Influence of physical activity on the immune system in breast cancer patients during chemotherapy

Thorsten Schmidt1 · Walter Jonat2 · Daniela Wesch3 · Hans-Heinrich Oberg3 · Sabine Adam-Klages3 · Lisa Keller2 · Christoph Röcken1 · Christoph Mundhenke2

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Abstract
Purpose Physical activity can impact the immune system in different ways, e.g. by alteration of the humoral and cellular immune response. Physical activity at medium intensity enhances numbers of cytotoxic T cells, NK cells and macrophages in healthy people. The aim of this study was to compare the effects of endurance and resistance training on the immune system in breast cancer patients during adjuvant chemotherapy.
Methods In a prospective, controlled and randomized intervention exploratory trial, 12-week supervised endurance or resistance training were compared with usual care twice a week. Endpoints were the absolute numbers of the immune cells such as CD3+ T lymphocytes including CD4+ and CD8+, αβ T cells, γδ T cells, CD3−/CD16+/56+ NK cells and CD19+ B cells, before and after 12 weeks of treatment. Cell numbers were analyzed using fluorescence-activated cell sorting.
Results Despite different physical interventions in all groups immune cell count decreased in CD3 T cells including TCR αβ and CD4 T cells, NK cells and CD19 B cells 12 weeks after initiation of chemotherapy and start of the physical intervention program, while the reduction of γδ T cells and CD8 T cells is less prominent in the RT and UC group.
Conclusion Chemotherapy led to a decrease in nearly all measured immune cells. In this study, physical intervention with endurance or resistance training did not suppress cellular immunity any further. Larger multicenter trials are needed to evaluate the exact impact of sports intervention on immune cell subpopulations.

Keywords Physical activity · Breast cancer · Immune system · Chemotherapy

Introduction
For primary prevention and the prevention of breast cancer recurrence it is important to assess the potential of new approaches to supportive care. Nowadays, physical activity is often used as adjunctive therapy during chemo- and radiotherapy to relieve disease and therapy related symptoms. In several randomized controlled trials the influence of physical activity of breast cancer patients during medical treatment on psychological and physical parameters has been evaluated. It has been suggested that physical activity can not only improve physical performance, but also influences factors as quality of life, depression and fatigue (Baumann et al. 2013; Courneya et al. 2013, 2014; Hayes et al. 2013; Markes et al. 2006).

The effector function of the immune system is impaired with advanced age and by exogenous agents. For instance, immunological reactions can be diminished by inactivating antigen-specific B and T cells through, e.g. altered presentation and costimulation by dendritic cells or macrophages as well as through influencing innate immune functions of natural killer (NK) cells and neutrophils (Brolinson and Elliott 2007; Pawelec et al. 2001). This appears to be important for the increased incidence of malignant diseases in the elderly persons (Senchina and Kohut 2007). Risk factors such as advanced age, hereditary factors, obesity, lifestyle, environmental pollution, nicotine and physical activity influence the immune system and play a role in carcinogenesis. While

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healthy athletes and older adults has already been studied well for many years (Brolinson and Elliott 2007; Gleeson and Walsh 2012; Pedersen 1991; Pedersen and Bruunsgaard 1995; Phillips et al. 2010), the impact on the immune system of cancer patients and on disease progression has not been adequately investigated. Initial findings on the immunological impact of physical activity in cancer patients have been made in the 1990s. (Nieman et al. 1995; Peters et al. 1994; Uhlenbruck and Order 1991).

Currently, only a small number of studies evaluated the effects on the immune system of breast cancer patients. Several authors described an enhanced immune function and a low susceptibility to cancer which occur with regular moderate exercise, whereas inactivity and/or exhaustive exercise suppress immune function, and elevate susceptibility to infections (Fairey et al. 2005, 2002; Hagstrom et al. 2016; Hutnick et al. 2005; McTiernan 2008; Peters et al. 1994). Most of these studies focus on the period after adjuvant therapy and investigated endurance training as the intervention method, whereas resistance training as intervention and the influence of physical activity during chemotherapy on the immune system are underrepresented (Fairey et al. 2002; Hagstrom et al. 2016; Hutnick et al. 2005; Mohamady et al. 2013; Nieman et al. 1995; Peters et al. 1995, 1994; Saxton et al. 2014; Zimmer et al. 2016).

The aim of the study was to compare the effects of resistance and endurance training with standard care on the immune system of women with primary breast cancer during adjuvant chemotherapy.

**Materials and methods**

**Design and procedures**

In this prospective, controlled and randomized intervention exploratory trial 12-week supervised resistance training (RT) or endurance training (ET) were compared with usual care (UC) in women with primary moderate or high risk breast cancer during adjuvant chemotherapy. An overview of the study flow is shown in Fig. 1. Patients were recruited at an academical breast unit in Germany. Inclusion criteria were: primary moderate or high risk breast cancer, planned adjuvant or neoadjuvant chemotherapy with epirubicine/cyclophosphamide (EC) (4×, q3w) followed by paclitaxel (12×, q1w), fluorouracil/epirubicine/cyclophosphamide (3×, q3w) followed by doxetaxel (3×, q3w) or further chemotherapy regimen 18–70 years old women and fitness to exercise. Exclusion criteria comprised, acute infectious disease, severe cardiac disease (New York Heart Association functional class III; myocardial infarction < 3 months), severe pulmonary or renal insufficiency (glomerular filtration rate < 30%), serious neurological disorders, less than 10,000 platelets per ml, hemoglobin < 8 g/dl and a planned radiotherapy during the study. The active study period was from the initiation of chemotherapy to the end of EC application. The study was approved by the local review board (registration number: AZ A 157/11). All participants were included in the study after providing written informed consent, as required by the Declaration of Helsinki (1975).

**Randomization**

After baseline assessments the patients were assigned randomly (1:1:1) to RT, ET UC using a computer-generated program. The allocation sequence was executed by the clinical research unit and concealed from the project team. To prevent possible bias, the investigators and study nurses did not have access to the randomization files.

**Statistical analysis**

The analyses included data of patients who attended a minimum of 70% of the training sessions according to the protocol. Immunological profiles were assessed at baseline on the day when chemotherapy (T1) was initiated, 12 week after initiation of chemotherapy and physical intervention (T2). Primary endpoints of this trial were the absolute number count of T cell receptor (TCR) αβ and TCR γδ CD3+ T cells (CD3+), CD3+ TCR γδ T cells alone (γδ T cells), CD3+ TCR αβ T cells (αβ T cells), αβ T helper cells (CD4+), αβ- and γδ cytotoxic T cells (CD8+), CD8- γδ T cells, NK cells (CD3−/CD16+/56+) and B cells (CD19). Obtained results at baseline were compared across the treatment and control groups using an independent t test for continuous outcomes. Statistical significance for the t test at T1 and T2 was set at the probability level of p < 0.05. The effects are expressed with mean and standard deviations. The analyses were performed using the SPSS system for windows (Version: PASW 18).
Setting and participants

Out of 100 patients screened between February 2012 and October 2013, 81 patients were enrolled in the study and randomized before the start of chemotherapy into the intervention groups ET and RT or usual care (UC). Nineteen patients did not enroll due to timing problems. Due to chemotherapy related side effects or withdrawal of consent 14 out of 81 patients dropped out: three withdrew from the RT, nine from the ET and two from the UC. The data of 67 patients were fully evaluable (21 patients in the RT, 20 in the ET and 26 in the SC). An overview of the patient cohort is shown in Tables 1, 2.

Exercise training intervention

RT and ET were performed during the period of chemotherapy. After the initiation of chemotherapy, both physical interventions took place for 60 min twice a week for 12 weeks. The training sessions of the RT and ET were supervised and documented by experienced exercise therapists. Before each resistance and endurance training the individual intensity levels were checked according to the exercise guidelines for cancer survivors of the American College of Sports Medicine (36).

To define the individual resistance for each exercise the therapist carried out the hypothetic one-repetition maximum (h1RM) according to the Brzycki Method (Brzycki 1993) in the first training session of the RT group. The h1RM is a dynamic maximum force test and was performed according to the repetition method. Hereby, the therapist chose the weight to avoid that the patient carry out more than 20 repeats (Gießing 2003). The h1RM test took place on all workout machines. At the beginning, patients of the RT completed one training set of 20 repetitions with a hypothetical 50% of the maximum weight. The training took place on the following devices: squat, chest press, leg curl, rowing, leg extension, upper arm curl, upper arm extensors, shoulder press, abdominal bench and lats pull down. Any further increase in intensity was based on the Borg scale (Borg 1998; Wahlund 1948).

The endurance training took place on an indoor bike (Tomahawk, Indoorcycling group, Nürnberg, Germany). The Borg-scale was used as a subjective reference point for the performance during the training. During the training, patients exercise for 45 min. After a 10-min warm-up, the patients exercise for 25–30 min followed by a 5 min cool down. The patients were encouraged to be active at Borg level 11–14 (Borg 1998; Wahlund 1948).

The training intervention took place on Monday and Wednesday, while the chemotherapy took place on Thursday.

Usual care

Participants in the usual care group were informed about the feasibility of physical activity and the impact of physical activity during chemotherapy. Patients did not receive a supervised training.

Determination of the immune parameter

The determination of the absolute cell number as immune parameters was made by flow cytometry (Fulwyler 1965) using a FACS Canto and the DIVA software. The BD Multitest 6-color TBNK (M6T) Reagent with BD Trucount™ Beads (http://www.bd.com/resource.aspx?IDX=17743 DX = 17,742, BD Biosciences, San Jose, CA, USA) was applied to determine the absolute number of αβ T

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Anamnestic and anthropometric parameters of the patients</th>
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<td>n</td>
<td>Age (years) (mean ± d)</td>
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<td>RT</td>
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<td>ET</td>
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<td>UC</td>
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<th>Table 2</th>
<th>Different Chemotherapies of the intervention groups and the standard care group</th>
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<tbody>
<tr>
<td>4×epirubicin/cyclophosphamid, q3w, followed by 12×taxol weekly</td>
<td>4×epirubicin/cyclophosphamid, q3w, followed by 4×docetaxel, q3w</td>
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<tr>
<td>3×fluorouracil/Epirubicin cyclophosphamide, q3w, followed by 3×docetaxel, q3w</td>
<td>3×fluorouracil/Epirubicin cyclophosphamide, q3w, followed by 3×docetaxel, q3w + herceptin</td>
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<tr>
<td>Further chemotherapy-regimen</td>
<td>Further chemotherapy-regimen + herceptin</td>
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<td>RT</td>
<td>10</td>
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<td>ET</td>
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<td>UC</td>
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Regarding the different CD3+ T cell subsets, αβ T cells cell number was highly significant in the ET and UC group, − 21.54%, p < 0.0001; UC: − 21.86%, p < 0.0001). The differences of all immune parameters between the arms are not significant.

Regarding the different CD3+ T cell subsets, αβ T cells highly significantly decreased in all groups with less extent in the RT group (RT: − 19.84%; p: 0.04; ET: − 26.22%; p: <0.0001; UC: − 21.86% p: <0.0001), whereas the absolute γδ T cell number was nearly stable, in contrast to αβ T cells within 12 weeks (RT: +0.89%; p: 0.95; ET: 16.16%, p: 0.14; UC: − 14.93%, p: 0.12). In detail, γδ T cells were stable within 12 weeks in the RT and only slightly decreased in the ET- and UC group. Interestingly, similar results as for γδ T cell population were measured for CD8+ T cells which co-express either the TCR αβ or occasionally TCR γδ(RT: − 10.93% p: 0.13; ET: − 16.89% p: 0.04; UC: − 4.00% p: 0.41) whereas a significant decrease of the CD4+ T cells was detected in all three groups (RT: − 31.96% p: 0.001; ET: − 35.14%; p: 0.001; UC: − 29.17% p: 0.001).

In addition, NK cells (CD16/CD56) were slightly reduced in the RT and UC group and highly significant in the ET group (RT: − 22.88% p: 0.53; ET: − 40.16% p: 0.001; UC: − 19.39% p: 0.05). Extremely striking was the highly significant reduction of the B cells (CD19) in all three groups (RT: − 86.60%; p: 0.001; ET: − 92.59%, p: 0.001; UC: − 88.76%, p: 0.001). The differences of all immune parameters between the arms are not significant.

Previous studies that investigated the influence of physical activity on the immune system of breast cancer patients focused mainly on the time after medical treatment and described the effect on the cells of the immune system and changes in cytotoxins. In a systematic review (Schmidt et al. 2017a, b) we identify ten studies, who investigate especially in the effects of physical training on the immune system (NK cells, monocytes macrophages, lymphocytes or the tumor-associated macrophages, interleukines and the tumor necrosis factor (TNF)) of breast cancer patients (Evans et al. 2015; Fairey et al. 2005; Hagstrom et al. 2016; Hutnick et al. 2005; Mohamady et al. 2013; Nieman et al. 1995; Peters et al. 1995, 1994; Saxton et al. 2014; Zimmer et al. 2016). The results of these studies show that the NK cell populations increase or their function improves due to different sports interventions. Fairey et al. and Peters et al. report in addition a change in the lymphocyte population. Both the NK-cells and also the lymphocytes play an important role in the immune system and the immunoreaction (Fairey et al. 2005; Peters et al. 1995, 1994).

Our study represents a first attempt to obtain information about the influence of several training programs on the immune system of breast cancer patients undergoing chemotherapy. In contrast to our results, Hagstrom et al. could determine a positive effect of physical training on the immune system of breast cancer patients in aftercare. 39 BC patients were randomized to an intervention and a control group. The 20 participants in the intervention group completed equipment training over 16 weeks at 80% of the “one repetition maximum”. The NK-cells, the “natural killer T-cells” (NKT) and the inflammation markers TNF-α, IL-6, IL-10 and CRP (C reactive protein) were measured before and after the intervention. The results showed an altered TNF-α expression in NK- and NKT cells of the intervention group compared to the control group (Hagstrom et al. 2016). This result corresponds to findings obtained in other studies (Fairey et al. 2002; Hagstrom et al. 2016; Hutnick et al. 2005; Mohamady et al. 2013; Saxton et al. 2014; Zimmer et al. 2016).

In our study the absolute cell number of NK cells, B cells and T cells decreased in the intervention groups as well in the control group with a lowest reduction of the CD3 T cells to T2 in the resistance group. While in the past, discouraged from physical activity during chemotherapy on the basis of a physical activity induced immunosuppression, our data describe that supervised physical activities has no influence on chemotherapy induced immunosuppression. Slightly no significant higher values or lower reduction of the subsets of immune parameter (γδ T cells and CD8 T cells) from T1 to T2 we observed in the resistance group.

The different results of the studies can be attributed to the various study designs. While the present study concentrates on the phase during chemotherapy, previous studies focused
Table 3  Immune cells at T1, T2, T3 in the RT, EC an UC-group

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<th>CD3</th>
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<th>CD4</th>
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<th>CD8</th>
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<tr>
<td></td>
<td>T1 vs. T2</td>
<td>p</td>
<td>% Change T1/T2</td>
<td>T1 vs. T2</td>
<td>p</td>
<td>% Change T1/T2</td>
<td>T1 vs. T2</td>
<td>p</td>
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<td>RT</td>
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<tr>
<td>T1</td>
<td>1252.82 ± 422.86</td>
<td>0.46</td>
<td>−19.32</td>
<td>827.33 ± 317.86</td>
<td>0.001</td>
<td>−31.96</td>
<td>359.67 ± 156.92</td>
<td>0.13</td>
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<tr>
<td>T2</td>
<td>1010.81 ± 484.96</td>
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<td></td>
<td>562.86 ± 210.31</td>
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<td></td>
<td>320.33 ± 208.24</td>
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<td>ET</td>
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<tr>
<td>T1</td>
<td>1153.40 ± 365.05</td>
<td>0.001</td>
<td>−25.78</td>
<td>753.60 ± 259.90</td>
<td>0.001</td>
<td>−35.14</td>
<td>339.40 ± 173.98</td>
<td>0.04</td>
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<tr>
<td>T2</td>
<td>856.00 ± 379.00</td>
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<td></td>
<td>488.75 ± 192.85</td>
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<td></td>
<td>282.05 ± 152.28</td>
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<tr>
<td>UC</td>
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<tr>
<td>T1</td>
<td>1255.48 ± 340.32</td>
<td>0.001</td>
<td>−21.54</td>
<td>788.60 ± 199.43</td>
<td>0.001</td>
<td>−29.17</td>
<td>369.84 ± 150.37</td>
<td>0.41</td>
</tr>
<tr>
<td>T2</td>
<td>985.00 ± 323.98</td>
<td>0.36</td>
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<td>558.60 ± 159.44</td>
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<td>355.00 ± 170.71</td>
<td>0.40</td>
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Between the groups p-value

<table>
<thead>
<tr>
<th></th>
<th>CD16/56</th>
<th></th>
<th>γδ</th>
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<th>αβ</th>
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<tr>
<td></td>
<td>T1 vs. T2</td>
<td>p</td>
<td>% Change T1/T2</td>
<td>T1 vs. T2</td>
<td>p</td>
<td>% Change T1/T2</td>
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<td>RT</td>
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<tr>
<td>T1</td>
<td>230.14 ± 118.26</td>
<td>0.53</td>
<td>−22.88</td>
<td>42.67 ± 25.96</td>
<td>0.95</td>
<td>+0.89</td>
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<tr>
<td>T2</td>
<td>177.48 ± 118.05</td>
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<td></td>
<td>43.05 ± 29.74</td>
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<tr>
<td>ET</td>
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<tr>
<td>T1</td>
<td>182.65 ± 82.44</td>
<td>0.001</td>
<td>−40.16</td>
<td>41.75 ± 47.66</td>
<td>0.14</td>
<td>−16.16</td>
</tr>
<tr>
<td>T2</td>
<td>109.30 ± 42.30</td>
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<td></td>
<td>35.00 ± 52.45</td>
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<td></td>
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<tr>
<td>UC</td>
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<tr>
<td>T1</td>
<td>188.76 ± 79.30</td>
<td>0.05</td>
<td>−19.39</td>
<td>53.84 ± 66.48</td>
<td>0.12</td>
<td>−14.93</td>
</tr>
<tr>
<td>T2</td>
<td>152.16 ± 99.20</td>
<td>0.72</td>
<td></td>
<td>45.80 ± 48.65</td>
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</table>

Between the groups p-value
on the time after the operation, chemotherapy or radiation therapy. Furthermore, the sport and exercise programs in the studies cited differ in several points, so that comparability is limited. The intervention programs differ with respect to their intensity, duration of the individual training sessions, their frequency and the overall extent of physical activity.

While Hagstrom et al. conducted a resistance training with an intensity of 80% of the 1RM, Zimmer et al. conducted a single intervention as a half-marathon, Evans et al. an interval training on a cycle ergometer with 60% of the VO2 max, Saxton et al. a progressive aerobic and strength training at 65–85% heart rate, Hutnick et al. an endurance and exercise program at 60–70% of the functional capacity, Niemann et al. a supervised walking training at 75% of HFmax and Peters et al. a cycle ergometer training at 60–80% HF max. Mohamady et al. performed a mobilization and mobility training, Fairey et al. a cycle training without specific details about the impact. Other differences can be observed with respect to the length of the individual training sessions (30–60 min), the frequency (three times per week–five times per week) and the overall duration (between 8 weeks and 7 months) (Evans et al. 2015; Fairey et al. 2005; Hagstrom et al. 2016; Hutnick et al. 2005; Mohamady et al. 2013; Saxton et al. 2014; Zimmer et al. 2016).

A further common limitation for the comparison of all the studies is the time at which blood samples were drawn (directly after training, 24 h after training or at some other time). The changes in the immune cell numbers are short-lived and are often determined by the type and duration of activity.

A limitation of this study is the small sample size with an inhomogeneous collective relating to the chemotherapy (Table 2) and the lack of attention to additional activity on the job, in everyday life and leisure during the study. Additionally, the blood sample were taken before the chemotherapy and not immediately after the resistance and endurance training, so that the acute influence of physical activity could not demonstrated. In the course of our study, we analyzed the effects of a resistance and endurance training over the first 12 weeks with the largest chemotherapy induced immunosuppression. Following studies should include an increased sample size for a subgroup analysis of chemotherapy-groups and should analyse the impact over the whole time of chemotherapy.

**Conclusion**

In conclusion, the results of the present study, support the current literature and show the possibility of a resistance and endurance training during chemotherapy without an immunosuppression. Scientific and more specific statements about the effect of targeted sports intervention after
a breast cancer diagnosis such as the dose/effect relationship are possible only after further prospective, standardized and controlled clinical studies confirming the assumption of an immunomodulating effect of physical activity. Further studies should be the focus of these points to enable more precise statements on the intensity, duration and extent of sport activities.

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Compliance with ethical standards Conflict of interest There are no conflicts of interest.

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