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BENEFITS OF LIFELONG EXERCISE TRAINING ON LEFT VENTRICULAR FUNCTION AFTER MYOCARDIAL INFARCTION

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ABSTRACT

BACKGROUND. Endurance exercise training induces cardio-protective effects, but athletes are not exempted from a myocardial infarction (MI). Evidence from animal studies suggests that exercise training attenuates pathological left ventricular (LV) remodelling following MI. We tested the hypothesis that lifelong exercise training is related to an attenuated pathological LV remodelling after MI as evidenced by a better LV systolic function in veteran athletes compared to sedentary peers.

DESIGN. Cross-sectional study

METHODS. Sixty-five males (60 ± 6 years) were included and allocated to four groups based on lifelong exercise training volumes: 1) athletes (ATH, $n=18$), 2) post-MI athletes (ATH+MI, $n=20$), 3) sedentary controls (SED, $n=13$), and 4) post-MI controls (SED+MI, $n=14$). Athletes were lifelong (≥ 20 years) highly physically active (≥ 30 MET-hours/week), whereas sedentary controls did not meet the exercise guidelines (< 10 MET-hours/week) for the past 20 years. LV systolic function, diastolic function, and wall strain were measured using echocardiography.

RESULTS. Cardiac enzyme markers (creatine-kinase, creatinine, aspartate transaminase, and lactate dehydrogenase) following MI and infarct location did not differ between ATH+MI and SED+MI. LV ejection fraction was significantly higher in ATH ($61\%\pm 4$), ATH+MI ($58\%\pm 4$), and SED ($57\%\pm 6$) compared to SED+MI ($51\%\pm 7$; $P<0.01$). LV circumferential strain was superior in ATH (-19% [-21% to -17%], ATH+MI (-16% [-20% to -12%]), and SED [-15% [-18% to -14%] compared to SED+MI (-13% [-15% to -8%], $P<0.01$). Diastolic function parameters did not differ across groups.

CONCLUSION. These findings suggest that lifelong exercise training may preserve LV systolic function and possibly attenuates or minimizes the deleterious effects of pathological post-MI LV remodelling in veteran athletes.

Keywords: coronary artery disease; physical activity; echocardiography; secondary prevention

1 INTRODUCTION

2 Regular exercise training leads to a favourable cardiovascular risk factor profile,¹ improves
3 cardiovascular function,^{2, 3} and lowers the risk for cardiovascular disease.^{4, 5} Despite the cardio-
4 protective effects of exercise training, athletes are not exempted from acute coronary syndromes or
5 myocardial infarction.⁶

6

7 After a myocardial infarction, the pathological LV remodelling starts within hours.^{7, 8} This process is
8 characterized by LV wall thinning, LV wall dilatation, reduced ejection fraction, and scar formation^{7, 8}
9 and eventually leads to impaired LV function. Preventing or reversing these maladaptations is of utmost
10 importance to recover and maintain LV function. Animal studies demonstrated that exercise training
11 before a myocardial infarction attenuates pathological LV remodelling.⁹ Trained rats had less cardiac
12 damage after ligation of the left anterior descending artery and fewer changes in cardiomyocyte
13 function.⁹ These results suggest that a physically active lifestyle before a myocardial infarction may
14 attenuate pathological LV remodelling. Confirmation of these findings in humans is lacking.

15

16 The primary aim of the study was to determine whether lifelong exercise training is related to an
17 attenuated pathological left ventricular remodelling after myocardial infarction. For this purpose, we
18 collected echocardiographic images in veteran athletes with and without a myocardial infarction and
19 sedentary controls with and without a myocardial infarction. We hypothesized that veteran athletes will
20 have a better LV systolic function compared to their sedentary peers after a myocardial infarction.

21

22 **METHODS**

23 **PARTICIPANTS**

24 Sixty-five male participants were included and stratified into four groups based on their lifelong physical
25 activity patterns and cardiac medical history: 1) veteran athletes (ATH, n=18), 2) veteran post-MI
26 athletes (ATH+MI, n=20), 3) sedentary controls (SED, n=13), and 4) sedentary post-MI controls
27 (SED+MI, n=14). To ensure that pathological LV remodelling was stabilized,⁷ post-MI participants with
28 a myocardial infarction diagnosis >6 months before the start of the study were included. Participants
29 were recruited via local newspapers, internet advertisement, and the *Nijmegen Exercise Study*.⁵
30 Individuals that expressed interest in study participation were screened by telephone and received a
31 questionnaire regarding their exercise history. Individuals that were more than 20 years physically active
32 and performed regular endurance exercise for ≥ 30 MET-hours per week were assigned to the athlete
33 group. Individuals that did not exceed the recommended exercise dose of the World Health Organisation
34 (<10 MET-hours/week) with habitual physical activities over the past 20 years, were assigned to the
35 sedentary control group.¹⁰ Individuals that could not be assigned to the athlete or sedentary group were
36 excluded from further study participation. Smokers and diabetics were not included in the study.
37 Additional exclusion criteria for the asymptomatic veteran athletes and sedentary controls was the use
38 of cardiovascular medication (e.g., antihypertensives, lipid-lowering medications). The Local Ethical
39 Committee of the region Arnhem-Nijmegen approved the study and all participants gave written
40 consent. All procedures performed in studies involving human participants were in accordance with the
41 ethical standards of the institutional and/or national research committee and with the 1964 Helsinki
42 declaration and its later amendments or comparable ethical standards.

43

44 **STUDY DESIGN**

45 Individuals that expressed interest in the study were first screened via telephone and completed a
46 questionnaire regarding their lifelong exercise history. Participants visited our laboratory on two days
47 during this cross-sectional study. On day 1, participants were medically screened for eligibility, followed

48 by an incremental maximal cycling test. On day 2, participants underwent a comprehensive assessment
49 of LV function using transthoracic echocardiography.

50

51 **MEASUREMENTS**

52 **MEDICAL SCREENING**

53 A physician screened the participants by taking a detailed medical history, physical examination, and
54 12-lead electrocardiogram. Blood samples were obtained, under fasting conditions, from an antecubital
55 vein for the analysis of total cholesterol, HDL, LDL, triglycerides, glucose, and HbA1c.

56

57 **LIFELONG PHYSICAL ACTIVITY PATTERNS**

58 Lifelong physical activity patterns were queried via an exercise history questionnaire, distinguishing
59 five age-periods: I) 20-29 years, II) 30-39 years, III) 40-49 years, IV) 50-59 years, and V) >60 years.
60 Each category consisted of three queries: 1) type of activity (*e.g.*, running, cycling, etc., or nothing), 2)
61 exercise time (hours) per activity per week, and (3) self-perceived intensity (light, moderate, or
62 vigorous) per activity. The corresponding metabolic equivalent of task (MET) score per exercise
63 activity was determined,¹¹ and exercise dose (MET-hours/week) was calculated by multiplying exercise
64 time with MET scores. Average exercise dose was calculated over the last 20 years. For post-MI
65 participants, exercise dose before and after the myocardial infarction diagnosis were calculated.

66

67 **INCREMENTAL MAXIMAL CYCLING TEST**

68 Cardiorespiratory fitness (VO_{2peak} , mL O_2 /min/kg) was assessed via an incremental maximal cycling
69 test. Participants cycled with 60-80 rotations per minute while the workload increased with 20 Watt/min
70 for athletes and 10 Watt/min for post-MI controls. Heart rate (12 lead-electrocardiogram), oxygen
71 uptake (VO_2 [ml/min]), carbon dioxide output (VCO_2 [ml/min]), and respiratory exchange ratio (RER)
72 were continuously measured (CPET, Cosmed v9.1b, Italy).¹² The anaerobic threshold was defined as a
73 RER above 1.0.¹² Participants were verbally encouraged to stimulate maximal exercise performance.
74 Lactate concentration (mmol/L) was measured via a capillary blood sample taken one-and-a-half minute
75 after exercise cessation (Arkray, type LT-1730, Japan).

76 CARDIAC MEDICAL HISTORY

77 Myocardial infarction characteristics were extracted from medical health records from the hospitals at
78 which the patients were admitted. Specifically, clinical diagnosis of the myocardial infarction, cardiac
79 enzyme levels (troponin-I, creatine kinase [CK], creatinine [CREAT], aspartate transaminase [ASAT],
80 and lactate dehydrogenase [LDH]), treatment strategy, and secondary events were identified and used
81 for data analyses.

82

83 ECHOCARDIOGRAPHY

84 Participants abstained from exercise 24 hours before the echocardiography assessment. Two-
85 dimensional Doppler and four-dimensional images were obtained by a single experienced cardiologist
86 using an ultrasound system (Vivid E9, General Electric Healthcare, Norway) equipped with a M5-S and
87 V4 probe. All measurements were performed according to the American Society of Echocardiography
88 (ASE) guidelines¹³ with the participant in the left lateral recumbent position. Images were taken at end-
89 expiratory breath hold, carefully avoiding Valsalva manoeuvre. A continuous three-lead
90 electrocardiogram registration was used to detect end-diastole time points (onset of QRS). Data were
91 transferred to a workstation for offline analysis (EchoPac PC version 113, General Electric Healthcare,
92 Norway). Data analysis of the echocardiographic images was performed by an independent, blinded
93 expert.

94

95 *Left ventricular systolic function*

96 LV ejection fraction (LVEF) was calculated from the LV end-diastolic volume (LVEDV) and LV end-
97 systolic volume (LVESV) using Simpson's biplane method. Based on ASE guidelines, a LVEF below
98 52% was defined as an impaired LVEF.¹³ Stroke volume was calculated by multiplying the time velocity
99 integral and cross-sectional area of the LV outflow tract. Cardiac output was calculated by multiplying
100 stroke volume with heart rate. Cardiac index was calculated by dividing cardiac output by body surface
101 area. Body surface area was calculated using DuBois' formula (equation 1).

102

$$0.007184 * (\text{body mass (kg)}^{0.425}) * (\text{height (m)}^{0.725})$$

Equation 1

103

104 Pulsed-wave tissue Doppler imaging measurements of peak systolic annular tissue velocities were
105 obtained at the septal and lateral mitral annulus from apical 4-chamber images and an average of both
106 sites is presented.

107

108 *Left ventricular wall strain*

109 Via the apical window, a 4D full volume R-wave 6 beat gated dataset of the LV was acquired. Volume-
110 rate was kept >30 Hz. The dataset was post-processed using 4D automated LV quantification tool
111 available in EchoPac to determine LV wall strain. From 4D images, endocardial border detection process
112 was initialized by manual alignment of the apex and mitral valves in a long-axis view at both end-
113 diastolic and end-systolic phase. The endocardial border was automatically generated throughout the
114 cardiac cycle. The proposed contour was evaluated via short-axis cut-planes of the 3D volume at base,
115 mid, and apex of the LV and cut-planes of the apical 4-, 3-, and 2-chamber views. Only major deviations
116 of the expected endocardial borders were operator corrected. Papillary muscles and major trabeculae
117 were included in the LV cavity. The epicardial border was automatically generated by the software,
118 which created a 3D region of interest of the LV wall. Speckle tracking was applied to determine global
119 longitudinal, circumferential, area, and radial strain.

120

121 *Left ventricular diastolic function*

122 Diastolic function was assessed with LV inflow pulsed-wave Doppler measurements at the mitral leaflet
123 tips, including peak flow velocity of the early rapid filling wave (E-wave), peak flow velocity of the late
124 filling wave due to atrial contraction (A-wave) and E/A ratio. Using pulsed-wave tissue Doppler, the
125 tissue velocity of the septal and lateral mitral annulus was registered. From these tracings, peak early
126 mitral annular tissue velocity (e'-wave), and peak late mitral annular tissue velocity during atrial
127 contraction (a'-wave) were measured. The ratio of E-wave and e' (E/e') was calculated.

128

129

130 STATISTICAL ANALYSIS

131 Data is reported as mean±standard deviation or median (interquartile range [IQR]). Categorical data
132 were analysed using the *Fisher's exact* test. Parameters were checked for normality using a *Shapiro-*
133 *Wilk* test. Skewed variables were log_e-transformed before analyses. Data that could not be transformed
134 into Gaussian distribution were analysed using nonparametric tests. An *independent Student's t* or *Mann-*
135 *Whitney-U* test were used to analyse cardiac enzyme levels between ATH+MI and SED+MI, when
136 appropriate. ANOVA with a *Tukey post hoc* or *Kruskal-Wallis* test were performed to determine
137 differences between groups, when appropriate. Statistical analyses were performed using SPSS 21.0
138 software (IBM Corp., Armonk, N.Y., USA).

139 **RESULTS**

140 **PARTICIPANT CHARACTERISTICS**

141 Participant characteristics of the four study groups are summarized in Table 1. Average exercise time
142 and dose were significantly higher in ATH and ATH+MI compared to SED and SED+MI (Supplement
143 Figure 1). Exercise time and dose before compared to after myocardial infarction increased in the
144 ATH+MI, but did not change in SED+MI. ATH and ATH+MI performed most of the time moderate
145 intensity exercise (65%), followed by vigorous intensity exercise (33%) and light intensity exercise
146 (2%). VO₂peak differed across groups, with ATH demonstrating the highest VO₂peak uptake (48.0±8.9
147 mL/min/kg), followed by ATH+MI (40.9±5.5 mL/min/kg), SED (31.6±4.8 mL/min/kg) and SED+MI
148 (29.7±6.5 mL/min/kg, *p*<0.01). VO₂peak did not differ between SED and SED+MI (Table 1).

149

150 [insert Table 1]

151

152 **MEDICAL HISTORY AND MEDICATION USAGE**

153 No differences were observed between ATH+MI and SED+MI for time between myocardial infarction
154 diagnosis and study participation, cardiac enzyme levels (Troponin-I, CK, CREAT, ASAT, and LDH),
155 and infarct location (Table 2). Percutaneous Coronary Intervention (PCI) treatment was applied in 94%
156 of the post-MI patients and prevalence did not differ between both post-MI groups (Table 2). None of
157 the participants received coronary artery bypass grafting surgery. 71% of the post-MI participants
158 completed a cardiac rehabilitation program and this did not differ between both post-MI groups (Table
159 2). Four post-MI controls needed an elective PCI and one of them reported a recurrent myocardial
160 infarction, whereas none of the post-MI athletes needed an elective PCI or reported a recurrent
161 myocardial infarction. Apart from ACE-inhibitors, medication use did not differ between post-MI
162 groups (Table 2).

163

164 [insert Table 2]

165

166 **ECHOCARDIOGRAPHY**

167 **LEFT VENTRICULAR SYSTOLIC FUNCTION**

168 Due to a low-quality echocardiogram, LVESV, and LVEDV of two ATH and two ATH+MI could not
169 be determined and were not included in the statistical analyses. LVESV was significantly lower in ATH
170 (38 mL [32 to 50]) and SED (39 mL [32 to 44]) compared to SED+MI (50 mL [44 to 69]) ($P < 0.01$),
171 but did not differ compared to ATH+MI (47 mL [42 to 52], $P > 0.10$). LVEF was significantly higher
172 in ATH (61% [57 to 62]), ATH+MI (59% [56 to 60]), and SED (58% [52 to 63]) compared to SED+MI
173 (51% [47 to 55], $P < 0.01$, Figure 1). Two (10%) ATH+MI *versus* eight (57%) SED+MI demonstrated
174 an impaired LVEF ($P < 0.01$). Stroke volume was significantly higher in ATH (83 mL [73 to 102])
175 compared to SED (71 mL [60 to 79]) and SED+MI (68 mL [57 to 82], $P < 0.05$), but stroke volume did
176 not differ between ATH+MI (82 mL [68 to 97]) and ATH, SED, and SED+MI ($P > 0.10$). Cardiac
177 output, cardiac index, and peak systolic annular tissue velocity did not differ across groups (Table 3).

178

179 [insert Figure 1]

180 [insert Table 3]

181

182 **LEFT VENTRICULAR WALL STRAIN**

183 LV longitudinal strain did not differ between ATH+MI (-13% [-18 to -10]), SED (-12% [-15 to -11]),
184 and SED+MI (-11% [-15 to -6], $P > 0.05$), but LV longitudinal strain was superior (*i.e.*, more negative
185 strain) in ATH (-16% [-18 to -14]) compared to SED+MI (Figure 2, $P < 0.05$). LV circumferential strain
186 was superior in ATH (-19% [-21 to -17]), ATH+MI (-16% [-20 to -12]), and SED [-15% [-18 to -14])
187 compared to SED+MI (-13% [-15 to -8], $P < 0.01$). LV area strain was superior in ATH (-31% [-34 to -
188 26]) and ATH+MI (-26% [-33 to -21]) compared to SED+MI (-20% [-26 to -13], $P < 0.05$), whereas LV
189 area strain did not differ between SED (-26% [-29 to -22]) and the other three groups (Figure 2, $P >$
190 0.05). LV radial strain did not differ between ATH+MI (37% [30 to 52]), SED (38% [31 to 45]), and
191 SED+MI (33% [24 to 38], $P > 0.05$), but LV radial strain was superior in ATH (47% [38 to 55])
192 compared to SED+MI (Figure 2, $P < 0.01$). LV longitudinal, circumferential, area, and radial strain did

193 not differ between ATH and ATH+MI ($P > 0.10$). LV circumferential strain was superior in SED
194 compared to SED+MI ($P < 0.05$).

195

196 [insert Figure 2]

197

198 LEFT VENTRICULAR DIASTOLIC FUNCTION

199 All diastolic function parameters (i.e. LVEDV, E-wave, A-wave, E/A ratio, e' LV, a' LV, and E/e' ratio)
200 did not differ across groups (Table 3).

201

202 DISCUSSION

203 The major finding of this study is that ATH+MI had a better ejection fraction and a superior global LV
204 wall strain compared to SED+MI. Ejection fraction and LV wall strain are important parameters for LV
205 systolic function.¹³ We found no differences in LV function between ATH and ATH+MI, whereas
206 ejection fraction and circumferential strain differed between SED and SED+MI. These findings suggest
207 that lifelong exercise training may protect against the deleterious effects of a myocardial infarction
208 and/or minimizes the effects of pathological LV remodelling after a myocardial infarction.

209

210 The magnitude of pathological LV remodelling is dependent on the severity of the myocardial
211 infarction,¹⁴ clinical treatment (PCI),¹⁵ medication use,¹⁶ and lifestyle changes following diagnosis.¹⁶
212 We found no difference in cardiac enzyme levels, PCI treatment, infarct location, and medication
213 (except ACE-inhibitors) between both post-MI groups, suggesting that myocardial infarction size was
214 comparable between ATH+MI and SED+MI. A potential explanation for the difference in ACE-
215 inhibitors may relate to the physically active lifestyle of the ATH-MI. Physical activity is related to a
216 favourable blood pressure,¹⁷ which may have enabled ATH-MI to reduce their medication.
217 Interestingly, ATH+MI reported an increase in activity levels after the myocardial infarction compared
218 to before, whereas the SED+MI did not change their physical activity behaviour. These findings suggest

219 that ATH+MI and SED+MI did not differ in clinical characteristics, while their habitual exercise levels
220 were significantly different.

221
222 Before the myocardial infarction, ATH+MI were highly physically active (49 [35-84] MET-
223 hours/week), whereas SED+MI were inactive (1 [0-4] MET-hours/week). Several studies support the
224 hypothesis that exercise training induces preconditioning effects against ischemia and reperfusion,^{18, 19}
225 which subsequently protects the myocardium against damage produced by ischemia and reperfusion.⁹
226 A reduction of the induced cardiac damage due to a myocardial infarction will promote the healing
227 process of the infarcted area.⁹ Indeed, evidence from animal studies suggests that exercise training
228 before a myocardial infarction attenuates LV remodelling⁹ and improves cardiac function⁹ after
229 myocardial infarction. Findings from our study support this hypothesis as LV function (i.e. LV ejection
230 fraction, global circumferential and area strain) was superior in ATH+MI compared to SED+MI. Our
231 results are indicative that lifelong exercise training may improve infarct healing after myocardial
232 infarction.

233
234 An alternative explanation for the better LV systolic function in ATH+MI *versus* SED+MI may relate
235 to their activity patterns after the myocardial infarction. Most cardiovascular professional societies
236 recommend post-MI patients to participate in a cardiac rehabilitation program, and advise post-MI
237 patients to remain physically active at a low-to-moderate endurance intensity level¹⁶ to improve
238 functional capacity and reduce (cardiovascular) mortality.^{20 21} An early start of cardiac rehabilitation
239 and prolonged exercise training (>12 weeks) is associated with larger improvements in LV
240 remodelling.²² In the present study, ATH+MI continued and even increased their high-level physical
241 activity patterns after MI, whereas SED+MI maintained their sedentary lifestyle. The VO₂peak of our
242 study population reinforces these observations; ATH+MI (40.9±5.5 mL/min/kg) showed a substantially
243 higher VO₂peak uptake compared to SED+MI (29.8±6.1 mL/min/kg). The physically active lifestyle
244 after the myocardial infarction may have contributed to the better LV systolic function in ATH+MI
245 compared to SED+MI. In fact, these observations may represent optimal cardiac rehabilitation, as LV
246 function of ATH+MI was not different from their non-MI peers.

247

248 In the current study, it is impossible to distinguish the independent effects of exercise training before
249 and after the myocardial infarction on LV function. To gain more information about post-infarction
250 cardiac function and lifelong exercise training, we correlated the training of the different age periods
251 with ejection fraction and the strain parameters. Overall, we observed that higher levels of physical
252 activity were related to improved LV function, which is in line with the reported results of this study
253 (supplement Table 1). The combination of exercise training before and after myocardial infarction may
254 be superior to exercise training before or after myocardial infarction only. One animal study suggests
255 that the combination of exercise training before and after myocardial infarction improves LV
256 remodelling by reducing the inflammatory response and scar thinning process.²³ Another animal study
257 demonstrated that the combination of exercise training before and after myocardial infarction improved
258 infarct healing and post-MI survival compared to no exercise training.⁹ However, ameliorating effects
259 on LV remodelling observed in mice that either exercised before or after myocardial infarction were lost
260 in mice that exercised before *and* after myocardial infarction.⁹ Absence of exercise benefits on LV
261 remodelling in this combination group most likely relate to a very early start of post-MI exercise training
262 accompanied with a high exercise intensity (~7 km/day in the first week post-MI) in this particular
263 study.⁹ Indeed, there is evidence that vigorous post-MI exercise may cause further deterioration of the
264 injured heart.²⁴ This negative effect seems to be dependent on the severity of the myocardial infarction
265 and timing of the exercise training.²⁵ Additional research is warranted to assess the relation between
266 exercise before and after the myocardial infarction in relation to LV remodelling in humans.

267

268 In contrast to LV systolic function, we did not observe statistical differences in diastolic function
269 between ATH+MI and SED+MI. A potential explanation could relate to the fact that not all post-MI
270 patients develop diastolic dysfunction after a myocardial infarction.²⁶ Specific treatment to improve
271 diastolic function following a myocardial infarction is not available.²⁷ Potentially the long period
272 between myocardial infarction and study participation (Q₅₀: 6 years [Q₂₅: 3 to Q₇₅: 10]), and adequate
273 cardiac medication use may have contributed to the null findings of diastolic function between groups.
274 Alternatively, aging has been associated with a progressive decline in diastolic function.^{28, 29} Aging may

275 lead to an impaired diastolic relaxation pattern^{28, 29} and lifelong exercise training can only partially
276 minimize the age-related decline.²⁸ Sub analysis of our results, revealed that indeed a higher age was
277 associated with a significantly lower E/A ratio ($r=-0.35$; $P < 0.01$) and a higher E/e' ratio ($r=0.42$; $P <$
278 0.01). These findings indicate that the inclusion of an older study population affected our results on
279 diastolic function. Collectively, the possibility that not all post-MI patients develop diastolic dysfunction
280 after a myocardial infarction and the influence of ageing on diastolic function, could have resulted into
281 the null findings in diastolic function in the present study.

282

283 **CLINICAL IMPLICATIONS**

284 In an event when exercise training '*fails*' to prevent a myocardial infarction, our data suggest that veteran
285 athletes may restore and/or maintain their LV systolic function after a myocardial infarction. Additional
286 benefits are improved secondary prevention, since none of the ATH+MI had an elective PCI or recurrent
287 myocardial infarction. The information of the current study that exercise training improves LV
288 remodelling after myocardial infarction might be another reason to motivate sedentary post-MI patients
289 or individuals at risk for cardiovascular disease to change their lifestyle and enjoy exercise training to
290 improve cardiovascular health.

291

292 **Limitations**

293 Presence of recall bias regarding exercise history of the participants is a potential study limitation. To
294 minimize this error, we did not elucidate our study hypothesis to the study participants.³⁰ Moreover, the
295 time span of exercise history was similar between the three groups and it is likely that recall bias was
296 similar across groups. This study was cross-sectional by design and is subject to the inherent limitations
297 of that approach. It is likely that over the last 20 years, lifestyle habits have changed, and this might
298 have influenced the risk for a myocardial infarction (*e.g.*, smoking or dietary habits). To avoid such
299 concerns, a longitudinal study design is preferred, but such a study would take too much time for
300 observations and tests. Ethical concerns would emerge during a longitudinal study design, because
301 individuals clearly at risk for myocardial infarction will receive preventative measures. These

302 individuals may not endure a myocardial infarction and will have no cardiac damage. Consequently, it
303 would be impossible to study the protective effects of lifelong exercise training against pathological LV
304 remodelling after the myocardial infarction. Therefore, we used the cross-sectional approach, coupled
305 with great effort to minimize bias. We could not retrieve information about other clinical markers (e.g.
306 LVEF) than the reported cardiac enzyme markers, which may have limited the comparison of infarct
307 size between post-MI groups. Although previous studies demonstrated that the cardiac enzyme markers
308 reported in this study are related to infarct size,³¹⁻³³ LVEF directly after the myocardial infarction would
309 have improved the comparison between post-MI groups. Unfortunately, these values could not be
310 provided by the different hospitals of the patients that were included in the present study. Finally, it is
311 important to keep in mind that of these results were generated from a relative small study population
312 and future work needs to confirm our findings in a large sample size. Nonetheless, we believe that this
313 study is a first step to confirm animal data that demonstrate that exercise may attenuate the deleterious
314 effects of MI

315

316 **CONCLUSIONS**

317 ATH+MI had a better LV systolic function compared to SED+MI and a similar LV systolic function
318 compared to ATH. SED+MI had a lower LVEF and circumferential wall strain compared to SED. These
319 findings suggest that lifelong exercise training may protect against the deleterious effects of a
320 myocardial infarction and/or minimizes the effects of pathological LV remodelling after a myocardial
321 infarction in veteran athletes.

322 **Conflicts of interest**

323 The authors MM, GS, AvD, and MH declare that they have no conflict of interest that are directly
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326

327 **Authorship**

328 MM, TE, AD, MH contributed to the conception or design of the work. All authors contributed to the
329 acquisition, analysis, and/or interpretation of data for the work. MM and TE drafted the manuscript. GS,
330 AD, MH critically revised the manuscript. All gave final approval and agreed to be accountable for all
331 aspects of work ensuring integrity and accuracy.

332

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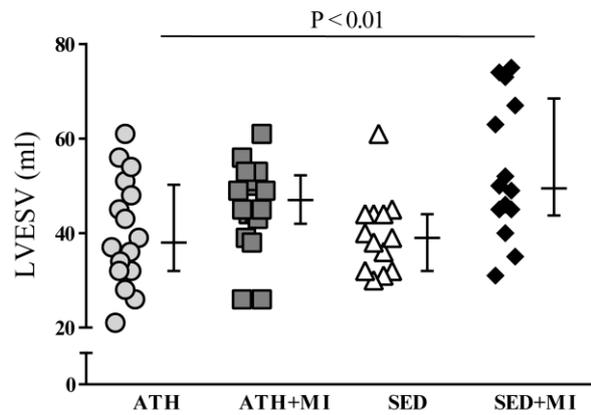
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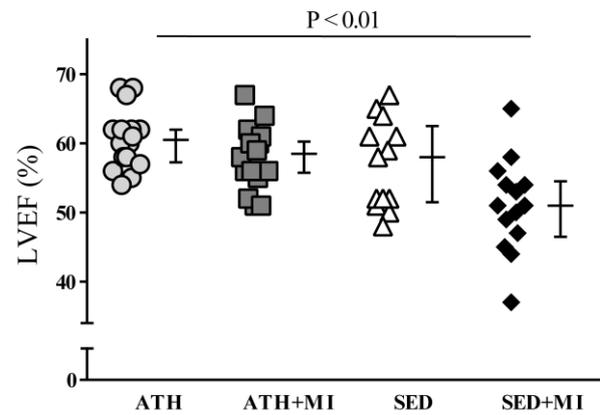
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419

420 **FIGURE LEGENDS**

A. LV End systolic volume



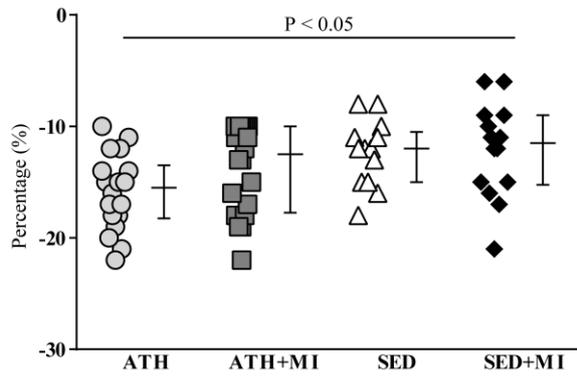
B. LV ejection fraction



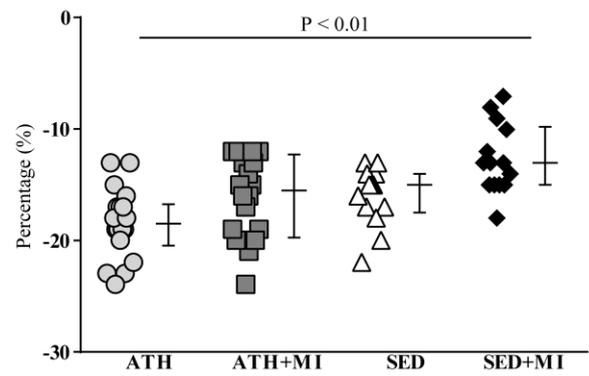
425 **Figure. 1** Individual and average values of A) left ventricular end systolic volume (LVESV) and B) left ventricular
426 ejection fraction (LVEF) of the veteran athletes (ATH, circles), veteran post-MI athletes (ATH+MI, squares),
427 sedentary controls (SED, triangles), and sedentary post-MI controls (SED+MI, diamonds). LVESV was
428 significantly lower in ATH and SED compared to SED+MI ($P < 0.01$), but did not differ compared to ATH+MI
($P > 0.10$). LVEF was significantly higher in ATH, ATH+MI, and SED compared to SED+MI ($P < 0.01$). Group
averages are reported as median and interquartile range.

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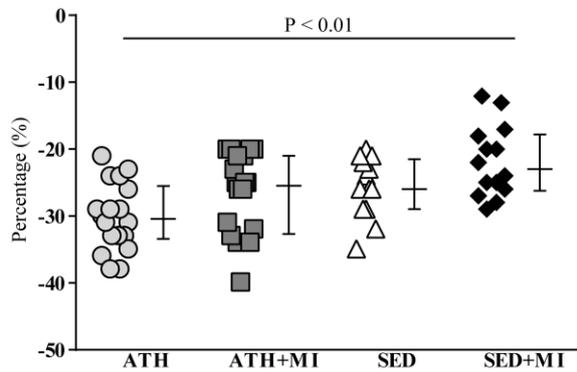
A. Longitudinal strain



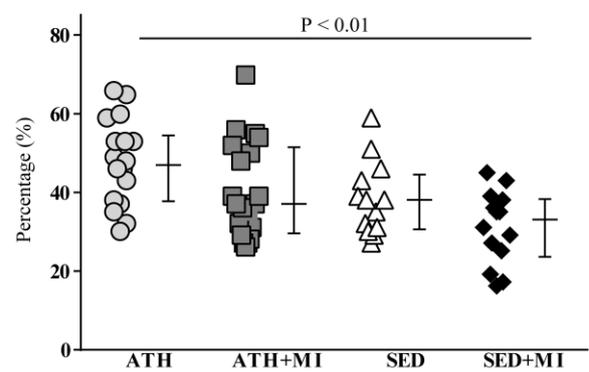
B. Circumferential strain



C. Area strain



D. Radial strain



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431

432 **Figure. 2** Individual and average values of A) LV longitudinal strain, B) circumferential strain, C) area strain, and

433 D) radial strain of the of the veteran athletes (ATH, circles), veteran post-MI athletes (ATH+MI, squares),

434 sedentary controls (SED, triangles), and sedentary post-MI controls (SED+MI, diamonds). LV longitudinal strain

435 did not differ between ATH+MI, SED, and SED+MI, but LV longitudinal strain was superior (*i.e.*, more negative

436 strain) in ATH compared to SED+MI. LV circumferential strain was superior in ATH, ATH+MI, and SED

437 compared to SED+MI. LV area strain was superior in ATH and ATH+MI compared to SED+MI, whereas LV area

438 strain did not differ between SED and the other three groups. LV radial strain did not differ between ATH+MI,

439 SED, and SED+MI, but LV radial strain was superior in ATH compared to SED+MI. Group averages are reported

440 as median and interquartile range.

441

Table 1. Participants' characteristics of the veteran athletes (ATH, $n=18$), veteran post-MI athletes (ATH+MI, $n=20$), sedentary controls (SED, $n=13$) and sedentary post-MI controls (SED+MI, $n=14$). P-value refers to a one-way ANOVA, (*) Kruskal-Wallis test, or (¥) Mann-Whitney-U test.

| <i>n</i> | ATH | ATH+MI | SED | SED+MI | <i>p</i> |
|--|------------------|-----------------------|-------------------------------|-------------------------------|----------|
| CHARACTERISTICS | | | | | |
| Age (years) | 61±7 | 60±6 | 58±7 | 61±6 | 0.67 |
| Height (cm) | 178±8 | 176±5 | 181±5 | 176±5 | 0.09 |
| Body mass (kg) | 74±8 | 77±7 | 88±9 ^{1,2} | 83±14 | <0.01 |
| Body Mass Index (kg/m ²) * | 23.3 (20.6-25.3) | 24.5 (23.9-26.0) | 26.9 (25.4-27.4) ¹ | 26.6 (22.5-28.8) ¹ | <0.01 |
| Body Surface Area (m ²) | 1.91±0.13 | 1.93±0.11 | 2.09±0.10 ^{1,2} | 1.99±0.18 | <0.01 |
| Mean arterial pressure (mmHg) * | 98 (89-108) | 95 (93-100) | 105 (94-109) | 92 (89-97) | 0.14 |
| Diastolic blood pressure (mmHg) | 82 (76-90) | 77 (74-81) | 88 (82-92) | 77 (73-82) | 0.06 |
| Systolic blood pressure (mmHg) | 130 (120-142) | 131 (126-142) | 137 (124-145) | 124 (118-132) | 0.22 |
| Resting heart rate (beats/min) * | 50 (48-55) | 57 (53-62) | 61 (54-71) ¹ | 59 (56-60) ¹ | <0.01 |
| Ever smoked (yes <i>n</i>) | 10 (56%) | 12 (60%) | 11 (85%) | 10 (71%) | 0.34 |
| Positive family history (yes <i>n</i>) | 9 (50%) | 15 (75%) | 6 (46%) | 11 (79%) | 0.13 |
| LIFELONG PHYSICAL ACTIVITY PATTERNS | | | | | |
| Exercise time | | | | | |
| Average (hours/week) * | 7.1 (5.8-11.9) | 5.7 (4.9-9.4) | 0.1 (0.0-0.9) ^{1,2} | 0.1 (0.0-0.4) ^{1,2} | <0.001 |
| Pre-MI (hours/week) ¥ | | 5.7 (4.6-8.6) | | 0.2 (0.1-1.1) | <0.001 |
| Post-MI (hours/week) ¥ | | 6.2 (5.3-10.3) | | 0.0 (0.0-0.6) | <0.001 |
| Exercise dose | | | | | |
| Average (MET-hours/week) * | 60 (47-110) | 51 (40-93) | 1 (0-6) ^{1,2} | 0 (0-3) ^{1,2} | <0.001 |
| Pre-MI (MET-hours/week) ¥ | | 49 (35-84) | | 1 (0-4) | <0.001 |
| Post-MI (MET-hours/week) ¥ | | 56 (43-93) | | 0 (0-4) | <0.001 |
| INCREMENTAL MAXIMAL CYCLING TEST | | | | | |
| VO ₂ peak (mL/min/kg) | 48.0±8.9 | 40.9±5.5 ¹ | 31.6±4.8 ^{1,2} | 29.7±6.5 ^{1,2} | <0.01 |
| % VO ₂ peak predicted (%) | 164±22 | 143±16 ¹ | 115±19 ^{1,2} | 111±22 ^{1,2} | <0.01 |
| Power Output (Watt) | 319±58 | 274±40 ¹ | 213±48 ^{1,2} | 188±43 ^{1,2} | <0.01 |
| Maximal heart rate (beats/min) | 165±13 | 164±15 | 168±15 | 147±20 ^{1,2,3} | <0.01 |
| Anaerobic threshold (Watt) | 224±63 | 200±44 | 145±41 ^{1,2} | 134±56 ^{1,2} | <0.01 |
| Respiratory Exchange Ratio (VCO ₂ / VO ₂) | 1.14±0.06 | 1.12±0.08 | 1.10±0.07 | 1.11±0.10 | 0.56 |
| Lactate (mmol/L) * | 11.6 (8.9-12.3) | 10.5 (9.2-11.2) | 11.3 (10.8-12.4) | 11.4 (9.9-12.4) | 0.28 |
| FASTING BLOOD LEVELS | | | | | |
| HbA1c (mmol/mol) * | 35.5 (34.4-39.4) | 36.6 (35.5-37.7) | 37.2 (35.5-38.8) | 37.7 (36.1-39.4) | 0.18 |
| Cholesterol (mmol/L) | 5.4±0.8 | 4.5±0.9 ¹ | 6.0±0.9 ² | 4.2±0.7 ^{1,3} | <0.01 |
| HDL (mmol/L) | 1.8±0.3 | 1.6±0.4 | 1.4±0.3 ¹ | 1.4±0.2 ¹ | <0.01 |
| LDL (mmol/L) | 3.3±0.8 | 2.6±0.8 ¹ | 4.1±0.7 ^{1,2} | 2.3±0.6 ^{1,3} | <0.01 |
| Triglycerides (mmol/L) * | 0.9 (0.7-1.3) | 0.9 (0.8-1.1) | 1.3 (1.0-2.2) ¹ | 1.2 (0.9-1.9) | <0.01 |
| Glucose (mmol/L) * | 4.6 (4.3-5.0) | 4.6 (4.5-5.0) | 4.7 (4.4-5.0) | 4.7 (4.3-5.0) | 0.79 |

MET: Metabolic Equivalent of Task; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; LDL: low-density lipoprotein.

¹Significant different from ATH; ²Significant different from ATH+MI; ³Significant different from SED.

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Table 2. Cardiac medical history data of the veteran post-MI athletes (ATH+MI, $n=20$) and sedentary post-MI controls (SED+MI, $n=14$). P-value refers to a (¥) *Mann-Whitney U* or *Fisher's exact* test (two-sided).

| | ATH+MI | | SED+MI | | <i>p</i> -value |
|-------------------------------------|----------|----------------|-----------|------------------|-----------------|
| Post-MI time (years) | 5 (3-10) | | 7 (4-10) | | 0.73 |
| ENZYME MARKERS* | | | | | |
| Troponin-I (µg/L) (median [IQR]) ¥ | $n=10$ | 7.5 (1.1-24.2) | $n=7$ | 17.9 (4.2-100.0) | 0.23 |
| CK (u/L) (median [IQR]) ¥ | $n=17$ | 775 (251-2029) | $n=14$ | 522 (399-2222) | 0.45 |
| CREAT (umol/L) (median [IQR]) ¥ | $n=14$ | 87 (78-103) | $n=13$ | 89 (71-97) | 0.49 |
| AST (u/L) (median [IQR]) ¥ | $n=14$ | 38 (26-135) | $n=12$ | 75 (35-117) | 0.44 |
| LDH (u/L) (median [IQR]) ¥ | $n=13$ | 407 (335-638) | $n=11$ | 382 (176-520) | 0.14 |
| INFARCT LOCATION | | | | | |
| Anterior (n) | 7 (35%) | | 8 (57%) | | 0.30 |
| Inferior (n) | 7 (35%) | | 5 (36%) | | 1.00 |
| Non-STEMI (n) | 6 (30%) | | 1 (7%) | | 0.20 |
| TREATMENT* | | | | | |
| PCI (n [%]) | 18 (95%) | | 12 (92%) | | 1.00 |
| Thrombolytic therapy (n [%]) | 1 (5%) | | 1 (8%) | | |
| CARDIAC REHABILITATION | | | | | |
| Cardiac rehabilitation (n [%]) | 13 (65%) | | 11 (79%) | | 0.47 |
| POST-MI INCIDENTS | | | | | |
| Elective PCI (n) | 0 (0%) | | 4 (29%) | | 0.022 |
| Recurrent myocardial infarction (n) | 0 (0%) | | 1 (7%) | | 0.41 |
| MEDICATION | | | | | |
| Anticoagulant (n) | 19 (95%) | | 14 (100%) | | 1.00 |
| Anti-platelet (n) | 18 (90%) | | 12 (86%) | | 1.00 |
| Vitamin K antagonist (n) | 1 (5%) | | 2 (14%) | | 0.56 |
| Antihypertensives (n) | 14 (70%) | | 13 (93%) | | 0.20 |
| ACE-inhibitor (n) | 5 (25%) | | 9 (64%) | | 0.035 |
| AT2-antagonist (n) | 3 (15%) | | 3 (21%) | | 0.67 |
| Beta-blocker (n) | 8 (40%) | | 10 (71%) | | 0.09 |
| Diuretic (n) | 1 (5%) | | 3 (21%) | | 0.28 |
| CCB (n) | 1 (5%) | | 0 (0%) | | 1.00 |
| Antihyperlipidemic agents (n) | 16 (80%) | | 14 (100%) | | 0.13 |
| Statins (n) | 16 (80%) | | 14 (100%) | | 0.13 |

*Based on a sub sample; hospital data were not available

MI: myocardial infarction; PCI: Percutaneous coronary intervention; CK: Creatine kinase; CREAT: Creatinine; ASAT: Aspartate transaminase; LDH: Lactate dehydrogenase; NON-STEMI: non-ST elevation myocardial infarction; ACE: angiotensin converting enzyme; AT: angiotensin; CCB: calcium channel blocker.

Table 3. Left ventricular systolic and diastolic function of the veteran athletes (ATH, *n*=18), veteran post-MI athletes (ATH+MI, *n*=20), sedentary controls (SED, *n*=13) and sedentary post-MI controls (SED+MI, *n*=14). P-value refers to a one-way ANOVA or (*) Kruskal-Wallis test.

| | ATH | ATH+MI | SED | SED+MI | <i>p</i> |
|---------------------------------------|------------------|------------------|-------------------------|-------------------------|----------|
| SYSTOLIC FUNCTION | | | | | |
| Stroke volume (mL) * | 83 (73-102) | 82 (68-97) | 71 (60-79) ¹ | 68 (57-82) ¹ | 0.045 |
| Cardiac output (L/min) * | 4.3 (3.7-5.8) | 4.7 (3.9-5.5) | 4.4 (4.1-6.1) | 3.6 (3.4-5.1) | 0.45 |
| Cardiac index (L/min/m ²) | 2.1 (1.9-2.7) | 2.4 (2.1-2.8) | 2.2 (1.9-2.8) | 1.9 (1.7-2.8) | 0.33 |
| s' velocity (cm/s) | 9.3±1.9 | 8.8±1.7 | 9.0±1.4 | 8.4±2.0 | 0.52 |
| DIASTOLIC FUNCTION | | | | | |
| LVEDV (mL) | 101±24 | 109±18 | 92±15 | 107±22 | 0.14 |
| E (m/s) | 63.0±11.9 | 62.9±16.3 | 62.7±15.7 | 68.9±15.0 | 0.61 |
| A (m/s) | 58 (46-71) | 59 (52-75) | 69 (54-81) | 70 (64-81) | 0.07 |
| E/A ratio | 1.10 (0.86-1.29) | 0.95 (0.80-1.27) | 0.92 (0.71-1.18) | 0.92 (0.80-1.05) | 0.51 |
| e' LV (cm/s) | 11.7 (9.7-13.3) | 9.3 (8.0-10.5) | 9.0 (7.3-10.5) | 10.3 (7.5-12.1) | 0.10 |
| a' LV (cm/s) | 11.3±2.5 | 10.4±1.7 | 11.2±2.0 | 10.4±1.2 | 0.41 |
| E/e' | 5.9 (5.0-6.5) | 6.4 (5.6-8.5) | 7.5 (6.1-8.7) | 6.7 (6.2-7.8) | 0.11 |

s' velocity: peak systolic annular tissue velocity; LVEDV: left ventricular end-diastolic volume; E: peak flow velocity of the early rapid filling wave at the mitral leaflet tips; A: peak flow velocity of the late filling wave at the mitral leaflet tips; e' LV: peak annular tissue velocity during early filling; a': peak annular tissue velocity during late diastolic atrial contraction; E/e': ratio of peak E velocity with e'. ¹Significant different from ATH.

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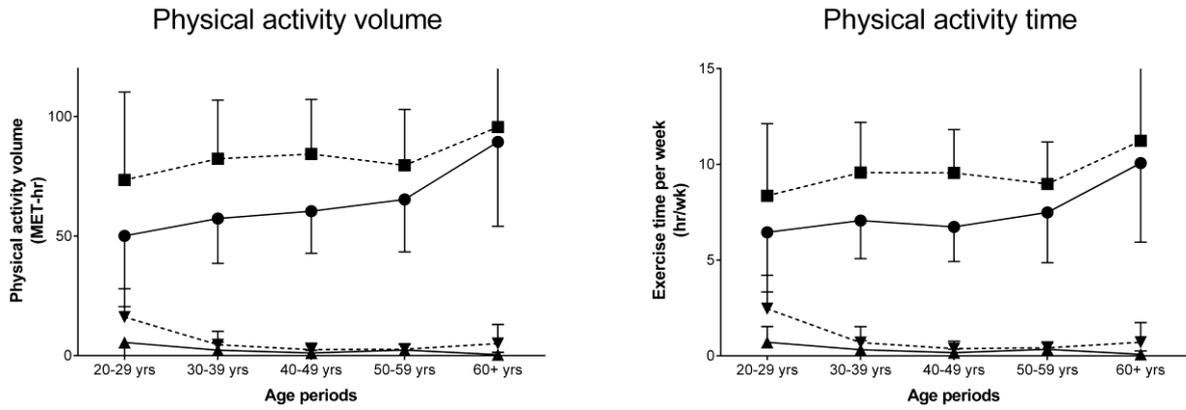
Supplementary Table 1. Correlation analysis between physical activity dose of the five different age periods and cardiac function parameters.

| Parameter | | EF% | GLS | GCS | AS | GRS |
|------------------|----------|------------|------------|------------|-----------|------------|
| P1 20-29 yrs | <i>r</i> | 0.33** | -0.24 | -0.30* | -0.28* | 0.25* |
| | <i>n</i> | 61 | 65 | 65 | 65 | 65 |
| P2 30-39 yrs | <i>r</i> | 0.41** | -0.34** | -0.36** | -0.36** | 0.33** |
| | <i>n</i> | 61 | 65 | 65 | 65 | 65 |
| P3 40-49 yrs | <i>r</i> | 0.44** | -0.39** | -0.37** | -0.40** | 0.36** |
| | <i>n</i> | 61 | 65 | 65 | 65 | 65 |
| P4 50-59 yrs | <i>r</i> | 0.51** | -0.42** | -0.34** | -0.41** | 0.39** |
| | <i>n</i> | 59 | 62 | 62 | 62 | 62 |
| P5 60+ yrs | <i>r</i> | 0.42** | -0.37* | -0.30 | -0.36* | 0.32* |
| | <i>n</i> | 38 | 38 | 38 | 38 | 38 |

***.* Correlation is significant at the 0.01 level (2-tailed).

**.* Correlation is significant at the 0.05 level (2-tailed).

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Supplementary Figure 1. Physical activity dose of the different age periods for ATH, ATH-MI, SED, and SED-MI. Athletes were more physically active throughout their life than the sedentary group and tended to increase their physical activity across their life. The sedentary groups tended to decrease their physical activity after their 30s.

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