with LDL-C, glucose, triglyceride, and blood pressure levels and negatively with HDL-C and physical activity. Menopausal status was positively associated with total cholesterol, LDL-C, and HDL-C.

4. Discussion

In this study, menopausal symptoms were observed to have modest positive associations with cholesterol levels and body fat mass measures. Remarkably, most of the observed associations disappeared after adjusting for confounders. Menopausal symptoms were not associated with blood pressure, blood glucose, triglycerides, and physical activity. Furthermore, menopausal symptoms at baseline did not predict the changes in most of the CMD risk factors during the follow-up.

In both cross-sectional and longitudinal analyses, we observed that menopausal symptoms, especially VMS, were positively associated with total cholesterol, LDL-C, and HDL-C but not with triglycerides and blood glucose. However, the observed associations disappeared after controlling for confounders with a higher number of VMS accounting only for −0.03 to 0.04 mmol/l change in all cholesterol levels. The previous evidence from cross-sectional and longitudinal studies focusing on night sweats and hot flashes has demonstrated positive associations of VMS with total cholesterol, LDL-C, HDL-C, and triglycerides [9,12], as well as with blood glucose [13,21] even after controlling for confounders. For instance, higher total cholesterol levels have been reported for women with hot flashes (0.27 mmol/l, 95 % CI [0.15, 0.39]) in large cross-sectional study [22] and for women with night sweats (0.17 mmol/l, 95 % CI [0.03, 0.31]) in meta-analysis including two large cross-sectional studies [9]. However, similarly to our results, one small study of Nordic women did not observe associations between VMS and blood lipids [23].

Previous meta-analysis of cross-sectional studies reported women with hot flashes and night sweat to have higher SBP and DBP [9]. Similar findings were also observed in one large-scale longitudinal study [14]. However, our longitudinal analyses indicated that women with a higher number of vasomotor symptoms might even have lower SBP and DBP. On the other hand, in all other symptoms categories, a higher number of symptoms tended to associated with higher SBP and DBP in our analyses. Furthermore, a higher physical activity level has previously been found to associate with fewer somatic and mood symptoms but the evidence of its association with VMS is contradictory [24]. Our analyses demonstrated a trend that the number of symptoms in all categories

Table 4
Associations of menopausal symptoms with blood-based biomarkers in longitudinal study design (n = 298).

		Total cholesterol [mmol/l]		LDL-C [mmol/l]		HDL-C [mmol/l]		Glucose [mmol/l]		Triglycerides [mmol/l]	
		B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI
Vasomotor symptoms											
Model 1	Main effect	0.15*	[0.02, 0.28]	0.12*	[0.01, 0.24]	0.03	[−0.04, 0.09]	−0.02	[−0.10, 0.05]	0.05	[−0.04, 0.15]
	Interaction with time	−0.03	[−0.16, 0.09]	−0.02	[−0.13, 0.09]	−0.02	[−0.08, 0.03]	−0.04	[−0.12, 0.03]	0.07	[−0.01, 0.14]
Model 2	Main effect	0.03	[−0.11, 0.18]	0.05	[−0.08, 0.17]	−0.03	[−0.10, 0.04]	−0.04	[−0.12, 0.04]	0.01	[−0.09, 0.11]
	Interaction with time	0.04	[−0.09, 0.17]	0.03	[−0.08, 0.15]	0.01	[−0.04, 0.07]	−0.02	[−0.11, 0.06]	0.09*	[0.01, 0.17]
Psychological symptoms											
Model 1	Main effect	0.05	[−0.06, 0.15]	0.06	[−0.03, 0.16]	−0.01	[−0.07, 0.04]	0.01	[−0.05, 0.07]	0.04	[−0.03, 0.12]
	Interaction with time	0.03	[−0.07, 0.13]	0.02	[−0.06, 0.11]	−0.01	[−0.05, 0.03]	0.00	[−0.06, 0.06]	0.01	[−0.05, 0.07]
Model 2	Main effect	0.01	[−0.10, 0.11]	0.04	[−0.06, 0.13]	−0.03	[−0.09, 0.02]	0.01	[−0.05, 0.07]	0.02	[−0.05, 0.10]
	Interaction with time	0.04	[−0.05, 0.14]	0.03	[−0.06, 0.12]	0.01	[−0.04, 0.05]	0.00	[−0.06, 0.06]	0.00	[−0.06, 0.07]
Somatic or pain symptoms											
Model 1	Main effect	0.12	[−0.09, 0.33]	0.09	[−0.09, 0.28]	0.00	[−0.11, 0.11]	0.02	[−0.10, 0.14]	0.11	[−0.04, 0.26]
	Interaction with time	0.00	[−0.20, 0.20]	0.00	[−0.17, 0.17]	−0.04	[−0.13, 0.05]	−0.06	[−0.19, 0.06]	−0.04	[−0.17, 0.08]
Model 2	Main effect	0.05	[−0.16, 0.26]	0.04	[−0.14, 0.23]	−0.03	[−0.14, 0.08]	0.00	[−0.12, 0.12]	0.09	[−0.07, 0.24]
	Interaction with time	0.05	[−0.15, 0.25]	0.03	[−0.14, 0.20]	0.00	[−0.10, 0.09]	−0.06	[−0.19, 0.06]	−0.05	[−0.18, 0.08]
Urogenital symptoms											
Model 1	Main effect	0.04	[−0.10, 0.17]	0.04	[−0.08, 0.15]	−0.01	[−0.08, 0.06]	0.04	[−0.04, 0.11]	0.04	[−0.05, 0.14]
	Interaction with time	−0.01	[−0.14, 0.11]	0.00	[−0.11, 0.11]	−0.05	[−0.11, 0.00]	−0.01	[−0.09, 0.06]	0.06	[−0.02, 0.14]
Model 2	Main effect	−0.03	[−0.17, 0.11]	−0.01	[−0.13, 0.11]	−0.04	[−0.11, 0.03]	0.04	[−0.04, 0.11]	0.02	[−0.08, 0.12]
	Interaction with time	0.01	[−0.11, 0.14]	0.01	[−0.10, 0.12]	−0.03	[−0.09, 0.03]	−0.01	[−0.09, 0.07]	0.07	[−0.01, 0.15]
Total number of symptoms											
Model 1	Main effect	0.04	[−0.01, 0.09]	0.04	[0.00, 0.08]	0.00	[−0.03, 0.02]	0.01	[−0.02, 0.03]	0.03	[−0.01, 0.06]
	Interaction with time	0.00	[−0.04, 0.05]	0.00	[−0.04, 0.04]	−0.01	[−0.03, 0.01]	−0.01	[−0.04, 0.02]	0.02	[−0.01, 0.05]
Model 2	Main effect	0.00	[−0.05, 0.06]	0.02	[−0.03, 0.06]	−0.02	[−0.04, 0.01]	0.00	[−0.03, 0.03]	0.02	[−0.02, 0.05]
	Interaction with time	0.02	[−0.03, 0.07]	0.01	[−0.03, 0.06]	0.00	[−0.02, 0.02]	−0.01	[−0.04, 0.02]	0.02	[−0.01, 0.05]

All models include menopausal symptoms, time, and their interaction as predictors. Model 2 is additionally adjusted with age, body mass index, menopausal status, use of hormonal contraception, education, smoking status, and alcohol consumption. LDL-C Low-density lipoprotein cholesterol, HDL-C High-density lipoprotein cholesterol, CI Confidence interval.

* $p \leq 0.05$.

Table 5
Associations of menopausal symptoms with blood pressure, body composition, and physical activity measures in longitudinal study design (n = 298).

		Systolic blood pressure [mm Hg]		Diastolic blood pressure [mm Hg]		Total fat mass [kg][a]		Android fat mass [kg][a]		Physical activity[b] [mg]	
		B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI	B	95 % CI
Vasomotor symptoms											
Model 1	Main effect	−0.91	[−3.52, 1.69]	−0.43	[−1.87, 1.02]	0.74	[−0.72, 2.21]	0.08	[−0.08, 0.24]	−0.67	[−2.06, 0.72]
	Interaction with time	−0.15	[−2.68, 2.37]	0.01	[−1.33, 1.35]	−0.21	[−1.49, 1.07]	−0.03	[−0.18, 0.12]	−0.27	[−1.72, 1.19]
Model 2	Main effect	−1.71	[−4.39, 0.98]	−1.16	[−2.62, 0.30]	0.29	[−1.28, 1.86]	0.02	[−0.15, 0.20]	−0.47	[−1.93, 1.00]
	Interaction with time	0.37	[−2.18, 2.91]	0.59	[−0.71, 1.90]	0.09	[−1.26, 1.44]	0.01	[−0.15, 0.16]	−0.35	[−1.80, 1.11]
Psychological symptoms											
Model 1	Main effect	1.30	[−0.80, 3.41]	0.93	[−0.22, 2.07]	0.53	[−0.62, 1.67]	0.04	[−0.09, 0.17]	0.03	[−1.07, 1.12]
	Interaction with time	−1.18	[−3.18, 0.83]	−0.55	[−1.61, 0.50]	0.46	[−0.52, 1.45]	0.05	[−0.06, 0.16]	−0.87	[−1.95, 0.22]
Model 2	Main effect	0.96	[−1.11, 3.03]	0.68	[−0.42, 1.78]	0.38	[−0.78, 1.54]	0.02	[−0.10, 0.15]	0.28	[−0.85, 1.42]
	Interaction with time	−1.22	[−3.16, 0.71]	−0.54	[−1.52, 0.45]	0.52	[−0.48, 1.51]	0.06	[−0.05, 0.17]	−0.81	[−1.91, 0.29]
Somatic or pain symptoms											
Model 1	Main effect	2.83	[−1.28, 6.94]	0.91	[−1.34, 3.17]	1.06	[−1.22, 3.35]	0.08	[−0.18, 0.34]	−0.02	[−2.20, 2.16]
	Interaction with time	−1.93	[−5.79, 1.93]	−0.31	[−2.35, 1.74]	−0.07	[−2.08, 1.94]	−0.02	[−0.25, 0.22]	0.31	[−1.98, 2.59]
Model 2	Main effect	1.95	[−2.09, 5.98]	0.23	[−1.93, 2.40]	0.62	[−1.69, 2.93]	0.03	[−0.23, 0.29]	0.24	[−1.96, 2.44]
	Interaction with time	−1.86	[−5.76, 2.04]	−0.08	[−2.08, 1.92]	0.15	[−1.90, 2.20]	0.01	[−0.23, 0.25]	0.34	[−1.90, 2.58]
Urogenital symptoms											
Model 1	Main effect	1.89	[−0.71, 4.48]	1.47	[0.00, 2.93]	0.43	[−1.00, 1.87]	0.05	[−0.11, 0.22]	−0.39	[−1.80, 1.03]
	Interaction with time	−0.07	[−2.56, 2.42]	0.10	[−1.25, 1.46]	−0.07	[−1.37, 1.22]	0.00	[−0.15, 0.15]	−0.61	[−2.05, 0.84]
Model 2	Main effect	1.45	[−1.12, 4.01]	1.08	[−0.32, 2.48]	0.16	[−1.30, 1.62]	0.02	[−0.14, 0.19]	−0.21	[−1.62, 1.20]
	Interaction with time	0.08	[−2.36, 2.53]	0.26	[−1.00, 1.52]	0.08	[−1.20, 1.36]	0.02	[−0.13, 0.17]	−0.57	[−2.00, 0.85]
Total number of symptoms											
Model 1	Main effect	0.58	[−0.37, 1.53]	0.40	[−0.12, 0.92]	0.34	[−0.18, 0.85]	0.03	[−0.03, 0.09]	−0.14	[−0.65, 0.38]
	Interaction with time	−0.40	[−1.29, 0.49]	−0.13	[−0.59, 0.34]	0.06	[−0.37, 0.49]	0.01	[−0.04, 0.06]	−0.29	[−0.82, 0.23]
Model 2	Main effect	0.34	[−0.63, 1.31]	0.18	[−0.35, 0.71]	0.18	[−0.36, 0.72]	0.01	[−0.05, 0.07]	0.00	[−0.55, 0.54]
	Interaction with time	−0.35	[−1.25, 0.55]	−0.03	[−0.48, 0.43]	0.15	[−0.30, 0.59]	0.02	[−0.03, 0.07]	−0.30	[−0.82, 0.23]

All models include menopausal symptoms, time, and their interaction as predictors. Model 2 is additionally adjusted with age, body mass index, menopausal status, use of hormonal contraception, education, smoking status, and alcohol consumption unless otherwise specified. CI confidence interval.
[a] Model 2 is additionally adjusted with age, menopausal status, use of hormonal contraception, education, smoking status, and alcohol consumption.
[b] Accelerometer-measured physical activity mean amplitude deviation, mg milligravity (0.00981 m/s^2).

might be associated with higher total and android fat mass. These results are partially in line with previous results showing associations of VMS with higher body fat percentage [25] and BMI [9].

The mechanisms behind the linkage between menopausal symptoms and CMD risk factors are not completely clear. However, this linkage could be explained by the change in the hormonal milieu and especially the decrease in systemic E2 levels during the menopausal transition. These hormonal changes are often considered to be one major contributor to the development of menopausal symptoms [2], and they may also contribute to the unhealthy changes in CMD risk factors during the menopausal transition [1,6]. Some potential mechanisms for how the hormonal changes could affect the relationship between menopausal symptoms and CMD risk factors are the menopause-related changes in endothelial function and sympathetic activity that are also associated with VMS [26,27] and may result in changes in blood pressure [28] and lipids [29]. Our findings, in which the studied associations diminished after adjusting for menopausal status and other confounders, support the hypothesis about the confounding role of the change in the hormonal milieu and its derivatives in associations between menopausal symptoms and CMD risk factors.

Additionally, menopausal transition and varied menopausal symptoms have been linked to changes in body adiposity and obesity [2]. The increased amount of adipose tissue that contributes to CMD risk and the development of a pro-inflammatory adipokine profile is associated with a variety of menopausal symptoms and may play a role in the development of VMS [2,30]. BMI has been reported to moderate the associations between VMS with blood lipids [12], which indicates that the amount of adipose tissue may play a role in the associations between menopausal symptoms and CMD risk factors. However, contradictory to our results, several previous studies have reported these associations to persist even after adjusting for BMI [9,12,14]. Also, in our analyses, BMI did not moderate the associations between menopausal symptoms and CMD risk factors.

Strengths of the study include the longitudinal study design, where a total of 148 out of 298 participants experienced menopause during the follow-up. Another upside of this study is the relatively large sample with a comprehensive set of CMD risk factors and measured confounders. Furthermore, the assessment of menopausal symptoms in our study was not limited only to VMS, but included a variety of other symptom types as well. However, the substantive limitation of the study is the assessment of the menopausal symptoms only at baseline with a questionnaire that has not been validated and does not capture the frequency or the severity of the symptoms. Furthermore, the homogeneous sample of white women with several health-related exclusion criteria limits the generalizability of the results and may affect the associations between menopausal symptoms and CMD risk factors.

5. Conclusion

This study shows that menopausal symptoms are associated with higher cholesterol levels and body adiposity in middle-aged women. However, the associations between menopausal symptoms and cholesterol levels were diminished after controlling for confounders, indicating that these associations are, at least partially, explained by differences in age, menopausal status, BMI, socioeconomic status, and lifestyle habits. According to our results, menopausal symptoms are not associated with blood glucose, triglycerides, blood pressure, and physical activity levels, and they do not predict changes in CMD risk factors

during the menopausal transition. The independent role of menopausal symptoms in explaining the CMD risk factors may therefore be smaller than what has been previously suggested. More large-scale longitudinal studies with a comprehensive set of confounders are needed to clarify the independent role of menopausal symptoms in CMD risk in women.

Contributors

Matti Hyvärinen prepared the data and original manuscript, and was the major contributor to the statistical analyses.

Juha Karvanen offered guidance for statistical analyses and contributed to the writing process.

Hanna-Kaarina Juppi contributed to the writing process.

Jari E. Karppinen contributed to the writing process.

Tuija H. Tammelin contributed to the writing process.

Vuokko Kovanen obtained funding for the project and contributed to the writing process.

Pauliina Aukee contributed to the writing process.

Sarianna Sipilä contributed to the writing process.

Timo Rantalainen contributed to the writing process.

Eija K. Laakkonen obtained funding for the project and contributed to the writing process.

All authors saw and approved the final version, and no other person made a substantial contribution to the paper.

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Ethical approval

The study was performed in accordance with the Declaration of Helsinki. Both ERMA and EsmiRs studies were approved by the ethical committee of the Central Finland Health Care District (ERMA 8U/2014 and EsmiRs 9U/2018).

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked datasets for this paper. The datasets generated and/or analyzed during the current study are not publicly available due to EU and Finnish legislation and the consent provided by the participants does not permit open access to individual-level personal data. However, they are available from the corresponding author on reasonable request. More information about the datasets: 10.17011/jyx/dataset/83491.

Declaration of competing interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2023.05.004.

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