BMJ Open  Long-term effect of physical activity on health-related quality of life among menopausal women: a 4-year follow-up study to a randomised controlled trial

Kirsi Mansikkamäki,1,2 Jani Raitanen,1,3 Clas-Håkan Nygård,3 Eija Tomás,4 Reetta Rutanen,3 Riitta Luoto1

ABSTRACT

Objectives: The aim of the study was to explore the long-term effects of physical activity intervention on quality of life (QoL) 4 years after an original randomised controlled trial (RCT).

Design: Cohort study after an RCT.

Setting: 95 of the 159 women from the original RCT participated in weight, height and waist circumference measurements, performed the UKK 2 km Walk Test and completed the SF-36 Health Survey questionnaire. Multilevel mixed regression models were performed in order to compare the original and current group in an RCT setting.

Participants: There were 159 participants in the original RCT; 2.5 years later, 102 of the women responded to a questionnaire and 4-year after the trial, there were 95 respondents. The inclusion criteria in the original RCT were: being symptomatic, experiencing daily hot flushes, age between 40 and 63 years, not using hormone therapy now or in the past 3 months, sedentary lifestyle and having last menstruated 3–36 months earlier.

Main outcome measure: Health-related QoL as measured with the SF-36 instrument.

Results: Women in the intervention group had a significantly higher probability of improved physical functioning (OR 1.41; 95% CI 1.00 to 1.99) as compared with women in the control group. In addition, women in the intervention group had higher odds of good role functioning (OR 1.21; 95% CI 0.88 to 1.67), physical health (OR 1.33; 95% CI 0.96 to 1.84) and general health (OR 1.14; 95% CI 0.81 to 1.62), relative to women in the control group, although the differences did not reach statistical significance.

Conclusions: Women in the intervention group showed positive long-term effects on physical and mental dimensions of QoL after 4 years.

Trial registration number: ISRCTN54690027.

INTRODUCTION

Many physiological and psychological signs and symptoms occur in the lives of middle-aged women.1 A positive association between physical activity (PA) and quality of life (QoL) has been explored in many studies.2–7 PA has been associated with lower rates of cognitive and physical decline among postmenopausal women.8 In addition, PA appears to have positive effects on work ability, both short and long terms.9 Hormone therapy (HRT) is widely used as treatment for menopause symptoms, even though exercise has been deemed an alternative option for alleviating their symptoms and improving QoL in midlife.11 In an 8-year follow-up study, PA has been found to be a significant factor among menopausal women who had stable weight or were highly educated.4 Increasing one’s level of PA during menopausal transition and the postmenopausal period or at least maintaining the recommended level has also been suggested to reduce various psychological symptoms.12

We previously reported results from our menopausal health and PA intervention randomised controlled trial (RCT)6 12 examining aerobic training, and improved menopausal and health-related QoL among menopausal women. Women in the intervention group showed significantly larger decrease in the frequency of night-time hot flushes. These
findings were based on information collected through mobile phone diaries. Additionally, the diaries pointed to better sleep quality among women in the intervention group as compared to those in the control group.\(^7\) We also reported that the 6-month exercise intervention had effects on work ability 2½ years after the RCT.\(^9\)

The aim of the follow-up study reported here was to explore the long-term effects of the PA intervention on QoL 4 years after the RCT.

**MATERIALS AND METHODS**

The study population consisted of a sample of women who participated in a follow-up 4 years after the beginning of the trial, which was in 2009.\(^6\) The intervention study in 2009 was a RCT (ISRCTN54690027, http://www.controlled-trials.com/) in which the women were randomised into an intervention and a control group. Criteria for inclusion in the intervention study were: being symptomatic, experiencing daily hot flushes, age between 40 and 63 years, not using HRT now or in the past 3 months, having a sedentary lifestyle (with aerobic training under twice a week) and having last menstruated 3–36 months earlier. Women who were physically active (exercising two or more times a week, at least 30 min at a time); whose body mass index (BMI) was active (exercising two or more times a week, at least 30 min at a time); whose body mass index (BMI) was active (exercising two or more times a week, at least 30 min at a time); whose body mass index (BMI) was.

The characteristics of the study population are described best in terms of means and SEMs, or frequencies and percentages (table 1). Multilevel mixed effects logistic regression models were constructed to account for the within-subject correlation between four time points. The odds model was used for analysis of the association between the outcomes both on the physical dimensions (physical functioning; role functioning; physical; freedom from pain; and physical health) and on the psychological dimensions (role functioning; emotional; vitality; emotional well-being; social functioning; general health; and mental health) over time and between the intervention versus the control group. Multilevel linear regression models could not be used, because the distributions of SF-36 variables were skewed or discrete. Since the conditions necessary for the use of multilevel ordinal logistic
regression models were not met, these models could not be used either.

The multilevel model for dichotomous outcome $y_{ij}$ at time $i$ for person $j$ can be expressed as

$$\text{logit}\{\Pr(y_{ij} = 1|\xi_j)\} = b_1 + b_2x_{2j} + b_3x_{3ij} + b_4x_2x_{3ij} + \xi_j,$$

where $x_{2j}$ represents group, $x_{3ij}$ represents time, $\mathbf{x}_j = (x_{2j}, x_{3ij})'$ is a vector containing both covariates, and $\xi_j$ is a person-specific random intercept. This model allows for a difference between groups at baseline $\beta_2$, and linear changes in the log odds of outcome over time with slope $\beta_3$ in the control group and slope $\beta_3 + \beta_4$ in the intervention group. Therefore, $\beta_4$, the difference in the rate of improvement (on the log odds scale) between groups, can be viewed as changing over time between groups.\textsuperscript{17}

Also second-order and third-order functions of time were included in the model, for testing of whether a model with a non-linear effect improved the fit. A likelihood-ratio test was used for models’ comparison, to identify the model fitting best. The parameter estimates were presented as ORs with 95% CIs.

The proportions for the physical and mental dimensions of QoL by time are shown in figures 1 and 2. The outcomes of QoL dimensions were classified in two categories according to medians. Proportions of women having higher or equal score than median are shown in figures. Higher score defines more favourable health state. The Wilson score method without continuity correction:

$$\left(\frac{2np + z^2 \pm z \sqrt{z^2 + 4npq}}{2(n + z^2)}\right),$$

where $n$ denotes the sample size, $p$ is a single proportion, $q = 1 - p$ and $z$ denotes the standard normal deviate.
associated with a two-tailed probability $\alpha$, was used to
calculate the 95% CIs for the proportions in figures 1 and 2.18
The significance of all tests was determined to be at a
$p$ value <0.05, and data analyses were performed with
Stata Statistical Software, Release 12 (from StataCorp LP,
College Station, Texas, USA).
In these models, we used all available responses from
women even if they had not responded to all points of
data collection. As sensitivity analyses, we performed
multilevel mixed effects logistic regression models also
for women who responded to all four time points
(N=75). We also analysed the results by using only the
second follow-up (without 2.5 years follow-up).

RESULTS
Most of the participants (68%) were employed or part-
time workers (9%) when the intervention began. Over
the course of the 4 years, 7–20% of the women were in
part-time employment.
The women participating in the 4-year follow-up
were, on average, 58 years of age, and their mean BMI
was 26–27 kg/m². In the follow-up, no significant
change in BMI was observed. The proportion of
women using HRT was higher at the 4-year follow-up
point than before the intervention. In the follow-up,
no significant differences were observed in use of
blood pressure and cholesterol medication. Use of
headache medicine and other painkillers, sedatives
and sleeping pills, and antidepressants, decreased within
the intervention group and also among those in the
control group. The intervention and the follow-up
showed increased use of vitamins and mineral prepara-
tions in the intervention group (from 55.1% to 68.9%)
while in the control group their use declined
(from 51.9% to 34.0%); these results are presented in
table 1.
The women in the intervention group had a greater
likelihood of improvement on the various QoL dimen-
sions from baseline to the end of 4-year follow-up.
Overall, the results show that women in the intervention
group sustained their improved QoL more often than
women in the control group did. Figures 2 and 3 show
the proportions observed for the physical and mental
dimensions of QoL.
With the follow-up measurements, we found that
women in the intervention group displayed an improve-
ment in physical functioning (OR 1.41; 95% CI 1.00 to
1.99) when compared with the control group. However,
no significant differences were observed between groups
for the other variables, as is indicated by table 2. Results
for mental dimensions of QoL did not reach statistical
significance (shown in table 3).
The women who did not participate in the 2½-year and
4-year follow-up studies (N=47, 28.1%) were younger at
baseline (53.0 years, in contrast to 54.5 years), they had a
higher BMI (28.0, in contrast to 26.3) and they were

### Table 1

Characteristics (mean and SEM or frequency and percentage) of all participants

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of intervention 2½ Years</th>
<th>4 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INT</td>
<td>CON</td>
<td>INT</td>
</tr>
<tr>
<td>N</td>
<td>7</td>
<td>88</td>
<td>17</td>
</tr>
<tr>
<td>Age, mean (SEM)</td>
<td>78</td>
<td>81</td>
<td>75</td>
</tr>
<tr>
<td>BMI, mean (SEM)</td>
<td>54.4 (0.42)</td>
<td>54.1 (0.41)</td>
<td>52.2 (0.53)</td>
</tr>
<tr>
<td>Use of medicine in the past 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy, N (%)</td>
<td>2 (2.6)</td>
<td>2 (2.8)</td>
<td>5 (7.7)</td>
</tr>
<tr>
<td>Blood pressure and cholesterol medication, N (%)</td>
<td>12 (18.8)</td>
<td>12 (18.5)</td>
<td>32 (40.7)</td>
</tr>
<tr>
<td>Headache medicine and other painkillers, sedatives and sleeping pills, and antidepressants, N (%)</td>
<td>33 (40.7)</td>
<td>30 (40.0)</td>
<td>12 (19.8)</td>
</tr>
<tr>
<td>Vitamin and mineral supplements, N (%)</td>
<td>33 (40.7)</td>
<td>30 (40.0)</td>
<td>12 (18.8)</td>
</tr>
<tr>
<td>BMI, body mass index</td>
<td>28.0</td>
<td>28.6 (0.79)</td>
<td>26.0 (0.56)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CON, control; INT, intervention.
regular smokers more often (27.3%, in contrast to 12.0%) than the women who participated in the follow-up study.

As sensitivity analyses, we performed multilevel mixed effects logistic regression models also for women who responded to all four time points (N=75). When these women with non-missing responses were taken in the analyses, intervention women had significantly higher probability of improved mental health functioning (OR 1.96; 95% CI 1.13 to 3.40) as compared with control women (not shown in the figures or tables). Results from the models including only 4-year follow-up responses without 2.5 year responses were similar to the results in the current tables and figures.

DISCUSSION
The physical exercise intervention may have long-term positive effects on health-related QoL among the group of menopausal women experiencing daily symptoms of menopause. Women in the intervention group had a higher probability of improvement in physical functioning dimension of QoL from baseline to the end of 4-year follow-up. Among a subsample of women who responded to both follow-up studies, significant results between the groups were found between mental health dimensions. Overall, the results show that women in the intervention group sustained their improved QoL on both physical-health and mental-health dimensions more often than did women in the control group.

Findings from previous studies have shown that getting physical exercise is correlated with lower estimates of the perceived severity of symptoms and that exercise moderates the psychological symptoms associated with menopause.19 20 Our study is in line with these findings both in physical and mental dimensions. A report on an 8-year population-based follow-up study from Finland4 states that motivation to increase one’s PA during menopausal transition might be an explanatory factor connected with improved QoL. According to that follow-up study, women whose PA increased or remained stable, had a higher probability of improved QoL than women whose PA decreased.4 Elavsky19 found, in a longitudinal study of middle-aged women, that PA was associated with self-worth and by this mechanism improved QoL. Furthermore, Stojanovska et al1 recently published a review of the role of PA in reducing symptoms of menopause. They considered both somatic and psychological dimensions. On the basis of their review, physical exercise has been proposed as an alternative to HRT, for improving the QoL of menopausal women.

Our study has its limitations, in the response rate (59.7%) and the fact that women with an adverse lifestyle were more likely to be found among non-responders. All initial participants were included in the analyses, even if they did not participate to the end of the study. The study did not account for confounding factors such as age, weight, or other health conditions that may influence QoL. Additionally, the study was not able to capture the long-term effects of the intervention, as the follow-up period was limited to 4 years.

The physical dimensions of quality of life (QoL) by time. Outcomes of QoL dimensions were classified into two categories according to medians. Proportions of women having higher or equal score than median are shown. Higher score defines more favourable health state.
the intervention or the 2.5-year follow-up study. The results of the study showed a tendency towards increased QoL, although there were no statistically significant differences for any cores on the physical and mental dimensions of QoL between the groups. Our findings are similar to those from a large multiethnic volunteer group.

**Figure 3** Proportions for mental dimensions of quality of life (QoL) by time. Outcomes of QoL dimensions were classified into two categories according to medians. Proportions of women having higher or equal score than median are shown. Higher score defines more favourable health state.

**Table 2** Multilevel mixed effects logistic regression, ORs and 95% CIs of physical dimensions of QoL

<table>
<thead>
<tr>
<th></th>
<th>Physical functioning</th>
<th>Physical role functioning</th>
<th>Freeness from pain</th>
<th>Physical health</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>159</td>
<td>159</td>
<td>159</td>
<td>159</td>
</tr>
<tr>
<td>Group_baseline</td>
<td>0.52 (0.17 to 1.61)</td>
<td>0.84 (0.33 to 2.12)</td>
<td>0.58 (0.22 to 1.54)</td>
<td>0.72 (0.28 to 1.81)</td>
</tr>
<tr>
<td>Time</td>
<td>1.03 (0.10 to 11.1)</td>
<td>0.93 (0.75 to 1.17)</td>
<td>1.07 (0.85 to 1.34)</td>
<td>0.97 (0.77 to 1.22)</td>
</tr>
<tr>
<td>Group_time_1</td>
<td>44.7 (1.45 to 1374)*</td>
<td>1.21 (0.88 to 1.67)</td>
<td>1.25 (0.90 to 1.73)</td>
<td>1.33 (0.96 to 1.84)</td>
</tr>
<tr>
<td>Time_2</td>
<td>0.86 (0.19 to 3.82)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group_time_2</td>
<td>0.11 (0.01 to 0.91)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time_3</td>
<td>1.04 (0.82 to 1.32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group_time_3</td>
<td>1.41 (1.00 to 1.99)*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05.
cohort of postmenopausal women, in which self-reported PA was, for the most part, stable over 8 years of follow-up. There was approximately 0.3 metabolic equivalent (MET) of actual growth in recreational PA per year×8 years=2.4 MET h/week, which represented 30 min of brisk walking in this case.21

Loss-to-follow-up analysis showed differences between participants and those lost to follow-up. Non-responding women differed from responding women in their weight, age and smoking status. Respondents were lighter, older and were less often regular smokers than non-responding women. These differences might have had an effect on the findings in the follow-up study. If all of the original participants had been studied, the differences between the groups might have been larger. When limiting the analyses to women responding to both follow-up measurements, the results differed. Explanation for this may be due to the fact that conscientious women responding to questionnaires may have benefited even more from available support to be physically active. A follow-up study in itself can be considered an intervention, producing a non-differential support to the original groups in the RCT.

The core strengths of the study reported here are its prospective study design and repeated assessments of PA behaviour, which made it possible to examine the differences between groups in the follow-up.17 Many studies have described PA patterns through the lens of cross-sectional data, while fewer studies have examined changes between several time points after an intervention. PA has been reported to decrease with age,22 but contrary findings have also been reported. Earlier, our research group published the finding6 that women in menopausal transition shifted their behaviour in the other direction. Therefore, increased PA could be explained by higher motivation for lifestyle changes during the menopausal transition. In a longitudinal study by Smith-DiJulio et al,23 the researchers found that a woman’s sense of control, of her life and satisfaction with it, and her ability to make use of the available social support, predicted greater well-being during menopause. This is consistent with our findings, as we observed improvement in vitality, emotional well-being and mental health during the follow-up, even though the results did not reach a level of statistical significance.

Our results may be generalised to menopausal women having daily vasomotor symptoms, such as hot flushes or sleep problems, according to the inclusion criteria in the original RCT.6 Overall, our study underlines the importance of PA during menopausal transition. In addition, it supports the assumption that menopause can be seen as a window of opportunity, since it may motivate women to modify their lifestyle. Menopausal women should be encouraged to participate in regular exercise and supported in this endeavour through development of easily implemented home-based exercise programmes or incorporation of PA programmes into public-health initiatives.10
CONCLUSION
Women in the intervention group showed positive long-term effects on physical and mental dimensions of QoL after 4 years. Menopause is a window of opportunity for increasing PA and thereby future QoL. This finding is important, since an increase in PA may be associated with a lower future disease burden.

Acknowledgements Biomedical laboratory scientists Ulla Hakala, Ulla Honkanen and Sirke Rasipinperä; research assistant Taru Helenius; and Katriina Ojala, MSc, of the UKK Institute laboratory, performed all the measurements for the research and handled contact with the participants. Anna Shefl performed language editing.

Contributors KM and RL prepared the first version of the manuscript. JR was responsible for the statistical analyses. C-HN, ET and RR participated in drafting the manuscript and have approved the final version.

Funding Financial support for the follow-up study was received from the Juho Vainio Foundation (Finland), the Pirkanmaa Competitive Research Fund (Tampere, Finland) and the Academy of Finland.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was granted ethics approval by the Pirkanmaa Hospital District Ethics Committee, Tampere, Finland.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are some data from the questionnaires that are unpublished but all data concerning the measurements are published.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES
Long-term effect of physical activity on health-related quality of life among menopausal women: a 4-year follow-up study to a randomised controlled trial

Kirsu Mansikkamäki, Jani Raitanen, Clas-Håkan Nygård, Eija Tomás, Reetta Rutanen and Riitta Luoto

*BMJ Open* 2015 5:
doi: 10.1136/bmjopen-2015-008232

Updated information and services can be found at:
http://bmjopen.bmj.com/content/5/9/e008232

These include:

**References**
This article cites 21 articles, 2 of which you can access for free at:
http://bmjopen.bmj.com/content/5/9/e008232#BIBL

**Open Access**
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Errata**
An erratum has been published regarding this article. Please see next page or:
http://bmjopen.bmj.com/content/6/1/e008232corr1.full.pdf

**Topic Collections**
Articles on similar topics can be found in the following collections:

- Public health (1531)
- Sports and exercise medicine (155)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/
Correction

Mansikkamäki K, Raitanen J, Nygård C-H, et al. Long-term effect of physical activity on health-related quality of life among menopausal women: a 4-year follow-up study to a randomised controlled trial. BMJ Open 2015;5:e008232. There are several errors in this manuscript and are described below.

1. On page 2, ‘Statistical analysis’ section the following sentence is incorrect:
   The odds model was used for analysis of the association between the outcomes both on the physical dimensions (physical functioning; role functioning, physical; freedom from pain; and physical health) and on the psychological dimensions (role functioning; emotional; vitality; emotional well-being; social functioning; general health; and mental health) over time and between the intervention versus the control group.
   The correct sentence is:
   The odds model was used for analysis of the association between the outcomes both on the physical dimensions (physical functioning; role functioning, physical; freedom from pain; and physical health) and on the psychological dimensions (role functioning, emotional; vitality; emotional well-being; social functioning; general health; and mental health) over time and between the intervention versus the control group.

2. On page 3, the sentence ‘The proportions for the physical and mental dimensions of QoL by time are shown in figures 1 and 2.’ should be ‘The proportions for the physical and mental dimensions of QoL by time are shown in figures 2 and 3.’

3. In figure 3, the middle left panel should be titled ‘Social functioning’ and the lower left panel should be titled ‘General health’.

4. Reference 7 is incorrect. The corrected reference is:

BMJ Open 2016;6:e008232corr1. doi:10.1136/bmjopen-2015-008232corr1