Published ahead of Print

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Accepted for Publication: 15 August 2024

Medicine & Science in Sports & Exercise, Publish Ahead of Print
DOI: 10.1249/MSS.0000000000003546

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Conflict of Interest and Funding Source: Ana Jessica Pinto, Tiago Peçanha, Fabiana Infante Smaira, and Bruno Gualano were supported by grants from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; 2015/26937-4 and 2018/19418-9; 2016/23319-0; 2017/17837-1; 2017/13552-2). Kamila Meireles dos Santos was supported by a grant from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). The authors have no conflict of interest to disclose.

ABSTRACT

Purpose: We investigated the effects of a 4-month intervention targeting sedentary behavior on sedentary time and physical activity level, clinical parameters, cardiometabolic risk factors, inflammatory markers, and health-related quality of life in post-menopausal women with rheumatoid arthritis. **Methods:** This was a 4-month, parallel-group, randomized controlled trial (ClinicalTrials.gov identifier: NCT03186924). One-hundred-and-three postmenopausal rheumatoid arthritis patients were randomized (1:1) to either a newly developed intervention targeting sedentary behavior (Take a STAND for Health; TS4H) or standard of care (SOC). Sedentary behavior (primary outcome) and physical activity levels, clinical parameters, anthropometric parameters and body composition, blood samples and oral glucose tolerance test, blood pressure, muscle function, and health-related quality of life were assessed at baseline (Pre) and after 4 months (Post). Between- and within-group differences were tested using linear mixed models following the intention-to-treat principle. **Results:** Total sedentary time, time in prolonged sitting bouts, standing, and stepping did not change in either group (all $p \geq 0.337$). No significant between- and within-group differences were detected for any of the clinical parameters, markers of cardiometabolic health and inflammation, and health-related quality of life variables (all $p \geq 0.136$). Among responders in TS4H group (those who reduced sedentary time by ≥30 min/d), Pre to Post IL-10 concentrations tended to reduce (group*time: p=0.086; estimated mean difference [EMD]: -12.0 pg/mL [-23.5 to -0.6], p=0.037), and general health (group*time: p=0.047; EMD: 10.9 A.U. [-1.1 to 22.9], p=0.086) and overall physical health tended to improve (group*time: p=0.067; EMD: 7.9 A.U. [-0.9 to 16.6], p=0.089). **Conclusions:** TS4H did not change sedentary behavior, physical activity levels, clinical, cardiometabolic,

inflammatory or health-related quality of life outcomes. However, TS4H tended to reduce IL-10 levels and improve health-related quality of life in responders.

Key-Words: ACTIVE BREAKS, INFLAMMATORY ARTHRITIS, LIGHT-INTENSITY PHYSICAL ACTIVITY, SITTING

INTRODUCTION

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation, joint damage, pain, fatigue, and physical disability (1). Rheumatoid arthritis patients have a greater risk of cardiovascular diseases and premature mortality, which is partially explained by the complex interplay between chronic inflammation, adverse effects of drug treatment, associated comorbidities, and inactive and sedentary lifestyle (2-5).

Although exercise training improves clinical symptoms and overall health (6-8), participation in exercise programs may not be feasible for patients with disabilities and active disease, as these conditions may preclude participation in moderate-to-vigorous physical activity. Participation in light-intensity physical activity has been associated with lower cardiovascular risk, disability, and disease activity in rheumatoid arthritis (9). Thus, interventions focused on replacing sedentary time with light-intensity physical activity could be of clinical relevance.

Controlled laboratory studies have shown that short, active breaks in sedentary time (e.g., 2-min light-walking breaks every 20 min) for 5-8 h can improve postprandial glucose and insulin responses in general and clinical populations (10). Long-term intervention studies focused on reducing sedentary time have shown improvements in insulin sensitivity, lipid profile, body composition, and blood pressure in general population and in individuals with obesity (10). However, the impact of sedentary behavior interventions in rheumatoid arthritis remains underexplored.

We recently showed that breaking up sitting time with 3-min bouts of light-intensity walking every 30 min (total: 42 min) throughout an 8-hour period decreased postprandial glucose and insulin responses, and plasma IL-1β and IL-10, and increased IL-1ra concentrations, but did not change blood pressure, triglycerides concentrations or other inflammatory markers, compared to uninterrupted 8-hour prolonged sitting in post-menopausal females with rheumatoid arthritis (11). In addition, a 4-month intervention involving general motivational counselling and text-messages reminders resulted in reduced sedentary time (-1.6 h/d), pain, fatigue, and total cholesterol, and improved quality of life in a Scandinavian cohort of rheumatoid arthritis individuals (12). The cross-cultural validation of this finding in a Latin-American cohort with a lower socioeconomic status is necessary.

We investigated the effects of a newly developed intervention targeting sedentary behavior on habitual sedentary time (primary outcome) and physical activity levels, clinical parameters, cardiometabolic risk factors, inflammatory markers, and health-related quality of life in post-menopausal women with rheumatoid arthritis. In addition, responders and non-responders (grouped according to their changes in habitual sedentary time) were compared to test the efficacy of reducing sedentary behavior on health-related outcomes in rheumatoid arthritis.

METHODS

Experimental design

We conducted a 4-month, parallel-group, randomized controlled trial (clinicaltrials.gov; NCT03186924). This manuscript is described according to the recommendations by the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see CONSORT checklist,

Supplemental Digital Content, http://links.lww.com/MSS/D80). The rationale and design of this study have been fully described elsewhere (13).

Sedentary behavior (primary outcome) and physical activity levels, clinical parameters, anthropometric parameters and body composition, fasting glucose, insulin, c-peptide, HbA1c, lipid panel, and inflammatory markers, post-load glucose, insulin and c-peptide responses by means oral glucose tolerance test, indexes of insulin resistance/sensitivity, blood pressure, and health-related quality of life were assessed at baseline (Pre) and after 4 months (Post). In addition, sedentary behavior and physical activity levels were also evaluated at the second month to check adherence to the intervention ($Post_{2mo}$). After baseline assessments, patients were randomly allocated to either a standard of care (SOC) or intervention group (TS4H) using a simple randomization (1:1 ratio) procedure. An external researcher generated the allocation sequence and placed into numbered opaque envelopes. All assessors were blinded to participants' allocation. The trained researchers who were responsible for assigning participants to and delivering the TS4H intervention were not blinded. The SOC group received standard care, including general advice on a healthy lifestyle. The TS4H group received standard care plus a specific personalized intervention aimed to reduce sedentary time (called Take a STAND for Health).

Participants

One-hundred-and-three post-menopausal women diagnosed with rheumatoid arthritis (14) were recruited from the Rheumatoid Arthritis Outpatient Clinic of the Rheumatology Division (Clinical Hospital, University of Sao Paulo, Brazil). Patients were enrolled from December 2017

to February 2022. Exclusion criteria were regular participation in structured exercise training programs within the last 12 months, unstable drug therapy in the last 3 months prior to and during the study, and Health Assessment Questionnaire (HAQ) score >2.0 (i.e., severe physical impairment). This trial has been approved by the local Ethical Committee (Commission for Analysis of Research Projects, CAPPesq; approval: 1.735.096). Patients signed an informed consent form before participation.

Intervention

The Take a STAND for Health program is a goal setting, behavioral intervention aimed at reducing sedentary behavior with very light and light-intensity physical activity, which incorporates the constructs of self-determination theory (15). The Take a STAND for Health intervention was based on the Small Steps program (67), which was developed on the same principles, and was shown to be effective in reducing sedentary time (51 min/day) in older adults. Prior to this trial, the Take a STAND for Health intervention was tested on a small pilot study with healthy young participants (8F/9M; age: 26.4±3.4 years; body mass index: 24.4±3.0 kg/m^2). We found that this program reduced sedentary time by 38 min/day after just two weeks. In this pilot study, participants were instructed to select 15 goals, but they reported it was excessive and that goals would not always fit in their routines (13). Based on this feedback, it was decided to remove the requirement of a minimum number of goals and maintain only those with the best chance of being effectively incorporated into participant' routines.

The intervention consisted of 5 face-to-face individual sessions, lasting ~15 minutes, and weekly supportive phone calls and/or text messages. During session 1, a trained researcher

explained the details of the intervention (e.g., aim, duration) to the participant. Subsequently, participants were asked to talk about their routines and choose goals to reduce time spent in sedentary behavior, including goals from the following domains: (1) transport, which involved reducing sedentary time during transportation (e.g., park further away from your destination except when carrying heavy weight, get off the bus a stop before or after your destination); (2) work, which involved reducing sedentary behavior at the workplace (e.g., get up every 30 min while performing activities in a seated position, stand up during meetings and invite your colleagues to join you); and (3) leisure/social activities, which involved reducing time spent in sedentary behavior during leisure time (e.g., stand up during ad breaks, walk your dog at least twice a week). Goals will be explained in more detail if necessary and all possible questions will be clarified before patients' setting of the goal. Participants were instructed to complete a diary log to record their adherence to the intervention. During the following face-to-face sessions (n=3), each participant was asked about the goals' execution and encouraged to report barriers and facilitators to achieving her goals. If a participant was adhering to the goals, she was encouraged to maintain her routine. If not, the researcher discussed ways of overcoming the reported barriers; if a barrier was unresolvable, the patient had the option to select a new goal. Patients received supportive phone calls and/or text messages on a weekly basis to check adherence to the goals. The Take a STAND for Health intervention has been fully described elsewhere (13).

Measurements

Sedentary behavior (primary outcome). Postural allocation (sitting, standing and stepping) was measured using activPAL micro™ (PAL Technology, Glasgow, UK) during 7 consecutive days

(24 h/d) before, during ($Post_{2mo}$), and over the last week of intervention. Participants were instructed to always wear the monitors, except when participating in water-based activities, and to fill out a diary log in which they indicated any period during which they removed the activity monitors (16). All participants accumulated at least 10 hours of valid activity recordings daily for at least 4 days, including one weekend day (16). Data were exported from the device using PALanalysis software, v. 7.2.32 (PAL Technology, Glasgow, UK). ActivPAL™. Data were reported as follows: time spent in sedentary behavior (h/d), prolonged sitting bouts (h/d), standing (h/d), and stepping (h/d), number of breaks to sitting, and daily step count. All data were standardized to a 16-h day to avoid bias from differences in participants' daily wear time, as previously described (13).

Physical activity level. Physical activity levels were objectively measured using the actiGraph GT3X® accelerometers (ActiGraph, Pensacola, Florida) during waking hours for 7 consecutive days before, during ($Post_{2mo}$), and over the last week of intervention, except when bathing or swimming. The device was worn on the waistline on the right side of the hip. Data were exported in 60-sec epochs using ActiLife 6 software, v. 6.11.9 (ActiGraph, Pensacola, Florida). All participants accumulated at least 10 h/d of valid activity recordings for at least 4 days, including one weekend day (17). Freedson cut-points were used to define cut points for light-intensity and moderate-to-vigorous physical activity (18). Data were analyzed and reported as previously described (13).

Clinical parameters. Disease duration, current use of medications and presence of comorbidities were obtained by medical records and interviewing participants. Disease activity was assessed by

the Disease Activity Score in 28 joints (DAS-28) (19) and the Clinical Disease Activity Index (CDAI) (20) questionnaires. Assessments were performed by an experienced rheumatologist who was blinded to participants' study group. Physical functioning was assessed by HAQ (21). Pain was assessed by the Visual Analogic Scale (VAS) (22). Fatigue severity was assessed by the Fatigue Severity Scale (FSS) (23). Overall, physical, and mental fatigue was assessed by Chalder's Self-rating Fatigue Scale (24). Muscle function was evaluated by the Timed-Stands, the Timed-Up-and-Go, and handgrip tests as previously described (13).

Anthropometry and body composition. Anthropometric measurements included height, weight, body mass index (BMI), and waist circumference. Measurements were performed as previously described (13). Body composition was measured by whole-body dual energy x-ray absorptiometry scan (DXA; GE Healthcare, WI, USA) using CoreScan™ software.

Markers of metabolic health and inflammation. Blood samples (40 ml) were collected after a 12-h overnight fast for measuring glucose, insulin, c-peptide, glycosylated hemoglobin (Hb_{A1C}), lipid profile, C-reactive protein, erythrocyte sedimentation rate, and cytokines (i.e., IL-1, IL-1ra, IL-4, IL-6, IL-10, and TNF-α). Blood samples were analyzed at the Clinical Hospital Central Laboratory (School of Medicine, University of Sao Paulo) as previously described (13).

Glucose tolerance and insulin sensitivity. A 2-hour oral glucose tolerance test was performed. Blood samples were collected after a 12-hour overnight fast, and 30, 60, 90, and 120 min following the ingestion of 75 g of glucose. Two-hour glucose was used as surrogate of glucose tolerance. Incremental area under the curve (iAUC) of glucose, insulin and C-peptide

concentrations over 2 hours, and Matsuda index, HOMA-IR and HOMA-B were calculated as surrogates of insulin sensitivity.

Blood pressure. Blood pressure was measured by the auscultatory technique using a non-mercury sphygmomanometer (25). All measurements were taken in the same arm by a trained evaluator.

Health-related quality of life. Physical, mental, and overall health-related quality of life were assessed by the SF-36 questionnaire (26), in which higher scores indicate better quality of life.

Safety of TS4H intervention. Safety of the TS4H intervention was determined based on changes from Pre to Post in disease activity parameters (i.e., DAS-28, CDAI, and inflammatory markers) and symptoms (i.e., physical functioning as assessed by HAQ, pain, and fatigue).

Statistical analysis

Twenty-four participants (12 per arm) were required to achieve a 95% power (α), with a significance level of 5% (β), and assuming an effect size of 0.58 (27) for the primary outcome (i.e., sedentary time). Estimating a dropout rate of 25%, we planned to recruit at least 30 participants. Considering that this sample size could be underpowered for some secondary outcomes, we increased this estimated sample based on the feasibilities of our laboratory (including funding, capacity of research staff and facilities, and available participants), in line with contemporary recommendations (28, 29).

Linear mixed model (LMM) analyses were performed for each dependent variable, with group, time and their interaction term as fixed factors, and participants as a random factor. The presence of extreme observations and the normal distribution of residuals was determined through residual analyses. In case of significant F-values, a *post-hoc* test with Tukey's adjustment for multiple comparisons was performed. Analyses were conducted according to the intention to treat principle, in which missing values were handled by LMM. *A priori* exploratory sensitivity analyses were performed to test the efficacy of reducing sedentary time on health-related outcomes. Participants were allocated into 'responders' and 'non-responders' sub-groups according to changes in habitual sedentary time: ≥ 30 min/d of reduction vs < 30 min/d or increases in sedentary time, given 30 min/day is the average reduction in sedentary time in published meta-analysis (30) and reallocating 30 min of sedentary time to light-intensity physical activity associates with improvements in cardiometabolic risk factors (31). Thereafter, differences between- and within-group for dependent variables were tested using LMM as described for intention-to-treat analyses.

Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for Windows. The researchers responsible for statistical analysis were not blinded to participants' allocation. Data are presented as mean ± standard deviation (SD) or standard error (SE), or as estimated mean difference (EMD) and 95% confidence interval (95%CI). Significance level was set at $p \leq 0.050$. $P \leq 0.100$ was interpreted as a trend toward significance for secondary outcomes.

RESULTS

A total of 1,461 patients were screened for participation. One-hundred-and-three participants met inclusion criteria and were randomized to TS4H (n=51) and SOC (n=52). Nine participants in TS4H and eleven in SOC were lost to follow-up, none of them due to study- or intervention-related reasons (Figure 1). Mean age was 61±8 years and body mass index (BMI) was 28±5 kg/m^2. Disease activity ranged from remission to high activity in both groups; mean DAS-28 was 3.2±1.2 and CDAI was 11.7±9.8. Most participants were taking prednisone (>80%), disease-modifying antirheumatic drugs (DMARDS) (>86%) and biologic agents (>49%), and had hypertension (>58%) and dyslipidemia (>51%). Demographic and clinical characteristics are presented in Table 1. TS4H and SOC groups were comparable regarding baseline characteristics.

All participants self-reported completing selected TS4H goals regularly. However, 27 participants (53%) reported not completing TS4H goals due to pain and fatigue attributed to typical disease activity exacerbation not to the intervention per se, which was recurrent barrier to perform the intervention protocol in 25 out of 27 participants.

Sedentary behavior and physical activity levels

Total sedentary time, time in prolonged sitting bouts (>30 and >60 min), and numbers of sit-to-stand transitions were not different between groups after the intervention (all $p \geq 0.983$; Table 2). Similarly, time spent standing and in physical activity remained unchanged in both groups (group*time: all $p \geq 0.337$; Table 2), except for moderate-to-vigorous physical activity

(group*time: p=0.062), which decreased from $Post_{2mo}$ to Post in SOC, but p-value was no longer significant after adjustment for multiple comparisons (within-group: p=0.148).

Clinical parameters, markers of cardiometabolic health and inflammation, and health-related quality of life

No significant between- and within-group differences were detected for any of the clinical parameters, markers of cardiometabolic health and inflammation, and health-related quality of life variables (group*time: all p≥0.136; Table 3), except for fasting LDL concentrations (group*time: p=0.038), which tended to decrease in SOC from Pre to Post (within-group: p=0.073). Importantly, no exacerbation in disease activity, inflammatory markers, and disease symptoms were observed in the TS4H group.

Exploratory sensitivity analyses: Responders vs non-responders

As expected due to the sub-groups classification, total sedentary time was significantly lower in responders after the intervention (group*time: p<0.001; EMD: -1.6 h/d [-2.2 to -1.1], within-group: p<0.001), and it was also significantly lower than that of non-responders at Post (between-group: p=0.003; Table 4). Similarly, time spent in prolonged sitting bouts >30 tended to reduce in responders at Post (group*time: p<0.001; EMD: -0.7 h/d [-1.5 to 0.0], within-group: p=0.068), and tended to be lower than that of non-responders at Post (between-group: p=0.052; Table 4). While time in prolonged sitting bouts >60 min did not change in responders (p=0.225), it significantly increased among non-responders at Post (group*time: p<0.001; EMD: 0.8 h/d [0.2 to 1.4], p=0.003). Sedentary time was primarily replaced by standing (group*time: p<0.001; EMD: 1.2 h/d [0.7 to 1.8], p<0.001), but time spent stepping also increased in responders from

Pre to Post (group*time: p<0.001; EMD: 0.4 h/d [0.1 to 0.7], p=0.001). Standing time was also higher among responders vs. non-responders in Post (EMD: 2.0 h/d [0.6 to 3.5], p=0.003; Table 4). However, no changes were observed for sit-to-stand transitions, and light and moderate-to-vigorous physical activity (group*time: all p≥0.097; Table 4).

No significant between- and within-group differences were detected for any of the clinical parameters, and most of the markers of cardiometabolic health and inflammation (group*time: all p≥0.174; Table 5). Despite significant group-by-time interaction (p=0.040), within- and between-group differences in post-load glucose iAUC were not significant after adjustment for multiple comparisons (all p>0.477). There was a tendency for group-by-time interaction for IL-10 (p=0.086). IL-10 concentrations significantly reduced in responders from Pre to Post (EMD: -12.0 pg/mL [-23.5 to -0.6], p=0.037). Similar to the main analysis, no exacerbation was observed in disease activity, inflammatory markers, and disease symptoms were observed in the TS4H group.

General health domain as assessed by the SF-36 questionnaire tended to improve in responders from Pre to Post (group*time: p=0.047; EMD: 10.9 A.U. [-1.1 to 22.9], p=0.086; Figure 2). Despite tendency for group-by-time interaction (both p>0.058), within- and between-group differences in pain domain and overall health-related quality of life score were not significant after adjustment for multiple comparisons (all p≥0.287). Overall physical health score tended to improve in responders at Post (group*time: p=0.067; EMD: 7.9 A.U. [-0.9 to 16.6], p=0.089). No changes were observed for other health-related quality of life domains as assessed by SF-36 (group*time: all p≥0.117; Table 5 and Figure 2).

DISCUSSION

The main findings were that, overall, TS4H was not effective at reducing sedentary time and increasing participation in physical activity; possibly as a consequence, no changes were observed in clinical, cardiometabolic, inflammatory, and health-related quality of life outcomes. However, TS4H tended to reduce IL-10 levels and improve indexes of health-related quality of life in those who reduced sedentary time by ≥30 min/d. Despite disease-related symptoms being a recurrent barrier to TS4H, no exacerbation in disease activity, inflammatory markers, and symptoms were observed following the intervention. Although future studies are still needed to identify effective strategies to promote active behaviors in participants with rheumatoid arthritis, our novel data suggest replacing sedentary behavior with standing is a safe strategy capable of promoting some benefits in participants who adhere to the intervention.

As pointed out, overall, the TS4H intervention was not effective at reducing sedentary time in participants with rheumatoid arthritis. Meta-analyses demonstrated that interventions targeting sedentary behavior reduce overall daily sedentary time by 22 to 32 min in adults and older adults (30, 32-34). However, effectiveness varies greatly across different studies. Factors such as poor study quality, short intervention duration, and use of subjective assessments of sedentary behavior result in more pronounced reductions in sedentary time (32). Given most published studies meet at least one of these characteristics (32), overall estimates of changes in sedentary time following interventions targeting sedentary behavior are likely overestimated in published meta-analyses. In addition, studies with men-only or both sexes, but not women-only, show significant decreases in sedentary time (-57.9 min/d [-86.1 to -29.7], -25.3 min/d [-42.9 to -7.7], and -6.0 min/d [-23.5 to 11.6], respectively). This suggests women may have distinct

barriers to engage in sedentary behavior interventions as compared to men. Finally, behavioral interventions, as used herein, have also been shown to result in lower reductions in sedentary time as compared to environmental and multicomponent analysis (30); future studies should take this into consideration when designing sedentary behavior interventions. High-quality studies are needed to elucidate the effectiveness of sedentary behavior interventions design and delivery, as well as determine barriers and facilitators to such interventions and factors that influence effectiveness (e.g., population group, baseline physical activity level, individual preferences, design of intervention), both in general population and in participants with rheumatoid arthritis.

To the best of our knowledge, a single randomized controlled trial targeting sedentary behavior has been conducted in participants with rheumatoid arthritis (12, 35). In this study, the sedentary behavior intervention involved motivational counselling and text messaging on daily sitting time. It resulted in a significant reduction in sedentary time (-1.6 h/d [-2.0 to -1.3]) (12), which persisted after a 22-month follow-up period (-1.1 h/d [-1.5 to -0.7]) (36). Contrary to our hypothesis, the TS4H intervention did not change sedentary time on average, although 17 (33%) participants did reduce sedentary time by at least 30 min/d. Some differences between intervention design and population across studies could partially explain differences in intervention effectiveness, as our intervention did not include motivational counseling and our participants had lower physical functioning as measured by HAQ (1.2 vs 0.7), higher disease duration (20 vs. 15 years), and lower sedentary time at baseline (8.5 vs. 9.8 h/d).

Although no changes were observed for disease activity and symptoms, 27 out of 51 participants (53%) reported not completing some of their assigned TS4H goals due to pain and

fatigue attributed to typical disease activity exacerbation, which was recurrent barrier. Indeed, disease-related factors (e.g., pain, fatigue, joint mobility and stiffness) are the main self-reported barriers to physical activity in participants with rheumatoid arthritis (37, 38). Yet, we cannot properly identify the cause of increased pain and fatigue in our participants (i.e., typical disease exacerbation vs the TS4H intervention). Interestingly, pain and fatigue are bi-directionally associated with sedentary time in participants with rheumatoid arthritis, which suggests these symptoms may be both a cause and consequence of participation in this behavior (39). Altogether, these data suggest that even very-light and light-intensity physical activity might not be feasible during periods of disease symptoms exacerbation, and modifications in sedentary behavior and physical activity goals might be necessary during these periods. Continued efforts should be made to identify physical activity strategies that are less impacted by symptoms exacerbation and to educate participants on the importance of regular participation in physical activity and limiting sedentary behavior.

Sedentary behavior interventions have been shown to reduce body weight, waist circumference, percent body fat, systolic blood pressure, and fasting insulin and HDL cholesterol levels in adults and older adults (40). However, these benefits are not consistent across studies suggesting not everyone may benefit from these strategies (10). In participants with rheumatoid arthritis, reducing sedentary time improved pain, fatigue, fasting total cholesterol concentrations, and health-related quality of life (12). Despite the lack of changes in our primary analysis, exploratory sensitivity analysis demonstrated a tendency to improve IL-10 concentration and indexes of health-related quality of life in those who were able reduce sedentary time by ≥30 min/d. Our findings related to health-related quality of life are in line with Thomsen et al. (12)

and emphasize the role of physical activity at improving health-related quality of life (41), an outcome that is usually reduced in individuals with rheumatoid arthritis (42). As for IL-10 concentrations, our group has demonstrated that breaking up prolonged sitting with 3-min bouts of light-intensity walking every 30 min acutely decreased plasma IL-10 concentrations in postmenopausal women with rheumatoid arthritis (11). Our current findings suggest these benefits may be sustained over the longer term. The effects of the TS4H in reducing resting levels of IL-10, an anti-inflammatory cytokine, could be interpreted as detrimental. Aerobic and resistance exercise training programs led to reductions in IL-10 levels in patients with rheumatoid arthritis, which was accompanied by a decrease in regulatory B cell populations and positively correlated with changes in C-reactive protein following the exercise program (43). Similarly, reductions in IL-10 following physical activity program have been reported in patients with multiple sclerosis (44) and systemic lupus erythematosus (45). Additionally, it has been suggested that pro-inflammatory cytokines may trigger IL-10 production (46). Although not statistically significant, several pro-inflammatory markers assessed herein were reduced following TS4H (see Table 5), which is suggestive that the reduced IL-10 levels may be a consequence of these reductions. Finally, high levels of IL-10 have been reported in rheumatoid arthritis patients as compared to those with osteoarthritis and healthy individuals (47). Although IL-10 has anti-inflammatory effects, it has been suggested that high concentrations of IL-10 might be insufficient to counteract the inflammatory cascade in rheumatoid arthritis and conversely, can contribute to disease progression, promoting autoimmunity, and perpetuating the inflammatory process (48-50). Because of these opposing roles of IL-10, further studies are necessary to elucidate whether reductions in IL-10 concentrations following physical activity interventions are beneficial or detrimental for patients with rheumatoid arthritis. Without

neglecting the importance and health benefits of regular exercise, replacing sedentary behavior with very-light intensity physical activity is safe and can potentially improve overall health in participants with rheumatoid arthritis.

The strengths of this study include the randomized, controlled design and a well-powered sample; the use of objective measures of sedentary behavior and physical activity; the comprehensive clinical and metabolic assessments; and the evaluation of a novel, individually tailored intervention that has the potential of being delivered in real-world contexts. However, this study is not free of limitations. Our findings are confined to the main participants' characteristics (i.e., postmenopausal women with rheumatoid arthritis with a generally lower level of education and economic status) and limited by the duration of the intervention period (i.e., 4 months), its focus on specific sedentary behavior domains, and its specific behavioral components that were not specific to individuals with rheumatoid arthritis. Finally, to determine the efficacy of intervention in those who reduced sedentary time ≥30 min/d, we conducted sub-group sensitivity analyses for which the sample size was relatively small (n=17), possibly hindering our power to detect potentially clinically relevant differences in secondary outcomes.

CONCLUSIONS

In conclusion, TS4H did not change sedentary behavior and physical activity levels, clinical, cardiometabolic, inflammatory, and health-related quality of life outcomes in participants with rheumatoid arthritis. Nonetheless, among those who did reduce sedentary time, TS4H tended to reduce IL-10 levels and improve indexes of health-related quality of life. The most common self-reported barriers to TS4H were disease-related pain and fatigue, yet no

changes were observed in disease activity, inflammatory markers, and symptoms following the intervention. Future studies should test the effectiveness of novel interventions aimed at modifying sedentary behavior in participants with rheumatoid arthritis and assess barriers and facilitators to implementation of these strategies, enabling to identify those who are more prone or refractory to this form of intervention.

Acknowledgments: Ana Jessica Pinto, Tiago Peçanha, Fabiana Infante Smaira, and Bruno Gualano were supported by grants from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; 2015/26937-4 and 2018/19418-9; 2016/23319-0; 2017/17837-1; 2017/13552-2). Kamila Meireles dos Santos was supported by a grant from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Funding sources were not involved in the study design, the collection, analysis and interpretation of data, the writing of the report, and the decision to submit the article for publication.

Competing interests: The authors have no conflict of interest to disclose. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

Data availability statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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FIGURE LEGENDS

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Abbreviations: SOC, standard of care group; TS4H, Take a STAND for Health intervention.

Figure 2. Radar plot of health-related quality of life domains as assessed by SF-36 at Pre and Post in responders and non-responders to TS4H intervention. *Indicate tendency for within-group difference from Pre to Post ($p<0.100$).

SUPPLEMENTAL DIGITAL CONTENT

SDC 1: CONSORT_TS4H.doc

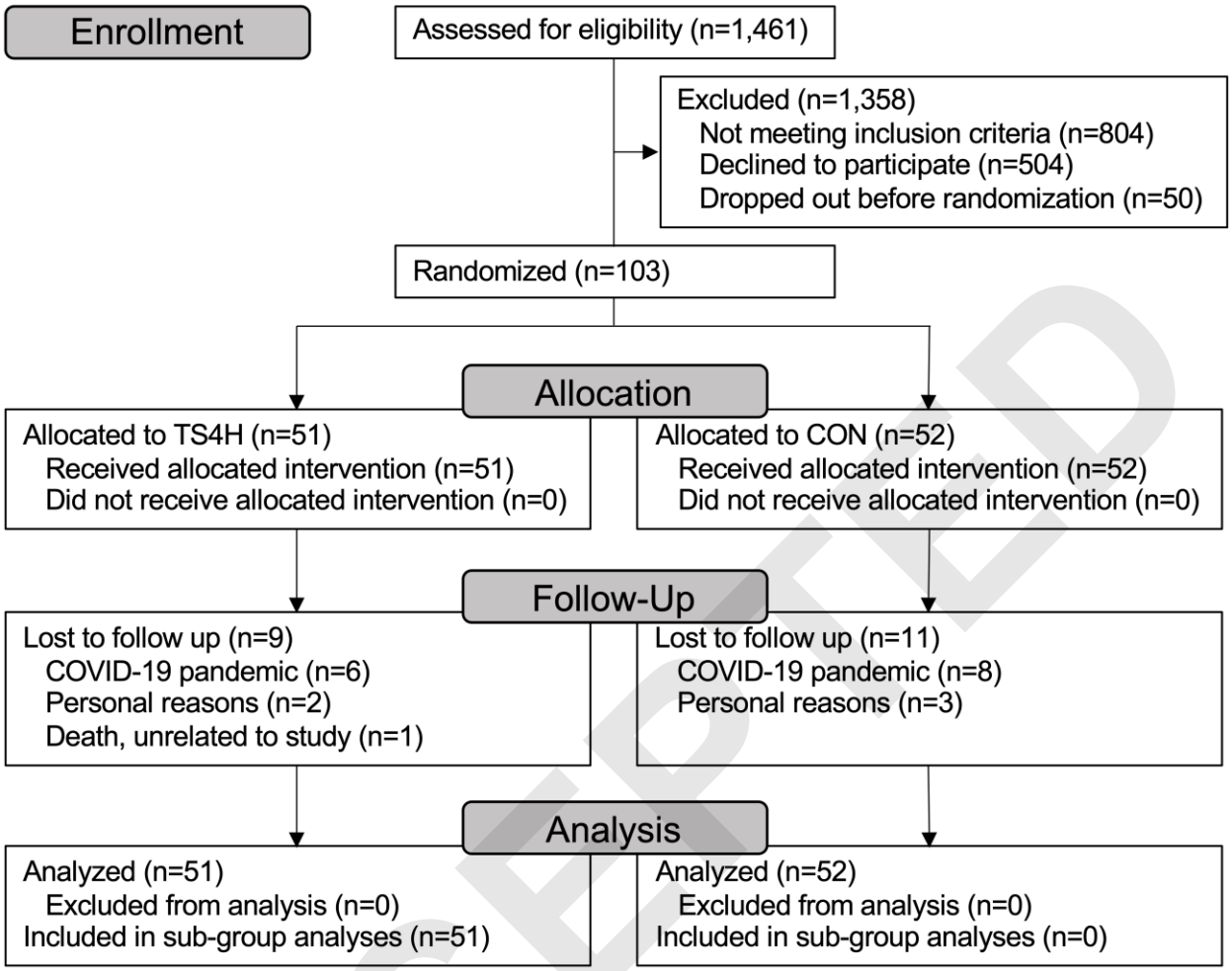

Figure 1

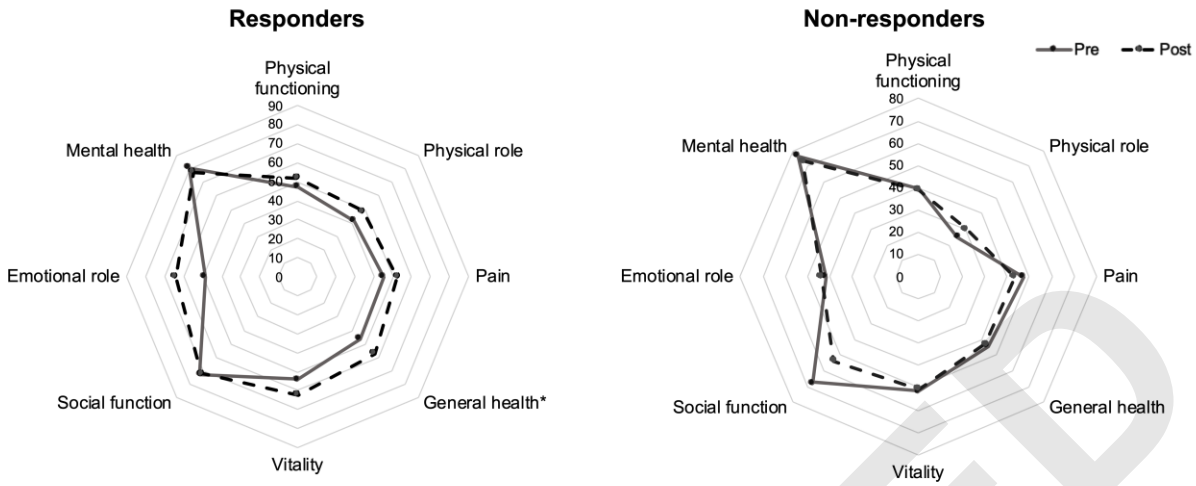

Figure 2

Table 1. Participants' characteristics.

Variables	TS4H (n=51)	SOC (n=52)	p-value
Age (years)	61.6±7.5	60.8±8.3	0.582
BMI (kg/m²)	28.5±5.6	28.3±5.2	0.831
Disease parameters			
Disease duration (years)	20.9±11.6	19.1±11.3	0.433
DAS-28 (A.U.)	3.3±1.3	3.1±1.2	0.335
CDAI (A.U.)	11.6±8.5	11.9±11.1	0.895
HAQ (A.U.)	1.2±0.6	1.2±0.6	0.807
Comorbidities [n(%)]			
Obesity	17 (33.3%)	15 (28.8%)	0.623
Hypertension	30 (58.8%)	31 (59.6%)	0.938
Dyslipidemias	27 (52.9%)	27 (51.9%)	0.913
Type 2 diabetes	7 (13.7%)	7 (13.5%)	0.964
Fibromyalgia	14 (27.5%)	12 (23.1%)	0.609
Osteoarthritis	17 (33.3%)	17 (32.7%)	0.938
Osteopenia or osteoporosis	14 (27.5%)	21 (40.4%)	0.166
Hypothyroidism	12 (23.5%)	11 (21.2%)	0.773
Depression	12 (23.5%)	13 (25.0%)	0.862
Medication [n(%)]			
Prednisone	41 (80.4%)	42 (80.8%)	0.964
Current dose (mg/d)	5.7±5.0	5.5±4.5	0.806
DMARDs	45 (88.2%)	49 (94.2%)	0.281
Leflunomide	22 (43.1%)	27 (51.9%)	0.372
Methotrexate	27 (52.9%)	33 (63.5%)	0.279
Azathioprine	7 (13.7%)	3 (5.8%)	0.173
Biological agents	25 (49.0%)	31 (59.6%)	0.280
Abatacept	12 (23.5%)	11 (21.2%)	0.773
Certolizumab	2 (3.9%)	3 (5.8%)	0.662

Etanercept	3 (5.9%)	3 (5.8%)	0.981
Rituximab	5 (9.8%)	4 (7.7%)	0.705
Tocilizumab	1 (2.0%)	6 (11.5%)	0.054
Tofacitinib	3 (5.9%)	2 (3.8%)	0.630
Non-steroidal anti-inflammatory drugs	21 (41.2%)	25 (48.1%)	0.481
Pain killers	34 (66.7%)	31 (59.6%)	0.459
Muscle relaxants	23 (45.1%)	23 (44.2%)	0.929
Antihypertensive drugs	29 (56.9%)	31 (59.6%)	0.233
Antidyslipidemic drugs	27 (52.9%)	26 (50.0%)	0.766
Antidiabetic drugs	9 (17.6%)	11 (21.2%)	0.653
Bisphosphonate	20 (39.2%)	23 (44.2%)	0.606
Thyroid hormone	10 (19.6%)	11 (21.2%)	0.845
Antidepressants	20 (39.2%)	19 (36.5%)	0.779

Data are presented as mean ± SD. Abbreviations: BMI, body mass index; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score in 28 joints; DMARDS, disease-modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; SOC, standard of care group; TS4H, Take a STAND for Health intervention.

Table 2. Sedentary behavior and physical activity level at Pre, $Post_{2mo}$, and Post in TS4H and SOC groups.

Variables	TS4H (n=51)			SOC (n=52)			p-value group*time	Post-intervention between-group differences	
	Pre	$Post_{2mo}$	Post	Pre	$Post_{2mo}$	Post		EMD (95%CI)	p-value
Sedentary behavior (h/d)	8.5±0.3	8.5±0.3	8.5±0.3	8.1±0.3	7.8±0.3	8.2±0.3	0.591	0.3 (-1.0 to 1.6)	0.983
Prolonged sitting bouts ≥30 min (h/d)	3.3±0.3	3.4±0.3	3.5±0.3	3.1±0.3	2.9±0.3	3.5±0.3	0.337	0.1 (-1.1 to 1.2)	1.000
Prolonged sitting bouts ≥60 min (h/d)	1.4±0.2	1.6±0.2	1.7±0.2	1.4±0.2	1.4±0.2	1.6±0.2	0.727	0.0 (-1.0 to 1.0)	1.000
Sit-to-stand transitions (number/d)	45.3±2.1	46.5±2.3	45.3±2.2	45.5±2.1	45.6±2.3	44.2±2.2	0.811	1.1 (-8.0 to 10.2)	0.999
Standing (h/d)	5.7±0.2	5.7±0.3	5.7±0.3	6.2±0.2	6.3±0.3	6.1±0.3	0.754	-0.4 (-1.4 to 0.6)	0.879
Stepping (h/d)	1.8±0.1	1.8±0.1	1.8±0.1	1.8±0.1	1.8±0.1	1.7±0.1	0.367	0.1 (-0.4 to 0.5)	0.994
Light-intensity PA (h/d)	5.1±0.2	5.2±0.2	5.1±0.2	5.6±0.2	5.6±0.2	5.4±0.2	0.529	-0.2 (-1.1 to 0.7)	0.980
Moderate-to-vigorous PA (min/d)	16.1±2.7	16.1±2.8	18.3±2.9	18.9±2.6	22.1±2.9	16.2±2.9	0.062	2.2 (-9.7 to 15.0)	0.995
Step count (steps/d)	7864±515	7796±541	7961±534	7409±510	7786±543	7347±536	0.483	614 (-1571 to 2799)	0.965

Data are presented as the estimated mean ± SE or EMD (95%CI), calculated by linear mixed models. Abbreviations: EMD, estimated mean difference; PA, physical activity; SOC, standard of care group; TS4H, Take a STAND for Health intervention; 95%CI, 95% confidence interval.

Table 3. Clinical parameters, metabolic risk factors, inflammatory markers, blood pressure, anthropometry and body composition, physical functioning, and health-related quality of life at Pre and Post in TS4H and SOC groups.

Variables	TS4H		SOC		p-value group*time	Post-intervention between-group differences	
	Pre	Post	Pre	Post		EMD (95%CI)	p-value
Clinical parameters	**n=51**		**n=52**				
DAS-28 (A.U.)	3.3±0.2	3.2±0.2	3.1±0.2	3.1±0.2	0.459	0.02 (-0.7 to 0.7)	0.999
CDAI (A.U.)	11.4±1.5	11.4±1.6	11.7±1.5	11.9±1.6	0.933	-0.5 (-6.4 to 5.5)	0.997
HAQ (A.U.)	1.2±0.1	1.1±0.1	1.2±0.1	1.2±0.1	0.974	-0.03 (-0.4 to 0.3)	0.996
VAS Pain (cm)	4.3±0.4	4.8±0.4	4.8±0.4	4.5±0.4	0.242	0.3 (-1.3 to 1.9)	0.972
Fatigue	**n=45**		**n=44**				
Fatigue severity (A.U.)	34.3±2.5	40.1±2.8	35.6±2.5	35.7±2.9	0.185	4.4 (-6.3 to 15.2)	0.696
Mental fatigue (A.U.)	5.5±0.4	4.9±0.4	5.5±0.4	5.4±0.4	0.358	-0.5 (-2.1 to 1.0)	0.818
Physical fatigue (A.U.)	9.7±0.6	9.9±0.7	9.3±0.6	11.1±0.7	0.145	-1.2 (-3.8 to 1.4)	0.613
Overall fatigue (A.U.)	15.3±0.8	14.0±0.9	14.7±0.8	15.8±1.0	0.118	-1.8 (-5.3 to 1.8)	0.561
Metabolic risk factors	**n=50**		**n=51**				
Fasting glucose (mg/dL)	101.6±4.7	97.9±4.8	94.5±4.7	94.2±4.9	0.394	3.7 (-14.2 to 21.7)	0.948
2-hour post-load glucose (mg/dL)	142.6±11.2	141.9±11.6	129.5±10.9	125.0±11.7	0.707	16.9 (-26.0 to 59.7)	0.736

Glucose iAUC (mg/dL*2h)	100.7±11.3	102.9±11.8	96.0±11.0	86.1±12.0	0.286	16.8 (-27.6 to 61.2)	0.750
Fasting insulin (μIU/mL)	13.1±1.4	13.3±1.5	12.8±1.4	14.4±1.5	0.521	-1.1 (-6.9 to 4.6)	0.955
Insulin iAUC (μIU/mL*2h)	13.0±2.6	18.0±2.8	12.8±2.5	14.5±2.9	0.500	3.5 (-7.2 to 14.3)	0.821
Fasting C-peptide (ηg/mL)	2.84±0.15	2.92±0.16	2.77±0.15	2.72±0.17	0.473	0.20 (-0.41 to 0.81)	0.826
C-peptide iAUC (ηg/mL*2h)	10.7±0.7	11.0±0.7	13.1±0.7	12.6±0.8	0.410	-1.6 (-4.4 to 1.1)	0.409
HbA1c (%)	6.0±0.2	6.0±0.2	5.7±0.2	5.8±0.2	0.136	0.2 (-0.6 to 1.0)	0.942
HOMA-IR (A.U.)	3.3±0.4	3.5±0.5	3.3±0.4	3.1±0.5	0.491	0.4 (-1.3 to 2.2)	0.922
HOMA-β (A.U.)	13.8±1.2	14.0±1.3	13.8±1.1	13.8±1.3	0.930	0.2 (-4.7 to 5.1)	0.999
Matsuda index (A.U.)	4.1±0.4	3.7±0.5	3.9±0.4	4.1±0.5	0.401	-0.4 (-2.2 to 1.4)	0.939
Triglycerides (mg/dL)	134.0±9.9	134.4±10.2	126.3±9.8	118.2±10.2	0.337	16.2 (-21.7 to 54.0)	0.677
Total cholesterol (mg/dL)	195.8±5.4	197.9±5.6	210.3±5.3	203.5±5.7	0.146	-5.6 (-26.6 to 15.4)	0.896
HDL (mg/dL)	62.2±2.4	62.6±2.4	63.4±2.3	65.3±2.4	0.481	-2.7 (-11.7 to 6.3)	0.860
LDL (mg/dL)	109.6±4.5	111.3±4.7	123.7±4.5	114.6±4.8	0.038	-3.3 (-20.8 to 14.3)	0.962
VLDL (mg/dL)	23.8±1.1	23.2±1.1	24.0±1.1	22.3±1.2	0.360	0.9 (-3.4 to 5.2)	0.942
Inflammatory markers	**n=47**		**n=46**				
C-reactive protein (mg/L)	7.8±1.4	6.9±1.5	7.5±1.4	10.9±1.5	0.059	-4.1 (-9.8 to 1.6)	0.249
IL-1β (pg/mL)	22.5±10.5	21.8±10.6	7.7±10.1	7.9±10.1	0.659	13.9 (-24.2 to 51.9)	0.778
IL-1ra (pg/mL)	136.7±54.5	122.68±54.6	55.9±53.4	52.0±53.5	0.271	70.7 (-127.9 to 270.4)	0.791

IL-4 (pg/mL)	277.2±129.3	254.4±129.6	85.3±127.8	76.7±1281	0.589	177.8 (-296.6 to 652.1)	0.764
IL-6 (pg/mL)	34.9±9.5	32.0±9.6	21.5±9.3	18.9±9.4	0.958	13.1 (-22.7 to 48.9)	0.766
IL-10 (pg/mL)	38.0±7.8	34.3±8.3	27.9±7.7	33.5±8.0	0.178	0.8 (-29.8 to 31.5)	0.999
TNF-α (pg/mL)	21.5±4.6	21.4 ±4.7	22.1±4.5	22.5±4.6	0.808	-1.1 (-18.6 to 16.3)	0.998
Blood pressure	**n=51**		**n=52**				
Systolic blood pressure (mmHg)	128.8±2.3	131.9±2.6	134.1±2.3	133.2±2.6	0.273	-1.3 (-10.9 to 8.3)	0.273
Diastolic blood pressure (mmHg)	75.5±1.2	74.1±1.3	78.4±1.2	76.6±1.4	0.812	-2.5 (-7.5 to 2.5)	0.564
Anthropometry and body composition	**n=51**		**n=52**				
Body mass (kg)	70.5±1.9	69.3±2.0	67.4±1.9	65.5±2.0	0.629	3.8 (-3.8 to 1.1)	0.545
BMI (kg/m2)	28.5±0.7	28.4±0.7	28.3±0.7	28.0±0.7	0.534	0.4 (-2.4 to 3.2)	0.982
Waist circumference (cm)	93.7±1.4	93.2±2.1	94.1±2.0	93.2±2.2	0.791	0.0 (-7.9 to 7.9)	1.000
Fat-free mass (kg)	40.9±0.8	38.6±0.9	39.5±0.8	37.5±0.9	0.732	1.1 (-2.3 to 4.5)	0.831
Bone mineral density (g/cm2)	0.996±0.018	1.003±0.018	0.993±0.017	0.991±0.019	0.485	0.013 (-0.057 to 0.082)	0.963
Fat mass (kg)	29.7±1.3	30.6±1.4	27.9±1.3	28.0±1.4	0.429	2.7 (-2.6 to 7.9)	0.536
Fat mass (%)	41.3±1.0	43.2±1.0	41.1±0.9	42.1±1.0	0.243	1.1 (-2.7 to 4.9)	0.862
Visceral adipose tissue (g)	909.6±83.6	1152.8±92.4	858.9±82.0	938.7±96.9	0.123	214.1 (-140.0 to 568.2)	0.387
Physical functioning	**n=48**		**n=51**				
Timed Stands (rep/min)	10.2±0.5	11.7±0.6	10.1±0.5	10.8±0.6	0.174	0.9 (-1.3 to 3.0)	0.735

Timed Up and Go (s)	9.33±0.66	8.99±0.73	10.01±0.64	10.61±0.73	0.229	-1.61 (-4.33 to 1.10)	0.401
Health-related quality of life	**n=45**		**n=44**				
Mental health score (A.U.)	64.8±4.3	63.6±4.6	61.9±4.3	61.2±4.8	0.914	2.3 (-15.1 to 19.8)	0.985
Physical health score (A.U.)	44.0±2.9	47.2±3.1	44.8±2.9	44.1±3.2	0.231	3.2 (-8.5 to 14.9)	0.890
Overall quality of life (A.U.)	52.0±3.2	53.4±3.3	51.4±3.2	50.6±3.5	0.511	2.8 (-9.9 to 15.5)	0.935

Data are presented as the estimated mean ± SE or EMD (95%CI), calculated by linear mixed models. Abbreviations: A.U., arbitrary unit; BMI, body mass index; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score in 28 joints; HAQ, Health Assessment Questionnaire; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; IL, interleukin; IR, insulin resistance; LDL, low-density lipoprotein; SOC, standard of care group; TS4H, Take a STAND for Health intervention; TNF, tumor necrosis factor; VAS, Visual Analogic Scale; VLDL, very-low-density lipoprotein.

Table 4. Sedentary behavior and physical activity level at Pre, $Post_{2mo}$, and Post in responders and non-responders to TS4H intervention.

Variables	Responders (n=17)		Non-responders (n=24)		p-value group*time	Post-intervention between-group differences	
	Pre	Post	Pre	Post		EMD (95%CI)	p-value
Sedentary behavior (h/d)	8.5±0.5	6.9±0.5	8.3±0.4	9.5±0.4	<0.001	-2.6 (-4.5 to -0.8)	0.003
Prolonged sitting bouts ≥30 min (h/d)	3.3±0.4	2.6±0.4	3.1±0.4	4.1±0.4	<0.001	-1.5 (-3.1 to 0.0)	0.052
Prolonged sitting bouts ≥60 min (h/d)	1.5±0.4	1.0±0.4	1.3±0.3	2.1±0.3	<0.001	-1.1 (-2.4 to 0.1)	0.089
Sit-to-stand transitions (number/d)	38.8±3.5	38.9±3.5	49.4±3.0	49.3±3.0	0.961	-10.4 (-22.7 to 1.9)	0.125
Standing (h/d)	5.7±0.4	6.9±0.4	5.8±0.3	4.9±0.3	<0.001	2.0 (0.6 to 3.5)	0.003
Stepping (h/d)	1.8±0.2	2.2±0.2	1.9±0.2	1.6±0.2	<0.001	0.6 (-0.2 to 1.3)	0.165
Light-intensity PA (h/d)	4.8±0.4	5.2±0.4	5.3±0.3	5.1±0.3	0.097	0.1 (-1.2 to 1.4)	0.998
Moderate-to-vigorous PA (min/d)	14.2±3.3	12.0±3.4	13.2±2.6	14.9±2.8	0.232	-2.8 (-14.9 to 9.3)	0.916
Step count (steps/d)	7835±1020	9644±1020	8079±859	6964±859	<0.001	2680 (-898 to 6257)	0.202

Data are presented as the estimated mean ± SE or EMD (95%CI), calculated by linear mixed models. Abbreviations: CON, control group; EMD, estimated mean difference; PA, physical activity; TS4H, Take a STAND for Health intervention; 95%CI, 95% confidence interval.

Table 5. Clinical parameters, metabolic risk factors, inflammatory markers, blood pressure, anthropometry and body composition, physical functioning, and health-related quality of life at Pre and Post in responders and non-responders to TS4H intervention.

Variables	Responders		Non-responders		p-value group*time	Post-intervention between-group differences	
	Pre	Post	Pre	Post		EMD (95%CI)	p-value
Clinical parameters	**n=17**		**n=24**				
DAS-28 (A.U.)	3.4±0.3	3.3±0.3	3.3±0.3	3.1±0.3	0.898	0.2 (-1.0 to 1.3)	0.985
CDAI (A.U.)	13.4±2.4	9.8±2.4	10.2±1.8	11.3±1.7	0.174	-1.5 (-9.7 to 6.8)	0.961
HAQ (A.U.)	1.1±0.1	1.1±0.1	1.3±0.1	1.2±0.1	0.940	-0.2 (-0.7 to 0.3)	0.775
VAS Pain (cm)	4.2±0.6	4.2±0.7	4.3±0.5	5.0±0.5	0.459	-0.8 (-3.1 to 1.5)	0.784
Fatigue	**n=15**		**n=20**				
Fatigue severity (A.U.)	28.9±4.2	40.6±4.6	38.9±3.6	42.8±3.9	0.198	-2.2 (-18.6 to 14.2)	0.983
Mental fatigue (A.U.)	5.6±0.6	4.5±0.7	5.7±0.5	5.1±0.5	0.553	-0.6 (-3.0 to 1.7)	0.870
Physical fatigue (A.U.)	9.3±1.0	8.0±1.1	10.3±0.9	11.0±0.9	0.241	-3.1 (-6.9 to 0.8)	0.152
Overall fatigue (A.U.)	14.9±1.4	12.4±1.5	16.1±1.3	15.3±1.3	0.482	-2.8 (-8.3 to 2.6)	0.497
Metabolic risk factors	**n=15**		**n=21**				
Fasting glucose (mg/dL)	98.8±6.9	92.2±10.5	106.3±8.9	104.1±8.9	0.519	-11.8 (-48.9 to 25.2)	0.826
2-hour post-load glucose (mg/dL)	132.6±25.7	123.9±25.9	154.8±19.7	158.2±20.0	0.434	-34.3 (-123.2 to 54.6)	0.723
Glucose iAUC (mg/dL*2h)	97.5±22.5	80.5±22.7	108.2±17.2	123.7±17.6	0.040	-43.1 (-121.1 to 34.8)	0.4475
Fasting insulin (μIU/mL)	10.2±2.2	11.4±2.1	14.1±1.9	14.7±1.9	0.863	-3.4 (-11.3 to 4.6)	0.645

Insulin iAUC (μIU/mL*2h)	96.0±18.1	99.9±18.8	119.2±15.2	115.3±16.0	0.811	-15.4 (-83.1 to 52.3)	0.924
Fasting C-peptide (ηg/mL)	2.61±0.30	2.67±0.29	2.99±0.25	3.10±0.25	0.885	-0.42 (-1.46 to 0.62)	0.684
C-peptide iAUC (ηg/mL*2h)	10.0±1.1	10.5±1.1	10.2±0.9	11.1±0.9	0.731	-0.6 (-4.6 to 3.4)	0.978
HbA1c (%)	6.0±0.4	5.9±0.4	6.2±0.3	6.2±0.3	0.651	-0.3 (-1.6 to 1.1)	0.946
HOMA-IR (A.U.)	2.7±0.7	2.8±0.7	3.7±0.6	3.9±0.6	0.871	-1.1 (-3.8 to 1.6)	0.659
HOMA-β (A.U.)	10.6±2.2	12.0±2.2	14.8±2.0	15.5±2.0	0.842	-3.5 (-11.8 to 4.8)	0.644
Matsuda index (A.U.)	4.4±0.6	4.5±0.6	3.7±0.5	3.2±0.6	0.490	1.3 (-1.1 to 3.7)	0.459
Triglycerides (mg/dL)	122.0±18.3	115.9±18.3	142.8±15.4	148.1±15.4	0.423	-32.1 (-96.2 to 32.0)	0.540
Total cholesterol (mg/dL)	189.5±9.3	195.5±9.3	205.1±7.9	203.9±7.9	0.368	-8.4 (-41.2 to 24.3)	0.900
HDL (mg/dL)	63.4±4.7	66.1±4.7	62.9±4.0	62.0±4.0	0.210	4.1 (-12.4 to 20.6)	0.909
LDL (mg/dL)	103.4±6.9	108.0±6.9	117.0±5.8	116.0±5.8	0.377	-8.0 (-32.2 to 16.2)	0.814
VLDL (mg/dL)	22.2±1.2	21.7±1.2	23.8±1.1	23.4±1.1	0.934	-1.7 (-6.0 to 2.7)	0.727
Inflammatory markers	**n=14**		**n=23**				
C-reactive protein (mg/L)	10.8±1.9	6.2±1.9	6.0±1.6	6.2±1.6	0.109	0.1 (-6.7 to 6.8)	1.000
IL-1β (pg/mL)	10.5±35.4	8.2±35.4	34.9±29.4	33.4±29.4	0.620	-25.2 (-124.0 to 73.7)	0.907
IL-1ra (pg/mL)	65.6±13.4	58.8±13.5	53.2±10.7	43.9±10.8	0.716	14.9 (-30.8 to 60.5)	0.825
IL-4 (pg/mL)	89.1±1320.7	72.7±1320.7	142.3±1064.7	92.5±1064.8	0.139	-19.8 (-4730.4 to 4690.8)	1.000

IL-6 (pg/mL)	33.6±24.5	27.0±24.5	42.6±20.2	41.3±20.2	0.293	-14.3 (-101.5 to 72.9)	0.969
IL-10 (pg/mL)	44.8±19.5	32.8±19.5	41.2±15.2	38.7±15.3	0.086	-5.9 (-74.3 to 62.5)	0.995
TNF-α (pg/mL)	17.7±2.1	16.0±2.2	15.7±1.8	16.8±1.8	0.254	-0.8 (-8.5 to 7.0)	0.993
Blood pressure	**n=17**		**n=24**				
Systolic blood pressure (mmHg)	126.1±4.6	132.3±4.8	128.7±3.8	130.8±3.8	0.489	1.5 (-14.9 to 18.0)	0.995
Diastolic blood pressure (mmHg)	76.2±2.1	76.6±2.3	76.9±1.8	73.5±1.8	0.213	3.1 (-4.7 to 10.9)	0.712
Anthropometry and body composition	**n=17**		**n=24**				
Body mass (kg)	65.7±3.7	64.9±3.7	71.2±3.1	71.2±3.1	0.468	-6.3 (-19.4 to 6.7)	0.570
BMI (kg/m^2)	27.1±1.3	26.7±1.3	28.6±1.1	28.5±1.1	0.476	-1.8 (-6.2 to 2.6)	0.696
Waist circumference (cm)	88.9±3.4	88.3±3.5	94.6±2.9	94.4±2.9	0.860	-6.1 (-18.4 to 6.3)	0.546
Fat-free mass (kg)	39.0±1.4	37.1±1.4	42.0±1.1	39.1±1.2	0.413	-2.0 (-7.1 to 3.0)	0.692
Bone mineral density (g/cm^2)	0.973±0.026	0.987±0.027	0.998±0.022	1.003±0.022	0.378	-0.016 (-0.110 to 0.077)	0.965
Fat mass (kg)	27.0±2.5	27.7±2.5	29.9±2.1	30.8±2.1	0.808	-3.1 (-12.0 to 5.8)	1.000
Fat mass (%)	40.0±1.7	41.8±1.7	41.1±1.4	43.1±1.5	0.846	-1.3 (-7.3 to 4.8)	0.941
Visceral adipose tissue (g)	706.2±133.3	887.1±138.6	938.8±112.2	1216.8±125.5	0.562	-329.7 (-838.1 to 178.7)	0.310
Physical functioning	**n=17**		**n=24**				

Timed Stands (rep/min)	9.9±0.8	11.6±0.8	10.1±0.7	11.6±0.7	0.702	-0.0 (-3.0 to 3.0)	1.000
Timed Up and Go (s)	9.0±0.8	9.1±0.8	9.8±0.7	9.1±0.8	0.397	0.0 (-3.1 to 3.1)	1.000
Health-related quality of life	**n=15**		**n=20**				
Mental health score (A.U.)	67.6±6.8	71.5±6.9	61.9±59	56.8±6.0	0.213	14.7 (-10.2 to 39.6)	0.394
Physical health score (A.U.)	47.0±4.8	54.9±4.9	41.4±4.2	41.2±42	0.067	13.7 (-3.8 to 31.1)	0.089
Overall quality of life (A.U.)	54.8±4.9	61.1±5.0	49.3±4.3	47.1±4.3	0.075	14.0 (-3.9 to 32.0)	0.170

Data are presented as the estimated mean ± SE or EMD (95%CI), calculated by linear mixed models. Abbreviations: A.U., arbitrary unit; BMI, body mass index; CDAI, Clinical Disease Activity Index; CON, control group; DAS28, Disease Activity Score in 28 joints; HAQ, Health Assessment Questionnaire; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; IL, interleukin; IR, insulin resistance; LDL, low-density lipoprotein; TS4H, Take a STAND for Health intervention; TNF, tumor necrosis factor; VAS, Visual Analogic Scale; VLDL, very-low-density lipoprotein.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	NR – not enough space as per MSSE guidelines
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 2-3
	2b	Specific objectives or hypotheses	Page 3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Page 4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	Page 5
	4b	Settings and locations where the data were collected	Page 5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Page 5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Pages 6-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	Page 8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA

Randomisation:			Page 4
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	See Pinto et al. *Trials* 2020
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	See Pinto et al. *Trials* 2020
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	See Pinto et al. *Trials* 2020
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Pages 8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Page 8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Page 9, Figure 1 and all Tables
	13b	For each group, losses and exclusions after randomisation, together with reasons	Page 9 and Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Page 5
	14b	Why the trial ended or was stopped	Page 5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	All Tables

		by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Pages 9-11 and all Tables
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Pages 10-11 and Tables 4 and 5
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Page 9
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Page 14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Page 14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pages 11-13
Other information			Pages 2 and 4
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	Page 4 and reference 13 – Pinto et al. Trials 2020
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Pages 14-15

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments,

herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.