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LETTER TO THE EDITOR

Response to Comment on: "Low Cardiorespiratory Fitness Post-COVID-19: A Narrative Review"

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Dear Editor,

We thank Gomes Neto et al. [1] for their comment on our recent narrative review and their lauding words. Our article outlined the current evidence provided by studies using cardiopulmonary exercise testing in patients post-COVID-19 [2]. Moreover, we discussed the contribution of the pulmonary system, cardiovascular system, and periphery to exercise intolerance and low cardiorespiratory fitness (CRF) post-COVID-19 [2].

In their letter, Gomes Neto et al. [1] meta-analysed eight studies previously included in our review. We greatly appreciate their work supporting the findings of our article. These meta-analytic data in combination with the findings of our review will help researchers and clinicians understand the magnitude of the difference in CRF between patients post-COVID-19 and controls. This may, in turn, be valuable for the development of targeted treatment strategies as well as policy making. In the following, we want to use the opportunity to contextualise the findings of Gomes Neto et al. [1] and discuss exercise as a treatment option for patients post-COVID-19.

1 Findings in Context

All eight studies meta-analysed by Gomes Neto et al. [1] compared patients post-COVID-19 with individuals without a history of COVID-19. Four studies matched controls for age, sex, and, in some cases, body mass index [3–6]. Controls in the other four studies were additionally matched for health status or comorbidities (see Table 1) [7–10].

Pooling these studies yielded higher peak oxygen uptake ($\dot{V}O_{2peak}$) (mean difference: 6.3 $mL \cdot min^{-1} \cdot kg^{-1}$; 95% confidence interval [CI]: 2.8–9.8 $mL \cdot min^{-1} \cdot kg^{-1}$) in controls as compared with patients post-COVID-19 [1]. Indeed, the observed between-group difference is considerable based on evidence suggesting a 1-$mL \cdot min^{-1} \cdot kg^{-1}$ increase in $\dot{V}O_{2peak}$ is associated with 11 and 15% reductions in all-cause and cardiovascular disease mortality, respectively [11]. Moreover, their subgroup analysis returned lower $\dot{V}O_{2peak}$ in patients followed-up after severe COVID-19 than in patients who had non-severe COVID-19 (mean difference: 3.7 $mL \cdot min^{-1} \cdot kg^{-1}$, 95% CI 1.9–5.5) [1]. However, these findings alone are not a testament to COVID-19 being the sole cause of low $\dot{V}O_{2peak}$. It is now well known that, among others, the presence of comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, chronic renal disease, and chronic obstructive pulmonary disease is associated with a greater risk of severe COVID-19 [12]. The

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Table 1 Description of matching procedures for controls in the respective studies

Study	Matched for age, sex, and
Alba et al. [7]	Unexplained dyspnoea and/or exercise intolerance unrelated to COVID-19 and/or unexplained dyspnoea
Cassar et al. [8]	Body mass index, and risk factors (i.e. smoking, hypertension, diabetes, coronary artery disease, and stroke)
Raman et al. [9]	Body mass index, and risk factors (i.e. smoking, hypertension, diabetes, coronary artery disease, and stroke)
Singh et al. [10]	Exercise intolerance unrelated to COVID-19

prevalence of comorbidities may thus be higher in patients than in controls not specifically matched for such. In turn, pathophysiological mechanisms of the respective comorbidities could have already impaired $\dot{V}O_{2peak}$ before COVID-19 [13].

To investigate a possible effect of COVID-19 on $\dot{V}O_{2peak}$, controls additionally matched for health status are needed. We therefore extended the findings of Gomes Neto et al. [1] by conducting another subgroup analysis of five studies (one with two follow-up examinations) including only comorbidity- or risk factor-matched controls. For this purpose, we ran a random effects meta-analysis [14]. Study-ID and a time point indicator were included as nested random effects in the model to address the studies by Cassar et al. [8] (two follow-ups) and Vonbank et al. [6] (two subgroups compared with one control group). For comparison, we reproduced the meta-analysis by Gomes Neto et al. [1] but excluded the two studies in athletes [5, 15] as not being representative of the general population. Moreover, we included the study by Szekely et al. [16] that reported $\dot{V}O_{2peak}$ in $L \cdot min^{-1}$. Hence, standardised mean difference was the outcome of choice. When standard deviation was not reported, the following formula was applied: standard deviation = interquartile range / 1.35 [17].

The first analysis comparing controls matched for health status to patients post-COVID-19 produced a standardised mean difference in $\dot{V}O_{2peak}$ of 0.93 (95% CI 0.46–1.40; see Fig. 1A) in favour of the healthy controls. The small number of available studies including health status-matched controls should be noted as a limitation of this analysis. The second analysis replicating the findings of Gomes Neto et al. [1] yielded a standardised mean difference in $\dot{V}O_{2peak}$ of 0.86 (95% CI 0.51–1.21; see Fig. 1B), likewise in favour of the healthy controls. Interestingly, standardised mean difference was similar in both analyses, suggesting pre-existing, presumably largely asymptomatic comorbidities in patients may play a minor role, whereas acute COVID-19 sequelae and post-COVID-19 symptoms may contribute considerably to low CRF and exercise intolerance. However, the presence of similar symptoms (i.e. dyspnoea) might lead to convergence of the observed between-cohort difference [7]. This is supported by a recent meta-analysis of nine studies in patients > 3 months after COVID-19 [18]. The authors compared patients with post-COVID-19 symptoms ($n = 464$) with those without symptoms ($n = 359$) and reported a 4.9-$mL \cdot min^{-1} \cdot kg^{-1}$ lower $\dot{V}O_{2peak}$ in the former group [18]. In sum, the available data point to a detrimental effect of COVID-19 sequelae on cardiorespiratory fitness and some of its determinants (highlighted in our review [2]).

Briefly, researchers and clinicians should also be aware of the large heterogeneity (see Fig. 2), predominantly small sample sizes, and lack of precision in this context when pooling the available studies. This again supports our premise of the one-size fits all principle being obsolete; individualised diagnosis and treatment are required.

2 Considerations Regarding Exercise as Medicine in Patients Post-COVID-19

We mostly agree with Gomes Neto et al. [1]. Exercise therapy may be a valuable tool to target low CRF as well as several underlying organ limitations in some patients post-COVID-19 [19]. However, we cannot stress enough the weight of adequate exercise therapy prescription. As with drug treatment, the right dosage is vital and governs the benefit–risk ratio. We recently highlighted this elsewhere and outlined the necessity of individualised and symptom-titrated exercise training [19]. The current symptom burden of patients and the risk for worsening of these symptoms post-exercise (i.e. post-exertional malaise) must be evaluated and considered in the prescription of exercise.

3 Conclusions

The analyses by Gomes Neto et al. [1] quantifying the level of CRF of patients post-COVID-19 in relation to healthy counterparts are a valuable addition to the findings of our review, although between-study heterogeneity was large (see test for heterogeneity in Figs. 1 and 2). Among other factors, differences in COVID-19 severity, prevalence and type of persisting symptoms, and follow-up period may contribute to the observed heterogeneity. Moreover, results of our subgroup analysis suggest that acute COVID-19 sequelae and

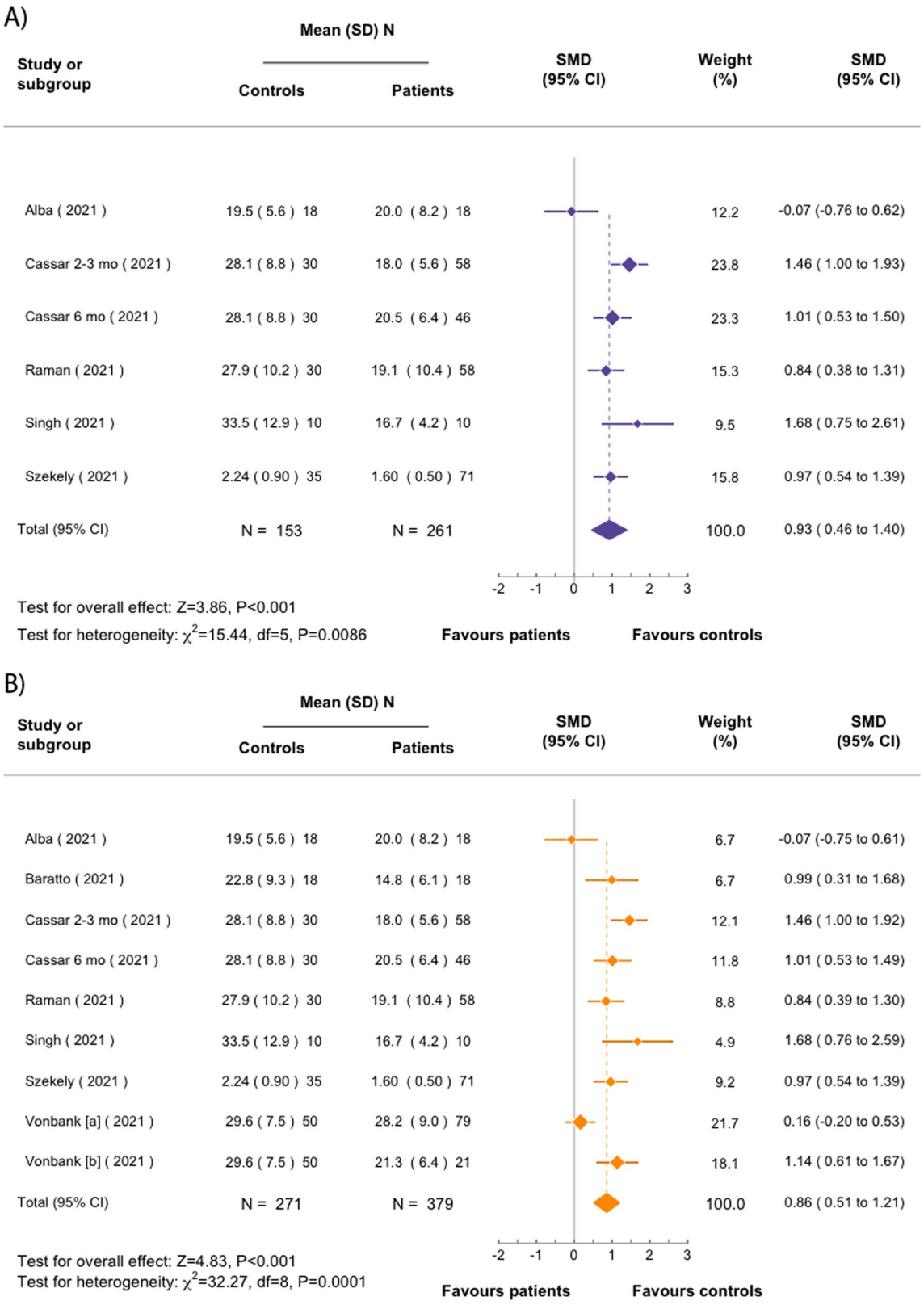

Fig. 1 Random effects meta-analyses. **A** Compares patients post-COVID-19 with controls matched for risk factors and/or health status. **B** Replication of Gomes Neto et al. [1] comparing patients post-COVID-19 with controls in general. No specific criteria applied for the inclusion of studies based on the control group. Vonbank [a] and [b] refers to data of their two study groups with mild and severe post-COVID-19, respectively compared to the same control group. *SMD* standardised mean difference

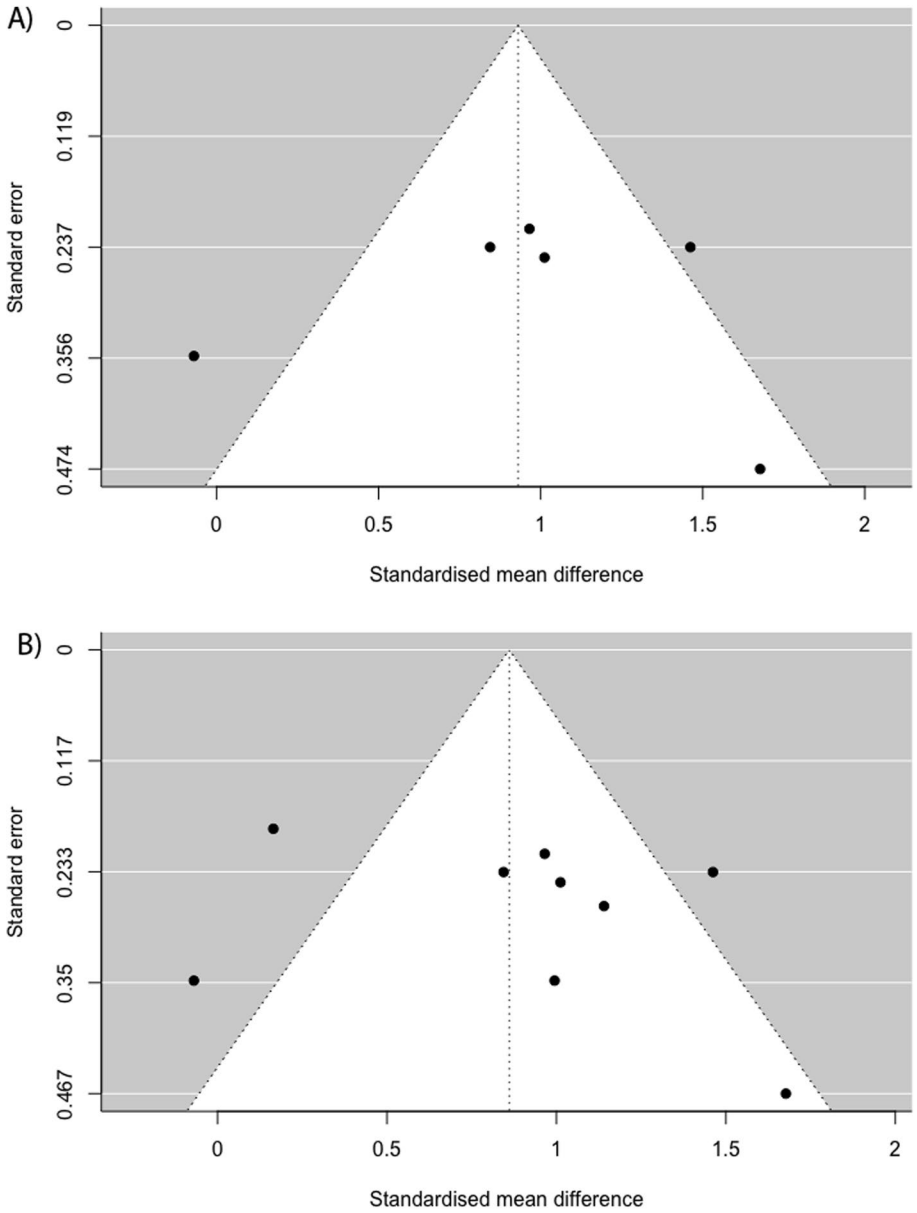

Fig. 2 Funnel plots illustrating heterogeneity. **A** Compares patients post-COVID-19 with controls matched for risk factors and/or health status. **B** Replication of Gomes Neto et al. [1] comparing patients post-COVID-19 with controls in general. No specific criteria applied for the inclusion of studies based on the control group

symptoms of post-COVID-19 may indeed be the main driver of low CRF post-COVID-19. The presence of especially asymptomatic comorbidities may contribute only minor to lower CRF compared with healthy controls.

Declarations

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Conflict of interest Fabian Schwendinger, Raphael Knaier, Thomas Radtke, and Arno Schmidt-Trucksäss declare that they have no conflicts of interest relevant to the content of this response.

Author contributions FS wrote the response, performed the statistical analyses, and interpreted the data. RK, TR, and AST contributed to data interpretation and revised the manuscript. All authors read and approved the final version of the response.

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