Physical activity associates with enhanced immunogenicity of an inactivated virus vaccine against SARS-CoV-2 in patients with autoimmune rheumatic diseases

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Abstract

Immunocompromised individuals show lower vaccine immunogenicity, which may be modulated by physical activity. This prospective cohort study within a phase-4 vaccination trial investigated whether physical activity is associated with enhanced immunogenicity of Coronavac (SARS-CoV-2 inactivated vaccine) in patients with autoimmune rheumatic diseases (ARD) (n=898) and non-ARD (n=197) individuals without pre-existing immunogenicity to SARS-CoV-2 after receiving a two-dose vaccine schedule. 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 were assessed. After controlling for covariates, active patients (≥150 min/week) 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 (≥150 min/week/<8h/day) vs. inactive/sedentary (<150 min/week/>8h/day) ARD. A dose-response was observed, with greater benefits for ≥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). 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. A physically active lifestyle may enhance SARS-CoV-2 vaccine immunogenicity, a finding of particular clinical relevance for immunocompromised individuals.

Introduction

Vaccines have played a vital role in controlling the COVID-19 pandemic, as observed in countries well-advanced in rolling out vaccination.¹⁻³ 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, transplant recipients and patients with HIV.

In fact, literature has been controversial regarding the SARS-CoV-2 vaccine responses in these groups. 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.⁴ 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.⁵,⁶ 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.⁷ 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 controls⁸. In line with this finding, we recently showed that an inactivated virus vaccine against SARS-CoV-2 (CoronaVac) – which accounts for ~45% of the administered vaccines in Brazil – elicited a lower but still clinically effective response in a large cohort of patients with ARD (n=910) compared to controls.⁹ Although the impact of this reduced
immunogenicity upon vaccine effectiveness remains unknown, efforts to determine modifiable factors potentially able to enhance vaccine response are of utmost importance, particularly in immunocompromised individuals.

There has been a long-stand notion that regular physical activity may enhance immune system response. Exercise has been shown to reduce 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.\(^{10}\) There is also evidence that physical activity can improve immune responses to influenza and pneumococcal vaccines, hastening the recovery following experimental rhinovirus infection.\(^{10}\) 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”.\(^{11}\)

To our knowledge, this is the first study to investigate the influence of physical activity on the immunogenicity of a vaccine against SARS-CoV-2 (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.

### Results

#### 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 1\(^{st}\) 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 Figure 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 more frequently used prednisone (P<.001) and biologic (P<.001) than inactive (n=404). Active (n=128) and inactive (n=69) non-ARD individuals did not statistically differ in age, sex and BMI (P=.397) (Table 2).
Unadjusted analysis

Figure 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 ($P=.038$).

Adjusted analysis

Figure 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 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 (Figure 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 Figure 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 (Figure 4).

Discussion

To our knowledge, this is the first evidence that being physically active may enhance immunogenicity of a vaccine against SARS-CoV-2 in a large cohort of patients with ARD. Additionally, a similar benefit was
observed in a small cohort of non-ARD individuals. This finding suggests that physical activity may boost vaccine response, which is particularly relevant to immunocompromised individuals who are prone to diminished immunogenicity.

Vaccination is a major strategy in reducing mortality and morbidity rates for several infectious diseases,\(^1\) including COVID-19.\(^2\) 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.\(^3\)\(^4\) mRNA vaccines against SARS-CoV-2 can elicit a reduced humoral response in older individuals and in ARD patients,\(^5\)\(^6\)\(^7\) a finding recently extended to CoronaVac,\(^8\) which has been largely used in highly populated countries, and recently approved for emergency use by WHO.\(^9\) 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.\(^8\) 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.\(^1\)\(^8\)\(^9\)\(^-\)\(^2\)\(^5\) 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,\(^1\)\(^2\)\(^6\)\(^7\) 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,\(^1\)\(^1\) 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.\textsuperscript{13} 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.\textsuperscript{13,28} Even a single bout of exercise can elicit substantial changes in the immune system.\textsuperscript{29} Described as the "acute-stress induced immunoenhancement hypothesis", the increases in epinephrine, cortisol, heart rate and blood pressure encompass the acute response to exercise.\textsuperscript{30} Alongside these physiological adjustments is the well-established 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,\textsuperscript{28,31} which may be of particular relevance to vaccination.\textsuperscript{30} 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.\textsuperscript{32} 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; 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. In this regard, CoronaVac seems to evoke less protective titer compared to others, a response associated with lower protection from SARS-CoV-2 infection.\textsuperscript{33} This underpins the clinical relevance of the current findings; conversely, it is uncertain whether physical activity may also associate with enhanced responses to other vaccine platforms able to elicit higher protective titer, as a ceiling effect may exist at least for healthy individuals.

Cumulative evidence has shown that physical activity is associated with better outcomes in COVID-19 patients. Consistently active individuals seem less susceptible to COVID-19-related ICU admission and mortality.\textsuperscript{34} This study brings novel evidence suggesting that a physical active lifestyle may also boost
SARS-CoV-2 vaccine immunogenicity, a finding of particular relevance for people with dysfunctional immune system. Collectively, these data reinforce the need for a global call for action to delivery physical activity during the COVID-19 pandemic, with particular emphasis to groups with reduced immune function. Randomized controlled trials are necessary to confirm the efficacy of physical activity in enhancing vaccine responses, and to establish the optimal dose to elicit the greatest benefits.

**Methods**

**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.

**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 Sáo Paulo, Brazil.

**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 antiphospholipid syndrome, following previously reported criteria. 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.

**Vaccination**

Participants underwent a two-dose schedule of CoronaVac (Sinovac Life Sciences, Beijing, China, batch #20200412) as previously described. 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 (20mL) 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.

**Physical activity level and sedentary behavior**
Physical activity and sedentary behavior were assessed by experienced researchers through telephone survey. Physical activity level survey comprised eight questions addressing four different physical activity domains: leisure-time, household activities, work, and commuting (Supplementary Material 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).

Sedentary behavior was assessed by asking participants how many hours/day were spent sitting throughout the week and weekend days. Sedentary status (yes: ≥8 hours/day; or no: <8 hours/day) 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.

**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.

**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).

**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 ≥ 30 or < 30%, respectively), as suggested by the manufacturer. Median (interquartile range) of the percentage of neutralizing activity was calculated for positive samples.

**Statistical analysis**

Baseline characteristics and outcomes for both ARD patients and non-ARD individuals measured after vaccination were compared across activity levels using $\chi^2$ 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 ≥ 60 years), sex, and BMI (< 25 kg/m²; 25–30 kg/m²; >30 kg/m²). 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).³⁶ DAG was developed from a priori knowledge to identify a minimum, but sufficient set of covariates to remove confounding from statistical analysis.³⁷ 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; ≥350 min) and immunogenicity data. Analyses were conducted using R-statistical environment (R-4.1.0 for Windows).

Declarations

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Author Contributions

N.E.A., S.G.P., A.C.M.R., C.G.S.S., E.F.N.Y, C.A.S. and E.B., conceived and designed the study, and supervised clinical data management. B.G., I.R.L., R.P.S., A.J.P., B.C.M., F.I.S., S.M.S., N.E.A., S.G.P., A.C.M.R., C.G.S.S., E.F.N.Y, C.A.S., H.R. and E.B participated in data collection. B.G., I.R.L., A.J.P., P.S., P.C.H. and H.R. analyzed and interpreted the data. B.G., H.R., and E.B. wrote the manuscript with inputs from all authors. All authors read and approved the final version.

Competing Interest Statement

The authors have no conflict of interests.

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Data availability

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

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

| ARD | (n = 898) |
|-----|----------|
| ears | 52.0 [41.0–62.0] |
| male | 683 (76.1) |
| t, kg | 71.4 [60.3–82.4] |
| , cm | 160.0 [155.0–166.0] |
| g/m² | 27.5 [24.2–31.2] |
| eight/offe | 567 (63.2) |
| sian race | 488 (54.3) |
| kg | 78 (8.7) |
| osteoarthritis | 408 (45.4) |
| oetes mellitus | 105 (11.7) |
| lipidemia | 247 (27.5) |
| diomyopathy | 54 (6.0) |
| onic renal disease | 44 (4.9) |
| onic obstructive pulmonary disease | 15 (1.7) |
| ima | 38 (4.2) |
| stial lung disease | 73 (8.1) |
| onary hypertension | 11 (1.2) |
| atologic disease | 3 (0.3) |
| atic disease | 36 (4.0) |
| cer | 9 (1.0) |
| ile | 28 (3.1) |
| erculosis | 2 (0.2) |

onic inflammatory arthritis (RA, axSpA, PsA) 483 (53.8)
er ARD (SLE, primary vasculitis, SSc, pSSj, IIMM, PAPS) 415 (46.2)

ct therapy

onisone 356 (39.6)
getic 327 (36.4)
unospressants 582 (64.8)

ysical activity, min per week 180.0 [10.0–450.0]
edentary time, hours per day 8.0 [5.0–10.0]

e presented as median [interquartile range] and n (%). ARD, autoimmune rheumatic disease; BMI, 2ss index; RA, rheumatoid arthritis; axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; SLE, c lupus erythematosus; SSc, systemic sclerosis; pSSj, primary Sjögren syndrome; IIMM, idiopathic itomyopathies; PAPS, primary antiphospholipid syndrome. Biologics include TNF inhibitor, pt, tocilizumab, belimumab, secukinumab, rituximab, ustekinumab. Immunosuppressants include e aute, leflunomide, mycophenolate mofetil, azathioprine, tofacitinib, cyclophosphamide, tacrolimus and rine. Missing data for weight and BMI (n = 1).
### Table 2. Characteristics of autoimmune rheumatic diseases (ARD) patients and non-ARD individuals according to physical activity status.

|                      | ARD Active (n = 494) | ARD Inactive (n = 404) | Non-ARD Active (n = 128) | Non-ARD Inactive (n = 69) | P-value |
|----------------------|----------------------|------------------------|--------------------------|---------------------------|---------|
| Age, years           | 47.0 [39.0-58.0]     | 56.0 [45.0-66.0]       | 48.0 [34.0-59.0]         | 47.0 [38.0-55.0]          | <.001   |
| Age, < 60 years      | 389 (78.7)           | 236 (58.4)             | 100 (78.1)               | 56 (81)                   | .617    |
| Sex, female          | 378 (76.5)           | 305 (75.5)             | 84 (65.6)                | 47 (68)                   | .845    |
| MI, kg/m²            | 27.5 [24.2-31.6]     | 27.5 [24.2-31.6]       | 26.4 [23.4-30.2]         | 26.8 [24.8-31.0]          | .397    |
| Prednisone           | 186 (37.7)           | 170 (42.1)             | -                        | -                         | <.001   |
| Biological           | 164 (33.2)           | 163 (40.3)             | -                        | -                         | .032    |
| Immunosuppressants   | 313 (63.4)           | 269 (66.6)             | -                        | -                         | .349    |

Results are expressed in median [interquartile range] and n (%). BMI, body mass index; ARD, autoimmune rheumatic diseases.

Note: Missing data for BMI (ARD, n = 1; non-ARD, n = 6).

### Figures
Figure 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 > 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). Data are expressed as median and CI 95% for frequency of SC and NAb positivity, and mean and individual data for neutralizing activity, GMT and FI-GMT.

**Figure 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).

**Figure 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).

![Figure 4](image_url)

**Figure 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).

**Supplementary Files**

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- Supplementaryinformation.pdf
- STROBEchecklistv4combined.docx