TITLE:

Acute effects of long-distance races on heart rate variability and arterial stiffness: a systematic review and meta-analysis.

AUTHORS:

Alberto CALLEJA-ROMERO[1]*, Germán VICENTE-RODRÍGUEZ[1,2,3,4], Nuria GARATACHEA[1,2,3,4]

[1]Faculty of Health and Sport Science (FCSD, Ronda Misericordia 5, 22001-Huesca, Spain), Department of Physiatry and Nursing, University of Zaragoza, Huesca, Spain; [2]Growth, Exercise, Nutrition and Development Group and IIS-Aragon, [3]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBER-Obn), Madrid, Spain; [4]Instituto Agroalimentario de Aragón -IA2- (CITA-Universidad de Zaragoza), Zaragoza, Spain;

Corresponding author: Alberto CALLEJA-ROMERO, Faculty of Health and Sport Science (FCSD), Department of Physiatry and Nursing, University of Zaragoza, Ronda Misericordia 5, 22001 Huesca, Spain. E-mail: calleja@unizar.es

ABSTRACT:

This study systematically reviewed and quantified the effects of running a long-distance race (LDR) on heart rate variability (HRV) and arterial stiffness (AS). All types of races of a distance equal to or greater than a marathon (≥42.2 km) were included. A total of 2,220 articles were identified, 52 were included in the qualitative analysis, and 48 were meta-analysed. The standardised mean difference pre- post-race of various time-domain and frequency-domain indices of HRV, mean arterial blood pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and carotid-femoral pulse wave velocity (cfPWV) was calculated. Regarding HRV, there was a significant decrease in most of the variables considered as markers of parasympathetic activity, indicating a shift of autonomic balance toward a reduced vagal tone. Regarding vascular variables, there was a significant drop in blood pressure and reduced AS. In conclusion, running an LDR seems to have a considerable acute effect on the autonomic nervous system, haemodynamics, and vascular properties. The observed effects could be categorised within the expected acute responses to long-lasting, strenuous exercise.

Keywords: Autonomic nervous system; heart rate variability; arterial stiffness; long-distance races; running

LIST OF ABBREVIATIONS

ANS	Autonomic nervous system
AS	Arterial stiffness
BP	Blood pressure
cfPWV	Carotid-femoral pulse wave velocity
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
HF	High-frequency band
HF/LF	Ratio high frequency/low frequency power
HR	Heart rate
HRV	Heart rate variability
ICROMS	Integrated quality criteria for the systematic review of multiple study designs
LDR	Long-distance race
LF	Low-frequency band
MAP	Mean arterial pressure
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
PWV	Pulse wave velocity
RMSSD	Square root of the mean squared differences of successive NN intervals
SBP	Systolic blood pressure
SD	Standard deviation
SDNN	Standard deviation of the NN intervals
SEM	Standard error of the mean
SMD	Standardized mean difference

Word count: 7,191 words

TEXT

1. INTRODUCTION

The positive effects of regular moderate aerobic exercise on cardiovascular (CV) health are well known[1]. Physical activity in general, and aerobic exercise in particular, causes a transient CV homeostatic disruption that, followed by an adequate recovery, produces positive adaptations in the CV system[2]. Nevertheless, prolonged strenuous exercise has been found to cause cardiac fatigue[3], arterial stiffness (AS)[4], and other increased CV disease (CVD) risk factors[5]. Thus, despite that many studies have investigated this topic, it is still unclear which dose of exercise (i.e., volume, intensity, and modality) optimises or counteracts CV health benefits[6].

Participation in a long-distance race (LDR), such as a marathon or an ultra-marathon, represent an external physiological stressor due to the high exercise volume and the intrinsic competitive nature of the race[7]. LDRs have increased substantially in popularity and number of participants over the last few years[8-10]. This fact has significantly increased the interest within the research community. However, there is currently no consensus on the beneficial, neutral, or negative impact of an LDR on some CV variables, such as systolic function, vascular function, or inflammatory markers[4, 11-13].

Exercise-induced changes in vascular properties, haemodynamics, and autonomic nervous system (ANS) regulation have been shown to play a fundamental role in CV adaptations after prolonged exercise[14, 15]. The ANS has an important influence on the regulation of heart rate (HR) and blood pressure (BP), and those are closely related to vascular properties and haemodynamics, both important parameters in the study of the CVD risk[16, 17].

HR variability (HRV) assessment is one of the most widely used methods employed to provide noninvasive indicators of ANS activity[18, 19] and its interpretation has been explained extensively in previous literature[18-21].

The stressful nature of the aerobic exercise associated with an LDR typically induces an increase in sympathetic activity and parasympathetic withdrawal in comparative terms to basal conditions[22, 23]. However, the magnitude of the autonomic balance disruption after an LDR requires greater description[24] given that it may be influenced by both methodological factors of the study design, such as the timing of the measurement post-exercise[15] or the position of the body during the assessments[25], and intrinsic characteristics of the LDR itself, such as distance[26] or characteristics of the terrain on which it is run (e.g., mountain[27], large altitude variation[28]). Of course, individual factors, such as aerobic fitness levels, also influence the responses[15].

The post-LDR HRV's timing of measurement is an important methodological factor to be considered when analysing ANS responses. The overall pattern of ANS following exercise shows an initial decrease of parasympathetic activity immediately post-exercise, followed by a progressive increase of its activity until it recovers the typical activity of the resting values[29]. Stanley et al.[15] quantitatively summarized the findings of eight studies that reported cardiac parasympathetic reactivation values in the acute recovery period following aerobic exercise. They found that the initial 10 min post-exercise elicits a very large to an extremely large reduction in cardiac parasympathetic activity. They also found that the recovery to near pre-exercise levels was produced within 90 min following low- and threshold-intensity exercise. However, it was required up to 24 h following low-intensity exercise and at least 48 h following high-intensity exercise for a complete recovery. In addition, other methodological factors such as body position during the assessment may influence the observed responses, with vagal modulations maximised in the supine position and significantly reduced in other protocols[25].

Exercise intensity has been proposed as a primary determinant of the post-exercise recovery of HRV[15, 26], but it is not clear how the interaction between intensity and exercise duration may influence the post-exercise recovery of HRV[26]. A recent review conducted by Michael et al.[26] has suggested that exercise duration may influence the magnitude of the effect on HRV post-exercise when it is prolonged beyond some critical length but, to date, the distance-dose response has not been clearly elucidated.

Regarding mountain LDRs, their main characteristic is that they are performed in a natural 'off-road' environment and involve running over positive and negative slopes[30]. Vernillo et al.[27] concluded that mountain races are more physiologically demanding than flat races, mainly because they involve running uphill and downhill. Additionally, some of these races can reach high altitudes, adding extra physiological stress. In this respect, Bärtsch et al.[28] established that altitude and the resulting hypoxia induce an increase in HR and sympathetic modulation. Nevertheless, Yamamoto et al.[31] found that only altitudes higher than 3,500m had an increment in HR and sympathetic nervous system indicator, and a decrement in parasympathetic nervous system indicator during exercise at simulated altitude and hypoxia.

Regular aerobic exercise training has shown to have positive effects on vascular properties, diminishing AS and BP[32, 33]. Regarding LDRs, despite a general trend toward decreased pulse wave velocity (PWV) after the race[4, 12, 34], a race distance influence has been observed, with greater reductions in AS after 45 km of running than those measured after an additional 30 km of running[4]. Conversely, some studies have reported acute reductions in large artery compliance (the inverse of AS) following the participation in ultra-marathon races[35, 36].

The overall objective of this paper is to provide an overview of the effects of LDRs on ANS and AS. This, in turn, will inform researchers, clinicians, coaches and practitioners about the magnitude of changes as a function of distance, altitude and running terrain, with important application in recreational and high-performance settings. Accordingly, we aimed to conduct a systematic review and meta-analysis on the impact of LDRs on HRV parameters and AS, and to identify race characteristics or methodological moderators that may explain a significant proportion of the magnitude of these changes.

2. METHODS

This systematic review and meta-analysis was performed according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions[37] and reported following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[38]. The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020192488).

2.1 Eligibility criteria

Studies were deemed eligible if they: (1) were published peer-reviewed in English or Spanish language; (2) included healthy human adults (≥ 18 years); (3) investigated the participation in a marathon or ultra-marathon footrace (≥ 42,2 km); and (4) reported pre- and post-race measurements or change values of HRV, the considered gold standard for non-invasive AS assessment, namely carotid-femoral PWV(cfPWV)[39], or BP. Exclusion criteria included studies that involved: (1) laboratory experiments (i.e. treadmill running); (2) no pre- or post-race measurements.

2.2 Data sources and search strategy

The electronic databases of PubMed (MEDLINE), Scopus, SPORTDiscus and Web of Science were systematically searched, covering the period from database inception to 18th January 2021. The search strategy included terms for the three key outcomes: "heart rate variability", "arterial stiffness", and "long-distance races". The different terms of the respective outcomes were searched individually with Boolean operator OR, then combined using Boolean operator AND (heart rate variability AND long-distance races; arterial stiffness AND long-distance races). The search strategies were modified for each database to maximize sensitivity. The full search strategy is detailed in the Supplementary Material Appendix S1.

Additionally, reference lists of relevant articles and reviews identified in the searches were checked to find potentially relevant studies. Two authors conducted the literature search, reviewed the titles and abstracts, and checked if the article could be included in the review according to the inclusion criteria. Relevant articles were obtained in full, and the same authors independently assessed for eligibility. Disagreements at any stage were resolved by discussion. When consensus was not reached, a third author reviewed the debated articles.

2.3 Outcome measures and data extraction

Sample sizes of the studies, characteristics of the subjects (age, sex and body mass index), LDR details (distance, terrain, and maximum altitude achieved during the race), details of the pre-post measurements (time before and after the race, technique and body position), and main outcome measures (HRV and AS) were extracted from study reports using a piloted extraction form. Outcome data were registered as means and standard deviation (SD) or standard error of the mean (SEM). If adequate data for meta-analysis was not reported, the corresponding author was contacted and asked for clarifications and to provide missing data. When a response could not be obtained and relevant data were graphed, Web Plot Digitizer[40] was used to obtain data from figures, as described previously[41]. If subjects were repeatedly tested after the race, only the first measurement following race cessation was used for analysis to avoid unit-of-analysis error[37].

2.4 Risk of bias assessment

The risk of bias within included studies was assessed using the integrated quality criteria for the systematic review of multiple study designs (ICROMS) tool[42]. Given the type of studies included in the review ('non-controlled before-after'), the 15 specific criteria established by the ICROMS tool were applied. According to the assessment scale used, the maximum quality score was 30, and according to the 'decision matrix' also included in the ICROMS tool, the minimum score for each study to be included in the review was 22. However, since no clear gold standard for quality assessment method in the review of observational studies exists, and misclassification of study quality may occur[43], we catalogued the studies that did not reach the minimum score as studies with a 'high risk of bias' rather than exclude them automatically. We then performed quantitative analyses by including and excluding studies classified as 'high risk of bias' to check whether they might be altering the meaning or magnitude of the results.

2.5 Statistical analysis

2.5.1 Assessment of effect size. Meta-analyses were performed using OpenMeta[Analyst][44, 45]. A random-effects model (DerSimonian-Laird method) was used to account for possible between-study heterogeneity regarding study design, the methodology used to assess HRV and AS, and subject's characteristics[37]. Hedges' g corrected standardized mean difference (SMD), and 95% confidence intervals (CI) values were calculated as the difference in means before and after the LDR divided by the pooled standard deviation. Separate meta-analyses were performed with those variables for which the effect size could be calculated from the reported results in at least four different studies. This was possible for HR, five HRV related variables (the standard deviation of the NN intervals (SDNN), the square root of the mean squared differences of successive NN intervals (RMSSD), power in the low-frequency band (LF), power in the high-frequency band (HF), LF/HF ratio), and for four AS related variables (cfPWV, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)). The SMD measure was used to express effect size pre-post LDR, and its interpretation followed Cohen's classification. Consequently, SMD values of 0.2-0.5, 0.5-0.8, and >0.8 were interpreted as small, moderated and large effect sizes, respectively[46]. Data originally reported as mean ± standard error or mean ± CI were converted to mean ± standard deviation for consistency following Cochrane guidelines[37]. Data reported in logarithm-scale were transformed to raw data as described by Higgins et al.[47] to enable meta-analysis on the raw-scale alongside other included studies. *P* values less than 0.05 were considered statistically significant.

2.5.2 Assessment of heterogeneity. The heterogeneity level in the network of studies was expressed via the magnitude of the between-study variance Tau-square[37]. The null hypothesis of homogeneity of true effects was tested using Q-test. The variability in effect estimates due to heterogeneity rather than sampling error (chance) was assessed by the I^2 statistic. The I^2 values of 30-50%, 50-75%, and >75% were interpreted as moderate, substantial and considerable heterogeneity, respectively[37].

2.5.3 Publication bias. We searched for potential publication bias by visually analysing funnel plots symmetry. Effect estimates were plotted against the standard error of the effect estimate on the vertical axis. Despite the well-documented limitations on this simplistic interpretation, asymmetrical funnel plots were considered to indicate a high risk of publication bias, while symmetrical funnels plots were considered to indicate low risk[37]. Egger's regression asymmetry test was also used, taking values of <0.10 as a reference to determine the possibility of publication bias[37, 48]. Additionally, and also despite its known limitations[37]. the Rosenthal's Fail-Safe N sensitivity test[49] was calculated to explore publication bias's potential when the funnel plot showed asymmetry.

2.5.4 Effect modifiers analysis. Moderator analyses were conducted using subgroups analyses and meta-regressions. Separate meta-analyses were performed for the relevant subgroups with those outcomes reported in more than ten studies[37]. Differences between subgroups were examined by checking the confidence interval of each summary mean difference[37]. In addition, differences between subgroups were also investigated via meta-regression. This was possible only for the following three outcomes: HR, SBP, and DBP. The pre-specified characteristics subject to subgroup analyses and meta-regression were: (i) time point of post-race assessment (≤ 30 minutes, 31-60 minutes, and > 60 minutes after race cessation); (ii) body position during assessments; (iii) race length (marathon, ultra-marathon); (iv) type of race (road, off-road); (v) maximum altitude above sea level achieved during the race (< 2000 m: "low altitude", > 2000 m: "moderate/high altitude")[28].

3. RESULTS

3.1 Study selection

The initial search identified 2,220 articles, and four additional articles were identified following inspection of the reference lists of relevant articles. After removing duplicates, 1,073 articles were screened by their titles, and 170 articles were selected. Abstracts of the selected articles were then screened, and 103 were excluded, leaving 67 articles for full-text review. Fifteen articles were excluded due to the following reasons: (i) reported outcome measures not included in the present review (n=10) ; (ii) no LDR (n=3) ; (iii) no pre- post-LDR assessment (n=2). A total of 52 articles were included in the qualitative analysis. Six studies provided data in an unsuitable form for SMD calculation, and their authors were contacted by e-mail. Two of them replied and provided the requested data[50, 51]. The other four could not be effectively contacted, or no response was received, and therefore could not be included in the quantitative analysis[10, 52-54]. Thus, a total of 48 studies were included in the meta-analysis. Figure 1 illustrates the study selection process in a PRISMA flow diagram.

Figure 1 around here

3.2 Study characteristics

The main characteristics of the fifty-two included articles are summarized in Table 1.

3.2.1 Population. This review includes 1,245 subjects in the quantitative analysis, of which 1,027 are men, 130 women, and 88 are unknown. All athletes were over 18 years of age, and the mean age ranged from 27.4 to 51.6 years of age.

3.2.2 LDR. Twenty-three studies assessed the effects of running a road marathon (42.2 km on flat course), one studied an off-road marathon (42.2 km on trail terrain with altitude changes), nine studied road ultra-marathons (> 42.2 km on flat course) ranging from 80 to 246 km, and twenty-five studied off-road ultra-marathons (> 42.2 km on trail terrain with altitude changes), ranging from 46 to 195 km. Note that the number of studies sums up to 58 because five articles reported the results of two subsamples separately[4, 36, 51, 54, 55] and one article of three subsamples separately[12]. From those studies which reported the maximum altitude above sea level achieved during the race, twenty-six were under 1,000 m of altitude, four ranged from 1,000 to 2,000 m, eight ranged from 2,000 to 3,000 m, and three achieved an altitude higher than 3,000 m (4,400 m maximum).

Table I around here

3.3 Risk of bias

The average ICROMS score for all studies was 25.3 out of a possible maximum score of 30. Thirty-five studies obtained a score greater than 25, of which five obtained the maximum score. Only two studies were classified as "high risk of bias" for receiving a score of less than 22. The summary of the risk of bias within studies is presented in Table 2.

Table II around here

Supplementary material Appendix S2 shows funnel plots for those outcomes with at least ten studies included in the meta-analysis, namely HR, RMSSD, MAP, SBP, and DBP. Visual inspection did not suggest publication bias for RMSSD, SBP and DBP, but showed a slight asymmetrical appearance for HR, and MAP, suggesting either publication bias or true nonexistence of the studies that would be located in the areas of the base where they are now missing. However, Egger’s test did not show potential publication bias neither for HR (p = 0.78) nor for MAP (p = 0.67). Furthermore, Rosenthal's fail-safe N test showed that 23,591 missing samples would be needed to make the correlation nonsignificant for HR, and 157 for MAP, suggesting that publication bias, if exists, would have only a minimal influence on the observed correlations.

3.4 Meta-analyses

3.4.1 HRV. HR and time-domain indices of HRV, such as RMSSD, and SDNN were reported in forty-eight, ten, and seven studies respectively. The pooled analysis revealed a significant large increase in HR (figure 2 ; SMD = 2.07 ; 95% CI 1.87, 2.27 ; p <0.01), and a significant large decrease in RMSSD (figure 3 (A); SMD = -0.81; 95% CI -1.18, -0.44; $p < 0.01$) and SDNN (figure 3 (B); SMD = -0.90; 95% CI -1.40, -0.41; $p < 0.01$). Significant substantial heterogeneity between studies was observed in the three outcomes: HR ($I^2 = 68.91\%$; $p < 0.01$), RMSSD ($I^2 = 55.31\%$; $p = 0.02$), and SDNN ($I^2 = 67.50\%$; $p < 0.01$). Frequency-domain variables such as LF and HF power were reported in nine studies, and LF/HF ratio was reported in eight studies. No significant change was observed in LF (figure 4 (A); SMD = -0.12; 95% CI -0.49, 0.24; $p = 0.51$), whereas a significant moderated decrease in HF (figure 4 (B); SMD = -0.64; 95% CI -0.90, -0.39; $p < 0.01$), and a significant small increase in LF/HF ratio (figure 4 (C); SMD = 0.42; 95% CI 0.08, 0.76; $p < 0.01$) was found. Significant moderate heterogeneity between studies was observed in LF ($I^2 = 49.45\%$; $p = 0.05$), whereas non-significant no heterogeneity was observed in HF ($I^2 = 0\%$; $p = 0.56$) and LF/HF ratio ($I^2 = 36.45\%$; $p = 0.14$).

Figure 2 around here

Figure 3 around here

Figure 4 around here

3.4.2 AS. CfPWV was reported in eight studies. As seen in figure 5, a small but significant decrease was observed post-race (SMD = -0.39; 95% CI -0.69, -0.09; $p = 0.01$). No significant moderate heterogeneity between studies was found ($I^2 = 34.89\%$; $p = 0.15$). Similarly, a significant reduction in BP was identified following an LDR, with significant negative SMD post-race compared to pre-race in SBP, DBP and MAP. As shown in figure 6 (A), there was a significant large decrease in SBP (SMD = -0.81; 95% CI -0.94, -0.67; $p < 0.01$), with significant moderate heterogeneity between studies ($I^2 = 51.68\%$; $p < 0.01$). A moderated significant decrease in DBP and MAP was also observed (figure 6 (B); SMD = -0.77; 95% CI -0.93, -0.60; p <0.01; and figure 6 (C); SMD = -0.74; 95% CI

-1.1, -0.39; $p < 0.01$ respectively), both with substantial heterogeneity between studies ($I^2 = 62.18\%$; $p < 0.01$; and $I^2 = 60.06\%$; $p < 0.01$ respectively).

Figure 5 around here

Figure 6 around here

3.5 Additional analyses

Subgroup analyses and meta-regressions were performed for outcomes reported in more than ten studies[37] (i.e. HR, SBP, and DBP). Supplementary material Appendix S3 shows bubble plots of meta-regressions that reached statistical significance.

3.5.1 Timepoint of post-race assessment. Subgroup analysis revealed a significant influence of the time point of post-race assessment on the magnitude of effects, only for HR. When the studies were clustered in three subgroups (≤ 30 minutes, 31-60 minutes, and > 60 minutes after race cessation), a difference between effect sizes pooled within subgroups was found. The SMD for the subgroup of studies which assessed HR up to 30 min after race cessation was 2.11 (95% CI 1.87, 2.35; $p < 0.01$); 2.07 (95% CI 1.58, 2.56; $p < 0.01$) within 31-60 min after the race; and 1.86 (95% CI 1.20, 2.52; $p < 0.01$) later than 60 min after race cessation. The meta-regression showed a small but significant association between time point of post-race assessment (min) and magnitude of effects (covariate coefficient = -0.001; 95% CI -0.02, 0.00; $p = 0.03$).

3.5.2 Body position during assessments. Subgroup analysis revealed influence of the body position during assessments pre- post-race on the magnitude of effects for BP. Supine positions induced greater effects than seated positions on SBP (SMD = -0.85; 95% CI -1.00, -0.71; $p < 0.01$ vs SMD = -0.49; 95% CI -0.76, -0.22; $p < 0.01$) and DBP (SMD = -0.67; 95% CI -0.84, -0.50; $p < 0.01$ vs SMD = -0.44; 95% CI -0.84, -0.03; $p = 0.03$). However, the effect on HR was practically identical in studies that assessed it in the supine position and those that assessed it in the seated position (SMD = 2.16; 95% CI -1.90, 2.41; $p < 0.01$ vs SMD = 2.19; 95% CI 1.72, 2.16; $p < 0.01$).

3.5.3 Race distance. Subgroup analysis revealed influence of the race distance on the magnitude of effects for HR, SBP, and DBP. When the studies were clustered in two subgroups (marathon, ultra-marathon), a difference between effect sizes pooled within subgroups was found. Marathon races induced greater effects than ultra-marathon races on HR (SMD = 2.41; 95% CI 2.11, 2.71; $p < 0.01$ vs SMD = 1.81; 95% CI 1.59, 2.02; p <0.01 respectively) and DBP (SMD = -0.77; 95% CI -1.04, -0.70; $p < 0.01$ vs SMD = -0.75; 95% CI -0.96, -0.26; $p < 0.01$ respectively), whereas ultra-marathon races produced greater effects than marathon races on SBP (SMD = -0.88; 95% CI -1.08, -0.67; $p < 0.01$ vs SMD = -0.73; 95% CI -0.89, -0.56; $p < 0.01$ respectively). The meta-regression showed a small but significant association between race distance (km) and magnitude of effects on HR (covariate coefficient = -0.004; 95% CI -0.08, 0.00; $p = 0.04$). Meta-regressions with SBP and DBP did not reach statistical significance.

3.5.4 Terrain. Subgroup analysis revealed influence of the type of race on the magnitude of effects for HR, SBP, and DBP. When the studies were clustered in two subgroups (road, off-road), a difference between effect sizes pooled within subgroups was found. Road races produced greater effects than off-road races on HR (SMD = 2.17; 95% CI 1.91, 2.44; $p < 0.01$ vs SMD = 1.95; 95% CI 1.66, 2.24; $p <0.01$ respectively) SBP (SMD = -0.87; 95% CI -1.04, -0.70; $p < 0.01$ vs SMD = -0.71; 95% CI -0.93, -0.49; $p < 0.01$ respectively), and DBP (SMD = -0.83; 95% CI -1.07, -0.58; $p < 0.01$ vs SMD = -0.67; 95% CI -0.85, -0.49; $p < 0.01$ respectively).

3.5.5 Altitude. Subgroup analysis revealed influence of the maximum altitude above sea level achieved during the race on the magnitude of effects for HR, SBP, and DBP. When the studies were clustered in two subgroups ("low altitude", "moderate/high altitude"), a difference between effect sizes pooled within subgroups was found. Low altitude races produced greater effects than moderate/high altitude races on HR (SMD = 2.13; 95% CI 1.87, 2.39; $p < 0.01$ vs SMD = 1.88; 95% CI 1.49, 2.28; $p < 0.01$ respectively), SBP (SMD = -0.90; 95% CI -1.06, -0.73; $p < 0.01$ vs SMD = -0.45; 95% CI -0.79, -0.20; $p < 0.01$ respectively), and DBP (SMD = -0.79; 95% CI -0.99, -0.59; $p < 0.01$ vs SMD = -0.61; 95% CI -0.85, -0.38; $p < 0.01$ respectively). However, meta-regressions with HR, SBP and DBP did not reach statistical significance.

3.6 Synthesis of results

In summary, as shown in Table III, a significant decrease in the time-domain measures (SDNN; RMSSD) and in the frequency-domain measure HF power, along with a significant increase in HR and in the ratio of LF to HF power, were observed following the participation in an LDR. Based on Cohen's classification, the effect was large (> 0.8) on HR, RMSSD, and SDNN post-race, moderated (0.5-0.8) on P_{HF}, and small (0.2-0.5) on LF/HF ratio.

Furthermore, a significant decrease in AS and BP was observed, with negative SMD pre-post-race in cfPWV, SBP, DBP and MAP. Based on Cohen's classification, the effect was large on SBP post-race, moderated on DBP and MAP, and small on cfPWV.

Subgroup analyses and meta-regressions revealed a small but significant association between timing of post-race measurement and pre-post change only for HR, indicating that early post-race measurements were more likely to show greater effects on HR compared to a later measurement. Pre- and post-race assessments in the supine position showed a greater decrease in SBP and DBP than those in the seated position. The race distance was associated with greater effects on SBP and with smaller effects on DBP and HR. The regression coefficient only reached statistical significance for race distance and HR, indicating that longer races (ultra-marathons) were more likely to show smaller effects on HR post-race than shorter ones (marathons). Road races were associated with greater HR, SBP, and DBP post-race decreases compared to off-road races. Finally, the maximum altitude reached during the race was inversely associated with pre-post changes on examined outcomes. Low altitude races showed greater decreases in HR, SBP, and DBP than moderate/high altitude races. However, the regression coefficient did not reach statistical significance A summary of subgroup analyses and meta-regressions is shown in Table IV.

Table III around here

Table IV around here

4. DISCUSSION

The current systematic review with meta-analysis showed that LDRs are associated with acute effects on HRV and AS. The pooled analysis identified reduced parasympathetic activity of the ANS, and reduced AS and BP post-race. Additionally, distance and altitude showed an inverse relationship with the effects' magnitude. Furthermore, road races seem to induce larger effects than off-road races. From a methodological point of view, the time elapsed between the end of the race and assessments showed an inverse relationship with the magnitude of the effects on HR and BP. In addition, supine assessments showed larger decreases in BP than those performed in a seated position.

The observed pre- post-LDR changes in ANS activity reflect the parasympathetic withdrawal expected to occur as a result of exercise (indicated by a decrease in HRV)[26]. Most of the studies have reported reduced HRV indices usually considered as markers of overall variability[26] such as SDNN[24, 66, 71, 78, 93, 94], and markers of parasympathetic activity[18] such as RMSSD[24, 61, 66, 71, 77-79, 91, 93], and HF[24, 57, 61, 63, 66, 71, 79, 91, 93], showing a typical acute response to a stressor stimulus (i.e. LDR)[18]. HR post-race, which may provide a quantifiable measure of disturbances in autonomic control in response to endurance exercise[23], showed the most remarkable change in the pooled analysis (SMD: 2.07). Current evidence indicates that HRV is more an indicator of parasympathetic than sympathetic activity[16, 23]. However, increased HR after exercise could also be an indicator of increased sympathetic activity[23]. Given our understanding of cardiac autonomic control, post-exercise tachycardia would be influenced by both the withdrawal of parasympathetic activity and the increase in sympathetic activity, among other factors[23, 26]. In this sense, since changes in parasympathetic activity are known to be quick and short-lived, whereas the sympathetic nervous system can attenuate the parasympathetic influence[22], this result suggests that increased HR post-race probably reflects the increase in sympathetic tone caused by the LDR. On a practical level, this means that, once the LDR has finished, even though the stressor stimulus of exercise has ceased, the sympathetic activity would remain increased for some time, returning to its basal level in a time-dependent manner[26]. Although these results indirectly support the hypothesis of increased sympathetic activity, this assumption should be interpreted with caution, as there are actually no HRV parameters that objectively assess sympathetic activity.[26, 95]

The vast majority of the included studies assessed HR and HRV within 60 minutes post-race. The HR showed an inverse relationship between the magnitude of the pre- post-race effects and the time delay between the end of the race and the post-assessment when studies were analysed by subgroups. That is, studies that evaluated later observed smaller effects. A previous review concluded that cardiac parasympathetic reactivation demonstrate a time-dependent recovery and eventual return to pre-exercise levels[15], and this is also confirmed by the results of our meta-regression, which showed a small but significant association between the time point of HR post-race assessment (min) and magnitude of effects (covariate coefficient = 0.001). From a methodological point of view, this enhances the importance of performing the post-exercise measurement at the earliest possible time after the completion of the LDR to assess the real effects that it has induced on the ANS. Additionally, it provides information regarding the monitoring of recovery in the minutes post-exercise that can be taken as a practical reference.

Regarding the race characteristics that showed an influence on the magnitude of ANS disturbance, our analysis suggests that marathon races cause greater disturbance than ultra-marathon races, road races greater disturbance than off-road races, and low altitude races greater disturbance than high altitude races. One possible explanation for these results is that exercise intensity is the key determinant of the ANS disturbance, in agreement with the conclusions of a previous review on cardiac autonomic responses conducted by Michael et al.[26]. Previous studies have concluded that an increase in the race time may reduce relative exercise intensity[93, 96], and this could explain the inverse correlation found between race length (km) and magnitude of effects pre-post on HR (covariate coefficient = -0.004). Road races causing greater ANS disturbance than off-road races could be explained by the higher pace on road races than on off-road ones[97], despite Vernillo et al.[27] concluded that uphill and downhill running causes greater physiological strain than level running. This difference may be because the dynamics of muscle recovery (as studied by Vernillo et al.) and ANS (as analysed in our meta-analysis), although related, do not follow a uniform linear relationship pattern, as seen in previous studies[24]. Similarly, low altitude races causing greater ANS disturbance than high altitude races may seem counterintuitive, since it is well established that altitude and acute hypoxia induce an increase in HR and sympathetic modulation[28, 61]. In this case, a higher intensity in low altitude races may explain, again, this correlation. In a practical sense, this compilation of results would indicate that, concerning the magnitude of the ANS's effect, the intensity at which an LDR is run is more important than the LDR characteristics, but bearing in mind that these characteristics, in turn, influence the intensity of the race. However, since the exercise intensity was not reported in most of the studies included in this review, interpretation of the correlations mentioned above should be made with care. To confirm the aforementioned correlations, future studies will need to be conducted controlling and assessing intensity in LDRs with different length, terrain characteristics, and achieved altitude.

Concerning the AS, the decrease in cfPWV indicates that after running an LDR, there is a decrease in the central (aortic) AS. This effect had previously been observed after moderate-intensity and short-duration exercise[98], and the results of this review confirm that it also occurs after long-duration and strenuous exercise, as is the characteristic of LDRs. The significant and large drop in SBP post-race and the moderated drop on DBP and MAP found in meta-analyses confirm a post-exercise hypotensive response, as previously described following prolonged exercise[99]. In a practical sense, it should be noted that this decrease in BP is considered a normal post-exercise physiological response. Besides, that increased hypotension is not neccesarily associated with an increased risk of syncope[99]. Interestingly, a recent review carried out by Mutter et al.[100] found that immediately post aerobic exercise (0-5 min), the AS of the central arterial segments is increased relative to resting values, and after that (>5 min) decreases to a level at or below resting values. Given the data reported in the studies included in our review and the intrinsic characteristics of assessments made at the end of a real race, we assume that these were made after a time post-exercise greater than 5 minutes. Thus, the results of our meta-analysis would be in line with the findings of this previous review. As happened before with HR post-race measurements, this shows the methodological importance to give consistent results. Even so, it should be noted that none of the reviewed studies by Mutter et al. included an LDR (or a protocol of similar duration and intensity) as the acute physical stressor.

Although most studies report reduced central AS following an LDR[4, 12, 34, 87], this issue remains open for debate since other important studies in the field have reported different outcomes. Vlachopoulos et al.[7] found no significant differences in AS following a marathon; Burr et al.[35] reported decreased arterial compliance (opposite to AS) following a mountain ultra-marathon (120-195 km), and Bonsignore et al.[36] found increased arterial compliance following an 80 km ultra-marathon, but decreased arterial compliance following a 195 km ultra-marathon. It has been proposed that particularly long duration races may have adverse effects on AS[4], however, this hypothesis has not been confirmed by subsequent studies, where a decrease has been observed following 50, 80 and 160 km[12]. Overall, the pooled analysis in our review has shown a decrease in central AS and, therefore, not supports the hypothesis of adverse effects on AS caused by long duration races. Nevertheless, we have analyzed AS through cfPWV assessment following an LDR, but we have not included arterial compliance outcomes. In this context, despite AS is the theoretical inverse of arterial compliance, it has been proposed that these measures may differ substantially because of the segments of the body where each method detect the properties of the vessels (cfPWV: aorta; arterial compliance: estimation of all capacitance vessels throughout the body)[4]. Thus, the hypothesis of a different effect on the aorta versus a general effect on the rest of the blood vessels could be maintained. Hence, further research analyzing differences in AS and arterial compliance assessment following a LDR is required to confirm and clarify potential differences.

Regarding the race characteristics which showed an influence on the magnitude of the drop on BP post-race, our analysis suggests that marathon races cause a greater reduction in DBP than ultra-marathon races, but a smaller drop on SBP; road races greater reduction on both SBP and DBP than off-road races; and low altitude races greater drop on both SBP and DBP than high altitude races. In essence, the studied race characteristics had the same moderator effects on BP as on the HR discussed above except for race distance, which positively correlates with the drop in SBP. That is, longer races produced a greater reduction in SBP than shorter ones, the opposite for DBP and HR as discussed above. Previous studies have found that systolic function requires a longer-term effort to be affected than diastolic filling[101]. Interestingly, Middleton et al.[102] concluded in their meta-analysis about left ventricular function immediately following prolonged exercise that exercise duration is an important factor in the impairment of the systolic function. However, they did not find the same impact on the diastolic filling. Nevertheless, it is worth noting that such correlations between race characteristics and BP were only found in our review in the subgroup analysis but did not reach statistical significance in any meta-regressions. Thus, we can conclude that analyzed race characteristics have a greater influence on the pre- post-race effects on HR than on haemodynamics. From a methodological point of view, it should be pointed out that differences were found in the magnitude of the decrease in BP related to the position of the body during the assessments (greater difference in the supine position than in the seated position). This not only confirms that body position influences blood pressure[103], but also highlights the need for pre- and post-race measurements to be conducted under identical conditions to avoid estimation errors due to methodological factors[104].

The relationship between ANS activity, PWV and BP is still a matter of discussion. It has been suggested that increased sympathetic vasoconstrictor mechanisms may increase AS by applying a constraint on the arterial wall[98]. Swierblewska et al.[105] proposed an independent relationship between ANS activity, PWV and BP, hypothesizing that the sympathetic nervous system may promote an increase in PWV by its effects on the renin-angiotensin-aldosterone system, promoting arterial wall fibrosis, and then sympathetic-mediated increases in PWV may precede and promote BP elevations. However, there is a coexistence of sympathetic activation and vasodilation in our results, which may lead to a decreased PWV and BP. This combination has been previously reported following aerobic exercise[98, 106], suggesting that vasodilator effect may offset reflex sympathetic activation directed to the vasculature, opposing excessive drops in BP following exercise. However, a recently publised review centered in resistance exercise, concluded that post-exercise hypotension is unlikely to be mediated by autonomic control[108]. Additionally, it should be noted that the decrease in post- aerobic exercise BP may also be mediated by other factors not included in this review, such as nitric oxide release, histamine release in active skeletal muscle, or increased blood flow to the skin directed to dissipate the temperature increase produced by exercise[107]. Another important possible reason for the diminished BP post-race is dehydration. The effects of fluid loss during exercise have been extensively studied in the literature and include alterations in autonomic regulation, with increased HR and decreased HRV[109], and vascular alterations, such as decreased BP[110] and AS[7]. Furthermore, since PWV is pressure dependent, diminished BP following endurance exercise has been proposed as a potential influencer and confounder in PWV measures[4, 7]. However, the close relationship between AS and BP does not allow the identifying of the true cause and effect relationship, which can be bidirectional[12]. Additionally, other factors may mediate the responses of the ANS and vascular system following an LDR not included in this review. For example, it is known that endurance exercise can alter different pro- and anti-inflammatory markers[13], and it is also known that inflammation interacts with the ANS and vascular system, adding more complexity to the mechanisms of interaction between these systems[111]. It would have been desirable to be able to include in the meta-analysis factors that may influence fluid loss, such as temperature or ambient humidity at the race location, or direct measures of dehydration such as athlete's body mass loss, or monitoring of serum osmolality and plasma sodium concentration[112]. However, because most studies do not specifically report these data, it has not been possible to include them in this review. This leads us to encourage their reporting in future research.

Our review has inherent limitations which need recognition. First, the quasi-experimental study design of included studies is an important limitation of this review and its meta-analyses. This aspect limits the strength of the conclusions, and it may have confounded the observed associations of the review in the same way that not true experimental studies may do so. Second, the noninvasive assessment of AS (i.e. cfPWV) introduces a possibility of estimation error or a misinterpretation of confounding factors. However, given the intrinsic characteristics of pre-post race field investigations and the validity of cfPWV measures for assessing AS (Class I, Level of Evidence A)[115], the use of this outcome is justified for its inclusion in the review and meta-analysis. Third, there was great heterogeneity amongst included studies in terms of participants, LDR characteristics, and outcome assessment. Finally, our subgroups and meta-regression analyses were only possible for HR, SBP and DBP, but not for any time domain or frequency domain HRV indices or specific PWV measurements. Nevertheless, this review's results may contribute to identifying the limitations of current research designs and thus improving the experimental approach of future studies. Furthermore, as a meta-analysis, the present study overcomes the potentially biased review and weighting of the studies' results to date to interpret evidence on these issues.

Summary and Conclusions

This systematic review and meta-analysis shows a shift of autonomic balance toward a reduced vagal tone, along with a drop in BP and reduced AS following an LDR. Furthermore, observed changes in the ANS, haemodynamics, and vascular properties were influenced by the timing of the measurement post-exercise, race distance, the position of the body during the assessments, the type of terrain (road or off-road), and the maximum altitude above sea level achieved during the race. As expected, the observed changes on the ANS and BP were time-dependent; that is, the later the post-race assessment, the smaller the observed changes pre- post-race. However, based on the scientific literature available to date, it is not yet possible to determine precisely the point in time when the effects are greatest and then return to baseline values. Assessments in the supine position showed a greater pre- post-race effect on BP than assessments in the seated position. Interestingly, marathons showed greater effects on the HR and DBP post-race than ultra-marathons, but smaller effects on the SBP. Road races caused greater effects on HR, systolic and diastolic BP than off-road races. Altitude also had an important effect on studied variables. Such is races achieving higher altitudes above sea level showed smaller effects on HR, systolic and diastolic BP than those achieving lower altitudes.

Nevertheless, given the quasi-experimental nature of the studies included in this review, these results should be interpreted cautiously. Future studies with a controlled experimental design are necessary, and further research should be undertaken to study the specific acute effects of running LDRs with different characteristics on the HRV and the AS. Also, in future research, it could be interesting to investigate the long-term effects and adaptations of training and running LDRs on the ANS and vascular properties of athletes. However, based on the acute responses studied, and considering that these responses would be repeated continuously overtime in training for LDRs, we believe that the long-term effects may be positive for both HRV improvement and vascular variables. Finally, in an attempt to standardise and improve further research, we have some practical methodological recommendations that we believe will help to enhance our understanding of the physiological responses in the LDRs studied in this review:

1. It is essential that pre- and post-race assessments be conducted under identical conditions, with particular attention to body position, which should always be reported in the studies. Special attention should be given to the timing of the post-race assessment, which should be carried out as early as possible after the end of the race, to assess the real effects of the race.
2. Given that intensity appears to be the variable with the most significant influence on the responses, it would be recommendable to monitor exercise intensity during the race. The use of heart rate monitors that allow the %HR max or %HR reserve[113] to be recorded would be desirable, but otherwise, it could be assessed with a rating-of-perceived-exertion scale[114].
3. Considering the importance of dehydration on physiological responses, aspects that can influence it, such as temperature and humidity, should be reported. If possible, it would be desirable to assess fluid loss directly by monitoring body mass loss, serum osmolality, or plasma sodium concentration.
4. To provide more exhaustive information and allow a more in-depth study of the causes of the effects, markers of inflammation before and after the race, such as interleukins or C reactive-protein[13], could also be assessed.

Overall, the most important consideration is that further studies on LDR should continue to accumulate more evidence that may confirm, refute or clarify the results obtained in this review.

REFERENCES

1. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol*. Aug 5 2014;64(5):472-81. doi:10.1016/j.jacc.2014.04.058
2. Lambert M, Borresen J. A Theoretical Basis of Monitoring Fatigue: A Practical Approach for Coaches. *International Journal of Sports Science & Coaching*. 2006;1(4):371-388. doi:10.1260/174795406779367684
3. Dawson EA, Whyte GP, Black MA, et al. Changes in vascular and cardiac function after prolonged strenuous exercise in humans. *Journal of applied physiology*. 2008 Nov 2008;105(5)doi:10.1152/japplphysiol.90837.2008
4. Burr JF, Phillips AA, Drury TC, Ivey AC, Warburton DE. Temporal response of arterial stiffness to ultra-marathon. *International journal of sports medicine*. 2014;35(08):658-663.
5. Christou GA, Pagourelias ED, Anifanti MA, et al. Exploring the determinants of the cardiac changes after ultra-long duration exercise: The echocardiographic Spartathlon study. *European Journal of Preventive Cardiology*. 2020:2047487319898782.
6. George K, Spence A, Naylor LH, Whyte GP, Green DJ. Cardiac adaptation to acute and chronic participation in endurance sports. *Heart*. Dec 2011;97(24):1999-2004. doi:10.1136/heartjnl-2011-300536
7. Vlachopoulos C, Kardara D, Anastasakis A, et al. Arterial stiffness and wave reflections in marathon runners. *Am J Hypertens*. Sep 2010;23(9):974-9. doi:10.1038/ajh.2010.99
8. Cejka N, Rüst C, Lepers R, Onywera V, Rosemann T, Knechtle B. Participation and performance trends in 100-km ultra-marathons worldwide. *Journal of sports sciences*. 2014 2014;32(4)doi:10.1080/02640414.2013.825729
9. Millet GP, Millet GY. Ultramarathon is an outstanding model for the study of adaptive responses to extreme load and stress. *BMC Med*. Jul 19 2012;10:77. doi:10.1186/1741-7015-10-77
10. Franco V, Callaway C, Salcido D, McEntire S, Roth R, Hostler D. Characterization of electrocardiogram changes throughout a marathon. *Eur J Appl Physiol*. Aug 2014;114(8):1725-35. doi:10.1007/s00421-014-2898-6
11. La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *European heart journal*. 2012;33(8):998-1006.
12. King TJ, Coates AM, Tremblay JC, et al. Vascular Function Is Differentially Altered by Distance following Prolonged Running. *Medicine and science in sports and exercise*. 08/15/2020 2020;doi:10.1249/MSS.0000000000002493
13. Barros ES, Nascimento DC, Prestes J, et al. Acute and Chronic Effects of Endurance Running on Inflammatory Markers: A Systematic Review. Systematic Review. *Frontiers in Physiology*. 2017-October-17 2017;8(779)doi:10.3389/fphys.2017.00779
14. Ashley EA, Kardos A, Jack ES, et al. Angiotensin-converting enzyme genotype predicts cardiac and autonomic responses to prolonged exercise. *Journal of the American College of Cardiology*. 08/01/2006 2006;48(3)doi:10.1016/j.jacc.2006.02.071
15. Stanley J, Peake JM, Buchheit M. Cardiac parasympathetic reactivation following exercise: implications for training prescription. *Sports medicine (Auckland, NZ)*. 2013 Dec 2013;43(12)doi:10.1007/s40279-013-0083-4
16. Weberruss H, Maucher J, Oberhoffer R, Müller J. Recovery of the cardiac autonomic nervous and vascular system after maximal cardiopulmonary exercise testing in recreational athletes. *Eur J Appl Physiol*. Jan 2018;118(1):205-211. doi:10.1007/s00421-017-3762-2

17. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *European Heart Journal*. 2006;27(21):2588-2605. doi:10.1093/eurheartj/ehl254

18. Malik M, Bigger JT, Camm AJ, et al. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *European Heart Journal*. 1996;17(3):354-381. doi:10.1093/oxfordjournals.eurheartj.a014868

19. Sassi R, Cerutti S, Lombardi F, et al. Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace*. Sep 2015;17(9):1341-53. doi:10.1093/europace/euv015

20. Singh N, Moneghetti KJ, Christle JW, Hadley D, Plews D, Froelicher V. Heart Rate Variability: An Old Metric with New Meaning in the Era of using mHealth Technologies for Health and Exercise Training Guidance. Part One: Physiology and Methods. *Arrhythm Electrophysiol Rev*. Aug 2018;7(3):193-198. doi:10.15420/aer.2018.27.2

21. Singh N, Moneghetti KJ, Christle JW, Hadley D, Froelicher V, Plews D. Heart Rate Variability: An Old Metric with New Meaning in the Era of Using mHealth technologies for Health and Exercise Training Guidance. Part Two: Prognosis and Training. *Arrhythm Electrophysiol Rev*. Dec 2018;7(4):247-255. doi:10.15420/aer.2018.30.2

22. White DW, Raven PB. Autonomic neural control of heart rate during dynamic exercise: revisited. *The Journal of physiology*. 2014;592(12):2491-2500.

23. Borresen J, Lambert MI. Autonomic control of heart rate during and after exercise. *Sports medicine*. 2008;38(8):633-646.

24. Fazackerley LA, Fell JW, Kitic CM. The effect of an ultra-endurance running race on heart rate variability. *Eur J Appl Physiol*. Sep 2019;119(9):2001-2009. doi:10.1007/s00421-019-04187-6

25. Medeiros AR, Leicht AS, Michael S, Boullosa D. Weekly vagal modulations and their associations with physical fitness and physical activity. *European Journal of Sport Science*. 2020:1-11.

26. Michael S, Graham KS, Davis GM. Cardiac Autonomic Responses during Exercise and Post-exercise Recovery Using Heart Rate Variability and Systolic Time Intervals—A Review. Review. *Frontiers in Physiology*. 2017-May-29 2017;8(301)doi:10.3389/fphys.2017.00301

27. Vernillo G, Giandolini M, Edwards WB, et al. Biomechanics and physiology of uphill and downhill running. *Sports Medicine*. 2017;47(4):615-629.

28. Bärtsch P, Saltin B. General introduction to altitude adaptation and mountain sickness. *Scand J Med Sci Sports*. Aug 2008;18 Suppl 1:1-10. doi:10.1111/j.1600-0838.2008.00827.x

29. Plews DJ, Laursen PB, Stanley J, Kilding AE, Buchheit M. Training adaptation and heart rate variability in elite endurance athletes: opening the door to effective monitoring. *Sports Med*. Sep 2013;43(9):773-81. doi:10.1007/s40279-013-0071-8

30. Athletics W. World Athletics | Our sport. @WorldAthletics. Accessed 31 January 2021, https://worldathletics.org/our-sport

31. Yamamoto Y, Hoshikawa Y, Miyashita M. Effects of acute exposure to simulated altitude on heart rate variability during exercise. *Journal of Applied Physiology*. 1996;81(3):1223-1229.

32. Bhuva AN, D'Silva A, Torlasco C, et al. Training for a first-time marathon reverses age-related aortic stiffening. *Journal of the American College of Cardiology*. 2020;75(1):60-71.

33. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation*. 09/12/2000 2000;102(11)doi:10.1161/01.cir.102.11.1270

34. Deiseroth A, Nussbaumer M, Drexel V, et al. Influence of body composition and physical fitness on arterial stiffness after marathon running. *Scand J Med Sci Sports*. Dec 2018;28(12):2651-2658. doi:10.1111/sms.13283

35. Burr JF, Bredin SS, Phillips A, et al. Systemic arterial compliance following ultra-marathon. *International journal of sports medicine*. 2012;33(03):224-229.

36. Bonsignore A, Bredin SS, Wollmann H, et al. The influence of race length on arterial compliance following an ultra-endurance marathon. *European journal of sport science*. 2017;17(4):441-446.

37. Higgins JP, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons; 2019.

38. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine*. 2009;151(4):264-269.

39. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert Consensus Document on the Measurement of Aortic Stiffness in Daily Practice Using Carotid-Femoral Pulse Wave Velocity. *Journal of hypertension*. 2012 Mar 2012;30(3)doi:10.1097/HJH.0b013e32834fa8b0

40. *WebPlotDigitizer*. Version 4.4. https://automeris.io/WebPlotDigitizer; 2020.

41. Kadic AJ, Vucic K, Dosenovic S, Sapunar D, Puljak L. Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. *Journal of clinical epidemiology*. 2016;74:119-123.

42. Zingg W, Castro-Sanchez E, Secci F, et al. Innovative tools for quality assessment: integrated quality criteria for review of multiple study designs (ICROMS). *Public Health*. 2016;133:19-37.

43. Egger M, Smith GD, Schneider M. Systematic reviews of observational studies. *Systematic reviews in health care: Meta-analysis in context*. 2001:211-227.

44. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of statistical software*. 2010;36(3):1-48.

45. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw*. 2012;49(5):1-15.

46. Cohen J. *Statistical power analysis for the behavioral sciences*. Academic press; 2013.

47. Higgins JP, White IR, Anzures-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. *Statistics in medicine*. 2008;27(29):6072-6092.

48. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. 1997;315(7109):629-634.

49. Rosenthal R. Meta-Analytic Procedures for Social Science Research Sage Publications: Beverly Hills, 1984, 148 pp. *Educational Researcher*. 1986;15(8):18-20.

50. Malek LA, Czajkowska A, Mróz A, Witek K, Nowicki D, Postuła M. Factors Related to Cardiac Troponin T Increase after Participation in a 100 Km Ultra-Marathon. *Diagnostics (Basel)*. Mar 19 2020;10(3)doi:10.3390/diagnostics10030167

51. Trullàs JC, Roca E, Guillermo A, Bové L, Gibert J. Ultra Pirineu 2017: Characteristics of elite and non-elite runners and effects on health of a mountain marathon: Serialmed-UP pilot study. *Apunts Medicina de l'Esport*. 2018;53(200):139-146.

52. Landman ZC, Landman GO, Fatehi P. Physiologic alterations and predictors of performance in a 160-km ultramarathon. *Clin J Sport Med*. Mar 2012;22(2):146-51. doi:10.1097/JSM.0b013e318243ffdc

53. Pressler A, Hanssen H, Dimitrova M, Krumm M, Halle M, Scherr J. Acute and chronic effects of marathon running on the retinal microcirculation. *Atherosclerosis*. 2011;219(2):864-868.

54. Stork TV, Mockel M, Eichstadt H, Muller RM, Hochrein H. Noninvasive assessment by pulsed Doppler ultrasound of left ventricular filling behavior in long distance runners during marathon race. *Am J Cardiol*. Nov 1 1991;68(11):1237-41. doi:10.1016/0002-9149(91)90203-w

55. Gratze G, Mayer H, Luft FC, Skrabal F. Determinants of fast marathon performance: low basal sympathetic drive, enhanced postcompetition vasodilatation and preserved cardiac performance after competition. *Br J Sports Med*. Nov 2008;42(11):882-8. doi:10.1136/bjsm.2007.044271

56. Belinchon-Demiguel P, Clemente-Suárez VJ. Psychophysiological, body composition, biomechanical and autonomic modulation analysis procedures in an ultraendurance mountain race. *Journal of medical systems*. 2018;42(2):32.

57. Bernardi L, Passino C, Robergs R, Appenzeller O. Acute and persistent effects of a 46-kilometer wilderness trail run at altitude: cardiovascular autonomic modulation and baroreflexes. *Cardiovasc Res*. May 1997;34(2):273-80. doi:10.1016/s0008-6363(97)00025-4

58. Blaber AP, Walsh ML, Carter JB, Seedhouse EL, Walker VE. Cardiopulmonary physiology and responses of ultramarathon athletes to prolonged exercise. *Can J Appl Physiol*. Oct 2004;29(5):544-63. doi:10.1139/h04-035

59. Calleja-Romero A, López-Laval I, Sitko S, et al. Effects of a 75-km mountain ultra-marathon on heart rate variability in amateur runners. *J Sports Med Phys Fitness*. Oct 2020;60(10):1401-1407. doi:10.23736/s0022-4707.20.10860-0

60. Christensen DL, Espino D, Infante-Ramirez R, et al. Transient cardiac dysfunction but elevated cardiac and kidney biomarkers 24 h following an ultra-distance running event in Mexican Tarahumara. *Extreme physiology & medicine*. 2017;6(1):3.

61. Cornolo J, Brugniaux JV, Macarlupu JL, Privat C, Leon-Velarde F, Richalet JP. Autonomic adaptations in andean trained participants to a 4220-m altitude marathon. *Med Sci Sports Exerc*. Dec 2005;37(12):2148-53. doi:10.1249/01.mss.0000179901.19280.85

62. Cote AT, Phillips AA, Foulds HJ, et al. Sex differences in cardiac function after prolonged strenuous exercise. *Clinical Journal of Sport Medicine*. 2015;25(3):276-283.

63. Daniłowicz-Szymanowicz L, Szwoch M, Ratkowski W, et al. A 100 km Run Does Not Induce Persistent Predominance of Sympathetic Activity During 24-Hour Recovery in Amateur Male Athletes. *Hellenic J Cardiol*. 2015;56:271-272.

64. Dávila-Román VG, Guest TM, Tuteur PG, Rowe WJ, Ladenson JH, Jaffe AS. Transient right but not left ventricular dysfunction after strenuous exercise at high altitude. *Journal of the American College of Cardiology*. 1997;30(2):468-473.

65. Faconti L, Parsons I, Farukh B, et al. Post-exertional increase in first-phase ejection fraction in recreational marathon runners. *JRSM Cardiovascular Disease*. 2020;9:2048004020926366.

66. Foulds HJ, Cote AT, Phillips AA, et al. Characterisation of baroreflex sensitivity of recreational ultra-endurance athletes. *Eur J Sport Sci*. 2014;14(7):686-94. doi:10.1080/17461391.2014.884169

67. George K, Oxborough D, Forster J, et al. Mitral annular myocardial velocity assessment of segmental left ventricular diastolic function after prolonged exercise in humans. *The Journal of physiology*. 2005;569(1):305-313.

68. Hanssen H, Keithahn A, Hertel G, et al. Magnetic resonance imaging of myocardial injury and ventricular torsion after marathon running. *Clinical science*. 2011;120(4):143-152.

69. Hart E, Shave R, Middleton N, George K, Whyte G, Oxborough D. Effect of preload augmentation on pulsed wave and tissue Doppler echocardiographic indices of diastolic function after a marathon. *Journal of the American Society of Echocardiography*. 2007;20(12):1393-1399.

70. Holtzhausen LM, Noakes TD. The prevalence and significance of post-exercise (postural) hypotension in ultramarathon runners. *Medicine and science in sports and exercise*. 1995 Dec 1995;27(12)

71. Hynynen E, Vesterinen V, Rusko H, Nummela A. Effects of moderate and heavy endurance exercise on nocturnal HRV. *International journal of sports medicine*. 2010;31(06):428-432.

72. Jouffroy R, Caille V, Perrot S, Vieillard-Baron A, Dubourg O, Mansencal N. Changes of cardiac function during ultradistance trail running. *The American journal of cardiology*. 2015;116(8):1284-1289.

73. Jung S-J, Park J-H, Lee S. Arterial stiffness is inversely associated with a better running record in a full course marathon race. *Journal of exercise nutrition & biochemistry*. 2014;18(4):355.

74. Kalliokoski KK, Laaksonen MS, Luotolahti M, et al. Myocardial perfusion after marathon running. *Scandinavian journal of medicine & science in sports*. 2004;14(4):208-214.

75. Krzemiński K, Buraczewska M, Miśkiewicz Z, et al. Effect of ultra-endurance exercise on left ventricular performance and plasma cytokines in healthy trained men. *Biology of Sport*. 2016;33(1):63.

76. Manier G, Wickers F, Lomenech AM, Cazorla G, Roudaut R. Echocardiographic assessment of myocardial performance after prolonged strenuous exercise. *Eur Heart J*. Nov 1991;12(11):1183-8. doi:10.1093/eurheartj/12.11.1183

77. Martínez-Navarro I, Chiva-Bartoll O, Hernando B, Collado E, Porcar V, Hernando C. Hydration Status, Executive Function, and Response to Orthostatism After a 118-km Mountain Race: Are They Interrelated? *The Journal of Strength & Conditioning Research*. 2018;32(2):441-449.

78. Martínez-Navarro I, Sanchez-Gomez JM, Collado-Boira EJ, Hernando B, Panizo N, Hernando C. Cardiac Damage Biomarkers and Heart Rate Variability Following a 118-Km Mountain Race: Relationship with Performance and Recovery. *J Sports Sci Med*. Dec 2019;18(4):615-622.

79. Mertová M, Botek M, Krejčí J, McKune AJ. Heart rate variability recovery after a skyrunning marathon and correlates of performance. *Acta Gymnica*. 2017;47(4):161-170.

80. Mydlík M, Derzsiová K, Bohus B. Renal function abnormalities after marathon run and 16-kilometre long-distance run. *Przegl Lek*. 2012;69(1):1-4.

81. Neilan TG, Yoerger DM, Douglas PS, et al. Persistent and reversible cardiac dysfunction among amateur marathon runners. *European heart journal*. 2006;27(9):1079-1084.

82. Nelson PB, Ellis D, Fu F, Bloom MD, O'Malley J. Fluid and electrolyte balance during a cool weather marathon. *The American journal of sports medicine*. Nov-Dec 1989 1989;17(6)doi:10.1177/036354658901700608

83. Niemela KO, Palatsi IJ, Ikaheimo MJ, Takkunen JT, Vuori JJ. Evidence of impaired left ventricular performance after an uninterrupted competitive 24 hour run. *Circulation*. Sep 1984;70(3):350-6. doi:10.1161/01.cir.70.3.350

84. Oxborough D, Shave R, Middleton N, Whyte G, Forster J, George K. The impact of marathon running upon ventricular function as assessed by 2D, Doppler, and tissue-Doppler echocardiography. *Echocardiography*. Sep 2006;23(8):635-41. doi:10.1111/j.1540-8175.2006.00282.x

85. Passaglia DG, Emed LGM, Barberato SH, et al. Acute effects of prolonged physical exercise: evaluation after a twenty-four-hour ultramarathon. *Arquivos brasileiros de cardiologia*. 2013;100(1):21-28.

86. Perrault H, Peronnet F, Lebeau R, Nadeau RA. Echocardiographic assessment of left ventricular performance before and after marathon running. *Am Heart J*. Nov 1986;112(5):1026-31. doi:10.1016/0002-8703(86)90316-9

87. Phillips AA, Cote AT, Foulds HJ, et al. A segmental evaluation of arterial stiffness before and after prolonged strenuous exercise. *Appl Physiol Nutr Metab*. Aug 2012;37(4):690-6. doi:10.1139/h2012-042

88. Privett SE, George KP, Middleton N, Whyte G, Cable N. The effect of prolonged endurance exercise upon blood pressure regulation during a postexercise orthostatic challenge. *British journal of sports medicine*. 2010;44(10):720-724.

89. Shave R, Dawson E, Whyte G, et al. Evidence of exercise-induced cardiac dysfunction and elevated cTnT in separate cohorts competing in an ultra-endurance mountain marathon race. *International journal of sports medicine*. 2002;23(07):489-494.

90. Roeh A, Schuster T, Jung P, Schneider J, Halle M, Scherr J. Two dimensional and real-time three dimensional ultrasound measurements of left ventricular diastolic function after marathon running: results from a substudy of the BeMaGIC trial. *Int J Cardiovasc Imaging*. Oct 2019;35(10):1861-1869. doi:10.1007/s10554-019-01634-5

91. Scott JM, Esch BT, Shave R, Warburton DE, Gaze D, George K. Cardiovascular consequences of completing a 160-km ultramarathon. *Med Sci Sports Exerc*. Jan 2009;41(1):26-34. doi:10.1249/MSS.0b013e31818313ff

92. Taksaudom N, Tongsiri N, Potikul A, Leampriboon C, Tantraworasin A, Chaiyasri A. Race predictors and hemodynamic alteration after an ultra-trail marathon race. *Open Access J Sports Med*. 2017;8:181-7. doi:10.2147/oajsm.s142040 http://dx.doi.org/10.2147/oajsm.s142040

93. Calleja-Romero A, López-Laval I, Sitko S, et al. Effects of a 75Km mountain ultra-marathon on heart rate variability in amateur runners. *The Journal of sports medicine and physical fitness*. 2020;

94. Martinez-Navarro I, Sanchez-Gomez JM, Collado-Boira EJ, Hernando B, Panizo N, Hernando C. Cardiac Damage Biomarkers and Heart Rate Variability Following a 118-Km Mountain Race: Relationship with Performance and Recovery. *J Sports Sci Med*. Dec 2019;18(4):615-622.

95. Martelli D, Silvani A, McAllen RM, May CN, Ramchandra R. The low frequency power of heart rate variability is neither a measure of cardiac sympathetic tone nor of baroreflex sensitivity. *American Journal of Physiology-Heart and Circulatory Physiology*. 2014;307(7):H1005-H1012.

96. Rodríguez-Marroyo JA, González-Lázaro J, Arribas-Cubero HF, Villa JG. Physiological demands of mountain running races. *Kinesiology*. 2018;50(1):60-66.

97. Staab JS, Agnew JW, Siconolfi SF. Metabolic and performance responses to uphill and downhill running in distance runners. *Medicine and Science in Sports and Exercise*. 1992;24(1):124-127.

98. Heffernan KS, Collier SR, Kelly EE, Jae SY, Fernhall B. Arterial stiffness and baroreflex sensitivity following bouts of aerobic and resistance exercise. *International journal of sports medicine*. 2007 Mar 2007;28(3)doi:10.1055/s-2006-924290

99. Murrell CJ, Cotter JD, George K, et al. Syncope is unrelated to supine and postural hypotension following prolonged exercise. *European journal of applied physiology*. 2011;111(3):469-476.

100. Mutter AF, Cooke AB, Saleh O, Gomez YH, Daskalopoulou SS. A systematic review on the effect of acute aerobic exercise on arterial stiffness reveals a differential response in the upper and lower arterial segments. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2017 Feb 2017;40(2)doi:10.1038/hr.2016.111

101. McGavock JM, Warburton DE, Taylor D, Welsh RC, Quinney H, Haykowsky MJ. The effects of prolonged strenuous exercise on left ventricular function: a brief review. *Heart & lung*. 2002;31(4):279-294.

102. Middleton N, Shave R, George K, Whyte G, Hart E, Atkinson G. Left ventricular function immediately following prolonged exercise: A meta-analysis. 2006.

103. Kallioinen N, Hill A, Horswill MS, Ward HE, Watson MO. Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: a systematic review. *Journal of hypertension*. 2017;35(3):421.

104. Laborde S, Mosley E, Thayer JF. Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Front Psychol*. 2017;8:213. doi:10.3389/fpsyg.2017.00213

105. Swierblewska E, Hering D, Kara T, et al. An independent relationship between muscle sympathetic nerve activity and pulse wave velocity in normal humans. *Journal of hypertension*. 2010;28(5):979-984.

106. Piepoli M, Coats A, Adamopoulos S, et al. Persistent peripheral vasodilation and sympathetic activity in hypotension after maximal exercise. *Journal of Applied Physiology*. 1993;75(4):1807-1814.

107. Brito LC, Fecchio RY, Peçanha T, Andrade-Lima A, Halliwill JR, Forjaz CL. Postexercise hypotension as a clinical tool: a "single brick" in the wall. *Journal of the American Society of Hypertension*. 2018;12(12):e59-e64.

108. Farinatti P, Polito MD, Massaferri R, et al. Postexercise hypotension due to resistance exercise is not mediated by autonomic control: A systematic review and meta-analysis. *Auton Neurosci*. Sep 2021;234:102825. doi:10.1016/j.autneu.2021.102825

109. Macartney MJ, Meade RD, Notley SR, Herry CL, Seely AJE, Kenny GP. Fluid Loss during Exercise-Heat Stress Reduces Cardiac Vagal Autonomic Modulation. *Med Sci Sports Exerc*. Feb 2020;52(2):362-369. doi:10.1249/mss.0000000000002136

110. Romero SA, Minson CT, Halliwill JR. The cardiovascular system after exercise. *Journal of Applied Physiology*. 2017;122(4):925-932.

111. Sheng Y, Zhu L. The crosstalk between autonomic nervous system and blood vessels. *Int J Physiol Pathophysiol Pharmacol*. 2018;10(1):17-28.

112. Bongers CC, Alsady M, Nijenhuis T, et al. Impact of acute versus prolonged exercise and dehydration on kidney function and injury. *Physiological reports*. 2018;6(11):e13734.

113. Karvonen MJ. The effects of training on heart rate: a longitudinal study. *Ann Med Exp Biol Fenn*. 1957;35:307-315.

114. Foster C, Boullosa D, McGuigan M, et al. 25 years of session rating of perceived exertion: Historical perspective and development. *International Journal of Sports Physiology and Performance*. 2021;16(5):612-621.

115. Townsend RR, Wilkinson IB, Schiffrin EL, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. *Hypertension*. 2015 Sep 2015;66(3)doi:10.1161/HYP.0000000000000033

NOTES

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Author's contributions: All authors have given substantial contributions to the conception and the design of the manuscript, acquisition, analysis and interpretation of the data. All authors have participated in drafting the manuscript and revised it critically. All authors read and approved the final version of the manuscript.

Acknowledgement: The authors would like to acknowledge the collaboration of the authors of the articles included in the review Dr Joan Carles Trullàs and Dr Lukasz A. Malek, for their help in providing data from their study when contacted. Also, the authors would like to acknowledge the assistance offered by Dr Jorge Marín-Puyalto in the statistical treatment of the data.

TABLES

Table I.- *Characteristics of the included studies.*

Study	n	Sex (men / women)	Age (years)	BMI (kg m^{-2})	LDR characteristics			Timepoint of measurements		Assessment body position	Main findings
					Length (km)	Terrain	Altitude (m)	PRE (before race)	POST (after race)		
Belinchón-deMiguel et al. (2018)[56]	11	NR	41.82±6.01	24.56±1.90	51.2	Off-road	1,920	NR	Immediately	NR	↑HR; ↓SBP; ↓DBP post-race
Bernardi et al. (1997)[57]	17	13/4	45.7±8.25	22.2±1.65	46	Off-road	3,300	1 day	30 min.	Supine	↑LF/HF ratio; ↓R-R; ↓SBP; ↓DBP 30 min. post-race
Blaber et al. (2004)[58]	8	7/1	35.8±7	20.36	100	Road	< 500	20 min.	5 min.	Seated	↑HR; ↓SBP; ↓DBP; ↓MAP post-race
Bonsignore et al. (2017)[36]	21	15/6	39.8±8.3	23.4±3.2	80	Off-road	2,200	1 day	30 min.	NR	- ↑HR; ↓SBP; ↓DBP; ↓MAP post-race
	25	22/3	43.7±9.8	23.5±2.3	195	Off-road	2,300	1 day	30 min.	NR	- Greater DBP decline following the 195-km race than the 80-km race
Burr et al. (2012)[35]	26	17/9	45±8.2	23.85	120; 195	Off-road	2,300	1 day	Immediately	Supine	↑HR; ↓SBP; ↓DBP post-race
Burr et al. (2014)[4]	9	9/0	43.1±13.4	23.04	75	Off-road	< 500	3 days	Immediately	Supine	- ↓ cfPWV at both the 45-km and the 75-km race - The lowest recorded value

	9	9/0	43.1±13.4	23.04	45	Off-road	< 500	3 days	Immediately	Supine	at the 45-km, but significantly increased towards baseline levels following completion of the full 75-km race
Calleja-Romero et al. (2020)[59]	8	8/0	47.8±7.4	23.1±0.9	75	Off-road	2,645	2 h.	20 min.	Supine	↑HR; ↓RMSSD post-race
Christensen et al. (2017)[60]	10	10/0	29.9±6.6	21.2±1.7	63	Off-road	2,400	1 day	30 min.	Seated	↑HR; ↓SBP post-race
Christou et al. (2020)[5]	27	19/8	45±7	NR	246	Road	1,053	24 h.	10 min.	Supine	↑HR; ↓SBP post-race
Cornolo et al. (2005)[61]	8	8/0	27.4±6.51	21.27±1.78	42.2	Road	4,400	NR	6-8 h.	Supine	Sympathetic predominance was observed after a high-altitude marathon but restored after 24h of recovery
Cote et al. (2015)[62]	25	17/8	44.8±6.6 (men) 45.9±10.2 (women)	24.6 (men) 22.3 (women)	100	Off-road	2,300	1 day	Immediately	Seated	- ↑HR; - Seated BP not significantly reduced post-race
Daniłowicz-Szymanowicz et al. (2015)[63]	17	17/0	42±15	NR	100	Road	NR	1 day	24 h.	NR	No statistically significant differences in HRV values pre- post-race
Dávila-Román et al. (1997)[64]	14	NR	43±8	NR	163	Off-road	4,300	NR	Immediately	NR	- ↑HR; ↓DBP - SBP not significantly different

Deiseroth et al. (2018)[34]	47	47/0	39 (37-44)[†]	24.2 (22.8-27.7)[†]	42.2	Road	< 500	NR	2 h.	NR	- ↓cfPWV post-race - The degree of cfPWV reduction was moderated by the athlete's body composition, with a lesser PWV reduction or even increase in athletes with higher BMI
Faconti et al. (2020)[65]	25	17/8	39.40±9.31	23.46±2.34	42.2	Road	< 500	1-2 days	30 min.	Supine	↑HR; ↓SBP; ↓DBP post-race
Fazackerley et al. (2019)[24]	13	8/5	36.6±7.6	23.1	65	Off-road	< 500	The average of day -4, -3, -2 before the race	Days 1 to 7	Supine	- A very likely: ↑HR; ↓R-R; ↓SDNN (ln); ↓P_{HF} (ln) - A likely: ↓RMSSD (ln); ↓P_{LF} (ln) - A possible: ↓LF/HF ratio
Foulds et al. (2014)[66]	25	17/8	44.6±8.3	23.8±2.1	120; 190	Off-road	2,300	1-4 days	20-30 min.	Seated	Decreased parasympathetic tone and cardiovagal baroreflex sensitivity after ultra-marathon competition with corresponding increases in sympathovagal balance
Franco et al. (2014)[10]	21	15/6	42±13	23±6	42.2	Road	< 500	1-3 h.	Immediately	NR	↑RMSSD post-race
George et al. (2005)[67]	29	23/6	33±10	25.39	42.2	Road	< 500	1 day	30 min.	Supine	↑HR; ↓SBP; ↓DBP post-race

Gratze et al. (2008)[55]	51	25/26	41.6±5.75 (men) 38.7±9.48 (women)	24.0±2.40 (men) 23.1±1.73 (women)	42.2	Road	< 500	1 day	2 h.	Supine	↑HR; ↓SBP; ↓DBP post-race
Hanssen et al. (2011)[68]	28	28/0	41±5	NR	42.2	Road	< 500	5 days	30 min.	Supine	↑HR; ↓SBP; ↓DBP 30post-race
Hart et al. (2007)[69]	14	13/1	34±7	24.9	42.2	Road	< 500	24 h.	30 min.	Supine	↑HR post-race
Holtzhausen et al. (1995)[70]	31	NR	38.9±7.8	NR	80	Road	< 500	1 day	5 min.	Supine	↑HR; ↓SBP post-race
Hynynen et al. (2010)[71]	10	10/0	37±5	24.0±1.8	42.2	Road	< 500	Night after a rest day	Night after the race (afternoon race)	Supine	- ↑Nocturnal HR - ↓ Most HRV indices after the marathon
Jouffroy et al. (2015)[72]	49	49/0	42.8±9.4	22.5±1.8	80	Road	< 500	1 day	Immediately	NR	↑HR; ↓SBP; ↓DBP post-race
Jung et al. (2014)[73]	30	28/2	51.6±8.8	23.1±1.5	42.2	Road	< 500	NR	Immediately	Seated	No significant changes in BP post-race
Kalliokoski et al. (2004)[74]	7	7/0	39±9	22.84	42.2	Road	< 500	In the morning of the race day	Immediately	Supine	- ↑HR post-race - ↓BP but not statistically different
King et al. (2020)[12]	21	11/10	42±10	24±3	50	Off-road	< 500	3 weeks	23-112 min.	Supine	↑HR; ↓SBP; ↓DBP; ↓cfPWV post-race
	13	9/4	44±8	24±3	80	Off-road	< 500	3 weeks	23-112 min.	Supine	
	11	9/2	46±10	25±2	160	Off-road	< 500	3 weeks	23-112 min.	Supine	
Krzemiński et al. (2016)[75]	9	9/0	30±3	22.6±1.20	100	Off-road	1,262	1 week	Immediately	NR	↑HR; ↓DBP post-race

Landman et al. (2012)[52]	52	NR	40 (24-61)‡	22.7(19-28.6)‡	160	Off-road	2,800	1 day	Immediately	Seated	↑HR post-race
Małek et al. (2020)[50]	18	15/3	43.55±10.6	24.5±2.4	100	Road	< 500	NR	Immediately	NR	↑HR; ↓SBP; ↓DBP post-race
Manier et al. (1991)[76]	11	10/1	37±7	21.3	42.2	Road	< 500	Day of the race	30 min.	Supine	↑HR; ↓SBP; ↓DBP post-race
Martínez-Navarro et al. (2018)[77]	16	NR	40.12±7.01	24.43±2.36	118	Off-road	1,280	1 day	30 min.	Supine	↑HR; ↓SDNN (ln); ↓RMSSD (ln); ↓SBP post-race
Martínez-Navarro et al. (2019)[78]	28	28/0	42±7.49	24.56±1.94	118	Off-road	1,280	1 day	5 min.	Supine	↑HR; ↓SDNN; ↓RMSSD post-race
Mertová et al. (2017)[79]	10	10/0	37.2 ±9.2	22.8±1.5	42.2	Off-road	1,027	In the morning of the race day	5 min.	Supine	↑LF/HF ratio; ↓RMSSD; ↓P_{HF} (ln) post-race
Mydlík et al. (2012)[80]	29	28/1	33.5±6	NR	42.2	Road	NR	NR	Immediately	NR	↓SBP; ↓DBP post-race
Neilan et al. (2006)[81]	20	10/10	34±10	NR	42.2	Road	< 500	1 week	Immediately	NR	↑HR; ↓SBP post-race
Nelson et al. (1989)[82]	45	39/6	39.3±12.28	NR	42.2	Road	< 500	Immediately	1 h.	NR	↓SBP; ↓DBP post-race
Niemela et al. (1984)[83]	13	13/0	38±8	22.8	173	Road	NR	NR	25 min.	Supine	↑HR; ↓SBP post-race
Oxborough et al. (2006)[84]	35	29/6	30±8	NR	42.2	Road	< 500	1 day	30 min.	Supine	↑HR; ↓SBP post-race
Passaglia et al. (2012)[85]	12	12/0	43.3±9.9	26±2.6	140.3	Road	900	1 day	Immediately	Supine	↓SBP; ↓DBP post-race
Perrault et al. (1986)[86]	13	13/0	30±5.77	NR	42.2	Road	< 500	3 days	40 min.	Supine	↑HR; ↓SBP post-race

Phillips et al. (2012)[87]	20	13/7	46±7	24±2	120; 195	Off-road	2,300	1-5 days	Immediately	Supine	↑HR; ↓SBP; ↓DBP; ↓MAP post-race
Pressler et al. (2011)[53]	85	85/0	44 (31-60)‡	23.8 (18.5-27.5)‡	42.2	Road	NR	4 weeks	Immediately	NR	↑HR; ↓SBP; ↓DBP post-race
Privett et al. (2010)[88]	10	10/0	29±4	24.6	42.2	Road	< 500	1 day	60 min.	Supine	↑HR post-race
Shave et al. (2002)[89]	11	11/0	42±11	23.82	70	Off-road	NR	1 day	Immediately	Supine	↑HR; ↓SBP; ↓DBP post-race
Roeh et al. (2019)[90]	212	212/0	42 (36-49)‡	23.6±2.1	42.2	Road	NR	In the week pre-race	1 h.	Supine	↑HR post-race
Scott et al. (2009)[91]	16	13/3	41.2±4.7	21.7±2.0	160	Road	NR	NR	Immediately	Supine	↑HR; ↓R-R post-race
Störk et al. (1991)[54]	12	12/0	34±5	NR	42.2	Road	NR	NR	10 min.	Standing	↑HR post-race
	11	11/0	32±7	NR	42.2	Road	NR	NR	10 min.	Standing	
Taksaudom et al. (2017)[92]	33	NR	NR	NR	66	Off-road	NR	1 day	15 min.	Seated	↑HR; ↓SBP post-race
Trullàs et al. (2018)[51]	7	5/2	30.8 (15.2)†	NR	45	Off-road	2,475	The evening before race	15 min.	Seated	- ↑HR post-race - ↓DBP post-race (only in non-elite runners)
	18	16/2	37.5 (9.6)†	NR	45	Off-road	2,475	The evening before race	15 min.	Seated	
Vlachopoulos et al. (2010)[7]	20	16/4	36±10	23.2±1.8	42.2	Road	< 500	2 days	10-15 min.	NR	↑HR; ↓SBP; ↓DBP post-race

Data are expressed in mean ± standard deviation, except if otherwise specified; †: data expressed in median (interquartile range); ‡: data expressed in median (range); NR: not reported; (ln): values underwent a logarithmic transformation.

Altitude: maximum altitude above sea level achieved during the race; BMI: body mass index; BP: blood pressure; cfPWV: carotid-femoral pulse wave velocity; DBP: diastolic blood pressure; HR: heart rate; LDR: long-distance race; MAP: mean arterial pressure; P_{HF}: power in the high-frequency band; P_{LF}: power in the low-frequency band; R-R: mean R-R intervals; RMSSD: square root of the mean squared differences of successive NN intervals; SBP: systolic blood pressure; SDNN: standard deviation of the NN intervals.

Table II.- *Risk of bias using ICROMS tool*[42]

Dimension	**1. Clear aims and justification**	**2. Managing bias in sampling**	**3. Managing bias in outcome measurements and blinding**	**4. Managing bias in follow-up**	**5. Managing bias in other study aspects**	**6. Analytical rigour**	**7. Managing bias in reporting / ethical considerations**	**FINAL SCORE**
Authors (year)	(max. score: 6)	(max. score: 2)	(max. score: 4)	(max. score: 2)	(max. score: 4)	(max. score: 2)	(max. score: 10)	(max. score: 30)
Belinchón-deMiguel et al. (2018)[53]	4	1	4	1	3	2	7	**22**
Bernardi et al. (1997)[54]	4	2	4	1	3	2	8	**24**
Blaber et al. (2004)[55]	4	1	4	2	3	2	10	**26**
Bonsignore et al. (2017)[33]	4	2	4	2	4	2	10	**28**
Burr et al. (2012)[32]	6	2	4	2	4	2	10	**30**
Burr et al. (2014)[4]	5	2	4	2	4	2	9	**28**
Calleja-Romero et al. (2020)[56]	4	2	4	2	3	2	10	**27**
Christensen et al. (2017)[57]	6	2	4	2	4	2	10	**30**
Christou et al. (2020)[5]	4	1	4	2	3	2	10	**26**
Cornolo et al. (2005)[58]	6	2	4	2	4	2	9	**29**
Cote et al. (2015)[59]	4	2	4	2	4	2	10	**28**
Daniłowicz-Szymanowicz et al. (2015)[60]	4	0	4	1	3	0	7	**19**
Dávila-Román et al. (1997)[61]	4	0	4	1	3	2	9	**23**
Deiseroth et al. (2018)[31]	4	2	4	2	4	2	10	**28**
Faconti et al. (2020)[62]	4	2	4	2	4	2	10	**28**
Fazackerley et al. (2019)[23]	4	2	4	2	3	2	9	**26**
Foulds et al. (2014)[63]	6	2	4	2	4	2	6	**26**
Franco et al. (2014)[10]	4	1	4	1	3	2	9	**24**
George et al. (2005)[64]	4	2	4	2	4	2	9	**27**
Gratze et al. (2008)[52]	4	2	4	1	3	2	9	**25**
Hanssen et al. (2011)[65]	4	2	4	2	3	2	8	**25**

Hart et al. (2007)[66]	4	2	4	1	3	2	8	**24**
Holtzhausen et al. (1995)[67]	4	1	4	1	3	2	7	**22**
Hynynen et al. (2010)[68]	4	1	4	1	3	2	10	**25**
Jouffroy et al. (2015)[69]	4	1	4	1	3	2	7	**22**
Jung et al. (2014)[70]	4	1	4	1	3	2	8	**23**
Kalliokoski et al. (2004)[71]	4	1	4	2	3	2	8	**24**
King et al. (2020)[12]	4	1	4	2	3	2	7	**23**
Krzemiński et al. (2016)[72]	6	2	4	2	4	2	10	**30**
Landman et al. (2012)[49]	4	1	4	1	3	2	9	**24**
Małek et al. (2020)[47]	4	1	4	1	3	2	10	**25**
Manier et al. (1991)[73]	4	1	4	1	3	2	10	**25**
Martínez-Navarro et al. (2018)[74]	4	1	4	2	3	2	10	**26**
Martínez-Navarro et al. (2019)[75]	4	1	4	2	3	2	10	**26**
Mertová et al. (2017)[76]	4	1	4	2	3	2	9	**25**
Mydlík et al. (2012)[77]	4	1	4	1	3	2	7	**22**
Neilan et al. (2006)[78]	4	2	4	2	3	1	9	**25**
Nelson et al. (1989)[79]	6	2	4	1	4	2	6	**25**
Niemela et al. (1984)[80]	4	1	4	1	3	2	7	**22**
Oxborough et al. (2006)[81]	4	1	4	2	3	2	7	**23**
Passaglia et al. (2012)[82]	4	1	4	2	3	2	10	**26**
Perrault et al. (1986)[83]	4	1	4	1	3	2	5	**20**
Phillips et al. (2012)[84]	6	2	4	2	4	2	10	**30**
Pressler et al. (2011)[50]	4	2	4	2	3	2	9	**26**
Privett et al. (2010)[85]	4	1	4	2	3	2	10	**26**
Roeh et al. (2019)[87]	4	1	4	2	3	2	9	**25**
Scott et al. (2009)[88]	4	2	4	2	3	2	9	**26**
Shave et al. (2002)[86]	4	1	4	2	3	2	10	**26**

Störk et al. (1991)[51]	6	2	4	2	4	2	4	**24**
Taksaudom et al. (2017)[89]	4	2	4	2	3	2	8	**25**
Trullàs et al. (2018)[48]	4	1	4	2	3	2	9	**25**
Vlachopoulos et al. (2010)[7]	6	2	4	2	4	2	10	**30**

Table III.- *Synthesis of results*

	N	n	Effect				Heterogeneity			
Outcome	Studies	Subjects	SMD	95% C.I.	S.E.	*p*-value	Tau^2	Q	*p*-value	I^2
HR	48	1,121	2.07	1.87; 2.27	0.10	< 0.01	0.31	151.17	<0.01	68.91%
RMSSD	10	151	-0.81	-1.18; -0.44	0.19	< 0.01	0.19	20.14	0.02	55.31%
SDNN	7	117	-0.90	-1.40; -0.41	0.25	< 0.01	0.29	18.46	<0.01	67.50%
P_{LF}	9	124	-0.12	-0.49; 0.24	0.19	0.51	0.15	15.83	0.05	49.45%
P_{HF}	9	124	-0.64	-0.90; -0.39	0.13	< 0.01	0.00	6.79	0.56	0.00%
LF/HF ratio	8	116	0.42	0.08; 0.76	0.17	0.01	0.08	11.02	0.14	36.45%
SBP	45	1,131	-0.81	-0.94; -0.67	0.07	< 0.01	0.10	91.06	<0.01	51.68%
DBP	44	919	-0.77	-0.93; -0.60	0.08	< 0.01	0.17	113.69	<0.01	62.18%
MAP	10	192	-0.74	-1.09; -0.39	0.18	< 0.01	0.18	22.53	<0.01	60.06%
cfPWV	8	150	-0.39	-0.69; -0.09	0.15	0.01	0.06	10.75	0.15	34.89%

N: number of studies included in meta-analysis; n: number of subjects included in meta-analysis; SMD: standardized mean difference; CI: confidence interval; SE: standard error. cfPWV: carotid-femoral pulse wave velocity; DBP: diastolic blood pressure; HR: heart rate; MAP: mean arterial pressure; P_{HF}: power in the high frecuency band; P_{LF}: power in the low frequency band; RMSSD: square root of the mean squared differences of successive NN intervals; SBP: systolic blood pressure; SDNN: standard deviation of the NN intervals.

Table IV.- *Synthesis of subgroup meta-analyses and meta-regressions*

	Subgroup analysis								Meta-regression					
Outcome	Subgroups		N	n	Effect				Timing post-race assessment		Distance		Altitude	
			Studies	Subjects	SMD	95% C.I.	S.E.	p-value	Effect	p-value	Effect	p-value	Effect	p-value
HR	Timing post-race assessment	≤ 30 min	35	667	2.11	1.87; 2.35	0.12	< 0.001	-0.001	0.03	-0.004	0.04	0	0.08
		31-60 min	7	325	2.07	1.58; 2.56	0.25	< 0.001						
		> 60 min	6	129	1.86	1.20; 2.52	0.34	< 0.001						
	Distance	Marathon	21	623	2.41	2.11; 2.71	0.15	< 0.001						
		Ultra-marathon	27	498	1.81	1.59; 2.02	0.11	< 0.001						
	Terrain	Road	26	759	2.17	1.91; 2.44	0.14	< 0.001						
		Off-road	22	362	1.95	1.66; 2.24	0.15	< 0.001						
	Altitude	Low	33	660	2.13	1.87; 2.39	0.13	< 0.001						
		Moderate/High	10	176	1.88	1.49; 2.28	0.20	< 0.001						
SBP	Timing post-race assessment	≤ 30 min	35	708	-0.82	-1.00; -0.64	0.09	< 0.001	0	0.83	0.001	0.48	0	0.04
		31-60 min	7	325	-0.65	-0.81; -0.49	0.08	< 0.001						
		> 60 min	3	98	-0.86	-1.15; -0.56	0.15	< 0.001						
	Distance	Marathon	19	640	-0.73	-0.89; -0.56	0.09	< 0.001						
		Ultra-marathon	26	491	-0.88	-1.08; -0.67	0.11	< 0.001						
	Terrain	Road	25	786	-0.87	-1.04; -0.70	0.09	< 0.001						
		Off-road	20	345	-0.71	-0.93; -0.49	0.11	< 0.001						
	Altitude	Low	29	615	-0.90	-1.06; -0.73	0.08	< 0.001						
		Moderate/High	10	202	-0.45	-0.79; -0.20	0.15	< 0.001						
DBP	Timing post-race assessment	≤ 30 min	35	708	-0.77	-0.96; -0.59	0.09	< 0.001	-0.001	0.71	0.001	0.58	0	0.4
		31-60 min	6	113	-0.53	-0.79; -0.26	0.14	< 0.001						
		> 60 min	3	98	-1.04	-1.77; -0.30	0.38	0.006						
	Distance	Marathon	18	428	-0.77	-1.04; -0.50	0.14	< 0.001						
		Ultra-marathon	26	491	-0.75	-0.96; -0.55	0.10	< 0.001						

	Terrain	Road	24	574	-0.83	-1.07; -0.58	0.13	< 0.001			
		Off-road	20	345	-0.67	-0.85; -0.49	0.09	< 0.001			
	Altitude	Low	29	615	-0.79	-0.99; -0.59	0.10	< 0.001			
		Moderate/High	10	202	-0.61	-0.85; -0.38	0.12	< 0.001			

N: number of studies included in meta-analysis; n: number of subjects included in meta-analysis; SMD: standardized mean difference; C.I.: confidence interval; SE: standard error.
HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Altitude: maximum altitude above sea level achieved during the race; low altitude: < 2000 m. above sea level; moderate/high altitude: > 2000 m. above sea level.

TITLES OF FIGURES

Figure 1.- *PRISMA flow diagram.*

Figure 2.- *Forest plot showing the effect of a long-distance race on heart rate.*

Figure 3.- *Forest plot showing the effect of a long-distance race on time-domain indices of the heart rate variability: (A) RMSSD: square root of the mean squared differences of successive NN intervals; (B) SDNN: standard deviation of the NN intervals.*

Figure 4.- *Forest plot showing the effect of a long-distance race on frequency-domain indices of the heart rate variability: (A)* P_{LF}*: power in the low-frequency band; (B)* P_{HF}*: power in the high-frequency band; (C) LF/HF: ratio low frequency/high frequency.*

Figure 5.- *Forest plot showing the effect of a long-distance race on the carotid-femoral pulse wave velocity (cfPWV)*

Figure 6.- *Forest plot showing the effect of a long-distance race on blood pressure: (A) SBP: systolic blood pressure; (B) DBP: diastolic blood pressure; (C) MAP: mean arterial pressure.*

FIGURES

Figure 1

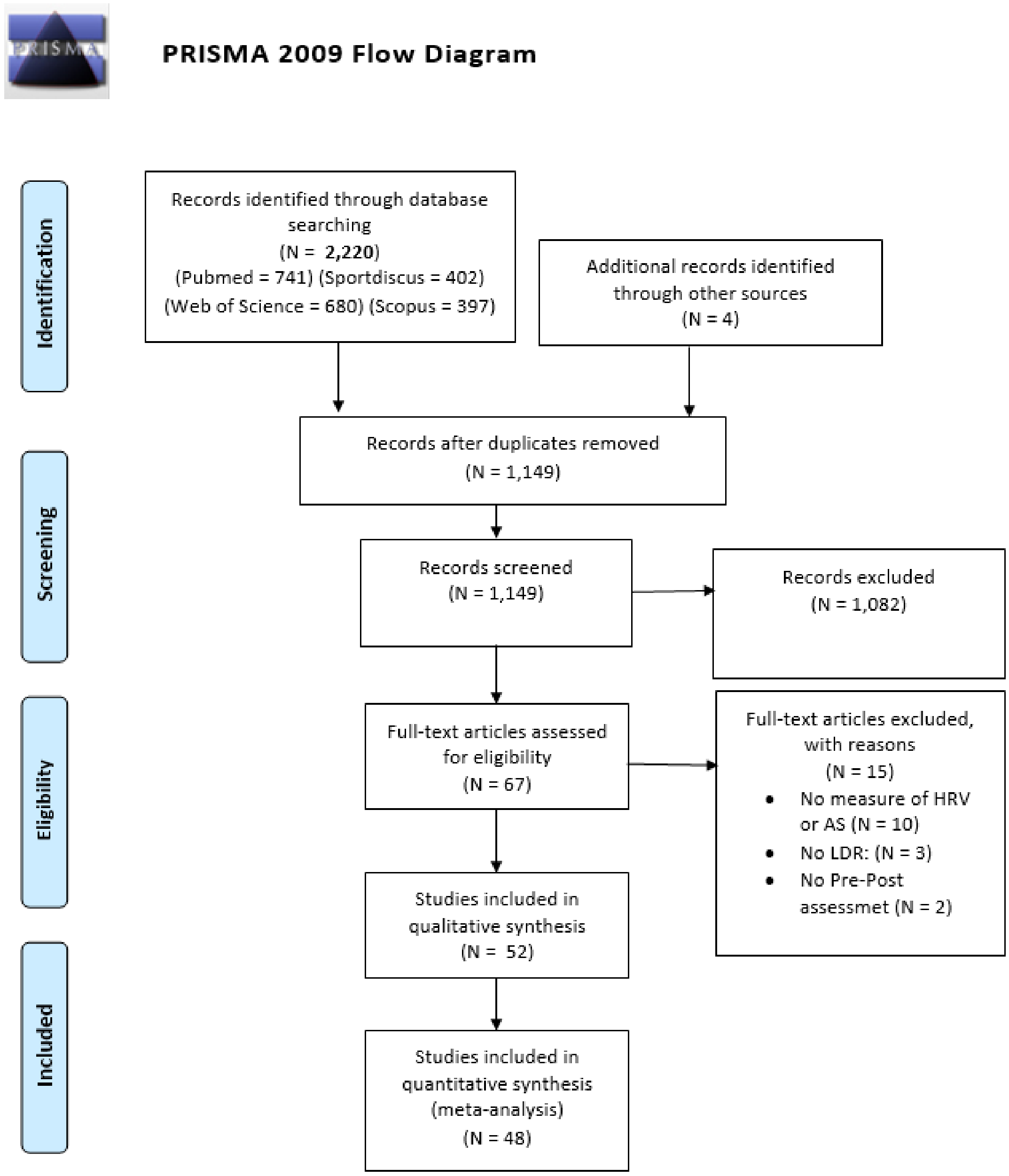
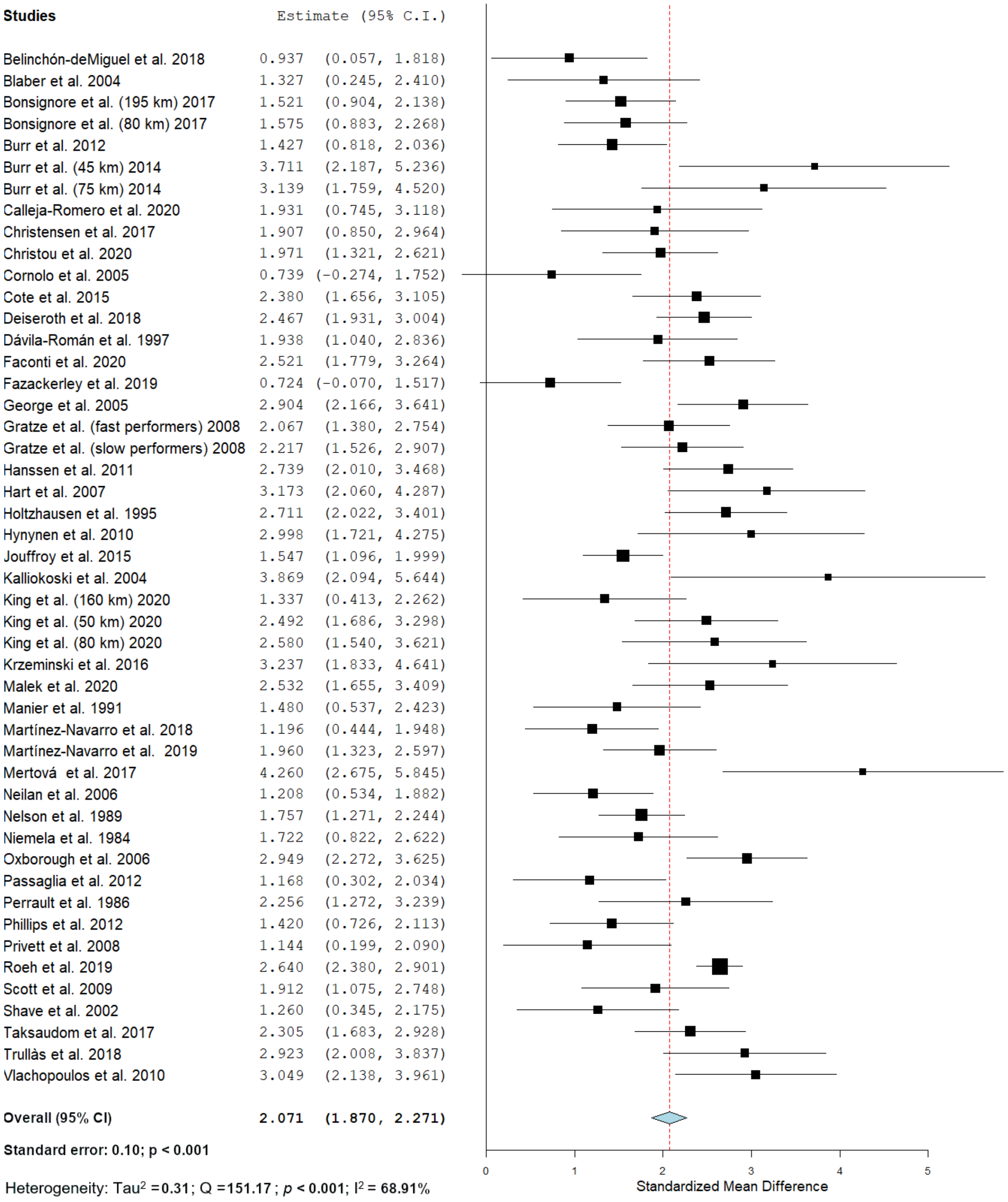


Figure 2



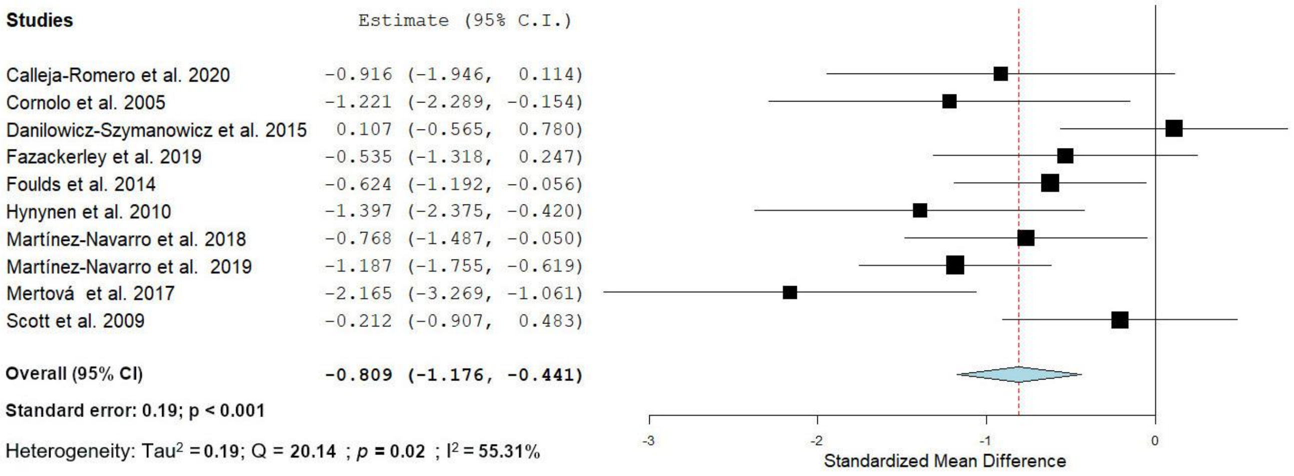
Studies	Estimate (95% C.I.)
Belinchón-deMiguel et al. 2018	0.937 (0.057, 1.818)
Blaber et al. 2004	1.327 (0.245, 2.410)
Bonsignore et al. (195 km) 2017	1.521 (0.904, 2.138)
Bonsignore et al. (80 km) 2017	1.575 (0.883, 2.268)
Burr et al. 2012	1.427 (0.818, 2.036)
Burr et al. (45 km) 2014	3.711 (2.187, 5.236)
Burr et al. (75 km) 2014	3.139 (1.759, 4.520)
Calleja-Romero et al. 2020	1.931 (0.745, 3.118)
Christensen et al. 2017	1.907 (0.850, 2.964)
Christou et al. 2020	1.971 (1.321, 2.621)
Cornolo et al. 2005	0.739 (-0.274, 1.752)
Cote et al. 2015	2.380 (1.656, 3.105)
Deiseroth et al. 2018	2.467 (1.931, 3.004)
Dávila-Román et al. 1997	1.938 (1.040, 2.836)
Faconti et al. 2020	2.521 (1.779, 3.264)
Fazackerley et al. 2019	0.724 (-0.070, 1.517)
George et al. 2005	2.904 (2.166, 3.641)
Gratze et al. (fast performers) 2008	2.067 (1.380, 2.754)
Gratze et al. (slow performers) 2008	2.217 (1.526, 2.907)
Hanssen et al. 2011	2.739 (2.010, 3.468)
Hart et al. 2007	3.173 (2.060, 4.287)
Holtzhausen et al. 1995	2.711 (2.022, 3.401)
Hynynen et al. 2010	2.998 (1.721, 4.275)
Jouffroy et al. 2015	1.547 (1.096, 1.999)
Kalliokoski et al. 2004	3.869 (2.094, 5.644)
King et al. (160 km) 2020	1.337 (0.413, 2.262)
King et al. (50 km) 2020	2.492 (1.686, 3.298)
King et al. (80 km) 2020	2.580 (1.540, 3.621)
Krzeminski et al. 2016	3.237 (1.833, 4.641)
Malek et al. 2020	2.532 (1.655, 3.409)
Manier et al. 1991	1.480 (0.537, 2.423)
Martínez-Navarro et al. 2018	1.196 (0.444, 1.948)
Martínez-Navarro et al. 2019	1.960 (1.323, 2.597)
Mertová et al. 2017	4.260 (2.675, 5.845)
Neilan et al. 2006	1.208 (0.534, 1.882)
Nelson et al. 1989	1.757 (1.271, 2.244)
Niemela et al. 1984	1.722 (0.822, 2.622)
Oxborough et al. 2006	2.949 (2.272, 3.625)
Passaglia et al. 2012	1.168 (0.302, 2.034)
Perrault et al. 1986	2.256 (1.272, 3.239)
Phillips et al. 2012	1.420 (0.726, 2.113)
Privett et al. 2008	1.144 (0.199, 2.090)
Roeh et al. 2019	2.640 (2.380, 2.901)
Scott et al. 2009	1.912 (1.075, 2.748)
Shave et al. 2002	1.260 (0.345, 2.175)
Taksaudom et al. 2017	2.305 (1.683, 2.928)
Trullàs et al. 2018	2.923 (2.008, 3.837)
Vlachopoulos et al. 2010	3.049 (2.138, 3.961)
Overall (95% CI)	**2.071 (1.870, 2.271)**

Standard error: 0.10; p < 0.001

Heterogeneity: Tau^2 =**0.31**; Q =**151.17**; *p* < **0.001**; I^2 = **68.91%**

Figure 3

(A) RMSSD

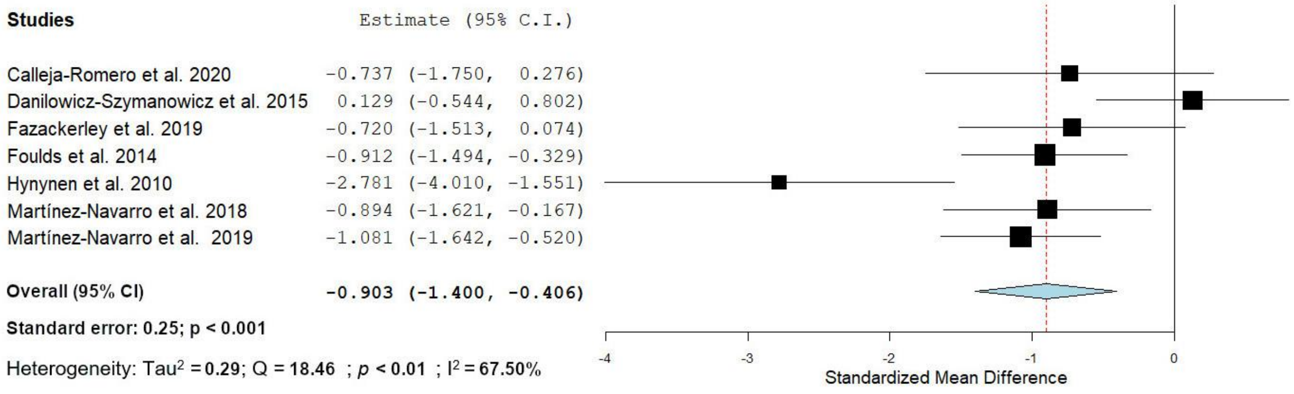


Studies	Estimate (95% C.I.)
Calleja-Romero et al. 2020	−0.916 (−1.946, 0.114)
Cornolo et al. 2005	−1.221 (−2.289, −0.154)
Danilowicz-Szymanowicz et al. 2015	0.107 (−0.565, 0.780)
Fazackerley et al. 2019	−0.535 (−1.318, 0.247)
Foulds et al. 2014	−0.624 (−1.192, −0.056)
Hynynen et al. 2010	−1.397 (−2.375, −0.420)
Martínez-Navarro et al. 2018	−0.768 (−1.487, −0.050)
Martínez-Navarro et al. 2019	−1.187 (−1.755, −0.619)
Mertová et al. 2017	−2.165 (−3.269, −1.061)
Scott et al. 2009	−0.212 (−0.907, 0.483)
Overall (95% CI)	**−0.809 (−1.176, −0.441)**

Standard error: 0.19; p < 0.001

Heterogeneity: Tau^2 = **0.19**; Q = **20.14** ; p **= 0.02** ; I^2 = **55.31%**

(B) SDNN



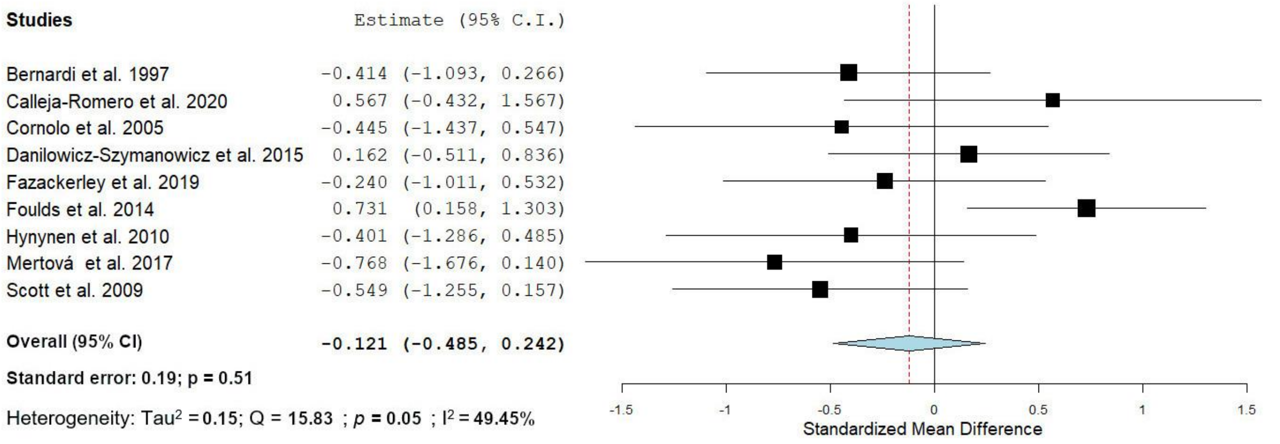
Studies	Estimate (95% C.I.)
Calleja-Romero et al. 2020	−0.737 (−1.750, 0.276)
Danilowicz-Szymanowicz et al. 2015	0.129 (−0.544, 0.802)
Fazackerley et al. 2019	−0.720 (−1.513, 0.074)
Foulds et al. 2014	−0.912 (−1.494, −0.329)
Hynynen et al. 2010	−2.781 (−4.010, −1.551)
Martínez-Navarro et al. 2018	−0.894 (−1.621, −0.167)
Martínez-Navarro et al. 2019	−1.081 (−1.642, −0.520)
Overall (95% CI)	**−0.903 (−1.400, −0.406)**

Standard error: 0.25; p < 0.001

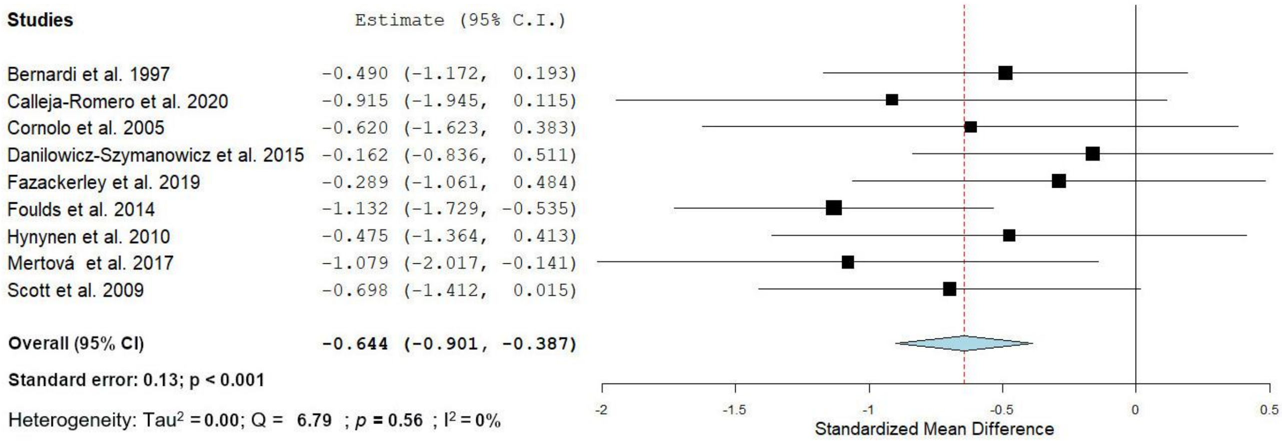
Heterogeneity: Tau^2 = **0.29**; Q = **18.46** ; p **< 0.01** ; I^2 = **67.50%**

Figure 4

(A) P_{LF}



(B) P_{HF}



(C) LF/HF

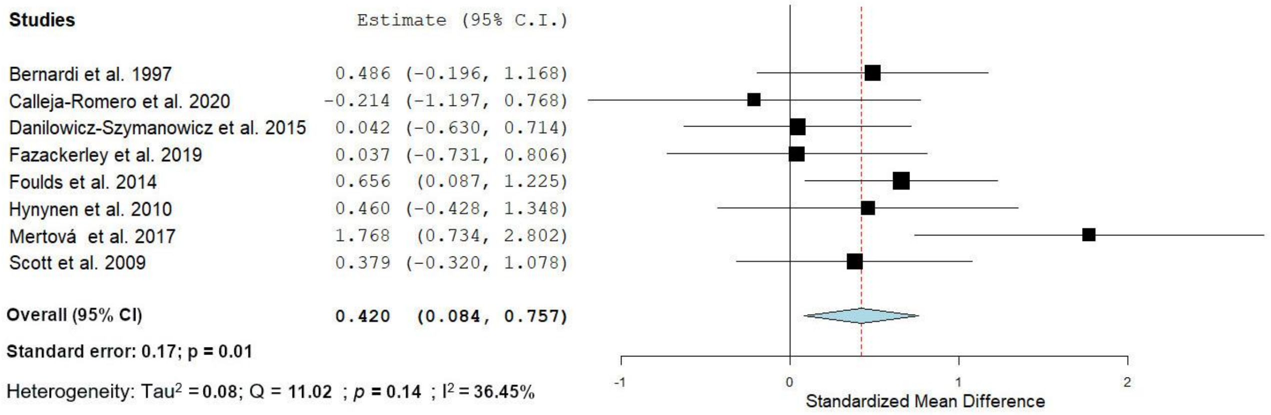
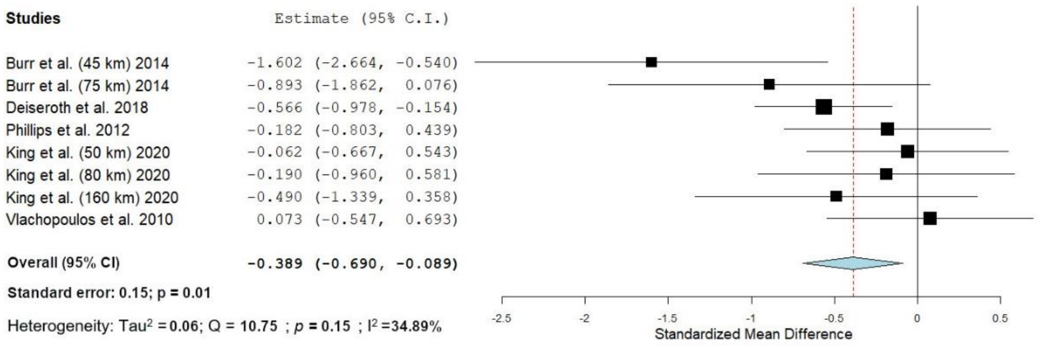


Figure 5

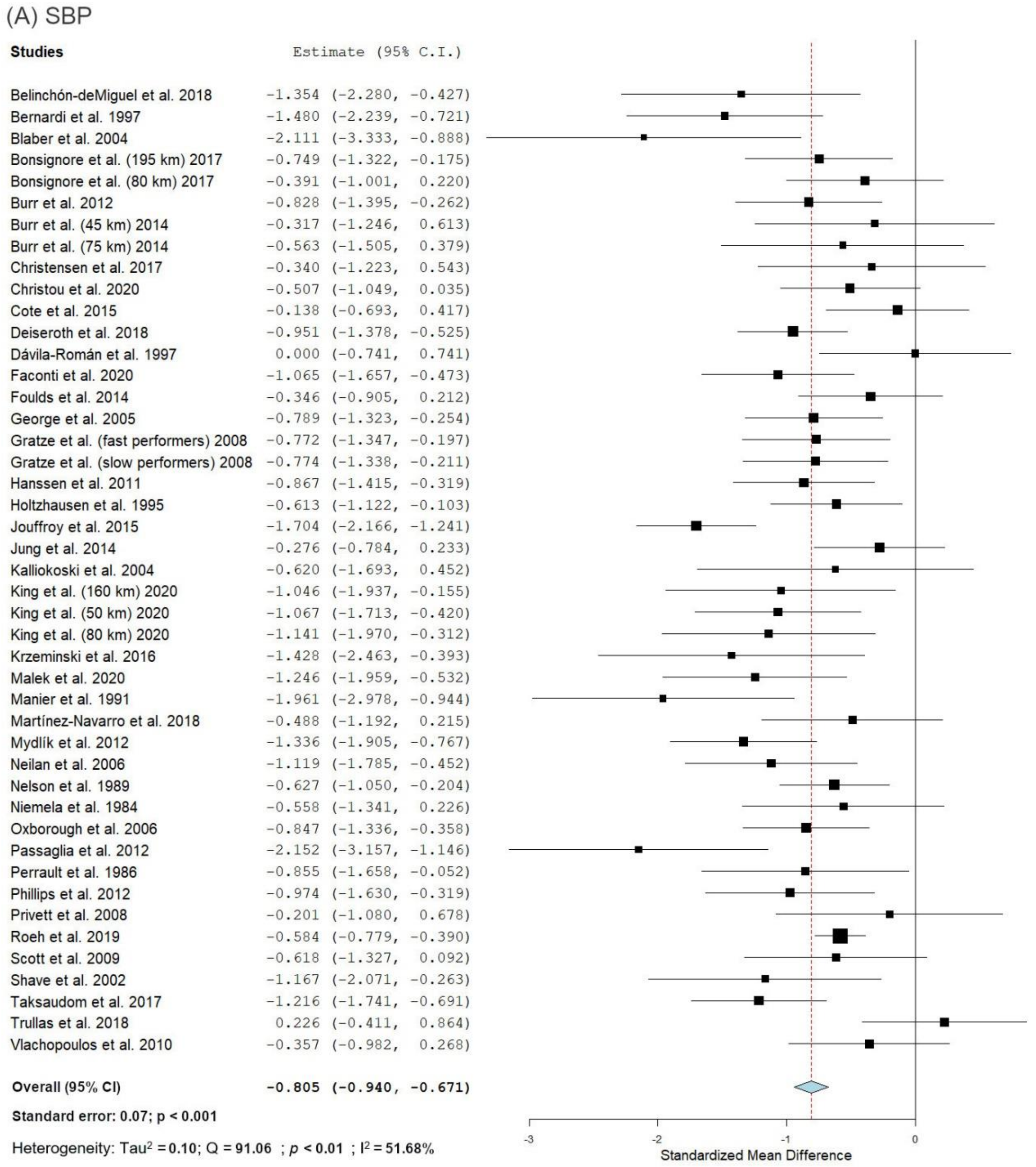


Studies	Estimate (95% C.I.)
Burr et al. (45 km) 2014	−1.602 (−2.664, −0.540)
Burr et al. (75 km) 2014	−0.893 (−1.862, 0.076)
Deiseroth et al. 2018	−0.566 (−0.978, −0.154)
Phillips et al. 2012	−0.182 (−0.803, 0.439)
King et al. (50 km) 2020	−0.062 (−0.667, 0.543)
King et al. (80 km) 2020	−0.190 (−0.960, 0.581)
King et al. (160 km) 2020	−0.490 (−1.339, 0.358)
Vlachopoulos et al. 2010	0.073 (−0.547, 0.693)
Overall (95% CI)	**−0.389 (−0.690, −0.089)**

Standard error: 0.15; p = 0.01

Heterogeneity: $Tau^2 = 0.06$; $Q = 10.75$; $p = 0.15$; $I^2 = 34.89\%$

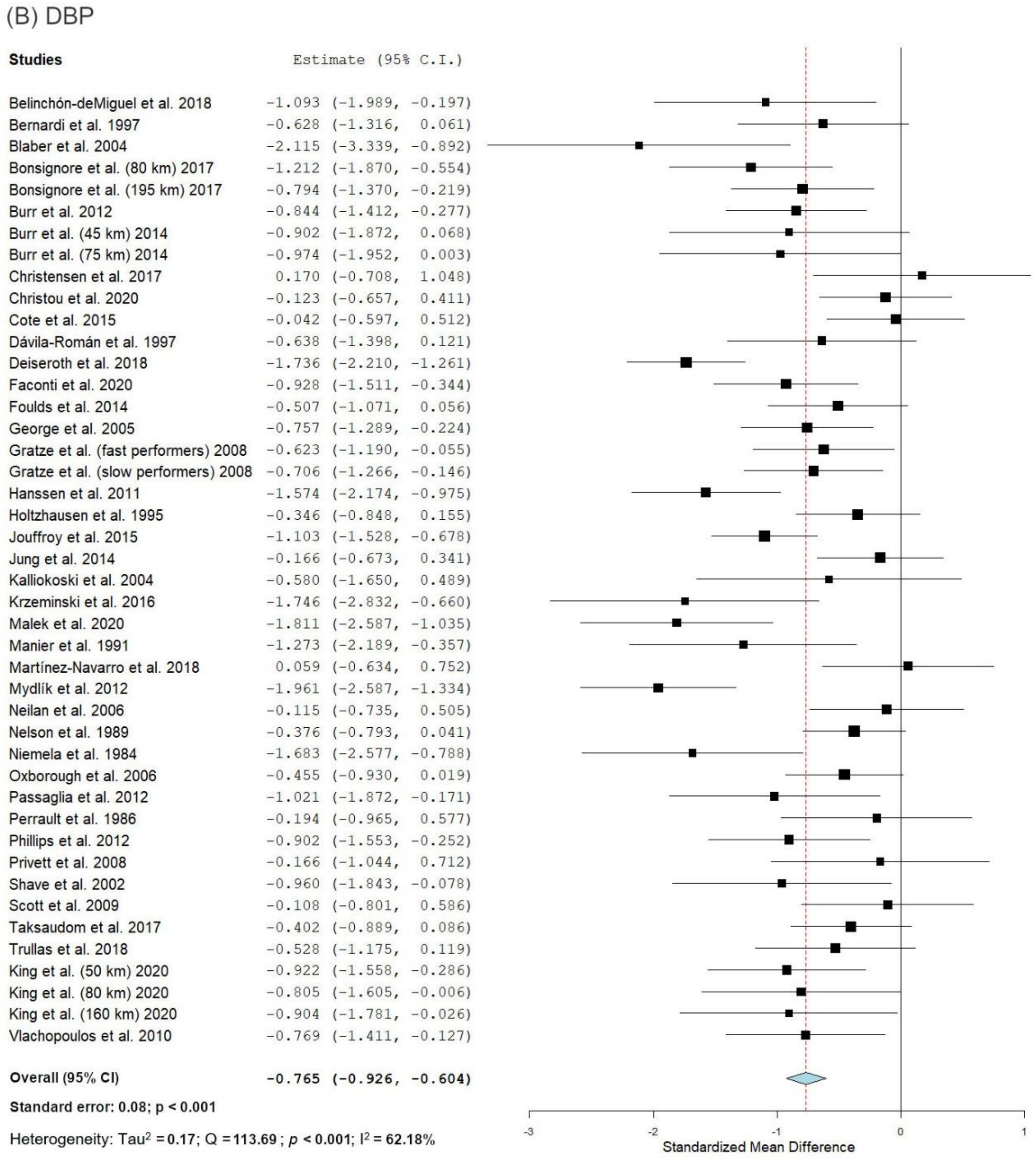
Figure 6



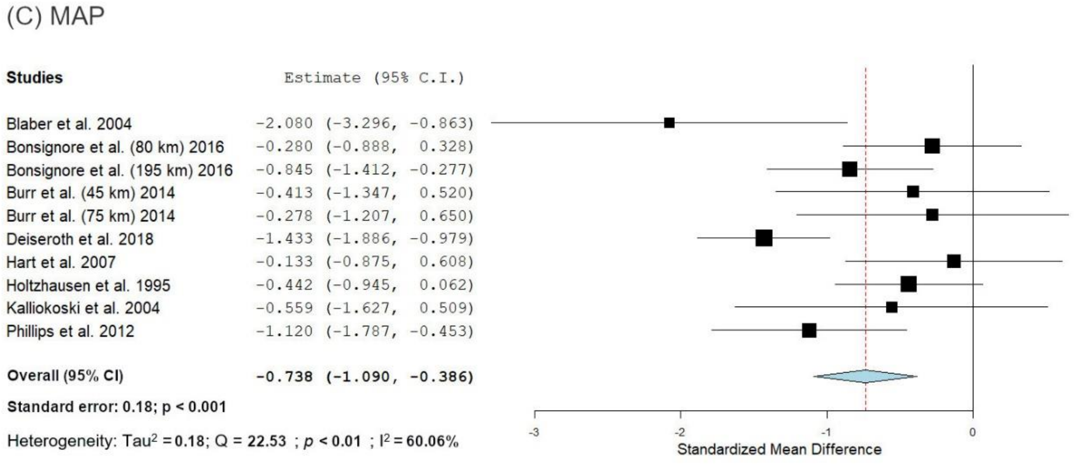
Studies	Estimate (95% C.I.)
Belinchón-deMiguel et al. 2018	−1.354 (−2.280, −0.427)
Bernardi et al. 1997	−1.480 (−2.239, −0.721)
Blaber et al. 2004	−2.111 (−3.333, −0.888)
Bonsignore et al. (195 km) 2017	−0.749 (−1.322, −0.175)
Bonsignore et al. (80 km) 2017	−0.391 (−1.001, 0.220)
Burr et al. 2012	−0.828 (−1.395, −0.262)
Burr et al. (45 km) 2014	−0.317 (−1.246, 0.613)
Burr et al. (75 km) 2014	−0.563 (−1.505, 0.379)
Christensen et al. 2017	−0.340 (−1.223, 0.543)
Christou et al. 2020	−0.507 (−1.049, 0.035)
Cote et al. 2015	−0.138 (−0.693, 0.417)
Deiseroth et al. 2018	−0.951 (−1.378, −0.525)
Dávila-Román et al. 1997	0.000 (−0.741, 0.741)
Faconti et al. 2020	−1.065 (−1.657, −0.473)
Foulds et al. 2014	−0.346 (−0.905, 0.212)
George et al. 2005	−0.789 (−1.323, −0.254)
Gratze et al. (fast performers) 2008	−0.772 (−1.347, −0.197)
Gratze et al. (slow performers) 2008	−0.774 (−1.338, −0.211)
Hanssen et al. 2011	−0.867 (−1.415, −0.319)
Holtzhausen et al. 1995	−0.613 (−1.122, −0.103)
Jouffroy et al. 2015	−1.704 (−2.166, −1.241)
Jung et al. 2014	−0.276 (−0.784, 0.233)
Kalliokoski et al. 2004	−0.620 (−1.693, 0.452)
King et al. (160 km) 2020	−1.046 (−1.937, −0.155)
King et al. (50 km) 2020	−1.067 (−1.713, −0.420)
King et al. (80 km) 2020	−1.141 (−1.970, −0.312)
Krzeminski et al. 2016	−1.428 (−2.463, −0.393)
Malek et al. 2020	−1.246 (−1.959, −0.532)
Manier et al. 1991	−1.961 (−2.978, −0.944)
Martínez-Navarro et al. 2018	−0.488 (−1.192, 0.215)
Mydlík et al. 2012	−1.336 (−1.905, −0.767)
Neilan et al. 2006	−1.119 (−1.785, −0.452)
Nelson et al. 1989	−0.627 (−1.050, −0.204)
Niemela et al. 1984	−0.558 (−1.341, 0.226)
Oxborough et al. 2006	−0.847 (−1.336, −0.358)
Passaglia et al. 2012	−2.152 (−3.157, −1.146)
Perrault et al. 1986	−0.855 (−1.658, −0.052)
Phillips et al. 2012	−0.974 (−1.630, −0.319)
Privett et al. 2008	−0.201 (−1.080, 0.678)
Roeh et al. 2019	−0.584 (−0.779, −0.390)
Scott et al. 2009	−0.618 (−1.327, 0.092)
Shave et al. 2002	−1.167 (−2.071, −0.263)
Taksaudom et al. 2017	−1.216 (−1.741, −0.691)
Trullas et al. 2018	0.226 (−0.411, 0.864)
Vlachopoulos et al. 2010	−0.357 (−0.982, 0.268)
Overall (95% CI)	**−0.805 (−0.940, −0.671)**

Standard error: 0.07; p < 0.001

Heterogeneity: Tau^2 = **0.10**; Q = **91.06** ; *p* **< 0.01** ; I^2 = **51.68%**


(B) DBP

Studies
Estimate (95% C.I.)
Belinchón-deMiguel et al. 2018 -1.093 (-1.989, -0.197)
Bernardi et al. 1997 -0.628 (-1.316, 0.061)
Blaber et al. 2004 -2.115 (-3.339, -0.892)
Bonsignore et al. (80 km) 2017 -1.212 (-1.870, -0.554)
Bonsignore et al. (195 km) 2017 -0.794 (-1.370, -0.219)
Burr et al. 2012 -0.844 (-1.412, -0.277)
Burr et al. (45 km) 2014 -0.902 (-1.872, 0.068)
Burr et al. (75 km) 2014 -0.974 (-1.952, 0.003)
Christensen et al. 2017 0.170 (-0.708, 1.048)
Christou et al. 2020 -0.123 (-0.657, 0.411)
Cote et al. 2015 -0.042 (-0.597, 0.512)
Dávila-Román et al. 1997 -0.638 (-1.398, 0.121)
Deiseroth et al. 2018 -1.736 (-2.210, -1.261)
Faconti et al. 2020 -0.928 (-1.511, -0.344)
Foulds et al. 2014 -0.507 (-1.071, 0.056)
George et al. 2005 -0.757 (-1.289, -0.224)
Gratze et al. (fast performers) 2008 -0.623 (-1.190, -0.055)
Gratze et al. (slow performers) 2008 -0.706 (-1.266, -0.146)
Hanssen et al. 2011 -1.574 (-2.174, -0.975)
Holtzhausen et al. 1995 -0.346 (-0.848, 0.155)
Jouffroy et al. 2015 -1.103 (-1.528, -0.678)
Jung et al. 2014 -0.166 (-0.673, 0.341)
Kalliokoski et al. 2004 -0.580 (-1.650, 0.489)
Krzeminski et al. 2016 -1.746 (-2.832, -0.660)
Malek et al. 2020 -1.811 (-2.587, -1.035)
Manier et al. 1991 -1.273 (-2.189, -0.357)
Martínez-Navarro et al. 2018 0.059 (-0.634, 0.752)
Mydlík et al. 2012 -1.961 (-2.587, -1.334)
Neilan et al. 2006 -0.115 (-0.735, 0.505)
Nelson et al. 1989 -0.376 (-0.793, 0.041)
Niemela et al. 1984 -1.683 (-2.577, -0.788)
Oxborough et al. 2006 -0.455 (-0.930, 0.019)
Passaglia et al. 2012 -1.021 (-1.872, -0.171)
Perrault et al. 1986 -0.194 (-0.965, 0.577)
Phillips et al. 2012 -0.902 (-1.553, -0.252)
Privett et al. 2008 -0.166 (-1.044, 0.712)
Shave et al. 2002 -0.960 (-1.843, -0.078)
Scott et al. 2009 -0.108 (-0.801, 0.586)
Taksaudom et al. 2017 -0.402 (-0.889, 0.086)
Trullas et al. 2018 -0.528 (-1.175, 0.119)
King et al. (50 km) 2020 -0.922 (-1.558, -0.286)
King et al. (80 km) 2020 -0.805 (-1.605, -0.006)
King et al. (160 km) 2020 -0.904 (-1.781, -0.026)
Vlachopoulos et al. 2010 -0.769 (-1.411, -0.127)
Overall (95% CI) -0.765 (-0.926, -0.604)
Standard error: 0.08; p < 0.001
Heterogeneity: Tau² = 0.17; Q = 113.69 ; p < 0.001; I² = 62.18%
-3
-2
-1
0
1
Standardized Mean Difference


(C) MAP

Studies
Estimate (95% C.I.)
Blaber et al. 2004 -2.080 (-3.296, -0.863)
Bonsignore et al. (80 km) 2016 -0.280 (-0.888, 0.328)
Bonsignore et al. (195 km) 2016 -0.845 (-1.412, -0.277)
Burr et al. (45 km) 2014 -0.413 (-1.347, 0.520)
Burr et al. (75 km) 2014 -0.278 (-1.207, 0.650)
Deiseroth et al. 2018 -1.433 (-1.886, -0.979)
Hart et al. 2007 -0.133 (-0.875, 0.608)
Holtzhausen et al. 1995 -0.442 (-0.945, 0.062)
Kalliokoski et al. 2004 -0.559 (-1.627, 0.509)
Phillips et al. 2012 -1.120 (-1.787, -0.453)
Overall (95% CI) -0.738 (-1.090, -0.386)
Standard error: 0.18; p < 0.001
Heterogeneity: Tau² = 0.18; Q = 22.53 ; p < 0.01 ; I² = 60.06%
-3
-2
-1
0
Standardized Mean Difference

SUPPLEMENTARY MATERIAL

Appendix S1.- *Search strategy*

HRV:

(“heart rate variability”) OR (“heart beat variability”) OR (hrv)) OR (“heart rate variation”) OR (“heart beat variation”) OR (“autonomic nervous system”[MeSH Terms] OR “autonomic nervous system”[Text Word])

Arterial Stiffness:

“vascular stiffness”[MeSH Terms] OR “arterial stiffness”[Text Word] OR “aortic stiffness”[Text Word] OR “pulse wave analysis”[MeSH Terms] OR “pulse wave velocity”[Text Word] OR “carotid-femoral pulse wave velocity”[MeSH Terms] OR “Carotid-Femoral Pulse Wave Velocity”[Text Word] OR (pwv) OR (cfpwv) OR “blood pressure”[MeSH Terms] OR “blood pressure determination”[MeSH Terms] OR “arterial pressure”[MeSH Terms] OR “blood pressure”[Text Word]

Marathon / Ultra-marathon:

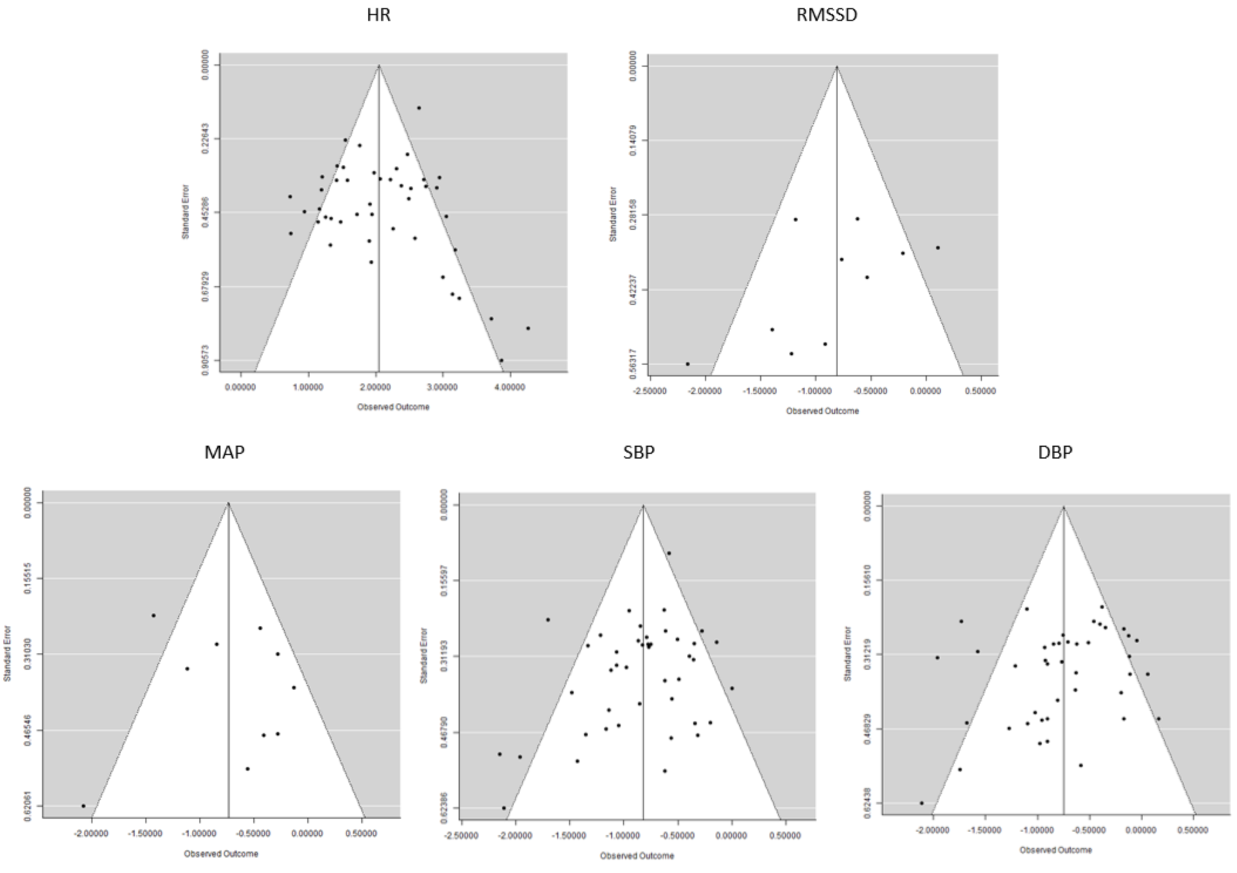
(marathon*) OR (ultra-marathon*) OR (ultramarathon*) OR (long distance runn*) OR (endurance runn*) OR (ultra-endurance) OR (ultraendurance) OR (ultra-runn*) OR (ultrarun*) OR (ultra-distance) OR (ultradistance) OR (ultra-race) OR (ultrarace)

1. **((“vascular stiffness”[MeSH Terms] OR “arterial stiffness”[Text Word] OR “aortic stiffness”[Text Word] OR “pulse wave analysis”[MeSH Terms] OR “pulse wave velocity”[Text Word] OR “carotid-femoral pulse wave velocity”[MeSH Terms] OR “Carotid-Femoral Pulse Wave Velocity”[Text Word] OR (pwv) OR (cfpwv) OR “blood pressure”[MeSH Terms] OR**

“blood pressure determination”[MeSH Terms] OR “arterial pressure”[MeSH Terms] OR “blood pressure”[Text Word])) AND ((marathon*) OR (ultra-marathon*) OR (ultramarathon*) OR (long distance runn*) OR (endurance runn*) OR (ultra-endurance) OR (ultraendurance) OR (ultra-runn*) OR (ultrarun*) OR (ultra-distance) OR (ultradistance) OR (ultra-race) OR (ultrarace))

2. **(((“heart rate variability”) OR (“heart beat variability”) OR (hrv) OR (“heart rate variation”) OR (“heart beat variation”)) OR (“autonomic nervous system”[MeSH Terms] OR “autonomic nervous system”[Text Word])) AND ((marathon*) OR (ultra-marathon*) OR (ultramarathon*) OR (long distance runn*) OR (endurance runn*) OR (ultra-endurance) OR (ultraendurance) OR (ultra-runn*) OR (ultrarun*) OR (ultra-distance) OR (ultradistance) OR (ultra-race) OR (ultrarace))**

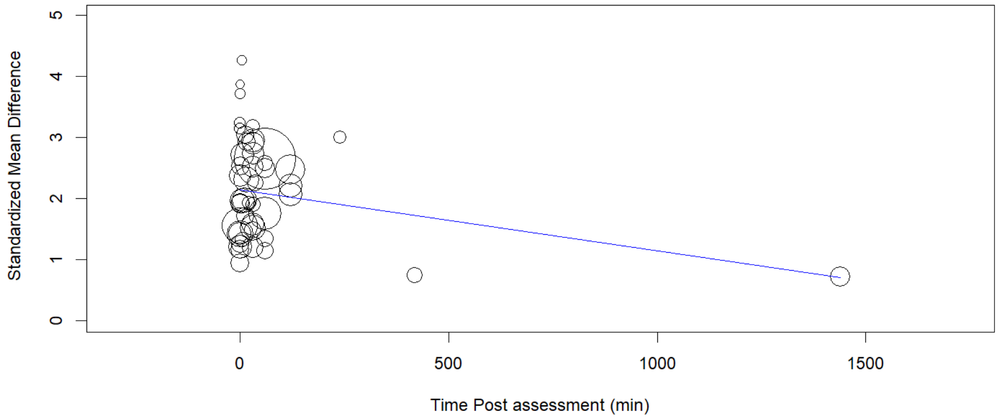
Appendix S2.- *Risk of bias assessed through funnel plots.*



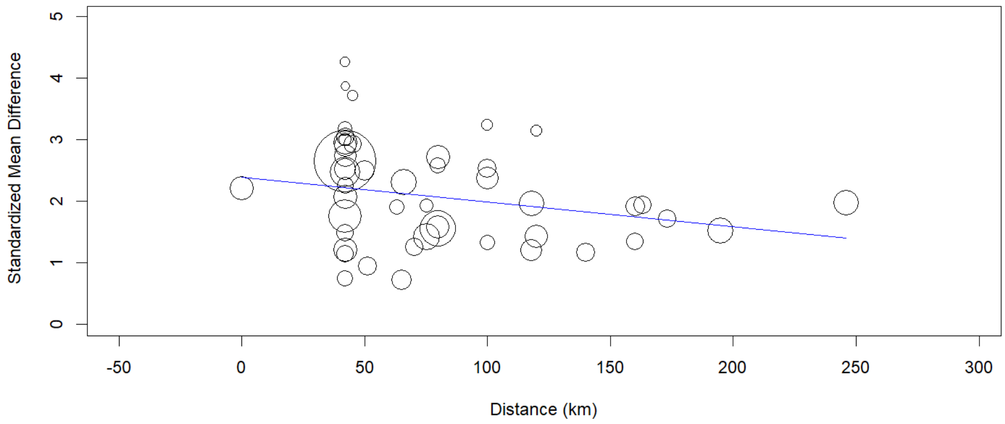
R-R: mean R-R intervals; RMSSD: root mean square of successive differences between adjacent NN intervals; MAP: mean arterial pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure

Appendix S3.- B*ubble plots of meta-regressions with statistical significance*

HEART RATE

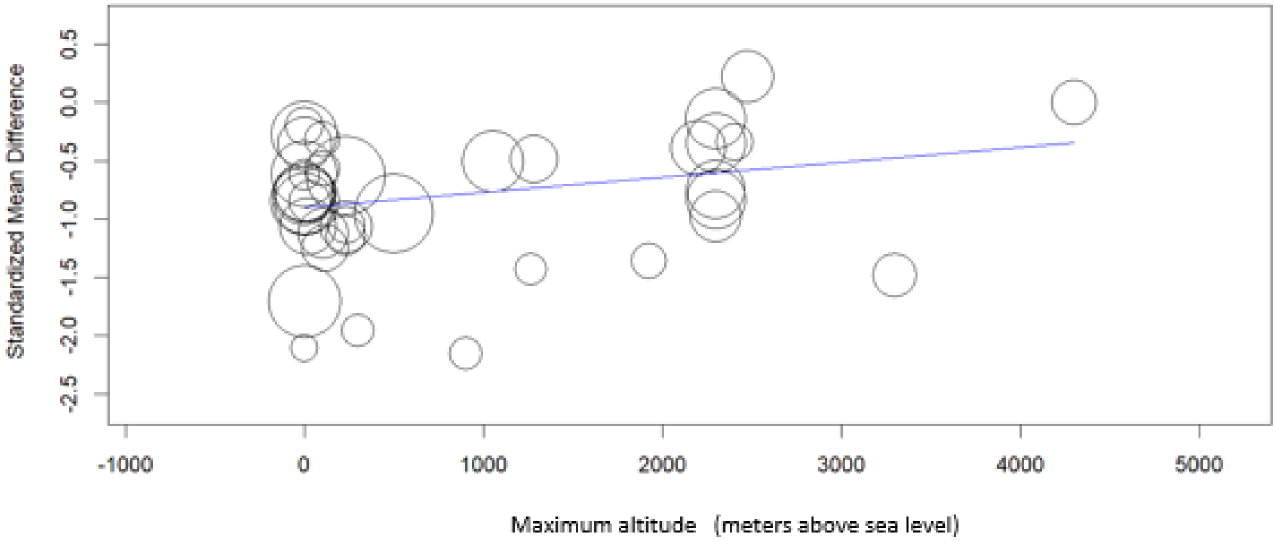


Regression coefficient: changes in heart rate pre- post-race with a unit increase of the minutes following the completion of the race until its evaluation.
Correlation coefficient (95% CI): -0.001 (-0.002, 0.000); Standard error < 0.001; *p*-value = 0.03



Regression coefficient: changes in heart rate pre- post-race with a unit increase of the race distance.
Correlation coefficient (95% CI): -0.004 (-0.008, -0.000); Standard error = 0.002; *p*-value = 0.04

SYSTOLIC BLOOD PRESSURE



Regression coefficient: changes in systolic blood pressure pre- post-race with a unit increase of the maximum altitude above sea level achieved during the race. Correlation coefficient (95% CI): < 0.001 (<0.001, <0.001); Standard error < 0.001; *p*-value = 0.04