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Effectiveness of a treadmill-based aerobic exercise intervention on pain, daily functioning, and quality of life in women with primary dysmenorrhea: A randomized controlled trial

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ABSTRACT

Objective: To evaluate the effectiveness of a treadmill-based aerobic exercise intervention on pain and associated symptoms of primary dysmenorrhea.
Methods: Seventy women with primary dysmenorrhea were included in the study. The experimental group underwent supervised aerobic training for 4 weeks followed by unsupervised home exercise for the next 6 months. The control group continued usual care. The primary outcome was pain. Secondary outcomes included quality of life (QoL), daily functioning, and sleep.
Results: After the 4-week training, compared to the control group exercise significantly improved primary outcomes pain quality (mean difference (MD) -1.9, 95% CI 3.8 to −0.04, $p < .05$), and intensity (MD -4.7, 95% CI -9.3 to −0.09, $p < .05$), but not present pain. Significant effects were also reported for pain interference (MD -1.7, 95% CI -3.4 to −0.02, $p < .05$) at 4 weeks; the other outcomes did not significantly differ between groups at this time. During the follow-up period of 7-months, the effect on pain improved to 22 mm (95% CI 18 to 25). Significant benefits of exercise were maintained up to 7-months for present pain, QoL and daily functioning.
Conclusion: Exercise has significant effects on primary dysmenorrhea-related pain, QoL and function.
Trial registration: ACTRN12613001195741.

1. Introduction

Primary dysmenorrhea is a common gynaecological problem among women of reproductive age and has a high socioeconomic impact. The International Federation of Gynecology and Obstetrics defines primary dysmenorrhea as *'painful cramps in the absence of any visible pelvic pathology that could account for it'* [1]. The prevalence of primary dysmenorrhea reported in the literature varies considerably, with greater prevalence among women in the age group 17 to 24 years, and estimates ranging from 67 to 90% [2]. The pathophysiology of primary dysmenorrhea is primarily linked to elevated levels of prostaglandins that induce hypercontractility of the myometrium, leading to ischemia and hypoxia of the uterine muscle. Aerobic exercise is thought to reduce pain by a number of different mechanisms influencing opioid and non-opioid systems [3]. Aerobic exercise has been shown to influence the production of beta-endorphins which are mainly associated with changes in pain perception [4]. Particularly vigorous aerobic exercises are reported to stimulate the largest concentration of beta-endorphins [5]. These beta-endorphins inhibit the release of substance P, a protein crucial for the transmission of pain, and gamma aminobutyric acid, an inhibitory neurotransmitter that is known for inhibiting the activity of pain controlling structures [4,6].

The effectiveness of aerobic exercise on the pain of primary dysmenorrhea is not completely understood. Empirical evidence about the effectiveness of aerobic exercise is needed to guide management of primary dysmenorrhea. Systematic reviews have confirmed the paucity of research in the field of aerobic exercise and primary dysmenorrhea [7,8]. To date, only two randomized controlled trials have evaluated the effect of aerobic exercise for primary dysmenorrhea. [9,10] One of these studies evaluated the effects of aerobic and stretching exercise on pain in primary dysmenorrhea but used non-validated pain intensity outcomes [9]. The other study, published over thirty years ago, investigated the effects of aerobic exercise on menstrual distress symptoms [10]. That study reported the effects of aerobic exercise on

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menstrual distress but did not isolate effects on pain. Both studies have been rated as having low methodological quality in the PEDro database, with scores of 4 and 2, respectively. The lack of high-quality studies justifies the need for a randomized, controlled trial to investigate the effects of aerobic exercise for primary dysmenorrhea.

The research questions were:

1. Does a 4-week aerobic exercise intervention improve pain, quality of life, daily functioning, and sleep in women with primary dysmenorrhea?
2. Are any gains maintained over the following 6-month period with a home exercise programme?

2. Methods

2.1. Design

This study was an assessor blinded, two arm, parallel group, randomized, controlled trial conducted in Dunedin, New Zealand between March 2014 and August 2015. The study protocol [11], based on a previously completed feasibility study [28], was prospectively registered and published [11]. Women with primary dysmenorrhea were randomly allocated to undertake regular aerobic exercise (experimental group) or usual care (control group) by a clinical research administrator using simple randomisation (generated using a random numbers list) with allocation concealment using opaque sealed envelopes. The clinical research administrator was an independent person with no other involvement in the study. Eligible women completed a screening questionnaire about demographic characteristics and details of menstrual pain and use of analgesics. Primary dysmenorrhea was confirmed based on information about the onset of primary dysmenorrhea, pain, and a history of analgesics use [11,12]. Participants then completed the validated short-form International Physical Activity Questionnaire [13] to determine their baseline physical activity levels. All participants were then provided with four sets of self-reported outcome questionnaires and return envelopes for assessment of study outcomes at the first (baseline, week 0) and second menstrual periods (post-intervention, week 4), and menstrual periods at the end of 4 and 7 months. The principal investigator was blinded to group allocation during data analysis, with the two groups being assigned a code which was revealed only after the analysis was completed. A research assistant double-entered raw data onto an electronic spreadsheet and prompted return of questionnaires.

2.2. Participants, therapists, centres

Potential participants were recruited through public and university campus advertising. Eligibility criteria for this study were based on the guidelines for diagnosing primary dysmenorrhea from the Society of Obstetrics and Gynecologists of Canada [14] and in accordance with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for clinical trials that evaluate the effect of interventions on pain [15]. The study included women with primary dysmenorrhea who: were in the age group 18 to 43 years; were not pregnant; were having regular menstrual cycles; and reported moderate-to-severe primary dysmenorrhea-associated pain, indicated by a score of ≥ 4 on a numerical rating scale ranging from 'no pain' (0) to 'unbearable pain' (10) for at least two previous consecutive menstrual periods [16,17]. The exclusion criteria applied during recruitment, including rationale for use are presented in Table 1. Baseline assessments of outcomes were completed during the first menstrual period following entry into the study. A detailed description of the outcomes was published [11] and is described further, below. The principal investigator – a registered physiotherapist with 3 years of specialist experience in the area of pain and women's health – provided the exercise intervention at the University of Otago's School of Physiotherapy.

2.3. Intervention

The clinical research administrator, upon receiving the completed baseline questionnaire, informed the experimental group participants of their group allocation by phone, and made appointments for the exercise intervention. The training period started on the day following the last day of menstruation of the first menstrual period, and ended before the start of the second menstrual period. Exercise intervention was provided as outlined in the protocol.[11] Participants were screened for exercise safety using the Physical Activity Readiness Questionnaire before starting the exercise programme to determine safety or possible risk of exercising. The exercise intervention was for 7 months. Participants underwent supervised aerobic training on a treadmill[2] for four weeks at the school, which was followed by an unsupervised, maintenance programme at home for 6 months. Treadmill training was preceded by warm-up exercises for 10 min and followed by cool down exercises for 10 min, including stretching for mid and lower back, stretches for the pelvic region and strengthening of abdominal and gluteal muscles. Participants performed exercise between menstrual periods, with no exercises during the week of menstruation. The aerobic training at the School of Physiotherapy was performed 3 times per week at 70 to 85% of their maximum heart rate, calculated as 206 minus 88% of age (in years) [18]. The conventional age-predicted formula (ie, 220 – age) was not used because it is not gender specific, and has also been criticised for overestimation of the maximum heart rate among young women and underestimation among older women [18]. During the sessions, participants recorded the distance covered on the treadmill via a pedometer[3] and their heart rate via a monitor[4] worn on the wrist. Owing to funding limitations, participants were not provided with pedometers for the unsupervised maintenance programme at home. The exercises and aerobic training were taught and supervised on a one-to-one basis at the School of Physiotherapy.

The Borg Rating of Perceived Exertion (RPE) Scale from 6 ('no exertion at all') to 20 ('maximal exertion') was used to regulate the exercise intensity on the treadmill. Participants were encouraged to increase the speed of the treadmill until they perceived their RPE to be between 14 and 16. Some study participants had access to a treadmill at the university gym. Other participants who did not have access to a treadmill were encouraged to continue with outdoor walking or jogging. Participants were provided with an adherence diary with the average distance covered on the treadmill at the School of Physiotherapy and were requested to adhere to the target intensity (RPE 14 to 16) and distance of aerobic training. Exercise group participants were requested to record the frequency (number of days per week) and duration of home exercise in the adherence diary. For ethical reasons, no restrictions were placed on the use or amount of analgesics by the exercise group participants.

Control group participants were informed of their group allocation by phone and requested to continue to manage their pain as usual, e.g. with analgesics. Women in the control group did not receive trial intervention but completed the study measures. As with the experimental group participants, no restrictions were placed on the use or amount of analgesics and activity undertaken by the control group participants. Monthly phone calls were made to control group participants to enquire about their pain and to remind them to complete the questionnaires.

2.4. Outcome measures

Assessments were done at baseline (Month 0), at the end of

[2] Weslo Cadence 920, ICON Fitness Lifestyle Limited, Leeds, UK
[3] Digi-Walker SW-700/701, Yamax Health & Sports Incorporated, San
[4] Polar FSI Fitness, Polar Electro Inc., New York, USA

Table 1
Exclusion criteria and justification for use of each criterion.

Exclusion criteria	Justification for use of the criterion
Pregnant women	Pregnant women will not have periods to assess.
Women with irregular menstrual cycles	Irregular cycles are indicative of secondary dysmenorrhea [42].
Menstrual cycles > 35 days apart	Prolonged gaps between menstrual cycles are suggestive of anovulatory cycles and oligomenorrhea [43,44]. Oligomenorrhea is associated with a pathology either in the reproductive system or brain (pituitary tumours) [45].
Women on OCP, hormonal therapy and women using intrauterine devices	These interventions are thought to affect ovulation and/or menstruation [46].
No pain relief with over the counter analgesics	No response to analgesics is suggestive of secondary dysmenorrhea [12].

OCP = oral contraceptive pills.

intervention period at the school (4 weeks), and Months 4 and 7.

2.4.1. Primary outcome

Pain was measured using the validated short-form McGill Pain Questionnaire [19]. The three sub-scales of this questionnaire are: pain quality, measured with the Pain Rating Index; pain intensity, measured with the 0–100 mm Visual Analogue Scale; and the 'present pain' measured with Present Pain Index [20]. A higher score on any sub-scales of the questionnaire indicates worse pain [20]. Participants were instructed to complete all three sub-scales of the questionnaire on the day of maximum pain of menstruation, rating their current pain.

2.4.2. Secondary outcomes

Quality of life was measured using the validated 12-Item Short-form Health Survey (SF-12) [21]. The SF-12 yields two different summary scores: the Physical Component Summary for physical health and the Mental Component Summary for mental health [22]. A higher score on the SF-12 indicates better health [22]. The impact of pain on daily functioning was measured using the Brief Pain Inventory-short form [23]. This questionnaire includes four pain severity items, seven interference items (general activity, mood, walking ability, normal work, relation with other people, sleep, and enjoyment of life) rated on a scale from 0 to 10, and the percentage pain relief obtained from analgesics in the past 24 h [11]. Participants were also required to record the name of the analgesic consumed for pain but dose or consumption was not recorded. A lower score on the questionnaire represents lower severity and less interference [23]. Sleep quality was measured using the Women's Health Initiative Insomnia Rating Scale (WHIIRS) [24]. A score of 9 or greater out of 20 on the WHIIRS indicates clinical insomnia [24,25]. Higher scores on WHIIRS indicate more severe insomnia symptoms [24]. The participants' perception of global improvement was measured using the Patient Global Impression of Change (PGIC) scale [26]. Because the PGIC measures improvement or deterioration, it was not completed at baseline. Based on a previous study, a rating of 6 ('much improved') or 7 ('very much improved) on the PGIC was nominated a priori as the smallest worthwhile effect [27]. Adherence to exercise sessions at the School of Physiotherapy was assessed through session attendance. An exercise adherence diary was used to record adherence to the unsupervised maintenance programme. An acceptable level of adherence of 80% was established a priori [9].

2.5. Data analysis

A power calculation was performed for the study, based on the 0–100 mm pain VAS outcome. The anticipated standard deviation was 18.14 mm, based on data from the feasibility study [28]. A between-group difference of 15 mm for pain on the VAS was nominated as the smallest worthwhile effect [29]. The required sample size was estimated to be 70 (35 in each group, assuming 90% power, a two-tailed 0.05 level of significance, and allowing for 15% dropouts. Statistical analysis was performed using SPSS version 22.0 (Armonk, NY) with an intention-to-treat approach. Statistical significance was established as $p < .05$. Missing data were replaced with group means. A sensitivity analysis using a 'last observation carried forward' approach was carried out for VAS. Weekly physical activity levels were based on the average metabolic equivalent tasks [13]. Statistical analysis followed a pre-specified protocol [11]. Statistical analyses was done using repeated-measures analysis of covariance (ANCOVA) with baseline score as the covariate for all primary and secondary outcomes except PGIC. For PGIC, numbers and percentages were calculated and compared across groups. Bonferroni correction was done for significant group-by-time interaction effects [30].

3. Results

Fig. 1 summarises the flow of participants flow through the study. Seventy-nine women were screened for inclusion in the study. Seventy women meeting the eligibility criteria were randomized to the experimental group ($n = 35$) and the control group (n = 35). Two, five, and seven participants were lost to follow-up in the control group at 1, 4 and 7 months respectively. Three, two, and eight participants were lost to follow-up in the intervention group at 1, 4 and 7 months respectively. Following the intention-to-treat protocol, final analysis was done for 35 participants in each group. The participants' baseline physical activity levels and pain for the two preceding menstrual cycles are presented in Table 2. The baseline values of the primary and secondary outcome measures are presented in Supplementary Table 1. No adverse events were reported. With regard to the unsupervised exercise sessions, participants performed exercises on an individual basis.

3.1. Effects of intervention

Table 3 shows the calculated between-group differences at one, four and seven months.

3.1.1. Primary outcome

Exercise provided statistically significant benefits at 1-month for pain quality (Pain Rating Index) and pain intensity (both $p < .05$) compared with the controls. These benefits were maintained at 4 and 7 months (all $p < .01$). The benefits at 7 months for pain intensity were also clinically worthwhile, with a mean benefit of a 21-mm reduction in pain intensity on the 100-mm VAS. A sensitivity analysis using the 'last observation carried forward' approach did not alter the results obtained on the VAS at 7 months ($p < .01$).

For the Present Pain Index, no significant effect was observed at 1 month ($p > .05$). Statistically significant benefits from exercise were observed at 4 and 7 months (both $p < .01$); however, the mean estimates and even the upper limits of the confidence intervals did not reach 1 point on the 5-point scale, suggesting that they may not be clinically worthwhile effects on their own.

3.1.2. Secondary outcomes

On the SF-12 quality of life questionnaire, the Physical Component Summary and the Mental Component Summary did not show a significant effect at 1 month ($p > .05$). Statistically significant benefits were observed at 4 and 7 months (all $p < .01$). Similarly, on the Brief

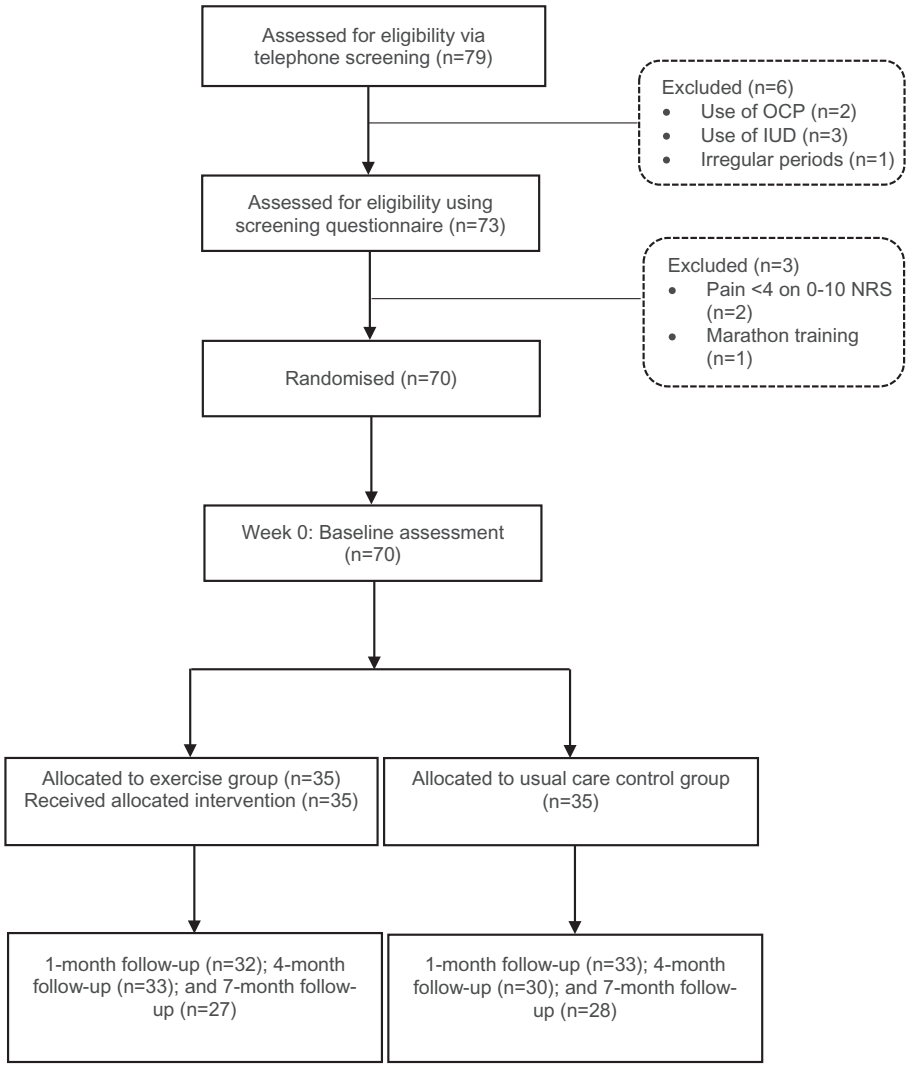

Fig. 1. Participant flow through the study.

Table 2
Baseline measurements of physical activity levels, and mean pain.

Outcomes	Exp (n = 35)	Con (n = 35)
Physical activity level, n (%)		
Low	23 (66)	21 (60)
Moderate	10 (29)	13 (37)
High	2 (6)	1 (3)
Past period pain *(0 to 10)*, mean (SD) [a]		
Period 1	6.5 (1.3)	6.5 (1.3)
Period 2	6.8 (1.3)	6.6 (1.0)

Con = control group, Exp = experimental group, NRS = Numerical Rating Scale.

[a] Period 1 and 2 represent the participant-reported pain intensity of two consecutive menstrual periods and were used to assess eligibility for study participation.

Pain Inventory-short form the pain severity data showed no significant effect at 1 month, but statistically significant benefits were observed at 4 and 7 months (all $p < .01$). Again, however, the mean estimates were < 4 points on the 40-point scale, so they may not be clinically worthwhile on their own. The pain interference data showed statistically significant benefits of exercise at 1 and 4 months ($p < .05$) and at 7 months ($p < .01$), while the data about percentage pain relief with analgesics showed statistically significant benefits at 4 and 7 months ($p < .01$). Again these effects did not exceed 10% of the scales on which they were measured. For the secondary outcome of sleep, there was no significant effect of exercise at months 1, 4 or 7.

For the scores of PGIC, based on the planned analysis of the absolute number of participants with a clinically significant change score, no significant effect of exercise was observed at 1 month ($p > .05$). However, significantly more participants rated their global change as 'much improved' or 'very much improved' in the experimental group compared with the control group at 4 months ($p < .05$) and 7 months ($p < .01$).

4. Discussion

This is the first randomized controlled trial to evaluate the effects of a treadmill-based exercise intervention on multiple domains affected by primary dysmenorrhea. The trial was able to demonstrate that exercise was significantly more effective than control in reducing pain quality, intensity, and interference at 4 weeks. By continuing the follow-up of participants for 6 more months, the trial was also able to demonstrate that this beneficial effect of exercise on pain was sustained to 4 and 7 months. In addition, from 4 months to the completion of the study, there were significant and sustained benefits of the exercise in quality of life, daily functioning, and PGIC. No beneficial effects of exercise were identified on sleep at any of the assessment time points.

This, study not only demonstrated statistically significant

Table 3
Mean (95% CI) of difference between groups at all time points.

Outcomes	Mean difference between groups		
	Month 1	Month 4	Month 7
Primary outcome			
PRI	-1.9 (−3.8 to −0.04)	−2.1 (−3.3 to −0.89)	−2.4 (−3.6 to −1.1)
VAS	−4.7 (−9.3 to −0.09)	−18.9 (−22.7 to −15.2)	−21.1 (−24.8 to −17.5)
PPI	−0.11 (−0.42 to 0.20)	−0.44 (−0.72 to −0.16)	−0.49 (−0.80 to −0.18)
Secondary outcomes			
PCS	2.0 (0.00 to 4.2)	4.0 (1.6 to 6.4)	4.8 (2.2 to 7.6)
MCS	1.3 (−0.42 to 3.1)	2.8 (1.0 to 4.7)	4.5 (2.4 to 6.6)
Pain severity	−0.40 (−0.80 to 1.2)	−2.3 (−3.9 to −0.78)	−3.1 (−4.6 to −1.6)
Pain interference	−1.7 (−3.4 to −0.02)	−2.0 (−3.6 to −0.43)	−2.2 (−3.7 to −0.81)
% pain relief	1.7 (−0.61 to 4.2)	5.1 (2.0 to 8.3)	6.3 (3.2 to 9.3)
Sleep	0.49 (−0.99 to 0.00)	0.49 (−1.0 to 0.02)	0.46 (−0.94 to 0.00)

Abbreviations Con: Control group; Exp: Experimental group; MCS: Mental Component Summary; PCS: Physical Component Summary; PPI: Present Pain Index; PRI: Pain Rating Index; QoL: Quality of Life; VAS: Visual Analogue Scale.
For pain and daily functioning, negative values favour the experimental group; for all other outcomes negative values favors the usual care group. Pain was measured using the short-form McGill Pain Questionnaire (SF-MPQ). Quality of life was assessed using the 12-Item Short-form Health Survey (SF-12). The impact of pain on daily functioning was assessed using the Brief Pain Inventory-short form (BPI-sf).

improvements in primary dysmenorrhea-associated pain with increasing benefit over a 6-month follow-up period, but additionally the best single estimate of the effect of exercise on the primary outcome for pain (VAS) surpassed the threshold for clinical significance (20 mm) [31]. The improvements observed in quality of life scores due to exercise at 7 months are noteworthy. There was a mean change of 4.8 points in the Mental Component Summary score of the SF-12 (Supplementary Table 1). A 5-point increase in the Physical Component Summary or Mental Component Summary of the SF-12 has been reported as predictive of satisfaction with intervention in women with non-cancerous pelvic pain [32].

Another important consideration in interpreting the results is that there were statistically significant and sustained benefits across many of the secondary outcome measures. These multiple benefits (ie, improved quality of life, less interference from pain in daily functioning, etc) could be considered as a 'package deal' by patients. Therefore, although many of these benefits may not be clinically worthwhile, sustained benefits together with the substantial and sustained effect on the primary outcome, use of exercise to help ameliorate pain and its sequelae may be appealing to many patients with primary dysmenorrhea.

One of the anticipated benefits of exercise for participants was improved sleep quality. Moderate to vigorous intensity aerobic exercises are generally thought to improve sleep [33]; However, this study found no improvements in sleep with the intervention. This lack of improvement in sleep could be due to the inclusion of participants with no sleep difficulties. The mean baseline score (3.2) of the experimental group participants (Supplementary Table 1) was less than the clinical insomnia score of 9 out of 20 for the WHIIRS [22], indicating those participants began the intervention with no insomnia symptoms. It is therefore recommended that minimum levels of sleep loss could be set as inclusion criteria for future primary dysmenorrhea trials attempting to measure sleep as an outcome.

Several pain relieving mechanisms, including non-opioid and opioid systems have been proposed for exercise-induced changes in pain sensitivity [3,34,35], and may explain the reductions in pain demonstrated in this study. Firstly, exercise is thought to induce release of endogenous opioids (beta-endorphins) at central, spinal and/or peripheral levels all of which contribute to pain modulation. [3, 35] Secondly, the endocannabinoid-mediated mechanism is thought to contribute to exercise-induced analgesia. [3] Endocannabinoids are receptors that contribute to the control of pain transmission within the brain and spinal cord [3]. Elevations in peripheral blood endocannabinoids concentrations have been reported following aerobic exercise, and it is has been suggested that the activation of cannabinoid receptors produces analgesia [3]. Finally, exercise also induces the release of regulatory macrophages in the physically active muscles [35]. These regulatory macrophages are known for their ability to secrete anti-inflammatory cytokines and counteract the effect of other activated macrophages which secrete pro-inflammatory cytokines [35]. Therefore, following physical activity the overall effect is an increase in anti-inflammatory cytokines which are responsible for pain reduction [34,35]. The intervention tested in this study has the capacity to induce any or all of these mechanisms.

The exercise intervention was employed in this study when women were not menstruating. Changes in hormone levels during different phases of the menstrual cycle are thought to be associated with decreased exercise performance and increased laxity in ligaments, particularly the anterior cruciate ligament (ACL) of the knee [36,37]. A study of ACL laxity related to the menstrual cycle confirmed the risk of ACL injury in the menstruation phase [38]. Despite ACL injuries being common in pivoting sports [39] and least common in sports without cutting or pivoting movements such as running, we restricted women from exercising during menstruation considering the impact of menstrual cycle on exercise performance and consistent with previous studies of aerobic exercise for primary dysmenorrhea [9,10]. Future studies are recommended and required for investigating the anecdotal belief that exercising during menstruation might decrease menstrual bleeding and discomforts of menstruation.

The main strengths of this study are that the methodology was robust, and the feasibility of providing the intervention was tested. There was also a good representation of participants in all the target age ranges, as well as an equal percentage of participants recruited from non-university settings in both groups (40%). Therefore, the findings of this study can be generalised across the age range of women with primary dysmenorrhea. We considered using exercise diaries or logs to evaluate compliance with the home exercise programme. However, the limitation of such methods has been reported in previous studies [40,41] and we therefore elected not to include these in our study. Lack of monitoring of the home exercise programme could be considered a limitation of the study. Another issue with using self-reported measures is that participants may over report their activity levels. In which case the results could be even greater if all prescribed exercise sessions were to be completed as intended. Another limitation may be that, although participants in the exercise and control groups were permitted to take analgesics to manage their pain, the amount or number of analgesics consumed was not monitored or recorded. It is therefore difficult to confirm if the amount of analgesics consumed was consistent between the groups. This is considered a potential limitation of the study

because the amount of analgesics consumed may have influenced the treatment effects reported for percentage pain relief with analgesics in this study. Another limitation of our study is that, participants and the principal investigator were not blinded to treatment groups. However, outcomes assessments were all self-reported and analysis was done blinded. Lastly, there were a number of participants who were lost to follow-up at 7 months in both the groups. The present study was powered to allow 15% dropouts however, the dropout rate was 21% at 7 months follow-up. Thus, the study would not be adequately powered according to per-protocol analysis. However, it is acknowledged that the study was adequately powered with intention-to-treat analysis. That is, whether the last observation was carried forwards (assuming there was no change from the last measurement point) or the mean of the group was imputed as missing data the effects of exercise were highly significant for most outcomes at 7-months. This provides a strong argument supporting the effects of exercise. Reasons for dropping out of study is not known, it is unlikely that it could be related to intervention parameters because our feasibility study identified good acceptance towards the intervention and intensity of training. We recommend future studies to conduct focus groups to obtain participants feedback about the intervention and monitor and record the name and number/amount of analgesics consumed.

The evidence supporting the use of aerobic exercise for managing pain, improving quality of life and improving daily functioning has been strengthened by the findings from this research. However, it is difficult to draw any definitive conclusion from a single randomized trial. Owing to the many benefits of aerobic exercise identified in this study, aerobic exercise could be considered a useful treatment option for the management of primary dysmenorrhea. This study found no evidence to support the use of aerobic exercise for improving sleep in women with primary dysmenorrhea.

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Ethics approval

The Health and Disability Ethics Committee of New Zealand approved this study. Ethics approval reference no.: 13/STH/206. Written informed consent was obtained from all participants prior to data collection.

Conflict of interests

Nil.

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References

[1] M.Y. Dawood, Dysmenorrhea the global library of Women's medicine, (2008) http://www.glowm.com/section_view/heading/Dysmenorrhea/item/9 (Accessed Sept 7, 2015).
[2] H. Ju, M. Jones, G. Mishra, The prevalence and risk factors of dysmenorrhea, Epidemiol. Rev. (2013) mxt009.
[3] K.F. Koltyn, A.G. Brellenthin, D.B. Cook, N. Sehgal, C. Hillard, Mechanisms of exercise-induced hypoalgesia, J. Pain 15 (2014) 1294–1304.
[4] K.M. Naugle, R.B. Fillingim, J.L. Riley, A meta-analytic review of the hypoalgesic effects of exercise, J. Pain 13 (2012) 1139–1150.
[5] L. Schwarz, W. Kindermann, Changes in β-endorphin levels in response to aerobic and anaerobic exercise, Sports Med. 13 (1992) 25–36.
[6] A.S. Sprouse-Blum, G. Smith, D. Sugai, F.D. Parsa, Understanding endorphins and their importance in pain management, Hawaii Med. J. 69 (2010) 70.
[7] J. Brown, S. Brown, Exercise for dysmenorrhoea, Cochrane Database Syst. Rev. (2) (2010).
[8] P. Kannan, L.S. Claydon, Some physiotherapy treatments may relieve menstrual pain in women with primary dysmenorrhea: a systematic review, J. Phys. 60 (2014) 13–21.
[9] F. Vaziri, A. Hoseini, F. Kamali, K. Abdali, M. Hadianfard, M. Sayadi, Comparing the effects of aerobic and stretching exercises on the intensity of primary dysmenorrhea in the students of universities of Bushehr, J Family Reprod Health 9 (2015) 23.
[10] R.G. Israel, M. Sutton, K.F. O'Brien, Effects of aerobic training on primary dysmenorrhea symptomatology in college females, J. Am. Coll. Heal. 33 (1985) 241–244.
[11] P. Kannan, C.M. Chapple, D. Miller, L.S. Claydon, G.D. Baxter, Menstrual pain and quality of life in women with primary dysmenorrhea: rationale, design, and interventions of a randomized controlled trial of effects of a treadmill-based exercise intervention, Contemp. Clin. Trials. 42 (2015) 81–89.
[12] M. Proctor, C. Farquhar, Diagnosis and management of dysmenorrhoea, BMJ. 332 (7550) (2006) 1134–1138.
[13] C.L. Craig, A.L. Marshall, M. Sjöström, A.E. Bauman, M.L. Booth, B.E. Ainsworth, et al., International physical activity questionnaire: 12-country reliability and validity, Med. Sci. Sports Exerc. 35 (2003) 1381–1395.
[14] G. Lefebvre, O. Pinsonneault, V. Antao, A. Black, M. Burnett, K. Feldman, et al., Primary dysmenorrhea consensus guideline, J. Obstet. Gynaecol. Can. 27 (2005) 1117–1146.
[15] R.H. Dworkin, D.C. Turk, S. Peirce-Sandner, R. Baron, N. Bellamy, L.B. Burke, et al., Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations, Pain. 149 (2010) 177–193.
[16] E.E. Krebs, T.S. Carey, M. Weinberger, Accuracy of the pain numeric rating scale as a screening test in primary care, J. Gen. Intern. Med. 22 (2007) 1453–1458.
[17] W.M. Scott Dam, Clin Pain Manag, CRC press, Florida, USA, 2008.
[18] M. Gulati, L.J. Shaw, R.A. Thisted, H.R. Black, C.N.B. Merz, M.F. Arnsdorf, Heart rate response to exercise stress testing in asymptomatic women the St. James women take heart project, Circulation. 122 (2010) 130–137.
[19] R. Melzack, The short-form McGill pain questionnaire, Pain. 30 (1987) 191–197.
[20] G.A. Hawker, S. Mian, T. Kendzerska, M. French, Measures of adult pain: visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap), Arthritis Care Res. 63 (S11) (2011) S240–S252.
[21] J.E. Ware, M. Kosinski, S.D. Keller, A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity, Med. Care 34 (1996) 220–233.
[22] E. Gibbons, A. Mackintosh, R. Fitzpatrick, A structured review of patient-reported outcome measures for people undergoing elective procedures for benign gynaecological conditions: report to the Department of Health [article online], 2010. phi uhce ox ac uk/pdf/electiveprocedures/proms_oxford_ gynaecological% 20procedures_012011 pdf Accessed (2011), p. 12.
[23] C. Cleeland, Measurement of pain by subjective report, Adv. Pain Res. Ther. 12 (1989) 391–403.
[24] D.W. Levine, R.M. Kaplan, D.F. Kripke, D.J. Bowen, M.J. Naughton, S.A. Shumaker, Factor structure and measurement invariance of the Women's Health Initiative insomnia rating scale, Psychol. Assess. 15 (2003) 123.
[25] W.A. Bardwell, J. Profant, D.R. Casden, J.E. Dimsdale, S. Ancoli-Israel, L. Natarajan, et al., The relative importance of specific risk factors for insomnia in women treated for early-stage breast cancer, Psycho-oncology. 17 (2008) 9.
[26] W. Guy, ECDEU Assessment Manual for Psychopharmacology US Department of Health, Education, and Welfare Publication, revised ed. National Institute of Mental Health, Rockville, MD, 1976.
[27] H. Hurst, J. Bolton, Assessing the clinical significance of change scores recorded on subjective outcome measures, J. Manipulative Physiol. Therapeut. 27 (2004) 26–35.
[28] P. Kannan, L.S. Claydon, D. Miller, C.M. Chapple, Vigorous exercises in the management of primary dysmenorrhea: a feasibility study, Disabil. Rehabil. 37 (2015) 1334–1339.
[29] M.A. Hondras, C.R. Long, P.C. Brennan, Spinal manipulative therapy versus a low force mimic maneuver for women with primary dysmenorrhea: a randomized, observer-blinded, clinical trial, Pain. 81 (1999) 105–114.
[30] A. Field, Discovering Statistics Using IBM SPSS Statistics, Sage, 2013.
[31] J.T. Farrar, J.P. Young, L. LaMoreaux, J.L. Werth, R.M. Poole, Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale, Pain 94 (2001) 149–158.
[32] M. Kuppermann, L.A. Learman, M. Schembri, S. Gregorich, A. Jacoby, R.A. Jackson, et al., Effect of noncancerous pelvic problems on health-related quality of life and sexual functioning, Obstet. Gynecol. 110 (2007) 633–642.
[33] H.S. Driver, S.R. Taylor, Exercise and sleep, Sleep Med. Rev. 4 (2000) 387–402.

[34] K.A. Sluka, J.M. O'Donnell, J. Danielson, L.A. Rasmussen, Regular physical activity prevents development of chronic pain and activation of central neurons, J. Appl. Physiol. 114 (2013) 725–733.
[35] A. Leung, N.S. Gregory, L.-A.H. Allen, K.A. Sluka, Regular physical activity prevents chronic pain by altering resident muscle macrophage phenotype and increasing interleukin-10 in mice, Pain 157 (2016) 70–79.
[36] D. Dimitriev, E. Saperova, A. Dimitriev, I. Karpenko, Features of cardiovascular functioning during different phases of the menstrual cycle, Rossiiskii fiziologicheskii zhurnal imeni IM Sechenova/Rossiiskaia akademiia nauk, vol. 93, (2007), pp. 300–305.
[37] Phillips A. The effect of menstrual cycle phase on athletic performance. http://www.pikeathletics.com/blog/the-effect-of-menstrual-cycle-phase-on-athletic-performance; 2013 Accessed September 2015.
[38] L. Belanger, D. Burt, J. Callaghan, S. Clifton, B.J. Gleberzon, Anterior cruciate ligament laxity related to the menstrual cycle: an updated systematic review of the literature, J. Can. Chiropr. Assoc. 57 (2013) 76.
[39] R. Bahr, T. Krosshaug, Understanding injury mechanisms: a key component of preventing injuries in sport, Brit. J. Sports Med. 39 (2005) 324–329.
[40] J.C. Bollen, S.G. Dean, R.J. Siegert, T.E. Howe, V.A. Goodwin, A systematic review of measures of self-reported adherence to unsupervised home-based rehabilitation exercise programmes, and their psychometric properties, BMJ Open 4 (2014) e005044.
[41] G.L. Moseley, Do training diaries affect and reflect adherence to home programs? Arthritis Care Res. 55 (2006) 662–664.
[42] J. Sanfilippo, T. Erb, Evaluation and management of dysmenorrhea in adolescents, Clin. Obstet. Gynecol. 51 (2008) 257–267.
[43] V.B. Popat, T. Prodanov, K.A. Calis, L.M. Nelson, The menstrual cycle, Ann. N. Y. Acad. Sci. 1135 (2008) 43–51.
[44] E. Devoto, L. Aravena, X. Gaete, Has oligomenorrhea a pathological meaning? The importance of this symptom in internal medicine, Rev. Med. Chil. 126 (1998) 943–951.
[45] H.P. Adams, L.M. Nelson, Adolescent girls, the menstrual cycle, and bone health, J. Pediatr. Endocrinol. Metab. 16 (2003) 673–681.
[46] S. Schrager, Abnormal uterine bleeding associated with hormonal contraception, Am. Fam. Physician 65 (2002) 2073–2081.