Association between regular physical activity and the protective effect of vaccination against SARS-CoV-2 in a South African case–control study

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ABSTRACT

Background Both vaccination and physical activity have been shown to independently decrease the likelihood of severe COVID-19 infection.

Objective To assess the association between regular physical activity and vaccination against COVID-19 among healthcare workers.

Methods A test negative case–control study design was used to estimate the risk of having an associated COVID-19-related hospital admission, among individuals who were unvaccinated compared with those who were fully vaccinated with Ad26.COV2.S (>28 days after a single dose). 196 444 participant tests were stratified into three measured physical activity subgroups with low, moderate and high activity, to test the hypothesis that physical activity is an effect modifier on the relationship between vaccination and hospitalisation.

Results Vaccine effectiveness against a COVID-19-related admission among vaccinated individuals within the low activity group was 60.0% (95% CI 39.0 to 73.8), 72.1% (95% CI 55.2 to 82.6) for the moderate activity group, and 85.8% (95% CI 74.1 to 92.2) for the high activity group. Compared with individuals with low activity levels, vaccinated individuals with moderate and high activity levels had a 1.4 (95% CI 1.36 to 1.51) and 2.8 (95% CI 2.35 to 3.35) times lower risk of COVID-19 admission, respectively (p value <0.001 for both groups).

Conclusions Regular physical activity was associated with improved vaccine effectiveness against COVID-19 hospitalisation, with higher levels of physical activity associated with greater vaccine effectiveness. Physical activity enhances vaccine effectiveness against severe COVID-19 outcomes and should be encouraged by greater public health messaging.

INTRODUCTION
Background

The damaging medical consequences, as well as the destructive economic and social ripple effects of the COVID-19 pandemic have been well described.[1] Individuals' physical and mental health, behaviour and social security have been impacted.[2] As of September 2022, over 6.5 million people have died from the disease.[3] Non-pharmacological interventions to control the spread of COVID-19 have included limiting citizens' movement ('lockdowns'), emphasising physical distancing, hand sanitising and mask wearing. The most effective non-pharmacological interventions appear to have been

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Regular physical activity has protective effects against severe COVID-19 outcomes (such as hospital admission, intensive care unit admission, ventilation and death).
⇒ Previous studies have shown associations between physical activity levels and antibody levels in response to COVID-19 vaccines.

WHAT THIS STUDY ADDS

⇒ Objectively measured regular physical activity is associated with enhanced effectiveness of vaccination with Ad26.COV2.S against COVID-19-related hospital admission and a possible dose–response is demonstrated.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Public health messaging should encourage physical activity as a simple, cost-effective way of enhancing vaccine effectiveness to mitigate the risk of severe COVID-19 illness requiring hospital admission.

lockdowns.[4] Counterintuitively, in the context of lockdowns, these interventions often significantly limited individuals' access to physical activity. There are now excellent data supporting the protective effects of regular physical activity against severe COVID-19 outcomes, such as hospital and intensive care unit admission, ventilation and death.[5–8]

For pharmacological interventions against COVID-19, vaccination remains a clinically effective and cost-effective modality. Recent studies show vaccine effectiveness against COVID-19-related hospital admissions at between 73% and 94%.[9] Healthcare workers across eight locations in the USA who were fully vaccinated (2 weeks after a second dose) with mRNA BNT162b2 (Pfizer-BioNTech) were 90% less likely to be infected than those who were unvaccinated.[10] Similar findings were shown with inactivated SARS-CoV-2 vaccines.[11] Vaccine effectiveness has been shown across age bands, ethnic groups, and risk categories.[12]

The emergence of the field of exercise immunology has enhanced understanding of how regular moderate intensity physical activity improves immunosurveillance with many pronounced health benefits.[13] These studies have extended to include

the effect of physical activity on vaccine effectiveness. The most studied vaccine in the context of chronic physical activity and vaccine effectiveness is the influenza vaccine. Regular high levels of physical activity have been shown to improve immune responses to influenza vaccination, especially in older adults.[14 15] A study evaluating the effects of physical activity in women administered the pneumococcal vaccine found no significant difference between women who embarked on a physical lifestyle intervention and those who did not, but acknowledged potential methodological limitations,[16] while the effects of physical activity on vaccines administered to younger people have been equivocal.[17] Most of these studies have measured antibody responses to determine vaccine efficacy and suggest that regular physical activity of moderate intensity enhances the protective effect of vaccines, especially in those with immune dysfunction, including the elderly.

In a South African patient cohort exposed to the 20 hours/501Y.V2 ('Beta') variant, the Ad26.COV2.S vaccine has been shown to be 64% effective against moderate to severe COVID-19 and 81.7% effective against severe to critical disease, 28 days or more after vaccination.[18]

To our knowledge, no study has assessed the association between measured physical activity and vaccination effectiveness against COVID-19 admission. This study's findings may inform guidance on physical activity for individuals with reduced immune function, including the elderly and those with comorbidities, cohorts shown to be particularly vulnerable to severe outcomes from COVID-19.

Objectives
In this study we tested the hypothesis that regular physical activity acts as an adjuvant to the immune-boosting effect of COVID-19 vaccines, reducing severe outcomes as measured by hospital admission. We aimed to assess whether differential vaccine effectiveness of a single dose of Ad26.COV2.S was observed among subpopulations with directly measured low, moderate and high physical activity levels.

METHODS
Study design
A test negative case–control study design was used to estimate the risk of having an associated COVID-19-related hospital admission, among individuals who were unvaccinated relative to those who were fully vaccinated with Ad26.COV2.S (>28 days after a single dose) stratified into three physical activity subgroups: low, moderate and high. The manuscript was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[19]

Test negative case–control study
Test negative case–control studies are commonly used to assess the annual effectiveness of the influenza vaccine, by assessing the odds of vaccination among pathology specimens testing positive for influenza to the odds of vaccination among negative specimens.[20] They provide estimates of vaccine effectiveness consistent with randomised control trials provided that the data are adequately adjusted for confounders (such as age, sex and comorbidities), which potentially influence the risk of the outcome being measured.[21]

Setting
The Ad26.COV2.S vaccine (Janssen/Johnson & Johnson) comprises a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector encoding a full-length, membrane-bound SARS-CoV-2 spike protein in a prefusion-stabilised conformation. The Ad26.COV2.S vaccine was administered to healthcare workers in South Africa under the Sisonke Study, a phase 3B open-label implementation study.[22]

This was a retrospective analysis using anonymised Discovery Health and Vitality client data from 16 February 2021 to 30 October 2021. Discovery Health Medical Scheme (DHMS) is the largest open medical plan in South Africa (just over 2.8 million beneficiaries as of December 2021), and 18 employer-based medical plans (an additional 700 500 beneficiaries). Vitality is a global health promotion and behavioural change programme that encourages and rewards members for engaging in healthy lifestyle choices. As part of this health promotion strategy, Vitality offers members incentives and rewards for taking steps towards a healthier lifestyle.[23] Members belonging to Vitality pay an additional monthly contribution fee.

Study population
Participants aged 18 years and older were members of Discovery Health and Vitality clients. Discovery Health-administered client records included information related to demographics, chronic condition registrations, pathology results and operational data. COVID-19 admission data were obtained from Discovery Health's pre-authorisation data records, which include related diagnosis and procedure information. Measured physical activity records were extracted for Vitality (which included data recorded by wearable devices, clocked gym sessions and mass participation events). COVID-19 PCR test results for 258 293 Discovery Health clients, with membership during 15 February to 31 October 2021 were analysed. This cohort was divided into low, moderate and high physical activity groups (based on physical activity minutes as defined below), each of these containing vaccinated and unvaccinated individuals. Vaccinated individuals were healthcare workers who received vaccination in the Sisonke phase 3B study. Unvaccinated individuals included both non-healthcare workers and healthcare workers.

Test exclusion criteria
COVID-19 PCR test results for vaccinated and unvaccinated individuals with physical activity logged were included. Individuals only contributed their first positive test result from the start of the study period, provided that they did not test positive up to 90 days prior. Test results for individuals vaccinated with vaccine types other than Ad26.COV2.S, indeterminate test results, negative test results within 21 days of a positive test result and negative test results within 7 days of each other were excluded. No more than three randomly selected negative test results per patient were included in the analysis.

Physical activity measurements
Minutes of physical activity, step count and heart rate data were obtained from Vitality clients' wearable devices. The physical activity of participants was measured, and activity type, frequency and duration recorded as part of the Vitality Health behaviour modification programme.[23]

Individuals were mapped to physical activity subgroups using their average monthly physical point allocation in the 2 years prior to the study start date (online supplemental table 1). The range of average monthly physical activity points associated with the required duration of physical activity at moderate intensity was defined using the Vitality point allocation system (online supplemental table 2).

The physical activity subgroups were defined as follows:
1. Low activity levels (those engaging in less than 60 min of at least moderate intensity physical activity per week).
2. Moderate activity levels (those engaging in 60 and 149 min of at least moderate intensity physical activity per week).
3. High activity levels (defined as engaging in ≥150 min of at least moderate intensity physical activity per week).

Based on various physical activity guidelines, the Vitality Programme defines moderate intensity as having an average heart rate between 70% and 79% of maximum.[24]

Statistical analysis

A modified Poisson regression model with robust standard errors for each of the levels of activity was used to estimate the risk ratio of vaccination among those testing positive and having COVID-19 admission relative to the risk ratio of vaccination among those pathology specimens without an associated COVID-19 admission. Vaccine effectiveness was then assessed as one minus the risk ratio of COVID-19-related admission among fully vaccinated Ad26.COV2.S recipients from the Poisson regression model.

Well-documented risk factors for COVID-19 admission were included in the model.[25 26] These include age, sex, number of Centre of Disease Control (CDC) defined COVID-19 risk factors (including cancer, cardiovascular disease, chronic renal disease, chronic respiratory disease, diabetes, HIV, hypertension, liver disease, neurological disorders, obesity, severe mental disorders and solid organ transplants) and documented prior infection (online supplemental table 3). In addition to these factors, calendar week and province were also included as factors in the model. The likelihood of testing positive over the study period, which included South Africa's third wave of infections (predominantly in the Gauteng province), varied significantly by these factors (online supplemental figures 1 and 2). All covariates included were analysed as categorical variables.

Vaccination status as at PCR collection date was divided into the following exposure periods post vaccination: 0–3, 4–6, 7–9, 10–13, 14–20, 21–27 and 28 or more days since vaccination, with 28 or more days being defined as fully vaccinated. Periods prior to 14 days were included to assess observational bias between those vaccinated and controls.

Observational bias, after adjusting for confounders, between the vaccinated and unvaccinated populations, was assessed by observing vaccine effectiveness estimates against COVID-19 infection 7–13 days post vaccination. Clinical effectiveness from the vaccine prior 14 days, was not expected to impact the relative risk between the vaccinated population and controls.[18]

Three sensitivity analyses were performed: first, among related possible COVID-19 admissions (eg, pneumonia and ventilation), to ascertain the consistency of differences in vaccine effectiveness estimates among symptomatic patients across physical activity category subgroups; the second sensitivity analysis was performed by a single modified multinomial Poisson regression model, combining all activity data with a two-way interaction term between vaccination status and Vitality activity; the third sensitivity analysis used a Bayesian network based on the hypothesised causal relationships between the model's variables defined in a directed acyclic graph. This allowed for the explicit modelling of confounding and mediating effects (online supplemental figure 3).

Continuous variables were described using means (SD) and medians (interquartile range), where appropriate. Categorical variables were described as frequency (percentage). For continuous variables, statistical comparisons were performed with an independent t-test for normally distributed data. Statistical analysis was performed using MS Excel 2016 (Microsoft, USA) and R (version 3·6 ·3) using the Grammar of Data Manipulation package (dplyr) and survival libraries.

Ethics

Permission for use of DHMS anonymised medical and physical activity data was obtained from the Research Governance Committee of Discovery Health. Ethical approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg (clearance certificate number M211188). The Ad26.COV2.S vaccine was administered under the Sisonke Study, a phase 3B implementation study administered to healthcare workers.[22] This Sisonke Study was approved by the South African Health Products Regulatory Authority (SAHPRA) and the research ethics committees associated with Sisonke clinical research sites. The trial was registered at South African National Clinical Trial Registry (DOH-27- 0 22 021–6844); clin. gov number (NCT04838795) and the Pan African Clinical Trials Registry (PACTR202102855526180).

Patient and public involvement

Patients and the public were not involved in the design or conduct of this study. All data were anonymised.

RESULTS

PCR test results were analysed for individuals with low (n=53 771), moderate (n=62 721) and high (n=79 952) physical activity
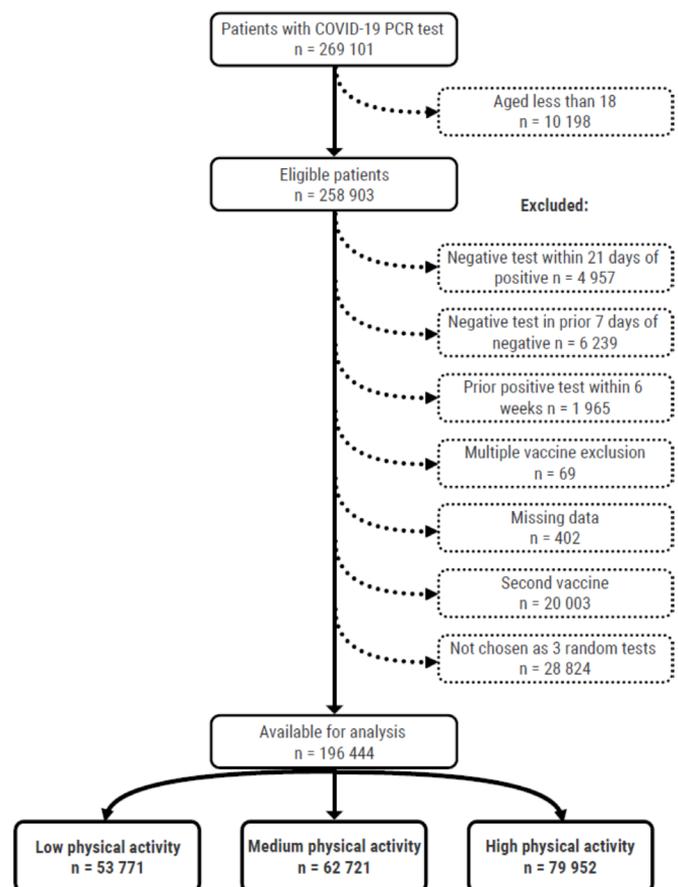
Figure 1 Consort flow diagram illustrating patient selection and breakdown.

Table 1 COVID-19 tests, characteristics and outcomes

	All COVID-19 tests			Admissions		
Characteristics	Low activity n (%)	Moderate activity n (%)	High activity n (%)	Low activity n (%)	Moderate activity n (%)	High activity n (%)
Age						
18–44	35 981 (66.9)	42 540 (67.8)	53 578 (67.0)	356 (36.1)	377 (38.3)	399 (40.3)
45–69	16 717 (31.1)	18 374 (29.3)	25 030 (31.3)	598 (60.6)	551 (55.9)	543 (54.8)
≥70	1073 (2.0)	1807 (2.9)	1344 (1.7)	32 (3.3)	57 (5.8)	49 (4.9)
Region*						
Gauteng	29 703 (55.2)	34 664 (55.3)	42 983 (53.8)	534 (54.2)	560 (56.9)	557 (56.2)
Other	24 068 (44.8)	28 057 (44.7)	36 969 (46.2)	452 (45.8)	425 (43.1)	434 (43.8)
Sex						
Female	34 456 (64.1)	35 365 (56.4)	40 708 (50.9)	417 (42.3)	364 (37.0)	301 (30.4)
Documented prior infection						
None	49 252 (91.6)	57 725 (92.0)	74 255 (92.9)	962 (97.6)	967 (98.2)	972 (98.1)
0 to 89 days	631 (1.1)	685 (1.1)	762 (1.0)	13 (1.3)	13 (1.3)	6 (0.6)
90 to 179 days	1224 (2.3)	1399 (2.2)	1605 (2.0)	6 (0.6)	1 (0.1)	4 (0.4)
≥180 days	2664 (5.0)	2912 (4.6)	3330 (4.1)	5 (0.5)	4 (0.4)	9 (0.9)
Number of COVID-19 risk factors†						
0	31 959 (59.4)	35 717 (56.9)	40 302 (50.4)	400 (40.6)	386 (39.2)	300 (30.2)
1	15 081 (28.1)	19 351 (30.9)	29 966 (37.5)	316 (32.0)	344 (34.9)	415 (41.9)
2	4880 (9.1)	5682 (9.1)	7568 (9.5)	186 (18.9)	180 (18.3)	182 (18.4)
≥3	1851 (3.4)	1971 (3.1)	2116 (2.6)	84 (8.5)	75 (7.6)	94 (9.5)

*Further regional breakdown as well as surveillance week is presented in online supplemental table 5 and online supplemental figures 1 and 2, respectively.
†See online supplemental table 1.

levels respectively, after restrictions were applied (figure 1). A total of 27 874, 5191 and 1362; 32 819, 5934 and 1353; and 42 873, 7092 and 1447 individuals contributed one, two and three negative test results, respectively, across the three stratified subgroups (online supplemental table 6). The median follow-up time since vaccination of Ad26.COV2.S recipients was 98 days (IQR 67–124 days).

Participants

Of the total test results analysed for the low activity group, 94.2% were unvaccinated and 5.0% fully vaccinated (table 1). This is similar to the 93.8% unvaccinated and 5.4% fully vaccinated in the moderate activity group and 92.4% unvaccinated and 6.7% fully vaccinated in the high activity group. Within the three activity groups (namely, low, moderate and high, respectively), 64.1%, 56.4% and 50.9% were female. For all three groups, most patients were in Gauteng province (55.2%, 55.3% and 53.8% (online supplemental table 7). The highest percentage of patients across all three groups was within the 18–44 year-old age group (66.9%, 67.8% and 67.0%). Similar percentages– namely 91.6%, 92.0% and 92.9%, had no documented prior COVID-19 infection. A slightly higher percentage of individuals with some COVID-19 risk factors were evident in the moderate and high activity groups. The distribution by PCR collection date, measured by calendar week, across the three groups were similar (online supplemental figure 1).

### Outcome data: hospital admissions

No observational bias was observed between the vaccinated and unvaccinated for low, moderate and high physical activity subgroups, as no statistically significant difference between the vaccinated population and the unvaccinated population was observed for categories: 7–9 days after vaccination and 10–13 days after vaccination for positive test outcomes (online supplemental table 4).

Vaccine effectiveness against COVID-19-related admission among fully vaccinated individuals with low activity levels was 60.0% (95% CI 39.0 to 73.8), moderate activity levels was 72.1% (95% CI 55.2 to 82.6) and high activity levels was 85.8% (95% CI 74.1 to 92.2) (figure 2 and table 2).

The risk ratio of COVID-19 admission for the vaccinated with high activity levels was 2.8 times lower than the risk ratio for those vaccinated individuals with low activity levels (p<0.001). Vaccinated individuals among those with moderate activity levels had a 1.4 times lower risk ratio of COVID-19 admission relative to the risk ratio of COVID-19 admission for the vaccinated among those with low activity levels (p<0.001).

Sensitivity analysis

The first sensitivity analysis, using PCR test results from an admitted patient cohort, had the following COVID-19 admission vaccine effectiveness among the fully vaccinated population in low, moderate and high physical activity subgroups,
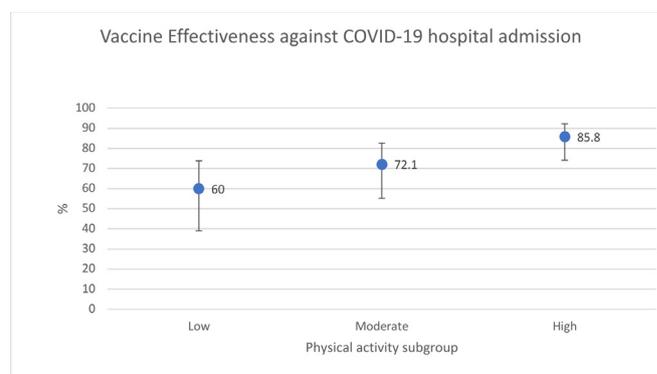
Figure 2 Vaccine effectiveness across physical activity subgroups 28 or more days since vaccination.

Table 2 Breakdown of physical activity level, vaccination status and COVID-19 outcomes

		COVID-19 tests total	Hospitalisations	Hospitalisations vaccine effectiveness (1-risk ratio) (95% CI)*	P value
Low	Not vaccinated	50 672	959	Reference	
	J&J Dose1 0–3 days	32	1	−122.8	0.43
	J&J Dose1 4–6 days	31	1	−240.1	0.22
	J&J Dose1 7–9 days	47	1	−134.5	0.40
	J&J Dose1 10–13 days	63	0	100.0	0.96
	J&J Dose1 14–20 days	93	0	100.0	0.95
	J&J Dose1 21–27 days	125	2	−14.7	0.85
	J&J Dose1 ≥28 days	2708	22	60.0 (39.0 to 73.8)	0.00
Moderate	Not vaccinated	58 814	968		
	J&J Dose1 0–3 days	58	0	100.0	0.98
	J&J Dose1 4–6 days	48	0	100.0	0.98
	J&J Dose1 7–9 days	52	0	100.0	0.98
	J&J Dose1 10–13 days	74	0	100.0	0.97
	J&J Dose1 14–20 days	115	0	100.0	0.97
	J&J Dose1 21–27 days	148	0	100.0	0.96
	J&J Dose1 ≥28 days	3412	17	72.1 (55.2 to 82.6)	<0.001
High	Not Vaccinated	73 857	975		
	J&J Dose1 0–3 days	67	0	100.0	0.98
	J&J Dose1 4–6 days	72	1	−72.1	0.59
	J&J Dose1 7–9 days	79	0	100.0	0.98
	J&J Dose1 10–13 days	133	2	−44.5	0.61
	J&J Dose1 14–20 days	193	2	−21.5	0.78
	J&J Dose1 21–27 days	190	0	100.0	0.97
	J&J Dose1 ≥28 days	5361	11	85.8 (74.1 to 92.2)	<0.001

*CIs are shown only for factors with p value ≤0.05.

respectively: 39.3% (95% CI 11.3% to 58.4%), 47.1% (95% CI 18.8% to 65.6%) and 69.7% (95% CI 48.1% to 82.3%). Each of the sensitivity point estimates were consistent with the vaccine estimates for low, moderate, and high physical activity categories using the full test dataset—that is, no statistical difference was observed between vaccine effectiveness estimates among the admitted population and the full test population (online supplemental table 4).

The second sensitivity analysis using a single multinomial modified Poisson regression model, demonstrated effectiveness of 91.5% (95% CI 70.2% to 97.6%) for vaccinated individuals with high activity relative to unvaccinated individuals with low activity. This was consistent with the primary finding of 85.8% (95% CI 74.1% to 92.2%). The difference in vaccine effectiveness between vaccinated individuals with high and low activity in the sensitivity was 91.5%–63.4%=28.1%, relative to the unvaccinated with low activity, while for the main result the difference was 85.8%–60.0%=25.8%, again showing a consistency between this sensitivity and the main result (online supplemental table 8).

The third and final sensitivity analysis using Bayesian modelling, allowed for the hypothesised causal relationships between the model's variables as defined in our directed acyclic graph (online supplemental figure 3). The difference in vaccine effectiveness between vaccinated individuals with high and low activity in the sensitivity was 95.6%–70.6%=25.0%, relative to the unvaccinated with low activity, while for the main result the difference was 85.8%–60.0%=25.8%, again showing a consistency between this sensitivity and the main result (online supplemental table 9).

DISCUSSION
Key findings
Vaccine effectiveness (as measured by avoidance of hospital admission) was compared between vaccinated and unvaccinated individuals in each of the three physical activity level categories. In fully vaccinated individuals, we found vaccine effectiveness against COVID-19 hospitalisation among those with high activity levels to be 86%, and significantly higher than for individuals with low activity levels, which was 60% (p<0.01). The results of all three of our sensitivity analyses confirmed these findings.

The findings suggest a possible dose–response. where high levels of physical activity were associated with higher vaccine effectiveness. This substantiates the WHO recommendations for regular physical activity—namely, that 150–300 min of moderate to intensity physical activity per week has meaningful health benefits in preventing severe disease, in this context against a communicable viral infection.[27]

Comparison with previous studies
Despite a dearth of science examining the association of COVID-19 vaccine effectiveness and physical activity, there are early signs emerging in the literature that vaccine effectiveness may be enhanced where physical activity is performed regularly and at an appropriate dose. However, in studies published thus far, physical activity has been self-reported through questionnaires, and serum antibody titres have been used as a measure of vaccine effectiveness.

Gualano *et al* described a dose–response when describing higher antibody levels on a cohort of physically active patients with autoimmune disease 2 months after vaccination with two

doses of CoronaVac when compared with inactive patients (OR=1.4 (95% CI 1.1 to 2.0)).[28] Physical activity levels were assessed by telephone interview. Physically active individuals were also younger and made less frequent use of medication.

In an open-label, single-arm, phase IV vaccination trial using two doses of the inactivated CoronaVac in immunocompromised patients, being physically active (self-reported via questionnaire) was associated with enhanced antibody persistence through 6 months.[29]

Possible explanation of our results

The reasons for the increased effect of vaccination in active individuals still have to be elucidated but may be a combination of enhanced antibody levels, improved T cell immunosurveillance and psychosocial factors. A recent systematic review by Chastin *et al* explored the effects of regular physical activity on the immune system, the risk of community-acquired infectious disease and the immune response to vaccination.[30] The review concluded that engaging regularly in moderate to vigorous physical activity is associated with a 31% risk reduction of community-acquired infectious disease and 37% risk reduction in infectious disease mortality, increases the strength of the immune barrier (salivary IgA immunoglobulin), increases the concentration of immune cells that regulate and effect immunity (CD4 T cells), and could strengthen the efficacy of immunisation. A median of three, 60 min physical activity sessions per week for 20 weeks prior to vaccination showed statistically significant higher antibody titres for H1N1, H3N2, influenza type B, pneumococcal and varicella zoster viruses.[30] Physical activity has been shown to have effects at many levels, including organelle level. Mitochondria play a particularly important part in immune function.[31–33] Physical activity regulates mitochondrial quality allowing the repair or elimination of damaged mitochondria and synthesising new ones, thus regulating mitochondrial biogenesis.[34]

Strengths and limitations

The study's main strength is the large sample of vaccinated individuals and almost all have directly measured physical activity data (only 3.8% of total recorded points evaluated were self-reported).

A limitation is that this analysis is based on a select group, probably of a higher socioeconomic status than both the insured population and general population in South Africa. The results therefore may not be generalisable to the South African population. Furthermore, data on consistently measured physical activity levels are not available for the full population. The results can therefore only be interpreted and compared relative to the three reported independent subgroups in this study.

The vaccinated and unvaccinated groups were also not directly comparable by occupation status; the vaccinated population included only healthcare workers while the unvaccinated control group included all Discovery Health members.

Owing to the observational nature of the study, other correlated factors might have contributed to, or explained, the higher vaccine effectiveness observed among the highly active population relative to the population with low physical activity. These possible correlates include diet, alcohol consumption and sleeping patterns.

These results may not be generalisable to new COVID-19 variants, such as Omicron, or other vaccine platforms, and the exact biological mechanism contributing to these observations is unknown owing to the lack of assessment of immunogenicity and cell-mediated responses in this study.

Suggestions for future research

There have been recent studies of waning vaccine effectiveness.[35] Given our follow-up period analysed, we did not investigate the extent of waning vaccine effectiveness among individuals of varying activity levels, which can be considered by investigators in future research. Furthermore, future research could look at the effectiveness of additional boosted Ad26.COV.S dose which is now a standard recommendation.[36]

CONCLUSIONS

Our study is the first to use recent, directly measured physical activity data to demonstrate an association between increased levels of regular physical activity and effectiveness of vaccination against COVID-19 hospitalisation, suggesting that regular physical activity may increase the effectiveness of COVID-19 vaccines and exhibit a dose–response. Public health messaging should encourage physical activity as a simple, cost-effective way of enhancing vaccine effectiveness to mitigate the risk of severe COVID-19 illness requiring hospital admission.

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