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Association between physical activity and immunogenicity of an inactivated virus vaccine against SARS-CoV-2 in patients with autoimmune rheumatic diseases

Bruno Gualano [a,b,*], Italo R. Lemes [a], Rafael P. Silva [a], Ana J. Pinto [a,c], Bruna C. Mazzolani [a], Fabiana I. Smaira [a], Sofia M. Sieczkowska [a], Nadia E. Aikawa [e], Sandra G. Pasoto [d], Ana C. Medeiros-Ribeiro [d], Carla G.S. Saad [d], Emily F.N. Yuki [d], Clovis A. Silva [d,e], Paul Swinton [f], Pedro C. Hallal [g], Hamilton Roschel [a], Eloisa Bonfa [d]

[a] Applied Physiology & Nutrition Research Group, University of São Paulo, Sao Paulo, Brazil
[b] Food Research Center, University of São Paulo, Sao Paulo, Brazil
[c] Division of Endocrinology, Metabolism, and Diabetes and Anschutz Health and Wellness Center, University of Colorado, School of Medicine, Aurora, CO, USA
[d] Rheumatology Division, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil
[e] Pediatric Rheumatology Unit, Instituto da Criança, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil
[f] Robert Gordon University, Garthdee Road, Aberdeen, UK
[g] Postgraduate Program in Epidemiology, Universidade Federal de Pelotas, Pelotas, Brazil

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ABSTRACT

Objectives: To investigate whether physical activity is associated with enhanced immunogenicity of a SARS-CoV-2 inactivated vaccine (Coronavac) in patients with autoimmune rheumatic diseases (ARD) (n = 898) and in non-ARD (n = 197) individuals without pre-existing immunogenicity to SARS-CoV-2.
Methods: This was a prospective cohort study within an open-label, single-arm, phase 4 vaccination trial. Immunogenicity was assessed after vaccination by measuring seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG (SC), geometric mean titers of anti-S1/S2 IgG (GMT), factor-increase in GMT (FI-GMT), frequency of neutralizing antibody (NAb), and median neutralizing activity. Physical activity (active being defined as ≥ 150 min/week) and sedentary behavior (>8h/day) were assessed by questionnaire.
Results: Physically active ARD patients (n = 494) were younger and less frequently used prednisone/biologics than inactive patients (n = 404). After controlling for covariates, active patients exhibited greater SC (OR: 1.4 [95%CI: 1.1–2.0]), GMT (32% [95%CI: 8.8–60) and FI-GMT (33% [95%CI: 9.6–63%]) vs. inactive. Cluster analysis (physical activity/sedentary status) revealed greater GMT (43.0% [95% CI: 11.0–84.0%) and FI-GMT (48.0% [95%CI: 14.0–92.0%]) in active/non-sedentary vs. inactive/sedentary ARD patients. A dose–response was observed, with greater benefits for the group of patients performing ≥ 350 min/week of physical activity (OR: 1.6 [95%CI: 1.1–2.4]; 41% [95%CI: 10–80%]; 35% [95%CI: 4.3–74], for SC, GMT, and FI-GMT, respectively) vs. the least active group (≤30 min/week). Greater SC (OR: 9.9 [95%CI: 1.1–89.0]) and GMT (26% [95% CI: 2.2–56.0%]) were observed in active vs. inactive non-ARD.
Conclusions: A physically active lifestyle may enhance SARS-CoV-2 vaccine immunogenicity, a finding of particular clinical relevance for immunocompromised patients.
Trial Registration: Clinicaltrials.gov #NCT04754698.

1. Introduction

Vaccines have played a vital role in controlling the COVID-19 pandemic, as observed in countries well-advanced in rolling out vaccination. (Haas et al., 2021; Hall et al., 2021; Vasileiou et al., 2021) However, a concern remains that vaccine-induced immunogenicity might not be as high in immunocompromised individuals, such as those with autoimmune rheumatic diseases (ARD), neoplasia, and

* Corresponding author at: Av. Dr. Arnaldo, 455, 3° andar, ZIP code: 01246-903, São Paulo, SP, Brazil.
E-mail address: gualano@usp.br (B. Gualano).

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transplant recipients.

In a small study involving patients with chronic inflammatory diseases (n = 26), all patients developed antibody responses after SARS-CoV-2 mRNA vaccination, but they exhibited reduced IgG and neutralizing antibodies levels compared to healthy controls. (Geisen et al., 2021) In addition, a reduced anti-spike antibody response was showed after the 1st (17%) and 2nd doses (54%) of SARS-CoV-2 mRNA 1273 or BNT162b2 vaccine in solid organ transplant recipients. (Geisen et al., 2021; Boyarsky et al., 2021a; Boyarsky et al., 2021b; Polack et al., 2020) In a retrospective cohort study of patients with a variety of immune-mediated inflammatory diseases including ARD (n = 84), 91% produced detectable neutralizing activity to BNT162b2 mRNA SARS-CoV-2 vaccine. (Simon et al., 2021) Furthermore, a non-controlled, prospective cohort study with ARD patients (n = 123) showed presence of anti-receptor-binding domain (RBD) antibodies in 74% of them, but lower IgG and neutralizing antibody levels compared to healthy controls (Boyarsky et al., 2021). In line with this finding, we recently showed that an inactivated virus vaccine against SARS-CoV-2 (CoronaVac, the most frequently administered vaccine worldwide) elicited a lower but still clinically effective response in a large cohort of patients with ARD (n = 910) compared to controls. (Medeiros-Ribeiro et al., 2021) Although the impact of this reduced immunogenicity (i.e., the type of immune responses that the vaccine generates and their magnitude over time) upon vaccine effectiveness (i.e., the vaccine's ability to prevent disease in the real world) remains unknown, efforts to determine modifiable factors potentially able to enhance vaccine response are of utmost importance, particularly in immunocompromised individuals.

Regular physical activity reduces chronic low-grade inflammation and has been linked to increased T-cell proliferation and cytokine production following antigenic stimulation, increased neutrophil phagocytic activity, and increased natural killer cell cytolytic activity. (Simpson et al., 2015) There is also evidence that physical activity can improve immune responses to influenza and pneumococcal vaccines, hastening the recovery following experimental rhinovirus infection. (Simpson et al., 2015) A recent meta-analysis from 6 studies involving 497 individuals vaccinated against H1N1, H3N2, influenza type-B, pneumococcal and varicella zoster virus showed that pooled antibody concentration after vaccination is higher with an adjunct physical activity program, leading to the speculation that physical activity may "strengthen the potency of immunization programs and help mitigate the impact of pandemics such as the COVID-19". (Chastin et al., 2021)

To our knowledge, this is the first study to investigate the influence of physical activity on the immunogenicity of CoronaVac in a large cohort of patients with ARD. As a secondary objective, we also assessed whether physical activity status affects immunogenicity in non-ARD individuals. Our working hypothesis was that physically active ARD patients would experience better vaccine-induced immune responses compared to their inactive peers.

2. Patients and methods

2.1. Ethics statement

The protocol was approved by the National and Institutional Ethical Committee of the Hospital das Clínicas. Written informed consent was obtained from each participant before enrollment.

2.2. Study design and setting

This was a prospective cohort study within the protocol of an open-label, single-arm, phase 4 vaccination trial (clinicaltrials.gov #NCT04754698), conducted at a tertiary referral hospital in São Paulo, Brazil.

2.3. Participants

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, systemic autoimmune myopathies and primary anti-phospholipid syndrome, following previously reported criteria. (Medeiros-Ribeiro et al., 2021) Additionally, a group of individuals without ARD, HIV or other conditions requiring immunosuppressive therapy were also studied. Exclusion criteria were: history of anaphylactic response to vaccine components, acute febrile illness or symptoms compatible to COVID-19 at vaccination, Guillain-Barré syndrome, decompensated heart failure (class III or IV), demyelinating disease, previous vaccination with any SARS-CoV-2 vaccine, history of live virus vaccine up to four weeks before, inactivated virus vaccine up to two weeks before, and receipt of blood products up to six months before the study, hospitalized patients, and pre-vaccination COVID-19 assessed by anti-SARS-CoV-2 S1/S2 IgG and/or neutralizing antibodies (NAb). Participants who had RT-PCR-confirmed COVID-19 after receiving 1st vaccine dose were excluded. (Medeiros-Ribeiro et al., 2021)

2.4. Vaccination

Participants underwent a two-dose schedule of CoronaVac (Sinovac Life Sciences, Beijing, China, batch #20200412) as previously described. (Medeiros-Ribeiro et al., 2021) The 1st dose was administered on February 9–10, 2021 (D0) and the 2nd dose was given on March 9–10, 2021 (D28). Blood samples (20 mL) from all participants were obtained at D0, D28, and D69 (six weeks after 2nd dose) at the Hospital Convention Center. Sera were stored in a −70 °C freezer for posterior analysis.

2.5. Physical activity level and sedentary behavior

Typical levels of physical activity and sedentary behavior prior to vaccination were assessed by experienced researchers through telephone survey. Physical activity survey comprised eight questions addressing four different physical activity domains: leisure-time, household activities, work, and commuting (**Supplementary Methods 1**). 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). (Bull et al., 2020)

Sedentary behavior was assessed by asking participants how many hours/day were spent sitting throughout the week and weekend days. Sedentary status (yes: ≥8 h/day; or no: <8 h/day) (Ekelund et al., 2016) was used in combination with physical activity to test whether these would additively influence the outcomes.

Six telephone calls and text messages were made to each participant before deeming the individual as a non-respondent.

2.6. Immunogenicity

Immunogenicity was assessed at D69 using seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG (SC), geometric mean titers of anti-S1/S2 IgG (GMT) and their factor-increase in GMT (FI-GMT), frequency of NAb and median (interquartile range) of neutralizing activity.

2.7. Anti-SARS-CoV-2 S1/S2 IgG antibodies

Human IgG antibodies against S1 and S2 proteins in RBD (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy) were assessed by chemiluminescent immunoassay. SC was defined as positive serology

(>15.0 UA/mL) post vaccination (considering all participants were negative for pre-vaccination serology at baseline). GMT was calculated attributing 1.9 UA/mL (half of the lower limit of quantification) to undetectable levels (<3.8 UA/mL). FI-GMT was determined as the ratio between GMT after and before vaccination and are presented as geometric means and 95% confidence intervals (CIs).

2.8. SARS-CoV-2 cPass virus-NAb

Circulating NAb against SARS-CoV-2 was assessed using the SARS-CoV-2 sVNT Kit (GenScript, Piscataway, NJ, USA), which detects neutralizing antibodies that block the interaction between RBD in the viral spike glycoprotein with angiotensin-converting enzyme 2 (ACE2) cell surface receptor. Tests were performed on ETI-MAX-3000 (DiaSorin, Italy). Samples were classified as either "positive" or "negative" (inhibition $\geq$ 30 or < 30%, respectively), as suggested by the manufacturer. Median (interquartile range) of the percentage of neutralizing activity was calculated.

2.9. Statistical analysis

Baseline characteristics and outcomes for both ARD patients and non-ARD individuals measured after vaccination were compared across activity levels using χ^2 test for categorical variables, exact test for categorical variables with a count < 5, and the Kruskal-Wallis test for continuous variables. Model-based analyses were then performed controlling for age (<60 or $\geq$ 60 years), sex, and body mass index (BMI) (<25 kg/m^2; 25–30 kg/m^2; >30 kg/m^2). For ARD patients, further controls included use of prednisone, immunosuppressants and biologics. Confounders were selected based on a Direct Acyclic Graph (DAG; www.dagitty.net) (**Supplementary** Fig. 1). (Joffe et al., 2012) DAG was developed from *a priori* knowledge to identify a minimum, but sufficient set of covariates to remove confounding from statistical analysis. (Robins, 2001) Data following vaccination and 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 frequency of IgG SC and NAb positivity. We conducted Tobit regression to account for floor effects and frequency minimum values obtained for neutralizing activity and natural log transformed IgG and FI-GMT. Tobit regression coefficients and 95%CIs for log transformed dependent variables were back transformed and presented as percent changes. An exploratory analysis clustering physical activity and sedentary status (active/sedentary; inactive/non-sedentary; active/non-sedentary; inactive/sedentary) was conducted for ARD patients. A further exploratory analysis tested a possible dose–response between total weekly volume of physical activity (0–30; 31–149; 150–349; $\geq$350 min) and immunogenicity data. Analyses were conducted using R-statistical environment (R-4.1.0 for Windows).

3. Results

3.1. Participants

A total of 1418 ARD patients were recruited, and 225 were excluded for the following reasons: 24 acute febrile illness/symptoms compatible to COVID-19 at vaccination day or real-time RT-PCR confirmed COVID-19 less than four weeks before vaccination day, 1 demyelinating disease, 25 previous vaccination with any SARS-Cov-2 vaccine, 1 inactivated virus vaccination, 161 individuals did not accept to participate in the study, and 13 hospitalized patients. Subsequently, 542 controls were recruited, but 50 refused to participate. The remaining 1193 ARD patients and 492 non-ARD individuals received the 1st dose, but 232 (19.4%) ARD patients and 191 (38.8%) non-ARD individuals had positive baseline IgG serology and/or NAb and were excluded. Also, 63 ARD (5.3%) patients and 104 non-ARD individuals (21.1%) did not respond to the physical activity survey and were excluded (**Supplementary** Fig. 2). The remaining ARD patients (n = 898; Table 1) and non-ARD individuals (n = 197; **Supplementary** Table 1) were analyzed.

Physically active ARD patients (n = 494) were significantly younger ($P < .001$), and less frequently used prednisone ($P < .001$) and biologic ($P < .032$) than inactive (n = 404). Active (n = 128) and inactive (n = 69) non-ARD individuals did not statistically differ in age, sex and BMI (**Supplementary** Table 2).

3.2. Unadjusted analysis

Fig. 1 presents immunogenicity data for active vs. inactive ARD patients and non-ARD individuals. After vaccination, frequency of SC ($P < .001$), GMT ($P < .001$), FI-GMT ($P < .001$), frequency of NAb ($P = .022$) and its neutralizing activity ($P < .001$) were greater in active vs. inactive ARD patients. Active non-ARD individuals exhibited greater SC than inactive ones ($P = .038$).

3.3. Adjusted analysis

Fig. 2 presents the regression models controlling for covariates in ARD patients. In general, older age, BMI > 30 kg/m^2, and use of prednisone, biologics and immunosuppressants were the factors more strongly associated with poor immunogenicity, while being physically

Table 1
Baseline characteristics of patients with autoimmune rheumatic diseases (ARD).

	ARD (n = 898)
Age, *years*	52.0 [41.0–62.0]
Sex, *female*	683 (76.1)
Weight, *kg*	71.4 [60.3–82.4]
Height, *cm*	160.0 [155.0–166.0]
BMI, *kg/m^2*	27.5 [24.2–31.2]
Overweight/obese	567 (63.2)
Caucasian race	488 (54.3)
Smoking	78 (8.7)
Comorbidities	
Systemic arterial hypertension	408 (45.4)
Diabetes mellitus	105 (11.7)
Dyslipidemia	247 (27.5)
Cardiomyopathy	54 (6.0)
Chronic renal disease	44 (4.9)
Chronic obstructive pulmonary disease	15 (1.7)
Asthma	38 (4.2)
Interstitial lung disease	73 (8.1)
Pulmonary hypertension	11 (1.2)
Hematologic disease	3 (0.3)
Hepatic disease	36 (4.0)
Cancer	9 (1.0)
Stroke	28 (3.1)
Tuberculosis	2 (0.2)
ARD	
Chronic inflammatory arthritis (RA, axSpA, PsA)	483 (53.8)
Other ARD (SLE, primary vasculitis, SSc, pSSj, IIMM, PAPS)	415 (46.2)
Current therapy	
Prednisone	356 (39.6)
Biologic	327 (36.4)
Immunosuppressants	582 (64.8)
Total physical activity, min *per week*	180.0 [10.0–450.0]
Total sedentary time, *hours per day*	8.0 [5.0–10.0]

Data are presented as median [interquartile range] and n (%). ARD, autoimmune rheumatic disease; BMI, body mass index; RA, rheumatoid arthritis; axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; pSSj, primary Sjögren syndrome; IIMM, idiopathic inflammatory myopathies; PAPS, primary antiphospholipid syndrome. Biologics include TNF inhibitor, abatacept, tocilizumab, belimumab, secukinumab, rituximab, ustekinumab. Immunosuppressants include methotrexate, leflunomide, mycophenolate mofetil, azathioprine, tofacitinib, cyclophosphamide, tacrolimus and cyclosporine.
Note: Missing data for weight and BMI (n = 1).

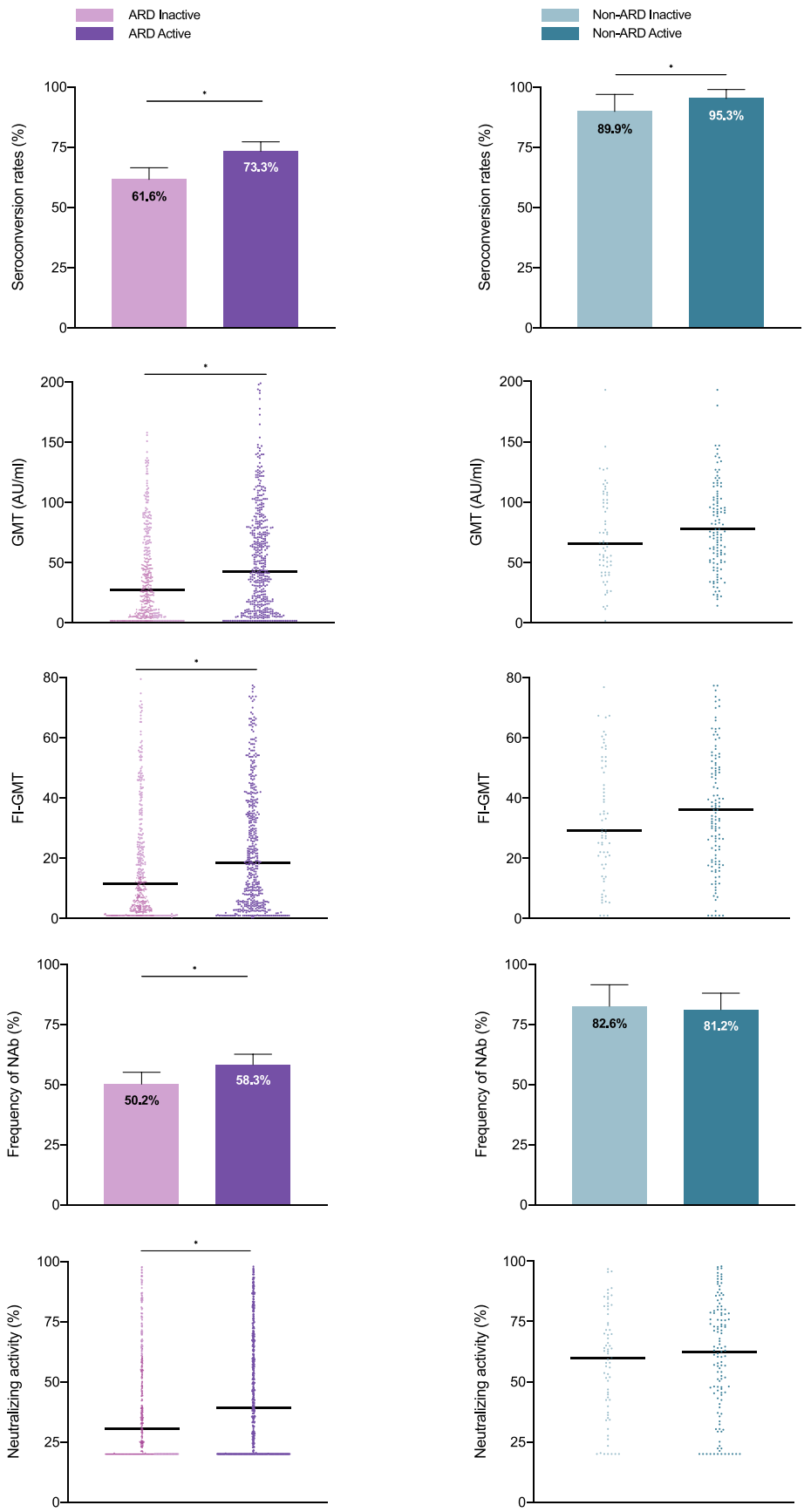

Fig. 1. Unadjusted analysis for immunogenicity data in autoimmune rheumatic diseases patients (ARD) (left) and in non-ARD individuals (right). *$P < .05$. Seroconversion was defined as a positive serology (IgG titer $\geq$ 15 AU/ml) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for NAb was defined as a neutralizing activity $\geq$ 30% (cPass sVNT Kit, GenScript, Piscataway, USA). Data are expressed as percentages and 95% CI for frequency of SC rates and NAb positivity, and individual data, median and interquartile range for neutralizing activity, GMT and FI-GMT.

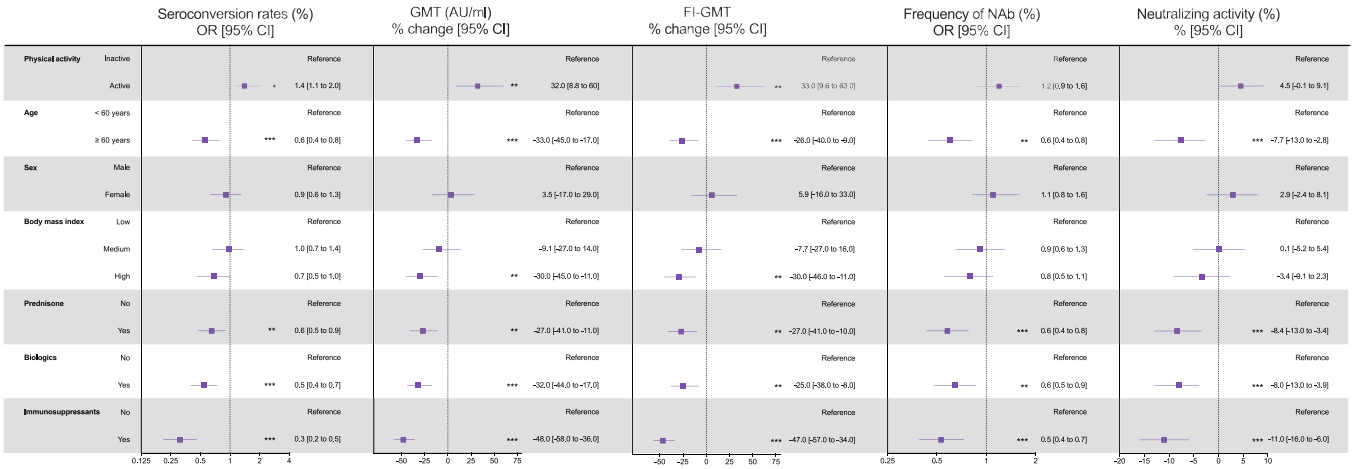

Fig. 2. Adjusted risk factors for immunogenicity data in autoimmune rheumatic diseases (ARD) patients. Logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) with binary data obtained for frequency of seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG (SC) and neutralizing antibodies (NAb) positivity. Tobit regression was used for natural log transformed GMT, FI-GMT and neutralizing activity. Data expressed as either percent or percent change [95% CI]) in patients with autoimmune rheumatic diseases following a vaccine against SARS-CoV-2. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$. Seroconversion was defined as a positive serology (IgG titer ≥ 15 AU/ml) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for NAb was defined as a neutralizing activity ≥ 30% (cPass sVNT Kit, GenScript, Piscataway, USA).

active was associated with better immunogenicity.

Point estimates from logistic regression models indicated greater odds of SC in physically active vs. inactive patients (OR: 1.4 [95%CI: 1.1 to 2.0]). ARD patients who were physically active also exhibited approximately 30% greater GMT (32% [95%CI: 8.8 to 60]) and FI-GMT (33% [95%CI: 9.6 to 63%]) than inactive ones. The associations between physical activity and neutralizing activity (4.5% [95%CI: −0.1 to 9.1%]) and neutralizing antibodies (OR: 1.2 [95%CI: 0.9 to 1.6]) were non-significant.

Cluster exploratory analysis of physical activity/sedentary status revealed significantly greater percent changes for GMT (43.0% [95%CI: 11.0 to 84.0%]) and FI-GMT (48.0% [95%CI: 14.0 to 92.0%]) in active/non-sedentary vs. inactive/sedentary ARD patients. Importantly, active/sedentary showed no difference in GMT and FI-GMT compared with inactive/sedentary, suggesting that sedentary behavior may have overridden the influence of physical activity (Fig. 3). The other exploratory analysis showed a dose–response between physical activity volumes and SC, GMT and FI-GMT, with the greatest benefits seen for ≥ 350 min/week of physical activity (OR: 1.6 [95%CI: 1.1 to 2.4], 41% [95%CI: 10 to 80%] and 35% [95%CI: 4.3 to 74] for SC, GMT and FI-GMT) (**Supplementary** Fig. 3).

Among non-ARD, point estimates from logistic regression models indicated greater odds of SC with a wide CI range in active vs. inactive individuals (OR: 9.9 [95%CI: 1.1 to 89.0]). Active individuals showed 26.0% greater GMT (95%CI: 2.2 to 56.0%) and 24.0% FI-GMT (95%CI: −9.4 to 71.0%) compared to inactive, although CIs overlapped 1 for FI-GMT. Frequency of NAb positivity and neutralizing activity did not significantly differ between active and inactive individuals (Fig. 4).

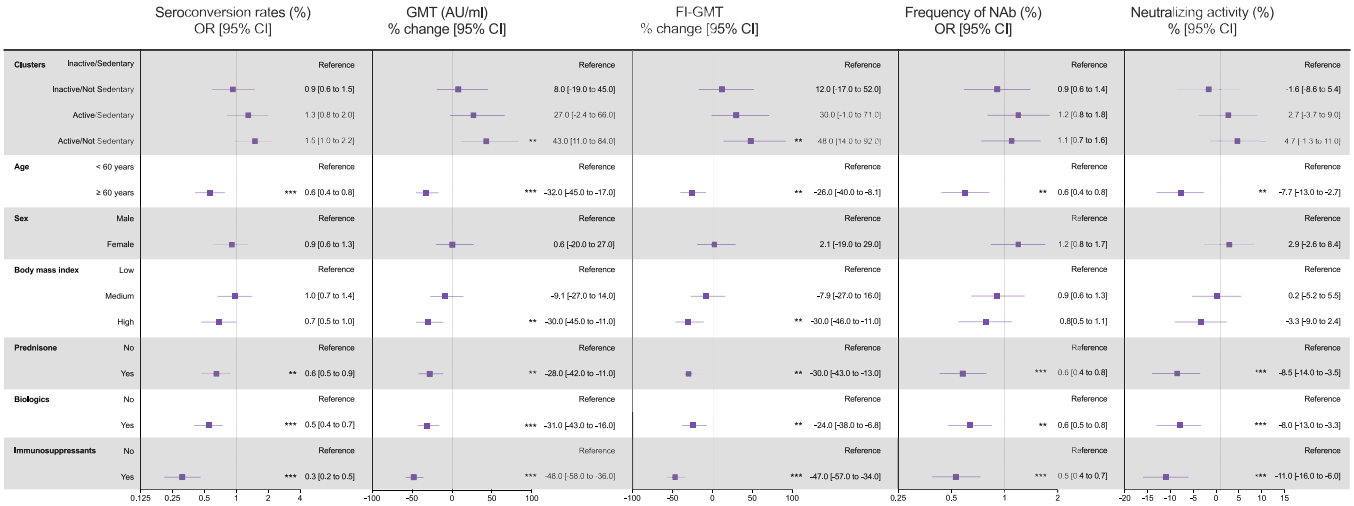

Fig. 3. Adjusted risk factors for immunogenicity data in autoimmune rheumatic diseases (ARD) patients clustered for physical activity and sedentary behavior. Logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) with binary data obtained for frequency of seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG (SC) and neutralizing antibodies (NAb) positivity. Tobit regression was used for natural log transformed GMT, FI-GMT and neutralizing activity. Data expressed as either percent or percent change [95%CI]) in patients with autoimmune rheumatic diseases following a vaccine against SARS-CoV-2. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$. Seroconversion was defined as a positive serology (IgG titer ≥ 15 AU/ml) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for NAb was defined as a neutralizing activity ≥ 30% (cPass sVNT Kit, GenScript, Piscataway, USA).

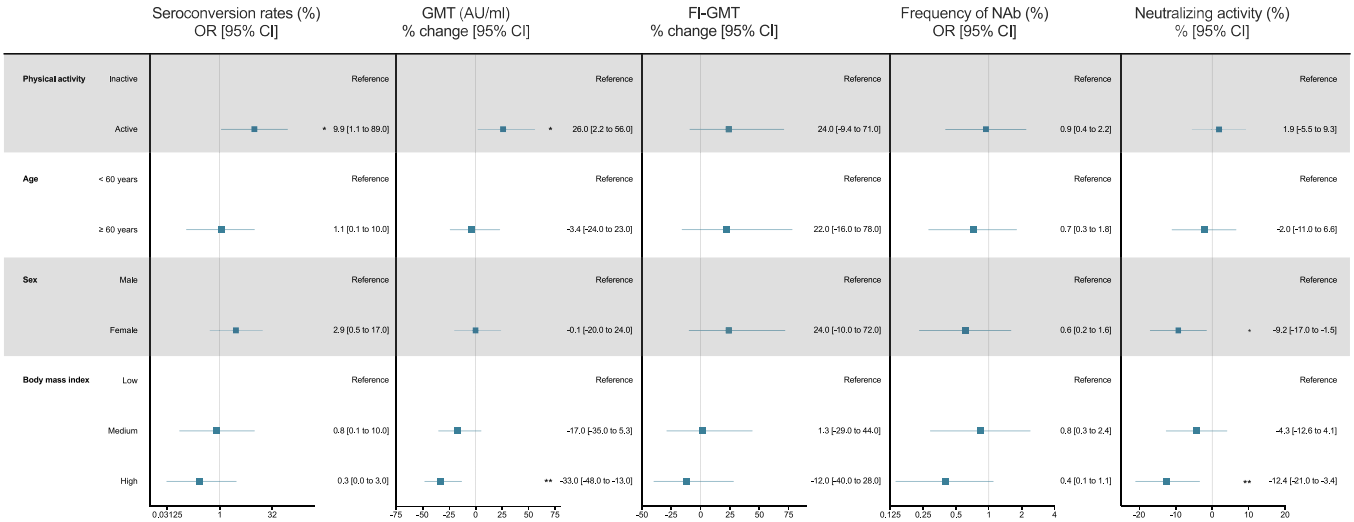

Fig. 4. Adjusted risk factors for immunogenicity data in non-autoimmune rheumatic diseases (non-ARD) individuals. Logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) with binary data was used for frequency of seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG (SC) and neutralizing antibodies (NAb) positivity. Tobit regression was used for natural log transformed GMT, FI-GMT and neutralizing activity. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$. Seroconversion was defined as a positive serology (IgG titer ≥ 15 AU/ml) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for NAb was defined as a neutralizing activity ≥ 30% (cPass sVNT Kit, GenScript, Piscataway, USA).

4. Discussion

To our knowledge, this is the first evidence that a physically active lifestyle may enhance immunogenicity of a vaccine against SARS-CoV-2 in a large cohort of patients with ARD.

Vaccination is a major strategy in reducing mortality and morbidity rates for several infectious diseases, (Nicholson et al., 2003) including COVID-19. (Pascoe et al., 2014) In countries with high capacity of vaccine acquisition and rapid rollouts, both new cases and deaths have been dramatically reduced. However, vaccine efficacy varies between individuals, with particularly low responses found in those with reduced immune function. (Hilleman, 2000; Villari et al., 2004) mRNA vaccines against SARS-CoV-2 can elicit a reduced humoral response in older individuals and in ARD patients, (Boyarsky et al., 2021; Boyarsky et al., 2021) a finding recently extended to CoronaVac, (Medeiros-Ribeiro et al., 2021) which has been largely used in highly populated countries, and recently approved for emergency use by WHO. (World Health Organization, 2021) Indeed, previous data from this trial point out to lower SC (70.4 vs. 95.5%) and titers (12.1 vs. 29.7), frequency of NAb positivity (56.3 vs. 79.3%) and neutralization activity (58.7 vs. 64.5%) in ARD patients vs. controls. (Medeiros-Ribeiro et al., 2021) It becomes clear that the search for adjuvants to enhance vaccine response and improve protection from disease infection is of great clinical importance. Chief amongst these is physical activity, which has been deemed as a behavioral intervention able to boost immune function in different scenarios, thereby potentially serving as an adjuvant to improve vaccine response, including that against SARS-CoV-2. This hypothesis was tested in the present study.

Both observational and interventional studies have shown that habitually physically active individuals, or those receiving exercise interventions, present with higher concentration of IgG and IgM following influenza and keyhole limpet haemocyanin (KLH) vaccination. (Grant et al., 2008; Keylock et al., 2007; Kohut et al., 2002; Kohut et al., 2004; Schuler et al., 2003; Smith et al., 2004; Woods et al., 2009; Yang et al., 2007) Apart from studies involving older individuals, evidence that physical activity may confer better vaccine responses in those with less functional immunity is lacking. In this regard, our data bring novel evidence that, compared to their inactive counterparts, physically active ARD patients may have higher SC rates, GMT and FI-GMT and a trend to higher neutralizing activity, even after controlling for several covariates, including age, sex, BMI and medications. Of relevance, the positive association of physical activity with GMT (+32%) was diametrically opposite to those of age (–33%), obesity (−30%) and medications (−27 to −48%), which underscores the potential importance of a physically active lifestyle in counteracting factors known to impair immunogenicity. Furthermore, our exploratory analysis suggests that the benefits of being physically active (i.e., meeting the minimum recommended amount of physical activity) on vaccine immunogenicity tends to wane owing to sedentary behavior (i.e., too much sitting), a finding that has been observed in population-based studies for all-cause mortality, (Ekelund et al., 2016; Stamatakis et al., 2019) and that requires confirmation for vaccines responses. We also observed a direct dose–response relationship between physical activity volume and SC, GMT, and FI-GMT. Although current evidence does not yet provide specific information about how intensity, frequency, duration and type of physical activity influence vaccine responses, (Chastin et al., 2021) the present findings suggest that engaging in at least 150 min/week of moderate-to-vigorous physical activity while avoiding excessive sitting time may enhance immunogenicity to vaccination against SARS-CoV-2, with higher physical activity amounts (≥350 min/week) possibly offering greater benefits.

Hypothetically, young healthy adults might be less responsive to the benefits of physical activity on immunogenicity, since the robust response to most vaccinations in this population may mask more subtle effects of exercise, whereas in those with weaker immune function and higher variability, the immunoenhancement effects may be more noticeable. (Pascoe et al., 2014) Similar to ARD patients, however, we observed a positive association between physical activity and SC rates and GMT in non-ARD individuals. This suggests the potential applicability of our findings in a more generalized context; nonetheless, these should be validated in a larger cohort of non-immunosuppressed individuals.

The mechanisms by which regular physical activity enhance vaccination responses are not fully understood. However, it is known that moderate-to-vigorous physical activity is able to improve immune function, which is reflected in greater antibody or cell-mediated responses to vaccination. (Pascoe et al., 2014; Edwards and Booy, 2013) Even a single bout of exercise can elicit substantial changes in the immune system. (Edwards et al., 2012) Described as the "acute-stress induced immunoenhancement hypothesis'', the increases in

epinephrine, cortisol, heart rate and blood pressure encompass the acute response to exercise. (Edwards et al., 2007) Alongside these physiological adjustments is the well-stablished leukocytosis response, the transient increase in muscle-secreted inflammatory cytokines, and the exercise-induced muscle damage leading to leukocyte trafficking to the tissue. These orchestrated adjustments have been postulated to stimulate the activation of immune surveillance in anticipation of antigen entry, (Edwards and Booy, 2013; Viswanathan et al., 2005) which may be of particular relevance to vaccination. (Edwards et al., 2007) Although the clinical benefit of physical activity on vaccines efficacy is commonly inferred from the quantified antibody, neutralization activity or cell-mediated responses, this postulation finds support in a population-based cohort study, in which moderately- and highly-active individuals were less likely to experience an influenza-coded visit to a physician or emergency department. (Siu et al., 2012) Whether SARS-CoV-2 vaccine efficacy may be modulated by physical activity and how it occurs remain to be investigated.

Our data is strengthened by the large prospective cohort of immunocompromised patients with ARD, the assessment of immunogenicity using both SARS-CoV-2 IgG and NAb, and the robust control for numerous covariates. Limitations include the use of questionnaire to assess physical activity, which is prone to recall bias and overreporting; the cross-sectional assessment of physical activity prior to vaccination, which may not accurately reflect the typical physical activity pattern before the pandemic; (Tison et al., 2020) lack of estimates of vaccine effectiveness to bridge to the immunogenicity data; short-term assessment of immunogenicity, precluding any firm conclusions on the persistency of the observed responses; lack of assessment of cell-mediated immune responses; observational nature of the study, hampering causative inferences; and the constraint of the results to the vaccine tested in this study. Regarding the latter, it is noteworthy that over 750 million doses of CoronaVac have been administered in >40 countries, (Wilder-Smith and Mulholland, 2021) with a prospective, national-cohort, phase 4 trial showing its excellent safety profile and effectiveness against severe cases and COVID-19-related death. (Jara et al., 2021) However, this vaccine seems to evoke less protective titer compared to others, a response associated with lower protection from SARS-CoV-2 infection. (Khoury et al., 2021) In addition, assessments of immune persistence of CoronaVac showed that prevalence of seropositivity decreased to 17% following 6 months. (World Health Organization (WHO), 2021) These observations underpin the clinical importance of the current findings, which point out to the potential utility of a safe, inexpensive, population-wide strategy (i.e., physical activity) in enhancing CoronaVac immunogenicity in patients with autoimmune disorders. Nonetheless, it is uncertain whether physical activity associates with enhanced responses to other vaccine platforms able to elicit higher protective titer, as a ceiling effect may exist, particularly for heathy individuals.

Recent evidence shows that active individuals seem less susceptible to COVID-19-related intensive care unit (ICU) admission and mortality. (Sallis et al., 2021) Now this study suggests that a physical active lifestyle may also enhance SARS-CoV-2 vaccine immunogenicity, a finding of particular relevance for patients with dysfunctional immune system living in countries facing vaccines scarcity, which hampers the immediate administration of additional doses. Our data reinforce the need for a global call for action to delivery physical activity during the COVID-19 pandemic, with emphasis to groups with reduced immune function. Randomized controlled trials (RCTs) should confirm the efficacy of physical activity to enhance vaccine responses, and to stablish the optimal dose to elicit the greatest benefits.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.12.016.

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