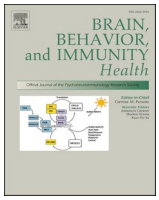
Brain, Behavior, & Immunity - Health 40 (2024) 100818

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Examining the association of vaccine-related mindsets and post-vaccination antibody response, side effects, and affective outcomes

Darwin A. Guevarra [a,b,c,*], Ethan G. Dutcher [b,c], Alia J. Crum [d], Aric A. Prather [b,c], Elissa S. Epel [b,c,**]

[a] Department of Psychology, Miami University, 90 North Patterson Avenue, Oxford, OH, 45056, USA
[b] Center for Health and Community, University of California, San Francisco, 675 18th Street, San Francisco, CA, 94107, USA
[c] Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, 675 18th Street, San Francisco, CA, 94107, USA
[d] Department of Psychology, Stanford University, Building 420, 450 Jane Stanford Way, Stanford, CA, 94305, USA

ARTICLE INFO

Keywords:
Mindsets
COVID-19
Vaccine
Antibody response
Side effects
Affect

ABSTRACT

Background: Although vaccines are largely effective and safe, there is variability in post-vaccination experience regarding antibody response, side effects, and affective outcomes. Vaccine mindsets, specific beliefs about the vaccine, may be associated with post-vaccination experience. This is important since mindsets are malleable and may help decrease vaccine hesitancy and improve post-vaccination experience.

Methods: In a prospective study, we measured overall positive vaccine mindset and specific mindsets regarding efficacy, body response, and side effects. We tested whether vaccine mindsets before vaccination predicted neutralizing antibody response, side effects, vaccine-related stress, and affective outcomes (general stress, sadness, and happiness). Antibody response was assessed one month and six months after participants completed a SARS-CoV-2 vaccination series. Side effect experience and affective reactions were assessed daily on the vaccination day and the subsequent five days.

Results: There was no significant association between the aggregate vaccine mindset score and neutralizing antibody response; however, people with a more positive vaccine mindset reported fewer side effects, less same-day vaccine-related anxiety, and improved affective outcomes after vaccination. In secondary analyses, when specific mindsets were explored, the mindset that vaccine side effects are a sign of treatment efficacy predicted higher antibodies, but not side effects experience and vaccine-related anxiety. Vaccine efficacy and body-response mindsets predicted fewer side effects, vaccine-related anxiety, and improved affective outcomes after vaccination.

Conclusion: These findings underscore the potential of vaccine mindsets in enhancing the overall post-vaccination experience and, in some cases, increasing antibody response.

1. Introduction

The SARS-CoV-2 virus has led to over 770 million infections and 6.9 million deaths (World Health Organization, 2023). To combat this pandemic, the United States Food and Drug Administration authorized the rapid development of three vaccines (Creech et al., 2021; Ghazy et al., 2022): Ad26.COV2.S (Janssen/Johnson & Johnson), mRNA-1273 (Moderna), and BNT162b2 (Pfizer/BioNTech). Although the vaccines are generally effective and safe (Lai et al., 2021), there is variability in vaccination response that has prompted researchers to identify modifiable psychosocial factors that may impact antibody response, side effects, and affective experience (Gallagher et al., 2022; Madison et al., 2021; Vedhara et al., 2021). These psychosocial factors can be tested as a non-pharmacological vaccine adjuvant to improve vaccination experience and decrease vaccine hesitancy (Madison et al., 2021; Stasiuk et al., 2021; Vedhara et al., 2021). Mindsets regarding vaccination are understudied as potential targets for improving biological and experiential vaccination outcomes.

* Corresponding author.
** Corresponding author. Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, 675 18th Street, San Francisco, CA, 94107, USA.
E-mail addresses: guevarda@miamioh.edu (D.A. Guevarra), elissa.epel@ucsf.edu (E.S. Epel).

https://doi.org/10.1016/j.bbih.2024.100818
Received 3 July 2024; Accepted 4 July 2024
Available online 16 July 2024

Mindsets are beliefs and assumptions about how the world works that can impact what people experience, feel, and do (Dweck and Yeager, 2019; Molden and Dweck, 2006; Zion and Crum, 2018). People can have beliefs and mindsets about many things, such as intelligence, stress, aging, illnesses, and medical treatments (Crum et al., 2013; Schroder, 2021; Zion and Crum, 2018; Zion et al., 2022). Mindsets can impact how people interpret and experience health-relevant situations and outcomes (Crum and Zuckerman, 2017; Crum et al., 2017a, b; Leibowitz et al., 2021). For example, people who are led to believe that stress is enhancing ('stress-is-enhancing' mindset) versus stress is harmful ('stress-is-debilitating' mindset) showed greater increases in positive affect, cognitive flexibility, and anabolic growth hormones after a stressful situation (Crum et al., 2017a, b; Crum et al., 2013). People can also have mindsets about clinical conditions that impact their experience and health-relevant outcomes. For example, people with the mindsets that 'cancer is an opportunity' and 'cancer is manageable' report better health-related quality of life compared to the mindset that 'cancer is a catastrophe' (Zeidman et al., 2022). Cancer patients who were randomized to a mindset intervention about cancer and their body, compared to a control group, reported better quality of life, increased adaptive coping behaviors and reduced psychological and physical distress (Zion et al., 2023).

In this study, we explore whether mindsets about the vaccine, both broad and specific mindsets, are associated with post-vaccination antibody levels, side effects, and affective experience. A broad positive mindset is a combination of people's positively valenced cognitions and affective reactions about the vaccine. People can also have more specific mindsets regarding different aspects of the vaccine and their relationship to it. An efficacy mindset is the belief that the vaccine will protect them from COVID-19. A body-response mindset refers to the belief their body is capable and will respond well to the vaccine. A side-effects mindset is the belief that the side effects or symptoms after receiving a vaccine are signs that the vaccine is working.

Vaccine mindsets can theoretically improve post-vaccination experience through placebo-related mechanisms (Geers et al., 2021; Petrie and Rief, 2019). In this context, placebo-related mechanisms include positive treatment expectations regarding the vaccine. Positive expectations regarding a treatment can often enhance their efficacy and other related health outcomes (Petrie and Rief, 2019; Price et al., 2008). For example, when the opioid remifentanil is administered with positive expectations, it more than doubles its analgesic effects compared to the control condition with no information (Bingel et al., 2011). Moreover, negative expectancy information eliminated remifentanil's analgesic effects. In another study, patients scheduled for heart surgery who were randomized to an optimized expectation group, compared to a support group and standard medical care, showed the best outcomes six months later in terms of better improvements in disability, mental quality of life, and fitness for work (Rief et al., 2017). The optimized expectation intervention also lowered postoperative adrenaline levels compared to standard medical care, and in turn, the adrenaline levels predicted lower disability six months after surgery (Salzmann et al., 2017). In summary, positive mindsets regarding a treatment can improve efficacy across a variety of domains, including increasing the effectiveness of morphine, diazepam, deep brain stimulation (Colloca et al., 2004), topical lidocaine (Petersen et al., 2014), acupuncture (Linde et al., 2007), and surgical interventions (Auer et al., 2016).

Mindsets may also influence the emotional response to vaccination. The vaccine hesitancy literature offers valuable insight regarding affective outcomes and side effects. Vaccine hesitancy refers to delaying or refusing vaccination despite its availability (MacDonald, 2015). In samples of individuals who received the COVID-19 vaccine, higher levels of vaccine hesitancy were associated with higher levels of anxiety and depressive symptoms (Palgi et al., 2021) and more side effects after vaccination (Hoffman et al., 2022a, b). One of the likely mechanisms is nocebo effects. The nocebo effect is the opposite of the placebo effect, in which harmful outcomes occur after a treatment resulting from negative expectations and related factors (Colloca, 2020; Geers et al., 2021; Petrie and Rief, 2019). In contrast to vaccine hesitancy and its underlying negative expectations, positively valenced vaccine mindsets should be associated with fewer side effects, lower anxiety and stress, and more positive mood.

Modifying mindsets regarding the meaning of symptoms has also been shown to reduce nocebo effects and improve treatment outcomes. In one study, children undergoing oral immunotherapy who learned that side effects are a positive signal of treatment efficacy experienced less anxiety, fewer symptoms, and improved treatment efficacy as measured by changes in IgG4 levels (Howe et al., 2019). In a study on the COVID-19 vaccine, a brief intervention explaining how side effects are related to vaccine efficacy resulted in decreased symptoms and greater intentions to vaccinate in the future compared to a control condition (Crum et al., 2023). To date, research has not explored the extent to which mindsets about vaccines are associated with vaccine efficacy.

In this prospective study, we examined whether mindsets about the vaccine would predict better post-vaccination experience, including vaccination efficacy, side-effect experience, and affective experience. We recruited a large community sample of adults who each arranged to receive one of three vaccines: Ad26.COV2.S (Janssen/Johnson & Johnson), mRNA-1273 (Moderna), or BNT162b2 (Pfizer/BioNTech). Blood draws occurred pre-vaccination and approximately one month and six months post-final vaccine injection. Vaccination efficacy was assessed using pseudovirus assays sensitive to SARS-CoV-2 neutralizing antibody (nAB) response one month and six months after the vaccination series. Side-effect experience and affective outcomes were assessed on each vaccination day and each of the five days after. We hypothesized that a positive vaccine mindset would be associated with higher antibody response, fewer side effects, less vaccine-related stress and anxiety, and more positive mood. We pre-registered our primary analysis on AsPredicted.org (#119976). We note any deviations from our pre-registration below.

2. Methods

2.1. Study design and participants

The findings presented are part of a larger study, the Building Optimal antibOdies Study (BOOST), designed to identify psychological, behavioral, and biological predictors of immune response to the COVID-19 vaccine (Prather et al., 2023). The study recruited 534 healthy adults in the San Francisco Bay Area from March 6 to April 17, 2021. To be eligible, participants had to be 18 years or older, have no history of SARS-CoV-2 infection, and have not received a COVID-19 vaccine. Participants with one of the following conditions were excluded: current pregnancy, history of immune-related diseases such as autoimmune conditions, viral hepatitis, HIV, and current cancer treatment. Participants taking medications that affected the immune system, such as immunomodulators and corticosteroids, were also excluded. All methods followed the policies and regulations approved by the University of California, San Francisco Institutional Review Board.

Eligible participants consented to complete daily questionnaires and blood draws at baseline before vaccination, one month (30 days, interquartile range 28–32 days), and six months (180 days, interquartile range 178–182 days) after the final vaccine injection. Participants forwarded information on their vaccination appointment date to the research team. Participants who received the Johnson & Johnson vaccine only received one injection ($n = 62$). Sociodemographic and behavioral factors of interest, including age, sex, and smoking status (current tobacco use, yes/no), were obtained by self-report. Body height and weight were measured during the baseline blood draw to calculate body mass index (BMI). Study data were collected and managed using REDCap electronic data capture tools hosted at the University of California, San Francisco (Harris et al., 2009, 2019). Participants were compensated $100 for each of the three assessments. The sample size

varied for each analysis depending on data available for each predictor and outcome measure: antibody response, side effects, and affective outcomes.

2.2. Predictors

2.2.1. Vaccine mindsets

Positive vaccine mindset was measured with four items (as pre-registered) on a 6-point Likert scale from 0 (Strongly agree) to 5 (Strongly disagree) at the first dose (D1) and second dose (D2). A positive vaccine mindset was assessed the morning participants were to receive their vaccine injection. Participants who received the Johnson & Johnson vaccine only reported their positive vaccine mindset at the first (and only) dose. The four items included efficacy mindset ("The vaccination will protect me from COVID-19"), body-response mindset ("My body is capable and will respond well to the vaccine"), and positive affective responses ("I feel positive/hopeful about receiving the vaccine" and "I feel grateful to receive this vaccination.").[1] The four items were used to create an average score regarding overall positive vaccine mindset (dose 1 $\alpha = 0.715$, $M = 4.53$, $SD = 0.53$; dose 2 $\alpha = 0.764$, $M = 4.55$, $SD = 0.53$; dose 1 and 2, $M = 4.53$, $SD = 0.50$). In addition, we had an additional side effects mindset item ("Side effects/symptoms are a sign that the vaccine is working") that was not included in the positive mindset scale.

2.3. Outcomes

2.3.1. SARS-CoV-2 neutralizing antibody (nAB) response

Sensitive, high-throughput pseudovirus assays were used to measure the serum levels of SARS-CoV-2 neutralizing antibody (nAB) response. Pseudoviruses were produced by co-transfection of 293 T cells with a plasmid expressing full-length spike protein of the Wuhan-1 strain (Weissman et al., 2021). Virus stocks were collected three days after transfection and stored in aliquots at −80 °C. For neutralization, a predetermined optimal dose of pseudovirus was incubated with serial threefold dilutions of heat-inactivated serum in 150 μl medium for 1 h at 37 °C in 96-well tissue culture plates. Sensitive, high-throughput pseudovirus assays were used to measure the serum levels of SARS-CoV-2 neutralizing antibody responses (nAB). Pseudoviruses were produced by co-transfection of 293 T cells with a plasmid expressing full-length spike protein of the Wuhan-1 strain (Weissman et al., 2021). Virus stocks were collected three days after transfection and stored in aliquots at −80 °C. For neutralization, a predetermined optimal dose of pseudovirus was incubated with serial threefold dilutions of heat-inactivated serum in 150 μl medium for 1 h at 37 °C in 96-well tissue culture plates. Subsequently, CHO/ACE2 cells, treated with TrypLE enzyme, were added to the wells with necessary controls. After incubating for 66-27 h, the medium was removed, and 100 μl of 1:6 diluted Promega BriteGlo in Glo lysis buffer was added. Plates sat for 7 min at room temperature before luminescence was recorded using a Biotek Synergy H1 Luminometer. Neutralizing antibody titers were defined as the serum dilution at which relative luminescence units (RLU) would be reduced by 50% compared to virus control wells after subtracting background RLUs. Neutralizing antibody (nAB) responses were transformed using a base 10 log before analyses. Please see Prather et al. (2023) for a detailed description of procedures for quantifying neutralizing antibodies.

2.3.2. Vaccine side effects

Vaccine side effects were measured on the day participants received the vaccine and the five days afterward (6 days total). Participants were asked at the end of each day if they experienced any of the following symptoms that day: tiredness; headache; muscle pain; chills; joint pain; fever; nausea/vomiting; feeling unwell; tender or swollen lymph nodes (lymphadenopathy); injection site pain, redness or swelling; pain or swelling in the arm that did not get the vaccination; other allergic reactions (difficulty breathing, swelling of face/throat, rash); stomachache; None of the above. To capture the range of side effects experienced, data were collapsed to reflect the presence or absence of each symptom on any of the six days for a range of scores from 0 to 13 with a mean (SD) of 2.62 (2.38) (Dutcher et al., 2024). The calculation did not include injection site pain, redness, or swelling because the count was intended to measure systemic rather than local symptoms.

2.3.3. Vaccine-related anxiety

Vaccine-related anxiety was measured by averaging participant answers to three questions, each scored on a 6-point Likert scale from 0 (Strongly agree) to 5 (Strongly disagree). Vaccine-related anxiety was reported on the day that participants received their vaccination. Participants who received the Johnson & Johnson vaccine only reported their vaccine-related anxiety at the first dose. The three items were "I am worried about potential side effects," "I feel anxious/nervous about receiving the vaccine," and "I feel mixed or ambivalent about receiving the vaccine" ($M = 1.73$, $SD = 1.11$).

2.3.4. General affective outcomes

General affective outcomes on the day of vaccination for the next five days were measured in the morning and night using three single items on a 5-point Likert scale from 0 (Not at all) to 4 (Extremely). General stress ($M = 0.79$, $SD = 0.98$) was measured with responses to "I feel stressed, anxious, overwhelmed," sadness ($M = 0.55$, $SD = 0.85$) was measured with responses to "I felt sad, downhearted, unhappy," and happiness ($M = 2.29$, $SD = 1.14$) was measured with responses to "I felt joyful, glad, happy."

2.3.5. Covariates

Participants reported psychosocial factors included as covariates such as age, sex, and smoking status. Height and weight were measured during baseline blood draws. Baseline anti-spike IgG was also used as a covariate to control for participants who may have been exposed to the SARS-CoV-2 virus. Antibodies to the SARS-CoV-2 spike protein at baseline were quantified by ELISA (Prather et al., 2023). Because vaccine mindsets may be related to an overall positive outlook, we used optimism as a covariate for side effects and affective outcomes. Optimism was measured with six items on a 5-point Likert scale from 0 (Does not describe me at all) to 4 (Describes me very well) from the Life-Orientation Test (Scheier et al., 1994).

2.4. Analysis

All analyses were conducted using R. Due to the repeated measures nature of the data, we conducted several mixed-effects models using the *lme4* package to predict neutralizing antibody response, side effects, vaccine-related stress, and affective outcomes (general stress, sadness, and happiness). For brevity, we focused on reporting the main effects and any interactions with vaccine mindsets. Due to the inclusion of categorical predictors in the models (vaccine type, dose time, time of day, and day), F statistics and partial eta squared (η_p^2) are provided for each predictor, and slopes were estimated with the emmeans package. F statistics used Type II sums of squares (Langsrud, 2003). Below, we provide details regarding each model and any deviations from our pre-registered analysis for each outcome.

2.4.1. SARS-CoV-2 neutralizing antibody (nAB) response

We conducted four linear mixed-effects models predicting nAB response with positive vaccine mindset (our primary predictor) and secondary predictors: efficacy mindset, body-response mindset, and side

[1] Feelings of hope and gratitude are conceptually viewed as affective responses to the specific efficacy and body-response mindsets. In this study, given their high correlation and proximity to the mindset measure we include them in an aggregate measure.

effects mindset. The model consisted of vaccine mindsets, a two-way interaction between vaccine type (Johnson & Johnson, Moderna, & Pfizer) and timepoint (one month, six months after vaccination series), while covarying for age, sex, BMI, smoking status, baseline anti-spike IgG. These covariates (including the vaccine type and timepoint interaction) were chosen from a previous analysis of this sample that established they were significantly associated with nAB response (Prather et al., 2023). We did not include trait-level optimism as a covariate since there is no evidence it is related to antibody response (Madison et al., 2021). For our primary analysis, we deviated from our pre-registration by adding the two-way interaction between vaccine type and time point due to their strong relationship (Prather et al., 2023). We also conducted the same analysis for vaccine mindsets at dose 2 and the average of doses 1 and 2 as primary predictors and reported them in Supplementary Materials Table 2.

2.4.2. Side-effects

We conducted four Poisson mixed-effects models to predict side effect experience. We covaried for dose time (dose 1, dose 2), vaccine type, and trait optimism.

2.4.3. Same-day vaccine-related anxiety

We conducted four linear mixed-effects models predicting same-day vaccine-related anxiety. We covaried for dose time (dose 1, dose 2), vaccine type, and trait optimism.

2.4.4. Affective outcomes from days 0–5

Lastly, we conducted four separate linear mixed-effects models for general stress, sadness, and happiness. We were also interested in potential interactions of vaccine mindset and day. The final model consisted of a two-way interaction between vaccine mindset and day while covarying for the dose time, vaccine type, time of day, and trait optimism.

3. Results

3.1. Participant demographics

Descriptive statistics for each primary outcome are provided in Table 1. The number of participants and observations varied depending on the analysis due to the availability of the data. Using the largest sample (affective outcomes), the mean (SD) age was 52.41 (11.95) and ranged from 18 to 76. A majority of the sample were female (63.99%) and White (56.06%).

3.2. Predicting neutralizing antibody response at one month and six months

Contrary to our hypothesis, positive vaccine mindset at the first dose (d1) did not predict nAB, F (1, 362.70) = 2.36, p = 0.13, η_p^2 = 0.006. Secondary analyses showed no effects for efficacy mindset, F (1, 365.19) = 2.49, p = 0.12, η_p^2 = 0.007, and body-response mindset, F (1, 366.46) = 3.63, p = 0.06, η_p^2 = 0.01. However, side effects mindset positively predicted nAB response, F (1, 364.64) = 5.36, p = 0.021, η_p^2 = 0.014 (see Table 2 for summary regression coefficients).

As reported in our original paper on this sample (Prather et al., 2023), age was negatively associated with nAB post-vaccination (ps < 0.05), and baseline anti-spike antibody level, a proxy for prior infection, was associated with higher nAB post-vaccination (ps < 0.05). Participants who were female at birth also had higher nAB post-vaccination (p < 0.05) (See Supplementary Materials Tables 1a–1d for detailed tables). We also report results for the mixed effects model at dose 2 and average of dose 1 and 2 in Supplementary Materials Table 2.

3.3. Predicting side effects

For side effects, we used a sample of n = 458 to 460 consisting of $n_{observations}$ = 755 to 759 depending on the data availability of predictor and covariates. Consistent with our hypothesis, a positive vaccine mindset (z = −3.04, β = −0.20, p < 0.001) negatively predicted the experience of side effects (See Table 2 for summary regression coefficients). Notably, these effects were significant when controlling for optimism. For context, a β = −0.20 (exponentiated value = 0.819) can be interpreted as a 18% decrease in the number of side effects per one-unit increase in positive vaccine mindset. In secondary analyses, efficacy mindset (z = −1.98, β = −0.10, p = 0.048), and body-response mindset (z = −3.99, β = −0.16, p < 0.001) predicted side effect count, but vaccine side effects mindset did not predict side effect count (z = 0.60, β = 0.02, p = 0.552). Optimism negatively predicted side effect count in all four models (ps < 0.001). See Supplementary Materials Table 3 for detailed results.

3.4. Predicting same-day vaccine-related anxiety

For vaccine-related anxiety, we used a sample of n = 457 and $n_{observations}$ = 759. Consistent with our hypothesis, positive vaccine mindset (β = −1.04, p < 0.001, η_p^2 = 0.257), efficacy mindset (β = −0.44, <0.001, η_p^2 = 0.082), and body-response mindset (β = −0.45, <0.001, η_p^2 = 0.138) negatively predicted vaccine-related anxiety. Notably, these associations hold even when controlling for optimism. Optimism negatively predicted side effects experienced in all three models (ps < 0.01).

Table 1
Demographic statistics for each outcome.

Demographics	Antibody response (n = 372)	Side effects (n = 460)	Affective outcomes (n = 462)
Age, mean (SD)	52.06 (11.92)	52.43 (11.89)	52.41 (11.95)
Age, min - max	18–76	18–76	18–76
Sex, n (%)			
Female	242 (65.05%)	294 (64.05%)	295 (63.99%)
Male	130 (34.95%)	165 (35.95%)	166 (36.01%)
Race and Ethnicity, n (%)			
Asian	99 (26.61%)	116 (25.22%)	116 (25.11%)
Black/African American	8 (2.15%)	15 (3.26%)	15 (3.25%)
Hispanic/Latinx	35 (9.41%)	40 (8.70%)	41 (8.87%)
White	205 (55.11%)	259 (56.30%)	259 (56.06%)
Other/Multiracial/Unknown	25 (6.72%)	30 (6.52%)	31 (6.71%)
Education, n (%)			
Some college or less	50 (13.44%)	67 (14.57%)	68 (14.72%)
4-year degree	151 (40.59%)	181 (39.35%)	181 (39.18%)
Professional degree/Doctorate	171 (45.97%)	212 (46.09%)	213 (46.10%)

Note: Sample size varies for each outcome measure. Sample size indicates total number in the sample in which age is calculated. Sample size also varies depending on availability of socio-demographic data. For example, for side effects, the total number of people who provided sex data was 459.

Table 2
Results of mixed effects models.

	Positive vaccine mindset			Vaccine efficacy mindset			Vaccine body-response mindset			Vaccine side effects mindset		
Outcome	*β*	*SE*	*p*	*β*	*SE*	*p*	*β*	*SE*	*p*	*β*	*SE*	*p*
Antibody response	0.06	0.04	0.126	0.05	0.03	0.116	0.05	0.03	0.058	**0.05**	**0.02**	**0.021**
Side effects	**−0.20**	**0.06**	**<0.001**	**−0.10**	**0.05**	**0.048**	**−0.16**	**0.04**	**<0.001**	0.02	0.03	0.552
Vaccine-related anxiety	**−1.04**	**0.07**	**<0.001**	**−0.44**	**0.05**	**<0.001**	**−0.45**	**0.04**	**<0.001**	−0.05	0.04	0.127
Stress	**−0.22**	**0.04**	**<0.001**	**−0.12**	**0.03**	**<0.001**	**−0.09**	**0.03**	**<0.001**	**−0.10**	**0.02**	**<0.001**
Sadness	**−0.16**	**0.04**	**<0.001**	**−0.08**	**0.03**	**<0.001**	**−0.07**	**0.02**	**0.002**	**−0.04**	**0.02**	**0.022**
Happiness	**0.32**	**0.05**	**<0.001**	**0.11**	**0.03**	**0.001**	**0.12**	**0.03**	**<0.001**	**0.05**	**0.02**	**0.015**

Notes: Unstandardized betas, standard error, and *p* values are reported for the main effects for each of the four mindsets. Mixed-effects models for antibody response controlled for timepoint (after month 1 and month 6 following the initial vaccine series), vaccine type (Janssen/Johnson & Johnson, Moderna, Pfizer/BioNTech), the timepoint by vaccine type interaction, baseline anti-spike IgG, age, sex, BMI, and smoking status. For side effects, a Poisson regression controlled for time of dose (Dose 1 vs. Dose 2), vaccine type, and optimism. For vaccine-related anxiety, a mixed-effects model was used for the time of dose (Dose 1 vs. Dose 2), vaccine type, and optimism. For general stress, sadness, and happiness across the 0–5 days, the mixed effects models controlled for interaction with day, time of dose (Dose 1 vs. Dose 2), vaccine type, time of day (morning vs. evening), and optimism. Significant findings at the $p \leq 0.05$ level are bolded.

However, the side effects mindset did not negatively predict vaccine-related anxiety ($\beta = -0.05$, $p = 0.127$, $\eta_p^2 = 0.003$). See Supplementary Materials Table 4 for detailed results.

3.5. Predicting affective outcomes from days 0–5

For affective outcomes, we used a sample $n = 462$ with $n_{observations} = 7822$ for stress, $n_{observations} = 7813$ for sadness, and $n_{observations} = 7809$ for happiness. See Table 2 for a summary of findings.

Stress. Consistent with our hypothesis, positive vaccine mindset ($\beta = -0.22, p < 0.001, \eta_p^2 = 0.007$), efficacy mindset ($\beta = -0.12, p < 0.001, \eta_p^2 = 0.002$), body-response mindset (β = -0.09, $p = 0.001$, $\eta_p^2 = 0.002$), and side effects mindset (β = -0.10, $p < 0.001$, $\eta_p^2 = 0.004$) were negatively associated with stress. A positive vaccine, efficacy, and side effects mindset, but not a body-response mindset, interacted with the day. The interaction reflects a pattern of mindset that has the strongest relationship with stress on day 0 and the weakest on day 5. Again, notably, these main effects findings were significant even when controlling for optimism. Optimism negatively predicted stress in all four models (*ps* < 0.01). See Supplementary Materials Tables 5a and 5b for detailed results.

Sadness. Consistent with our hypothesis, positive vaccine mindset ($\beta = -0.16$, $p < 0.001$, $\eta_p^2 = 0.004$), efficacy mindset ($\beta = -0.08$, $p = 0.003$, $\eta_p^2 = 0.001$), body-response mindset (β = -0.07, $p = 0.002$, $\eta_p^2 = 0.001$), and side effects mindset (β = -0.04, $p = 0.022$, $\eta_p^2 = 0.001$) were negatively associated with sadness. Positive vaccine mindset and efficacy mindset, but not body-response mindset and side effects mindset interacted with the day. The interaction reflects a pattern of mindset with the strongest relationship with sadness on day 0 and the weakest on day 5. Again, notably, these main effects findings were significant even when controlling for optimism. Optimism negatively predicted stress in all four models (*ps* < 0.01). See Supplementary Materials Tables 6a and 6b for detailed results.

Happiness. Consistent with our hypothesis, positive vaccine mindset ($\beta = 0.32$, $p < 0.001$, $\eta_p^2 = 0.011$), efficacy mindset ($\beta = 0.11$, $p = 0.001$, $\eta_p^2 = 0.002$), body-response mindset ($\beta = 0.12$, $p < 0.001$, $\eta_p^2 = 0.003$), and side effects mindset ($\beta = 0.04$, $p = 0.015$, $\eta_p^2 = 0.001$) were positively associated with happiness. Positive vaccine, efficacy, and body-response mindset, but not body-response mindset interacted with the day. The interaction reflects a pattern of mindset, with the strongest relationship with happiness on day 0 and the weakest on day 5. Again, notably, these main effects findings were significant even when controlling for optimism. Optimism negatively predicted stress in all four models (*ps* < 0.01). See Supplementary Materials Tables 7a and 7b for detailed result.

4. Discussion

We investigated the association between vaccine mindsets and post-vaccination outcomes. The relationships between positive vaccine, efficacy, and body-response mindsets and neutralizing antibody response was not statistically significant. However, the side effects mindset—the mindset that vaccine side effects are a sign that the vaccine is working—positively predicted stronger antibody response at one and six months later. This finding of side effect mindsets predicting antibody response needs replication. However, it is consistent with previous research from Howe et al. (2019) suggesting that side effects mindsets are associated with more positive immunological responses to oral immunotherapy treatment for peanut allergies. The lack of a statistically significant associations between the other vaccine-related mindsets and antibody response may be due to reduced variability in the mindset measures. Participants in our sample generally scored high on vaccine-related mindsets. Future studies with a broader range of mindsets would be useful.

Positive vaccine mindset was strongly associated with decreased anxiety about and experience of side effects. This finding is particularly noteworthy as the experience of side effects is one of the reasons people are reluctant to receive the vaccine (Crum et al., 2023; Solís Arce et al., 2021). Reducing side-effect experience is also particularly important since severe COVID-19 vaccine side effects are linked with depressive symptoms in older adults (Hoffman et al., 2022a, b). Interestingly, while the side effects mindset was the only predictor of antibody response, it was the only mindset not associated with side effect experience. This is not completely surprising as this mindset is about the *meaning* of the side effects (the extent to which people believe the experience of side effects means the vaccine is working) and not about the likelihood of side effects (believing you will or will not receive side effects). Previous research on this mindset has shown mixed results with respect to side effects, with associations between this mindset and the prevalence of symptoms happening at various times and not at others (e.g., no associations with side effects during the beginning of treatment but decreases at the end of treatment). This underscores the important distinction between mindsets regarding the meaning of a topic and expectations regarding a particular outcome (Crum et al., 2023; Howe et al., 2017; Leibowitz et al., 2021).

We also assessed post-vaccination subjective experience. Here, we found that an overall positive mindset and each specific mindset were associated with less stress and sadness and more happiness during the day of vaccination and subsequent days after (0–5 days). These effects were strongest closest to vaccination day and decreased over time. These findings on affect are important because the COVID-19 pandemic has brought a complex set of stressors, including fear of getting COVID-19, social isolation, as well as vaccine-related stress, anxiety, and worry (Chou and Budenz, 2020; Daly and Robinson, 2021a, 2021b; McGinty et al., 2020). It is not surprising that a positive vaccine mindset is associated with less vaccine-related anxiety. However, given this complex and long list of stressors, it is noteworthy that a positive vaccine mindset was associated with less stress and sadness on the day of the

vaccination and even five days afterward. Moreover, vaccine mindset also predicted more happiness post-vaccination and five days after. The interaction between vaccine mindset and day is also notable. The association between vaccine mindset and affective outcomes was strongest at vaccination day zero and weakest at day five, suggesting it serves a more protective effect around the days of vaccination. In summary, all four vaccine-related mindsets were associated with a better affective response post-vaccination. It is also important to note that these effects hold controlling for general optimism. This highlight the value of a more specific mindset about the efficacy of the vaccination over and above a more global measure of dispositional tendency to expect positive outcomes.

Although the study has several strengths, there are several limitations to the current research. First, although we recruited a sociodemographically diverse community sample, our sample had generally positive mindsets regarding the vaccine. Future studies should recruit samples with less favorable views of vaccines in general. Second, although this was a prospective cohort study, leveraging predictors that temporally preceded our outcomes, we could not make causal claims. However, like many mindsets, vaccine-related mindsets are theoretically amenable to educational interventions (Crum et al., 2023; Zion and Crum, 2018). For instance, Crum et al. (2023) found that a 4-min video to improve people's mindsets about vaccine side effects (in this case, the mindsets that 'symptoms are positive signals') reduced symptoms' worry and frequency. Future studies might test whether similar educational material targeted at vaccine mindsets can casually impact post-vaccination outcomes.

Vaccination is an important measure to prevent future disease and promote public health. Although much remains to be explored, these findings underscore the importance of understanding mindsets in shaping vaccine experiences and outcomes. Future research should further probe these findings. Examining the relationships between a range of mindsets and expectations about vaccination and considering how best to design psychological interventions to optimize the post-vaccination experience to help improve population health.

Funding sources

This work was supported by the National Institute of Aging of the National Institute of Health under award number R24AG048024 and U24AG072699-03S1 and the LSP Family Foundation.

CRediT authorship contribution statement

Darwin A. Guevarra: Formal analysis, Writing – original draft, Writing – review & editing. **Ethan G. Dutcher:** Data curation, Formal analysis, Writing – review & editing. **Alia J. Crum:** Conceptualization, Supervision, Writing – review & editing. **Aric A. Prather:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Elissa S. Epel:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

There are no conflict of interest among all authors.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100818.

References

Auer, C.J., Glombiewski, J.A., Doering, B.K., Winkler, A., Laferton, J.A.C., Broadbent, E., Rief, W., 2016. Patients' expectations predict surgery outcomes: a meta-analysis. Int. J. Behav. Med. 23, 49–62.
Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M.C., Ploner, M., Tracey, I., 2011. The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. Sci. Transl. Med. 3 (70), 70ra14-70ra14.
Chou, W.-Y.S., Budenz, A., 2020. Considering emotion in COVID-19 vaccine communication: Addressing vaccine hesitancy and fostering vaccine confidence. Health Commun. 35 (14), 1718–1722.
Colloca, L., 2020. Placebo and nocebo effects. N. Engl. J. Med. 382 (6), 554–561.
Colloca, L., Lopiano, L., Lanotte, M., Benedetti, F., 2004. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. Lancet Neurol. 3 (11), 679–684.
Creech, C.B., Walker, S.C., Samuels, R.J., 2021. SARS-CoV-2 vaccines. JAMA 325 (13), 1318–1320.
Crum, A., Zuckerman, B., 2017. Changing mindsets to enhance treatment effectiveness. JAMA Netw. Open 317 (20), 2063–2064.
Crum, A.J., Akinola, M., Martin, A., Fath, S., 2017a. The role of stress mindset in shaping cognitive, emotional, and physiological responses to challenging and threatening stress. Hist. Philos. Logic 30 (4), 379–395.
Crum, A.J., Heathcote, L.C., Morrison, Z., Yielder, R., Leibowitz, K., Petousis-Harris, H., Thomas, M.G., Prober, C.G., Berek, J.S., Petrie, K.J., 2023. Changing mindsets about side effects of the COVID-19 vaccination: a randomized controlled trial. Ann. Behav. Med., kaad020
Crum, A.J., Leibowitz, K.A., Verghese, A., 2017b. Making mindset matter. BMJ 356, j674.
Crum, A.J., Salovey, P., Achor, S., 2013. Rethinking stress: the role of mindsets in determining the stress response. Journal of Personality and Social Psychology 104 (4), 716–733.
Daly, M., Robinson, E., 2021a. Anxiety reported by US adults in 2019 and during the 2020 COVID-19 pandemic: population-based evidence from two nationally representative samples. J. Affect. Disord. 286, 296–300.
Daly, M., Robinson, E., 2021b. Psychological distress and adaptation to the COVID-19 crisis in the United States. J. Psychiatr. Res. 136, 603–609.
Dutcher, E.G., Epel, E.S., Mason, A.E., Hecht, F.M., Robinson, J.E., Drury, S.S., Prather, A.A., 2024. COVID-19 vaccine side effects and long-term neutralizing antibody response: a prospective cohort study. Ann. Intern. Med.
Dweck, C.S., Yeager, D.S., 2019. Mindsets: a view from two eras. Perspect. Psychol. Sci. 14 (3), 481–496.
Gallagher, S., Howard, S., Muldoon, O.T., Whittaker, A.C., 2022. Social cohesion and loneliness are associated with the antibody response to COVID-19 vaccination. Brain Behav. Immun. 103, 179–185.
Geers, A.L., Faasse, K., Guevarra, D.A., Clemens, K.S., Helfer, S.G., Colagiuri, B., 2021. Affect and emotions in placebo and nocebo effects: what do we know so far? Social and Personality Psychology Compass, e12575.
Ghazy, R.M., Ashmawy, R., Hamdy, N.A., Elhadi, Y.A.M., Reyad, O.A., Elmalawany, D., Almaghraby, A., Shaaban, R., Taha, S.H.N., 2022. Efficacy and effectiveness of SARS-CoV-2 vaccines: a systematic review and meta-analysis. Vaccines 10 (350).
Harris, P.A., Taylor, R., Minor, B.L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., 2019. The REDCap consortium: Building an international community of software platform partners. J. Biomed. Inf. 95, 103208.
Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inf. 42 (2), 377–381.
Hoffman, Y., Levin, Y., Palgi, Y., Goodwin, R., Ben-Ezra, M., Greenblatt-Kimron, L., 2022a. Vaccine hesitancy prospectively predicts nocebo side-effects following COVID-19 vaccination. Sci. Rep. 12 (1), 20018.
Hoffman, Y., Palgi, Y., Goodwin, R., Ben-Ezra, M., Greenblatt-Kimron, L., 2022b. Severe Covid-19 vaccine side-effects are rare in older adults yet are linked with depressive symptoms. Am. J. Geriatr. Psychiatr. 30 (1), 115–116.
Howe, L.C., Goyer, J.P., Crum, A.J., 2017. Harnessing the placebo effect: Exploring the influence of physician characteristics on placebo response. Health Psychol. 36 (11), 1074–1082.
Howe, L.C., Leibowitz, K.A., Perry, M.A., Bitler, J.M., Block, W., Kaptchuk, T.J., Nadeau, K.C., Crum, A.J., 2019. Changing patient Mindsets about Non–Life-Threatening symptoms during oral immunotherapy: a randomized clinical trial. J. Allergy Clin. Immunol. Pract. 7 (5), 1550–1559.
Lai, C.-C., Chen, I.-T., Chao, C.-M., Lee, P.-I., Ko, W.-C., Hsueh, P.-R., 2021. COVID-19 vaccines: Concerns beyond protective efficacy and safety. Expet Rev. Vaccine 20 (8), 1013–1025.
Langsrud, Ø., 2003. ANOVA for unbalanced data: use Type II instead of Type III sums of squares. Stat. Comput. 13 (2), 163–167.
Leibowitz, K.A., Howe, L.C., Crum, A.J., 2021. Changing mindsets about side effects. BMJ Open 11 (2), e040134.
Linde, K., Witt, C.M., Streng, A., Weidenhammer, W., Wagenpfeil, S., Brinkhaus, B., Willich, S.N., Melchart, D., 2007. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. Pain 128 (3), 264–271.
MacDonald, N.E., 2015. Vaccine hesitancy: Definition, scope and determinants. Vaccine 33 (34), 4161–4164.
Madison, A.A., Shrout, M.R., Renna, M.E., Kiecolt-Glaser, J.K., 2021. Psychological and behavioral predictors of vaccine efficacy: Considerations for COVID-19. Perspect. Psychol. Sci. 16 (2), 191–203.

McGinty, E.E., Presskreischer, R., Han, H., Barry, C.L., 2020. Psychological distress and loneliness reported by US adults in 2018 and April 2020. JAMA 324 (1), 93–94.
Molden, D.C., Dweck, C.S., 2006. Finding meaning in psychology: a lay theories approach to self-regulation, social perception, and social development. Am. Psychol. 61 (3), 192–203.
Palgi, Y., Bergman, Y.S., Ben-David, B., Bodner, E., 2021. No psychological vaccination: vaccine hesitancy is associated with negative psychiatric outcomes among Israelis who received COVID-19 vaccination. J. Affect. Disord. 287, 352–353.
Petersen, G.L., Finnerup, N.B., Grosen, K., Pilegaard, H.K., Tracey, I., Benedetti, F., Price, D.D., Jensen, T.S., Vase, L., 2014. Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. Pain 155 (12), 2687–2698.
Petrie, K.J., Rief, W., 2019. Psychobiological mechanisms of placebo and nocebo effects: Pathways to improve treatments and reduce side effects. Annu. Rev. Psychol. 70 (0), 1–27.
Prather, A.A., Dutcher, E.G., Robinson, J., Lin, J., Blackburn, E., Hecht, F.M., Mason, A. E., Fromer, E., Merino, B., Frazier, R., 2023. Predictors of long-term neutralizing antibody titers following COVID-19 vaccination by three vaccine types: the BOOST study. Sci. Rep. 13 (1), 1–9.
Price, D.D., Finniss, D.G., Benedetti, F., 2008. A comprehensive review of the placebo effect: Recent advances and current thought. Annu. Rev. Psychol. 59, 565–590.
Rief, W., Shedden-Mora, M.C., Laferton, J.A., Auer, C., Petrie, K.J., Salzmann, S., Schedlowski, M., Moosdorf, R., 2017. Preoperative optimization of patient expectations improves long-term outcome in heart surgery patients: results of the randomized controlled PSY-HEART trial. BMC Med. 15 (1), 1–13.
Salzmann, S., Euteneuer, F., Laferton, J.A., Auer, C.J., Shedden-Mora, M.C., Schedlowski, M., Moosdorf, R., Rief, W., 2017. Effects of preoperative psychological interventions on catecholamine and cortisol levels after surgery in coronary artery bypass graft patients: the randomized controlled PSY-HEART trial. Psychosom. Med. 79 (7), 806–814.
Scheier, M.F., Carver, C.S., Bridges, M.W., 1994. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the life orientation test. Journal of Personality and Social Psychology 67 (6), 1063–1078.
Schroder, H.S., 2021. Mindsets in the clinic: Applying mindset theory to clinical psychology. Clin. Psychol. Rev. 83, 101957.
Solís Arce, J.S., Warren, S.S., Meriggi, N.F., Scacco, A., McMurry, N., Voors, M., Syunyaev, G., Malik, A.A., Aboutajdine, S., Adeojo, O., 2021. COVID-19 vaccine acceptance and hesitancy in low-and middle-income countries. Nat. Med. 27 (8), 1385–1394.
Stasiuk, K., Maciuszek, J., Polak, M., Doliński, D., 2021. Profiles of vaccine hesitancy: the relation between personal experience with vaccines, attitude towards mandatory vaccination, and support for anti-vaccine arguments among vaccine hesitant individuals. Social Psychological Bulletin 16 (2), 1–20.
Vedhara, K., Royal, S., Sunger, K., Caldwell, D.M., Halliday, V., Taylor, C.M., Fairclough, L., Avery, A., Welton, N.J., 2021. Effects of non-pharmacological interventions as vaccine adjuvants in humans: a systematic review and network meta-analysis. Health Psychol. Rev. 15 (2), 245–271.
World Health Organization, 2023. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/.
Zeidman, A., Benedict, C., Zion, S.R., Fisher, S., Tolby, L., Kurian, A.W., Berek, J.S., Woldeamanuel, Y.W., Schapira, L., Palesh, O., 2022. Association of illness mindsets with health-related quality of life in cancer survivors. Health Psychol. 41 (6), 389–395.
Zion, S.R., Crum, A.J., 2018. Mindsets Matter: a new framework for harnessing the placebo effect in modern medicine. In: Colloca, L. (Ed.), International Review of Neurobiology, vol. 138. Elsevier, pp. 137–160.
Zion, S.R., Louis, K., Horii, R., Leibowitz, K., Heathcote, L.C., Crum, A.J., 2022. Making sense of a pandemic: mindsets influence emotions, behaviors, health, and wellbeing during the COVID-19 pandemic. Soc. Sci. Med. 301, 114889.
Zion, S.R., Schapira, L., Berek, J.S., Spiegel, D., Dweck, C.S., Crum, A.J., 2023. Changing cancer mindsets: a randomized controlled feasibility and efficacy trial. Psycho Oncol. 32 (9), 1433–1442.