

# Effect of BNT162b2 mRNA booster vaccination on $VO_{2max}$ in recreational athletes: A prospective cohort study

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## Abstract

**Background and Aims:** The goal of the present study was to systematically evaluate the effect of a booster vaccination with the BNT162b2 messenger RNA (mRNA; Pfizer-BioNTech®) vaccine on maximum oxygen uptake ( $VO_{2max}$ ), potential signs of (peri)myocarditis, and sports participation.

**Methods:** Recreational athletes who were scheduled to undergo booster vaccination were evaluated with transthoracic echocardiography, serum measurements of high-sensitivity C-reactive protein (hsCRP) and high-sensitivity troponin I, and a bicycle cardiopulmonary exercise test (CPET) with serum lactate evaluation before the booster vaccine administration. Seven days postvaccination the test battery was repeated. Additionally, the subjects were asked to fill in a questionnaire on side effects and a subjective evaluation of their relative training volume and intensity as compared to the weeks before vaccination.

**Results:** A group of 42 analysed athletes showed a statistically significant 2.7% decrease in  $VO_{2max}$  after vaccination (mean standard error of mean pre: 48.6 (1.4) ml/kg/min; post: 47.3 (1.4) ml/kg/min;  $p = 0.004$ ). A potentially clinically relevant decrease of 8.6% or more occurred in 8 (19%) athletes. Other CPET parameters and lactate curves were comparable. We found no serological or echocardiographic evidence of (peri)myocarditis. A slight but significant increase in hsCRP was noted 1 week after vaccination. Side effects were mild and sports participation was generally unchanged or mildly decreased after vaccination.

**Conclusion:** In our population of recreational endurance athletes, booster vaccination with the BNT162b2 mRNA vaccine resulted in a statistically significant decrease in  $VO_{2max}$  7 days after vaccination. The clinical impact hereof needs to be further determined. No major adverse events were observed.

## KEYWORDS

athlete, COVID-19, SARS-CoV-2, vaccination,  $VO_{2max}$

## 1 | INTRODUCTION

Vaccination is highly recommended for athletes. It is advised that this should be done outside the competition period to minimize interference with training and competition as a result of potential side effects.<sup>1</sup> Recent recommendations, however, state that delaying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination until sports/competition is complete may not be desirable.<sup>2</sup> This is of course due to the ongoing pandemic with greater health risks from the disease (COVID-19) than from vaccination.<sup>3</sup>

The COVID-19 pandemic has caused uncertainties regarding sports participation, both concerning the disease itself and the vaccination against it. The disease can give rise to potentially dangerous cardiac complications such as (peri)myocarditis. The reported prevalence of this condition in athletes ranges between 0% and 15%.<sup>4</sup> More recently, SARS-CoV-2 vaccination (specifically with messenger RNA [mRNA] vaccines) has been identified as a potential etiology of a similar clinical syndrome, most frequently in younger males who received their second vaccine.<sup>5,6</sup>

Although SARS-CoV-2 vaccination generally is well-tolerated among athletes, the fear of performance loss, an impaired immune response as a result of sports participation, or side effects following vaccination may lead to postponement or cancelation of vaccination.<sup>7</sup> Contrary to the increasing knowledge of cardiac side effects, the impact of vaccination on exercise capacity has not been studied extensively. Recent evidence demonstrates that athletes should anticipate modification of training regimens for 2 days after influenza vaccination.<sup>8</sup> Even more recently, a negative association between vaccination status and calculated maximum oxygen uptake capacity ( $VO_{2max}$ ) has been reported.<sup>9</sup>

To gain more insight into this matter we aimed to evaluate the effect of BNT162b2 mRNA (Pfizer-BioNTech®) booster vaccination on  $VO_{2max}$  (defined as the maximum value of the 30 s rolling average of the  $VO_2$  uptake) in a group of recreational endurance athletes (individuals performing endurance sports, such as cycling, running, or swimming for  $\geq 4$  h/week and having done so for at least 4 years<sup>10</sup>).

## 2 | MATERIALS AND METHODS

We used the strengthening of the reporting of observational studies in the epidemiology cohort checklist when writing our report.<sup>11</sup> Inclusion criteria for the study participants were (1) age  $\geq 18$  years old, (2) full vaccination status before the start of the study, and (3) planned booster vaccination with the BNT162b2 mRNA vaccine. Recruitment was done in two University Hospitals (Site A: Antwerp and Site B: Leuven, Belgium). Within 7 days before the booster vaccine administration, three evaluations were performed: (1) a blood sample for high-sensitivity C-reactive protein (hsCRP; Atellica; Siemens®) and high-sensitivity troponin I (hsTnI; Atellica; Siemens®), (2) transthoracic echocardiography (TTE) followed by (3) a cardiopulmonary exercise test (CPET) with serum lactate evaluation. Seven days after booster vaccination the same test battery was repeated in

the same institution as the first test. Athletes were advised not to perform any intensive exercise during the first 3 days after vaccination.

Additionally, the athletes were asked to fill in a short questionnaire regarding the side effects of vaccination (presence and duration of pain or swelling at the injection site, palpable or sore axillary lymph node(s) on the side of the injection, body temperature  $>37.5^\circ\text{C}$ , fatigue, myalgia, chest pain, headache, palpitations, or dizziness) and subjective impact on training volume and intensity in the week following vaccination (1: none, 2: much less, 3: somewhat less, 4: same as always, 5: somewhat more, and 6: much more).

### 2.1 | CPET and lactate measurement

Participants were requested to refrain from intense exercise 48 h before the CPET. The test was performed on a bicycle ergometer with breath-by-breath gas analysis (Site A: Lode-Excalibur Sport® and Ergostik; Geratherm®; Site B: ER900® and Oxycon Alpha®; Jaeger). After adjustment of the saddle and fitting of the mask, the subjects sat still on the bicycle for 1 min. During this stage, a resting lactate measurement was performed (20  $\mu\text{l}$  end-to-end capillary whole blood sample taken from the hyperaemised left ear lobe, EKF Biosen) and measurement of pretest heart rate (HR). Next, the subjects started cycling without resistance for 1 min. At Site A, the test started at 30 W with a gradual increase in resistance depending on the subject's weight: for individuals weighing less than 70 kg, the increase was 20 W/min, otherwise 25 W/min by means of a raise, activate, mobilise, potentiate protocol. At Site B, a 50 + 25 W STEP protocol was used. Rotations were kept at 75–85/min. Depending on the site (and the technical possibilities) further lactate measurements were performed: At Site A, lactate was measured at the end of each stage up to the maximum exercise, resulting in a lactate curve. At Site B, lactate was measured at respiratory exchange ratio (RER) = 1, at maximum exercise and 30 min after reaching maximum exercise. After achieving maximal volitional fatigue, subjects were asked to continue cycling for another 2 min at 30 W followed by a single (Site A) to 3 min (Site B) passive recovery resting phase. Care was given to perform the repeat CPET at the same time of day (with a margin of 1 h earlier or later) as the baseline test to minimize confounding of diurnal variations in  $VO_{2max}$ .<sup>12</sup> A test was considered maximal if  $\text{RER} \geq 1.10$ <sup>13</sup> and a plateau of the  $VO_2$  curve was observed despite increases in work output. The maximum workload was determined at exhaustion. Determination of the ventilatory thresholds (VT) was done semiautomatically on the  $VCO_2/VO_2$  (VT1) and  $VCO_2/VE$  (VT2) plots by one observer, using the method described by Beaver et al.<sup>14</sup>

### 2.2 | Echocardiography

TTE was performed by experienced sonographers (Site A: Philips® IE 33 MATRIX, Site B: GE® Vivid E95) following recent guidelines.<sup>15</sup> To eliminate intraobserver variability for each test person, the pre- and

postvaccination TTE were performed by the same operator. The focus was placed on parameters potentially affected by (peri) myocarditis: presence or absence of pericardial fluid, intraventricular septum thickness, left ventricular (LV) posterior wall thickness, LV ejection fraction (using biplane Simpson's method), LV end-diastolic volume, LV end-systolic volume, global longitudinal strain, mitral E and A wave amplitude, tissue Doppler-derived early diastolic velocity at the basal inferoseptum (septal e'), right ventricular (RV) end-diastolic area, RV end-systolic area (with the calculation of fractional area change), RV free wall longitudinal strain, and tricuspid annular plane systolic excursion.

### 2.3 | Endpoints

The primary endpoint of the study was the change in  $VO_{2max}$  after vaccination. Secondary endpoints included changes in VT1 and VT2, peak HR and power output, and evaluation of the lactate and HR recovery data. In a separate analysis, echocardiographic data and serum markers were evaluated for signs of (peri)myocarditis.

### 2.4 | Statistical analysis

All analyses were performed using SPSS® 27.0.1.0. Only the data from participants who performed two maximal CPET's were included. Continuous data were evaluated for normal distribution using the Shapiro–Wilk test. Paired analysis of normally distributed data was performed with the paired *t*-test, otherwise the related samples Wilcoxon signed rank test was used. Correction for multiple testing was done with the Holm–Bonferroni method. To compare the data obtained in both CPETs between subjects, the lactate values were interpolated for each decile of maximum workload. From this standardized lactate, curves were drawn. These curves were then analyzed with repeated measures analysis of variance (ANOVA). Interactions of the site of inclusion and gender with the primary outcome ( $VO_{2max}$ ) were also tested with repeated measures ANOVA with status (pre–post vaccination) as a within-subject factor and site or gender as a between-subject factor. A two-tailed  $p < 0.05$  was considered statistically significant. All data are reported as mean (standard error of mean [SEM]) unless stated otherwise.

### 2.5 | Sample size calculation

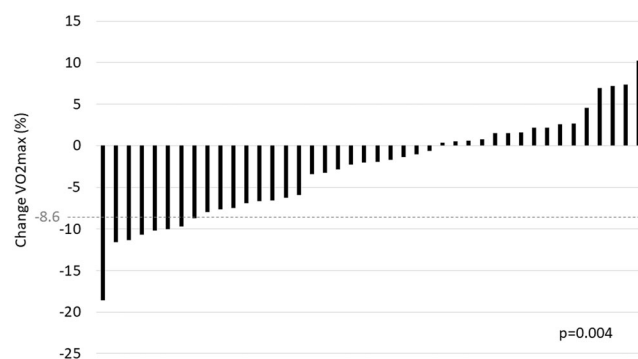
A typical “average  $VO_{2max}$ ” (for active men) is 46.4 (8.4) ml/kg/min.<sup>16</sup> As we found no formal data on the magnitude of a clinically relevant change in  $VO_{2max}$  for an athletic population, we used the following reasoning: the  $VO_{2max}$  decreases with 4 ml/kg/min/decade in men (8.6%).<sup>16</sup> If an individual would go down 10 years in exercise capacity, that could be considered a clinically relevant change. Using G\*Power® Version 3.1.9.4, we calculated a sample size of 50 for a power of 0.80 and a significance level of 0.05.

## 3 | RESULTS

A group of 47 athletes was recruited (27 Site A, 20 Site B). Three did not deliver two maximal tests (one male before, one female before, and one female after vaccination (RER: 1.25 to >1.05 and  $VO_{2max}$ : 50.24 to >46.06 ml/kg/min). Additionally, one male athlete eventually did not get vaccinated and one male athlete caught COVID-19 immediately after his first vaccination, resulting in 42 individuals (71% male) forming the study cohort. The mean age was 37.0 (1.8) years and the mean body mass index was 22.7 (0.4) kg/m<sup>2</sup>. None of the study participants were current smokers and seven of them had previously suffered from COVID-19. On average they performed 7.4 (SEM: 0.5, range 4–15) h of sports per week (almost everyone performed more than one type of sports: 88% cycling, 54% running, 20% swimming, and 44% other). The prevaccination evaluation was performed at a median of 0 days (interquartile range [IQR]: 2 days) before vaccination.

### 3.1 | Cardiopulmonary exercise test

We found a statistically significant reduction in  $VO_{2max}$  after vaccination (−2.7%; pre: 48.6 [1.4] ml/kg/min, post 47.3 [1.4] ml/kg/min;  $p = 0.004$ ; Figure 1, Table 1), without a significant difference in peak RER or peak lactate values. There was no interaction of the inclusion site with these results ( $p_{status} = 0.006$ ,  $p_{status \times site} = 0.31$ ). The same was true for the interaction of gender ( $p_{status} = 0.008$ ;  $p_{status \times gender} = 0.95$ ). When only athletes who did not report a decrease in training volume and intensity (i.e., a score  $\geq 4$  for both intensity and volume [ $n = 22$ ]) were analyzed, the decrease in  $VO_{2max}$  was confirmed (from 46.1 [1.8] to 44.7 [1.8] ml/kg/min [ $p = 0.04$ ]). The same was true if only athletes without a history of previous SARS-CoV-2 infection ( $n = 35$ ) were evaluated (from 48.5 [1.6] to 46.8 [1.6] ml/kg/min [ $p = 0.001$ ]). A potentially clinically relevant decrease of 8.6% or more was found in 8 (19%) subjects.



**FIGURE 1** Percentage change  $VO_{2max}$ . Percentage change in  $VO_{2max}$  (abscissa) after vaccination ranked from most negative to most positive. The dashed line denotes the cutoff of −8.6% for a clinically relevant change in  $VO_{2max}$ .  $VO_{2max}$ , maximum oxygen uptake.

TABLE 1 CPET results

|                                    | Overall (n = 42) |              |       | Male (n = 30) |              |       | Female (n = 12) |              |       |
|------------------------------------|------------------|--------------|-------|---------------|--------------|-------|-----------------|--------------|-------|
|                                    | Pre              | Post         | p     | Pre           | Post         | p     | Pre             | Post         | p     |
| VO <sub>2max</sub> (ml/kg/min)     | 48.6 (1.4)       | 47.3 (1.4)   | 0.004 | 51.3 (1.5)    | 50.0 (1.6)   | 0.019 | 41.9 (1.8)      | 40.5 (1.6)   | 0.097 |
| O <sub>2</sub> pulse max (ml/beat) | 19.2 (0.7)       | 18.2 (0.7)   | 0.010 | 21.2 (0.5)    | 20.3 (0.5)   | 0.06  | 14.0 (0.8)      | 13.0 (0.6)   | 0.048 |
| RER                                | 1.23 (0.01)      | 1.24 (0.01)  | 0.68  | 1.25 (0.01)   | 1.25 (0.01)  | 0.77  | 1.21 (0.02)     | 1.21 (0.02)  | 0.71  |
| Watt VT1 (W)                       | 196.9 (8.3)      | 198.4 (8.8)  | 0.74  | 217.7 (7.7)   | 219.3 (9.4)  | 0.79  | 144.8 (12.3)    | 146.2 (9.2)  | 0.83  |
| Watt VT2 (W)                       | 269.8 (12.1)     | 266.7 (11.2) | 0.85  | 302.2 (11.9)  | 295.6 (11.0) | 0.40  | 194.2 (13.5)    | 199.2 (14.3) | 0.52  |
| Watt Max (W)                       | 337.7 (11.3)     | 340.0 (11.3) | 0.43  | 371.9 (9.1)   | 374.5 (8.9)  | 0.50  | 252.1 (13.3)    | 253.8 (13.9) | 0.71  |
| HR Pre (BPM)                       | 70.6 (1.8)       | 73.0 (2.2)   | 0.21  | 69.8 (2.2)    | 71.6 (2.5)   | 0.45  | 72.4 (3.4)      | 76.4 (4.7)   | 0.26  |
| HR VT1 (BPM)                       | 143.2 (3.0)      | 140.1 (2.7)  | 0.17  | 142.6 (3.6)   | 138.4 (3.3)  | 0.20  | 144.8 (5.6)     | 143.8 (4.9)  | 0.65  |
| HR VT2 (BPM)                       | 165.3 (3.1)      | 163.2 (2.8)  | 0.30  | 165.7 (3.8)   | 162.6 (3.5)  | 0.13  | 163.8 (5.7)     | 164.7 (5.1)  | 0.71  |
| HR Max (BPM)                       | 181.1 (2.0)      | 181.1 (2.1)  | 0.96  | 181.6 (2.5)   | 181.1 (2.5)  | 0.60  | 179.7 (3.6)     | 181.3 (4.2)  | 0.52  |
| HR Rec1 (BPM)                      | 160.6 (2.4)      | 157.3 (2.4)  | 0.06  | 160.3 (2.8)   | 157.2 (5.2)  | 0.30  | 161.1 (4.9)     | 120.1 (3.2)  | 0.02  |
| HR Rec3 (BPM)                      | 118.7 (2.8)      | 118.6 (2.4)  | 0.82  | 120.1 (3.2)   | 119.6 (2.6)  | 0.87  | 115.1 (5.9)     | 116.0 (5.2)  | 0.82  |
| VE/VCO <sub>2</sub> slope          | 23.4 (0.5)       | 24.0 (0.5)   | 0.78  | 23.8 (0.6)    | 23.9 (0.6)   | 0.89  | 24.0 (0.9)      | 24.2 (0.8)   | 0.71  |

Note: Results are shown as mean (SEM). For clarification *p* values in the table are raw values, thus before correction.

VE/VCO<sub>2</sub> slope: Number of liters of air being breathed to eliminate 1 L of CO<sub>2</sub>; O<sub>2</sub> pulse max = VO<sub>2max</sub> (ml/min)/HR<sub>max</sub>(beats/min).

Abbreviations: BPM, beats per minute; CPET, cardiopulmonary exercise test; HR Max, maximum heart rate; HR Pre, pretest heart rate; HR Rec1, heart rate 1 min after peak exercise; HR Rec3, heart rate 3 min after peak exercise; HR VT1, heart rate at the first anaerobic threshold; HR VT2, heart rate at the second anaerobic threshold; RER, respiratory exchange ratio; W, Watt; Watt Max, maximum power; Watt VT1, power at the first anaerobic threshold; Watt VT2, power at second anaerobic threshold.

O<sub>2</sub> pulse was also significantly lower 1 week after vaccination (from 19.2 [0.7] to 18.2 [0.7] ml/beat; *p* = 0.010). This difference reached statistical significance in females, but not in males (Table 1).

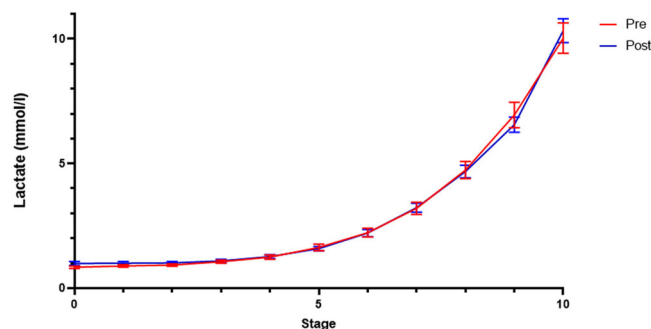
After Holm-Bonferroni correction for multiple testing, no significant differences in any of the other measured CPET parameters were found.

### 3.2 | Serum lactate

The analysis of the lactate data of Site 1 did show that lactate significantly increased with exercise stage (*p*<sub>stage</sub> < 0.001), without any difference according to vaccination status (*p*<sub>status</sub> = 0.89; *p*<sub>status×stage</sub> = 0.21; Figure 2). These results did not change after the addition of the Site 2 data: There were no significant differences in rest, RER = 1 and peak lactate. Only five individuals completed the 30' lactate test, with, after correction, no significant alteration after vaccination (median [IQR] pre: 3.2 [1.85 mmol/L; post: 4.36 [2.6] mmol/L; *p* = 0.045 × 4 = 0.18).

### 3.3 | Serum analysis

For the hsTnI assay, the upper limit of normal is 45 ng/ml. We found no value over 25 ng/ml (median [IQR] pre = post 4.0 [4.0] ng/ml; *p* = 0.82). For the hsCRP assay, the upper limit of normal is 10 mg/L. One female participant had a hsCRP of 10 mg/L before vaccination.



**FIGURE 2** Lactate curves. Lactate concentrations (ordinate; mmol/L) according to relative exercise stage (in deciles of maximum workload). Red line: Prevaccination and blue line: postvaccination. Error bars represent mean ± 2 SE.

Overall, there was a slight increase in hsCRP after vaccination (median [IQR]: 0.6 [0.8] and 0.8 [1.1] mg/L for pre- and postvaccination, respectively; *p* = 0.004 after correction).

### 3.4 | Echocardiography

As shown in Table 2, we found no evidence of myocarditis on TTE. All measured structural and functional parameters of the LV and RV were comparable before and 1 week after booster vaccination. None of the participants showed pericardial fluid.

**TABLE 2** Echocardiographic results

|             | Pre         | Post        | p    |
|-------------|-------------|-------------|------|
| IVSt (mm)   | 9.2 (0.2)   | 9.2 (0.2)   | 0.70 |
| LVPWt (mm)  | 9.2 (0.2)   | 9.2 (0.2)   | 0.72 |
| LVEF (%)    | 61.0 (0.8)  | 59.8 (1.2)  | 0.21 |
| LVEDV (ml)  | 132.1 (4.2) | 133.3 (5.1) | 0.71 |
| LVESV (ml)  | 52.0 (2.3)  | 52.6 (2.4)  | 0.64 |
| GLS (%)     | -20.9 (0.4) | -21.2 (0.5) | 0.49 |
| E/A         | 1.62 (0.07) | 1.66 (0.08) | 0.55 |
| E/e'        | 7.95 (0.35) | 7.48 (0.29) | 0.07 |
| RV FAC (%)  | 46.0 (0.01) | 45.9 (0.01) | 0.94 |
| RVFW LS (%) | -26.7 (0.5) | -28.1 (0.6) | 0.05 |
| TAPSE (mm)  | 24.3 (0.5)  | 24.9 (0.5)  | 0.27 |

Note: Data are shown as mean (SEM).

Abbreviations: E/A, mitral E-wave amplitude divided by mitral A wave amplitude; E/e', mitral E-wave amplitude divided by septal e' amplitude; GLS, global longitudinal strain; IVSt, intraventricular septum thickness; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVPWt, left ventricular posterior wall thickness; RV FAC, right ventricular fractional area change; RVFW LS, right ventricular free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

**TABLE 3** Side effects

|              | Subjects | %    | 1d | 2d | 3d | 4d | 5d | 6d | 7d |
|--------------|----------|------|----|----|----|----|----|----|----|
| Local pain   | 34       | 80.1 | 15 | 12 | 5  |    | 2  |    |    |
| Fatigue      | 24       | 57.1 | 13 | 5  | 2  |    | 2  |    | 1  |
| Myalgia      | 9        | 21.4 | 7  | 1  | 1  |    |    |    |    |
| Headache     | 6        | 14.3 | 5  |    | 1  |    |    |    |    |
| Swelling LN  | 5        | 11.9 | 1  | 1  | 2  |    | 1  |    |    |
| Fever >37.5  | 5        | 11.9 | 5  |    |    |    |    |    |    |
| Chest pain   | 4        | 9.5  | 2  |    |    | 1  |    |    | 1  |
| Palpitations | 1        | 2.4  |    |    |    |    | 1  |    |    |
| Dizziness    | 1        | 2.4  |    |    | 1  |    |    |    |    |

Note: Subjects: Number of subjects reporting the side effect; %: percentage of subjects reporting the side effect. 1d–7d: Number of subjects reporting the specific number of days with the side effect. Abbreviation: LN, lymph nodes.

### 3.5 | Vaccination side effects

The most prevalent side effects were local pain for a median of 2 days (81%) and fatigue for a median of 1 day (57%; Table 3). Most participants reported no change in their training volume or intensity in the week after their vaccination, with a median score for intensity and volume of 4 (both IQR 1). Two athletes (5%) did not perform any exercise (one for reasons unrelated to the vaccination, and one because of extreme fatigue).

## 4 | DISCUSSION

In our study, we found a statistically significant decrease in  $\text{VO}_{2\text{max}}$  1 week after booster vaccination with BNT162b2 mRNA. A clinically relevant decrease was found in 19% of subjects. We did not observe any major side effects from this vaccination.

### 4.1 | Exercise capacity

Data on the effect of vaccination on exercise capacity is scarce, specifically for SARS-CoV-2 vaccines. A recent report on a small group of athletes (18 athletes, 9 male, age 24–43 years old, 12 vaccinated, 6 controls) evaluated with a different CPET protocol (4–5 min stages at 50%, 60%, 70%, and 80% of predicted  $\text{VO}_{2\text{max}}$ ) found elevation of the HR with 5 beats/min at the 70% exercise stage, together with increased norepinephrine levels at the 80% stage.<sup>17</sup> The authors state that this might have implications for athletes at the elite level. There was no significant effect on other parameters such as RER, time to the VT, and serum lactate. A formal analysis of the evolution of  $\text{VO}_{2\text{max}}$  was not performed.

In our series, we did not observe a difference in HR at VT1 (which prevaccination was at 78.9 [7.1]% and postvaccination at 77.3 [7.2]% of  $\text{HR}_{\text{max}}$ ;  $p = 0.22$ ; Table 1). We found a significant 2.7% decrease in  $\text{VO}_{2\text{max}}$  after administration of the booster vaccine. The underlying mechanisms and clinical consequences of this finding remain unclear.

First of all, the statistically significant 1.3 ml/kg/min reduction in  $\text{VO}_{2\text{max}}$  may not be considered clinically relevant in our population. Indeed, a small and potentially temporary decline in  $\text{VO}_{2\text{max}}$  does not necessarily imply a decline in athletic performance. While  $\text{VO}_{2\text{max}}$  is one determinant of athletic performance, other important factors include exercise economy and fractional utilization of  $\text{VO}_{2\text{max}}$ , depending on exercise conditions.<sup>18,19</sup> Furthermore, a potentially clinically relevant decrease in  $\text{VO}_{2\text{max}}$  of 8.6% or more was only found in 19%.

From our data, the mechanism of this reduction remains unclear. In fact on linear regression analysis, only 17% of the variance of the difference in  $\text{VO}_{2\text{max}}$  after vaccination could be explained through the variance in  $\text{O}_2\text{pulse max}$  ( $p = 0.007$ ). This suggests that other factors, such as the peripheral efficiency of  $\text{O}_2$  extraction play a role. This has been described in COVID-19<sup>20</sup> and in long-COVID.<sup>21</sup> These findings certainly warrant future clarification.

Second, as we did not include a sham-vaccinated group (see also under limitations), we cannot firmly state that the administration of the booster vaccine caused the decrease in  $\text{VO}_{2\text{max}}$ . An alternative explanation could be a detraining effect as the result of our advice not to perform intensive exercise during the first 3 days after vaccination. However, whereas a period of 2–4 weeks of detraining can result in a decline of  $\text{VO}_{2\text{max}}$ , short periods of relative rest have not been shown to impact exercise capacity in well-trained athletes.<sup>22,23</sup> Moreover, most of the participants in our study did not report an important decrease in either training volume or training

intensity. A post hoc subanalysis of those athletes in our series who reported no decrease in sports participation after vaccination confirmed the decrease in  $VO_{2max}$ , suggesting that detraining is not the most important explanation for this finding.

Finally, as we only tested our subjects 7 days after booster administration, it is still uncertain how long the observed decline in  $VO_{2max}$  lasts. This could be the subject of future studies in this field.

## 4.2 | Immune response

As for a lower immune response in athletes after vaccination, the majority of the current evidence points towards a similar or even heightened response in athletes.<sup>1,24</sup> In our series, we did not specifically evaluate this, although we found a statistically significant small increase in hsCRP levels, which is commonly observed after antiviral vaccination and suggestive of an immune reaction.<sup>25</sup>

## 4.3 | Side effects

We observed similar side effects as reported by others after the second vaccination in an athletic population: Local pain was most prevalent (81% in our study; 94% of athletes in a prior series).<sup>7</sup> Our study participants reported more fatigue (57% vs. 37%) and less myalgia and headaches (respectively, 24% vs. 33% and 14% vs. 34%). Overall the side effects were benign and did not cause the vast majority of athletes to discontinue their training: Only one athlete did not train at all during the week after vaccination for reasons related to the vaccination.

Importantly, in our small cohort of athletes, we did not see any biochemical or echocardiographic sign of (sub)clinical (peri)myocarditis after booster vaccination with the BNT162b2 mRNA vaccine. This does not fully exclude subclinical myocarditis in the absence of cardiac magnetic resonance imaging (MRI) data.

## 5 | LIMITATIONS

The current study had no control group of athletes receiving a sham booster vaccination (including the postvaccination training advice) undergoing the same evaluation process. As pointed out above, a short period of detraining does not affect  $VO_{2max}$  in well-trained athletes. Furthermore, we did not deem it ethical to withhold booster vaccination from our population of healthcare workers on the brim of a potential new COVID-19 wave.

The two participating centers used slightly different exercise protocols. As each individual was in his/her own control and a paired analysis were performed this does not affect the conclusions.

As the prevalence of (peri)myocarditis postvaccination is low, we chose to not include this condition as a primary endpoint of the current study, including not performing a cardiac MRI. This results in

the study being underpowered to draw firm conclusions as to the occurrence of this condition.

We cannot formally exclude the occurrence of (sub)clinical SARS-CoV-2 infection just before or during the period after the booster vaccination. However, as the study took place in the setting of two university hospitals, the threshold for polymerase chain reaction testing was very low. Indeed, we found one (excluded) subject to actually suffer from COVID-19 after his vaccine. This at least suggests a high a priori suspicion of the disease. Furthermore, the time frame between the two test moments was relatively short and took place in a period of strict governmental preventive measures, such as social distancing and wearing protective masks. As such, we expect the risk of intercurrent infections to be low.

Our cohort comprised recreational athletes in whom  $VO_{2max}$  was tested as the primary outcome measure. It is unclear to what extent these results can be extrapolated to the effect of vaccination on other exercise modalities (such as time-trial performance) and to a more elite group of athletes.

## 6 | PERSPECTIVE

In our population of well-trained recreational endurance athletes, booster vaccination with the BNT162b2 mRNA vaccine was safe and generally well-tolerated. One week after administration of the vaccine  $VO_{2max}$  was 2.7% or 1.3 ml/kg/min lower, the clinical significance and underlying mechanisms of which remain to be determined. However, in the context of professional athletes every second counts, so in spite of the remaining uncertainties regarding the implications of the observed decrease in  $VO_{2max}$  in our study, we would suggest (if epidemiologically justifiable) scheduling BNT162b2 mRNA booster vaccination outside major competition periods, until more data have been obtained on the effect of (booster) vaccination on (higher level) athletic performance.

## AUTHOR CONTRIBUTIONS

**Hielko Miljoen:** Conceptualization; data curation; formal analysis; investigation; methodology; supervision; validation; visualization; writing – original draft; and writing – review and editing. **Youri Bekhuis:** Data curation; formal analysis; investigation; validation; and writing – review and editing. **Johan Roeykens:** Data curation; formal analysis; investigation; methodology; and writing – review and editing. **Karim Taha:** Formal analysis; investigation; validation; and writing – review and editing. **Rudi Frankinouille:** Formal analysis; project administration; resources; validation; and writing – review and editing. **Matthijs Michielsen:** Investigation; resources; validation; and writing – review and editing. **Caroline M. Van de Heyning:** Resources; supervision; validation; and writing – review and editing. **Véronique Cornelissen:** Formal analysis; resources; supervision; validation; and writing – review and editing. **Kasper Favere:** Writing – review and editing. **Sander Eens:** Writing – review and editing. **Jan Gielen:** Resources; supervision; validation; and writing – review and

editing. **Kaatje Goetschalckx**: Formal analysis; investigation; supervision; validation; and writing – review and editing. **Hein Heidebuchel**: Resources; supervision; validation; and writing – review and editing. **Guido Claessen**: Conceptualization; formal analysis; methodology; resources; supervision; validation; and writing – review and editing. All authors have read and approved the final version of the manuscript.

## CONFLICTS OF INTEREST

Dr. Hein Heidebuchel did receive personal lecture and consultancy fees from Abbott, Biotronik, Daiichi-Sankyo, Pfizer-BMS, Medscape, Pfizer-BMS, and Springer Healthcare Ltd. He received unconditional research grants through the University of Antwerp and/or the University of Hasselt from Abbott, Bayer, Biotronik, Biosense-Webster, Boston-Scientific, Boehringer-Ingelheim, Daiichi-Sankyo, Fibricheck/Qompium, Medtronic, and Pfizer-BMS, all outside the scope of this work. Dr. Hielko Miljoen did receive personal lectures and consultancy fees from Pfizer-BMS and Abbott outside the scope of this work.

## DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request to the corresponding author. Hielko Miljoen had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

## ETHICS STATEMENT

For this study, approval of the local ethics committee was obtained. The trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04726150). All participants gave written informed consent.

## TRANSPARENCY STATEMENT

Hielko Miljoen affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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**How to cite this article:** Miljoen H, Bekhuis Y, Roeykens J, et al. Effect of BNT162b2 mRNA booster vaccination on  $VO_{2max}$  in recreational athletes: a prospective cohort study. *Health Sci Rep.* 2022;5:e929. doi:10.1002/hsr2.929

## APPENDIX

### Covivax Study Group

#### Antwerp

|                      |                        |                                                                          |
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