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**FINAL AUTHOR VERSION OF PAPER ACCEPTED IN MEDICINE AND SCIENCE  
IN SPORTS AND EXERCISE**

**The effects of an injected placebo on endurance running performance**

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## **ABSTRACT:**

**PURPOSE:** To quantify the placebo effect magnitude on endurance running performance, in ‘real-world’ field-based head-to-head competition settings, of an injected placebo (‘OxyRBX’) purporting to have similar effects to recombinant human erythropoietin (r-HuEPO). **METHODS:** 15 endurance-trained club-level men (age:  $27.5 \pm 6.8$  years, BMI:  $22.9 \pm 2.0$  kg·m<sup>-2</sup>), with personal best 10 km times of  $39.3 \pm 4.4$  min (mean±SD), completed the randomised cross-over study design of 3 km races before and after 7-day ‘control’ and ‘placebo’ phases. During the placebo phase participants self-administered subcutaneous saline injections daily, believing it to be OxyRBX, with no intervention during the control phase. At the start and end of each 7-day phase 3 km running performance was assessed. Qualitative assessments of participants’ perceptions and experiences were recorded throughout and in semi-structured interviews on completion. **RESULTS:** Race time improved significantly more in response to the placebo intervention ( $9.73 \pm 1.96$  s faster,  $P=0.0005$ ), than in response to control ( $1.82 \pm 1.94$  s faster,  $P=0.41$ ) ( $P_{interaction}=0.02$ ). In response to the placebo, participants reported reductions in physical effort, increased potential motivation and improved recovery. Beliefs and congruence between positive expectations of the effects of the placebo and perceptions of physical change during training also appeared to impact on competitive performance. **CONCLUSIONS:** Compared to control, the injected placebo improved 3 km race time by 1.2%. This change is of clear sporting relevance, but is smaller than the performance improvement elicited by r-HuEPO administration. The qualitative data suggest that placebo may have improved performance by both reducing perception of effort and increasing potential motivation, in accord with the psychobiological model for exercise performance, and that cognitive and non-cognitive processes appear to have influenced placebo response.

**KEY WORDS:** injection; erythropoietin; potential motivation; psychobiological model;  
perceived effort; competition

**Paragraph 1: INTRODUCTION:** The placebo effect is acknowledged as a key factor in medical research and, as a consequence, its effect has been controlled in clinical trials for over 50 years (26). The placebo effect has also been recognised in the context of sports performance, with a number of studies reporting statistically significant improvements in endurance, sprint or strength performance with placebo interventions (reviewed in (4)).

**Paragraph 2:** Orally administered placebos have been typically shown to improve endurance performance by ~2% in participants who are at least moderately well-trained (5, 11, 17, 22, 39). However, these studies have all assessed performance using either cycle ergometer or running time-trial performance assessments with tests performed on individual performing alone, and unaware of the performances of others, rather than assessment during head-to-head field-based competition scenarios – in other words, studies are often not performed under conditions which best reflect the ‘real-world’ sporting competition for that particular event. It is known that performance is often improved in head-to-head competition settings, compared to settings without a competitive element (12, 13, 34, 37, 38). The mechanisms responsible for this ‘competition effect’ are not fully understood but could conceivably be explained in the context of the psychobiological model (8, 20, 29), which applies Motivational Intensity Theory (40), to a sporting context. Motivational Intensity Theory predicts that maximum exercise tolerance will be increased when either perception of effort is reduced or ‘potential motivation’ (i.e. the greatest effort an individual is prepared to exert) is increased (8, 20, 29). Consistent with increased potential motivation, there is evidence that competition results in increased allocation of effort to an exercise task (12), increased positive emotions (12), a similar rate of perceived exertion (RPE) at a

greater workload (37) and reduced internal attentional focus (37), together with performance-facilitating physiological changes such as enhanced sympatho-adrenal system activation (12, 34), increased heart rate (12, 37), and higher peak oxygen uptake (34), although performance improvements with competition have also been observed in absence of changes to peak heart rate and oxygen uptake (38). Thus, it is likely that the ergogenic benefit of competition is the result of motivational or dissociative effects enabling a greater amount of the 'reserve' capacity between volitional maximal effort and true physiological capability to be utilized (13, 32, 33). Placebo may also reduce perception of effort via its positive effect on perceived ability, and thus act, at least in part, on the same psychological mediator as competition to improve performance. Thus, the effects of placebo and competition may not be additive and the effects of placebo on performance in a head-to-head competitive environment may be less marked than previously observed. It is therefore important to study the magnitude of the placebo effect in a competitive setting to provide a clearer measure of the likely magnitude of the placebo effect on sporting performance in a real-world competition setting.

**Paragraph 3:** There are reports of increasing use of performance enhancing drugs in both elite and recreational level sport (10, 30). One such drug, which is banned for use in sport by the World Anti-Doping Code, is recombinant human erythropoietin (r-HuEpo), which stimulates renal erythrocyte production (15). Studies have shown that r-HuEpo administration increases haematocrit (Hct) which, in turn, can lead to an increase in oxygen-carrying capacity by between 7 and 13% (14, 18, 24, 28). Such impacts often also result in the improvement of endurance performance in athletes (2, 14). However, studies on the effects of r-HuEpo administration on sporting performance in field-based tests are limited (14), and no study has assessed its effects on performance in a placebo-

controlled trial using field-based head-to-head competition setting. Such studies are needed to assess the true effects of r-HuEpo on 'real-life' sporting performance.

**Paragraph 4:** A key feature of r-HuEpo administration is that it is given by injection. There is clear evidence from clinical medicine that the route of delivery is a key mediator of the size of a placebo effect, with placebos administered by injection inducing larger effects than placebos administered orally (43). For example, Benedetti and colleagues effectively demonstrated that an intramuscular placebo injection improved pain tolerance to a greater extent than oral placebo administration (6). It is, therefore, conceivable that at least some of the performance benefits of r-HuEpo administration could be attributable to an additional conditioned response related to route of administration (36). However, Benedetti and colleagues did not include any measure of physical performance and did not involve competitive athletes. In the context of sports performance, the authors are only aware of one study which assessed the effect of an injected placebo (a sham spinal injection purporting to be fentanyl – an opioid analgesic) on endurance sporting performance (1). This found no effect of placebo on 5 km cycling performance (1), however there has been subsequent criticism of the efficacy of the placebo procedure employed, as it was argued that the leg pain experienced during the placebo cycling time-trial (which would not have been experienced with the fentanyl condition) may have unmasked the sham nature of the placebo intervention (19). Thus, to the authors' knowledge, there have been no appropriately designed studies assessing the effect of an injected placebo, purporting to be a performance-enhancing ergogenic aid, on endurance performance.

**Paragraph 5:** The aim of this study was therefore to quantify the magnitude of the placebo effect on endurance running performance, in a field-based head-to-head competition setting, of an injected placebo (that we called ‘OxyRBX’) purporting to have a similar effect to r-HuEpo. In addition, to further our qualitative understanding of how placebo injections may influence endurance running performance, members of the research team recorded detailed notes of any comments made to them by participants about their perceptions and experiences of training and competition during the study; and on completion of the study, participants were interviewed in-depth about their experiences of ‘taking OxyRBX’.

**Paragraph 6: METHODS: Participants:** Nineteen endurance-trained male volunteers were initially recruited to take part in the study. Four participants dropped out of the study prior the commencement of ‘OxyRBX’ administration. Three of the four drop-outs mentioned ‘fear’ of the possible complications (e.g. blood clotting) associated with OxyRBX use. One individual did not give a reason for dropping-out. Thus, fifteen participants (age  $27.5 \pm 6.8$  years, height  $1.79 \pm 0.05$  m, body mass  $73.4 \pm 7.6$  kg and BMI  $22.9 \pm 2.0$  kg·m<sup>-2</sup>; mean  $\pm$  SD) successfully completed the experimental protocol. The fifteen participants were well-trained club-level athletes, who reported engaging in  $213 \pm 129$  minutes of endurance-based training and  $50 \pm 58$  minutes of resistance training per week, with personal record times for running 10 km of  $39.3 \pm 4.4$  min (mean  $\pm$  SD). All participants were healthy non-smokers and none were taking any medications or supplements at the start of the study. Participants provided written informed consent on the basis that they were undertaking a trial to investigate the effects of the legal EPO-like substance ‘OxyRBX’ on sporting performance, rather than a trial of the placebo effect. This deception was essential for the study to be successfully

undertaken and is standard practice in published studies of the placebo effect (7). The dropout of three participants due to fear of complications of 'OxyRBX' administration provides an illustration of the effectiveness of the procedures employed to induce the belief in participants that they were taking a powerful drug. Participants were fully debriefed about the true nature of the study, on completion of a post-study qualitative interview (see below – one participant who did not attend the interview was debriefed by email), and were instructed not to discuss anything related to the trial with others until given permission by the research team (granted when all participants had completed the study). As a further precaution, participants were given specific instructions and directions about how to enter and vacate the final interview room to ensure no crossing of paths between participants. The study was approved by the research ethics committee of the College of Medical, Veterinary and Life Sciences at the University of Glasgow and was performed according to the World Medical Association (Declaration of Helsinki) code of ethics.

**Paragraph 7: Preliminary Study Brief.** Prior the commencement of the performance trials, the effects of r-HuEpo administration on exercise performance were described to participants and discussions took place concerning its alleged use particularly amongst elite cyclists. Each preliminary study brief was carried out by the same investigator (RR), on a one-to-one basis and followed a semi-structured approach. Participants were initially provided with a detailed information sheet about the study, described as 'A study to assess the effects of OxyRBX on sporting performance in well trained individuals' and a 'Drug Information Sheet' on OxyRBX describing its purported effects, dosage and safety information. This was reinforced by a semi-structured discussion about the purported benefits of 'OxyRBX' on performance, which was

described as being a legal r-HuEpo-like substance, which had been shown to induce similar benefits to r-HuEpo in animal studies and which extensive testing had shown to be safe to use in humans. Potential side effects of OxyRBX (e.g. rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue) were also described, but it was emphasised that these were extremely rare (less than one case in a million). Participants were encouraged to ask questions and discuss issues/topics that felt important to them about the study, to ensure an effective tailored priming process for each individual. This briefing process was carried out in order to reinforce beliefs about the effects of OxyRBX on exercise performance and the similarity of these effects to those of administering r-HuEpo.

**Paragraph 8: Experimental Design.** The experimental design is outlined in Figure 1. Participants initially underwent an individual familiarisation 3 km time-trial run on an indoor 200 m running track located at the Kelvin Hall Arena (Glasgow, UK). This was carried out to familiarise participants to the running track used for the four competition runs and to racing over the 3 km distance. With participants unaware, individual 3 km completion times for this time-trial were used for handicapping purposes for the 3 km competition runs in the main study. Participants then followed a randomised cross-over study design where each participant underwent tests before and after a 7-day ‘control’ phase, during which no intervention was given; and before and after a 7-day ‘placebo’ phase, in which participants came to the laboratory every day to receive daily subcutaneous saline injections (0.5 ml sterile 0.9% NaCl). Participants were informed that these injections contained OxyRBX, which should elicit similar effects as r-HuEpo. Eight participants underwent the control phase before the placebo phase, with the other seven undergoing the placebo phase before the control phase. There was a 2-week

interval between the two study phases and participants were told that this was to ensure a suitable OxyRBX ‘wash-out period’ for the participants who started with the OxyRBX administration phase. Participants were regularly informed not to discuss which group they have been assigned and, as far as possible, were monitored to ensure that no such discussions took place.

**Paragraph 9: 3 km Running Races.** Each participant in each cohort undertook four performance tests as competitive 3 km running races (in groups of 7 or 8 participants) on an indoor 200 m running track. During the races, which took place at the start and end of both the placebo and control weeks, ambient temperature and humidity conditions were  $17.9 \pm 0.8^{\circ}\text{C}$  and  $39.6 \pm 3.4\%$ , respectively. Participants were asked to prepare for each race as they would normally for competition and were instructed to refrain from consuming alcohol 48 hours preceding each race. No specific instructions were given to participants regarding hydration and caffeine intake other than being told to prepare as they would normally for a competitive event. Participants were asked to undertake the same preparation for all the races. To ensure that the 3 km races were competitive, participant starting times were handicapped based on the times achieved during the individual 3 km time trial familiarisation runs (i.e. a participant who completed that familiarisation run in 11:00 would start 30 seconds before a participant who completed the familiarisation run in 10:30; this handicapping remained constant throughout the study), and small monetary prizes (£35 (~\$50) for first place, decreasing by £5 per position down to seventh place) were provided according to finishing position. Participants were instructed to aim to achieve as high a finishing position as possible and to complete the race in the shortest possible time. Heart rates were recorded on a second-by-second basis throughout using a telemetry system (Fitpulse, TT Sport S.R.L,

Italy) and lap times were recorded manually by the investigators. Ratings of perceived exertion (RPE) were collected, from each participant, immediately after finishing each race (including familiarisation run) by a member of the research team. Participants were asked to report their RPE at the end of the race, using the Borg scale from 6-20 (9), with '6' indicating 'no effort at all' and '20' indicating 'maximal exertion' effort. They were briefed before each race that this rating should reflect their overall perception of effort taking into account all sensations. During each race, participants were given positive verbal encouragement by members of the research team who were blinded to the participants' condition allocation and received verbal information on the number of laps remaining. Participants were not given any further information (e.g. lap times, heart rates, etc) or results until completion of the study.

**Paragraph 10: Haematological Measures.** Venous blood samples (~4 ml) were collected into EDTA tubes, from an antecubital vein, after 10 minutes of supine rest, 60-120 minutes before each 3 km race. Red blood cell count (RBC), haemoglobin concentration [Hb], haematocrit Hct, mean cell volume (MCV) and mean corpuscular volume (MCH) were quantified using a haematology analyser (Sysmex XT-2000i, Norderstedt, Germany).

**Paragraph 11: Training and Diet.** Participants were instructed to maintain their normal training and diet regimen throughout the study and were asked to record all training sessions in a diary that was provided by the experimenters. Participants were asked to replicate training for the week, and food intake for the two days, leading up to each 3 km race.

**Paragraph 12: Qualitative Assessments.** During the placebo week, when they attended the University to receive their daily placebo injection, participants were asked to describe any changes they had noticed whilst ‘taking OxyRBX’. Immediately following each 3 km race (both during the placebo and control week), participants were asked to assess their performance during the race. Notes of the daily and post-race accounts were taken by members of the research team and written up electronically. All 15 participants provided accounts during the placebo week; 9/15 provided accounts during the control week. In addition, 14/15 participants took part in an in-depth, semi-structured interview on completion of the study, prior to their being informed of the true nature of the experiment. The interviews were audio-recorded with participant consent and transcribed verbatim. Questions were asked in two stages. Firstly, participants were asked about their experiences of ‘taking OxyRBX’ during the trial, including whether they had any anxieties about taking the substance; whether they thought it would improve their performance; whether they felt different when ‘taking’ the substance; how they felt during training and the races; whether they felt that their recovery was different; and whether they experienced any positive or negative side effects. Then, after their race times were revealed to them, they were asked further questions including the extent to which they felt that any improvement was due to the substance allowing them to work harder. After completion of the interview, participants were fully debriefed about the nature of the study.

**Paragraph 13: Quantitative Data Analysis.** Statistical analyses were conducted using Statistica 6.0 (Tulsa, OK). Data are presented as mean  $\pm$  SEM (unless otherwise indicated). All data were tested for normality and homogeneity of variance prior to statistical analysis and were found to conform to assumptions for parametric statistical

testing. Two-way repeated measures ANOVAs (intervention condition (control vs placebo) x test (pre- vs post-)) were used to identify any differences between trials in 3 km race time, mean heart rate, RPE and haematological variables. The intervention condition x test interaction term was used to assess whether changes from pre- to post-intervention in the placebo condition differed from the control condition. Three-way repeated measures ANOVA (intervention condition x test x race-segment (first, second, third 1000 m)) was used to identify any differences between trials in running speed and heart rate throughout the races. For all ANOVAs, *post-hoc* Fisher tests were used to identify where any differences lay. Statistical significance was accepted at  $P < 0.05$ .

**Paragraph 14: Qualitative Data Analysis.** The notes of participants' accounts and interview transcripts were read repeatedly (by RR and CMG) to identify questions of interest (e.g., the physical effects of 'taking OxyRBX') and any emerging issues (e.g., the impact of regular competition on performance). A thematic analysis was conducted using an adapted Framework Approach (27), where data are coded, indexed, charted systematically, and then organised using matrices in which each participant is represented by a row and each theme by a column. NVivo10 software was used to assist data coding and organisation. Constant comparison (checking the emerging analysis against every instance of similarly indexed data) ensured that all perspectives were represented (31).

**Paragraph 15:** Summary analyses of four key themes are relevant here: '*Expectations*', which captured participants' views of 'taking OxyRBX' prior to the placebo week; '*Physical effects*', which include all references to physical changes experienced by participants during the study (both the placebo and control weeks); '*Psychological*

*effects*', which included all references to non-physical changes experienced by participants during the study; and '*Competition*', which includes participants' views of the competitive element of the study. To compare and contrast the accounts of participants whose performance improved during the placebo week, and those who showed no improvement, participants were grouped according to change in race times during the placebo week. Participants were assigned to one of three 'performance' groups: the 'Marked Improvement' group (n = 6) included those whose race times decreased by  $\geq 10$  seconds; the 'Slight Improvement' group's (n = 5) race times decreased by  $< 10$  seconds; and the 'No Improvement' group's (n = 4) race times increased during the placebo week compared to the control week. Participant numbers were assigned on recruitment to the study and not reassigned when a participant dropped out, thus participant numbers for the interviews in the results are recorded as P01 to P19. Accordingly, extracts are presented with labels to indicate the participant's ID (P01-P19), data type ('Log' = researcher notes, 'Int' = post-study interview) and performance during the placebo week ('Improver' = Marked Improvement, 'Slight' = Slight Improvement, 'No' = No Improvement).

**Paragraph 16: RESULTS. Quantitative Results.** Completion times for the 3 km races pre- and post-intervention in the control and placebo conditions are shown in Table 1. There was a significantly greater improvement in race time from pre- to post-intervention in response to the placebo intervention than in response to the control intervention (intervention condition x test interaction,  $F_{1,14} = 6.82$ ,  $p = 0.02$ ). Post-hoc tests revealed that race time was significantly faster, by 9.73 s (95% confidence interval (CI): 5.14 to 14.33.57 s faster), in response to the placebo intervention ( $p = 0.0005$ ); but did not improve significantly in response to the control condition (1.82 s faster (95% CI:

2.77 s slower to 6.41 s faster),  $p = 0.41$ ). Figure 2a shows the mean ( $\pm$  SEM) change in 3 km race time in response to the control and placebo interventions (i.e. post-intervention minus pre-intervention); Figure 2b shows the changes for individual participants. Eleven participants improved performance more in response to the placebo intervention than in response to the control intervention; change in performance was similar in response to both interventions for one participant; and three participants had greater performance increases in response to the control intervention.

**Paragraph 17:** Figures 3a and 3b show the participants' running speeds in the first, second and third 1000 m segments of the 3 km races before and after the control and placebo interventions, respectively. In three-way repeated measures ANOVA (intervention condition  $\times$  test  $\times$  race-segment), a significant intervention condition  $\times$  test interaction for running speed was observed ( $F_{1,14} = 7.117$ ,  $p = 0.018$ ). Intervention condition  $\times$  race-segment ( $F_{2,28} = 0.085$ ,  $p = 0.92$ ); test  $\times$  race-segment ( $F_{2,28} = 0.645$ ,  $p = 0.53$ ); and intervention condition  $\times$  test  $\times$  race-segment ( $F_{2,28} = 0.378$ ,  $p = 0.69$ ) interaction terms were not significant. Post-hoc tests revealed that participants started the 3 km race more aggressively following the placebo intervention, running the first 1000 m at a 2% faster pace than pre-intervention (0.094  $\text{m}\cdot\text{s}^{-1}$  faster (95%CI: 0.032 to 0.156  $\text{m}\cdot\text{s}^{-1}$  faster),  $p = 0.004$ ), and maintaining a running speed 1.4% faster than pre-intervention in the second (0.061  $\text{m}\cdot\text{s}^{-1}$  faster (95%CI: 0.001  $\text{m}\cdot\text{s}^{-1}$  slower to 0.123  $\text{m}\cdot\text{s}^{-1}$  faster),  $p = 0.053$ ) and third (0.062  $\text{m}\cdot\text{s}^{-1}$  faster (95%CI: 0.000 to 0.124  $\text{m}\cdot\text{s}^{-1}$  faster),  $p = 0.050$ ) 1000 m segments (Figure 3b). In contrast, there was no significant difference in running speed in any of the three 1000 m segments of the post-intervention 3 km race, compared to pre-intervention in the control condition (Figure 3a).

**Paragraph 18:** Figures 4a and 4b show participants' heart rates during the first, second and third 1000 m segments of the 3 km races before and after the control and placebo interventions, respectively, for participants in whom complete sets of heart rate data across all four races were obtained (n = 10). In three-way repeated measures ANOVA (intervention condition x test x race-segment), there was a significant main effect of race-segment on heart rate ( $F_{2,18} = 51.058, p < 0.0005$ ), but no significant two- or three-way interactions indicating that heart rate responses during the 3 km races were not significantly influenced by the placebo intervention. There were also no significant differences in RPE between pre- and post-intervention races in either the control or placebo condition (Table 1). As expected, there were no significant differences in any haematological variables between control and placebo conditions, either pre- or post-intervention (Table 1). Participants' training remained constant throughout the period of the study and did not differ significantly between the weeks preceding each of the four 3 km races (Table 2).

**Paragraph 19: Qualitative Results.** In the post-study interviews, despite consenting to take part in the study, a few participants admitted they had felt: '*worried about taking the injections*' (P07\_Int\_Improver); '*a wee (a little) bit guilty I suppose, putting something in my body that's not always going to be there*' (P16\_Int\_Improver); or '*a wee bit scared, just because I didn't know anything about OxyRBX*' (P09\_Int\_No). Almost all of the participants reported that they thought they were taking a real performance enhancing substance during the study, providing further evidence that the briefing procedures used were highly effective in inducing participants' beliefs that the substance would enhance their performance. Almost all of those who recorded a marked improvement or who showed no improvement in their race times had expected they

would see positive changes when ‘taking OxyRBX’. Many said they had been interested to see if and how OxyRBX would work for them. Some whose performance had improved markedly described a real sense of anticipation beforehand:

P13\_Int\_Improver: *“I wanted to, kind of like count down until I was going to take it, and see if there was any differences in my performance and in like everyday general life. So yeah, I was really looking forward to seeing differences... the advantages of it.”*

**Paragraph 20:** Amongst those whose performance improved less markedly, expectations tended to be more measured. Some admitted they had not anticipated any changes from ‘taking OxyRBX’:

P15\_Int\_Slight: *“I didn’t think taking the drug would have any effects at all because it was a tenth of the normal dose tested before. Ethically, I thought you couldn’t give any therapeutic doses, so didn’t think... I wouldn’t expect anything to happen, not through any evidence, just thought the dose was too small in comparison to therapeutic doses.”*

**Paragraph 21:** In describing their experiences of ‘taking OxyRBX’, although a few participants reported minor negative effects (changing sleep patterns, slight pain at the injection site, nausea), almost all mentioned at least some positive effects. During the placebo week, participants whose race times improved (both markedly and slightly) reported back to research team members that they were feeling ‘*more comfortable*’ (P13, Improver) both during training and in competition:

P15\_Log\_Slight: *Run today outdoor about 3 mile easy run in approximately 30 minutes, last 10 minutes more difficult, however much better than normal. This was a repeated route. A lot easier, at beginning took him longer to get tired [...] Breathing was easier during running, noticeably different.*

P16\_Log\_Improver: *Thinks best run was today. Doesn't know why, says the only thing that's different is the drug, so drug potentially had effect. Breathing was better, utilising oxygen really well. Muscles more efficient, good push off every step.*

**Paragraph 22:** This reduction in perceived physical effort both during training and the competitive races was also evident in the post-study interviews, where some participants described how 'taking OxyRBX' had increased their enjoyment of training sessions:

P01\_Int\_Slight: “ ... when I started taking the drug, particularly noticed in the gym that I was doing a lot more in my sets than normal, and also running I did feel less tired even when I was on the treadmill... I don't like running inside, but I felt I could run longer than normal. Even in training sessions, I felt I was running better, felt less out of breath, enjoying the sessions more. One session, it was windy, but I was still running well, coach said I was running faster.”

**Paragraph 23:** In contrast, participants whose race times did not improve often appeared less convinced that 'taking OxyRBX' had had a positive physical effect, particularly during training (P19\_Log\_No: *Alright, nothing to report really. Feels no difference really*). One (who had expected the placebo to work) even suggested an increase in perceived effort (or a nocebo effect) during the placebo week:

P10\_Int\_No: *I thought the week when I was taking the supplement, I felt like my legs were really heavy, felt like it was working against me, particularly the drug week. The following weeks I was getting better, maybe like a delayed effect ...like my legs felt better.*

**Paragraph 24:** Another noticeable physical effect that many participants experienced during the placebo week (including those whose race times showed no improvement) was enhanced recovery both following training sessions and after the races:

P15\_Int\_Slight: *“... the last race we did, recovery was pretty poor... that was post control, compared to taking the drug; you seemed to regenerate really quickly. After one or two days on drug I started thinking the drug was having an effect.”*

**Paragraph 25:** Many participants also described enhanced potential motivation, particularly during the competitive races. They commonly reported ‘pushing’ themselves harder during the placebo week races, and some felt ‘taking OxyRBX’ presented an opportunity for them to experience their full potential as an endurance athlete:

P07\_Int\_Improver: *“ I don’t know, I was always had it in my head, when I run, psychology is what stops me, but I think having this in me just made me push harder, I was knackered (tired) throughout that race, but I just kept pushing. It didn’t make the race easier to get that time, I don’t know, worked hard...”*

**Paragraph 26:** Only a couple of participants reported that their potential motivation had increased during training. However, one reported that he had almost found this counterproductive:

P02\_Int\_Slight: *“I think the training effect of the substance, everything was much quicker, I have to admit when I was on the substance I was on the verge of injury, I kept pushing myself too hard, just because I could...and because it was fun.”*

**Paragraph 27:** In addition to increased potential motivation, some participants reported feeling greater confidence in their ability during the placebo week race. However, this perceived advantage did not always translate into an improved time:

P09\_Int\_No Improver: *“During the races, I always gave it all, so you’re finishing the same way. Just, when I was doing the runs....when on the drug I thought, I thought there are at least 2 or 3 guys that I should have an advantage over.”*

**Paragraph 28:** A number of participants also described how the competitive element of the study had had an effect in itself. As is revealed in this participant’s account, the regular races appeared to act as an additional spur for some during training:

P04\_Log\_Slight: *Feeling really good. Drug is having an effect. Feels more up for it, especially due to competition tomorrow.*

**Paragraph 29:** Indeed, one participant who had taken part in a previous performance-enhancing drug trial and remained sceptical throughout the study (...*having done the EPO*

*trial and having a medic on board... this time not having one, seemed a bit unreal*), showed a marked improvement in his race time despite reporting no physical or psychological effects during the placebo week. He maintained that competition and regular assessment was enough in itself to improve performance:

*P5\_Int\_Improver: The biggest change in training was the knowledge that you're competing every week etc... You try and do race prep... Interval sessions improved noticeably one day. When you get onto one of these trials [research studies], you tend to find you can push harder, there's something to focus on, prepare for.*

**Paragraph 30: DISCUSSION.** The aim of this study was to determine whether an injectable placebo, claiming to be a legal substance with similar effects to r-HuEpo, would improve endurance running performance. The principal finding was that participants completed the 3 km distance 1.2% faster in the post-placebo condition compared to the post-control condition (and 1.5% faster compared to the pre-placebo condition) – a difference that is statistically significant, physiologically relevant and of clear importance in a competitive sporting setting. To put these results into context, in the 2012 Olympics the difference between the gold medal and fourth place was less than 1% in all track events from 1500m to 10000m for both men and women.

**Paragraph 31:** The ergogenic effects of placebo in the present study can potentially be explained within the framework of the psychobiological model, which postulates that maximum exercise tolerance will be increased when either perception of effort is reduced or potential motivation (i.e. the greatest effort an individual is prepared to exert) is increased (8, 20, 29). This model attempts to provide an overarching paradigm which

encompasses both physiological and psychological factors affecting performance. For example, according to the psychobiological model, physiological factors such as exercise training (16) or carbohydrate ingestion (3) would ultimately act to improve performance by reducing perception of effort for a given absolute exercise intensity. Similarly, psychological interventions such as motivational 'self-talk' lead to a lower RPE for equivalent work rate and enhanced endurance performance (8). Consistent with these previous observations, improved exercise performance for the same degree of perceived effort was observed following placebo administration in the present study. This suggests that placebo facilitated an enhancement in performance by providing a degree of decoupling in the normal relationship between RPE and exercise intensity, an observation which is supported by the qualitative data in which a number of participants described reduced physical effort (and enhanced recovery) when taking the placebo both during training and the competitive races.

**Paragraph 32:** It was not the intention of this study to establish the potential underlying neurological mechanisms for this reduction in effort perception; however previous work on the effects of placebo analgesia on pain perception using functional magnetic resonance imaging (fMRI) may provide some insights in this regard. Wager and colleagues used fMRI to reveal decreased activity in pain-sensitive areas of the brain in response to a placebo analgesic cream (35) demonstrating a measurable effect of placebo on brain function. Thus, given the evidence that pharmaceutical interventions which act to elevate the pain threshold also reduce RPE and improve exercise performance (21, 33), it is conceivable that the effect of placebo on effort perception may act, at least in part, via the same neurological mechanisms (i.e. reduction in pain sensitivity). However, further study is needed to establish whether this is the case.

**Paragraph 33:** In addition to reducing perceived effort, evidence from the qualitative data suggests that placebo administration increased potential motivation. Participants commonly reported pushing themselves harder during the races at the end of the placebo intervention week. This may be related to the effect of placebo on perceived ability – a number of participants also reported increased confidence in their ability after taking placebo – which has been shown to increase willingness to exert effort in challenging tasks (41, 42). Thus, the evidence from the present study suggests that placebo administration potentially acts to improve performance by both reducing perception of effort *and* increasing potential motivation.

**Paragraph 34:** The 1.2% improvement in performance with the injected placebo is of similar magnitude to the performance improvements seen in response to orally administered placebos (5, 11, 17, 22, 39). One interpretation of this finding is that route of placebo administration does not substantially influence the magnitude of the placebo effect on endurance sporting performance. However, the lack of head-to-head competition in the lab-based performance assessments following oral placebo administration in earlier studies may have led to the observed placebo effect being greater than would have been observed under true competitive conditions. The present findings suggest that placebo administration is likely to improve performance by reducing perception of effort and increasing potential motivation – the same psychological mediators thought to be responsible for the ergogenic effect of competition (12, 13, 32, 33, 37). Thus, as capacity to reduce effort perception and increase potential motivation is likely to be finite, the beneficial effects of competition

and placebo are likely not to be independent nor fully additive. Thus, the present findings uniquely provide an estimate of the likely magnitude of the effect of an injected placebo on endurance sporting performance in a real-world competition setting. Further study is needed to determine whether any differences exist between the effects of orally and injected placebos on performance under such 'real world' conditions.

**Paragraph 35:** Analysis of the qualitative data provided insights which help explain how placebo influenced participants approach and perceptions to training and racing, revealing that endurance athletes taking a placebo drug experienced reductions in perceptions of physical effort during training and competition, an increase in potential motivation during competition, and perceptions of increased recovery both during training and after races. According to the Conditioned Response Model (36), the method of administration (injection) (the conditioned stimulus) and the credibility of the University setting may have contributed to performance improvement, but interestingly, the participants' accounts suggest that an interaction between their expectations from taking a placebo and their actual experiences of physical changes during training influenced performance outcomes. Those who anticipated greatest positive change from taking the placebo *and* also perceived decreased physical effort during training tended to demonstrate the greatest improvement in performance; those with more moderate expectations who perceived decreased physical effort during training, showed some improvement in performance; whereas those whose expectations of positive change were not supported by their experiences (i.e. they did not perceive decreased physical effort during training) did not show any improvement in their race times. These findings are in line with experimental evidence that the placebo effect is mediated by cognitive processes when conscious physiological processes (e.g. motor performance or pain) are

targeted (7, 23). However, it has previously been suggested that a nocebo response (i.e. where an inert substance produces a ‘harmful’ effect) is the result of negative expectations (7). Our study suggests the relationship is not so straightforward, and that where experience thwarts expectations, then a negative outcome may be observed. Previous research on placebo analgesia has demonstrated that verbal instructions on the effect of a placebo can also influence placebo response, with participants who receive the strongest suggestion that a placebo will be effective, showing the greatest pain reduction (25). In the current study, the initial detailed documentation and verbal reinforcement of participants’ beliefs that the placebo could produce a similar effect as the well-known (illegal) performance enhancer, r-HuEpo, served to heighten emotions and expectations of the outcomes of taking the placebo. This, in turn, will likely have been an important mediator of the physical, motivational and performance outcomes (26).

**Paragraph 36:** Only one study, to the authors’ knowledge, has determined the effect of r-HuEPO administration on running performance in a field-based test (14). In that report, by Durussel and colleagues, r-HuEPO administration improved performance in a 3 km running time trial by ~6%, compared to baseline, in a group of men of similar ability to the participants in the present study (3 km race time  $668 \pm 75$  seconds at baseline) (14). However, the Durussel study did not include a placebo intervention arm and therefore the performance improvement from baseline would have reflected the true ergogenic effect of the drug, *plus* any additional cognitive (i.e. placebo) effects associated with expectations and beliefs related to the impact of r-HuEPO administration (14). The results of the present study indicate that this cognitive component is real. In addition, the performance trial employed in the Durussel study

did not include head-to-head competition, so represents an experimental model in which potential placebo effects are likely to be maximised. Thus taking the results of the present study and the Durussel study together, it would seem that the likely true effect of r-HuEPO administration on endurance performance is somewhat less than 5%, and further study using a placebo controlled trial and performance testing in a competitive environment is needed to quantify the true ergogenic effect of r-HuEPO on endurance performance in real-life sporting context.

**Paragraph 37:** The present study has a number of strengths. We used a randomised cross-over design to determine the true effect of placebo over and above any familiarisation or order of testing effects. We also used a field-based performance test that included head-to-head competition and prizes to simulate real competition. Thus, the results should provide an estimate of the true magnitude of changes to performance from an injected placebo in a competitive setting. In addition, we adopted a mixed-methods approach which supplemented quantitative data with qualitative insights into the participants' experiences following placebo administration. However, an important limitation of the study is that although the participants were well-trained, they were not elite runners. Thus, further study is needed to determine whether the placebo effect size would be comparable in elite athletes who may have greater experience in providing maximal physical effects, and thus may have higher baseline potential motivation with less capacity for this to be augmented.

**Paragraph 38:** In conclusion, this study provided novel insights into the effects of an injected placebo, purporting to be performance enhancing agent similar to r-HuEPO, on endurance performance in a head-to-head competitive setting. The magnitude of

benefit, at 1.2%, is of clear sporting relevance, but is substantially smaller than the performance improvement elicited by r-HuEPO administration. The data are consistent with placebo acting to improve competitive performance by both reducing perception of effort *and* increasing potential motivation, in accord with the psychobiological model for exercise performance (8, 20, 29), but also suggest that other factors (including cognitive beliefs and expectations) may mediate the placebo response. Further study is needed to determine whether the magnitude of the placebo effect is similar in athletes at the elite level.

**Paragraph 39: ACKNOWLEDGMENTS.** We thank the participants for their time and effort; their cooperation was greatly appreciated. This work received no external funding. The results of the present investigation do not in any way constitute endorsement by the American College of Sports Medicine (ACSM).

## **DISCLOSURES**

None.

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1 **FIGURE LEGENDS:**

2

3 **Figure 1:** Representation of the study design. Participants underwent the Control and Placebo  
4 phases in randomised order. Placebo injections were self-administered by participants, on  
5 each day of the Placebo phase. No intervention was provided during the Control phase.

6

7 **Figure 2:** Panel (A): Mean ( $\pm$  SEM) change in 3 km race completion time from pre- to post-  
8 intervention in the Placebo and Control trials. Panel (B): Individual changes 3 km race  
9 completion time from pre- to post-intervention in the Placebo and Control trials.

10

11 **Figure 3:** Running speeds in the first, second and third 1000 m segments of the 3 km races  
12 before and after (A) control and (B) placebo interventions. Values are mean  $\pm$  SEM.

13

14 **Figure 4:** Heart rates in the first, second and third 1000 m segments of the 3 km races before  
15 and after (A) control and (B) placebo interventions. Values are mean  $\pm$  SEM.

16

17

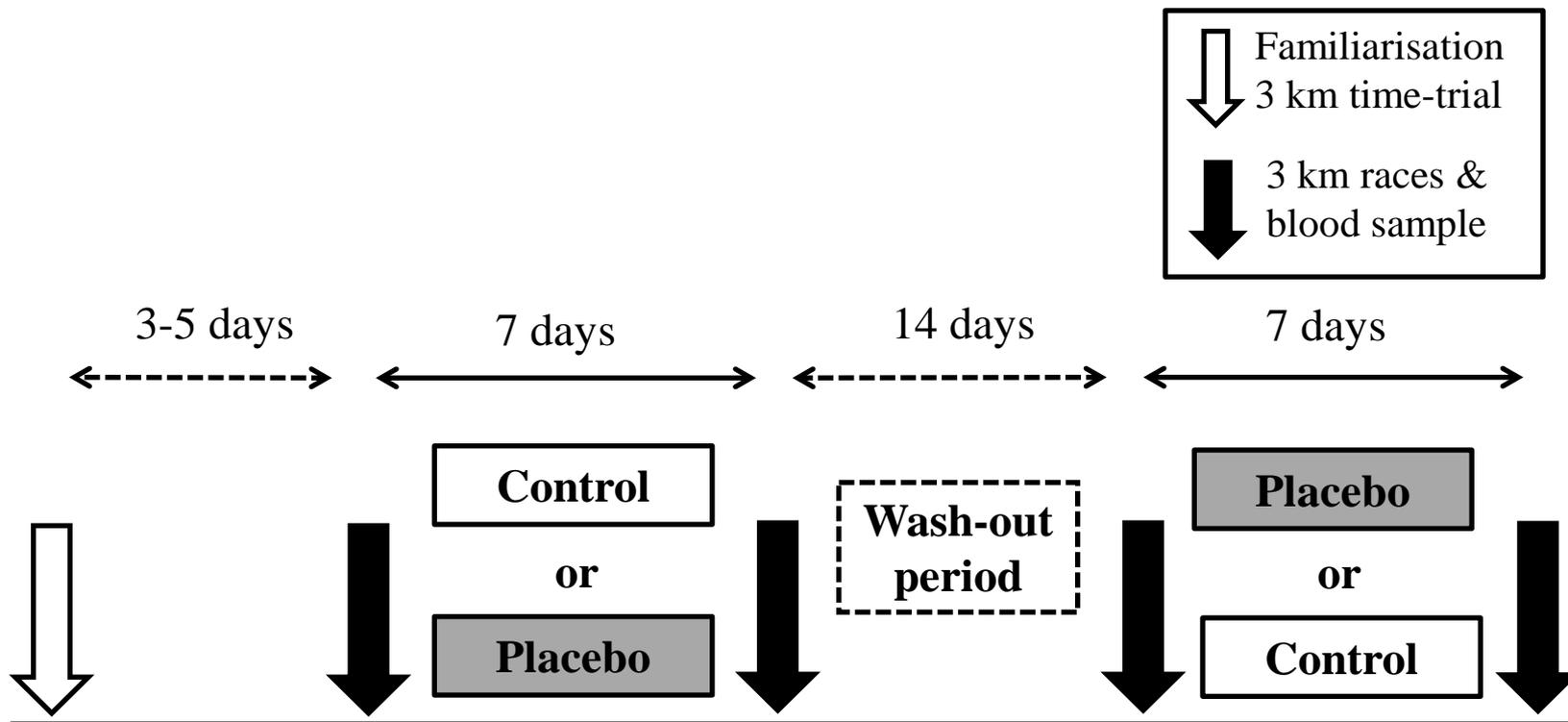


Figure 1

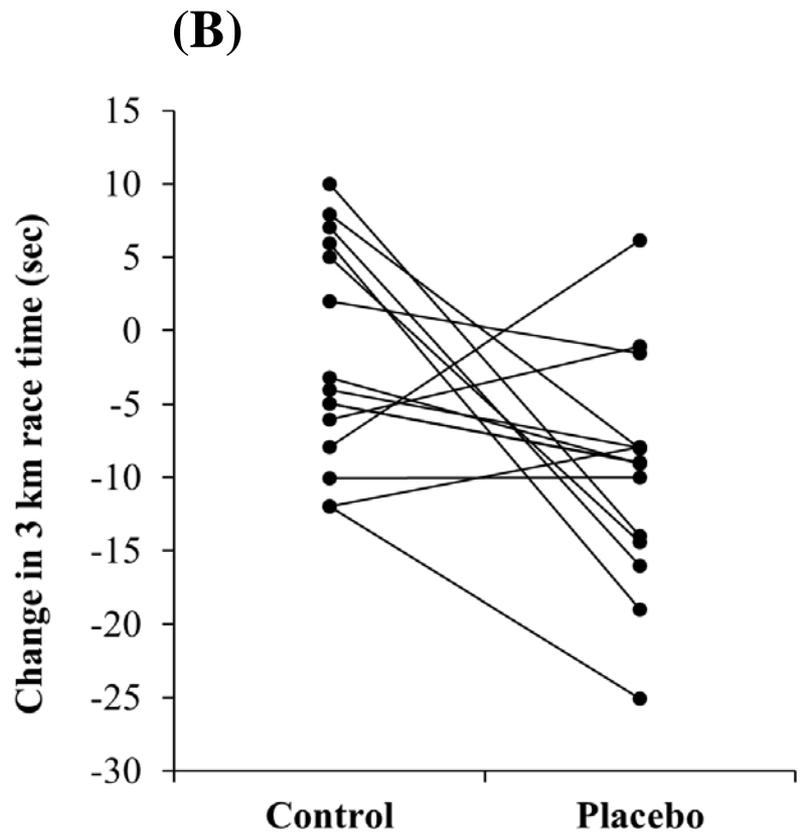
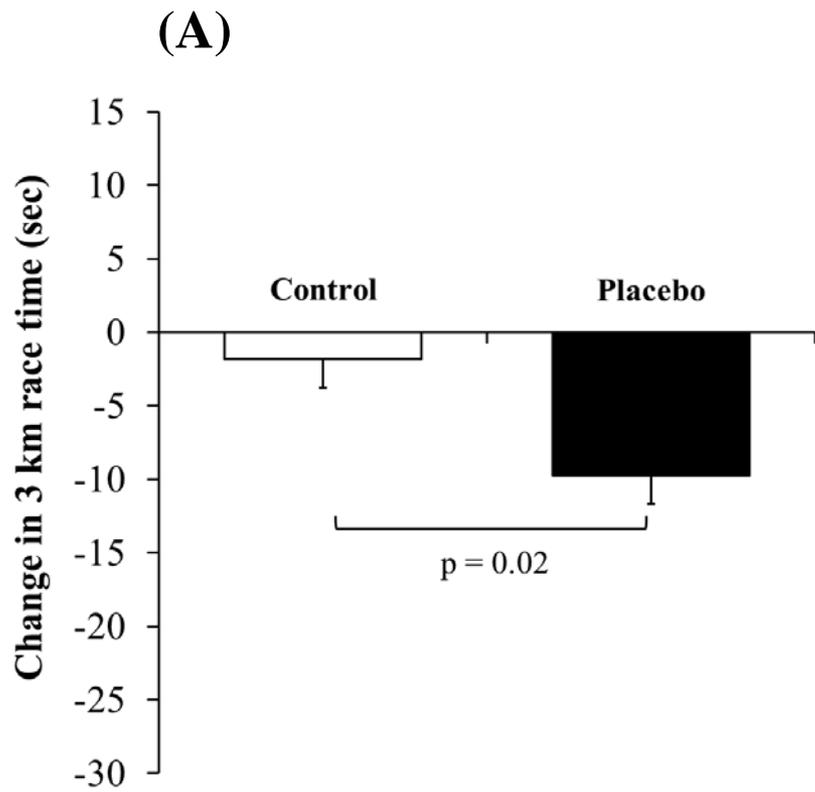
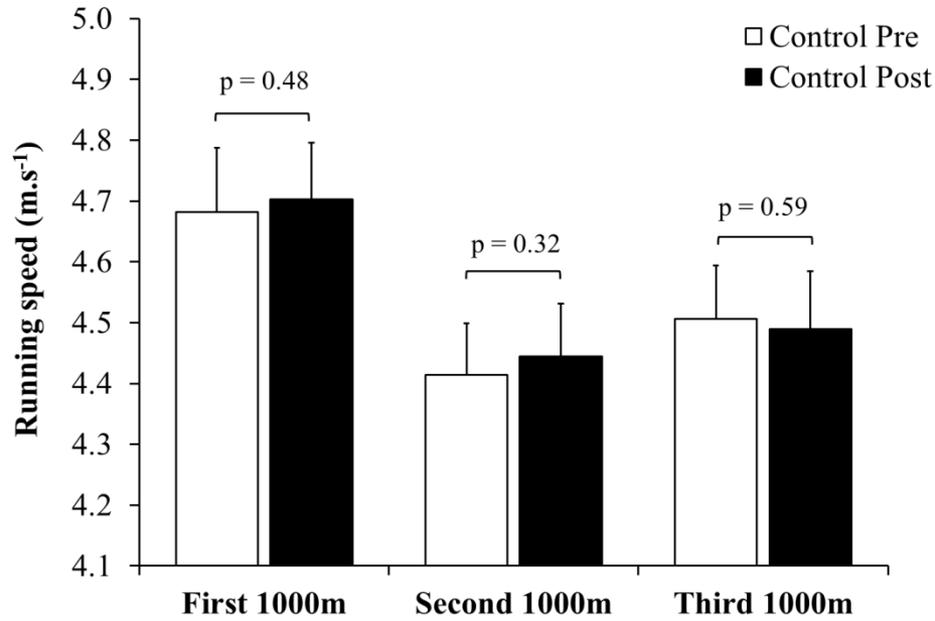


Figure 2

### (A) Control



### (B) Placebo

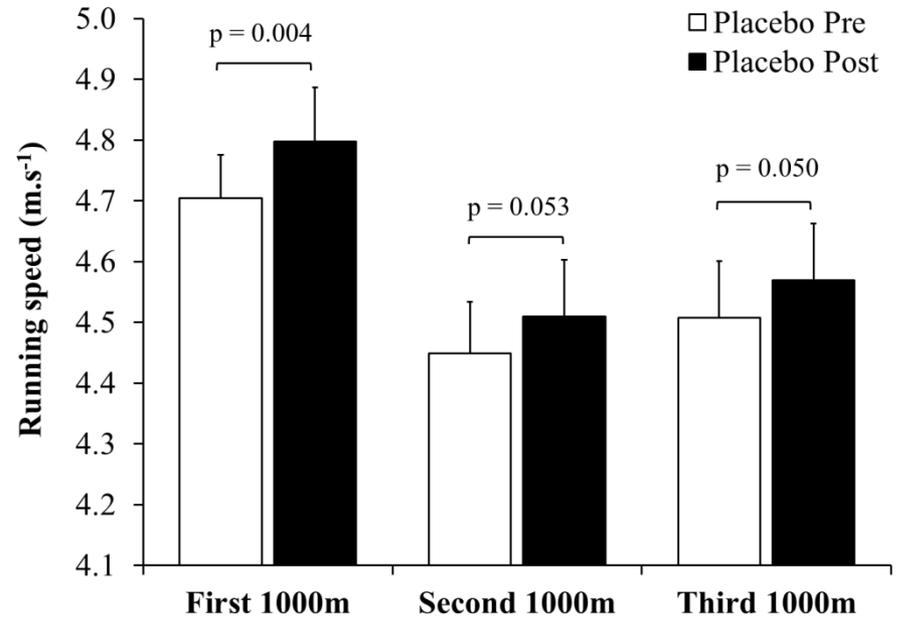
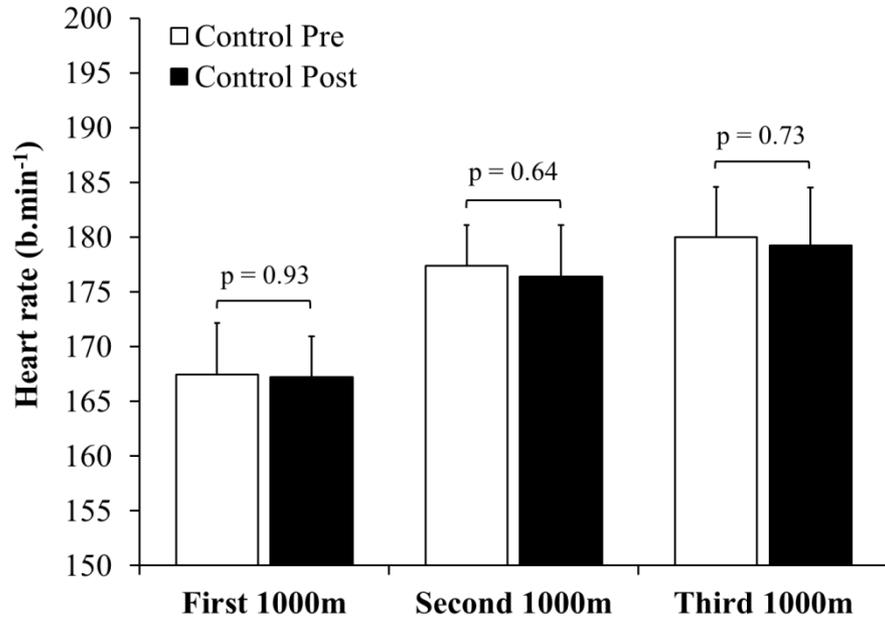


Figure 3

### (A) Control



### (B) Placebo

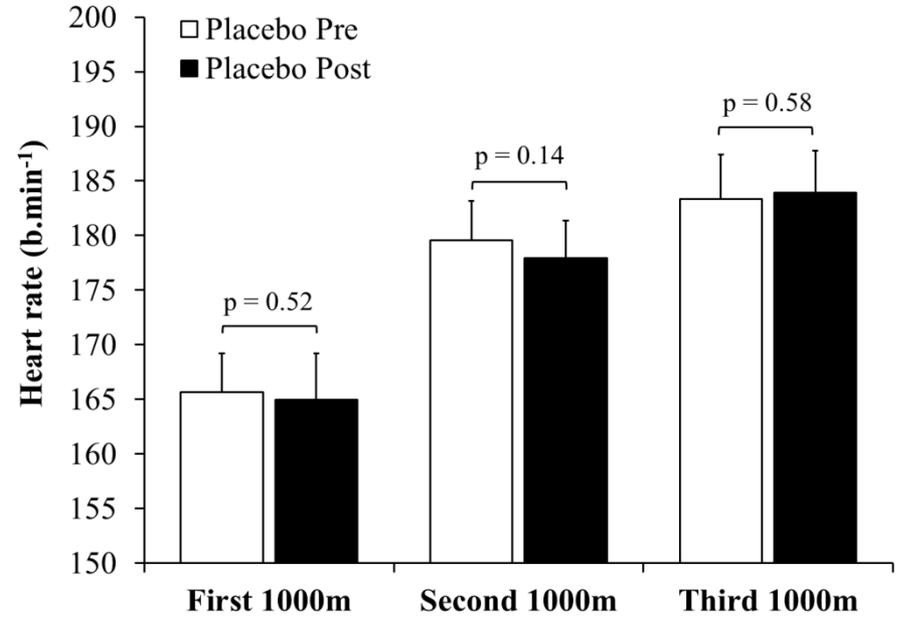


Figure 4