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Psychological correlates of antibody response to mRNA SARS-CoV-2 vaccination: A prospective observational cohort study

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ABSTRACT

Background: Vaccines fundamentally changed the course of the COVID-19 pandemic, saving > 14 million lives within a year. However, vaccine-conferred protection showed inter-individual variability, with many identified correlates of protection (e.g., age) not amenable to change. This prospective observational cohort study examined whether modifiable psychological factors (depressive symptoms, anxiety, perceived stress and positive mood), which predict antibody responses to other vaccines, also influenced the effectiveness of COVID-19 vaccines. We focussed on novel mRNA vaccines as these conferred greater clinical protection and psychological correlates have not been investigated in these vaccines previously.

Methods: One-hundred and eighty-four adults attending a mass-vaccination centre in the UK received a two-dose BNT162b2 mRNA SARS-CoV-2 vaccine course, completed validated psychological measures, and provided blood samples prior to vaccination and 4 weeks following the second vaccine dose.

Results: In separate linear regression models controlling for pre-vaccination antibody levels, demographic and clinical factors, higher levels of depressive symptoms (β = -0.15 [95 % CI: −0.30, −0.01], $p = 0.041$, partial $f^2 = 0.009$) and lower levels of positive mood (β = 0.16 [95 % CI: 0.01, 0.30], $p = 0.036$, partial $f^2 = 0.011$) were significantly associated with lower SARS-CoV-2 spike-specific antibody levels following vaccination. No significant relationships were observed between measures of anxiety or perceived stress and antibody responses.

Conclusions: Lower levels of depressive symptoms and greater positive mood were associated with larger antibody responses following mRNA SARS-CoV-2 vaccination in a community sample attending for their first course of COVID-19 vaccinations. As both are amenable to change, they could offer mechanisms for enhancing vaccine effectiveness particularly among populations at greater risk of vaccine failure.

1. Introduction

The introduction of effective SARS-CoV-2 vaccines in late 2020 turned the tide on the COVID-19 pandemic, saving at least 1.4 million lives in Europe alone (The WHO European Respiratory Surveillance Network, 2024) and an estimated 14.4 million worldwide within a year of their first use outside of clinical trials (Watson et al., 2022). Central to this was the first large scale deployment of messenger ribonucleic acid (mRNA) vaccines which accounted for approximately 90 % of all COVID-19 vaccine doses administered globally (Our World in Data. Our World in Data., 2024). SARS-CoV-2 mRNA vaccines developed during the pandemic proved to be more effective and immunogenic than non-mRNA equivalents (Naranbhai et al., 2021). However, as with non-mRNA vaccines, the immune response and the clinical effectiveness of these vaccines demonstrate considerable inter-individual variability (Krüttgen et al., 2022; Wheeler et al., 2021). To date, vaccine-induced antibody responses to these mRNA vaccines have been found to be associated with a number of non-modifiable clinical and demographic factors including age (Kodde et al., 2023), prior infection (Callegaro et al., 2021), and a number of comorbidities (Kim et al., 2024). Many of

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these factors have also been found to predict an increased likelihood of vaccine-breakthrough, and in turn, hospitalisation and death (Bea et al., 2023; Butt et al., 2021; DeSantis et al., 2023; Martín Pérez et al., 2024; Smits et al., 2023; Dorjee et al., 2020). What is less clear is whether modifiable characteristics can also influence the effectiveness of mRNA vaccines. Establishing this would be important, as such evidence would signal potential for the development of non-pharmacological vaccine adjuvants (Vedhara et al., 2019) to enhance mRNA vaccines, particularly in populations where immunogenicity is sub-optimal.

In non-mRNA vaccines, multiple modifiable psychological factors have been found to predict antibody responses following vaccination. Historically, much of this evidence has been concerned with indices of psychological distress, including depression (Segerstrom et al., 2008; Li et al., 2007), anxiety (Glaser et al., 1992) and stress (Pedersen et al., 2009). For example, a *meta*-analysis of 13 studies exploring the relationship between psychological stress and antibody response to influenza vaccination found a significant negative relationship across vaccine strains and in both young and older adults (Pedersen et al., 2009). However, more recently there has been growing evidence that measures of positive affect are positively and independently associated with antibody responses to non-mRNA vaccines (Ayling et al., 2018; Marsland et al., 2006).

In terms of SARS-CoV-2 vaccines, a small number of studies have started to consider psychological factors as potential correlates of vaccine immune responses. Early studies suggest that lower social cohesion/increased loneliness (Gallagher et al., 2022) and greater psychological distress [as measured by the Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS] (Pearce et al., 2023) are associated with reduced antibody responses to SARS-CoV-2 vaccines. However, these findings are based on cross-sectional analyses relying on post-vaccination antibody measures only and thus could not control adequately for antibody levels prior to vaccination. They also do not distinguish between non-mRNA and mRNA vaccines in their findings. To our knowledge only one small study of 78 Japanese healthcare workers has reported specifically on mRNA SARS-CoV-2 vaccines, and observed evidence of a negative association between distress [as measured by the Hospital Anxiety and Depression Scale (HADS)] and vaccine-induced antibody responses (Kaneko and Tsuboi, 2023), although again these analyses did not control for prior exposure/pre-vaccination antibody levels.

Here, we present findings from a longitudinal prospective community cohort study exploring for the first time the relationship between not one, but multiple psychological parameters and antibody responses to a two-dose course of SARS-CoV-2 mRNA vaccination. Our focus was on psychological factors which have commonly and reliably been associated with indices of vaccine effectiveness in previous research with non-mRNA vaccines (e.g., Ayling et al., 2018; Marsland et al., 2006; Pedersen et al., 2009) and with COVID-19 infection (Ayling et al., 2022). We report on relationships between perceived stress, anxiety, depressive symptoms, and positive mood measured on the day of initial vaccination and subsequent anti-SARS-CoV-2 spike antibody responses after completing a two-dose course of BNT162b2 mRNA SARS-CoV-2 vaccines (Comirnaty®, Pfizer, Inc., and BioNTech). In our analyses we examine these relationships controlling for a range of demographic and clinical factors including age, gender, immunosuppressive medication use, and pre-vaccine antibody levels resulting from prior exposure.

2. Methods and Materials

2.1. Study Design & participants

A longitudinal prospective observational cohort study of potential correlates of antibody responses to SARS-CoV-2 vaccination was conducted in May 2021. This corresponded to a period when mass vaccination of individuals regarded as being at greater risk of COVID-19 infection as a result of their occupation (e.g., those working in healthcare) or having health conditions that increased their COVID-19 risk ('clinically vulnerable') had been underway for several months in the UK, and the vaccines were being made available to all those aged > 40 years. During the recruitment period, however, eligibility rules for the vaccines changed rapidly, making the vaccines available to increasingly younger adults, such that by the end of recruitment all those aged > 30 years were eligible. Exclusion criteria for the study were minimal to maximise the diversity of the sample. Thus, exclusion was limited to individuals for whom the collection of blood samples was contraindicated; deemed too physically frail by healthcare staff to participate or had insufficient command of English or a cognitive condition which would prohibit engagement with surveys and/or ability to provide informed consent.

Ethical and research governance approvals were obtained prior to study commencement (REC ID: 21/NW/0048, IRAS ID: 295272).

Three hundred and eighty-nine participants, due to receive a mRNA SARS-CoV-2 vaccination course as part of usual care, were opportunistically recruited into the study from individuals attending for appointments at a mass vaccination centre in the East Midlands, UK. We excluded 30 participants (8 %) who consented but did not complete the baseline questionnaire which assessed psychological and demographic factors, 134 (34 %) participants who did not provide a follow-up blood sample for analysis at 4 weeks post-vaccination course, and 41 (11 %) participants for whom either baseline or 4-week post-vaccination course antibody levels were not calculable (i.e., when analysed they fell outside the reliable detection range of the immunoassay). Thus, a total of 184 participants are the focus of these analyses. Table 1 shows the characteristics of both those for whom post-vaccination antibody level data were available and those whom it was not. There were no statistically significant differences between these two groups in pre-vaccination SARS-CoV-2 spike or nucleocapsid antibody levels, demographic, clinical, or any psychological variables measured.

2.2. Procedure

Fig. 1 provides on overview of the study. In brief, participants gave consent and entered the study prior to receipt of their first SARS-CoV-2 vaccine dose and had a fingerprick blood sample taken for the assessment of pre-vaccination antibodies. Following skin puncture with a disposable lancet, samples were collected using a 10 μ L Mitra stick volumetric absorptive microsampling device (Neoteryx), allowing the sample to dry onto the device. Participants were instructed on how to take future fingerprick blood samples themselves at home using the same method. Participants then received a standard dose SARS-CoV-2 mRNA vaccine BNT162b2 (Comirnaty®, Pfizer, Inc., and BioNTech) administered by clinic staff.

Participant questionnaires (see Measures) were completed via an online survey platform immediately *following* receipt of this first vaccine dose while in the post-vaccination waiting zone. At this time, it was policy that individuals should wait on site for at least 15 min post-vaccination in case of complications. Participants could access the questionnaires on their personal devices or where required on a tablet device provided by the research team. While this is not truly a baseline questionnaire, in that it was completed by participants a few minutes following, rather than prior to, their first vaccine administration for ease of understanding we will refer to this as a baseline questionnaire hereafter. Details were also collected as to where and when the participant had an appointment for their second SARS-CoV-2 vaccine dose.

At the time of the second vaccine dose, participants were provided with a home blood sampling fingerprick kit, instructions for its use and were requested to collect their blood sample 4 weeks after the date of this second vaccine. In the event that second doses were administered when a researcher could not be present, the blood sampling kit was sent by post. All participants received a text reminder at 4 weeks post vaccination to collect their blood sample and to return it via freepost or to a local GP practice.

Table 1
Participant Characteristics by Availability of Post-Vaccination Antibody Data.

	With Post-Vaccination Antibody Data	Without Post-Vaccination Antibody Data	
Gender			
Female	82 (44.3 %)	82 (47.4 %)	
Male	99 (53.5 %)	91 (52.6 %)	
Prefer not to say	1 (0.5 %)	0 (0 %)	
Prefer to self-describe	3 (1.6 %)	0 (0 %)	χ^2 (3) = 3.99, p = 0.268
Age			
Mean (SD)	36.4 (2.72)	35.9 (3.28)	*t (335.02)* = 1.57, p = 0.118
Median [Min, Max]	36.3 [27.2, 47.6]	35.6 [20.8, 53.2]	
Ethnicity			
Asian/Asian British	7 (3.8 %)	12 (6.9 %)	
Black/Black British	1 (0.5 %)	1 (0.6 %)	
Chinese/Chinese British	5 (2.7 %)	1 (0.6 %)	
Middle Eastern	0 (0 %)	2 (1.2 %)	
Mixed Race	1 (0.5 %)	6 (3.5 %)	
Other ethnic group	2 (1.1 %)	4 (2.3 %)	
Prefer to self-describe	0 (0 %)	1 (0.6 %)	
White/White British	169 (91.4 %)	146 (84.4 %)	χ^2 (7) = 12.51, p = 0.085
Taking Immunosuppressive Medication			
No	183 (98.9 %)	170 (98.3 %)	
Unsure	1 (0.5 %)	2 (1.2 %)	
Yes	1 (0.5 %)	1 (0.6 %)	χ^2 (2) = 0.41, p = 0.814
Smoker	23 (12.4 %)	22 (12.7 %)	
Alcohol Intake[†]			
Mean (SD)	2.30 (1.47)	2.41 (1.61)	H = 0.44, p = 0.507
Median [Min, Max]	2.00 [0, 5]	3.00 [0, 7]	
Self-reported General Health[‡]			
Mean (SD)	3.97 (0.76)	3.8 (0.90)	H = 2.45, p = 0.118
Median [Min, Max]	4.00 (The WHO European Respiratory Surveillance Network, 2024; Krüttgen et al., 2022)	4 (The WHO European Respiratory Surveillance Network, 2024; Krüttgen et al., 2022)	
Physical Health Comorbidity	24 (13.0 %)	24 (13.9 %)	χ^2 (1) = 0.01, p = 0.925
Depressive Symptoms (PHQ-9)			
Mean (SD)	4.67 (4.22)	5.53 (4.74)	H = 2.69, p = 0.101
Minimal (0–4)	110 (59.5 %)	87 (50.3 %)	
Mild (5–9)	52 (28.1 %)	58 (33.5 %)	
Moderate (10–14)	18 (9.7 %)	16 (9.2 %)	
Moderately Severe (15–19)	2 (1.1 %)	11 (6.4 %)	
Severe (≥20)	3 (1.6 %)	1 (0.6 %)	
Anxiety (GAD-7)			
Mean (SD)	4.17 (4.29)	4.95 (4.58)	H = 3.24, p = 0.072
Minimal (0–4)	117 (63.2 %)	100 (57.8 %)	
Mild (5–9)	49 (26.5 %)	46 (26.6 %)	
Moderate (10–14)	12 (6.5 %)	18 (10.4 %)	
Severe (≥15)	7 (3.8 %)	9 (5.2 %)	
Perceived Stress (PSS-4)			
Mean (SD)	5.51 (3.36)	5.21 (2.95)	H = 0.25, p = 0.615
Positive Mood (SPANE-P)			
Mean (SD)	21.3 (4.90)	21.6 (4.87)	*t (354.67)* = -0.46, p = 0.645

[†] Derived from summing the first two items of the **Alcohol Use Disorder identification test,** higher scores indicate greater intake.
[‡] Participants rated their general health as Poor (1), Fair (2), Good (3), Very Good (4) or Excellent (5).

2.3. Measures

2.3.1. Baseline questionnaire

Participants completed a range of validated measures as well as several individual items relating to demographics (e.g., age, gender) and clinical factors (e.g., if on any immuno-suppressive medications) as part of the baseline questionnaire. With regards psychological factors, depressive symptoms were measured via Patient Health Questionnaire (PHQ-9, α = 0.83) (Kroenke et al., 2001), anxiety was measured via the General Anxiety Disorder Scale (GAD-7, α = 0.89) (Spitzer et al., 2006), stress was measured using the Perceived Stress Scale (PSS-4, α = 0.67) (Cohen et al., 1983), and positive mood was measured via the positive sub-scale of the Scale for Positive and Negative Experience (SPANE-P, α = 0.94) (Jovanović, 2015). While a range of validated measures exist for these psychological factors, these specific measures were selected either because they have been frequently deployed in prior research exploring psychological correlates of immune response, are particularly brief while remaining reliable, or in the case of PHQ-9 and GAD-7, are commonly used as a screening tool in UK primary care. We opted to not include the negative sub-scale of the SPANE instrument due to anticipated collinearity with the PHQ-9 and seeking to minimise participant burden. All questionnaires instructed participants to respond in relation to their experiences over the previous two weeks. The online survey platform was set-up such that psychological scales required a response to all items to progress, as such there was no potential for missing data.

2.3.2. Anti-SARS-CoV-2 antibodies

SARS-CoV-2 specific antibodies were assessed in dried blood samples (DBS). This approach has previously been validated and found to have very high levels of comparability to traditional serum sampling (Morley et al., 2020). We assessed both Anti-SARS-CoV-2 spike and nucleocapsid specific antibodies in all samples. While COVID-19 infections would be expected to lead to rises in both protein and nucleocapsid antibodies specific to the virus, the BNT162b2 mRNA COVID-19 vaccine is based on the SARS-CoV-2 spike protein specifically (Polack et al., 2020), and thus vaccination alone would not be expected to induce large increases in nucleocapsid-specific antibodies. Dried blood samples were eluted in 150 μL PBS 25 % Tritron-X100, with two hours of shaking at 400 rpm at room temperature (RT). Anti-SARS-CoV-2 spike protein and nucleocapsid specific antibodies were measured via ELISA performed using Opentrons OT-2 liquid handling robots for reagent and/or sample additions at each step. All samples were run in duplicate (intra-assay coefficients of variation: Spike = 5.98 %, Nucleocapsid = 6.19 %). Separate Maxisorp (NUNC) 384-well assay plates were coated with either 20 μL per well of 1μgmL-1 of Wuhan strain SARS-CoV-2 full length spike protein (His tagged, CHO expressed, native antigen company) or Wuhan strain SARS-CoV-2 nucleocapsid protein (His tagged, Baculovirus expressed, Sino Biological, Stratech UK) respectively, in carbonate-bicarbonate buffer (CBC; Merck). Plates were sealed and incubated overnight at 4 °C. Plates then underwent a three-cycle wash in an automated plate washer (Biochrom ASYS Atlantis) with Phosphate-Buffered Saline with 0.05 % Tween 20 (PBS-T) before being filled

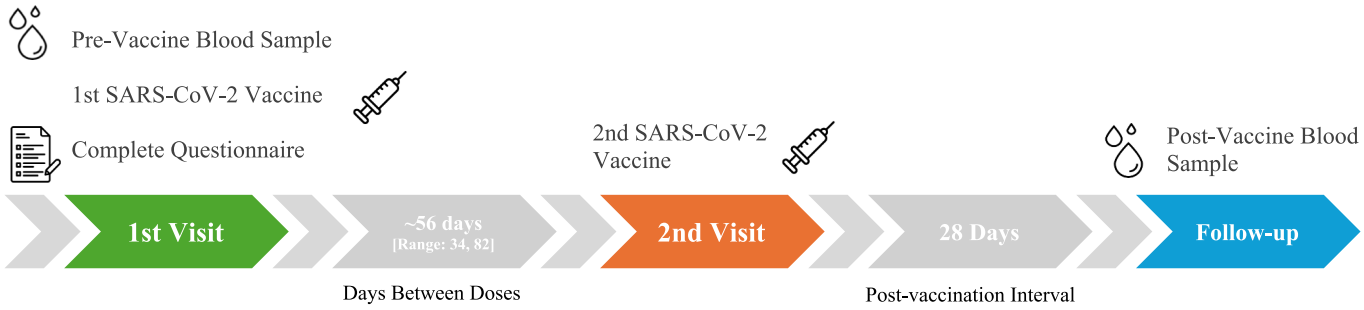

Fig. 1. Study Procedure.

with 100 μL of blocking solution (3 % whey powder in PBS containing 0.05 % Tween 20, 0.05 % sodium azide, and 0.01 % EDTA) and left overnight at 4 °C. Plates were then washed 3 times with PBS with 0.05 % Tween 20 (PBS-T) using a Biochrom ASYS Atlantis plate washing robot with a 16-channel manifold. Wells were immediately filled with 100 μL of blocking solution, containing 3 % whey powder (w/v) in PBS containing 0.05 % Tween 20, 0.05 % sodium azide, and 0.01 % EDTA and blocked overnight at 4 °C. Plates were washed a further 3 times and 20 μL of diluted sample added in duplicate wells, alongside a 12-point standard curve of SARS-CoV-2 antibody positive control sample, and a negative control sample (National Institute of Biological Standards and Controls, UK). After incubating for one hour at RT, the plate went through the same washing process before 20 μL of gamma chain-specific anti-human IgG HRP conjugate (Sigma, A0170) at a 1:30,000 dilution in PBS was added to all wells. This was incubated for 30 min at RT. Plates were then washed again, with 40 μL One-step Ultra-3,3′,5,5′-tetramethylbenzidine (TMB) substrate solution (Thermo Fisher Scientific) then added to each well. After incubating for 20 min at RT, 40 μL of stop solution (2 N H2SO4) was added and absorbance read at 450 and 600 nm using an EPOCH microplate reader (BioTek, UK). Data were presented as a conversion of delta optical density values (450 nm-600 nm) into BAU (binding antibody units) by interpolating against the SARS-CoV-2 antibody positive control standard curve (National Institute of Biological Standards and Controls, UK, Ref: 20/162).

2.4. Statistical analyses

All analyses were completed using R (version 4.3.2) via RStudio (version 2024.09.0 + 375). Differences between participants with and without post-vaccination antibody data were examined using independent sample t-tests (or non-parametric equivalent) and chi-squared tests as appropriate. Spike and nucleocapsid antibody levels were $\log_2$ transformed to improve distribution normality. To examine responses to vaccination, paired t-tests were used to compare baseline and 4 week post-second vaccine dose anti-SARS-CoV-2 spike and nucleocapsid antibody levels. To assess relationships between pre-vaccination anti-SARS-CoV-2 spike and nucleocapsid antibody levels and baseline psychological factors we conducted bivariate correlational analyses. To assess relationships between anti-SARS-CoV-2 spike antibody responses following vaccination and baseline psychological factors, first we conducted bivariate correlational analyses followed by a series of linear regression models predicting anti-SARS-CoV-2 spike antibodies at 4 weeks post-second vaccination. Age, gender (male/female/self-described), number of days between vaccine doses, and whether that participant self-reported being on immunosuppressive medications (yes/no/unsure) were entered alongside anti-SARS-CoV-2 spike and nucleocapsid antibody levels as measured at baseline and each psychological factor individually (depressive symptoms, anxiety, perceived stress, positive mood). Those psychological factors which were statistically significant in individual models were added together in a final combined model to assess if they were independently significant predictors.

As there was some evidence of non-normality of residuals in regression models, we conducted sensitivity analyses using robust regression (R Package: MASS) – examination of these results did not show any substantive differences in estimated coefficients and thus are not reported here. We also conducted further sensitivity analyses including other participant reported health-related covariates including current smoking status, alcohol intake, self-reported general health, and physical health co-morbidity status in the models (for full details see supplementary appendix).

3. Results

3.1. Responses to vaccination

Pre- and post-vaccination antibody levels are shown in Table 2. There was a significant increase in $\log_2$-transformed anti-SARS-CoV-2 spike antibody levels from baseline to 4 weeks post-second vaccination ($t(183)$ = -59.92, $p < 0.001$, d = -6.34 [95 % CI: −6.55, −6.13]). There was no significant change in anti-SARS-CoV-2 nucleocapsid antibody levels following vaccination ($t(183) = 1.12$, $p = 0.26$, d = 0.10 [95 % CI: −0.07, 0.26]). This is consistent with these effects being due to vaccination rather than natural infection, given the BNT162b2 mRNA SARS-CoV-2 vaccine was developed to induce antibody responses against the full-length spike protein of SARS-CoV-2 specifically (Polack et al., 2020).

3.2. Relationships between psychological factors and anti-SARS-CoV-2 antibody levels pre-vaccination

Bivariate correlations indicated no statistically significant relationships between pre-vaccination anti-SARS-CoV-2 spike or nucleocapsid antibody levels and psychological factors [depressive symptoms: spike (rho = 0.02 [95 % CI: −0.08, 0.13], $p = 0.66$), nucleocapsid (rho = 0.03 [95 % CI: −0.08, 0.13], $p = 0.61$); anxiety: spike (rho = − 0.005 [95 % CI: −0.11, 0.10], $p = 0.93$), nucleocapsid (rho = 0.01 [95 % CI: −0.09, −0.12], $p = 0.80$); stress: spike (rho = 0.03 [95 % CI: −0.07, 0.14], $p = 0.51$), nucleocapsid (rho = 0.02 [95 % CI: −0.09, 0.12], $p = 0.74$); positive mood: spike ($r = 0.08$ [95 % CI: −0.03, 0.18], $p = 0.14$), nucleocapsid ($r = 0.01$ [95 % CI: −0.10, 0.11], $p = 0.89$).

Table 2
Log-2 Transformed Antibody Levels (Binding Antibody Units) Pre- and 4 weeks Post-Vaccination Course – Mean (SD).

	Pre-Vaccination	Post-Vaccination
Anti-Spike SARS-CoV-2 Antibodies	2.57 (1.16)	8.91 (0.96)
Anti-Nucleocapsid SARS-CoV-2 Antibodies	4.18 (0.93)	4.08 (0.99)

Note: Values based on n = 184 with both pre- and post-vaccination antibody data.

3.3. Relationships between psychological factors and anti-SARS-CoV-2 spike responses to vaccination

At 4 weeks post-second vaccination, bivariate correlations indicated statistically significant relationships between anti-SARS-CoV-2 spike antibody levels with depressive symptoms (rho = − 0.17 [95 % CI: −0.31, −0.03], $p = 0.024$), but not anxiety (rho = − 0.11 [95 % CI: −0.25, 0.04], $p = 0.144$), perceived stress (rho = − 0.10 [95 % CI: −0.25, 0.05], $p = 0.175$), or positive mood ($r = 0.14$ [95 % CI: −0.001, 0.28] ; $p = 0.051$). Individual linear regression models (see Table 3) showed that both greater depressive symptoms ($p = 0.041$, partial $f^2 = 0.009$) and lower positive mood ($p = 0.036$, partial $f^2 = 0.011$) were statistically significant predictors of lower anti-SARS-CoV-2 spike antibody levels at 4 weeks post-second vaccination in models also controlling for age, gender, days between vaccine doses, self-reported immunosuppressive medication use and baseline spike and nucleocapsid antibodies. Anxiety and perceived stress did not significantly predict anti-SARS-CoV-2 spike antibody response to vaccination in these models. In a combined regression model, depressive symptoms and positive mood were no-longer independent significant predictors, likely explained by multicollinearity between these two measures (r = -0.71, 95 % CI [-0.77, −0.63], $p < 0.001$).

3.3.1. Sensitivity analyses

We conducted sensitivity analyses adding additional health-related variables (smoking, alcohol intake, self-reported health and presence of physical co-morbidities) in all models. For full details see the supplementary appendix. None of these health-related variables were found to independently predict antibody responses, with the overall models including these factors all becoming statistically non-significant due to poorer fit to the data. Findings in relation to psychological factors remained robust, however, with depressive symptoms and positive mood remaining statistically significant predictors of anti-SARS-CoV-2 antibody responses within their individual models.

4. Discussion

This study is, to our knowledge, the first prospective examination of psychological correlates of antibody responses to mRNA SARS-CoV-2 vaccination. We observed that higher depressive symptoms and lower positive mood pre-vaccination were associated with weaker antibody responses 4 weeks following two doses of mRNA SARS-CoV-2 vaccine. These effects were not independent of each other, given the overlap between depressive symptoms and low mood, but were separately independent of several established demographic and clinical predictors of antibody responses. We found no evidence to support either anxiety or perceived stress as measured at the point of first vaccination as correlates of antibody responses to mRNA SARS-CoV-2 vaccination in this cohort.

Our findings in relation to depressive symptoms and positive mood are consistent with the limited data reported to date in relation to psychological correlates of SARS-CoV-2 vaccine responses (e.g., Gallagher et al., 2022; Kaneko and Tsuboi, 2023; Pearce et al., 2023)) and the larger literature in relation to these factors as correlates of non-mRNA vaccine responses (Ayling et al., 2018; Marsland et al., 2006; Afsar et al., 2009; Irwin et al., 2013). While the effect sizes observed were small and the proportion of variance in post-vaccination antibody levels explained by the models was modest, this is consistent with comparable non-mRNA vaccine studies (e.g., Ayling et al., 2018). It is also important to highlight that these relationships were observed in an mRNA SARS-CoV-2 vaccine that proved considerably more immunogenic than non-mRNA vaccines developed at the same time (Naranbhai et al., 2021); in a cohort predominately made up of young to middle aged adults (mean age 36 years) who described themselves as healthy (>75 % rated their general health as ‘very good’ or ‘excellent’) and in whom both mRNA and non-mRNA vaccine immunogenicity could be expected to be optimal (Goodwin et al., 2006; Wang et al., 2021). This is arguably the most stringent conditions in which the effects of psychological factors may be observed. Indeed, in non-mRNA vaccines, psychological factors have repeatedly been shown to have larger associations with antibody responses in less immunogenic vaccines and in those in whom responses are least robust (e.g., older adults, Pedersen et al., 2009). While it is yet to be determined whether small effects in this context could potentially be of clinical relevance, further research is warranted to see if effect sizes are larger in populations where immunogenicity is low.

Mechanistically, the relationships underlying psychological factors and antibody responses to vaccination are likely to be complex – comprising both indirect effects mediated through health behaviours (Clayborne and Colman, 2019; Grant et al., 2009) and more direct and bidirectional interactions between the immune and the central nervous systems (Madison et al., 2021; Pressman et al., 2019). Indeed, experimental studies have demonstrated both depression and positive mood act as potent immune modulators influencing many aspects of the immune cascade that lead to antibody formation following immune challenge (Ayling et al., 2020; Zorrilla et al., 2001). In non-mRNA vaccines, researchers have begun to examine the potential utility of psychological

Table 3
Linear Regression Models Predicting Post-Vaccination Anti-SARS-CoV-2 Spike Antibody Levels (log_2 transformed).

	Depressive Symptoms Model	Anxiety Model	Stress Model	Positive Mood Model	Combined model
(Intercept)	**6.204*****	**6.151*****	**6.039*****	**5.300*****	**5.694*****
Age	0.030	0.029	0.034	0.033	0.031
Gender					
Male vs Female	−0.018	−0.063	−0.043	−0.003	−0.008
Prefer to self-describe vs Female	0.130	0.064	0.070	0.083	0.110
Days between Doses	0.015	0.016	0.014	0.015	0.015
Immunosuppressive Medications					
Unsure vs No	−0.799	−0.745	−0.857	−0.826	−0.821
Yes vs No	0.375	0.396	0.358	0.344	0.350
Baseline Spike Antibodies	−0.032	−0.032	−0.020	−0.030	−0.033
Baseline Nucleocapsid Antibodies	**0.241***	**0.241***	**0.235***	**0.236***	**0.241***
Depressive Symptoms	**−0.034***				−0.019
Anxiety		−0.027			
Stress			−0.035		
Positive Mood				**0.031** *	0.019
R^2	0.093	0.084	0.085	0.094	0.097
Adj. R^2	0.045	0.036	0.037	0.046	0.044
F	1.94	1.75	1.76	1.97	1.83
p	**0.049***	0.082	0.079	**0.046***	0.059

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.
Values are unstandardised coefficients (*b*).

interventions for enhancing vaccination responses, with early evidence suggesting promise (Vedhara et al., 2019). Future research is needed to explore whether such approaches may be of benefit in the context of mRNA vaccines – noting there may be differences to be elucidated given mechanistic distinctions in how mRNA and non-mRNA vaccines induce antibody formation.

In summary, the present study is the first, to our knowledge, to involve a prospective examination of the effects of a range of psychological factors on the antibody response to mRNA SARS-CoV-2 vaccinations. Strengths of our approach include that we controlled for prior infection exposure via baseline assessments of spike and nucleocapsid anti-SARS-CoV-2 antibodies as well as including several demographic and clinical factors in our models and sensitivity analyses. We acknowledge several limitations. We observed high levels of dropout across the study which limits the statistical power of our analyses and prevented us from conducting more robust sub-group modelling (e.g., by age groups or gender). However, we did not observe statistically significant differences between those who remained in the study and those who dropped out (see Table 1). We also note that the self-selected nature of our recruitment and the time-limited sampling approach for this cohort study limits, to some extent, the confidence we can have in extrapolating our findings to a wider general population. While we controlled for pre-vaccination antibody levels as well as some demographic and health-related covariates in our analyses, there remain numerous participant characteristics that we were unable to assess for reasons of practicality and burden. For example, body mass index has previously been associated with both antibody responses following vaccination and psychological factors (Jaison et al., 2024; Ou et al., 2023). Finally, we note that IgG antibody levels, while a well-established correlate of clinical protection post-vaccination, are not the only outcome relevant to protection following vaccination. Indeed, in both mRNA and non-mRNA vaccines alike there is a need for additional research on the relationships between psychological factors and cell-mediated immunity following vaccination (Verschoor et al., 2021). Despite these limitations, this research provides evidence that positive mood and depressive symptoms are associated with the potency of the antibody response to mRNA SARS CoV-2 vaccines, even among adults younger and ostensibly more healthy than the populations in whom impaired responses to vaccination are usually observed.

CRediT authorship contribution statement

Kieran Ayling: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hannah Jackson:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Ru Jia:** Writing – review & editing, Investigation, Data curation. **Simon Royal:** Writing – review & editing, Resources, Investigation. **Lucy Fairclough:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Kavita Vedhara:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The present study had no dedicated funding source and was supported by the goodwill and unused consumables of co-authors purchased as part of other related research projects during the COVID-19 pandemic. As such no specific funder played any role in the design, collection, analysis or interpretation of data in this study. KA, LF, and KV conceived and designed the study. KA led the in-person data collection, supported by RJ and SR, and conducted overall data analysis. HJ conducted all antibody assays and subsequent antibody data processing overseen by LF. KA drafted the first version of the manuscript which was then reviewed and revised by all authors. All authors had full access to all the data in the study and agreed to submit for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.03.011.

Data availability

Data will be made available on request.

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