scientific reports

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A mediating role of visceral adipose tissue on the association of health behaviours and metabolic inflammation in menopause: a population-based cross-sectional study

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Fat distribution changes with advancing menopause, which predisposes to metabolic inflammation. However, it remains unclear, how health behaviours, including sleeping, eating and physical activity, or their combinations contribute to metabolic inflammation caused by visceral adipose tissue (VAT). The aim of the present study was to examine whether health behaviours are associated with metabolic inflammation and whether VAT mediates these associations in menopausal women. This cross-sectional study consisted of a sample of middle-aged women ($n = 124$). Health behaviours were assessed by self-report questionnaire with measures of sleeping, eating (Eating Disorder Examination Questionnaire, EDE-Q), and physical activity behaviours. Metabolic inflammation was measured using GlycA, a composite biomarker of inflammation, and bioimpedance device was used to assess VAT. Structural equation modelling was used to examine the direct and indirect associations of health behaviours with inflammation, as well as the moderation effect of health behaviours on VAT and metabolic inflammation. VAT was directly associated with inflammation. Two indirect pathways were found: eating and physical activity behaviours were both inversely associated with inflammation through VAT, whereas sleeping behaviour was not. Physical activity moderated the association between VAT and metabolic inflammation. The association was stronger in those who were physically less active. Furthermore, eating behaviour and physical activity had an interaction on VAT. Physical activity was negatively associated with VAT among women with normal eating behaviour, but the association was less clear among women with features of disordered eating behaviour. It is possible to impede the menopausal shift to adverse visceral adiposity through increased physical activity and further decrease the risk of metabolic inflammation in menopausal women. The present study offers potential hypotheses for future longitudinal research.

Keywords Visceral fat, Inflammatory biomarker, Physical inactivity, Dimensions of sleep, Eating disorder examination questionnaire, Menopause

In the premenopausal stage, sex hormone estrogen has a protective impact on cardiometabolic health[1], and plays an important role in immune and inflammatory processes[2]. The transition across menopause to the postmenopausal stage shifts fat distribution from gynoid area to the adverse android obesity[3,4]. This alteration predisposes women to various adverse health outcomes such as metabolic inflammation that precedes and contributes to cardiovascular and metabolic diseases[1,2,5]. Contrary to acute inflammation, chronic metabolic inflammation is a physiological state observed without an infection. Metabolic inflammation is considered a hallmark of metabolic disorders, such as obesity and type II diabetes[6], occurring when proinflammatory cytokines are secreted from the visceral adipose tissue (VAT)[7]. It is well established that VAT is associated with metabolic

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inflammation[8–10]. However, mechanisms behind the association between VAT and metabolic inflammation lie in molecular processes leading to the secretion of cytokines by adipose tissue. Previous research suggests that exercise[11], weight loss[12] and whole grain diet[13] can reduce systemic levels of proinflammatory cytokines. Thus, exploring the impact of health behaviours as potential factors affecting the accumulation of excessive VAT and further metabolic inflammation is of great importance.

While health behaviours including sleeping, eating and physical activity contribute to various health outcomes as independent factors, they are known to interact with each other[14–18]. However, in the context of inflammation, previous research has focused on their separate associations instead of investigating them together in one study[19]. It is known that changes in sleep duration or quality, eating behaviour and physical activity behaviour contribute significantly to body composition[15,20,21]. An increasing body of knowledge suggests that dimensions of sleep (duration and quality) contribute to immune functions[22,23]. Furthermore, eating behaviour and nutrition have been associated with metabolic inflammation[24–26]. The role of physical activity in inflammation is also recognized[27]. For example, Bruunsgaard and Nimmo et al. have suggested that it is possible to reduce inflammation by modifying the level of physical activity[28,29]. Oftedal et al. also[30] suggested that poor sleep, in combination with either both poor diet (assessed with diet quality score) and physical inactivity (assessed with International Physical Activity Questionnaire Short Form) or with only one of these is a health risk. Similar results were found by Loprinzi[19] in their cross-sectional study where the combination of healthy diet (assessed with Healthy Eating Index, HEI) and adequate sleep was associated with lower high-sensitive C-reactive protein (hs-CRP), a marker of inflammation. However, these studies have concentrated on food intake and healthy diets, rather than eating behaviour per se. In the context of menopause, the behavioural aspect should be considered, since previous research indicates that estrogen may influence eating behaviour by reducing appetite and food intake[31,32]. However, it is not clear, in what magnitude health behaviours could modify the association between VAT and inflammation in the context of menopause. Furthermore, since for example balanced and moderate caloric restriction might serve as a feasible tool for reducing inflammation[33], it could be hypothesized that eating behaviour in general might modify the association between VAT and inflammation. The association between sleep and inflammation is less clear, thus more uncertainty is connected to the association of sleep with metabolic inflammation.

GlycA (glycoprotein acetylation) is a novel nuclear magnetic resonance (NMR) -based biomarker of inflammation, that assesses systemic inflammation by evaluating the glycosylation status of acute phase proteins[34,35]. As GlycA concentrations correlates with metabolically adverse conditions such as insulin resistance, body mass index, metabolic syndrome, it is a plausible general indicator of body's metabolic inflammation status[36]. Previously hs-CRP has been widely used as an indicator of metabolic inflammation, yet there may be some limitations concerning CRP. An assay that is based on measuring only individual acute-phase proteins, is more prone to exhibit higher intra-individual variability[37,38]. Considering that GlycA is a composite biomarker that integrates several acute phase proteins, it may serve as a more stable indicator of metabolic inflammation compared to a single marker such as CRP[34,39–41].

Metabolic risk factors outlined above emphasize the importance of examining possible pathways between health behaviour and inflammation. The purpose of this study was to investigate whether sleeping, eating and physical activity behaviours are associated with metabolic inflammation in menopause. We hypothesized that sleeping, eating, and physical activity behaviours have direct and indirect associations through VAT on inflammation, and that these behaviours may moderate the association between VAT and inflammation. Furthermore, we hypothesized that health behaviours have interactions with each other, and they moderate each other's associations with VAT and inflammation. A structural equation model (SEM) (Fig. 1) was constructed with hypotheses as followed:

H1: VAT is positively associated with inflammation.
H2: Sleeping, eating and physical activity behaviours are directly associated with inflammation.
H3: VAT mediates the hypothesized association (H2) between sleeping, eating and physical activity behaviours and inflammation.
H4: Sleeping, eating and physical activity behaviours moderate the hypothesized association (H1) between VAT and inflammation.
H5: Sleeping, eating and physical activity behaviours moderate each other's associations with VAT and inflammation.

Methods

Study participants

The study sample is part of the EsmiRs (Estrogen, MicroRNAs, and the Risk of Metabolic Dysfunction) study[42] including 494 Caucasian 51–59-year-old women. EsmiRs study was collected in 2018–2020 via postal invitations addressed to women who had earlier participated in the ERMA (Estrogenic Regulation of Muscle Apoptosis) study[43] and had consented to be contacted later with potential new study invitations ($n = 811$).

The flow chart of the study participants is shown in Fig. 2. Recruiting and questionnaire data collection for the EsmiRs study started in November 2018. Eventually, 494 women returned questionnaires including most health behaviour questions used in the current study. The laboratory visits began in January 2019. Since laboratory visits were discontinued due to the COVID-19 pandemic in March 2020, we lost the opportunity to measure 99 women. Furthermore, based on the obtained questionnaire data, we excluded 46 women who had more than seven years since menopause and ten women due to severe illness. In addition, 25 women did not consent for laboratory visits, and 16 discontinued at this point. Thus, laboratory measures, some questionnaires and blood sampling were obtained from 292 to 298 participants altogether. The actual analytic sample of the current study was 124 women, since it was the number of blood samples analysed with NMR to acquire a measure for the

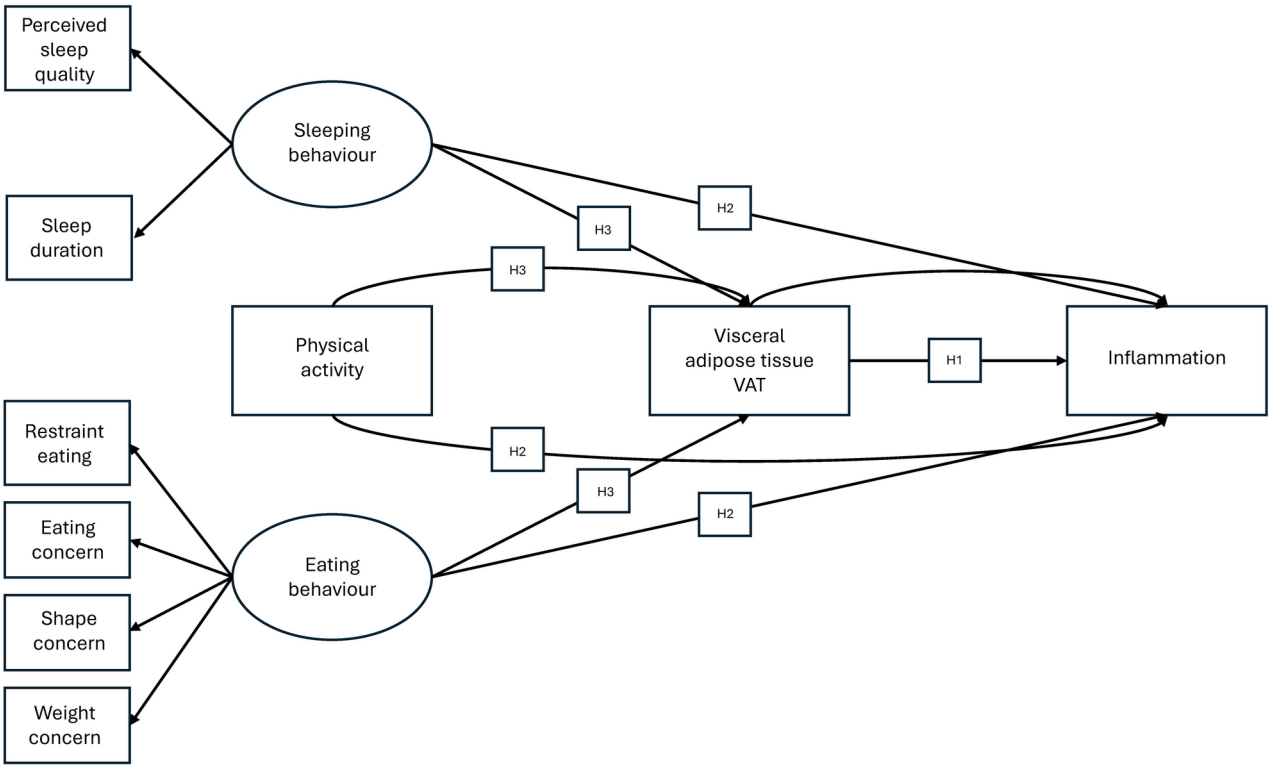

Fig. 1. Hypothesized path model.

GlycA, which was used as a marker of metabolic inflammation (Fig. 2). The reason for limiting NMR analyses to the lower number of samples was purely financial but did not occur completely random. We selected those participants who also had NMR measurements available from the earlier ERMA study ($n = 87$) and those who were willing and eligible to participate in the EsmiRs metabolism substudy ($n = 42$)[44]. Considering some overlap, the final number of participants with available GlycA measurements was 124. We performed sensitivity analyses to assess potential selection bias by comparing the analytic sample with the remaining women, who were excluded from the analysis (Table 1). More specific information about the representativeness of the participating women is represented in Additional file 1.

All participants provided written informed consent. The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Central Finland Health Care District (9U/2018). The STROBE-nut Statement[45] was followed to ensure transparency while reporting the present study (See Additional file 2).

Metabolic inflammation

GlycA measured from the serum blood samples, was used as an outcome to indicate metabolic inflammation. Blood samples were collected during the laboratory visits in the morning after a minimum of 10 h overnight fasting, aliquoted and stored at − 80 °C until analysis. GlycA was analysed with NMR spectroscopy (Nightingale Health Ltd., Helsinki, Finland)[46].

Health behaviour measures

Sleeping behaviour was assessed with a self-administered questionnaire that included questions about perceived sleep quality and sleep duration. For the sleep duration question ('on average, how many hours do you sleep?'), participants chose from six answering options: under 5 h, 5, 6, 7, 8, and 9 or more than 9 h. Participants' perceived sleep quality was evaluated by asking about their typical sleep experience. Respondents could choose from five options: 'good,' 'fairly good,' 'fairly poorly,' 'poorly,' or 'can't tell.' Women who selected 'can't tell' ($n = 3$) were grouped into the 'fairly good' category, since it was considered that a participant would report if experiencing significant problems in their sleep quality.

Eating behaviour was assessed using a self-administered Eating Disorder Examination Questionnaire (EDE-Q)[47,48] that included altogether 28 questions forming four subscales: *restraint eating* (e.g. 'Have you gone for long periods of time without eating anything at all in order to influence your shape or weight?'), *eating concerns* (e.g. 'Have you had a definite fear of losing control over eating?'), *shape concerns* (e.g. 'Have you had a definite desire to have a totally flat stomach?') and *weight concerns* (e.g. 'Has your weight influenced how you think about yourself as a person?'). Participants provided answers using a 7-point Likert scale where 0 indicated the absence of eating disorder symptoms and 6 indicated the daily presence of symptoms during the past 28 days. Subscales were formed from items 1–12 and 19–28. There were five items in each of the subscales for restraint

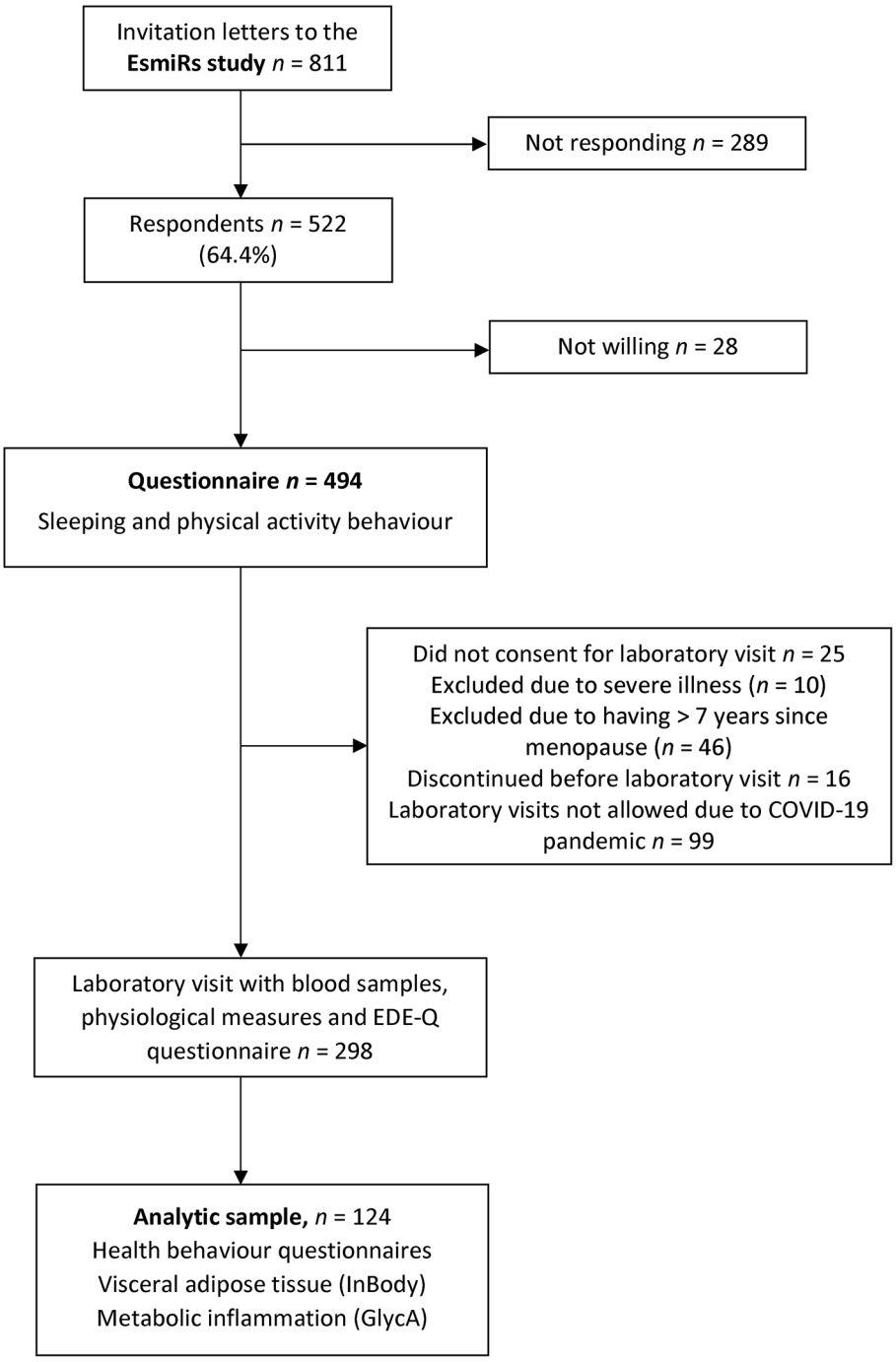

Fig. 2. Flow chart of the study participants.

eating, eating concern and weight concern, and 8 items in the subscale for shape concern. Items 13–18 relate to behaviour associated with binge-eating and compensatory actions but are not considered in the present study[47]. Score of each subscale was calculated as the mean of the subscale in question. The overall score (global score) was calculated as the mean of all four subscales. Reliability analyses were run for eating behaviour subscales. Cronbach's alpha was 0.84 for the overall score, 0.73 for the restraint eating, 0.59 for the eating concern, 0.91 for the shape concern, and 0.84 for the weight concern.

Physical activity was reported as metabolic equivalent hours per day (MET-h/d) based on the intensity, duration and frequency of current leisure-time physical activity including active commute[49] obtained from the self-administered questionnaire.

	Analytic sample (n = 124)		Excluded from the analysis (n = 370)		Difference
	Mean/n	SD/%	Mean/n	SD/%	*p*
Self-reported measurements					
Age	55.3	1.7	54.9	2.1	0.028
MET-h/d	4.9	3.6	4.6	3.8	0.464
Alcohol doses per week	3.2	3.7	3.3	3.6	0.780
CES-D score	0.4	0.4	0.5	0.4	0.311
Missing	0		1		
Diet quality score, DQS	6.0	2.1	5.7	2.3	0.220
Income					0.108
≤ 35,000	54	43.5	171	46.7	
35,001–45,000	38	30.6	79	21.6	
> 45,000	32	25.8	116	31.7	
Missing	0		4		
Education					0.468
Secondary or lower	74	59.7	207	55.9	
Tertiary or higher	50	40.3	163	44.1	
Menopausal status					< 0.001
Premenopausal	2	1.6	25	6.8	
Perimenopausal	6	4.8	66	17.8	
Postmenopausal	116	93.5	279	75.4	
Vasomotor symptoms					0.927
Yes	101	81.5	300	81.1	
No	23	18.5	70	18.9	
Smoking					0.399
Never	88	71.0	238	64.3	
Former	30	24.2	109	29.5	
Current	6	4.8	23	6.2	
Sleep duration					0.168
< 6 h	2	1.6	17	4.6	
6–8 h	121	97.6	344	93.0	
> 8 h	1	0.8	9	2.4	
Perceived sleep quality					0.288
Good	20	16.1	66	17.8	
Fairly good	81	65.3	208	56.2	
Fairly poorly	19	15.3	83	22.4	
Poorly	4	3.2	13	3.5	
Use of HT					0.028
No	89	71.8	225	60.8	
Yes[a]	35	28.2	145	39.2	
Use of sleep medication					0.022
No	114	91.9	305	82.4	
Yes, occasionally	9	7.3	45	12.2	
Yes, regularly	1	0.8	20	5.4	
Laboratory visits (available from *n* = 298)					
EDE-Q restraint eating	1.0	1.0	1.3	1.2	0.101
Missing	4		8		
EDE-Q eating concern	0.2	0.3	0.3	0.4	0.309
Missing	4		8		
EDE-Q shape concern	1.3	1.2	1.4	1.1	0.286
Missing	4		8		
EDE-Q weight concern	1.1	1.2	1.1	1.0	0.687
Missing	4		8		
EDE-Q global score	0.9	0.8	1.0	0.8	0.218
Missing	4		8		
BMI (InBody)	25.7	3.9	25.9	4.2	0.646
Continued					

	Analytic sample (n = 124)		Excluded from the analysis (n = 370)		Difference
	Mean/n	SD/%	Mean/n	SD/%	*p*
Missing	2		–		
Visceral fat	120.6	25.1	118.8	26.3	0.559
Missing	2		–		

Table 1. Comparison between the analytic sample (n = 124) and the women excluded from the analysis (n = 370). Group differences are assessed by conducting independent t-tests for continuous variables and chi-square tests for categorical variables. MET-h/d, metabolic equivalent of task hours per day; CES-D, Center for Epidemiologic Studies Depression scale; [a]Either estrogen, or progestogen, or both.

Body composition

Body composition was measured in the morning between 7:00 and 10:00 AM after overnight fasting, participants wearing only undergarments/light clothing, using a bioimpedance device (InBody720; Biospace, Seoul, Korea). Of the body composition variables, the amount of VAT was used in the analyses.

Covariates

Based on previous literature, age, income and the use of hormone therapy (HT) were selected as confounding factors. We decided to include income as a covariate because socioeconomic gradient is considered to contribute to one's health choices[50,51], and socioeconomic position has also been linked to inflammation[52]. HT is used to alleviate menopausal symptoms and is likely to improve sleep quality worsened by vasomotor symptoms[53]. It is also suggested that estrogen is engaged in eating behaviour[32] and metabolic conditions[53,54].

The menopausal status of the participants was determined based on the participant's follicle stimulating hormone concentration and using the Stages of Reproductive Aging Workshop + 10 guidelines[55]. Participants were categorized as premenopausal ($n = 27$), early perimenopausal ($n = 37$), late perimenopausal ($n = 35$) or postmenopausal ($n = 395$).

Statistical analysis

Continuous data are expressed as means ± standard deviation (SD), and categorical data as percentages. Group differences were assessed by conducting independent t-tests for continuous variables and chi-square tests for categorical variables. Pearson's bivariate correlations were tested between the study variables. The structural equation modelling (Fig. 1) using maximum likelihood estimation with robust standard errors (MLR) was conducted using Mplus (version 7.3) to test the hypothesized associations. All models were adjusted for age, income and the use of HT.

First, we constructed a model with three health behaviours as predictors, VAT as a mediator, and GlycA as an outcome. Physical activity was used as an observed variable, eating as a categorical latent variable formed by four EDE-Q subscales, and sleeping as a categorical latent variable formed by quality and duration. Second, the moderation analysis was performed to test the moderating role of sleeping, eating and physical activity between the association of VAT and inflammation. The moderation models were estimated separately for each health behaviour. For physical activity, an interaction term between the observed variables physical activity and VAT was included in the model. For eating and sleeping behaviour, the latent moderated SEM were used[56]. Third, to find out if any combined effects of health behaviour on inflammation should occur, we ran interaction analyses for them using the latent moderated SEM[56]. Combined effects of health behaviours were tested with three interactions: eating * physical activity behaviour, sleeping * physical activity behaviour and eating * sleeping behaviour on inflammation and VAT. The moderation plots were created using Mplus.

The data were expected to be completely missing at random. There were four missing observations in eating behaviour measurements, and two in body composition measurements. Since the amount of missing data was no more than 3%, it was considered acceptable, and no imputation or data removal was done.

Results

Characteristics of the participants

The representativeness of the analytic sample in several socioeconomic, health behavioural and other characteristics of the full EsmiRs study sample are shown in Tables 1 and S1 (see Additional file 3). The mean age of the participants was 55.3 years (SD = 1.7) for the analytic sample ($n = 124$). The mean body mass index (BMI) was 25.7 (SD = 3.9). The analytic sample did not differ from the women excluded from analyses except that the women included were a bit older ($P = 0.028$), more likely to be postmenopausal ($P < 0.001$) and less likely to use medication for sleeping problems ($P = 0.022$) or menopausal symptoms ($P = 0.028$). Altogether, 94% of the women in the analytic sample were postmenopausal, hence for the analyses of the present study, we did not use menopausal status as a covariate.

Altogether, 28% of the analytic sample used some form of HT for menopausal symptoms. The most common form was combined estrogen + progestogen therapy (14%). A total of 15% of women had cardiovascular medication such as statins or antihypertensive medication. When conducting a sensitivity analysis, there were no differences in metabolic health between the HT users and non-users except for the blood serum glucose, which was slightly higher for those using HT (Additional file 3, Table S2). No differences in metabolic profile

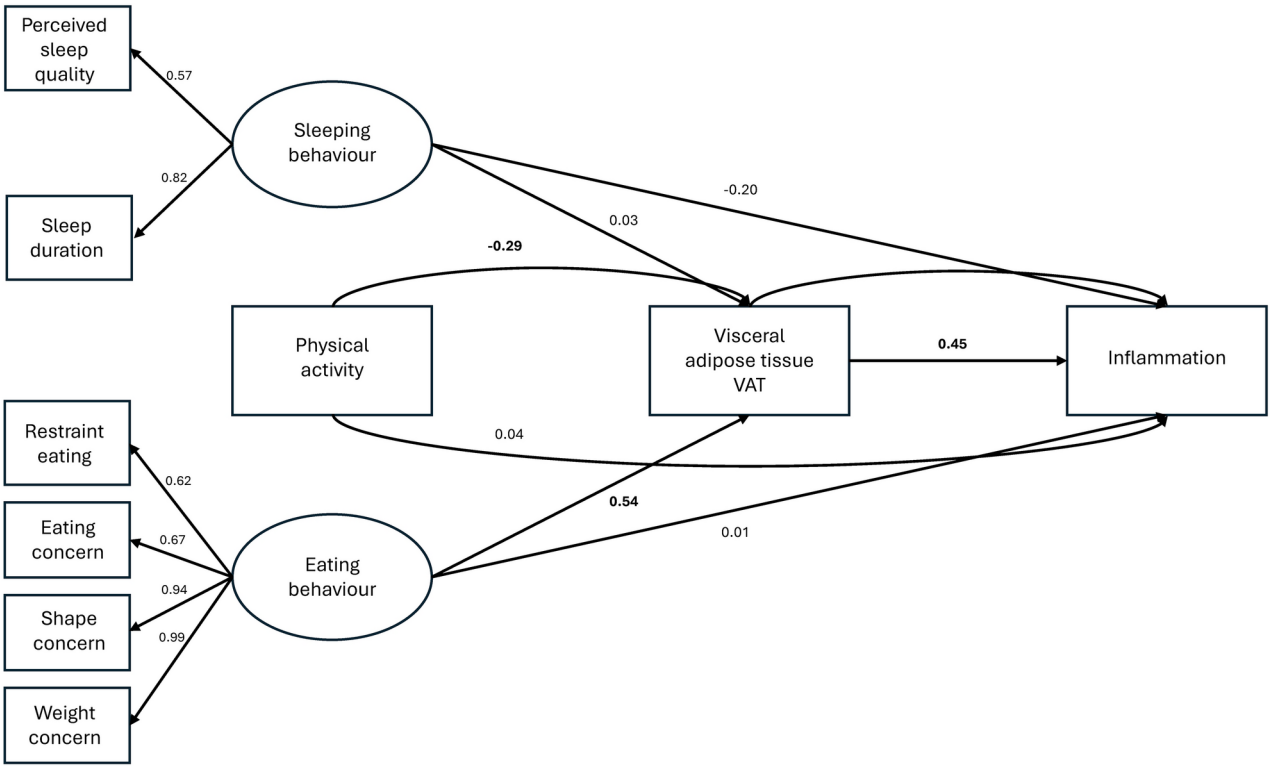

Fig. 3. Model results from the structural equation model. *Note*: Coefficients are standardized parameter estimates. Statistically significant ($P < 0.05$) parameter estimates are bolded. Factor loadings of each health behaviour subgroups are presented for latent sleeping and eating behaviour variable.

Effects	β	SE	*p*
Direct effects			
Sleeping behaviour → inflammation	−0.007	0.004	0.119
Eating behaviour → inflammation	0.001	0.009	0.900
Physical activity → inflammation	0.001	0.003	0.718
Visceral adipose tissue → inflammation	0.454	0.096	< 0.001
Indirect effects			
Sleeping behaviour → inflammation	0.000	0.002	0.826
Eating behaviour → inflammation	0.020	0.006	< 0.001
Physical activity → inflammation	−0.004	0.001	0.004
Total effects			
Sleeping behaviour → inflammation	−0.006	0.004	0.119
Eating behaviour → inflammation	0.022	0.007	0.003
Physical activity → inflammation	−0.003	0.002	0.265

Table 2. Unstandardized parameter estimates for direct and indirect effects for the model (n = 124). β = Unstandardized parameter estimate; SE = Standard error of the unstandardized parameter estimate. Total effects equal the sum of direct effects and indirect effects.

were found between sleep medication users and non-users (Additional file 3, Table S3). Bivariate correlations between health behaviours, VAT, and inflammation are presented in the Supplementary file 3, Table S4. Briefly, eating and physical activity behaviour correlated with VAT, but sleeping behaviour did not. Furthermore, sleep duration and all of the eating behaviour subscales, except the restraint eating, correlated with GlycA.

Direct and indirect associations between heath behaviour and inflammation

Figure 3 presents standardized parameter estimates for the model. Unstandardized model results are presented in Table 2. Consistent with our hypothesis (H1), VAT was positively associated with inflammation ($\beta = 0.454$, $P < 0.001$). Instead, contrary to our hypothesis, direct associations (H2) between eating, sleeping or physical

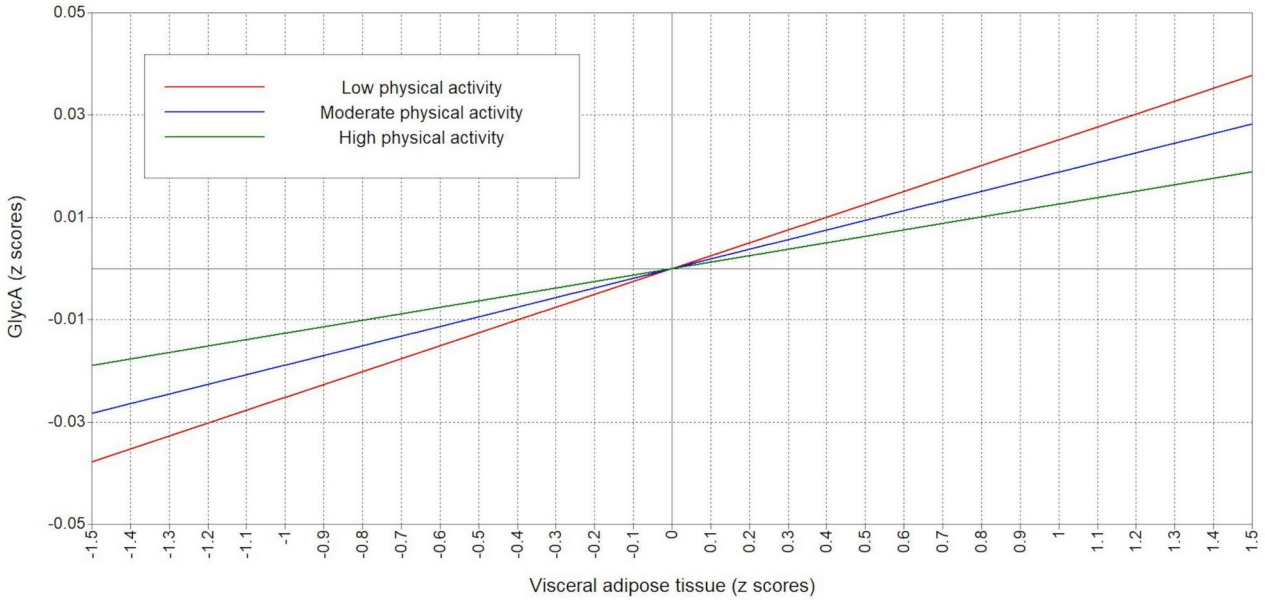

Fig. 4. Moderation effect of physical activity on inflammation. Units are presented as *z* scores.

Interactions	Estimate	SE	*p*
Eating * Physical activity —> GlycA	−0.00	0.00	0.265
Sleeping behaviour * Physical activity —> GlycA	−0.00	0.00	0.524
Eating behaviour * Sleeping behaviour —> GlycA	−0.00	0.00	0.641
Eating * Physical activity —> VAT	0.08	0.02	0.001
Sleeping behaviour * Physical activity —> VAT	0.00	0.03	0.989
Eating behaviour * Sleeping behaviour —> VAT	0.02	0.03	0.425

Table 3. Health behaviour interactions on inflammation (GlycA) and visceral adipose tissue (VAT). Unstandardized estimates are presented. SE = Standard error of the unstandardized parameter estimate.

activity behaviours and inflammation were not detected when VAT was considered. More disordered eating behaviour (β = 0.020, *P* = < 0.001) and lower physical activity (β = − 0.004, *P* = 0.004) were associated with higher inflammation through higher VAT (Table 2). The model explained 29% of the variance in inflammation.

Moderation between VAT and inflammation

Physical activity moderated the association between VAT and inflammation (β = − 0.002, *P* = 0.001) whereas sleeping and eating did not (Additional file 3, Table S5). The association between VAT and inflammation was more pronounced in those who were physically less active (Fig. 4). Next, a combined effects analysis was performed to test interactions between health behaviours on both inflammation and VAT (Table 3). The association between eating behaviour and VAT was influenced by the amount of physical activity (β = 0.08, *P* = 0.001). This interaction is illustrated in Fig. 5. To better understand this interaction, an additional model using the EDE-Q global score cut-off value ≥ 2.3 indicating disordered eating[57] was performed. In this additional interaction model, a higher amount of physical activity was associated with lower amount of VAT among women without features of disordered eating, while the association was less clear among women with a higher global score (Additional file 3, Fig. S1).

Discussion

This cross-sectional study aimed to investigate whether health behaviours are associated with metabolic inflammation in menopause. Using a structural equation modeling, we observed a direct association between VAT and inflammation. Furthermore, indirect associations between eating and physical activity behaviours and inflammation that were mediated by VAT, were observed. In the moderation analysis, physical activity moderated the association between VAT and inflammation. Furthermore, physical activity was identified as a moderator of the association between eating behaviour and VAT. As far as we know, this is the pioneering study investigating the associations of these combined effects of health behaviours and inflammation in menopause.

Consistent with our hypothesis, we observed that VAT had a positive direct association with metabolic inflammation. As already proven earlier, adipose tissue, located around the viscera, secretes inflammatory

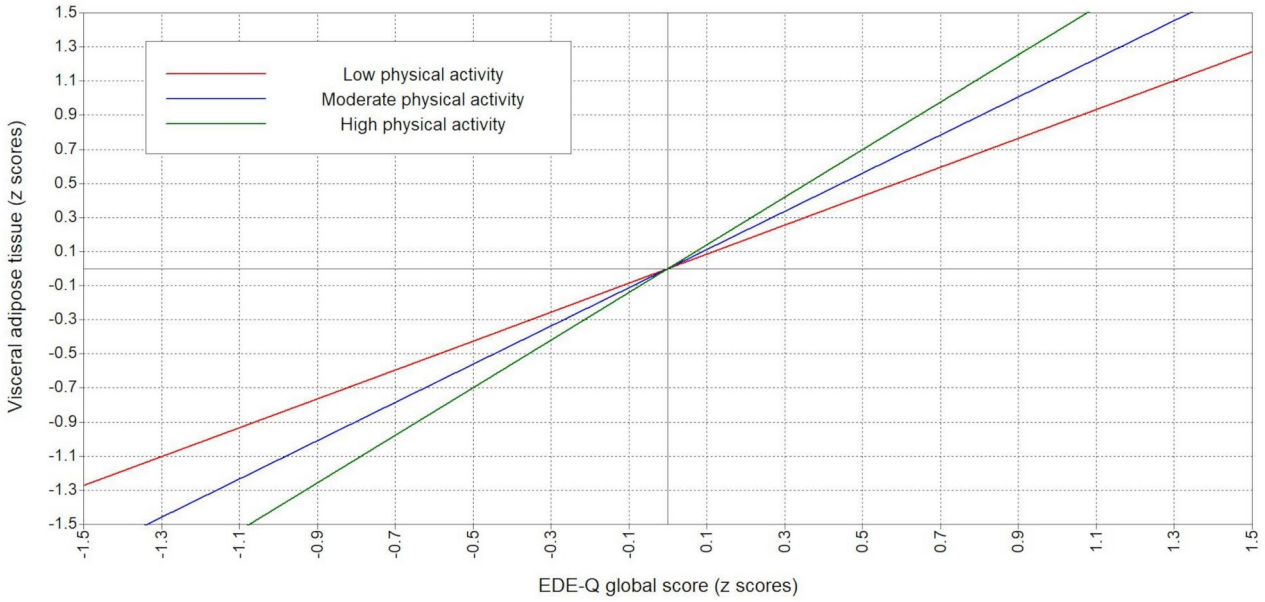

Fig. 5. Interaction between eating and physical activity behaviour on visceral adipose tissue (VAT). Units are presented as *z* scores.

cytokines in circulation and is a significant risk factor for metabolic abnormalities[58,59]. In this study, we wanted to further elucidate the role of health behaviours on the phenomena.

While sleeping is suggested to contribute inflammation, it is known that in menopausal stage, women report increasingly sleep problems[23]. Contrary to our hypothesis, sleeping behaviour was not directly nor indirectly associated with inflammation through VAT. There are various potential reasons for this. In one study sleep inconsistency was associated with inflammation, but this association did not remain significant after controlling for age, sex, BMI, health, and medications[17]. This implies the presence of other factors contributing to inflammation among poorly sleeping women. Contrary to the present study, in Liu et al.' research, experiencing poor sleep quality was associated with higher levels of hs-CRP in women[60]. However, in their study, they were not able to control the amount of physical activity, which is known to influence on the quality of sleep[61], and which was included in our statistical model. In the present study, we utilized self-reported sleep duration in addition to the perceived sleep quality. In one earlier study, longer self-reported sleep duration has been suggested to be positively associated with markers of inflammation, such as CRP and interleukin-6[62], while other study found no association[63]. However, it is worth noting that the dimensions of sleep are not all the same. Indeed, as Dolsen et al.[64] have pointed out, not all measures of sleep are plausibly associated with markers of inflammation. Previous studies have used various methodologies and measures such as sleep disturbances, sleep duration or sleep restriction, and sleep efficiency. Furthermore, both laboratory settings with objective measures and subjective self-report assessment at home have been used to examine the association between sleep and inflammation[64]. Hence, the results have been variable, and the comparison between the studies is rather problematic.

In the present study, we did not observe direct association between eating behaviour and inflammation. Instead, more disordered eating (i.e. scoring higher in EDE-Q) behaviour was associated with higher inflammation through VAT. The absence of a direct association between eating behaviour and inflammation when VAT was considered, suggests that there are other factors contributing this phenomenon. Contrary to the present study, at least a few studies have suggested that women with eating disorders (regardless of diagnosis) have altered inflammatory profiles[65,66]. However, the study population in these studies consisted of young women with diagnosed eating disorder. Healthy eating behaviour is characterized by flexible restraint. It is a dialogue between satiety and hunger, allowing flexibility regarding the quality and quantity of foods eaten[67,68]. The EDE questionnaire evaluates eating pathology and assesses behavioural problems concerning eating[47]. More specifically, questions assess the severity of disordered eating and body image and weight concerns. To our knowledge, the present study is the first to use EDE-Q to investigate the association between eating behaviour and inflammation in the context of menopause. Earlier studies such as by Succurro et al.[26] have, for example, investigated binge eating among women and men. Study participants with obesity and binge-eating disorder (BED) had worse metabolic and inflammatory profile compared to participants with obesity but without BED. As EDE-Q describes disordered eating, the results are somewhat comparable in terms of studies concerning BED.

We did not find a direct link between physical activity and inflammation when VAT was considered. A potential reason could be the relatively high level of activity of our study population, as suggested in some other studies. For example, Barber et al.[69] conducted a combined analysis of 14 exercise interventions. In their study, GlycA level decreased with increased physical activity in previously sedentary people. Our study sample, however, was quite physically active. This could be the reason physical activity was not directly associated

with higher level of GlycA, when mediating factor was considered. Vella et al.[70] for their part, suggested that moderate-to-vigorous physical activity might be associated with a favourable inflammatory profile independent of central adiposity. However, on average, the participants had higher BMI and had more metabolic risk factors or diseases compared to the present study population. Instead of a direct association, it seems that the link between health behaviour and inflammation goes through VAT.

In the present study, the moderation of physical activity on the association of VAT and inflammation was more pronounced in women who were less physically active. This further affects inflammation and is in line with previous research, where replacing sedentary time with physical activity produced significant improvements on inflammation in older women[27]. Physical activity enhances the mobility of energy reserves from the adipose tissue, which is suggested to be more pronounced in visceral fat[8,71]. In line with this, as Freedland[72] has pointed out, weight loss, especially loss of VAT, is more noticeable among persons with greater amount of VAT. Furthermore, aerobic exercise has been suggested to contribute favorably to adipose distribution profile that reduces the risk of metabolic syndrome[8]. These findings support the results of the present study, as VAT had a stronger association with GlycA among women who were less active, and weaker association with GlycA among women who were more physically active. More importantly, exercise even without weight loss is a feasible method for reducing VAT[73] and further metabolic inflammation.

In the present study, we acknowledged three aforementioned health behaviours at the same time but did not cluster them. Instead, we decided to carry out an interaction analysis. We noticed a combined effect in eating and physical activity behaviours, but not in sleeping with either eating or physical activity behaviour. Contrary to the present study, Van Strien and Koenders[20] have found an interaction between emotional eating and sleep duration on BMI change in women. It could be hypothesized that any health behaviour alone is less powerful to prevent the development of inflammation, especially, when it is known that health behaviours are prone to cluster[74,75]. There is a synergistic effect when it comes to both adverse and beneficial health behaviour. As they intersect by their physiological pathways, health behaviours further effect on similar health issues, such as cardiovascular diseases and diabetes[76]. For the analysis, we applied EDE-Q global score cut-off value of ≥ 2.3 indicating eating disturbances. The other cut-off values have been used as well[77], but the aforementioned is used in an earlier study, in a similar population, hence we decided to choose that one[57]. In the present study, 8% of women reached that score indicating that quite many women in our study experience eating disturbances. The association between physical activity and VAT was more pronounced among women without eating disorder (i.e. EDE-Q global score value ≤ 2.3). As for the women with higher global score, the amount of physical activity was less significant. In other words, higher physical activity along with healthy eating behaviour was associated with lower VAT. This adds up to the research concerning the synergistic effect of health behaviours and their beneficial role in prevention of chronic diseases.

To our knowledge, the combined effects of health behaviours, and the mediation of VAT on inflammation, has not been studied before in the context of menopausal women. We utilized a population-based sample, that was drawn from the Population Register Center of Finland. The use of composite marker GlycA as an indicator of inflammation instead of hs-CRP or other traditional single molecule biomarkers of metabolic inflammation is another strength. The physiological connection between VAT and GlycA is fairly strong. GlycA shows a stronger link to dysfunction in adipose tissue compared to hs-CRP[78]. Furthermore, since GlycA senses changes in several acute-phase proteins in serum, it has a stronger predictability of cardiovascular diseases than traditional biomarkers[34,79]. The serum levels of GlycA also respond to non-pharmacological interventions such as physical activity and weight loss[40].

However, there are certain limitations to be considered while interpreting these results. We acknowledge that the size of the analytic sample remained rather small, which may have increased the risk of Type II error. Hence it is possible there were associations that remained unobserved. It is also worth noting, that the current study is a secondary analysis, thus, not all of the health behaviour questionnaires of the observational EsmiRs study, were optimal as the compromises taken to avoid overly lengthy questionnaires. Furthermore, since the present study is cross-sectional, it does not comprise the temporal aspects of the studied phenomenon and the results cannot be interpreted causally. Health behaviour measurements were all obtained by self-administered questionnaires, which, as such, may not capture all the necessary information. Self-report, however, is a widely used way of gathering information about health behaviour due to its cost-effectiveness and effortlessness, but the validity of these questionnaires is partly limited at least concerning the assessment of physical activity[80]. While the questionnaire captures leisure-time and active commute physical activity, it does not comprise the overall daily activity. The validation study of the Finnish version of EDE-Q conducted in 2014[47] showed that it is a reliable and valid tool among adolescents, adult men and women, as well as eating disorder patients. However, in food intake questionnaires underreporting is a valid concern[81], and the embellishment of one's answers might be the case in eating behaviour questionnaires as well. Sleeping behaviour was assessed with two questions resembling the validated Pittsburgh Sleep Quality Index[82], however, using only two questions might limit the results obtained. This is one plausible reason why we did not see the association between sleep behaviour and inflammation. Poor sleep is associated with increased use of sleep medication[83]. In that sense, compared to women excluded in the analyses, women in the analytic sample were better sleepers, since the use of sleep medication was lesser. Furthermore, the average BMI of the participating women in the present study, was moderate (25.7). This might have affected the results obtained, since metabolic inflammation largely applies to persons with severe obesity. It is also worth noting that social factors are often behind the health behaviours, and the link between socioeconomic position and inflammation has been recognised[52]. This might be a plausible source of selection bias, therefore, we attempted to control it by using income as a controllable covariant. However, since participants recruited in health behaviour studies tend to be more active and healthier rather than inactive and unhealthy some residual confounding compared to full population is likely to have remained.

To further the generalizability of the results, combined effects research with larger study populations and longitudinal design focusing on modifiable health behaviours is necessary to elucidate the existing pathways between health behaviour and metabolic inflammation, and further aiming to prevent cardiovascular and metabolic diseases in menopause.

It is important to recognize the adverse effects of disordered eating and sleeping behaviour and the lack of physical activity on visceral adiposity accumulation. According to the present study, health behaviours, especially physical activity combined with eating behaviour could have a modifiable role on inflammation. With physical activity, it is possible to reduce the amount of VAT, and further help to prevent metabolic and cardiovascular diseases. It is also noteworthy that even 5–10% weight loss especially around the viscera is able to mitigate the risk of aforementioned diseases[72]. In the light of the present study, VAT is strongly associated with inflammation, but with a higher level of physical activity, it is possible to mitigate the adverse effects of inflammation, regardless of obesity. When combined with healthy eating behaviour, higher physical activity may have even a bigger role in reducing inflammation. Although the studied population consisted of menopausal women, it is important to note that the contributing factor for inflammation is VAT rather than menopause itself. The present study increases knowledge about the importance of comprehensive investments in health, since for example changing one's eating behaviour is not necessarily enough, but when combined with other health behaviours, the overall effect might be adequate.

In conclusion, these results build on existing evidence of advantages in increasing physical activity especially among sedentary women to control excess adipose tissue. This is important, since menopausal stage is characterized by excessive adiposity around the viscera, and furthermore, women with sedentary behaviour are more likely to be in higher risk of metabolic inflammation and further cardiometabolic diseases. The present study offers potential hypotheses for future longitudinal study designs.

Data availability

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Received: 10 September 2024; Accepted: 1 January 2025
Published online: 15 January 2025

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Acknowledgements

The authors want to thank the laboratory staff in the Faculty of Sport and Health Sciences for their invaluable help with the data collection, as well as the participants of the ERMA and EsmiRs studies who volunteered their time and effort.

Author contributions

Conceptualization, H.L., T.K., E.M.H. and E.K.L.; Methodology, Formal analysis, H.L. and T.K.; Writing—original draft, H.L.; Writing—Review and Editing, H.L., T.K., E.-M.H. and E.K.L.; Visualization, T.K. and H.L.; Supervision, T.K., E.M.H. and E.K.L.; Funding Acquisition, E.M.H. and E.K.L.; Project Administration, E.K.L. All authors read and approved the final manuscript.

Funding

The study was supported by the Academy of Finland and Juho Vainio Foundation.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Ethical approval for the ERMA and EsmiRs studies were provided by the ethical committee of the Central Finland Health Care District (Dnro 8U/2014 and 9U/2018, respectively). Written informed consent was obtained from all individual participants in the study.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-85134-8.

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