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One year of Football Fitness improves L1-L4 BMD, postural balance and muscle strength in women treated for breast cancer

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Abstract

Purpose. To examine efficacy of 12 months Football Fitness offered twice per week on bone mineral density (BMD), bone turnover markers (BTM), postural balance, muscle strength and body composition in women treated for early-stage breast cancer (BC).

Methods. Women treated for early-stage BC were randomised to Football Fitness (FFG, n=46) or control (CON, n=22) in a 2:1 ratio for 12 months, with assessments performed at baseline, 6 months and 12 months. Outcomes were total body-, lumbar spine- and proximal femur BMD, total body lean and fat mass, leg muscle strength, postural balance, and plasma amino-terminal propeptide of type 1 procollagen (P1NP), osteocalcin and C-terminal telopeptide of type 1 collagen (CTX). Intention-to-treat (ITT) analyses and per-protocol analyses (≥50% attendance in FFG) were performed using linear mixed models.

Results. Participants in FFG completing the 12-month intervention (n=33) attended 0.8 (SD=0.4) sessions per week. Intention to treat analysis of mean changes over 12 months showed significant differences in L1-L4 BMD (0.029 g/cm^2, 95%CI: 0.001 to 0.057), leg press strength (7.2 kg, 95%CI: 0.1 to 14.3) and postural balance (-4.3 n need of support, 95%CI: -8.0 to -0.7) favouring FFG compared to CON. In the per-protocol analyses, L1-L4 and trochanter major BMD were improved (p=0.012 and 0.030, respectively) in FFG compared to CON. No differences were observed between groups in BTMs in the ITT or per protocol analyses.

Conclusion. One year of Football Fitness training may improve L1-L4 BMD, leg muscle strength and postural balance in women treated for early-stage breast cancer.

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Trial registration number

The trial was registered at ClinicalTrials.gov with identifier NCT03284567.

Keywords: bone mineral density, breast cancer rehabilitation, soccer, bone turnover, flamingo balance test, bone turnover markers

1 Introduction

Breast cancer is the most common cancer in Danish women, with around 4,700 new cases annually. In recent decades, early diagnosis and improved treatment have led to higher survival rates, with a current 5-year survival rate of 87%, and currently 66,000 women in Denmark are living with a diagnosis of breast cancer [1]. While improvements in survival rates are inherently positive, adjuvant chemo- and endocrine therapy are associated with detrimental effects on body composition and skeletal health [2,3]. Specifically, premenopausal women may lose up to 8% of lumbar spine bone mass in the first year after chemotherapy-induced amenorrhea [4]. In postmenopausal women with hormone-receptor-positive breast cancer, aromatase inhibitors (AIs) are standard treatment for 5 years after surgery and adjuvant therapy, i.e. chemo- and radiation therapy [5]. While AIs improve disease-free survival, postmenopausal women on this treatment have an accelerated annual loss of bone mineral density (BMD) of ~1.5% together with increased fracture risk in addition to the normal age-related ~0.5-1% annually decline of BMD[6]. This is associated with increased osteoclast differentiation and activity, leading to increased bone resorption and a negative net balance in bone mass associated with remodelling [7,8]. As in healthy individuals, weight-bearing activities involving high-impact exercises, such as running and jumping, combined with resistance exercise are recommended training for breast cancer patients receiving AIs. The overall aim for the training is to prevent the age-related reduction in BMD leading to increased risk of osteoporosis and to improve muscle strength and postural balance to avoid risk of falling and fractures [9,10]. However, the role of exercise in managing late effects of cancer treatment has been less studied. A meta-analysis of seven randomised controlled trials (RCTs) of exercise interventions lasting at least 12 months in pre- and postmenopausal women treated for early-stage breast cancer showed that exercise does not maintain BMD at any site in postmenopausal women, while it may maintain femoral neck but not spine BMD in premenopausal women diagnosed with early-stage breast cancer [11]. However, the small number of trials and the heterogeneity of interventions and included populations warrant further studies before the role of exercise in bone health management in breast cancer patients can be defined.

In general, an osteogenic exercise stimulus is associated with dynamic mechanical loading that induces bone strain, preferentially with a high strain magnitude and -rate, which is covered by high-impact exercises with large ground-reaction forces and heavy resistance exercises with large joint-reaction forces [12]. Over the past 15 years, a comprehensive body of evidence has shown that small-sided recreational football combines endurance and high-intensity aerobic exercise, high-impact and resistance exercise, which altogether result in broad-spectrum health-promoting impact, including osteogenic effects [13]. Thus, the frequent high intensity bouts with accelerations and decelerations over short distances and in varied directions [14] induce osteogenic bone strain along varied strain axes on the weight-bearing skeleton [12].

To achieve more knowledge on osteogenic mechanisms in humans and specifically to investigate acute and short-term effects on bone remodelling and modelling, the assessment of bone turnover markers (BTMs) is recommended. Thus, it is recommended to evaluate bone formation by the amino-terminal propeptide of type 1 procollagen (P1NP) and bone resorption by the C-terminal telopeptide of type 1 collagen (CTX), which are related to changes in habitual loading pattern of the skeleton [15].

Football training performed 2–3 times per week for 3–4 months has been shown to improve femoral shaft and trochanter BMD in healthy, sedentary, middle-aged women [16] and femoral neck and femoral shaft BMD in middle-aged men and women with prediabetes [17], and to improve tibial BMD, jump power and muscle strength in healthy, untrained, premenopausal women [18]. In the latter study, further positive effects on bone mineralisation and muscle strength was reported after 16 months of football [19(p2010)].

In men with prostate cancer, we previously tested the feasibility and efficacy of football as a novel approach to promote an active lifestyle that included high-intensity exercise, camaraderie and, potentially, long-term adherence [20]. We found that football was a feasible and intense exercise modality that improved muscle mass, muscle strength, physical performance, and femur shaft and total hip BMD in men undergoing androgen deprivation therapy for prostate cancer [14,21], and that the effects on BMD were maintained 5 years after the initial baseline in those participants who continued to play football after the end of the supervised intervention period [22]. A subsequent multi-centre study (n=214) confirmed the efficacy of football as an osteogenic mode of exercise in men with prostate cancer [23].

Taking this into account, in this secondary study of the Football Fitness After Breast Cancer trial we aimed to evaluate the effects of one year Football Fitness offered twice per week, compared to usual care, on total body, spine and hip BMD, BTMs, lean body mass, postural balance and muscle strength in women treated for stage I-III breast cancer. We hypothesised that Football Fitness would be superior to usual care with regard to effects on lumbar spine and hip BMD, muscle strength and postural balance.

2 Methods

2.1 Trial design, setting, recruitment and participants

Football Fitness After Breast Cancer was a randomised trial comparing Football Fitness with standard care. Women managed with either lumpectomy or mastectomy for stage I-III breast cancer were recruited from the outpatient clinic of the Department of Oncology at Copenhagen University Hospital, Rigshospitalet. When attending control visits after completion of adjuvant chemotherapy and/or radiation therapy, the women were invited by a nurse to contact the project staff for eligibility screening for the present trial. The trial was also advertised in Facebook groups for breast cancer survivors, via public news outlets and on the Danish Cancer Society's webpage. The full list of criteria for inclusion was completion of adjuvant chemotherapy and/or radiation therapy within 5 years prior to randomisation, ability to read and understand Danish, age between 18 and 76 years, and WHO performance status 0-1. Exclusion criteria included planned treatment with chemotherapy or radiation therapy in the intervention period, stage IV breast cancer, osteoporosis, ongoing treatment with anticoagulants, serious cardiac morbidity including ischaemic heart disease, heart failure, poorly controlled hypertension, cardiac arrythmia, tendency to syncope and cardiac pacemaker. Participants with a T-score of < -2.5 in total hip or L1-L4 at baseline were excluded from the trial and encouraged to consult with their treating doctor for further screening for osteoporosis. Recruitment of participants began in March 2017 and ended in October 2018.

2.2 Randomisation, blinding, and sample size

After screening and baseline testing, the participants were randomised in a 2:1 ratio to either the Football Fitness group (FFG) or the control group (CON). The unequal allocation ratio was chosen to increase the volume of data from the intervention group, as this was the first study of its kind in this patient group. Furthermore, an unequal allocation leading to more participants to the FFG than CON ensured enough participants in FFG to form sufficiently large teams needed to carry out the intervention. A detailed description of the randomization process is reported elsewhere [24]. Assessment of muscle strength and postural balance was performed by study personnel blinded to group allocation, whereas DXA scans and blood sampling were performed by unblinded study personnel. Sample size was based on expected differences in changes of the primary outcome, VO_2max which is reported elsewhere [24]. In brief, we calculated that 50 women should be included in FFG and 25 women in CON to obtain a power of 0.8. To account for attrition, we aimed to include 90 women treated for breast cancer.

2.3 Ethics approval

The trial was conducted in accordance with the Helsinki Declaration and approved by the ethics committee of the Capital Region of Copenhagen, Denmark (Registration number H-16029533). All participants gave written informed consent before any study procedures were performed.

2.4 Intervention

Participants in FFG were offered Football Fitness twice weekly for 12 months. Each session consisted of a 10–15-min warm-up (running, squats, sit-ups, back extensions, core-strength exercises and balance exercises), 15 min of pair- or group-based football drills (passing, dribbling, shooting) and 3–4 x 7 min of small-sided (4–5-a-side) football matches on a 15-m wide, 20-m long pitch with 2-min breaks between matches. In order to prevent injuries, participants were instructed to avoid hard tackles and to refrain from placing the foot sole on top of the ball. From mid-October to late March, sessions were performed indoors on a 15-m wide, 20-m long pitch with boundaries. Sessions were instructed and supervised by exercise physiologists or physiotherapists who also recorded attendance at each session.

2.5 Usual care

The participants in CON were not given any restrictions on physical activity during the intervention period and were invited to participate in Football Fitness after the 12-month intervention period.

2.6 Injuries

Injuries occurring in relation to Football Fitness were recorded by the instructor and, in addition, the participants in both FFG and CON filled out a questionnaire at the 12-month follow-up assessment concerning musculoskeletal injuries sustained during the intervention period.

2.7 Activity profile during Football Fitness

The participants' movement patterns during outdoor small-sided matches were evaluated by portable global positioning system (GPS) units (MinimaxX s5, Catapult Innovations, Canberra, Australia) with a time resolution of 10 Hz. The units were placed in a vest worn by the participants. GPS data were analysed using proprietary software (Catapult Sprints version 5.1.7 team sports). Total distance, distance of single bouts and number of accelerations in the intensity zones 0–1, 1–2, 2–4 and > 4 m/s^2 were recorded. Limited access to the GPS system meant that only a subgroup of participants was included in measurements of activity profile. Heart rate during the 3–4 × 7-min small-sided matches was measured in a subsample of 15 participants in 15 sessions with a Polar Team 2 system and analysed with Polar Team 2 version 1.4.5 software.

2.8 Study outcomes

All assessments performed at baseline were repeated at 6- and 12-month follow-ups. The participants were instructed to avoid strenuous exercise for 48 hours before the test day and to avoid intake of alcohol for 24 hours prior to the test. The participants were also instructed to fast for at least 8 hours prior to the test and to avoid smoking and intake of caffeine and medicine, including anti-hypertensive drugs, until after the tests of the specific day were completed. DXA scans, blood pressure measurements and blood sampling were carried out in the morning between 7:30 and 10:00 a.m. The participants were offered a meal, e.g. a sandwich or fruit and yoghurt, drank water and/or fruit juice and filled out questionnaires before performing tests regarding muscle strength and postural balance (see below).

2.8.1. Body composition and regional bone mineral density

Height was measured with a stadiometer and weight with a digital platform. Total body BMD, fat percentage and lean mass were assessed with a whole-body DXA scan (iDXA, Lunar Corporation, Madison, WI, USA), and separate scans were performed to measure BMD of the lumbar spine and proximal femur. BMD values of the upper femur region are reported as means of the right and left sides. The coefficient of variation for measurement of BMD is 1.0% according to the manufacturer.

2.8.2. Bone turnover markers

Blood was obtained from an antecubital vein and analysed for procollagen type 1 amino-terminal propeptide (P1NP), osteocalcin and C-terminal telopeptide of type 1 collagen (CTX) by a chemiluminescence method using a fully automated immunoassay system (iSYS, Immunodiagnostic Systems Ltd, Boldon, England).

2.8.3. Muscle strength

Maximal leg muscle strength was assessed using the one repetition maximum (1RM) test for leg extension and leg press using conventional resistance training machines from Technogym (Cesena, Italy). 1RM was defined as the maximum weight lifted through a full range of motion with correct technique.

2.8.4. Postural balance

Postural balance was assessed using the flamingo balance test [25]. The test has previously been used to measure postural balance in numerous populations, including men with prostate cancer [14] and premenopausal women [18]. The participants were instructed to stand with eyes open and barefooted on their dominant leg on a 5-cm high and 3-cm wide plastic bar for 1 min while keeping the opposite knee flexed supported by one hand. The timing was paused each time a participant lost her balance and stepped off the bar or needed support. The number of times a participant stepped off the bar or needed support before a total of 1-min in balance was fulfilled was recorded as a measure of postural balance.

2.9 Statistical analyses

Descriptive statistics were reported as mean (SD) or n (%), unless stated otherwise. Differences in numeric variables at baseline were assessed by Welch two-sample t-tests, while categorial variables were assessed by Chi-squared tests. Within-group changes in outcome and differences between mean changes of groups were assessed by linear mixed-model analyses, where an unstructured covariance was assumed. Goodness of fit was assessed by residual diagnostics. Distributions of BTM were skewed and therefore log-transformed before statistical analysis and represented as median with interquartile ranges (IQR), range and outliers (>1.5 × IQR). Within-group changes in outcome and differences between mean changes of groups were reported as mean (95% confidence intervals). For translatability, estimated differences between mean changes of the groups are accompanied by percentage change. To test the efficacy of Football Fitness, a per-protocol analysis was performed, including only participants who participated in ≥ 50% of the possible Football Fitness sessions and, from the control group, only participants who attended all test days. Change values between participants who participated in ≥ 50% were compared to those who participated less with Welch two-sample t-tests. An additional secondary analysis excluding all participants receiving bisphosphonates were performed for BMD and BTM outcomes. To further explore responsiveness, participants in the intervention group were grouped in responders and non-responders. Statistical significance was considered as $P<0.05$. Linear mixed-model analyses were statistically processed using SAS software, version 7.1 (SAS Institute, Cary, NC), while the other above-mentioned statistical analyses and generation of figures were processed in R (RStudio Team, Inc., Boston, MA).

3. Results

3.1 Study sample

From March 2017 to October 2018, 81 women treated for breast cancer and interested in the study were screened for eligibility (see Fig. 1). The first and last participants were baseline-tested on 29 March 2017 and 3 October 2018, respectively. Reasons for exclusion before baseline assessment were lack of time or long travel distance (n=7), self-reported low BMD (n=1) and musculoskeletal injury (n=1). Of 72 women assessed at baseline, 4 were excluded due to BMD ≤ -2.5 or feeling uncomfortable after completing the tests while fasting. In total, 68 women were randomised to either the Football Fitness group (n=46) or the control group (n=22) after baseline assessment. Five participants allocated to FFG did not start the Football Fitness intervention. One participant broke her leg while hiking on vacation after the baseline test and before the intervention started, and 4 regretted signing up to the trial for personal reasons, e.g. family and work obligations. Demographic and clinical characteristics are presented in Table 1. Retention in FFG was 76% and 72% at 6 and 12 months, respectively. The corresponding numbers for CON were 86% and 73%. 50% and 45% received calcium supplementation in FFG and CON, respectively. 54% and 45% received Vitamin D supplementation in FFG and CON, respectively. Some participants received multivitamins (n=20), magnesium (n=7), regular analgesics (n=2), blood pressure medications (n=3), and zinc (n=1).

3.2 Adherence to the Football Fitness intervention

Adherence to Football Fitness over 12 months was 44% (SD 21.6) of 92.5 (5.1) possible sessions for the 33 participants in FFG who completed the 12-month assessment, corresponding to 0.8 (0.4) sessions per week, of which 17 (52%) of the 33 participants attended >50% of possible sessions, corresponding to 1 session per week on average. Participation in the first 6 months was 50% (22.0) of 49.0 (0.8) possible sessions, corresponding to 0.9 (0.4) sessions per week for the 35 participants in FFG completing the 6-month follow-up. Six participants completing the 6-month follow-up had participated in ≤ 5 sessions. In the last 6 months, attendance was 43% (26.4) of 43.5 (4.7) possible sessions, corresponding to 0.7 (0.5) sessions per week.

3.3 Injuries

During 1 year of Football Fitness, 21 injuries were recorded in 15 participants (See Table 1 in the Electronic Supplementary Material (ESM)). Most injuries were related to football drills (n=6) or matches (n=6), and most were related to the ankle or knee joints or thigh muscles and resulted in a median time refraining from Football Fitness of 2 weeks (interquartile range (IQR) 1.0–3.0). One participant did not resume Football Fitness after a fall during an indoor warm-up that resulted in a meniscus lesion. All injuries were managed conservatively. After 12 months, 3 injuries were reported in 2 participants in CON (see Table 1 ESM).

3.4 Activity profile during Football Fitness

GPS measurements showed that during a session an average of 3.4 (0.5) small-sided matches of 7 min each were played, during which the participants covered 1459 m (447) and performed 80.8 accelerations >1 m/s^2 in addition to a total of 157.3 (28.6) activity bouts. Of the activity bouts, 87.5 (23.0) bouts covered 0–5 m, 52.2 (21.2) covered 5–10 m and 17.6 (12.4) covered 10–40 m (see Fig. 2). Mean heart rate (HR) of the sessions was 82.5% (7.3) of maximal HR. Intensity assessed by time in HR zones has been reported elsewhere [19].

3.5 Study outcomes

At the 6-month follow-up, the intention-to-treat analyses showed no differences between groups in any outcomes (see Table 2). At the 12-month follow-up, the analyses showed a significant difference in mean changes between groups in L1-L4 BMD of 0.029 g/cm^2 (95% CI: 0.001 to 0.057, p=0.040) favouring FFG, whereas a difference in mean changes between groups in trochanter major BMD of 0.032 g/cm^2 (-0.004 to 0.069, p=0.082) favouring FFG did not reach statistical significance. At baseline, P1NP was 61.9 (43.3) and 45.7 (28.2) ug/L, CTX was 353.9 (274.5) and 280.0 (228.1) ng/L, and osteocalcin was 20.8 (14.5) and 16.9 (8.5) ug/L in FFG and CON, respectively. There were no differences between groups at baseline in BTMs (See Fig. 3). No differences in mean changes between groups were observed in BTMs at either 6 months (p=0.706, 0.844, and 0.754 for CTX, osteocalcin, and P1NP, respectively) or 12 months (p=0.671, 0.846, and 0.692 for CTX, osteocalcin, and P1NP, respectively). Regarding physical performance outcomes, we observed significant differences in mean changes between groups of 7.2 kg (0.1 to 14.3, p=0.046) in 1RM leg press and – 4.3 n NoS (-8.0 to – 0.7, p=0.021) in postural balance, both favouring FFG.

The per-protocol analyses showed significant differences between mean changes of groups in L1-L4 and trochanter major BMD of 0.041 g/cm^2 (0.010 to 0.073, p=0.012) and 0.036 g/cm^2 (0.004 to 0.068, p=0.030), respectively, favouring FFG (see Table 2 in the ESM and Fig. 4). In total body and total hip BMD, differences between mean changes of groups of 0.015 g/cm^2 (-0.001 to 0.031, p=0.061) and 0.039 g/cm^2 (-0.006 to 0.084, p=0.085), respectively, favoured FFG, but did not reach statistical significance (see Table 2 in the ESM). Similarly, differences between mean changes of groups in 1RM leg press of 7.9 kg (-0.3 to 16.0, p=0.059) favouring FFG approached significance (see Table 2 ESM).

No significant differences were observed when comparing those who participated >50% of sessions with those who participated in <50% of sessions, yet absolute mean relative change values for BMD, maximal muscle strength, and postural balance outcomes were superior in those who participated in >50% of sessions (see Table 3 ESM).

To assess responsiveness of the Football Fitness, participants were grouped in responders and non-responders according to their individual differences from baseline to 12 months. At all regions, more than 70% had increased BMD values and ~90% had improved postural balance (See Table 4 ESM).

In the secondary analysis excluding participants receiving bisphosphonates there was a significant difference in mean changes after 12 months in trochanter major BMD of 0.042 g/cm^2 (0.004 to 0.08, p=0.03) while a difference in mean changes in L1-L4 BMD between groups of 0.030 g/cm^2 (-0.002 to 0.06) favoured the FFG but did not reach significance (p=0.07; data not shown). The corresponding per-protocol analysis showed a significant effect in both trochanter major (p=0.02) and L1-L4 (p=0.03) BMD favouring FFG. As with the analyses of the full study population, no differences in changes between groups in BTMs were observed at any time point in the secondary analyses, neither in the per protocol nor with bisphosphonate-treated participants excluded (data not shown).

4 Discussion

In this trial we found that 12 months of Football Fitness carried out approximately one hour per week improved lumbar spine BMD, leg muscle strength and postural balance, but not body composition, in women treated for breast cancer, compared to usual care. No differences between the two groups in any outcomes were observed at 6 months. Importantly, Football Fitness was feasible for this group of participants, yet mean attendance was only half of the offered sessions. In addition to the intention-to-treat improvement in lumbar spine BMD, the per-protocol analyses including women participating in at least 1 session per week for 12 months showed significant improvements in trochanter major BMD compared to CON. The positive effect on BMD is in accordance with our hypothesis that football has prominent osteogenic potential, even with modest exercise volumes, over a prolonged period. Contrary to our hypothesis, we found no benefits of Football Fitness on total body lean or fat mass. As for changes in BMD, this may be due to the low overall attendance to the intervention of 0.8 sessions per week over the 12-month period.

The benefits of Football Fitness on BMD, muscle strength and postural balance are important findings given the detrimental effects of breast cancer treatment, including chemotherapy and aromatase inhibitors, which 88% and 28%, respectively, of the participants had been or were being treated with in the present trial. We have previously shown the efficacy of recreational football on hip mineralisation in men with prostate cancer undergoing androgen deprivation therapy [14], and that finding was confirmed in a subsequent pragmatic multi-centre trial including men with both localized and advanced prostate cancer [23]. However, in the current trial the ITT analyses showed an osteogenic effect on lumbar spine BMD, not on hip BMD. The biomechanical loading pattern during football has been suggested as an explanation for the effect on hip BMD, which may also count for the spine as a load-bearing part of the axial skeleton [26]. The results of our per-protocol analyses, where both lumbar spine and trochanter major BMD were improved in FFG compared to CON after 12 months, are consistent with this theory, and considering the individual responsiveness with caution, it seemed that, especially the improved BMD values, were associated to higher adherence to the Football Fitness offer. Moreover, between-group differences favouring FFG in total body and total hip BMD of 0.015 g/cm^2 and 0.039 g/cm^2, respectively, approached significance ($p=0.061$ and $p=0.085$), supporting the potential benefits for bone mineralization of participation in football for women treated for breast cancer. It is likely that the Football Fitness with frequent high intensity bouts with accelerations and decelerations over short distances and in varied directions induced osteogenic bone strain of the lumbar spine resulting in a positive net balance in bone remodelling. Unfortunately, this was not supported by our findings in BTMs. No differences between groups in BTMs were observed at any time point in the ITT, per protocol, or without participants receiving bisphosphonates. This may be due to lack of sample power, timing of the test days, lack of training progression in musculoskeletal stimuli, but also the ability of BTMs to detect impact of treatment or behaviour on bone turnover over short periods of time, e.g. 4-12 weeks, whereas the 6-month intervals may not reflect the change in osteogenic stimuli induced by the Football Fitness, but may instead reflect the subsequent normalisation of the BTMs [27].

The concurrent effects on muscle strength and postural balance are of further importance, as improved muscle strength and postural balance may reduce the occurrence of future falls. Combined with improved BMD, this may ultimately reduce the risk of fractures in this population of women treated for breast cancer. Indeed, based on epidemiological studies on the association between changes in BMD and fracture risk [28], changes in Z-scores in FFG of 0.301 for L1-L4 and 0.09 for femoral neck in the current trial (data not shown) correspond to estimated reductions of fracture risk of 30 % and 9 % for lumbar spine and femoral neck, respectively. The positive effects on BMD seen in the present trial are particularly noteworthy given the lack of improvements described in the majority of previous exercise trials that included both pre- and postmenopausal breast cancer survivors undertaking exercise programmes lasting at least 1 year [11]. One trial successfully prevented femoral neck bone loss in premenopausal breast cancer survivors who performed a median number of 3.3 exercise sessions per week combining step aerobics, jumps and leaps, and circuit-training either supervised or home-based [29]. In comparison, the participants in the present trial achieved significant improvements in L1-L4 BMD with a mean of only 0.8 (0.4) weekly sessions, which underscores the potential of football as an osteogenic exercise modality. Furthermore, when inspecting individual data, ~70% in FFG had positive BMD values across all assessed regions (see Table 4 ESM).

Some important limitations of the present trial should be emphasised. Most of the participants had completed at least 3 years of higher education and their mean age was lower than the average for women treated for breast cancer. The results may therefore not be generalisable to the overall population of breast cancer survivors. The aim to include 90 women was not achieved due to a lower than expected recruitment rate, which resulted in a lower study power. Information on menstrual status was not provided by all participants, which is another limitation because oestrogen may have a positive influence on bone mineral turnover over 1 year. However, the number of participants providing this information was ~ 70% in both FFG and CON and the distribution across the categories “regular monthly cycle”, “irregular cycle” and “no menstruation for ≥ 1 year” was not significantly different between the two groups. Finally, the number of injuries reported by participants in FFG was higher than in CON. While this raises concern about the safety of Football Fitness it should also be noted that injuries in FFG were recorded on an ongoing basis and by a questionnaire at 12 months, while participants in CON only were asked to report musculoskeletal injuries at 12-months follow-up and the data on injuries in CON may therefore be more prone to recall bias.

5 Conclusion

We conclude that 1 year of Football Fitness training improves L1-L4 BMD, leg muscle strength and postural balance in women treated for stage I-III breast cancer. Per-protocol analyses suggest that participation in at least one weekly session has additional benefits for hip BMD.

6 Perspectives

While regular exercise may counteract some late effects of breast cancer treatment, only few studies have successfully shown improved BMD with exercise interventions in women treated for breast cancer [11]. In the present study we show that Football Fitness may be a feasible intervention to improve both postural balance, muscle strength, and BMD which ultimately may prevent falls, osteoporosis, and bone fractures. This knowledge adds to the existing evidence on football as a mean to reduce risk factors for bone fracture in untrained healthy women [18] and elderly men with prostate cancer, [23,30] and it provides further evidence to the "Football is Medicine" framework recently suggested by Krustrup et al.[13]

Conflicts of interest:
Jacob Uth, Bjørn Fristrup, Victor Sørensen, Eva Wulff Helge, Maja Kjærgaard Christensen, Julie Boye Kjærgaard, Trine Kjeldgaard Møller, Jørn Wulff Helge, Niklas Rye Jørgensen, Mikael Rørth, Eva Soelberg Vadstrup, and Peter Krustrup declare that they have no conflict of interest.

Authors' contributions
JU and PK developed the study concept and initiated the project together with MR and ESV. EWH, JWH, BF, and NRJ further developed the protocol. JU and PK applied for funding. BF and JU set up the trial database. BF, MKC, JKT, TKM, and JU collected the study data and carried out the intervention. VS performed the statistical analysis and prepared the tables and figures. JU, VS, and PK drafted the paper. All authors contributed to and approved the final paper.

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Figure Captions:

Fig. 1 CONSORT flowchart

Fig. 2 Activity profile during Football Fitness training matches

Fig. 3 Boxplot of P1NP, CTX, and Osteocalcin values at baseline, 6- and 12 months showing median, interquartile ranges (IQR; 0.25 and 0.75), minimal and maximal values as whiskers, and outliers as dots (>1.5 × IQR). No differences of mean changes between groups were observed. Mean changes relative to baseline measurements of CTX were 28.7% and -5.3% for FFG and 14.7% and -21.9% for CON at 6 and 12 months, respectively. Mean changes relative to baseline measurements of P1NP were 11.3% and -14.1% for FFG and 29.0% and -9.8% for CON at 6 and 12 months, respectively. Mean changes relative to baseline measurements of osteocalcin were 2.5% and -17.2% for FFG and 9.2% and -7.1% for CON at 6 and 12 months, respectively.

Fig. 4 Per-protocol analysis of changes in BMD from baseline to 12 months in FFG (n = 17) and CON (n = 16)

Data availability

All data are available upon request.

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Table 1. Demographics, medical characteristics, and baseline values of outcomes.

	Football Fitness group (n=46)			Control group (n=22)		
	N	n/mean	SD/%	N	n/mean	SD/%
Demographic characteristics						
Age (years)	46	47.4	(9.4)	22	50.0	(9.3)
Married, cohabiting, or in a relationship	46	30	(65.2%)	22	17	(77.3%)
Ethnicity	46			22		
Danish		42	(91.3%)		20	(90.9%)
Other		4	(4.7%)		2	(9.1%)
Educational and working status	46			21		
> 3 years of higher education		39	(84.8%)		14	(63.6%)
Working	46	34	(73.9%)	22	15	(68.2%)
Sick leave	46	5	(10.9%)	22	4	(18.2%)
Use of addictive substances						
Smoking	46	4	(8.7%)	22	1	(4.5%)
Alcohol intake (≥ 8 units/week)	45	6	(13.3%)	21	3	(13.6%)
Menstrual status	32			15		
Regular monthly cycle		0	(0.0%)		0	(0.0%)
Unregular cycle		5	(10.9%)		5	(22.7%)
No menstruation ≥ 1 year		27	(58.7%)		10	(45.5%)
Medical characteristics						
Diagnosed stage of cancer	46			22		
I		18	(39.1%)		10	(45.5%)
II		18	(39.1%)		12	(54.5%)
III		10	(21.7%)*		0	(0.0%)
Surgery						
Time since surgery (years)	46	3.1	(1.9)	22	3.4	(3.0)
Mastectomy	46	19	(41.3%)	22	9	(40.9%)
Lumpectomy	46	27	(58.7%)	22	13	(59.1%)
Previous therapy						
Radiotherapy	46	38	(82.6%)	22	17	(77.3%)
Chemotherapy	46	43	(93.5%)	21	18	(81.8%)
Current treatment						
Tamoxifen	46	25	(54.3%)	22	11	(50.0%)
Aromatase inhibitors	46	11	(23.9%)	22	7	(31.8%)
Trastuzumab	46	15	(32.6%)	22	6	(27.3%)
Zoledronic acid	46			22		
Before inclusion (days)	7	180	(111)	2	70	(10)
After inclusion (days)	7	123	(99)	2	88	(93)
Baseline measurements						
Bone densitometry						
Total body BMD (g/cm^2)	46	1.190	(0.103)	22	1.200	(0.101)
T-score		1.010	(1.030)		1.170	(1.000)

Z-score		1.050	(1.020)		1.080	(0.851)
L1-L4 BMD (g/cm^2)	44	1.150	(0.128)	21	1.200	(0.153)
T-score		-0.252	(1.070)		0.176	(1.270)
Z-score		-0.056	(1.230)		0.287	(1.160)
Total hip BMD (g/cm^2)	45	0.973	(0.111)	22	1.000	(0.112)
Femoral neck BMD (g/cm^2)	46	0.941	(0.109)	22	0.980	(0.118)
T-score		-0.342	(0.906)		-0.001	(0.979)
Z-score		0.078	(0.791)		0.271	(0.916)
Trochanter major BMD (g/cm^2)	46	0.782	(0.106)	22	0.814	(0.100)
Femoral shaft BMD (g/cm^2)	45	1.160	(0.136)	22	1.180	(0.145)
Body composition						
Body mass index (kg/m^2)	46	25.5	(4.9)	22	26.4	(4.6)
Lean body mass (kg)	46	42.6	(4.0)	22	43.5	(5.2)
Fat percentage (%)	46	38.0	(7.7)	22	40.4	(7.0)
Physical function						
1RM leg press (kg)	45	86.2	(23.5)	21	85.7	(25.6)
1RM leg extension (kg)	46	43.1	(7.7)	22	44.3	(9.4)
Postural balance (n NoS)	46	15.5	(9.1)	22	15.9	(7.1)

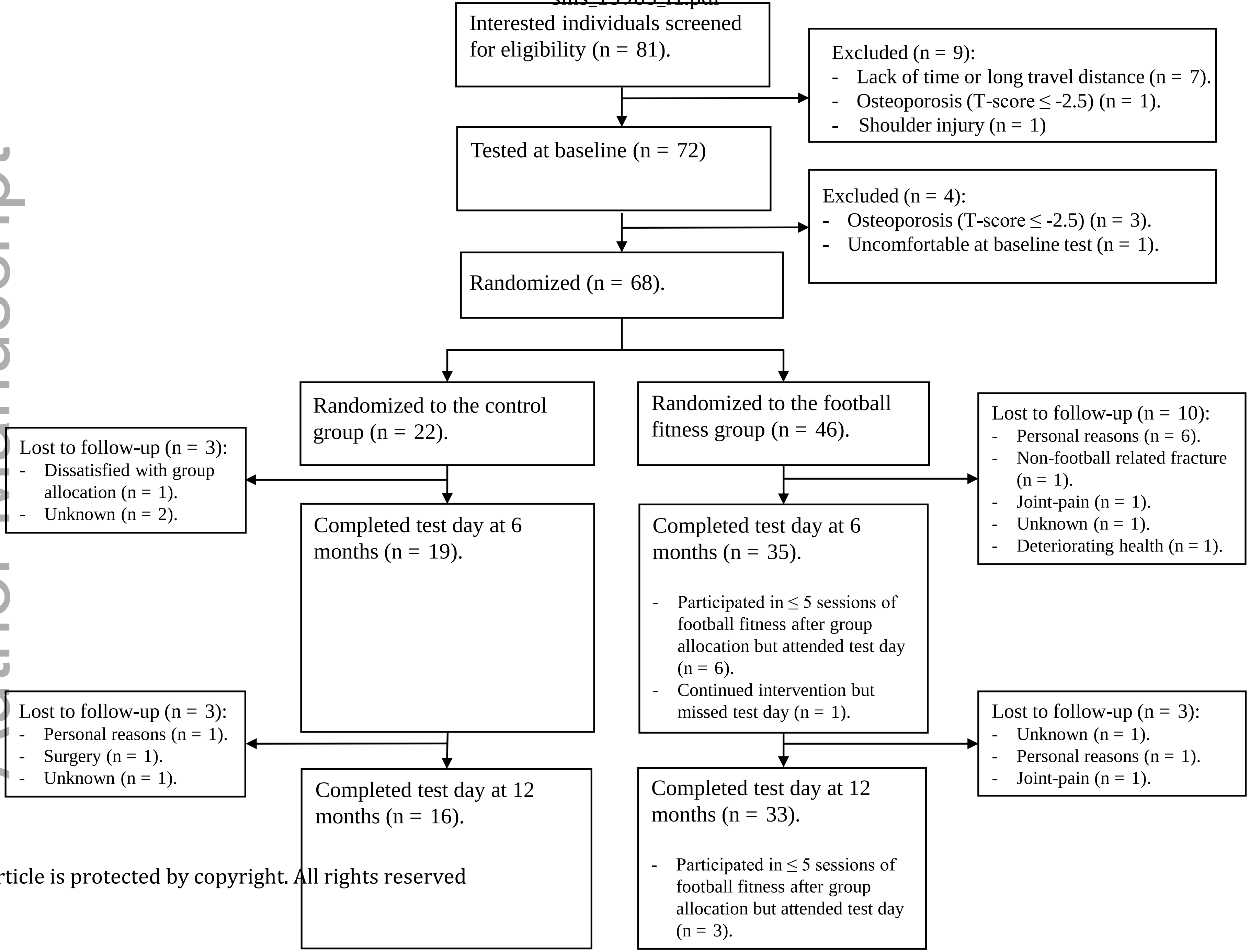
Difference between groups are annotated with * ($P < 0.05$). Continuous variables were analysed with two-sample t-tests. Categorial variables were analysed with Chi^2-tests. Measurements of BMD of lower limbs are reported as the mean of the left and right values. Abbreviations: Bone mineral density (BMD), 1 repetition maximum (1RM), need of support (NoS).

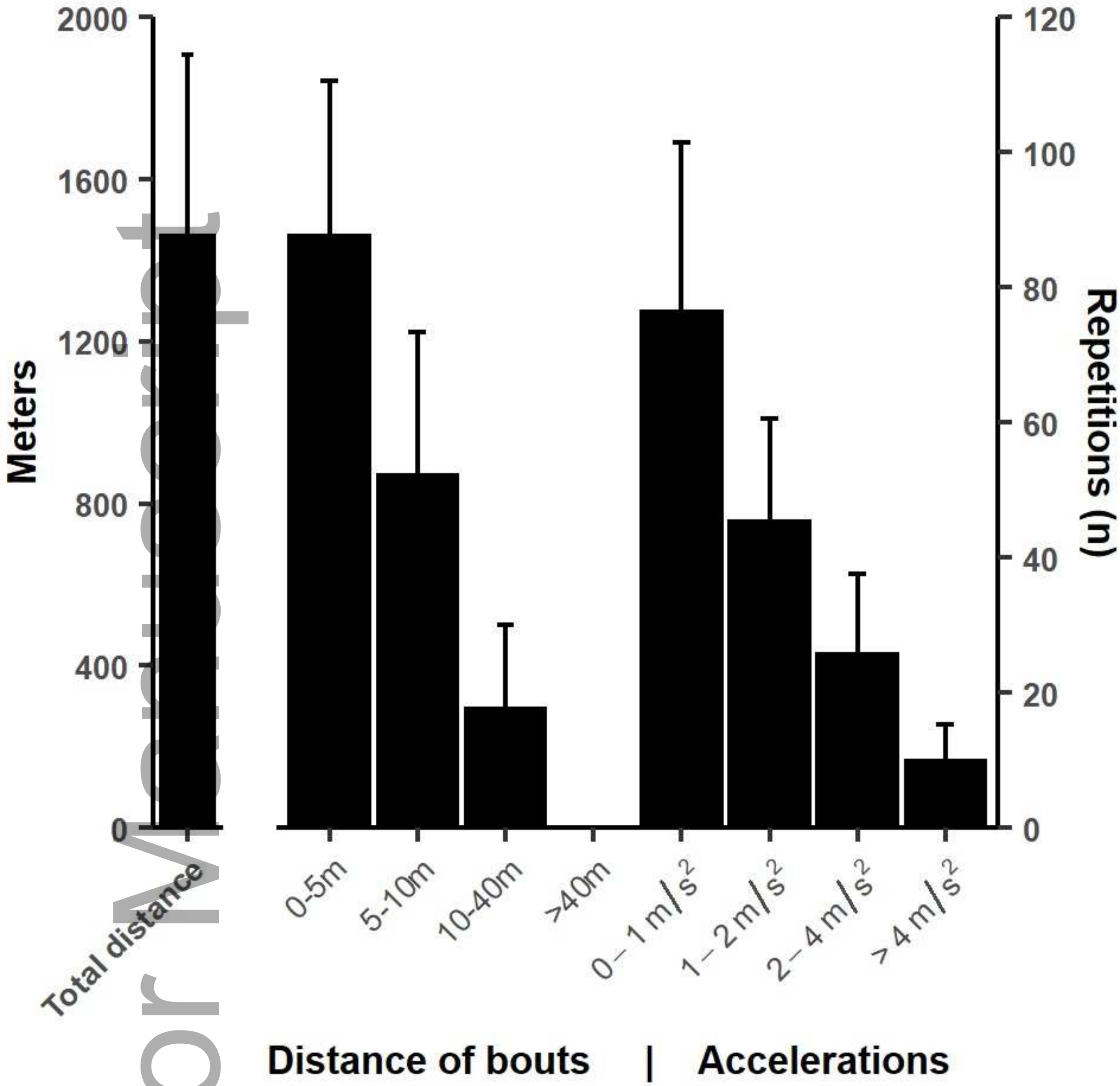
Table 2. Estimated mean differences within and between groups at 6 and 12 months.

	Football Fitness group			Control group			Est. Δ between mean changes of groups			
Measurements	n	Est. mean Δ	0.95 CI	n	Est. mean Δ	0.95 CI	Est. mean Δ	0.95 CI	P value	%
0-6 months										
Bone densitometry (g/cm^2)										
Total body BMD	35	0.004	(-0.004 to 0.012)	19	-0.005	(-0.015 to 0.006)	0.009	(-0.004 to 0.022)	0.175	0.8%
L1-L4 BMD	33	0.013	(0.003 to 0.023)	18	0.001	(-0.012 to 0.015)	0.011	(-0.005 to 0.028)	0.184	0.9%
Total hip BMD	35	0.002	(-0.024 to 0.028)	18	-0.013	(-0.049 to 0.023)	0.015	(-0.030 to 0.059)	0.512	1.5%
Femoral neck BMD	35	-0.005	(-0.038 to 0.028)	18	-0.012	(-0.058 to 0.034)	0.007	(-0.049 to 0.064)	0.800	0.7%
Trochanter m. BMD	35	0.010	(-0.012 to 0.030)	18	-0.015	(-0.044 to 0.014)	0.025	(-0.011 to 0.061)	0.170	3.2%
Femoral shaft BMD	35	-0.001	(-0.036 to 0.034)	18	-0.011	(-0.06 to 0.037)	0.011	(-0.049 to 0.071)	0.724	0.9%
Body composition										
Body mass index (kg/m^2)	35	-0.1	(-0.4 to 0.2)	19	-0.2	(-0.6 to 0.2)	0.1	(-0.4 to 0.6)	0.593	0.4%
Lean body mass (kg)	35	0.3	(-0.3 to 0.8)	19	0.0	(-0.8 to 0.7)	0.3	(-0.6 to 1.2)	0.536	0.7%
Fat percentage (%)	35	-0.7	(-1.4 to 0.0)	19	-0.5	(-1.4 to 0.5)	-0.2	(-1.4 to 1.0)	0.700	-0.5%
Physical function										
1RM leg press (kg)	35	1.0	(-2.8 to 4.7)	19	-3.1	(-8.2 to 2.0)	4.1	(-2.3 to 10.4)	0.206	4.8%
1RM leg extension (kg)	35	1.7	(0.1 to 3.3)	19	2.2	(0.1 to 4.4)	-0.5	(-3.2 to 2.2)	0.696	-1.1%
Postural balance (n NoS)	35	-4.3	(-6.0 to -2.6)	18	-2.6	(-5.1 to -0.2)	-1.7	(-4.7 to 1.4)	0.272	-10.9%
0-12 months										
Bone densitometry (g/cm^2)										
Total body BMD	33	0.015	(0.007 to 0.023)	16	0.008	(-0.004 to 0.019)	0.007	(-0.007 to 0.021)	0.314	0.6%
L1-L4 BMD	32	0.027	(0.011 to 0.043)	16	-0.002	(-0.025 to 0.021)	0.029	(0.001 to 0.057)	**0.040**	**2.5%**
Total hip BMD	33	0.011	(-0.015 to 0.038)	16	-0.009	(-0.045 to 0.028)	0.020	(-0.025 to 0.065)	0.371	2.0%
Femoral neck BMD	33	0.004	(-0.028 to 0.037)	16	-0.007	(-0.053 to 0.038)	0.011	(-0.045 to 0.068)	0.683	1.2%
Trochanter m. BMD	33	0.018	(-0.003 to 0.040)	16	-0.014	(-0.043 to 0.016)	0.032	(-0.004 to 0.069)	0.082	4.0%
Femoral shaft BMD	33	0.010	(-0.026 to 0.045)	16	-0.003	(-0.052 to 0.047)	0.012	(-0.049 to 0.073)	0.695	1.0%

Body composition										
Body mass index (kg/m^2)	33	-0.2	(-0.6 to 0.2)	16	-0.1	(-0.7 to 0.5)	-0.1	(-0.8 to 0.6)	0.808	-0.4%
Lean body mass (kg)	33	-0.2	(-0.8 to 0.3)	16	0.0	(-0.8 to 0.8)	-0.2	(-1.2 to 0.8)	0.663	-0.5%
Fat percentage (%)	33	-0.3	(-1.2 to 0.6)	16	0.0	(-1.3 to 1.3)	-0.3	(-1.8 to 1.3)	0.742	-0.8%
Physical function										
1RM leg press (kg)	28	2.2	(-1.9 to 6.4)	14	-5.0	(-10.8 to 0.8)	7.2	(0.1 to 14.3)	**0.046**	**8.4%**
1RM leg extension (kg)	28	4.3	(0.6 to 8.0)	14	6.4	(1.2 to 11.6)	-2.1	(-8.5 to 4.3)	0.509	-4.8%
Postural balance (n NoS)	27	-5.9	(-8.0 to -3.9)	13	-1.6	(-4.6 to 1.4)	-4.3	(-8.0 to -0.7)	**0.021**	**-27.5%**

Intention-to-treat analyses of outcomes were performed with linear mixed model analyses including all available data. Hence, reported n's are available data at endpoints of time intervals (6 and 12 months, respectively). Measurements of BMD of lower limbs are reported as the mean of the left and right values. Abbreviations: bone mineral density (BMD), one repetition maximum (1RM), need of support (NoS).


Interested individuals screened for eligibility (n = 81).
Excluded (n = 9):
- Lack of time or long travel distance (n = 7).
- Osteoporosis (T-score ≤ -2.5) (n = 1).
- Shoulder injury (n = 1)
Tested at baseline (n = 72)
Excluded (n = 4):
- Osteoporosis (T-score ≤ -2.5) (n = 3).
- Uncomfortable at baseline test (n = 1).
Randomized (n = 68).
Randomized to the control group (n = 22).
Randomized to the football fitness group (n = 46).
Lost to follow-up (n = 3):
- Dissatisfied with group allocation (n = 1).
- Unknown (n = 2).
Lost to follow-up (n = 10):
- Personal reasons (n = 6).
- Non-football related fracture (n = 1).
- Joint-pain (n = 1).
- Unknown (n = 1).
- Deteriorating health (n = 1).
Completed test day at 6 months (n = 19).
Completed test day at 6 months (n = 35).
- Participated in ≤ 5 sessions of football fitness after group allocation but attended test day (n = 6).
- Continued intervention but missed test day (n = 1).
Lost to follow-up (n = 3):
- Personal reasons (n = 1).
- Surgery (n = 1).
- Unknown (n = 1).
Lost to follow-up (n = 3):
- Unknown (n = 1).
- Personal reasons (n = 1).
- Joint-pain (n = 1).
Completed test day at 12 months (n = 16).
Completed test day at 12 months (n = 33).
- Participated in ≤ 5 sessions of football fitness after group allocation but attended test day (n = 3).



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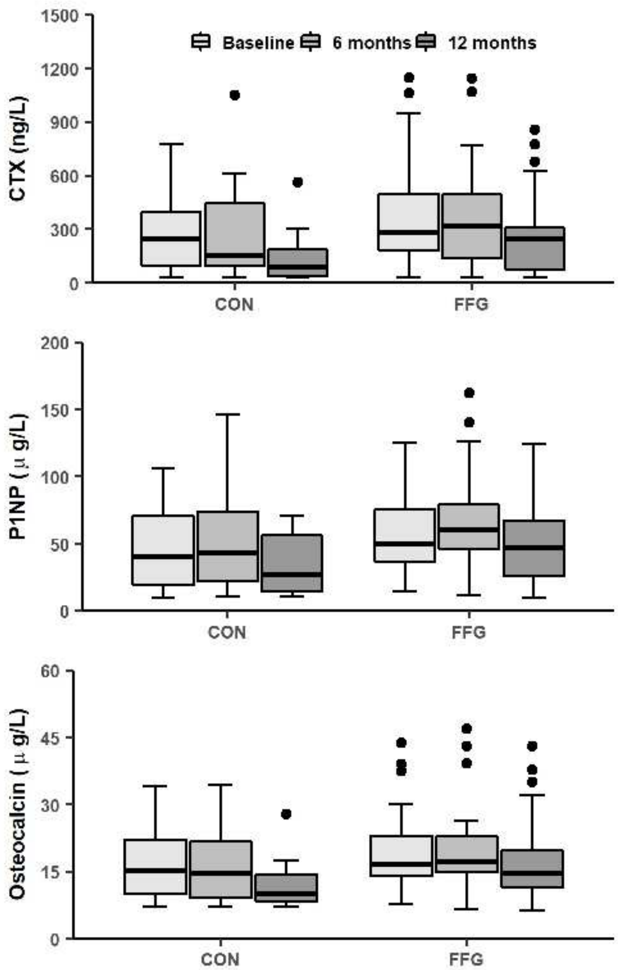

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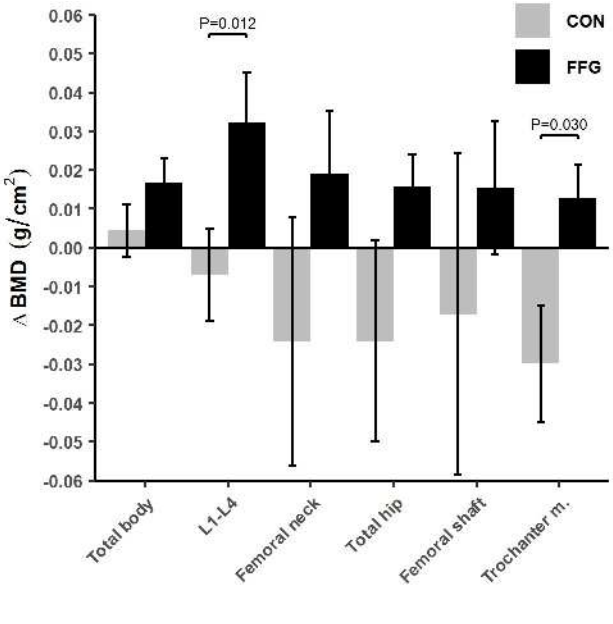

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