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Meireles, K, Peçanha, T , Pinto, A J , Santos, L P, Mazzolani, B C, Smaira, F I , Rezende, D, Ribeiro, A C M, Pinto, A L S , Lima, F R, Silva Junior, N D, Forjaz, C L M , Gualano, B and Roschel, H (2024) Improved vascular health linked to increased physical activity levels and reduced sedentary behavior in rheumatoid arthritis. American Journal of Physiology - Heart and Circulatory Physiology. ISSN 0363-6135

DOI: https://doi.org/10.1152/ajpheart.00640.2024

Publisher: American Physiological Society

Version: Accepted Version

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Additional Information: This is an open access article which first appeared in American Journal of Physiology - Heart and Circulatory Physiology

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1	TITLE PAGE
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3	Improved vascular health linked to increased physical activity levels and reduced
4	sedentary behavior in rheumatoid arthritis
5	
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38 ABSTRACT

Rheumatoid arthritis (RA) is characterized by deteriorated vascular health and increased 39 40 cardiovascular risk. Physical activity (PA) is recommended for cardiovascular management in RA, but evidence on the associations between objectively-measured PA 41 and vascular health markers in RA is limited. In this cross-sectional study, eighty-two 42 post-menopausal women with RA (62±7 years) undertook ultrasound assessments of 43 vascular function and structure, including brachial and superficial femoral artery (BA 44 45 and SFA) flow-mediated dilation; baseline and post-hyperemia peak diameters; and 46 carotid intima-media thickness. Participants also performed a 7-day accelerometerbased assessment of PA and sedentary behavior (SB). Fitted regression models 47 controlled for age, body mass index and disease activity were conducted to examine 48 associations between vascular and PA outcomes. Regression analyses revealed that 49 50 prolonged SB (bouts>60min) and total sedentary time were inversely associated with both baseline and peak BA diameters, with each additional hour of SB resulting in 51 52 decreases of 0.08-0.1mm in these diameters ($p \le 0.01$). Total sedentary time also showed similar negative associations with peak SFA diameters (β =-0.14[-0.24-0.05], p<0.01). 53 54 Conversely, light-intensity PA and stepping time were positively associated with both 55 baseline and peak BA diameters, with each additional hour increasing these diameters 56 by 0.10-0.24mm (p≤0.02). Finally, standing time was positively associated with SFA peak diameter (\beta=0.11[0.01-0.20], p=0.02). No associations were found between 57 moderate-to-vigorous PA and vascular outcomes. In conclusion, in patients with RA, 58 SB was negatively, while light PA was positively, associated with BA and SFA 59 60 diameters. These findings suggest that reducing SB and increasing PA, even at light 61 intensities, may improve vascular health in RA.

- 62
- Key-words: inflammation, atherosclerosis, inflammatory rheumatic diseases,autoimmune rheumatic diseases, vasculature, exercise.

65 NEW & NOTEWORTHY

This was the first study to investigate associations between objectively-measured physical activity and markers of vascular health in rheumatoid arthritis (RA). The findings suggest that reducing sedentary behavior and increasing light or total physical activity are associated with improved vascular outcomes in RA. These results support further investigation into interventions aimed at reducing sedentary time and replacing with any type of physical activity as a potential strategy for improving cardiovascular outcomes in individuals with RA.

73

74 INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder characterized by accelerated atherosclerosis and increased cardiovascular risk (1, 2). Interventions aimed to reduce cardiovascular risk in RA should target the initial stages of the atherosclerosis continuum, which are characterized by endothelial dysfunction, subclinical atherosclerosis, and inward vascular remodeling (3).

Moderate-to-vigorous physical activity (MVPA) has been listed as an effective intervention to support the management of cardiovascular disease and to improve vascular health in the general population (4) and in patients with RA (5). However, individuals with RA usually present with low levels of MVPA (6), which may be due to disease-specific barriers for performing higher intensity physical activity, such as high levels of fatigue, and joint pain and stiffness (7).

86 More recent evidence suggests that in addition to performing MVPA, reducing sedentary time (e.g., sitting or lying down) and replacing it with lighter activities (e.g., 87 88 standing or mild stepping) offers significant health benefits for individuals with RA (8, 9). For instance, a previous study from our group demonstrated that brief active breaks 89 90 during prolonged sitting improve glycemic control and reduce inflammatory markers in 91 women with RA (8). These benefits may also extend to the vasculature (10). However, 92 potential associations between sedentary behavior/physical activity and markers of vascular function and structure in RA remain largely unexplored, warranting further 93 research to inform the design of appropriate behavioral interventions. 94

To the best of our knowledge, only one previous study investigated the associations 95 96 between sedentary time and vascular outcomes in RA, demonstrating that increased 97 time spent in sitting position is associated with impaired endothelial function in the micro- but not in the macrovasculature (11). However, the previous study used self-98 reported sitting time to estimate sedentary behavior, which varies significantly between 99 individuals, is less accurate than objective device-based methods (12), and lacks details 100 101 on physical activity intensity, limiting the study's findings. Additionally, it measured 102 vascular function in upper limb vessels by assessing forearm skin blood flow velocity in response to iontophoresis of acetylcholine and sodium nitroprusside, along with brachial 103 artery flow-mediated dilation (FMD). However, evidence suggests that lower-limb 104 arteries may benefit more from reducing sitting time due to restoration of leg blood 105 106 flow, which enhances shear stress and endothelial function (13).

Therefore, our study aimed to expand previous findings and investigate the associations 107 between objectively-measured sedentary behavior and physical activity levels and upper 108 109 and lower limb endothelial function (i.e., FMD and associated measurements) and markers of subclinical atherosclerosis (i.e., carotid intima-media thickness [cIMT]) in 110 post-menopausal women with RA. We hypothesized that increased sedentary behavior 111 and reduced physical activity levels would associate with deteriorated endothelial 112 113 function (i.e., reduced FMD), inward vascular remodelling (i.e., reduced arterial 114 diameters) and accelerated atherosclerosis, while reduced sedentary behavior and higher 115 levels of physical activity would associate with an improved vascular profile in post-116 menopausal women RA.

117

118 MATERIALS AND METHODS

119 Study design

This was a cross-sectional exploratory study nested within a randomized controlled trial (NCT03186924) (14, 15) conducted at the Laboratory of Assessment and Conditioning in Rheumatology (Clinical Hospital, University of Sao Paulo, Brazil). The participants included in this study represent a sub-sample of the trial and were recruited between July 2018 and February 2022. All data collected for the present study and reported herein refers to the pre-intervention assessment of the previous trial.

126

127 Participant recruitment and ethical approval

Postmenopausal women diagnosed with rheumatoid arthritis (16) were recruited from the Rheumatoid Arthritis Outpatient Clinic of the Clinical Hospital (University of Sao Paulo, Brazil). The exclusion criteria included: 1) participation in structured exercise training programs within the last 12 months; 2) unstable drug therapy in the last 3 months prior to and during the study; 3) Health Assessment Questionnaire score >2.0; and 4) presence of heart or renal disease, and stroke.

Prior to participation in the study, participants received a detailed explanation about the experimental procedures and provided their written consent. The study followed the principles of the Declaration of Helsinki and was approved by the local Institutional Ethics Committee.

138

139 Assessments and procedures

Assessments took place in two separated visits to the laboratory. During the first visit,
clinical parameters were assessed, and participants were provided with accelerometers
to monitor sedentary behavior and physical activity. The second visit was scheduled for
the vascular assessment. Both visits were booked within a two-week interval.

144

145 *Clinical parameters*

Disease activity was assessed by the Disease Activity Score-28 for Rheumatoid Arthritis with C reactive protein (DAS28-CRP) (17) and the Clinical Disease Activity Index (CDAI) (18). Pain levels were assessed through a 10-point Visual Analog Scale (VAS). The Health Assessment Questionnaire (HAQ) (19) was used to evaluate functional capacity in different domains of daily life. Additional clinical data (e.g., disease duration, comorbidities, medication use) were obtained by the review of recent (<6 months) medical records.

153

154 Sedentary behavior and physical activity levels

155 Sedentary behavior (lying down and sitting), standing, and stepping time were measured using activPAL-microTM (PAL Technology, Glasgow, UK). Patients wore the 156 157 accelerometer on the right medial front thigh for 7 consecutive days (24 hours/day). The 158 accelerometer data was imported into and analyzed using the PALanalysis software (v.7.2.32, PAL Technology, UK). The following data was reported: time spent in 159 160 sedentary behavior (i.e., sitting and lying down, h/day), time spent in prolonged sitting in bouts $>60 \min (h/day)$, standing (h/day), and stepping (h/day), and number of breaks 161 162 in sedentary time.

- 163 All data were standardized to a 16-h day to avoid bias from differences in participants'
- 164 daily wear time, using the formula: $(data \times 16)$ /wear time (14).
- 165

166 *Physical activity level*

Physical activity levels were objectively measured using actiGraph GT3X® (ActiGraph, US). All patients were instructed to wear the accelerometer during waking hours for 7 consecutive days. The device was worn on a belt at the waistline on the right side of the hip. Data were exported in 60-s epochs using ActiLife 6 software (v. 6.11.9, ActiGraph, US). Participants had to accumulate at least 10 hours of valid activity recordings per day for at least 4 days, including one weekend day. Freedson cut-points were used to define

time spent in each exercise intensity, as follows: light-intensity physical activity (LPA)

- 174 (≥100 to <1952 counts/min), and MVPA (≥1952 counts/min) (20). Data were reported
- as follows: LPA (h/day) and MVPA (min/day).
- 176 All data were standardized to a 16-h day to avoid bias from differences in patients' wear
- time, using the formula: $(data \times 16)$ /wear time (14).
- 178
- 179
- 180 Vascular ultrasound assessments

181 Participants reported to the laboratory in the afternoon for the assessment of brachial 182 (BA) and superficial femoral artery (SFA) flow-mediated dilation (FMD), as well as common carotid artery intima-media thickness (cIMT). These assessments were 183 performed by an experienced sonographer using a high-resolution ultrasound machine 184 (LOGIO-e PRO, GE-Healthcare, US) equipped with a 4.0-12.0-MHz linear transducer. 185 186 The experiments were conducted in the afternoon between 12:00 and 6:00 PM. Participants were instructed to abstain from eating food for a minimum of 4 hours, 187 188 smoking for a minimum of 6 hours, avoid caffeine-containing beverages for at least 12 189 hours and intense exercise for 24 hours prior to the tests, while maintaining their regular 190 medication regimen. They were asked before the assessment whether they had followed 191 these instructions and if they had changed their medication regimen in the days prior. If 192 participants did not adhere to the instructions or altered their medication routine, the test was rescheduled to a later date to ensure compliance with the protocol. 193

194

195 *Brachial and superficial femoral artery flow-mediated dilation - FMD*

196 Assessments of FMD in BA and SFA were performed according to current guidelines

197 (21). Testing was performed first in BA, with a 15-minute interval between tests.

For BA, participants extended their right arm $\sim 80^{\circ}$ from the torso and researchers 198 immobilized it with foam supports. The ultrasound transducer was positioned on the 199 200 distal third of the participant's arm while a manual pneumatic cuff was positioned at the forearm (2-3cm below the elbow) to provide the ischemic stimulus. For SFA, 201 202 participants were positioned with their right thigh externally rotated. The ultrasound transducer was placed on the mid-thigh and the cuff was positioned 1-2cm above the 203 knee. Longitudinal images of BA and SFA diameters were taken using the B-mode 204 ultrasound, and simultaneous pulse-waved Doppler blood flow velocity were obtained 205 206 using a $< 60^{\circ}$ insonation angle with the sample volume placed in the center of the artery 207 and aligned with the blood flow. Initially, a 1-min baseline recording of diameter and blood flow velocity of each investigated artery were performed and then the cuffs were
inflated to ~200 mmHg for 5 minutes. After cuff release, data was recorded for 3
minutes for BA and 5 minutes for SFA.

Offline analyses of artery diameters and shear rates were performed using a semi-211 automatic edge detection and wall tracking software (Cardiovascular Suite, Quipu®, 212 Italy). Baseline diameter was defined as the average vessel diameter measured during 213 the 1-min baseline recording. Peak diameter was defined as the largest diameter 214 215 observed following cuff release. FMD% was calculated as the percentage change of the 216 vessel diameter after cuff release in relation to baseline vessel diameter [FMD=(peak diameter-baseline diameter/baseline diameter)x100]. Shear rate was calculated as 8 217 218 times the mean blood velocity divided by the internal diameter (Shear rate = 8×10^{-10} x mean blood velocity/internal diameter) (21). The relevant shear rate stimulus for the FMD 219 220 response was calculated as the area under the curve of the shear rate up to the peak diameter (SRAUC). SRAUC was reported separately and was also used to normalize 221 222 the FMD response (i.e., FMD/SRAUC).

223

224 <u>Common carotid artery intima-media thickness - cIMT</u>

The assessment of cIMT was performed according to current guidelines (22). For that, patients remained with the head rotated and the ultrasound transducer was positioned longitudinally to the right common carotid artery (i.e., longitudinal plane), 1-2cm below the carotid bulb. Ultrasound parameters (e.g., gain, depth, and focal zone) were modified to optimize the appearance of the intima border along the vessel.

230 Once a clear image of the vessel was obtained using B-mode ultrasound, 20-30s video 231 recordings were made at three distinct angles (anterior, lateral and posterior(22)) for subsequent analysis. Analysis of cIMT was performed using an edge detection and wall 232 tracking software (Cardiovascular Suite, Quipu®, Italy). cIMT was measured at the 233 234 distal wall of the common carotid artery (from the lumen-intima interface to the media-235 adventitia interface) and calculated as the average thickness over a vessel segment 236 >10mm in each of the three recorded angles across the 20-30s of recording. cIMT_{mean} was calculated as the average of the cIMT in the three measured angles. Additionally, 237 common carotid diameter was calculated as the distance between the media-adventitia 238 interfaces of both the near and far walls of the common carotid artery obtained 239 throughout the video recordings. Common carotid artery wall-to-lumen ratio was 240 241 calculated as the cIMT_{mean} divided by the mean carotid diameter.

242

243 Statistical analysis

244 Linear regression models were used to determine the association between sedentary behavior/physical activity variables and vascular outcomes, while controlling for 245 potential cofounders. Firstly, a simple linear model was fitted with the exposure 246 (sedentary behavior/physical activity variables) as the outcome predictor (Model 1). 247 248 Then, a multiple linear regression model was constructed, including body mass index 249 (BMI), age and disease activity (DAS28-CRP) as additional covariates (Model 2). 250 Multicollinearity was assessed using variance inflation factor (VIF), and collinearity was disregarded if VIF<5. All analyses were conducted in R (v.4.3.2), running in 251 RStudio (v.2023.12.0.369, Posit Software, Boston, MA), using 'car' library (v.3.1-2). 252 Statistical significance was set as P<0.05. Data are presented as means \pm standard 253 254 deviation or as otherwise specified.

255

256 **RESULTS**

257 Of the 103 individuals who participated in our previous randomized trial (14), 82 agreed 258 to take part and were included in the analysis of the present study. Importantly, 28 of 259 the participants were recruited during the COVID-19 pandemic. All participants were 260 asked whether they had experienced symptoms or received a diagnosis of COVID-19, and all reported that they did not have the virus at the time of their participation in the 261 study. Participants' characteristics are reported in Table 1. Average sample age was 62 262 years and participants were mostly overweight (i.e., 72% had a BMI ≥ 25.0 kg/m²). 263 Disease activity ranged from remission to high activity (mean DAS28-CRP was 264 265 3.4±3.0, CDAI was 10.8±9.9).

Sedentary behavior and physical activity levels are reported in Table 1. On average, participants spent a total of 8.2 h/day in sedentary behavior, of which 1.6 h/day were spent in prolonged (>60min) bouts. Participants averaged 18 min/day in MVPA. Data from the assessments of vascular function and structure are reported in Table 2.

Results from the regression analyses examining the associations between objectivelymeasured sedentary behavior and vascular outcomes are reported in Table 3. Prolonged sedentary behavior (in bouts >60 min) was inversely associated with both baseline and peak BA diameters. Each additional hour/day of prolonged sedentary behavior corresponded to reductions of 0.07 mm and 0.08 mm in baseline and peak BA diameters, respectively, in model 1 (p=0.03 for both). These associations persisted after

adjusting for confounders in model 2, in which each additional hour/day of prolonged 276 sedentary behavior was associated with a 0.1 mm decrease in both baseline and peak 277 BA diameters (p < 0.01 for both). In the adjusted model, total sedentary time was also 278 inversely associated with BA diameters, with each additional hour of sedentary 279 behavior corresponding to reductions of 0.08 mm in baseline and peak BA diameters 280 (p=0.01 and p<0.01, respectively). A similar relationship was observed for SFA peak 281 diameter and total sedentary time, in which each additional hour of sedentary behavior 282 283 associated with a 0.14 mm reduction in peak SFA diameter (p < 0.01) in model 2. BA 284 FMD/SRAUC was positively associated with number of breaks in sedentary time in model 1, however these associations were no longer present after adjusting for 285 286 confounders (in model 2). There were no significant associations between sedentary behavior and any of the other FMD-related variables or any of the cIMT parameters 287 288 across all models.

No associations were observed between physical activity and any vascular parameters in 289 290 model 1, as shown in Table 4. After adjusting for confounders, SFA peak diameter was 291 positively associated with standing time, with each additional hour of standing 292 corresponding to a 0.11 mm increase in peak SFA diameter (p=0.02). BA diameters 293 were positively associated with LPA, with each additional hour of LPA corresponding 294 to increases in 0.1 mm in both baseline and peak diameters (p=0.02). Finally, BA diameters were also positively associated with stepping time, with each hour increase in 295 this activity corresponding to increases of 0.24 and 0.17 mm in baseline and peak 296 diameter, respectively ($p \le 0.01$). There were no significant associations between 297 298 physical activity and either FMD or any of the cIMT parameters across all models 299 (Table 4).

300

301 DISCUSSION

The present study tested the associations between objectively-measured sedentary behavior and physical activity and markers of macrovascular endothelial function and carotid artery structure in RA. Our results indicated that sedentary behaviors were inversely associated, while light forms of physical activity (LPA and standing) and total physical activity (stepping time) were directly correlated with BA and SFA diameters, both at rest and after reactive hyperemia. These associations were independent of BMI, disease severity and age. On the other hand, there were no significant associations between physical activity or sedentary behavior with FMD or any of the cIMTparameters.

Lack of associations between FMD in the BA and SFA and physical activity and 311 sedentary behavior contradicts the study hypothesis and previous studies showing 312 positive associations between physical activity and FMD (5, 23). However, this finding 313 should be interpreted in light of the observed associations between physical activity, 314 315 sedentary behavior, and the diameters of the BA and SFA. Previous studies have 316 reported complementary and reciprocal changes in FMD and arterial diameters in 317 response to physical activity (24-26). These studies suggest that FMD and arterial diameters adapt to physical activity according to two distinct time courses, with initial 318 319 improvements in FMD being replaced over time by increase in artery diameters (i.e., arterial remodelling) and return of FMD towards baseline levels. Due to the cross-320 321 sectional nature of this study, it is not possible to capture these time-related associations between physical activity data and FMD and arterial diameter. However, based in our 322 323 results, it is possible to speculate that the participants with lower sedentary behavior and 324 higher physical activity levels had already gone through this adaptive process, reaching 325 the point of increased arterial diameters and return of FMD to baseline levels. This 326 would explain the observed associations between physical activity data and BA and 327 SFA diameters, alongside the absence of associations with FMD. This hypothesis should be tested in longitudinal studies exploring the temporal relationship between 328 329 physical activity, FMD and arterial remodeling in RA.

330 The observed associations between increased physical activity levels and/or reduced 331 sedentary behavior with increased BA and SFA diameters, nevertheless, suggest that 332 various PA behaviors (e.g., reducing prolonged or total sedentary time or increasing light intensity PA or stepping time) may positively affect vascular phenotype in RA. 333 Importantly, RA is associated with an elevated cardiovascular risk (1, 2), partly due to 334 an altered vascular profile caused by both (dys)functional changes (e.g., endothelial 335 336 dysfunction(1), vessel inflammation(27), sympathetic hyperactivity(28)) and structural inward vascular remodeling (29). Indeed, the average FMD in our study sample was 337 338 4.3% for the brachial artery, which is below the age-adjusted 50th percentile for brachial FMD in females (30) and aligns with a classification of impaired endothelial 339 function (31), confirming the presence of endothelial dysfunction in the study sample. 340 341 These vascular alterations represent key hallmarks of the early stages of the 342 cardiovascular disease continuum, which may culminate with the development of advanced cardiovascular disease. Therefore, the results of the present study suggest a
potential counteracting role of physical activity on these adverse vascular changes,
which may contribute to reduce cardiovascular risk in RA.

346 The results of the present study indicate that reduced sedentary behavior and increased light physical activity are associated with improved vascular markers in both upper- and 347 lower-limb arteries. Previous studies that modulated sedentary time through prolonged 348 sitting and/or via active breaks in these prolonged sitting have suggested that lower limb 349 350 arteries may be more responsive than upper limb arteries to changes in sedentary time 351 and physical activity (10, 13). However, this trend was not confirmed by our regression analyses. The observational design and tools used in the present study do not allow us to 352 353 draw definitive conclusions about the absence of these expected limb-specific associations between vascular parameters with sedentary behavior and physical activity. 354 355 However, inconsistencies between our findings and those of previous studies may reflect the different types of sedentary behaviors captured in our study, which may 356 357 include not only sitting but also reclining and lying down positions. Sitting is more 358 likely to reduce shear rate and affect the function of lower limb arteries (10, 13, 32), 359 while reclining and lying down may not have the same impact on these arteries.

360 The lack of significant associations between physical activity or sedentary behavior and cIMT- a marker of subclinical atherosclerosis - is inconsistent with the study 361 hypothesis. However, this indicates that physical activity alone does not appear to be 362 associated with an improved atherosclerotic profile in RA. This finding aligns with the 363 notion that a combination of multiple factors (e.g., physical activity, smoking cessation, 364 365 dietary changes, and lipid-lowering drugs) (33) may be required to reverse 366 atherosclerosis in clinical populations, an hypothesis that need to be tested by studies using multi-component interventions. Alternatively, longer-duration physical activity 367 behavior (>6 months) may also be associated with an improved atherosclerotic profile 368 (34), which should be tested in longitudinal studies. 369

Interestingly, while our study found associations between lighter forms of physical activity and total physical activity with some vascular outcomes, no association was observed between MVPA and any vascular outcome. Although it's widely understood that all forms of physical activity positively impact health, evidence also suggests a dose-response relationship, with higher intensities yielding the greatest benefits (35), a finding not supported by the present study on postmenopausal women with RA. These results, however, need to be interpreted considering that average daily time spent in MVPA was low, with only approximately 25% of subjects meeting recommendations from guidelines (i.e., 150 min/week of MVPA), a fact that may have blunted potential associations. Notwithstanding, device-derived MVPA is associated with all-cause mortality risk reduction even at lower levels of activity (35), and increases of any magnitude in this behavior should be encouraged in this population.

Taken together, our findings emphasize the potential benefits of promoting physical 382 383 activity of any intensity in RA patients. The observed associations between reducing 384 sedentary time and increasing lighter forms of PA with improved vascular diameters are 385 encouraging, as some patients with RA may find it challenging to perform MVPA due to recurrent pain and fatigue (7). In contrast, engagement in light physical activity may 386 be more easily achievable by these patients and may possibly modulate cardiovascular 387 risk in people with RA. Additionally, engagement in light physical activity may, over 388 389 time, increase patients' confidence and physical capacity to participate in moderate or vigorous activities. In this way, light activity may serve as a gateway to more intense 390 391 physical activity. These notions align with current exercise guidelines for RA, which 392 emphasize the importance of tailoring exercise programs to each patient's capabilities (36). 393

394 Our study does not come without limitations, including its cross-sectional approach, 395 inherently hindering causal inferences. The study sample included only postmenopausal women with RA, so the findings cannot be directly generalized to other 396 populations, such as men or women of reproductive age. Specifically related to the 397 FMD assessments, the study employed a manual pneumatic cuff, which arguably results 398 399 in slower cuff inflation/deflation compared to automatic systems, potentially affecting 400 the shear stress response and the resulting dilation. The study results should also be interpreted considering the potential effects of cardiovascular, antihypertensive, and 401 lipid-lowering medications, which may have influenced vascular outcomes and 402 modulated the associations between physical activity and vascular function in our study 403 404 sample. Additionally, caution should be exercised when interpreting the study findings, 405 considering that physical activity/sedentary behavior showed no associations with more broadly used measures of vascular health (i.e., FMD and cIMT). Furthermore, the low 406 levels of MVPA observed in the sample might have affected possible associations 407 between this behavior and vascular outcomes, as previously discussed. Nonetheless, 408 409 our study is the first, to the best of our knowledge, to explore and demonstrate existing 410 associations between objectively measured sedentary and physical activity with vascular 411 outcomes in RA, advancing the current knowledge with more reliable and accurate412 measures of physical activity and sedentary behavior.

In conclusion, reduced sedentary behavior and increased light-intensity and total physical activity are associated with improved vascular outcomes in RA. Our results suggest the potential role of replacing sedentary behavior with light physical activity to improve vascular health markers in RA. However, as this was a cross-sectional study, these findings need to be tested in specific intervention trials before they can be recommended as a standard strategy for managing vascular health in RA patients.

419

Author contributions: KM, TP, AJP, ACMR, ALSP, FRL, CLMF, BG, and HR
conceived and designed research. KM, TP, AJP, BCM, FIS, DR, NDSJ performed
experiments. KM, AJP, LPS analyzed data. KM, TP, AJP, LPS interpreted the results of
experiments. KM and LPS prepared the tables, KM, TP, AJP and LPS drafted and
edited manuscript. All authors revised and approved the final version of manuscript.

425

426 **Conflict of interest:** None

427

428 Acknowledgments: Kamila Meireles dos Santos was supported by a grant from the 429 Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Ana Jessica Pinto, Tiago Peçanha, Lucas Porto Santos and Bruno Gualano were supported by grants 430 431 from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; 2015/26937-4 and 2018/19418-9; 2016/23319-0 and 2019/07150-4; 2022/12890-0; 432 433 2017/13552-2). Tiago Pecanha and Hamilton Roschel were supported by grants from 434 the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; 406196/2018-4; 428242/2018-9). Claudia L. M. Forjaz was supported by grants from 435 the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 436 302309/2022-5). We thank all the individuals who participated in this study and the 437 438 health professionals who assisted with participant recruitment. The graphical abstract developed using BioRender. 439 was

Variables	All participants
n	82
Age(years)	62 ± 7.6
$BMI(kg/m^2)$	28.8±5.4
Disease parameters	
DAS28-CRP(A.U.)	$3.4{\pm}3.0$
CDAI(A.U.)	10.8 ± 9.9
HAQ(A.U.)	$1.1{\pm}0.6$
Disease duration (years)	$20{\pm}11.0$
Comorbidities	n(%)
Hypertension	47(57%)
Dyslipidemia	42(51%)
Type 2 diabetes	17(21%)
Cardiovascular diseases	10(12%)
Hypothyroidism	17(21%)
Osteoarthritis	25(30%)
Osteopenia or osteoporosis	23(28%)
Fibromyalgia	17(21%)
Lung diseases	9(11%)
Sjögren syndrome	7(9%)
Systemic lupus erythematosus	3(4%)
Medication	n(%)
DMARDs	70(85%)
Prednisone	61(74%)
Biological agents	45(55%)
Non-steroidal anti-inflammatory drugs	32(39%)
Antihypertensive drugs	47(57%)
Antidyslipidemic drugs	42(51%)
Antidiabetic drugs	17(21%)
Pain killers	54(66%)
Muscle relaxants	29(35%)
Sedentary behavior and physical activity level	
Total sedentary behavior (h/day)	$8.2{\pm}2.0$
Prolonged sedentary behavior (bouts >60 min)	$1.6{\pm}1.8$
(h/day)	
Breaks in sedentary behavior (number/day)	45.2±14.5
Standing time (h/day)	5.9±1.7
LPA (h/day)	6.1±1.5
MVPA (min/day)	18.0 ± 15.2
Stepping time (h/day)	1.71 ± 0.67

441 Data are presented as mean±SD. Abbreviations: BMI, body mass index; CDAI, Clinical Disease Activity Index;
442 DAS28, Disease Activity Score in 28 joints; DMARDS, disease-modifying antirheumatic drugs; HAQ, Health
443 Assessment Questionnaire; LPA, light intensity physical activity; MVPA, Moderate-to-vigorous physical activity;

444 PA, physical activity.

445

446

447 Table 2. Vascular parameters

Variables	All participants
Brachial artery(BA)	
BA baseline diameter(mm)	3.7 ± 0.5
BA peak diameter(mm)	3.9 ± 0.5
BA-FMD(%)	4.3 ± 3.0
BA-shear rate AUC (AU. 10^3)	38.7 ± 21.1
BA-FMD/ shear rate AUC (AU. 10^{-5})	0.156 ± 0.197
Superficial femoral artery (SFA)	
SFA baseline diameter(mm)	5.3 ± 1.0
SFA peak diameter(mm)	5.6 ± 0.8
SFA-FMD(%)	3.7 ± 2.2
SFA-shear rate AUC (AU. 10^3)	22.1 ± 17.5
SFA-FMD/ shear rate AUC (AU.10 ⁻⁵)	0.303 ± 0.426
Common carotid artery	
Carotid diameter mean(mm)	6.8 ± 0.7
cIMT _{mean} (mm)	0.7 ± 0.1
Wall-to-lumen ratio	0.108 ± 0.017

448 Data are presented as mean±SD. cIMT_{mean}, mean common carotid intima-media thickness. FMD, flow-mediated dilation.

		S	edentary beha	vior			Prolon	ged sedentary	behavi	or	Breaks					
			(h/day)					(h/day)								
	В	Р	95% CI	R ²	p model	β	р	95% CI	R ²	p model	β	р	95% CI	\mathbf{R}^2	p model	
Model 1																
BA baseline diameter(mm)	-0.05	0.07	-0.11;0.01	0.04	0.07	-0.07	0.03	-0.14;-0.01	0.06	0.03	0.00	0.73	-0.01;0.01	0.00	0.73	
BA peak diameter(mm)	-0.05	0.12	-0.11;0.01	0.03	0.12	-0.08	0.03	-0.14;-0.01	0.06	0.03	0.00	0.71	-0.01;0.01	0.00	0.71	
BA-FMD(%)	0.20	0.24	-0.14;0.53	0.02	0.24	-0.02	0.93	-0.40;0.37	0.00	0.93	0.01	0.81	-0.04;0.06	0.00	0.81	
BA SRAUC (AU).10 ³	0.66	0.58	-1.74;3.01	0.00	0.58	1.97	0.15	-0.70;4.64	0.03	0.15	-0.15	0.38	-0.50;0.19	0.01	0.38	
BA-FMD/SRAUC (AU).10 ⁻⁵	0.79	0.49	-1.46;0.03	0.01	0.49	-1.26	0.33	-3.78;1.27	0.01	0.33	0.31	0.05	0.00;0.63	0.05	0.05	
SFA baseline diameter(mm)	-0.05	0.41	-0.16;0.06	0.01	0.41	-0.02	0.75	-0.14;0.10	0.00	0.75	-0.01	0.47	-0.02;0.01	0.01	0.47	
SFA peak diameter(mm)	-0.09	0.05	-0.18;0.00	0.05	0.05	-0.06	0.24	-0.16;0.04	0.02	0.24	-0.01	0.27	-0.02;0.01	0.02	0.27	
SFA-FMD(%)	0.12	0.35	-0.13;0.36	0.01	0.35	0.02	0.87	-0.26;0.30	0.00	0.87	0.03	0.12	-0.01;0.06	0.03	0.12	
SFA SRAUC (AU).10 ³	0.23	0.82	-1.81;2.28	0.00	0.82	0.46	0.69	-1.80;2.73	0.00	0.69	0.03	0.99	-0.30;0.30	0.00	0.99	
SFA-FMD/SRAUC (AU).10 ⁻⁵	0.60	0.81	-5.60;4.42	0.00	0.81	1.69	0.55	-7.22;3.84	0.00	0.55	-0.17	0.64	-0.93;0.58	0.00	0.64	
Mean common carotid diameter(mm)	0.06	0.16	-0.02;0.14	0.02	0.16	0.04	0.38	-0.05;0.14	0.01	0.38	0.00	0.64	-0.02;0.01	0.00	0.64	
cIMT(mm)	0.01	0.40	-0.01;0.02	0.01	0.40	0.01	0.11	0.00;0.02	0.03	0.11	0.00	0.90	0.00;0.00	0.00	0.90	
Common carotid wall-to-lumen ratio	0.00	0.55	0.00;0.00	0.00	0.55	0.00	0.42	0.00;0.00	0.01	0.42	0.00	0.73	0.00;0.00	0.00	0.73	
Model 2																
BA baseline diameter(mm)	-0.08	<0.01	-0.14;-0.02	0.16	<0.01	-0.10	<0.01	-0.16;-0.03	0.17	<0.01	0.00	0.48	-0.01;0.01	0.08	0.17	
BA peak diameter(mm)	-0.08	0.01	-0.14;-0.02	0.12	<0.01	-0.10	< 0.01	-0.17;-0.03	0.18	<0.01	0.00	0.44	-0.01;0.01	0.09	0.13	
BA-FMD(%)	0.17	0.36	-0.19;0.52	0.04	0.58	0.05	0.81	-0.36;0.46	0.03	0.71	0.01	0.75	-0.04;0.06	0.03	0.71	
BA SRAUC (AU).10 ³	0.66	0.61	-1.94;3.26	0.01	0.96	1.84	0.21	-1.10;4.74	0.03	0.74	-0.15	0.42	-0.51;0.21	0.01	0.91	
BA-FMD/SRAUC (AU).10 ⁻⁵	1.14	0.34	-1.24;3.52	0.05	0.40	-0.59	0.66	-3.28;2.10	0.04	0.51	0.29	0.08	-0.03;0.62	0.08	0.18	
SFA baseline diameter(mm)	-0.09	0.14	-0.21;0.03	0.08	0.20	-0.02	0.72	-0.16;0.11	0.05	0.42	0.00	0.65	-0.02;0.00	0.05	0.41	
SFA peak diameter(mm)	-0.14	< 0.01	-0.24;-0.05	0.18	<0.01	-0.07	0.21	-0.18;0.04	0.09	0.13	-0.01	0.42	-0.02;0.01	0.08	0.19	
SFA-FMD(%)	0.18	0.19	-0.10;0.45	0.04	0.58	0.05	0.77	-0.25;0.34	0.04	0.87	0.03	0.16	-0.01;0.06	0.04	0.54	
SFA SRAUC (AU).10 ³	0.60	0.58	-1.56;2.75	0.05	0.45	0.60	0.58	-1.56;2.57	0.05	0.45	0.00	0.78	-0.04;0.03	0.05	0.48	
SFA-FMD/SRAUC (AU).10 ⁻⁵	-1.25	0.64	-6.56;4.05	0.05	0.48	-1.39	0.63	-7.22;4.43	0.05	0.48	0.11	0.78	-0.88;0.66	0.04	0.50	
Mean common carotid diameter(mm)	0.06	0.11	-0.01;0.15	0.13	0.03	0.03	0.57	-0.06;0.12	0.10	0.09	0.00	0.95	-0.01;0.01	0.10	0.10	
cIMT(mm)	0.00	0.37	-0.01;0.02	0.15	0.02	0.01	0.45	-0.01;0.02	0.15	0.02	0.00	0.58	0.00;0.00	0.15	0.02	
Common carotid wall-to-lumen ratio	0.00	0.06	0.00.0.00	0.00	0.43	0.00	0.65	0.00.0.00	0.00	0.40	0.00	0.74	0.00.0.00	0.00	0.42	

450	Table 3. Results of	f regression an	alyses examining	s associations	between	sedentary	behavior	and vascu	lar function	and structure
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 Common carotid wall-to-lumen ratio
 0.00
 0.96
 0.00;0.00
 0.00
 0.43
 0.00
 0.65
 0.00;0.00
 0.00
 0.42

 Model
 1: simple linear regression. Model
 2: adjusted by age, BMI and disease activity. P-values in bold indicate statistical significance. BA, brachial artery; SFA, superficial femoral artery; cIMTmean, mean common carotid intima-media thickness; FMD, flow-mediated dilation; SR. shear rate; AUC, area under curve until the peak dilation; AU, arbitrary units.

			Standing		Light-intensity PA							Mod	lerate-to-vigor	ous PA		Stepping time				
			(h/day)	D ²				(h/day)	D ²		•		(min/day)	D ²				(h/day)	D ²	
	ß	р	95% CI	R-	p model	ß	р	95% CI	R-	p model	þ	р	95% CI	R-	p model	в	р	95% CI	R-	P
Model 1					mouer					mouer					mouer					mouer
BA baseline diameter(mm)	0.03	0.36	-0.03.0.08	0.01	0.36	0.07	0.10	-0.01:0.15	0.04	0.10	0.00	0.37	-0.01.0.00	0.01	0.37	0.13	0.14	-0.04.0.30	0.03	0.14
BA peak diameter(mm)	0.02	0.56	-0.04.0.08	0.01	0.56	0.07	0.10	-0.02:0.15	0.03	0.10	0.00	0.41	-0.01:0.00	0.01	0.41	0.12	0.20	-0.06:0.29	0.02	0.20
BA-FMD(%)	-0.15	0.35	-0.48.0.17	0.01	0.35	-0.11	0.65	-0 57:0 35	0.00	0.65	0.00	0.76	-0.04.0.05	0.00	0.76	-0.50	0.32	-1 49.0 49	0.01	0.20
BA SRAUC (AU). 10^3	1.03	0.38	-3.38:1.31	0.01	0.38	-1.51	0.36	-4.77:1.75	0.01	0.36	0.11	0.51	-0.22:0.44	0.01	0.51	-3.99	0.26	-11.07:3.10	0.02	0.26
BA-FMD/SRAUC (AU).10 ⁻⁵	0.79	0.48	-2.98:1.42	0.01	0.48	0.14	0.93	-2.97:3.24	0.00	0.93	0.15	0.36	-0.17:0.46	0.01	0.36	1.10	0.74	-5.60:7.80	0.00	0.74
SFA baseline diameter(mm)	0.03	0.62	-0.08:0.14	0.00	0.62	0.03	0.71	-0.12:0.18	0.00	0.71	-0.01	0.25	-0.02:0.01	0.02	0.25	-0.14	0.39	-0.47:0.19	0.01	0.39
SFA peak diameter(mm)	0.07	0.11	-0.02:0.16	0.03	0.11	0.07	0.26	-0.05:0.20	0.02	0.26	0.00	0.49	-0.02:0.01	0.01	0.49	0.14	0.30	-0.13:0.42	0.01	0.30
SFA-FMD(%)	-0.05	0.66	-0.30:0.19	0.00	0.66	0.04	0.83	-0.31:0.38	0.00	0.83	0.00	0.80	-0.04:0.03	0.00	0.80	-0.34	0.36	-1.07:0.39	0.01	0.36
SFA SRAUC (AU). 10^3	0.04	0.97	-1.98:2.06	0.00	0.97	-0.64	0.65	-3.46:2.18	0.00	0.65	-0.01	0.95	-0.03:0.03	0.00	0.95	0.96	0.76	-5.18:7.09	0.00	0.76
SFA-FMD/SRAUC (AU).10-5	2.78	0.26	-2.12;7.69	0.02	0.26	0.68	0.84	-6.27;7.63	0.00	0.84	-0.23	0.51	-0.92;0.00	0.01	0.17	-0.10	0.17	0.00;4.43	0.03	0.17
Mean common carotid diameter(mm)	-0.06	0.18	-0.14;0.03	0.02	0.18	-0.10	0.08	-0.22;0.01	0.04	0.08	0.00	0.50	-0.02;0.01	0.01	0.50	-0.02	0.86	-0.27;023	0.00	0.86
cIMT(mm)	0.00	0.87	-0.01;0.01	0.00	0.87	-0.01	0.40	-0.02; 0.01	0.01	0.40	0.00	0.12	0.00;0.00	0.03	0.12	-0.02	0.21	-0.06;0.01	0.02	0.21
Common carotid wall-to-lumen ratio	0.00	0.22	0.00;0.00	0.02	0.22	0.00	0.47	0.00; 0.00	0.01	0.47	0.00	0.51	0.00;0.00	0.01	0.51	0.00	0.41	-0.01;0.00	0.01	0.41
Model 2																				
BA baseline diameter(mm)	0.04	0.15	-0.02;0.10	0.10	0.09	0.10	0.02	0.01;0.18	0.13	0.04	0.00	0.81	-0.01;0.01	0.06	0.34	0.24	<0.01	0.06;0.42	0.16	0.01
BA peak diameter(mm)	0.04	0.18	-0.02;0.10	0.10	0.08	0.10	0.02	0.01;0.18	0.13	0.04	0.00	0.87	-0.01;0.01	0.06	0.30	0.17	0.01	0.05;0.42	0.16	0.01
BA-FMD(%)	-0.12	0.50	-0.47;0.23	0.03	0.64	-0.12	0.63	-0.62;0.38	0.02	0.84	0.01	0.70	-0.04;0.06	0.02	0.85	-0.48	0.38	-1.56;0.60	0.04	0.58
BA SRAUC (AU).10 ³	-1.21	0.33	-3.71;1.27	0.02	0.86	-1.50	0.40	-5.04;2.05	0.02	0.83	0.16	0.38	-0.20;0.52	0.02	0.82	-4.28	0.27	-12.00;3.45	0.02	0.81
BA-FMD/SRAUC (AU).10-5	-0.72	0.53	-3.02;1.58	0.05	0.48	-0.43	0.80	-3.75;2.88	0.05	0.49	0.09	0.61	-3.75;2.88	0.05	0.46	-1.20	0.97	-7.29;7.04	0.04	0.54
SFA baseline diameter(mm)	0.06	0.35	-0.06;0.17	0.06	0.32	0.05	0.50	-0.11;0.22	0.04	0.59	-0.01	0.36	-0.02;0.01	0.04	0.52	-0.08	0.64	-0.44;0.27	0.05	0.41
SFA peak diameter(mm)	0.11	0.02	0.01;0.20	0.14	0.03	0.10	0.12	-0.03;0.23	0.08	0.20	0.00	0.68	-0.02;0.01	0.06	0.43	0.24	0.10	-0.05;0.53	0.10	0.08
SFA-FMD(%)	-0.09	0.50	-0.35;0.17	0.02	0.81	-0.02	0.91	-0.39;0.35	0.01	0.94	0.01	0.79	-0.04;0.03	0.01	0.93	-0.50	0.22	-1.30;0.31	0.04	0.61
SFA SRAUC (AU).10 ³	0.28	0.79	-2.37;1.81	0.05	0.48	-0.83	0.58	-3.79;2.13	0.04	0.58	0.03	0.85	-0.33;0.27	0.03	0.63	0.52	0.87	-5.89;6.93	0.05	0.49
SFA-FMD/SRAUC (AU).10 ⁻⁵	3.69	0.15	-1.38;8.75	0.07	0.25	1.15	0.75	-6.15;8.45	0.05	0.51	0.25	0.51	-0.98;0.49	0.05	0.46	-0.10	0.17	-0.26;4.83	0.07	0.27
Mean common carotid diameter(mm)	-0.07	0.09	-0.14;0.01	0.14	0.03	-0.11	0.05	-0.21;0.01	0.15	0.02	0.00	0.91	-0.01;0.01	0.11	0.08	-0.03	0.79	-0.28;0.21	0.10	0.09
cIMT(mm)	0.00	0.67	-0.01;0.01	0.15	0.02	-0.01	0.33	-0.02;0.01	0.16	0.02	0.00	0.38	0.00;0.00	0.15	0.02	-0.02	0.23	-0.06;0.01	0.16	0.01
Common carotid wall-to-lumen ratio	0.00	0.39	0.00;0.00	0.05	0.46	0.00	0.71	0.00;0.00	0.06	0.40	0.00	0.43	0.00;0.00	0.06	0.33	0.00	0.33	-0.01;0.00	0.05	0.43
455 bodel 1: simple linear regression. Mo	odel 2: adju	usted by	age, BMI and	d diseas	e activity	. P-valu	es in bo	old indicate s	tatistica	l signific	ance. B	A, brach	ial artery; SF.	A, super	ficial fem	oral artery	; cIMTm	ean, mean con	nmon car	otid
4 56 ima-media thickness; FMI	D, flov	v-media	ted dilati	on.	SR.	shear	rate;	AUC,	area	unde	r th	e cu	rve until	the	peak	dilati	on; A	.U, arbitra	ry u	nits.

454 Table 4. Results of regression analyses examining associations between physical activity levels and function and vascular structure

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567

Physical activity, sedentary behavior and vascular health in rheumatoid arthritis

METHODS

Accelerometer-measured physical activity and sedentary behavior (over 7 days)



Vascular ultrasound assessment

Flow-mediated dilation (FMD) (diameter and blood velocity data)

Carotid intima-media thickness (cIMT)



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OUTCOME



CONCLUSION

Reducing sedentary behavior and increasing physical activity, even at light intensities, may improve vascular health in RA

Take a stand for health (TS4H)

