



## LJMU Research Online

**Cirer-Sastre, R, Legaz-Arrese, A, Corbi, F, George, KP, Nie, J, Carranza-García, LE and Reverter-Masià, J**

**Cardiac Biomarker Release After Exercise in Healthy Children and Adolescents: A Systematic Review and Meta-Analysis.**

<http://researchonline.ljmu.ac.uk/id/eprint/9464/>

### Article

**Citation** (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

**Cirer-Sastre, R, Legaz-Arrese, A, Corbi, F, George, KP, Nie, J, Carranza-García, LE and Reverter-Masià, J (2018) Cardiac Biomarker Release After Exercise in Healthy Children and Adolescents: A Systematic Review and Meta-Analysis. Pediatric Exercise Science. ISSN 1543-2920**

LJMU has developed [LJMU Research Online](http://researchonline.ljmu.ac.uk/) for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact [researchonline@ljmu.ac.uk](mailto:researchonline@ljmu.ac.uk)

<http://researchonline.ljmu.ac.uk/>

1           **Cardiac Biomarker Release after Exercise in Healthy Children and**  
2           **Adolescents: A Systematic Review and Meta-analysis**

3   **Running head:** Cardiac biomarkers after exercise in youth

#### 4 **Abstract**

5 **Purpose:** We evaluated the impact of acute exercise and 24 h recovery on serum  
6 concentration of cardiac troponins (cTnT; cTnI) and NT-proBNP in healthy children  
7 and adolescents. We also determined the proportion of participants exceeding the upper  
8 reference limits (URL) and acute myocardial infarction (AMI) cut-off for each assay.

9 **Method:** Web of Science, SPORTDiscus, MEDLINE, ScienceDirect and Scopus  
10 databases were systematically searched up to November 2017. Studies were screened,  
11 quality-assessed and data was systematically extracted and analyzed. **Results:** From 751  
12 studies initially identified, 14 met the inclusion criteria for data extraction. All three  
13 biomarkers were increased significantly after exercise. A decrease from post-exercise to  
14 24 h was noted in cTnT and cTnI, although this decrease was only statistically  
15 significant for cTnT. The URL was exceeded by a 76% of participants for cTnT, a 51%  
16 for cTnI and a 13% for NT-proBNP. Furthermore, the cut-off value for AMI was  
17 exceeded by 39% for cTnT and a 11% for cTnI. Post exercise peak values of cTnT were  
18 associated with duration and intensity ( $Q_{(3)} = 28.3, P < .001$ ) while NT-proBNP peak  
19 values were associated with duration ( $Q_{(2)} = 11.9, P = .003$ ). **Conclusion:** Exercise  
20 results in the appearance of elevated levels of cTnT, cTnI and NT-proBNP in children  
21 and adolescents. Post-exercise elevations of cTnT and NT-proBNP are associated with  
22 exercise characteristics.

23

24

25

26

## 27 **Background**

28 Cardiac troponin T and I (cTnT and cTnI) are accepted indicators of myocyte necrosis  
29 and are considered sensitive markers of acute myocardial injury (MI) and infarction  
30 (AMI) (75). Serum cTnT and cTnI are elevated after irreversible heart muscle damage  
31 and levels peak during the subsequent days (1,60). The N-terminal fragment of the  
32 prohormone brain natriuretic peptide (NT-proBNP) is a marker accepted to reflect  
33 myocardial stretch (74), which is currently used to detect heart failure and  
34 asymptomatic left ventricular dysfunction (14,53) with the magnitude and duration of  
35 release dependent on the severity of stretch and stress (3).

36 The lower detection limits of cTnT and cTnI assays have been greatly reduced in recent  
37 years (59) with new high sensitivity assays available for both biomarkers. These assays  
38 can detect the 99<sup>th</sup> percentile with a CV < 10% and measure cTn concentrations in at  
39 least a 50% of a healthy population at rest (59). Although the higher sensitivity of these  
40 assays enables better rates of true positive detection (40), a decline in specificity has  
41 been reported such that cTn appearance might be related to etiologies other than AMI  
42 (1,16,40). This can include physical exercise as a known non-pathological cause of cTn  
43 increase (1).

44 Numerous investigations have described the serological release of cTnT, cTnI and NT-  
45 proBNP after physical exercise and its kinetics (15,22,63). Contrary to an AMI-related  
46 release, cTn values normally peak within 2-5 h (cTnT) and 3-6 h (cTnI) post-exercise  
47 and then decrease returning to basal levels after 24 h of recovery in most participants  
48 (15,25). The differences between cTnT and cTnI peaks might be related to differences  
49 in their molecular weights (11). NT-proBNP release normally peaks immediately after  
50 exercise and remains elevated during the subsequent 72 h; and its clearance, that seems  
51 to take longer than cTn, has been related to a temporary reduction in kidney function

52 subsequent to exercise (9,11). These observations have important clinical implications,  
53 since the elevation of these cardiac biomarkers for several hours after physical exercise  
54 might be misinterpreted in physically active patients, admitted to the emergency  
55 department for chest pain of origins other than acute coronary syndrome and heart  
56 failure.

57 The 99<sup>th</sup> percentile of a normal reference population, considered the upper reference  
58 limit (URL), is designated as the decision level for the diagnosis of MI for both general  
59 and paediatrics populations (34,75). In this respect, the reported 99<sup>th</sup> percentiles for  
60 children are lower than in adults for cTn and NT-proBNP (17,26,50), and both are used  
61 for clinical diagnostic (24). The magnitude of cTn and NT-proBNP post-exercise  
62 release, as well as the prevalence of data above clinical cut-offs have been extensively  
63 studied in healthy adults. Only a limited number of studies addressing the cardiac  
64 biomarker response to exercise in children and adolescents are currently available.  
65 Moreover, these studies are heterogeneous in terms of exercise exposure and often  
66 occur with small sample sizes and thus a limited statistical power. As a result, the  
67 association of cTn and NT-proBNP with exercise is currently controversial  
68 (7,29,44,52,61,65,67,69) and might be confounded with either individual as well as  
69 exercise characteristics.

70 Based on studies with adult participants other individual characteristics, other than age,  
71 might influence cardiac biomarkers release. Sex differences in cTn and NT-proBNP are  
72 controversial (4,6,10,23,30,36,56,80). Previous exercise experience has been negatively  
73 associated with cTn release (10,21,47,76) while training load might be not associated  
74 with biomarker appearance (18,21,28,33,68,79). NT-proBNP is not associated with  
75 previous exercise experience either (62,68,77) while its association with training load  
76 remains controversial (18,28,43,61,62,64,65,68). Finally, fitness condition has not been

77 associated with cTn or NT-proBNP data (68,70). Exercise characteristics have also been  
78 studied as to their influence on cardiac biomarker release (15,71). Exercise intensity was  
79 mentioned as a predictor for cTn release while exercise duration has been correlated  
80 with both cTn and NT-proBNP data (8,9,12,64,68,83). Exercise mode and type have not  
81 been fully evaluated and any associations remain controversial (31,55,85).

82 Previous systematic reviews and meta-analyses related to cardiac biomarker release  
83 after exercise have been focused on adult participants (15,66,71,82). To the best our  
84 knowledge no systematic review or meta-analysis has been published addressing the  
85 cardiac biomarkers response to exercise in children and adolescents. Considering that  
86 children and adolescents have a low cardiovascular risk (2), we selected this special  
87 group in order to get a “clean” background and preclude the potential effects of  
88 concealed cardiovascular diseases and get "pure" effect of exercise on cardiac  
89 biomarkers. Due to variations in sample size and the diversity of participant and  
90 exercise characteristics a systematic review with a meta-analysis could contribute to the  
91 current knowledge by synthesizing available data into single, more powerful estimates  
92 of effect. Moreover, secondary analysis might help to identify possible associations with  
93 individual and exercise characteristics that could explain a certain degree of  
94 heterogeneity between the current findings.

95 In accordance with the PRISMA statement (41) the main objective of this study was to  
96 systematically review studies whose participants were healthy children and adolescents  
97 that were exposed to physical exercise and whose resting and post-exercise measures of  
98 cTnT, cTnI and NT-proBNP were described. A secondary objective was to analyse the  
99 moderator effects of a) age, b) pubertal status, c) sex, d) previous training (years), e)  
100 current training (h/week or km/week), f) exercise duration (minutes), g) exercise

101 intensity (average HR), h) maximum oxygen uptake (VO<sub>2</sub>max), and i) exercise mode on  
102 the pooled effects determined by the main objective.

### 103 **Methods**

#### 104 **Search strategy**

105 We searched Web of Science, SPORTDiscus, MEDLINE, ScienceDirect and Scopus  
106 databases between July 1, 2017 and November 30, 2017. A three-component additive  
107 search key (*#A AND #B AND #C*) was used with: #A, measurement; #B, intervention;  
108 and #C, population. All searches were restricted to title or abstract, and keywords were  
109 stated in English. Measurement was defined with the expression "*cardiac biomarker\**"  
110 *OR Troponin OR TnT OR TnI OR cTn\* OR hs-cTn\* OR "N-terminal prohormone of*  
111 *brain natriuretic peptide" OR "NT-proBNP" OR "NT-pro-BNP"*. Intervention was  
112 specified with: *exercise OR sport\* OR "physical activity" OR running OR marathon*  
113 *OR soccer OR swim\* OR athletes*. Finally, population was stated with "*children OR*  
114 *adolescent\* OR young*".

#### 115 **Inclusion and exclusion criteria**

116 We selected observational or experimental studies with a repeated measures design.  
117 Participants (or a subset of them) must be under the age of 18, not have personal history  
118 or clinical evidences of cardiovascular disease and have a normal 12-lead  
119 electrocardiogram and/or echocardiogram at rest (72). Interventions of interest were  
120 those which involved exposure to physical exercise, including sport events and  
121 laboratory tests. We searched primarily for studies that reported serum cardiac  
122 biomarkers responses to exercise. Specifically, those which reported cTnT and/or cTnI  
123 and/or NT-proBNP before and after exercise. Inclusion criteria included the necessity to  
124 report some quantitative measure of location and variation (mean with standard  
125 deviation (sd); median with range; or median with inter quartile range) of the

126 biomarker's value for a minimum of one time point post-intervention. Studies where  
127 participants were exposed to specific pharmacological or nutritional interventions were  
128 excluded and the remaining articles were included in our review.

#### 129 **Data extraction**

130 Studies were inspected to gather the data for (where available): sample size, sex,  
131 maturational status, age, training status (years of previous experience, weekly hours of  
132 training, weekly km of training), VO<sub>2</sub> max, performed exercise, exposure duration  
133 (minutes), average heart rate (surrogate of intensity) and absolute concentration of  
134 cTnT, cTnI or NT-proBNP before and after exercise. We also recorded the proportion  
135 of participants above the URL for each biomarker, and rate of participants above the  
136 cut-off for AMI for cTnT and cTnI. Outcomes reported as median [range] were  
137 transformed to mean (SD) using Wan et al.'s formulas (84). All concentrations were  
138 expressed in ng/L (75), and concentrations of cTn reported as "under limits of detection  
139 of 10 ng/L" were represented as 5 ng/L (12,48).

#### 140 **Quality assessment**

141 We analysed the methodological quality of studies that met all inclusion criteria in order  
142 to detect possible methodological discrepancies that might explain a degree of  
143 heterogeneity between studies. In this sense, studies' quality was assessed by two  
144 authors independently, filling the Quality Assessment Tool for before-after (Pre-Post)  
145 studies with no control group from the National Heart Lung and Blood Institute (42).  
146 This scale considers 12 binary items, which average scores each article from 0  
147 indicating *high risk of bias*, to 1 indicating *low risk of bias* (QAT<sub>i</sub>). Discrepancies  
148 between assessors were resolved by a third author.



## 149 **Statistical analysis**

150 All analyses were performed in R (54) using Viechtbauer's "metafor" package (81).  
151 Random effects meta-analyses were conducted by biomarker (cTnT, cTnI and NT-  
152 proBNP) using the following estimates: the baseline concentration, the peak  
153 concentration, the concentration at 24 h, the absolute mean difference between baseline  
154 and peak concentrations, the absolute mean difference between baseline and  
155 concentration after 24 h recovery, the absolute mean difference between peak  
156 concentrations and concentrations at 24 h post exercise, the rate of participants whose  
157 peak concentration exceeded the assay URL and the rate of participants exceeding the  
158 cut-off for AMI. Rates were log-transformed for statistical comparisons and estimates  
159 were then back transformed for ease of interpretation. Heterogeneity was measured with  
160 Cochrane's  $Q$  statistic and  $I^2$  values (19). We assessed publication bias using Egger's  
161 regression test for funnel plot asymmetry (5,57). Subgroup analyses were conducted  
162 when heterogeneity was significant to assess the possible influence of exercise mode,  
163 age, intensity and duration on the absolute mean difference between baseline and peak  
164 concentrations. In addition, when data was available, we investigated for the possible  
165 influence of Tanner stage, sex,  $VO_{2max}$ , years of previous training, weekly hours of  
166 training and weekly km of training, regardless of exercise mode, age, intensity and  
167 duration. Outcome multiplicity from the same groups (12) was controlled introducing a  
168 study identification as a random effect (51,81). Measures are expressed as mean  $\pm$  95%  
169 confidence intervals (CI) unless otherwise stated and we considered statistically  
170 significant differences when  $P < .05$ .

## 171 **Results**

172 The search process appears outlined in Figure 1. Fourteen studies met the  
173 inclusion/exclusion criteria that included 21 groups covering a total sample of 336

174 participants (72 females) who had a mean age of  $15.1 \pm 2.3$  years (12,13,49,76–  
175 78,20,27,30,38,39,46–48). Two studies provided complete data from more than one  
176 subgroups contributing with different estimates by sex (27,78) or Tanner stage (30),  
177 which were treated as different units for the analysis. One study provided four outcome  
178 measurements from the same group at different exposures (12), which were controlled  
179 for multiplicity within the models (51,81). Interventions were based on five different  
180 modalities: in nine studies participants ran [three treadmill protocols (45 to 90 min)  
181 (13,46,77), five half marathons (12,27,47,48,76) and one full marathon (78)], in two  
182 studies basketball was employed (38,49), in one a soccer match (20), in one study  
183 participants swam for 60 min (30) and one included a set of table tennis exercises (39).  
184 Table 1 shows the number of groups available for each comparison ( $k$ ) as well as their  
185 respective pooled effect sizes.

186 **\*\*Figure 1\*\***

187 Figure 1. Flowchart for study inclusion and exclusion stages.

188

189 Table 1. Estimated pooled effect sizes (95% CI) by biomarker.

|                           | <b>K</b> | <b>Pooled Effect Size</b> | <b>Z</b> | <b>p(z)</b> | <b>Q</b> | <b>p(Q)</b> | <b>I<sup>2</sup></b> |
|---------------------------|----------|---------------------------|----------|-------------|----------|-------------|----------------------|
| <b>Cardiac Troponin T</b> |          |                           |          |             |          |             |                      |
| Mean baseline (ng/L)      | 16       | 5 (4, 6)                  | 11.84    | < .001      | 206.47   | < .001      | 98.7%                |
| Mean peak (ng/L)          | 14       | 144 (83, 205)             | 4.65     | < .001      | 105.78   | < .001      | 96.5%                |
| Mean at 24 h (ng/L)       | 9        | 11 (5, 16)                | 3.86     | < .001      | 146.52   | < .001      | 98.2%                |
| Dif. Peak - Pre (ng/L)    | 14       | 139 (79, 198)             | 4.53     | < .001      | 102.72   | < .001      | 96.4%                |
| Dif. 24 h - Peak (ng/L)   | 7        | -89 (-147, -32)           | -3.04    | .002        | 33.85    | < .001      | 93%                  |
| Dif. 24 h - Pre (ng/L)    | 9        | 7 (1, 12)                 | 2.5      | .01         | 87.22    | < .001      | 96.3%                |
| MI threshold IR           | 18       | .76 (.66, .87)            | -3.83    | < .001      | 27.86    | .047        | 13.5%                |
| AMI threshold IR          | 14       | .39 (.26, .6)             | -4.38    | < .001      | 39.1     | < .001      | 75.4%                |
| <b>Cardiac Troponin I</b> |          |                           |          |             |          |             |                      |
| Mean baseline (ng/L)      | 7        | 16 (10, 22)               | 5.15     | < .001      | 89.67    | < .001      | 96.4%                |
| Mean peak (ng/L)          | 5        | 248 (17, 478)             | 2.1      | .04         | 61.42    | < .001      | 99 %                 |
| Mean at 24 h (ng/L)       | 7        | 38 (19, 56)               | 4.05     | < .001      | 348.01   | < .001      | 97.7%                |
| Dif. Peak - Pre (ng/L)    | 5        | 228 (6, 450)              | 2.01     | .04         | 54.53    | < .001      | 98.9%                |
| Dif. 24 h - Peak (ng/L)   | 5        | -199 (-404, 5)            | -1.91    | .06         | 42.56    | < .001      | 98.2%                |
| Dif. 24 h - Pre (ng/L)    | 7        | 21 (8, 33)                | 3.23     | .001        | 100.97   | < .001      | 93.2%                |
| MI threshold IR           | 7        | .51 (.32, .81)            | -2.85    | .004        | 16.74    | .01         | 60.5%                |
| AMI threshold IR          | 4        | .11 (.05, .24)            | -5.4     | < .001      | 3.41     | .33         | 24.4%                |
| <b>NT-proBNP</b>          |          |                           |          |             |          |             |                      |
| Mean baseline (ng/L)      | 6        | 77 (14, 140)              | 2.38     | .02         | 217.98   | < .001      | 99.5%                |
| Mean peak (ng/L)          | 6        | 106 (17, 195)             | 2.34     | .02         | 288.19   | < .001      | 99.5%                |
| Mean at 24 h (ng/L)       | 4        | 83 (0*, 182)              | 1.63     | .10         | 173.89   | < .001      | 99.6%                |
| Dif. Peak - Pre (ng/L)    | 6        | 20 (2, 38)                | 2.20     | .03         | 13.64    | .02         | 79.2%                |
| Dif. 24 h - Peak (ng/L)   | 4        | -2 (-11, 7)               | -0.48    | .63         | 7.26     | .06         | 0.1%                 |
| Dif. 24 h - Pre (ng/L)    | 4        | 4 (-8, 28)                | 1.55     | .44         | 0.65     | .88         | 0%                   |
| MI threshold IR           | 6        | .13 (.04, .44)            | -3.32    | < .001      | 18.02    | .003        | 74.1%                |

190 Note: Estimated effects for Incidence Rates (IR) were back transformed for easier interpretation.

191 \* Mathematically negative and truncated to 0 avoiding values outside the parameter space.

## 192 **Quality assessment and risk of publication bias**

193 Studies had a mean quality score of .61 (SD = .07). Pre-specification of sample  
194 eligibility criteria, enrollment of all eligible participants and sample size calculation  
195 were rated as *high risks of bias* in all studies. Other concurrent items rated as *high risk*  
196 *of bias* were blinding of outcome assessors, controlling for confounding variables in  
197 statistical analysis, reporting main effect of time with *p* values, and validity and  
198 reliability of outcome measures, in 12, 9, 3 and 1 cases, respectively. On the other hand,  
199 Egger's regression test was significant for all three biomarkers cTnT, cTnI and NT-  
200 proBNP ( $P < .001$ ), suggesting that current literature was still unrepresentative of the  
201 population of completed studies.

## 202 **Cardiac troponin T**

203 Participants had an overall cTnT concentration at baseline of 5 ng/L (4 ng/L to 6 ng/L).  
204 This concentration was increased ( $P < .001$ ) after 2-5 h, reaching a peak of 144 ng/L (83  
205 ng/L to 205 ng/L). Finally, 24 h after exercise cTnT was reduced ( $P < .002$ ) with a  
206 pooled concentration of 11 ng/L (5 ng/L to 16 ng/L), which was slightly higher than at  
207 baseline ( $P = .01$ ) (Figure 2). All three pooled concentrations as well as their differences  
208 were heterogeneous between studies ( $P < .001$  in all comparisons). Overall 76% (66%  
209 to 87%,  $P < .001$ ) of participants had a cTnT peak above the assays URL, and a 39%  
210 (26% to 60%,  $P < .001$ ) exceeded the cut-off for AMI. Again, both rates, for MI and for  
211 AMI, were heterogeneous between studies ( $P = .047$  and  $P < .001$ , respectively).  
212 In the subgroups analyses, cTnT was measured in four exercise modes, namely half  
213 marathon, treadmill running, table tennis and swimming. Exercise mode, available in *k*  
214 = 14 units with a total of  $n = 193$  participants, had a main effect on cTnT increase-to-

215 peak ( $Q_{(3)} = 9.98$ ,  $P = .02$ ). Post-hoc analysis revealed that after a half marathon and  
216 treadmill run cTnT increases were higher than after intermittent table tennis and  
217 swimming ( $P < .001$  and  $P = .004$ , respectively). Multiple regression with exercise  
218 mode as a random effect ( $k = 11$ ,  $n = 138$ ), revealed that age had a negative association  
219 ( $P < .001$ ) while intensity and duration were positively associated ( $P < .001$  and  $P =$   
220  $.003$ , respectively) with cTnT increase ( $Q_{(3)} = 28.3$ ,  $P < .001$ ). Moreover, participants'  
221  $VO_{2max}$  correlated negatively with cTnT increase ( $k = 7$ ,  $n = 60$ ,  $P = .04$ ). We did not  
222 find associations between cTnT increase and sex ( $k = 11$ ,  $n = 138$ ,  $P = .3$ ), Tanner stage  
223 ( $k = 4$ ,  $n = 63$ ,  $P = .5$ ), years of previous training ( $P = .16$ ) or weekly km of training ( $k =$   
224  $10$ ,  $n = 110$ ,  $P = .32$ ).

225 **\*\*Figure 2\*\***

226 Figure 2. Estimated kinetics by biomarker before, at peak value and 24 h after exercise,  
227 with their respective 95% IC. Note: a = significant increase; b = significant decrease; c  
228 = higher than at baseline.

### 229 **Cardiac troponin I**

230 The pooled baseline concentration for cTnI was 16 ng/L (10 ng/L to 22 ng/L). After 3-6  
231 h of exercise exposure participants increased this concentration ( $P = .04$ ) up to a peak of  
232 248 ng/L (17 ng/L to 478 ng/L). After 24 h recovery, this reduced to 38 ng/L (19 ng/L  
233 to 56 ng/L) which was not statistically different from the estimated peak concentration  
234 ( $P = .06$ ) (Figure 2). However, all three pooled concentrations as well as their  
235 differences were heterogeneous between studies ( $P < .001$  in all comparisons). The  
236 proportion of participants with cTnI above the URL was 51% (32% to 81%) and the rate  
237 exceeding the cut-off for AMI was 11% (5% to 24%). The rate for MI was  
238 heterogeneous ( $P = .01$ ) while the rate for AMI was not ( $P = .33$ ) between individual  
239 studies.

240 In the subgroup analysis, cTnI was measured in four exercise modes, namely half  
241 marathon, basketball, table tennis and soccer. The cTnI increase to peak did not differ  
242 between exercise modes ( $k = 5$ ,  $n = 83$ ,  $Q(4) = 4.75$ ,  $P = .31$ ), and did not either in a  
243 multiple comparison ( $k = 4$ ,  $n = 61$ ) at different ages ( $P = .33$ ), intensities ( $P = .6$ ) or  
244 durations ( $P = .31$ ). In addition, we did not find differences due to years of training ( $k =$   
245  $3$ ,  $n = 33$ ,  $P = .37$ ) or participants'  $VO_{2max}$  ( $k = 3$ ,  $n = 33$ ,  $P = .54$ ). Tanner stage and  
246 weekly training load data were not available to be modelled.

### 247 **N-terminal prohormone Brain Natriuretic Peptide**

248 The pooled baseline concentration for NT-proBNP corresponded to 77 ng/L (14 ng/L to  
249 140 ng/L). This concentration was increased immediately after exercise ( $P = .03$ )  
250 achieving a peak of 106 ng/L (17 ng/L to 195 ng/L). Finally, 24 h after exercise NT-  
251 proBNP concentration did not differ from its peak ( $P = .63$ ) or baseline ( $P = .44$ ) with  
252 an estimate of 83 ng/L (0 ng/L to 182 ng/L) (Figure 2). All three concentrations were  
253 heterogeneous ( $P < .001$ ). The rate of participants with NT-proBNP concentration  
254 above the URL was 13% (4% to 44%,  $P < .001$ ), and studies were heterogeneous ( $P =$   
255  $.003$ ).

256 In the subgroup analysis, NT-proBNP was present in four different exercise modes,  
257 namely half marathon, treadmill running, swimming and soccer. Exercise mode, had a  
258 main effect on the NT-proBNP post exercise increase ( $k = 6$ ,  $n = 101$ ,  $Q(4) = 25.06$ ,  $P <$   
259  $.001$ ). Post-hoc comparisons revealed that the higher NT-proBNP increases were related  
260 with soccer (estimated increase of 83 ng/L, 95%CI from 34 ng/L to 131 ng/L,  $P < .05$ )  
261 followed by half marathon (estimated increase of 59 ng/L, 95%CI from 12 ng/L to 105  
262 ng/L,  $P = .01$ ) and finally followed by swimming (estimated increase of 11 ng/L,  
263 95%CI from 3 ng/L to 18 ng/L,  $P = .006$ ), with no differences in the mode of treadmill  
264 running ( $P = .9$ ). Moreover, in a multiple regression with exercise mode as a random

265 effect ( $k = 4$ ,  $n = 62$ ), duration had a positive association with the estimate ( $P < .001$ )  
266 while age ( $P = .34$ ) and intensity ( $P = .37$ ) were not associated with NT-proBNP ( $Q_{(2)} =$   
267  $11.9$ ,  $P = .003$ ). Finally, we did not find differences in NT-proBNP for sex ( $k = 4$ ,  $n =$   
268  $62$ ,  $P = .3$ ), Tanner stage ( $k = 3$ ,  $n = 50$ ,  $P = .6$ ) and years of previous training ( $k = 4$ ,  $n =$   
269  $62$ ,  $P = .5$ ).  $VO_{2max}$ , and weekly training load data were not available to be modelled.

## 270 **Discussion**

271 The main purpose of this systematic review and meta-analysis was to estimate how  
272 exercise modulated the blood concentration of cTnT, cTnI and NT-proBNP in children  
273 and adolescents. Overall, this review found: 1) all three biomarkers were significantly  
274 elevated after exercise; 2) a decrease from peak values after 24 h recovery was only  
275 significant for cTnT; 3) the rate of participants exceeding the biomarkers' URL were  
276 76% for cTnT, 51% for cTnI and 13% for NT-proBNP; 4) the rate of participants  
277 exceeding the cut-off value for AMI were 39% for cTnT and 11% for cTnI; 5)  
278 individual variability was observed between studies; and 6) exercise duration influenced  
279 both cTnT and NT-proBNP while intensity influenced only cTnT. Despite these  
280 findings, the quality assessment of studies together with the analysis for publication bias  
281 revealed that current studies have a fair degree of quality with limited bias.

## 282 **Cardiac troponin T and I**

283 Our results indicate that cTn release in children and adolescents is inherent to physical  
284 exercise. Data reflect a fast increase of cTnT during the early hours of recovery, with  
285 close to complete recovery to baseline at 24 h. Similar results were appreciable for cTnI,  
286 although statistical power was limited and lead to only marginally significant  
287 differences between peak and 24 h values. Such observations suggest that cTn kinetics  
288 in children and adolescents during a 24 h recovery are comparable with the observed in  
289 adults (15,25). Our results coincide with previous research observing the highest cTnT

290 and cTnI concentrations about 2-3 and 3-5 h post exercise, respectively (15,25). Based  
291 upon the foregoing, when repeated blood sampling are not possible, single samples  
292 taken within such interval might detect concentrations close to the kinetics peak.

293 The current data suggest that, as in the case of adults (31,33), there is a marked  
294 individual variability regarding the exercise induced release of cTn, with a high  
295 proportion of participants with values exceeding the URL for MI and AMI. As  
296 evidenced in controlled studies with adolescents (12) and adults (68), cTnT variability  
297 could be partially explained by exercise intensity and duration, what likely reflects an  
298 impact of exercise volume on cardiac work. We also observed a higher cTnT release in  
299 the younger participants, and this could explain that the proportion of participants  
300 exceeding the URL in our study is higher than the reported by a recent meta-analysis  
301 without age restrictions (66). This would suggest a role for maturity mediating the post  
302 exercise cTn release. However, direct comparisons of the release of cTn after exercise  
303 in adults and adolescents have disclosed contradictory findings (30,38,77). Moreover,  
304 with the scarce data currently available we did not find any association between cTnT  
305 release and pubertal status. At all events, associations with pubertal status require  
306 further investigation. Running seems to induce higher cTnT releases than other modes  
307 as it was noticed in a previous meta-analysis based on adult participants (71);  
308 nevertheless, such assertion is complex to verify through direct comparisons. Although  
309 we observed lower cTnT releases in participants with greater VO<sub>2</sub>max, we could not  
310 corroborate whether the cTnT increase is mediated by current training or training  
311 history. It was not evident whether there were any sex differences in the cTn release.  
312 This coincides with previous studies in adults which reported a limited influence of sex  
313 and training history on the release of cTn (4,27,30,32,33,38,78). The scarce number of



314 studies did not allow to explain the between-subjects variability regarding the release of  
315 cTnI.

### 316 **N-terminal prohormone Brain Natriuretic Peptide**

317 An increase in NT-proBNP immediately after exercise was confirmed without a  
318 significant reduction within the 24 h recovery period that supports past research with  
319 adults (32,37). NT-proBNP may have a longer clearance period than cTn possibly  
320 extended to 72 h (9,11). In this regard, it has been suggested that BNP may play an  
321 important role in homeostasis during the transition of the circulation from children to  
322 maturity as a marker of myocardial growth (73). This might reflect an early myocardial  
323 adaptation to the intense training stimulus in children and adolescents. In either case,  
324 these possibilities require further study.

325 We noted that NT-proBNP changes with exercise were lower than the observed in cTn.  
326 Therefore, the proportion of participants exceeding the URL of NT-proBNP was lower  
327 than the reported in studies with adults (11,63). These differences might be associated  
328 with age. However, neither our analysis nor previous studies comparing directly  
329 adolescents with adults found NT-proBNP differences for age and pubertal status  
330 (30,77). It is therefore plausible to think that these differences might be related to  
331 exercises with less duration in studies conducted with adolescents compared with their  
332 equivalents with adults. Our results confirm indeed that in adolescents the release of  
333 NT-proBNP is largely associated with exercise duration, as it was reported previously in  
334 studies with adults (67,68). Given the close relationship between pre- and post-exercise  
335 values (32,33), baseline differences between studies might explain part of the  
336 differences we observed across NT-proBNP peak values depending on the exercise  
337 mode. Our results also confirmed that as in adults (4,30,32,33,67,68) exercise intensity,

338 training, fitness and sex have limited influence on the release of NT-proBNP with  
339 exercise.

#### 340 **Clinical implications**

341 A cardiac biomarker release was observed in most of the participants in all included  
342 studies, despite a certain degree of between-study variability. Importantly, this analysis  
343 shows that in children and adolescents, the factors mediating cardiac biomarkers after  
344 exercise as well as their kinetics, are comparable with the observed in previous studies  
345 in adults and differ from the observed after MI and AMI (74,75). It has been suggested  
346 that this reflects a reversible cellular process triggered by a normal physiological  
347 response to exercise (9,45,58,62). Likewise, the increase of cTn might reflect an  
348 increased rate and force of cardiac contraction during exercise that causes transient  
349 membrane damage and enables cystolic cTn to pass into circulation (69). On the other  
350 hand, a release of NT-proBNP from the ventricular cardiomyocytes might reflect a  
351 volume overload and cardiac wall stretch during exercise (11). Furthermore, some  
352 authors suggested that the use of the general population values as a reference might not  
353 be appropriate for adult athletes being evaluated for medical conditions using blood  
354 indices of cardiac biomarkers. This has prompted the reflection that cardiac biomarkers  
355 values might be stratified according to the physical activity of the adult subjects for  
356 improving the clinical usefulness of the biomarker (35). In this sense, our analysis  
357 extends this to children and adolescents, and suggests that when evaluating cTnT, cTnI  
358 and NT-proBNP in emergency settings, detailed information regarding any recent  
359 exercise should be obtained (38).

#### 360 **Limitations**

361 The main limitation of this systematic review and meta-analysis derives from the  
362 incomplete data provided by a range of heterogeneous studies. Moderator analyses were

363 performed with reduced numbers that decreased statistical power. This lack of statistical  
364 power might explain some non-significant results such as the inconclusive decrease in  
365 cTnI within a 24 h post-exercise recovery. We did not incorporate assay precision to our  
366 meta-analysis which could have explained certain degree of the study-to-study  
367 heterogeneity (71). Finally, we found differences between studies regarding when peak  
368 concentrations were taken or noted. In conclusion, more research should be conducted  
369 with children and adolescents analyzing such covariate parameters.

### 370 **Conclusion**

371 In conclusion, cardiac biomarkers in children and adolescents are significantly increased  
372 from rest to post-exercise with the URL exceeded by a 76% of participants for cTnT, a  
373 51% for cTnI and a 13% for NT-proBNP and the cut-off value for AMI exceeded by  
374 39% for cTnT and a 11% for cTnI. Finally, we confirmed that the cTnT release is  
375 mainly associated with exercise duration and intensity, while the NT-proBNP release  
376 remains influenced only by exercise duration.

377

378

379 **References**

- 380 1. Alquézar Arbé A, Santaló Bel M, Sionis A. Interpretación clínica de la  
381 determinación de troponina T de elevada sensibilidad. *Med Clin (Barc)*.  
382 2015;145(6):258–63. doi: 10.1016/j.medcli.2014.11.004
- 383 2. Andersen LB, Lauersen JB, Brønd JC, Anderssen SA, Sardinha LB, Steene-  
384 Johannessen J, et al. A New Approach to Define and Diagnose Cardiometabolic  
385 Disorder in Children. *J Diabetes Res*. 2015;2015(Cvd):1–10. PubMed: 25945355  
386 doi: 10.1155/2015/539835
- 387 3. Bayés-Genís A. The Circulating NTproBNP Level, a New Biomarker for the  
388 Diagnosis of Heart Failure in Patients With Acute Shortness of Breath. *Rev*  
389 *Española Cardiol*. 2005;58(10):1142–4. PubMed: 16238980 doi: 10.1016/S1885-  
390 5857(06)60391-5
- 391 4. Carranza-García LE, George K, Serrano-Ostáriz E, Casado-Arroyo R, Caballero-  
392 Navarro AL, Legaz-Arrese A. Cardiac Biomarker Response to Intermittent  
393 Exercise Bouts. *Int J Sports Med*. 2011;32(05):327–31. PubMed: 21547864 doi:  
394 10.1055/s-0030-1263138
- 395 5. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis  
396 detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–34. PubMed:  
397 9310563
- 398 6. Eijsvogels T, George K, Shave R, Gaze D, Levine BD, Hopman MTE, et al.  
399 Effect of Prolonged Walking on Cardiac Troponin Levels. *Am J Cardiol*.  
400 2010;105(2):267–72. PubMed: 20102930 doi: 10.1016/j.amjcard.2009.08.679
- 401 7. Eijsvogels TMH, Hoogerwerf MD, Maessen MFH, Seeger JPH, George KP,  
402 Hopman MTE, et al. Predictors of cardiac troponin release after a marathon. *J Sci*

- 403 Med Sport. 2015;18(1):88–92. PubMed: 24440407 doi:  
404 10.1016/j.jsams.2013.12.002
- 405 8. Eijsvogels TMH, Hoogerwerf MD, Oudegeest-Sander MH, Hopman MTE,  
406 Thijssen DHJ. The impact of exercise intensity on cardiac troponin I release. *Int J*  
407 *Cardiol.* 2014;171(1):e3–4. doi: 10.1016/j.ijcard.2013.11.050
- 408 9. Eijsvogels TMH, Fernandez AB, Thompson PD. Are There Deleterious Cardiac  
409 Effects of Acute and Chronic Endurance Exercise? *Physiol Rev.* 2016;96(1):99–  
410 125. PubMed: 26607287 doi: 10.1152/physrev.00029.2014
- 411 10. Fortescue EB, Shin AY, Greenes DS, Mannix RC, Agarwal S, Feldman BJ, et al.  
412 Cardiac Troponin Increases Among Runners in the Boston Marathon. *Ann Emerg*  
413 *Med.* 2007;49(2):137–143.e1. PubMed: 17145114 doi:  
414 10.1016/j.annemergmed.2006.09.024
- 415 11. Frassl W, Kowoll R, Katz N, Speth M, Stangl A, Brechtel L, et al. Cardiac  
416 markers (BNP, NT-pro-BNP, Troponin I, Troponin T) in female amateur runners  
417 before and up until three days after a marathon. *Clin Lab.* 2008;54(3–4):81–7.  
418 PubMed: 18630737
- 419 12. Fu F, Nie J, Tong T. Serum Cardiac Troponin T in Adolescent Runners: Effects  
420 of Exercise Intensity and Duration. *Int J Sports Med.* 2009;30(3):168–72.  
421 PubMed: 19199217 doi: 10.1055/s-0028-1104586
- 422 13. Fu FH, Nie J, George K, Tong TK, Lin H, Shi Q. Impact of a 21-km Run on  
423 Cardiac Biomarkers in Adolescent Runners. *J Exerc Sci Fit.* 2010;8(2):61–6.  
424 doi: 10.1016/S1728-869X(10)60009-3
- 425 14. Gaggin HK, Januzzi JL. Biomarkers and diagnostics in heart failure. *Biochim*  
426 *Biophys Acta - Mol Basis Dis.* 2013;1832(12):2442–50. PubMed: 23313577 doi:  
427 10.1016/j.bbadis.2012.12.014

- 428 15. Gresslien T, Agewall S. Troponin and exercise. *Int J Cardiol.* 2016;221:609–21.  
429 doi: 10.1016/j.ijcard.2016.06.243
- 430 16. Haider DG, Klemenz T, Fiedler GM, Nakas CT, Exadaktylos AK, Leichtle AB.  
431 High sensitive cardiac troponin T: Testing the test. *Int J Cardiol.* 2017;228:779–  
432 83. doi: 10.1016/j.ijcard.2016.10.043
- 433 17. Hess G, Runkel S, Zdunek D, Hitzler WE. Reference interval determination for  
434 N-terminal-B-type natriuretic peptide (NT-proBNP): A study in blood donors.  
435 *Clin Chim Acta.* 2005;360(1–2):187–93. PubMed: 15963969 doi:  
436 10.1016/j.cccn.2005.04.031
- 437 18. Hewing B, Schattke S, Spethmann S, Sanad W, Schroeckh S, Schimke I, et al.  
438 Cardiac and renal function in a large cohort of amateur marathon runners.  
439 *Cardiovasc Ultrasound.* 2015;13(1):13. doi: 10.1186/s12947-015-0007-6
- 440 19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in  
441 meta-analyses. *BMJ.* 2003;327(7414):557–60. PubMed: 12958120 doi:  
442 10.1136/bmj.327.7414.557
- 443 20. Hosseini SM, Azizi M, Samadi A, Talebi N, Hannes G, Burtscher M. Impact of a  
444 Soccer Game on Cardiac Biomarkers in Adolescent Players. *Pediatr Exerc Sci.*  
445 2017;1–16. doi: 10.1123/pes.2017-0060
- 446 21. Hubble KM, Fatovich DM, Grasko JM, Vasikaran SD. Cardiac troponin  
447 increases among marathon runners in the Perth Marathon: the Troponin in  
448 Marathons (TRIM) study. *Med J Aust.* 2009;190(2):91–3. PubMed: 19236297
- 449 22. Jarolim P, Morrow DA. Use of high sensitivity cardiac troponin assays as an  
450 adjunct to cardiac stress testing. *Clin Biochem.* 2016;49(6):419–20. PubMed:  
451 26969798 doi: 10.1016/j.clinbiochem.2016.03.001
- 452 23. Jassal D, Moffat D, Krahn J, Ahmadie R, Fang T, Eschun G, et al. Cardiac Injury

- 453 Markers in Non-elite Marathon Runners. *Int J Sports Med.* 2009;30(02):75–9.  
454 PubMed: 19177312 doi: 10.1055/s-0028-1104572
- 455 24. Kirk R, Dipchand AI, Rosenthal DN, Addonizio L, Burch M, Chrisant M, et al.  
456 The International Society for Heart and Lung Transplantation Guidelines for the  
457 management of pediatric heart failure: Executive summary. *J Hear Lung*  
458 *Transplant.* 2014;33(9):888–909. PubMed: 25110323 doi:  
459 10.1016/j.healun.2014.06.002
- 460 25. Klinkenberg LJJ, Luyten P, van der Linden N, Urgel K, Snijders DPC,  
461 Knackstedt C, et al. Cardiac Troponin T and I Release After a 30-km Run. *Am J*  
462 *Cardiol.* 2016;118(2):281–7. PubMed: 27282835 doi:  
463 10.1016/j.amjcard.2016.04.030
- 464 26. Koerbin G, Potter JM, Abhayaratna WP, Telford RD, Badrick T, Apple FS, et al.  
465 Longitudinal Studies of Cardiac Troponin I in a Large Cohort of Healthy  
466 Children. *Clin Chem.* 2012;58(12):1665–72. PubMed: 23019308 doi:  
467 10.1373/clinchem.2012.192054
- 468 27. Kong Z, Nie J, Lin H, George K, Zhao G, Zhang H, et al. Sex differences in  
469 release of cardiac troponin T after endurance exercise. *Biomarkers.* 2017;22(3–  
470 4):345–50. PubMed: 27879166 doi: 10.1080/1354750X.2016.1265007
- 471 28. König D, Neubauer O, Nics L, Kern N, Berg A, Bisse E, et al. Biomarkers of  
472 exercise-induced myocardial stress in relation to inflammatory and oxidative  
473 stress. *Exerc Immunol Rev.* 2007;13(February):15–36. PubMed: 18198658
- 474 29. Leers MPG, Schepers R, Baumgarten R. Effects of a long-distance run on cardiac  
475 markers in healthy athletes. *Clin Chem Lab Med.* 2006;44(8):999–1003.  
476 PubMed: 16879068 doi: 10.1515/CCLM.2006.179
- 477 30. Legaz-Arrese A, Carranza-García LE, Navarro-Orocio R, Valadez-Lira A,

- 478 Mayolas-Pi C, Munguía-Izquierdo D, et al. Cardiac Biomarker Release after  
479 Endurance Exercise in Male and Female Adults and Adolescents. *J Pediatr.*  
480 2017;191:96–102. doi: 10.1016/j.jpeds.2017.08.061
- 481 31. Legaz-Arrese A, López-Laval I, George K, José Puente-Lanzarote J, Castellar-  
482 Otín C, Reverter-Masià J, et al. Individual variability of high-sensitivity cardiac  
483 troponin levels after aerobic exercise is not mediated by exercise mode.  
484 *Biomarkers.* 2015;20(4):219–24. doi: 10.3109/1354750X.2015.1068851
- 485 32. Legaz-Arrese A, López-Laval I, George K, Puente-Lanzarote JJ, Mayolas-Pi C,  
486 Serrano-Ostáriz E, et al. Impact of an endurance training program on exercise-  
487 induced cardiac biomarker release. *Am J Physiol Circ Physiol.*  
488 2015;308(8):H913–20. PubMed: 25681432 doi: 10.1152/ajpheart.00914.2014
- 489 33. Legaz-Arrese A, López-Laval I, George K, Puente-Lanzarote JJ, Moliner-  
490 Urdiales D, Ayala-Tajuelo VJ, et al. Individual variability in cardiac biomarker  
491 release after 30 min of high-intensity rowing in elite and amateur athletes. *Appl*  
492 *Physiol Nutr Metab.* 2015;40(9):951–8. PubMed: 26307519 doi: 10.1139/apnm-  
493 2015-0055
- 494 34. Lin KY. Biomarkers in paediatric heart failure: is there value? *Cardiol Young.*  
495 2015;25(08):1469–72. doi: 10.1017/S1047951115002358
- 496 35. Lippi G, Banfi G. Exercise-related increase of cardiac troponin release in sports:  
497 An apparent paradox finally elucidated? *Clin Chim Acta.* 2010;411(7–8):610–1.  
498 doi: 10.1016/j.cca.2010.01.009
- 499 36. Lippi G, Schena F, Dipalo M, Montagnana M, Salvagno GL, Aloe R, et al.  
500 Troponin I measured with a high sensitivity immunoassay is significantly  
501 increased after a half marathon run. *Scand J Clin Lab Invest.* 2012;72(6):467–70.  
502 PubMed: 22794031 doi: 10.3109/00365513.2012.697575



- 503 37. Lippi G, Schena F, Salvagno GL, Montagnana M, Gelati M, Tarperi C, et al.  
504 Influence of a half-marathon run on NT-proBNP and troponin T. *Clin Lab*.  
505 2008;54(7–8):251–4. PubMed: 18942493
- 506 38. López-Laval I, Legaz-Arrese A, George K, Serveto-Galindo O, González-Rave  
507 JM, Reverter-Masia J, et al. Cardiac troponin I release after a basketball match in  
508 elite, amateur and junior players. *Clin Chem Lab Med*. 2016;54(2):333–8. doi:  
509 10.1515/cclm-2015-0304
- 510 39. Ma G, Liu Y, Liu K, G. M, Y. L, K. L, et al. Influence of repeated bouts of table  
511 tennis training on cardiac biomarkers in children. *Pediatr Cardiol*.  
512 2014;35(4):711–8. PubMed: 24272170 doi: 10.1007/s00246-013-0842-x
- 513 40. Meigher S, Thode HC, Peacock WF, Bock JL, Gruberg L, Singer AJ. Causes of  
514 Elevated Cardiac Troponins in the Emergency Department and Their Associated  
515 Mortality. Hiestand BC, editor. *Acad Emerg Med*. 2016;23(11):1267–73.  
516 PubMed: 27320126 doi: 10.1111/acem.13033
- 517 41. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred  
518 reporting items for systematic reviews and meta-analyses: the PRISMA  
519 statement. *Ann Intern Med*. 2009;151(4):264–9, W64. PubMed: 19622511
- 520 42. National Heart Lung and Blood Institute. Quality Assessment Tool for Before-  
521 After (Pre-Post) Studies With No Control Group [Internet]. 2014 [cited 2017 Jun  
522 1].
- 523 43. Neilan TG, Januzzi JL, Lee-Lewandrowski E, Ton-Nu T-T, Yoerger DM, Jassal  
524 DS, et al. Myocardial Injury and Ventricular Dysfunction Related to Training  
525 Levels Among Nonelite Participants in the Boston Marathon. *Circulation*.  
526 2006;114(22):2325–33. PubMed: 17101848 doi:  
527 10.1161/CIRCULATIONAHA.106.647461

- 528 44. Neumayr G, Pfister R, Mitterbauer G, Eibl G, Hoertnagl H. Effect of Competitive  
529 Marathon Cycling on Plasma N-Terminal Pro-Brain Natriuretic Peptide and  
530 Cardiac Troponin T in Healthy Recreational Cyclists. *Am J Cardiol.*  
531 2005;96(5):732–5. PubMed: 16125505 doi: 10.1016/j.amjcard.2005.04.054
- 532 45. Nie J, George K, Duan F, Tong TK, Tian Y. Histological evidence for reversible  
533 cardiomyocyte changes and serum cardiac troponin T elevation after exercise in  
534 rats. *Physiol Rep.* 2016;4(24):e13083. doi: 10.14814/phy2.13083
- 535 46. Nie J, George K, Tong TK, Tian Y, Shi Q. Effect of Repeated Endurance Runs  
536 on Cardiac Biomarkers and Function in Adolescents. *Med Sci Sports Exerc.*  
537 2011;43(11):2081–8. PubMed: 21502895 doi: 10.1249/MSS.0b013e31821d4a82
- 538 47. Nie J, P. George K, K. Tong T, Gaze D, Tian Y, Lin H, et al. The Influence of a  
539 Half-Marathon Race Upon Cardiac Troponin T Release in Adolescent Runners.  
540 *Curr Med Chem.* 2011;18(23):3452–6. PubMed: 21756240 doi:  
541 10.2174/092986711796642625
- 542 48. Nie J, Tong TK, George K, Fu FH, Lin H, Shi Q. Resting and post-exercise  
543 serum biomarkers of cardiac and skeletal muscle damage in adolescent runners.  
544 *Scand J Med Sci Sports.* 2011;21(5):625–9. PubMed: 20459466 doi:  
545 10.1111/j.1600-0838.2010.01096.x
- 546 49. Nie J, Tong TK, Shi Q, Lin H, Zhao J, Tian Y, et al. Serum cardiac troponin  
547 response in adolescents playing basketball. *Int J Sports Med.* 2008;29(6):449–52.  
548 PubMed: 18004684 doi: 10.1055/s-2007-989236
- 549 50. Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, et al. NT-Pro-B-  
550 type Natriuretic Peptide in Infants and Children: Reference Values Based on  
551 Combined Data from Four Studies. *Pediatr Cardiol.* 2009;30(1):3–8. PubMed:  
552 18600369 doi: 10.1007/s00246-008-9258-4

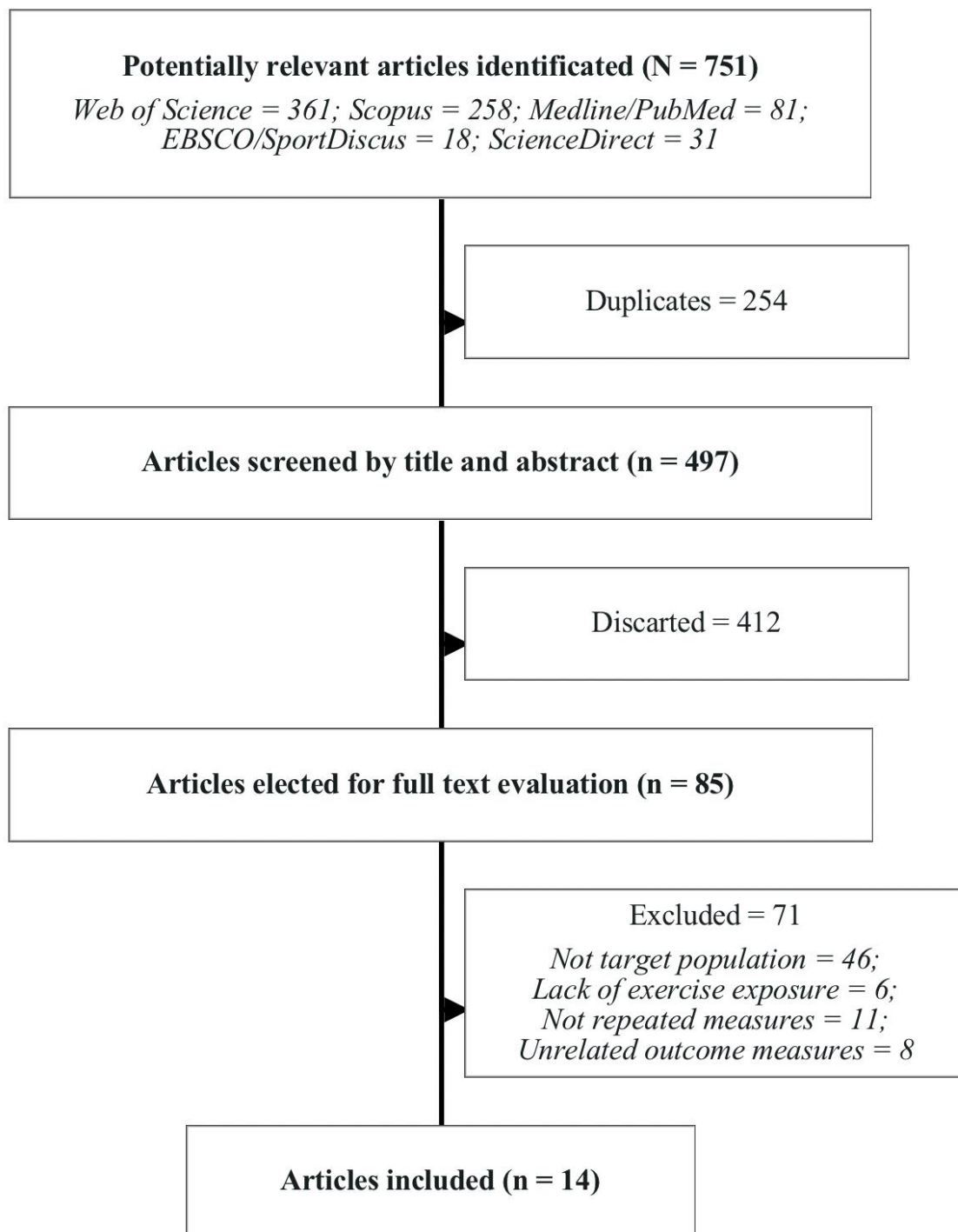
- 553 51. Van den Noortgate W, López-López JA, Marín-Martínez F, Sánchez-Meca J.  
554 Meta-analysis of multiple outcomes: a multilevel approach. *Behav Res Methods*.  
555 2015;47(4):1274–94. PubMed: 25361866 doi: 10.3758/s13428-014-0527-2
- 556 52. Ohba H, Takada H, Musha H, Nagashima J, Mori N, Awaya T, et al. Effects of  
557 prolonged strenuous exercise on plasma levels of atrial natriuretic peptide and  
558 brain natriuretic peptide in healthy men. *Am Heart J*. 2001;141(5):751–8.  
559 PubMed: 11320362 doi: 10.1067/mhj.2001.114371
- 560 53. Panagopoulou V, Deftereos S, Kossyvakis C, Raisakis K, Giannopoulos G,  
561 Bouras G, et al. NTproBNP: An Important Biomarker in Cardiac Diseases. *Curr*  
562 *Top Med Chem*. 2013;13(2):82–94. doi: 10.2174/1568026611313020002
- 563 54. R Core Team. R: A language and environment for statistical computing  
564 [Internet]. Vienna, Australia: R Foundation for Statistical Computing; 2016.
- 565 55. Ranjbar R, Ahmadi MA, Zar A, Krstrup P. Acute effect of intermittent and  
566 continuous aerobic exercise on release of cardiac troponin T in sedentary men.  
567 *Int J Cardiol*. 2017;236(PG-493-497):493–7. PubMed: 28096042 doi:  
568 10.1016/j.ijcard.2017.01.065
- 569 56. Roca E, Nescolarde L, Lupón J, Barallat J, Januzzi JL, Liu P, et al. The  
570 Dynamics of Cardiovascular Biomarkers in non-Elite Marathon Runners. *J*  
571 *Cardiovasc Transl Res*. 2017;10(2):206–8. PubMed: 28382580 doi:  
572 10.1007/s12265-017-9744-2
- 573 57. Rothstein HR. Publication Bias in Prevention, Assessment and Adjustments  
574 [Internet]. Assessment. 2005. 75-98 p. PubMed: 15296515 doi:  
575 10.1002/0470870168
- 576 58. Sanchis-Gomar F, López-Ramón M, Alis R, Garatachea N, Pareja-Galeano H,  
577 Santos-Lozano A, et al. No evidence of adverse cardiac remodeling in former

- 578 elite endurance athletes. *Int J Cardiol.* 2016;222(PG-171-7):171–7. doi:  
579 10.1016/j.ijcard.2016.07.197
- 580 59. Sandoval Y, Smith SW, Apple FS. Present and Future of Cardiac Troponin in  
581 Clinical Practice: A Paradigm Shift to High-Sensitivity Assays. *Am J Med.*  
582 2016;129(4):354–65. PubMed: 26743351 doi: 10.1016/j.amjmed.2015.12.005
- 583 60. Sandoval Y, Smith SW, Love SA, Sexter A, Schulz K, Apple FS. Single High-  
584 Sensitivity Cardiac Troponin I to Rule Out Acute Myocardial Infarction. *Am J*  
585 *Med.* 2017;130(9):1076–1083.e1. doi: 10.1016/j.amjmed.2017.02.032
- 586 61. Scharhag J, Urhausen A, Schneider G, Herrmann M, Schumacher K, Haschke M,  
587 et al. Reproducibility and clinical significance of exercise-induced increases in  
588 cardiac troponins and N-terminal pro brain natriuretic peptide in endurance  
589 athletes. *Eur J Cardiovasc Prev Rehabil.* 2006;13(3):388–97. PubMed: 16926669  
590 doi: 10.1097/00149831-200606000-00015
- 591 62. Scharhag J, Urhausen A, Herrmann M, Schneider G, Kramann B, Herrmann W,  
592 et al. No difference in N-terminal pro-brain natriuretic peptide (NT-proBNP)  
593 concentrations between endurance athletes with athlete's heart and healthy  
594 untrained controls. *Heart.* 2004;90(9):1055–6. PubMed: 15310701 doi:  
595 10.1136/hrt.2003.020420
- 596 63. Scharhag J, George K, Shave R, Urhausen A, Kindermann W. Exercise-  
597 associated increases in cardiac biomarkers. *Med Sci Sports Exerc.*  
598 2008;40(8):1408–15. PubMed: 18614952 doi: 10.1249/MSS.0b013e318172cf22
- 599 64. Scharhag J, Herrmann M, Urhausen A, Haschke M, Herrmann W, Kindermann  
600 W. Independent elevations of N-terminal pro-brain natriuretic peptide and  
601 cardiac troponins in endurance athletes after prolonged strenuous exercise. *Am*  
602 *Heart J.* 2005;150(6):1128–34. PubMed: 16338248 doi:

- 603 10.1016/j.ahj.2005.01.051
- 604 65. Scott JM, Esch BTA, Shave R, Warburton DER, Gaze D, George K.  
605 Cardiovascular consequences of completing a 160-km ultramarathon. *Med Sci*  
606 *Sports Exerc.* 2009;41(1):26–34. PubMed: 19092706 doi:  
607 10.1249/MSS.0b013e31818313ff
- 608 66. Sedaghat-Hamedani F, Kayvanpour E, Frankenstein L, Mereles D, Amr A, Buss  
609 S, et al. Biomarker Changes after Strenuous Exercise Can Mimic Pulmonary  
610 Embolism and Cardiac Injury--A Metaanalysis of 45 Studies. *Clin Chem.*  
611 2015;61(10):1246–55. PubMed: 2015420576 doi:  
612 10.1373/clinchem.2015.240796
- 613 67. Serrano-Ostáriz E, Legaz-Arrese A, Terreros-Blanco JL, López-Ramón M,  
614 Cremades-Arroyos D, Álvarez-Izquierdo S, et al. Cardiac Biomarkers and  
615 Exercise Duration and Intensity During a Cycle-Touring Event. *Clin J Sport*  
616 *Med.* 2009;19(4):293–9. doi: 10.1097/JSM.0b013e3181ab3c9d
- 617 68. Serrano-Ostáriz E, Terreros-Blanco JL, Legaz-Arrese A, George K, Shave R,  
618 Bocos-Terraz P, et al. The impact of exercise duration and intensity on the  
619 release of cardiac biomarkers. *Scand J Med Sci Sports.* 2011;21(2):244–9.  
620 PubMed: 19919634 doi: 10.1111/j.1600-0838.2009.01042.x
- 621 69. Shave R, George K, Gaze D. The Influence of Exercise Upon Cardiac  
622 Biomarkers: A Practical Guide for Clinicians and Scientists. *Curr Med Chem.*  
623 2007;14(13):1427–36. doi: 10.2174/092986707780831177
- 624 70. Shave R, Ross P, Low D, George K, Gaze D. Cardiac troponin I is released  
625 following high-intensity short-duration exercise in healthy humans. *Int J Cardiol.*  
626 2010;145(2):337–9. PubMed: 20079546 doi: 10.1016/j.ijcard.2009.12.001
- 627 71. Shave R, George K, Atkinson G, Hart E, Middleton N, Whyte G, et al. Exercise-

- 628 induced cardiac troponin T release: a meta-analysis. *Med Sci Sports Exerc.*  
629 2007;39(12):2099–106. PubMed: 18046180 doi: 10.1249/mss.0b013e318153ff78
- 630 72. Siddiqui S, Patel DR. Cardiovascular Screening of Adolescent Athletes. *Pediatr*  
631 *Clin North Am.* 2010;57(3):635–47. PubMed: 20538148 doi:  
632 10.1016/j.pcl.2010.03.001
- 633 73. Socrates T, Arenja N, Mueller C. B-Type Natriuretic Peptide in Children. *J Am*  
634 *Coll Cardiol.* 2009;54(15):1476–7. PubMed: 19796741 doi:  
635 10.1016/j.jacc.2009.04.092
- 636 74. Thomas MR, Lip GYH. Novel Risk Markers and Risk Assessments for  
637 Cardiovascular Disease. *Circ Res.* 2017;120(1):133–49. doi:  
638 10.1161/CIRCRESAHA.116.309955
- 639 75. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al.  
640 Third Universal Definition of Myocardial Infarction. *Circulation.*  
641 2012;126(16):2020–35. PubMed: 18653580 doi:  
642 10.1161/CIR.0b013e31826e1058
- 643 76. Tian Y, Nie J, Tong TK, Cao J, Gao Q, Man J, et al. Changes in serum cardiac  
644 troponins following a 21-km run in junior male runners. *J Sports Med Phys*  
645 *Fitness.* 2006;46(3):481–8. PubMed: 16998456
- 646 77. Tian Y, Nie J, Huang C, George KP. The kinetics of highly sensitive cardiac  
647 troponin T release after prolonged treadmill exercise in adolescent and adult  
648 athletes. *J Appl Physiol.* 2012;113(3):418–25. PubMed: 22653984 doi:  
649 10.1152/jappphysiol.00247.2012
- 650 78. Traiperm N, Gatterer H, Wille M, Burtscher M. Cardiac Troponins in Young  
651 Marathon Runners. *Am J Cardiol.* 2012;110(4):594–8. PubMed: 22579084 doi:  
652 10.1016/j.amjcard.2012.03.052

- 653 79. Urhausen A, Scharhag J, Herrmann M, Kindermann W. Clinical significance of  
654 increased cardiac troponins T and I in participants of ultra-endurance events. *Am*  
655 *J Cardiol.* 2004;94(5):696–8. PubMed: 15342317 doi:  
656 10.1016/j.amjcard.2004.05.050
- 657 80. Vidotto C, Tschan H, Atamaniuk J, Pokan R, Bachl N, Müller MM. Responses of  
658 N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) and Cardiac Troponin I  
659 (cTnI) to Competitive Endurance Exercise in Recreational Athletes. *Int J Sports*  
660 *Med.* 2005;26(8):645–50. PubMed: 16158369 doi: 10.1055/s-2004-830491
- 661 81. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat*  
662 *Softw.* 2010;36(3):1–48. PubMed: 18291371 doi: 10.1002/sim.6001>
- 663 82. Vilela EM, Bastos JCC, Rodrigues RP, Nunes JPL. High-sensitivity troponin  
664 after running--a systematic review. *Neth J Med.* 2014;72(1):5–9. PubMed:  
665 24457432
- 666 83. Voets PJGM, Maas RPPWM. Serum cardiac troponin I analysis to determine the  
667 excessiveness of exercise intensity: A novel equation. *J Theor Biol.*  
668 2016;392:48–52. doi: 10.1016/j.jtbi.2015.12.009
- 669 84. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard  
670 deviation from the sample size, median, range and/or interquartile range. *BMC*  
671 *Med Res Methodol.* 2014;14(1):135. PubMed: 25524443 doi: 10.1186/1471-  
672 2288-14-135
- 673 85. Weippert M, Divchev D, Schmidt P, Gettel H, Neugebauer A, Behrens K, et al.  
674 Cardiac troponin T and echocardiographic dimensions after repeated sprint vs.  
675 moderate intensity continuous exercise in healthy young males. *Sci Rep.*  
676 2016;6(1):24614. doi: 10.1038/srep24614
- 677



678

679

680

681

682

683



