Physical Activity at Different Life Stages and Its Consequence on the Initial Immunization and Inflammatory Response Against COVID-19

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Background: To evaluate the influence of previous physical activity (PA) during childhood, adolescence, and current PA practice on the production of antibodies and inflammatory response between the first and second doses of the COVID-19 vaccine. Methods: Fifty-nine men and 56 women were evaluated before the first vaccine, and 12 weeks later, blood samples were taken to quantify production of anti-severe acute respiratory syndrome coronavirus-2 immunoglobulin G antibodies and cytokines. Previous PA during childhood and adolescence was self-referred, and current PA was assessed using the International Physical Activity Questionnaire. Results: A positive and significant association was observed only between PA practice during adolescence and an increase in antibody production in adulthood (β = 2012.077, 95% confidence interval, 257.7953–3766.358, P = .025). Individuals who practiced PA during adolescence showed higher production of antibodies between the first and second vaccine dose compared to nonpractitioners (P = .025) and those that accumulated ≥150 minutes per week of current moderate–vigorous PA (MVPA), and presented higher antibody production in relation to who did <150 minutes per week of MVPA (P = .046). Individuals that were practitioners during childhood produced higher G-CSF (P = .047), and those that accumulated ≥150 minutes per week of current MVPA demonstrated lower IP-10 levels (P = .033). However, PA practitioners during adolescence presented higher G-CSF (P = .025), IL-17 (P = .038), IL-1RA (P = .005), IL-1β (P = .020), and IL-2 (P = .026) levels. Conclusion: Our results suggest that adults that accumulated at least 150 minutes of MVPA per week or practiced PA during adolescence developed an improved immune and inflammatory response against COVID-19 vaccination.

Keywords: antibodies, teenager, exercise, vaccine

At the end of 2019, a new viral pneumonia, named COVID-19 (Coronavirus Disease 2019), caused by the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus-2), emerged in the city of Wuhan, China, gaining notoriety for its rapid dissemination capacity.1-2 As a result of the high virulence and transmissibility, on January 30, 2020, the World Health Organization (WHO) declared it a public health emergency of international concern, which according to Health Regulations “constitutes an extraordinary event that may constitute a public health risk” to other countries due to the international spread of disease, and potentially requires an immediate and coordinated international response.” On March 11, 2020, WHO declared COVID-19 a pandemic.3,4

In order to prevent contagion and complications by COVID-19, several vaccines were produced in the last years, showing better efficacy and increase of antibody production after the second booster dose.5 The antibody response may also vary according to the specificity of the vaccine (28 d between the first and second doses or 3–4 mo between doses). In addition, physical activity (PA) practice has been reported as an important “adjuvant” for antibody
production, reducing the cytokine storm, an exaggerated immune and inflammatory response often observed in viral infections, minimizing the symptoms resulting from COVID-19. PA practice was also associated with a better immunogenicity 6 months after a 2-dose schedule of inactivated SARS-CoV-2 vaccine, especially in patients with systemic immunodeficiency. In a systematic review with meta-analysis conducted by Bohn-Goldbaum et al., they concluded that PA significantly increased seroconversion for the H1 strain and the antibody response. Also, Chastin et al. conducted a meta-analysis and demonstrated that PA has been associated with a healthier immune profile, observed by an increased CD4 cell count, which may speed the immunologic response to microbes and sustain the memory response; increased salivary immunoglobulin A concentration that strengthens mucosal defenses; and decreased levels of C-reactive protein and interleukin (IL)-6 that reduce chronic inflammation and its negative immunomodulatory effects.

Barroso et al. in a cohort study with adolescents found lower number of white blood cells and neutrophils and higher percentage of eosinophils and lymphocytes. On the other hand, those that did not engage in sports practice, as well as children with obesity and adolescents that reported a disease condition, showed higher total white blood cell levels and percentage of neutrophils, as well as lower percentage of lymphocytes. Therefore, the authors reinforce the importance of sports engagement and healthy habits to improve the immune system.

Previous PA practice is related to PA practice tracking, which is the maintenance of a leisure practice throughout life (from childhood, through adolescence to adulthood). During childhood and adolescence, PA practice is important for disease prevention, such as obesity. It is known that pediatric obesity can cause health complications and can be a predictor for developing type 2 diabetes mellitus, arterial hypertension, and dyslipidemia later during adulthood.

Studies indicate that adolescents involved in sports activities tend to become more physically active adults, highlighting the relevance of promoting public strategies aimed mainly at children and adolescents in the primary aspects of health promotion. In addition, since childhood and adolescence are key periods for immune development, where the immune system is likely to be programmed to respond to microbial challenges, it is important to understand the potential influence of previous PA practice during childhood and adolescence on antibody production in response to vaccines such as COVID-19.

The aim of this study is to investigate the influence of PA activity on the antibody and inflammatory response against COVID-19 vaccines, evaluating whether the practice of exercise in previous life stages (childhood and adolescence) and current PA practice would have any impact on the immune and inflammatory response in adults.

Methods

Sample

The study was developed in accordance with the Declaration of Helsinki and was submitted to the Research Ethics Committee of the Federal University of Piauí, Teresina, Piauí, Brazil, with approval under protocol (Approval: 5.017.799) and Certificado de Apresentação de Apreciação Etica (46115421.1.0000.5214).

The invitation to participate in the research occurred when individuals were at the vaccination station, through personal contact with the researcher. The study was explained, and the objectives and the procedures detailed. The criteria for participating in the study were: (1) being an adult aged over 18 years on the date of the first vaccination and agreed to participate in the study, by signing the Informed Consent Form. (2) The participants that were excluded from the study: (1) individuals who were absent from the second dose of vaccination on the predetermined date and (2) not answering any of the information from the questionnaire.

To assess immunization failure estimated at least in 10%, with 5% precision and 95% confidence G*Power software (version 3.1.9.2) was used. It was estimated that at least 139 participants prevaccination and postvaccination were necessary. A total of 173 volunteers agreed to participate in the study, at the vaccination station located at the Associação dos Professors of the Federal University of Piauí, in the city of Teresina—PI, Brazil, to be immunized against COVID-19 between June and October 2021. A total of 115 individuals, 59 males and 56 females, that met the criteria previously established and mentioned above were included in this study. Of these, 105 (91.3%) volunteers were vaccinated with the AstraZeneca/Oxford COVID-19 vaccine and 10 (8.7%) with the Pfizer COVID-19 vaccine. This difference is justified by the fact that the AstraZeneca/Oxford vaccine had more doses available on June 2021, at this immunization station, in the city of Teresina—PI, Brazil. In addition, it is important to mention that there were several challenges during COVID-19 vaccination in Brazil, such as people not returning for the second dose and a lack of logistic coordination at the federal level, which impaired vaccine distribution.

Experimental Design

It is a longitudinal study with an interval of 84 days (12 wk) between the first and second doses of the AstraZeneca/Oxford and Pfizer vaccine against COVID-19. After agreeing to participate in the study, volunteers were directed to a reserved room for the following procedures: (1) socioeconomic level and anthropometric assessment, (2) evaluation of previous and current PA practice through questionnaires, and (3) blood collection for subsequent determination of antibody and cytokine production levels. Upon the previously determined date for the second dose (84 d after the first dose), the volunteers were contacted again and on the day of the second dose, and all procedures previously described were repeated. The experimental design is illustrated in Figure 1.

Socioeconomic Level and Anthropometric Evaluation

The socioeconomic level was assessed according to the Associação Brasileira de Pesquisa de Mercado or Associação Brasileira de Institutos de Pesquisa de Mercado system, widely used to classify socioeconomic level from A to E based on ownership of household assets.

The total body mass (in kilograms) was measured using a Filizola digital scale, with a maximum capacity of 150 kg, with graduations of 100 g. Height was measured using a stadiometer, graduated in centimeters, with a vertical and fixed wooden bar, with a movable square. The body mass index (BMI) was also calculated (in kilograms per meter squared).

Previous and Current PA Practice

The current PA practice was assessed using the International Physical Activity Questionnaire—Short Form, that inquiries...
about PA in the past 7 days. Participants were classified as physically active (moderate to vigorous PA [MVPA] ≥ 150 min/wk) or inactive (MVPA < 150 min/wk) according to WHO guidelines. Evaluation of the previous PA practice was self-referred, and 2 questions were asked: (1) assessment of previous PA practice during childhood: ‘Between the ages of seven and 10, outside of school, did you engage in any supervised sports activity, for an uninterrupted year?’ (2) questions about previous PA practice during adolescence: ‘Between the ages of 11 and 17, outside of school, did you engage in any supervised sports activity for an uninterrupted year?’ From the answers, 2 categories were created: not having practiced (No = 0) or having practiced (Yes = 1), as used by Fernandes and Zanesco.11

### Blood Samples and Analysis of Antibody Production

The blood samples were collected in 10-mm vacutainer tubes (Becton Dickinson) before the first and second vaccine shot. Next, the tubes were centrifuged at 3000 rpm for 15 minutes at 4 °C, and plasma and serum samples were stored at −40 °C until analysis. The detection of IgG anti-N is a qualitative assay that relies on an assay-specific calibrator to report a ratio of specimen absorbance to calibrator absorbance. Results interpretation was determined by an index (S/CO) value, a ratio over the threshold value. An index of <1.4 was considered negative, and ≥1.4 was considered positive. The SARS-CoV-2 IgG II Quant Assay (Abbott) is a quantitative assay that measures antibodies against the receptor-binding domain of the S1-subunit of the SARS-CoV-2 S protein and presents 100% positive agreement with the plaque reduction neutralization test.

The antibody concentration is expressed as arbitrary concentration units (in arbitrary units per milliliter). Results ≥50 AU/mL (cutoff value) were reported as positive, and results <50 AU/mL were reported as negative. All steps of the assays were performed according to the manufacturer’s instructions. The chemiluminescence signals were detected by the ARCHITECT i2000SR equipment (Abbott, https://www.abbott.com).

### Western Blotting

Western blot analysis was performed using recombinant Spike (S1) and gamma (γ) proteins from Wuhan and was kindly provided by Dr Leda Castilho from Laboratório de Engenharia e Cultivo Celular from the Federal University of Rio de Janeiro (Rio de Janeiro, Brazil). Electrophoresis of each recombinant protein (2 μg/well) was performed on a 4% to 20% Tris-glycine gel separately. After transfer to nitrocellulose membrane, the membrane was blocked with 5% nonfat milk in phosphate-buffered saline —0.05% Tween, pH 8.0, overnight at 4 °C. After a washing step, the membrane strips were incubated with serum (1:100) for 2 hours at room temperature. This was followed by incubation with anti-human alkaline phosphatase-conjugated antibody (1:1000) for 2 hours at room temperature (Sigma). Bands were visualized using alkaline phosphatase substrate (Promega), and the reaction was interrupted by washing the membrane with deionized water.

### Cytokine and Chemokine Evaluation

Cytokine and chemokine serum levels were measured using a predefined Luminex-based multiparametric kit (MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel—Premixed 29 Plex, Merck Millipore). The markers examined were Epidermal Growth Factor, Granulocyte Colony-Stimulating Factor, Granulo
cyte-Macrophage Colony-Stimulating Factor, interferon (IFN)-α2, IFN-γ, IL-1α, IL-1β, IL-1RA, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, Interferon-γ-induced Protein-10, MCP-1, Macrophage Inflamma
tory Protein-1α, Macrophage Inflammatory Protein-1β, Tumor Necrosis Factor-α, Tumor Necrosis Factor-β, Vascular Endothelial Growth Factor, and Eotaxin/Chemokine (C-C motif) Ligand. Assays were performed according to the manufacturer’s instructions and measured on a Luminex 200 System (Lumi
nex Corp).

### Statistical Analysis

To verify the association between previous and current PA practice and the antibody production, a linear regression model was used with the outcome of absolute variation in antibody titers (titers after 12 wk of IgG minus baseline IgG titers) adjusted by baseline titers and PA practice as an independent variable, using 2 categories (does not practice PA = 0) or practice or have practiced (Yes = 1). Comparison of antibody production after the first vaccine shot
between practitioners and nonpractitioners or those that meet MVPA was performed using an analysis of covariance adjusted for antibody production before first shot. A multiple linear regression model was used to obtain regression coefficients adjusted by age, sex, and BMI. We provided standardized regression coefficients to re-express coefficients as the effect of a 1-SD change in the independent variables. Statistical significance was set at $P<.05$.

Data were analyzed using the Stata/MP (version 15.1) and GraphPad Prism (GraphPad Software Inc).

### Results

Initially, 173 volunteers were evaluated; however, only 115 individuals, 59 males and 56 females, completed the vaccination schedule, taking both vaccine doses within a 12-week period and completed the questionnaires regarding previous and current PA practice. Socioeconomic levels ranged between A (17, 15.2%), B1 (20, 17.9%), B2 (39, 34.8%), C1 (23, 20.5%), C2 (8, 7.1%), D–E (5, 4.5%), according to the socioeconomic index. There was no statistically significant gender difference regarding age and BMI; however, men had greater body mass ($P<.001$) and height ($P<.001$) compared with women, as shown in Table 1.

There was a statistically significant increase in antibody production between the first and second dose of the vaccine, in both males (Pre = 199.6 [355.9]; Post = 5065 [7296.7]; $P<.001$) and females (Pre = 105.4 [283.6]; Post = 1937.7 [3156.4]; $P<.001$).

Table 2 presents the association between previous and current PA practice and antibody production between the first and second doses of the COVID-19 vaccine in adults.

According to Table 2, a positive and significant association can be observed between PA practice during adolescence and the increase of antibody production in adulthood in the unadjusted regression analysis ($B = 2012.077$, 95% CI, 293.33–3730.81, $P = .022$). There was no influence of PA practice during childhood and current PA practice on the production of antibodies in the analyzed population. Furthermore, when the outcomes were adjusted by sex, BMI, and age, and when previous and current PA practice were inserted as independent variables and at the same time in the model, there were no significant associations.

Figure 2 shows detection of antibody against COVID-19 before and after COVID-19 vaccination.

Production of antibody was determined against 2 different COVID-19 antigens, the N protein and the S1 subunit (S protein). We did not observe a difference on the levels of antibody production against the N protein before and after the first vaccine dose. However, a significant difference was observed against the S1 subunit protein (Figure 2A and 2B).

Since the response against the N protein was not able to detect an increase of antibody production between blood collections, we decided to verify the antibody specificity against a different COVID-19 antigen, the γ protein and the S1 protein by Western blot analysis. We observed a strong detection of both γ and S1 subunit recombinant proteins by antibodies from individuals that tested positive with high titles for the S1 subunit protein by Enzyme-Linked Immunosorbent Assay (ELISA), after the first and second blood collections. Additionally, individuals with low titles for the S1 subunit protein by ELISA did not detect both γ and S1 subunit recombinant proteins. Interestingly, serum from individuals that reported having COVID-19 infection before vaccination also detected both recombinant proteins (γ and S1; Figure 2C).

Figure 3 presents the comparison on the antibodies against COVID-19 after first shot adjusted by antibodies analyzed before first shot at different stages of life.

The analysis of variance demonstrated that individuals who have accumulated ≥150 minutes per week of current MVPA presented higher antibodies against COVID-19 after the first injection in relation to those who practiced less than 150 minutes per week (panel A). Analyzing the overall increase of antibody production against the S1 subunit protein by ELISA after the first vaccine shot, according to previous PA practice, we observed that individuals that were practitioners during adolescence produced higher titles of anti-S1 antibodies after the first vaccine shot compared with

<table>
<thead>
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<th>Variables</th>
<th>Men (n = 59) MD ± DP</th>
<th>Women (n = 56) MD ± DP</th>
<th>$P$</th>
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<tr>
<td>Age, y</td>
<td>40.1 ± 9.9</td>
<td>43.9 ± 7.7</td>
<td>.027</td>
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<tr>
<td>Body mass, kg</td>
<td>82.5 ± 12.9</td>
<td>67.2 ± 12.0</td>
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<tr>
<td>Stature, cm</td>
<td>172.5 ± 7.4</td>
<td>158.3 ± 5.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5 ± 4.6</td>
<td>26.5 ± 4.8</td>
<td>.302</td>
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<td>COVID-19 infection</td>
<td>No 45 (76.3)</td>
<td>49 (87.5)</td>
<td></td>
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<tr>
<td></td>
<td>Yes 14 (23.7)</td>
<td>7 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>No 39 (66.1)</td>
<td>33 (58.9)</td>
<td></td>
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<tr>
<td></td>
<td>Yes 20 (33.9)</td>
<td>23 (41.1)</td>
<td></td>
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<tr>
<td>Medicine</td>
<td>No 39 (66.1)</td>
<td>32 (57.1)</td>
<td></td>
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<td></td>
<td>Yes 20 (33.9)</td>
<td>24 (42.9)</td>
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<td>Tobacco</td>
<td>No 53 (89.8)</td>
<td>51 (91.1)</td>
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<td></td>
<td>Yes 6 (10.2)</td>
<td>5 (8.9)</td>
<td></td>
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<tr>
<td>Alcoholic drink</td>
<td>No 22 (37.3)</td>
<td>38 (67.9)</td>
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<td></td>
<td>Yes 37 (62.7)</td>
<td>18 (32.1)</td>
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</table>

Abbreviation: BMI = body mass index.

(Ahead of Print)
nonpractitioners (panel B). However, there was no significant difference on PA practice during childhood (panel C).

Figure 4 shows a comparison of the inflammatory response after the first shot adjusted by antibody detection before first shot at different life stages.

When we analyzed circulating cytokines and chemokines (Figure 4), individuals that accumulated ≥150 minutes per week of current MVPA demonstrated lower IP-10 (P = .033) and higher IL-1β (P = .057) levels, although without a significant difference (Figure 4A). Individuals that practiced PA during adolescence presented higher G-CSF (P = .025), IL-17 (P = .038), IL-1RA (P = .005), IL-1β (P = .020), IL-2 (P = .026), MIP-1α (P = .050), IL-15 (P = .061), and TNF-α (P = .059) levels (Figure 4B). Individuals that were practitioners during childhood produced higher G-CSF (P = .047), IL-15 (P = .051), and MIP-1α (P = .061) levels, but there was no significant difference in the last 2 variables (Figure 4C).

Table 2 Association Between Previous and Current Practice of PA and Antibodies Production Against COVID-19 Vaccine in Adults

<table>
<thead>
<tr>
<th>Variable</th>
<th>Antibody production</th>
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</thead>
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<td>Regression coefficient (95%CI)</td>
<td>Standardized coefficient</td>
<td>P</td>
<td>Regression coefficient (95%CI)</td>
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<tr>
<td>PA practice during childhood</td>
<td>851.41 (1180.10–2882.92)</td>
<td>0.071</td>
<td>.408</td>
<td>271.04 (1912.12–2454.20)</td>
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<td>PA practice during adolescence</td>
<td>2012.077 (293.33–3730.81)</td>
<td>0.174</td>
<td>.022</td>
<td>1351.11 (670.99–3373.21)</td>
</tr>
<tr>
<td>Current PA practice</td>
<td>1364.512 (232.84–2961.86)</td>
<td>0.114</td>
<td>.093</td>
<td>1541.54 (104.59–3187.68)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; 95% CI, 95% confidence interval; PA, physical activity.

*Model 1: adjusted by baseline antibody level.
**Model 2: adjusted by baseline antibody level, sex, age, and BMI.

Figure 2 — Detection of specific antibodies (total IgG) before and after vaccination against COVID-19. (A) Antibodies against the N protein antigen before and after the first dose. (B) Antibodies against the S1 subunit antigen before and after the first dose. (C) Western blotting analysis of the volunteers’ sera before and after vaccination. Each group has a pool of 10 serum that showed high antibody titles. The group COVID is composed of volunteers that reported having COVID-19 infection previously. Volunteers that did not report having COVID infection previously were divided in 2 groups based on the detection of antibodies against COVID-19: (−) negative volunteers, (+) positive before the vaccination. (−) negative volunteers, (+) positive volunteers after vaccination. Significance was considered at P < .05. IgG indicates immunoglobulin G; N, nucleocapsid protein; S1, Spike.
indicates analysis of covariance; PA, physical activity.

Figure 3 — Production of antibodies against COVID-19 by volunteers with PA practice during different life stages. Comparison on the antibodies against COVID-19 after first shot adjusted by antibodies analyzed before first shot using the ANCOVA analysis, at different stages of life: current (panel A), adolescence (panel B), and childhood (panel C). ANCOVA indicates analysis of covariance; PA, physical activity.

Discussion

The present study verified the influence of previous PA practice during childhood, adolescence, and current PA practice and antibody production against COVID-19 between the first and second doses of the COVID-19 vaccine in adults. The main findings partly confirm our hypothesis since PA practice during adolescence was positively associated with an increase of antibody titles specific to the COVID-19 vaccine in adulthood with a 12-week interval between the first and second vaccine dose. Participants that accumulated ≥150 minutes per week of current MVPA presented higher antibodies against COVID-19 after the first shot in relation to those that practiced <150 minutes per week. Furthermore, individuals that were practitioners during childhood produced higher levels of G-CSF and individuals that accumulated ≥150 minutes per week of current MVPA demonstrated lower levels of IP-10. However, individuals that were practitioners during adolescence presented higher G-CSF, IL-17, IL-1rRA, IL-1β, and IL-2 levels.

Previous studies have shown that PA practice during childhood and adolescence is a protective factor for development of cardiometabolic diseases, such as diabetes, hypertension,11 and dyslipidemia21 in adulthood, suggesting that previous PA practice is even more important than current practice in disease prevention.8 Although several studies related current PA practice and antibody production,6,22 this is the first study demonstrating that individuals that practiced PA during adolescence showed an increase in antibody production against COVID-19 during adulthood.

Although, the impact of sports practice during youth on health in adulthood is systematically underestimated in the literature,23 sports engagement during youth and current PA has a significant impact on body fat in adulthood.24 Previous studies have demonstrated the importance of previous sport and PA practices on the cardiovascular,25 metabolic, and inflammatory pathways.26 Lima et al25 evaluated 55 healthy subjects of both genders and found that participants that engaged in sports activities during early life had lower values of very low-density lipoprotein and carotid intima-media thickness than subjects that did not engage in PA practices. Werneck et al26 investigated 101 adults (59 men) between 30 and 50 years old and concluded that early engagement in sports (during childhood and/or adolescence, but not adulthood) was associated with reduced body fat, and PA during childhood, adolescence, and adulthood was associated with lower body fat and C-reactive protein. Therefore, previous PA practice early in life seems to be an important strategy to impact also cardiovascular health, metabolic, and inflammatory response in adulthood.

The immune system development involves the innate immunity, that engages the background (genetic) information ready to act and protect the newborn,27 and the acquired immunity, developed throughout the individual’s life, based on continuous exposure to immune-eliciting factors.28 It has been suggested that PA practice during life may play an important role to improve antibody’s response and that the immune memory generated by other vaccines, in particular by live-attenuated vaccines such as measles, mumps, and rubella, may confer a nonspecific protective effect against SARS-CoV-2.29,30

The mechanisms involved from the practice of PA during adolescence associated with an increase of antibody titles to the COVID-19 vaccine in adulthood with a 12-week interval between the first and second vaccine dose are unclear. It is during this stage of life that the human body can have several health benefits from habitual practice of exercise, such as improved immune-modulatory factors that may lower inflammatory and oxidative stress, as well as improving homeostasis, lipid profile, and blood pressure in order to prevent metabolic and cardiovascular complications and block the virus entering the cell.31

Furthermore, engaging regularly in MVPA is associated with increased strength of the mucosal immune barrier (salivary IgA immunoglobulin) and higher concentration of immune cells that prepare, orchestrate and regulate immunity (CD4 T-cells).8 Therefore, engaging in MVPA during the early stage of life could induce an immunovigilance and improved immune competence, that could help eliminate pathogens and strengthen the effect of vaccination. In agreement with Damiot et al,32 we believe that individuals that
remained active throughout their lives have a protection factor against the virus that could also prevent the immunosenescence effect, a possible protective factor against the development of complications caused by COVID-19 infection.

In addition, Weisberg and Connors33 demonstrated that pediatric patients generated limited antibody responses to infection in terms of isotypes, which were largely limited to IgG anti-S antibodies, and an overall lower level of antibody neutralizing response than adults. Therefore, engagement of children and teenagers in regular PA could offer benefits to the immune system not only in the magnitude of total antibody and IgG levels but also to antibody neutralizing activity during adulthood.34

Regular PA practice can have a beneficial effect on the immune system, increasing IL-2 and natural killer cells, that can act together destroying tumor cells, as well as virus-infected cells.35 Dinas et al.36 found that physically active individuals developed antibodies against influenza in response to vaccination over a period of >4 weeks postvaccination (Standardized Mean Difference = 0.64, 95% CI, 0.30–0.98, Z = 3.72, F = 83%, P < .01) as opposed to a period of <4 weeks (P > .05; \( \chi^2 = 13.40, F = 92.5\%, P < .01\)). In addition, a resistance training session with exercises for the deltoid muscle and biceps brachii in the nondominant arm, performed 6 hours before the first flu vaccine dose, demonstrated improvement in the IFN-\( \gamma \) cell-mediated response in men and increased antibody responses in women, suggesting that other exercise strategies seem to potentiate the immune response to the vaccine.37

In a systematic review with meta-analysis, conducted by Bohn-Goldbaum et al.6 that analyzed randomized clinical trials
with acute exercise intervention and antibody production after vaccination against influenza, the authors concluded that PA practice increased antibody production by 1.2 times. Interestingly, results were more expressive in active but not sedentary individuals and, mainly in those engaged in regular physical exercise programs, corroborating with our data, since individuals who accumulated ≥150 minutes per week of current MVPA presented higher antibody titres against COVID-19 after the first shot in relation to those who did <150 minutes per week.

Hallam et al reported the effect of aerobic exercise from light to moderate intensity for 90 minutes performed on a cycle ergometer after immunization to different vaccines to evaluate the antibody response. The exercise was performed after influenza vaccination or after the first dose of the Pfizer-BioNTech COVID-19 vaccine. The results showed that practicing 90 minutes of exercise after immunization increased serum antibodies to each vaccine for several weeks, and increased IFN-α production that could partially contribute to the improved immune response. These findings suggest that adults who exercise regularly may increase the antibody response to influenza or COVID-19 vaccine by performing PA postimmunization from light to moderate intensity.

Apparently, SARS-COV-2 tends to trigger a series of inflammatory episodes through the excessive production of cytokines that can lead to lung injury causing chronic obstructive respiratory disease, edema, thrombus formation in the pulmonary endothelium, and tissue fibrosis. On the other hand, PA practice is able to improve the individual’s health status, a strategy used to increase the antibody response and reduce the risk of developing comorbidities that may further compromise the immune function of individuals. In the current study, individuals that were PA practitioners during childhood produced higher G-CSF levels and those that accumulated ≥150 minutes per week of current MVPA demonstrated lower IP-10 levels. However, individuals that were PA practitioners during adolescence presented higher G-CSF, demonstrated lower IP-10 levels. However, individuals that were PA practitioners during adolescence showed a higher production of circulating inflammatory and anti-inflammatory cytokines. This important effect on the vaccine response in individuals that practiced PA during adolescence or had a current PA practice further reinforces the importance of implementing public health programs and strategies that encourage the practice of PA throughout life.

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**Ethical Approval Information, Institution(s) and Number(s):** The study was developed and conducted in accordance with the Declaration of Helsinki and was submitted to the Research Ethics Committee of the Federal University of Piauí, Teresina, Piauí, Brazil, with approval under protocol (Approval: 5.017.799) and Certificate of Apresentação de Aprovação Ética (46115421.1.0000.5214).

**Data Availability Statement:** Data and publication materials can be provided upon request. Please contact corresponding author for this information.

**References**


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