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## ABSTRACT

This prospective cohort study within an open-label, single-arm, phase 4 vaccination trial (clinicaltrials.gov #NCT04754698) aimed to investigate the association between physical activity and persistent anti-SARS-CoV-2 antibodies 6 months after two-dose schedule of CoronaVac in autoimmune rheumatic diseases (ARD) patients (n=748). Persistent immunogenicity 6 months after the full-course vaccination was assessed using seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG, geometric mean titers of anti-S1/S2 IgG (GMT), and frequency of positive neutralizing antibodies (NAb). Physical activity was assessed trough questionnaire. Adjusted point estimates from logistic regression models indicated greater odds of seroconversion rates (OR: 1.5 [95%CI: 1.1 to 2.1]) and NAb positivity (OR: 1.5 [95%CI: 1.0 to 2.1]) in physically active patients and approximately 43% greater GMT (42.8% [95%CI: 11.9 to 82.2]) than inactive ones. In conclusion, among immunocompromised patients, being physically active was associated with an increment in antibody persistence through 6 months after a full-course of an inactivated SARS-CoV-2 vaccine.

## INTRODUCTION

Vaccine-induced antibody titers and effectiveness against symptomatic COVID-19 have been shown to wane over time. For instance, individuals who received a two-dose schedule of CoronaVac (Sinovac's inactivated vaccine) – a WHO-approved vaccine that is effective in preventing severe cases of COVID-19 and is increasing the global supply through COVAX – exhibited a decline in neutralizing antibodies (NAb) seropositivity 6 months after full course of vaccination in the general population[1] and in patients with autoimmune rheumatic disease (ARD).[2]

In a global scenario with inequity of vaccines and heterogeneous responses to vaccination, it is key to gathering knowledge on potential risk factors associated with poor persistence of immunity to develop strategies to enhance immunogenicity durability, as well as to prioritize individuals to receive booster doses. In this context, a physically active lifestyle emerges as a potential candidate. Physical activity is linked to reduced chronic low-grade inflammation, increased T-cell proliferation and cytokine production following antigenic stimulation, increased neutrophil phagocytic activity, and increased natural killer cell cytolytic activity.[3] In addition, a meta-analysis showed that antibody concentration after vaccination (H1N1, H3N2, influenza type-B, pneumococcal and varicella zoster virus) is higher when accompanied by a physical activity program, suggesting that physical activity may act as an adjuvant to vaccines[4]. However, little is known about the potential benefits of physical activity on the responses to COVID-19 vaccines. Recently, we showed that, among immunocompromised patients vaccinated with CoronaVac, those who were physically active exhibited higher titers and seroconversion rates than their inactive counterparts.[5] However, whether active individuals show a greater persistence of antibodies than inactive ones remain unclear.

This study aimed to investigate the association between physical activity and persistent humoral immune response 6 months after a two-dose schedule of CoronaVac in patients with ARD.

## MATERIALS AND METHODS

This was a prospective cohort study within an open-label, single-arm, phase 4 vaccination trial (clinicaltrials.gov #NCT04754698), conducted at a tertiary referral hospital in Sao Paulo, Brazil. The protocol was approved by the National and Institutional Ethical Committee of Hospital das Clínicas HCFMUSP, CAAE: 42566621.0.0000.0068). Written informed consent was obtained before participants' enrollment.

ARD patients aged ≥18 years and diagnosed with rheumatoid arthritis, systemic lupus erythematosus, axial spondyloarthritis, psoriatic arthritis, primary vasculitis, primary Sjögren's syndrome, systemic sclerosis, idiopathic inflammatory myopathies, and primary antiphospholipid syndrome were eligible. Detailed exclusion and inclusion criteria were described elsewhere.[6]

Patients underwent a two-dose schedule of CoronaVac (Sinovac Life Sciences, Beijing, China, batch #20200412).[6] The 1$^{st}$ dose was administered on February 9-10, 2021, and the 2$^{nd}$ dose was given on March 9-10, 2021. Blood samples (20mL) from all participants were obtained 6 months after the full-course vaccination at the Hospital Convention Center. The persistent immunogenicity was assessed using seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG (considering values > 15.0 UA/mL), geometric mean titers of anti-S1/S2 IgG (GMT), and frequency of positive NAb (inhibition ≥ 30%). GMT and NAb assays are thoroughly described elsewhere.[6,7]

Using a telephone-based survey, typical levels of physical activity prior to vaccination were assessed by experienced researchers. Physical activity survey comprised 8 questions addressing 4 different physical activity domains: leisure time, household activities, work, and commuting. Participants were asked how many days/week and minutes/day were spent in moderate-to-vigorous intensity activities in each domain, and summed for total time spent in moderate-to-vigorous physical activity. Participants were classified as physically active or inactive according to WHO Guidelines (i.e., physical inactivity defined as <150 min/week of moderate-to-vigorous intensity aerobic activity).[8]

Unadjusted analyses comparing active vs. inactive patients were performed using $\chi^2$ test for categorical variables and the Kruskal-Wallis test for continuous variables. Model-based analyses were performed controlling for age (<60 or ≥60 years), sex, and body mass index (BMI) (<25 kg/m$^2$; 25–30 kg/m$^2$; >30 kg/m$^2$), use of prednisone, immunosuppressants and biologics. Immunogenicity data and physical activity status were added as fixed effects and we conducted logistic regression to estimate odds ratios (ORs) and 95%CIs with binary data obtained for rates of IgG seroconversion and NAb positivity. Also, we conducted linear regressions for log transformed IgG. Linear regression coefficients and 95%CIs for log transformed dependent variables were back transformed and presented as percent changes. A further exploratory analysis tested a possible dose–response between total weekly volume of physical activity (0–30; 31–149; 150–349; ≥350 min) and immunogenicity data. Analyses were conducted using R-statistical environment (R-4.1.0 for Windows).

## RESULTS

A total of 748 ARD patients returned for data collection at the 6-month follow-up period and were analyzed. Physically active (n=421) and inactive (n=327) ARD patients were similar for most characteristics; however, active patients were significantly younger ($p$<0.001) had a lower frequency of chronic inflammatory arthritis ($p$<0.001), and less frequently used biologic ($p$<0.001) than inactive ones (**Table 1**).

Six months after vaccination, seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG (53.1 vs. 40.7%; $p$=0.001), frequency of positive NAb (31.2 vs. 22.0%; $p$=0.007), and GMT (p<0.001) were significantly greater in ARD active vs. inactive patients (**Figure 1**).

Adjusted models showed that being male ($p$<0.001) and use of prednisone ($p$<0.01) and biologics ($p$<0.001) were associated with poor immunogenicity, while being physically active was associated with better immunogenicity ($p$<0.01).

Adjusted point estimates indicated greater odds of seroconversion rates (OR: 1.5 [95%CI: 1.1 to 2.1]) and NAb positivity (OR: 1.5 [95%CI: 1.0 to 2.1]), and approximately 43% greater GMT (42.8% [95%CI: 11.9 to 82.2]) in physically active patients vs. inactive ones (**Figure 2**). Overall, the exploratory analysis showed a dose-response pattern between the amount of physical activity and immunogenicity responses, with the greatest benefits seen for ≥ 350 min/week of physical activity (seroconversion rates: OR: 1.6 [95%CI: 1.1 to 2.4]; GMT: 75% [95%CI: 28% to 139%]; NAb positivity: OR: 2.1% [95%CI: 1.3 to 3.4]) (**Supplementary Figure 1**).

## DISCUSSION

We recently showed that the ARD patients who were physically active exhibited greater seroconversion rates (OR: 1.4) and GMT (32%) vs. their inactive counterparts 6 weeks after the full course of vaccination.[6] Now, we extended this notion by showing that being physically active is also associated with greater persistent immune response 6 months after vaccination, evidenced by higher rates of seroconversion and neutralizing antibodies. Considering that the prevalence of seropositivity in response to CoronaVac decreased to 17% following 6 months in general population and 23.8% in immunocompromised patients,[9] the 50% greater odds of IgG and NAb positivity rates observed herein in active vs. inactive ARD patients appears to be clinically meaningful. The associations observed also suggest that physical activity status may be more influential on antibody persistence than classical factors related to vaccine immunogenicity, such as older age and use of immunosuppressants. One may speculate that our results may be generalizable to other vaccine platforms that yield greater immunogenicity but that at the same time show a more pronounced 6-month decay in immunocompromised patients than Coronovac [6,9,10], suggesting a greater room for improvement with the other platforms.

Even though the mechanisms underlying the potential benefits of regular physical activity on vaccine responses remain unclear, it appears to involve greater antibody concentrations and/or cell-mediated adaptations.[11,12] Literature shows that both structured and non-structured physical activity are associated with higher concentration of IgG and IgM following influenza and keyhole limpet haemocyanin (KLH) vaccination.[13–15] A recent meta-analysis corroborated these findings, leading the authors to speculate that physical activity could also potentiate immunization programs in the context of the COVID-19 pandemic.[4] In line with this hypothesis, our studies conducted within this phase-4 trial suggest that physical activity may not only enhance the humoral immunity to COVID-19 vaccination[7], but also help sustain its effects over time, as now evidenced. Of relevance, we have observed a dose-response pattern for the benefits of physical activity, with higher volumes (≥350 min/week) being associated with better immunogenicity, which suggests the importance of engaging in WHO guidelines and increasing the amount of activity as much as possible. In addition to its potential ability of improving vaccine responses, physical

activity is associated with other numerous health benefits, which include prevention of several chronic diseases and protection against severe cases of COVID-19.[5,16] In light of this, global strategies and public health policies focused on tackling physical inactivity become even more relevant and urgent, with special emphasis to individuals with dysfunctional immune systems.

The main limitations of this study include its observational design, the lack of estimates of vaccine effectiveness and cell-mediated immune markers and the assessment of physical activity using a subjective tool.

In conclusion, among immunocompromised ARD patients, being physically activity was associated with greater antibody persistence through 6 months after a full-course of an inactivated SARS-CoV-2 vaccine.

## DECLARATION OF INTEREST STATEMENT

None declared.


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## Data availability statement

All background and clinical information for ARD patients in this study are available from the corresponding author on reasonable request.

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**Table 1.** Baseline characteristics of ARD patients according to physical activity status.

| | Active ARD (*n* = 421) | Inactive ARD (*n* = 327) |
|---|---|---|
| Age, *years* | 47.0 [39.0–59.0] | 56.0 [45.0–65.0]* |
| Sex, f*emale* | 322 (76.5) | 248 (75.8) |
| Weight, *kg* | 71.2 [61.3–82.0] | 72.0 [60.0–83.6] |
| Height, *cm* | 160.0 [155.0–166.0] | 160.0 [154.0–167.0] |
| Body mass index, *kg/m*$^2$ | 27.5 [24.0–30.9] | 27.5 [24.2–31.6] |
| Overweight/obese | 267 (63.6) | 209 (63.9) |
| Caucasian race | 218 (51.8) | 187 (57.2) |
| Smoking | 34 (8.1) | 32 (9.8) |
| Comorbidities | | |
| Systemic arterial hypertension | 176 (41.8) | 151 (46.2) |
| Diabetes mellitus | 40 (9.5) | 45 (13.8) |
| Dyslipidemia | 114 (27.1) | 99 (30.3) |
| Cardiomyopathy | 27 (6.4) | 19 (5.8) |
| Chronic renal disease | 14 (3.3) | 23 (7.0)* |
| Chronic obstructive pulmonary disease | 3 (0.7) | 12 (3.7)* |
| Asthma | 17 (4.0) | 12 (3.7) |
| Interstitial lung disease | 21 (5.0) | 39 (11.9)* |
| Pulmonary hypertension | 2 (0.5) | 6 (1.8) |
| Hematologic disease | 1 (0.2) | 1 (0.3) |
| Hepatic disease | 11 (2.6) | 20 (6.1)* |
| Cancer | 4 (1.0) | 4 (1.2) |
| Stroke | 12 (2.9) | 11 (3.4) |
| Tuberculosis | 0 (0) | 2 (0.6) |
| Current therapy | | |
| Prednisone | 155 (36.8) | 138 (42.3) |
| Biologic | 145 (34.4) | 138 (42.2)* |
| Immunosuppressants | 263 (62.5) | 216 (66.1) |
| Total physical activity, *min per week* | 400.0 [252.0–720.0] | 0.0 [0.0–75.0]* |

Data are presented as median [interquartile range] and *n* (%). Biologics include TNF inhibitor, abatacept, tocilizumab, belimumab, secukinumab, rituximab, ustekinumab. Immunosuppressants include methotrexate, leflunomide, mycophenolate mofetil, azathioprine, tofacitinib, cyclophosphamide, tacrolimus and cyclosporine.

* *p*-value <0.05

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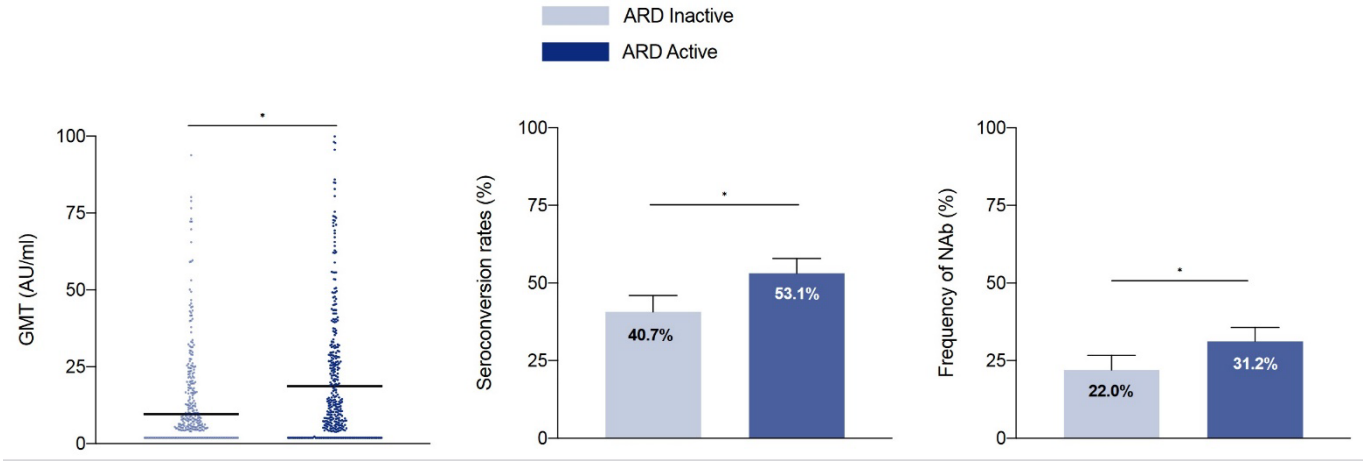
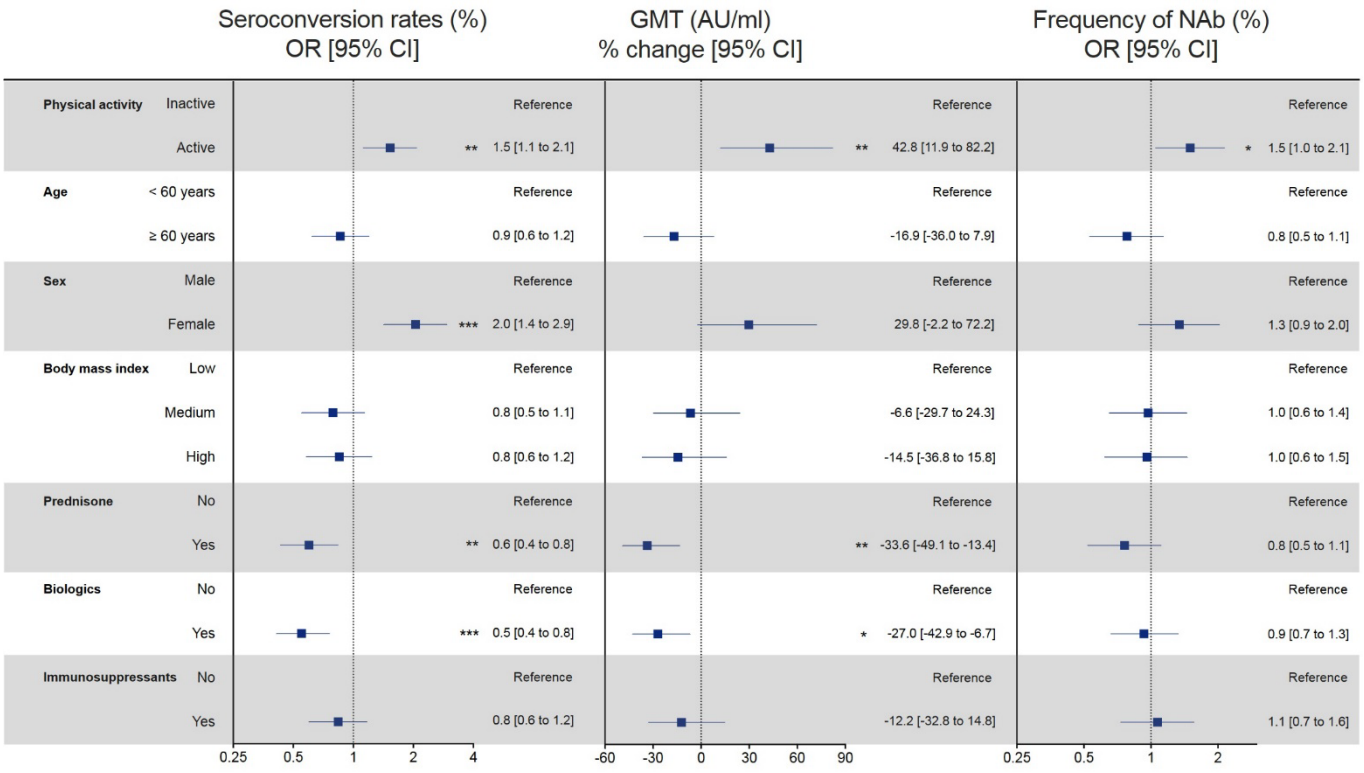
## FIGURE LEGENDS

**Figure 1.** Unadjusted analysis for immunogenicity data in autoimmune rheumatic diseases patients (ARD) six months after full vaccination with CoronaVac.




*$P$<.05. Missing data for IgG ($n$ = 3) and NAb ($n$ = 43).

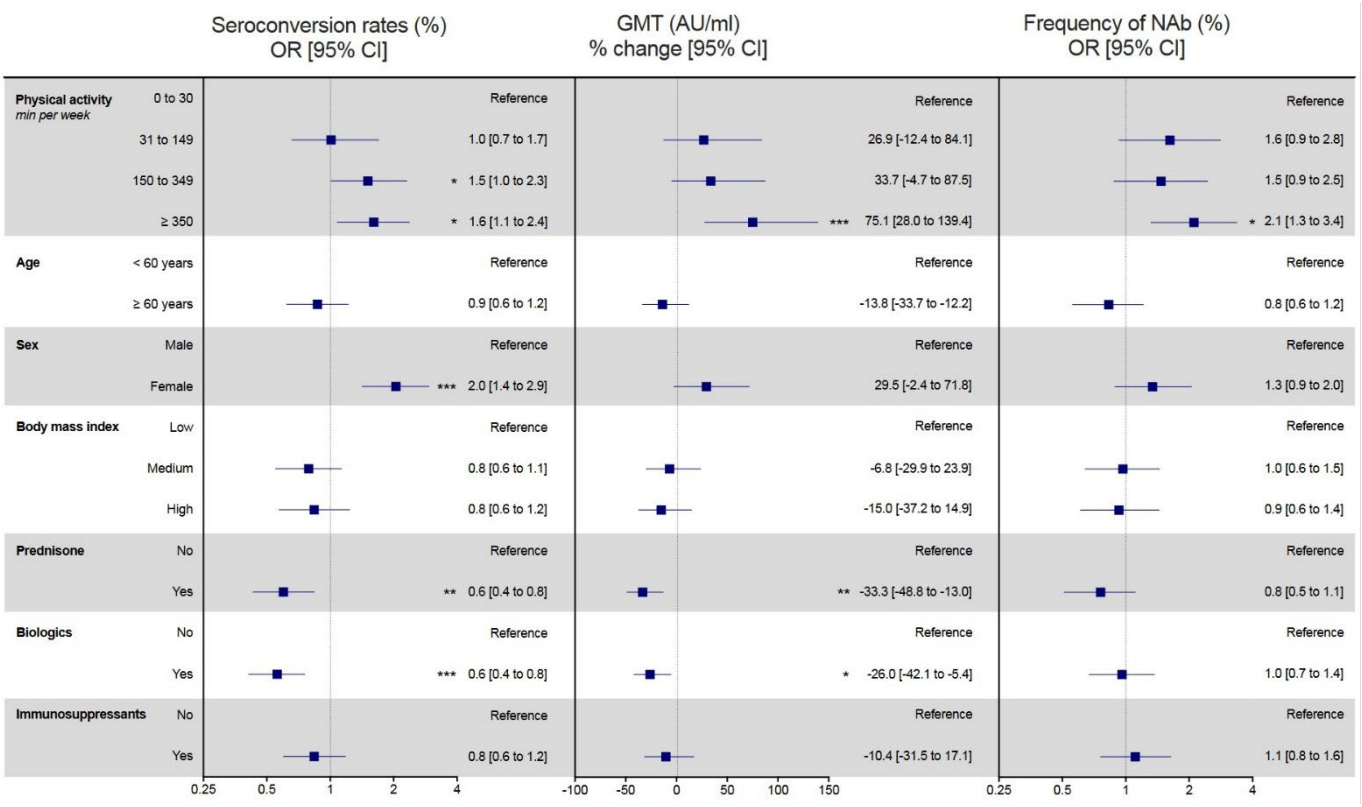
**Figure 2.** Adjusted risk factors for immunogenicity data in autoimmune rheumatic diseases (ARD) patients six months after full vaccination with CoronaVac.




Data expressed as OR [95% CI] or percent change [95% CI]). Adjusted for age, sex, BMI, use of prednisone, immunosuppressants and biologics. *$P$<.05, **$P$<.01, ***$P$<.001. Missing data for IgG ($n$ = 3) and NAb ($n$ = 43).

Supplementary Figure

Adjusted risk factors for immunogenicity data in autoimmune rheumatic diseases (ARD) patients six months after full vaccination with CoronaVac.




Data expressed as OR [95% CI] or percent change [95% CI]). Adjusted for age, sex, BMI, use of prednisone, immunosuppressants and biologics. **P*<.05, ***P*<.01, ****P*<.001. Missing data for IgG (*n* = 3) and NAb (*n* = 43).