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Short Communication

Depressive symptoms predict antibody titers after a second dose of the SARS-CoV-2 BNT162b2 vaccine among hospital workers in Japan

Hiroshi Kaneko [a], Hirohito Tsuboi [b,*]

[a] Division of Internal Medicine & Psychosomatic Internal Medicine, Hoshigaoka Maternity Hospital, Nagoya 464-0026, Japan
[b] Graduate School of Human Nursing, The University of Shiga Prefecture, 2500 Hassaka-cho, Hikone 522-8533, Japan

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ABSTRACT

Background: Although factors associated with the antibody response to the BNT162b2 mRNA COVID-19 vaccine have been reported, psychological factors have not been examined. Depression or anxiety may affect vaccine reactions because these factors influence immune responses. This study aimed to determine whether psychological status at the time of vaccination predicts antibody responses.

Methods: A prospective observational study of the BNT162b2 mRNA COVID-19 vaccine response was carried out among individuals attending for an annual health check-up. Participants included 78 volunteers out of 80 hospital workers in Nagoya, Japan. No participants had been infected with COVID-19 and all gave written informed consent to participate in the study. Blood samples were obtained approximately 28 days after the second dose of the vaccine, and antibody titers of the SARS-CoV-2 spike protein were determined using the SARS-CoV-2 IgG II Quant assay. Participants completed the Japanese version of the hospital anxiety and depression scale (HADS) questionnaire, one day before both vaccinations. Participants also recorded any adverse reactions, such as body temperature and other side effects, every day for two weeks after each dose. The relationships between antibody titers and the predictive factors were analyzed using multiple linear regression analysis, with the antibody titers as the dependent variables, followed by univariate analysis.

Results: Multiple linear regression analysis revealed that no or excessive alcohol intake ($p = 0.039$), poor results from a health check-up ($p = 0.011$), a longer duration between the second dose and blood collection ($p = 0.039$), and increased degree of depressive symptoms ($p = 0.041$) were significant negative predictors of antibody titers, while body temperature one day after the second dose as a significant positive predictor of antibody titers ($p < 0.0005$).

Conclusion: We identified that depressive symptoms just before the second dose of the BNT162b2 mRNA COVID-19 were an independent negative predictor of antibody responses, in addition to other factors. Our results highlight the importance of mental health at the time of vaccination to achieve the higher antibody responses necessary to acquire humoral immunity.

1. Introduction

The BNT162b2 mRNA vaccine against coronavirus disease 2019 (COVID-19) has shown promising efficacy in both a clinical trial (Polack et al., 2020) and nationwide mass vaccination settings (Dagan et al., 2021). Several factors, including age, duration from the second dose to sample collection, immunosuppressants, and alcohol consumption, can predict antibody titers following vaccination (Kageyama et al., 2021). Psychological factors have been shown to be related to antibody responses following influenza vaccination (Moynihan et al., 2004; Vedhara et al., 1999). Therefore, psychological factors may also affect the cellular immune responses to the BNT162b1 mRNA COID-19 vaccine (Sahin et al., 2020). Whether psychological factors modify humoral responses to COVID-19 vaccination remains unknown. Anxiety and depression are typical mental health conditions that may affect humoral immunity (Phillips et al., 2008). Thus, we hypothesized that anxiety and depression affect antibody response after COVID-19 vaccination.

The present research surveyed factors that predicted IgG antibody titers to the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein after two doses of mRNA vaccine, focusing on

* Corresponding author.
E-mail addresses: hkaneko@fujita-hu.ac.jp (H. Kaneko), tohtori17@gmail.com (H. Tsuboi).

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depression and anxiety among hospital workers.

2. Participants and methods

A prospective observational study was performed with volunteer workers in Hoshigaoka Maternity Hospital in Nagoya, Japan. The study protocol was approved by the Ethical Committee at Hoshigaoka Maternity Hospital (receipt number 2021–19).

Basic data and blood samples were collected from workers in April 2021 at their annual health check-up. The procedures are summarized in Fig. 1. A self-administered questionnaire about health and lifestyle factors was distributed to the participants and was completed prior to their health check-up. On the day or one day before both the first and second doses of vaccine, the Japanese version of the hospital anxiety and depression scale (HADS) questionnaire was completed by participants (Higashi et al., 1996; Zigmond and Snaith, 1983). Participants recorded their health status every day for two weeks following each dose, including their body temperature and any other side effects. Approximately 28 days (mean 28.5 days (S.D. 3.79), range 21–40 days) after the second dose, blood samples were collected to assess the levels of COVID-19 S-protein IgG.

Among 91 participants who completed the health examination, eleven individuals who rejected the vaccination, one who rejected antibody titer tests, and one who could have been infected with COVID-19 were excluded from the analysis. Consequently, 78 participants were included in the analysis (Fig. 1). The sample consisted of 11 men and 67 women, with mean ages of 51.7 years (S.D. 16.44) and 41.4 years (11.58), respectively (Table 1).

Table 1
Characteristics of participants and correlation with serum S-protein IgG levels after the second dose of vaccine.

Variable	N (men)	Mean (S.D.)	Range
Age (years)*	78 (11)	42.9 (12.77)	22 – 73
BMI (kg/m^2)	73 (10)	22.2 (3.54)	14.7 – 35.4
Duration from second dose to blood sampling (days) *	76 (9)	28.5 (3.79)	21 – 40
Temperature one day after the second dose *	76 (11)	37.0 (0.77)	35.2 – 38.8
Anxiety (at first dose) †	76 (9)	4.7 (2.94)	1 – 18
Depression (at first dose)	76 (9)	4.3 (2.88)	0 – 12
Anxiety (at second dose)	78 (11)	4.1 (2.89)	0 – 19
Depression (at second dose) †	78 (11)	4.9 (3.45)	0 – 13

Simple correlations between serum S–protein IgG levels after the second dose and continuous variables were calculated.
* $p < 0.05$.
† $p < 0.01$.

Participants received two doses (0.3 mL each), intramuscularly, of the BNT162b2 mRNA COVID-19 vaccine (Comirnaty®, Pfizer, Inc., and BioNTech). Blood samples were immediately transferred to the laboratory (FALCO, Nagoya, Japan), where antibody titers (including IgG) to the SARS-CoV-2 S-protein were determined using the SARS-CoV-2 IgG II Quant assay (Abbott Laboratories) (Eliakim-Raz et al., 2021). Seropositivity was defined as ≥ 50 arbitrary units (AU)/mL. As three participants showed > 50 AU/mL S-protein in the health check-up, we also

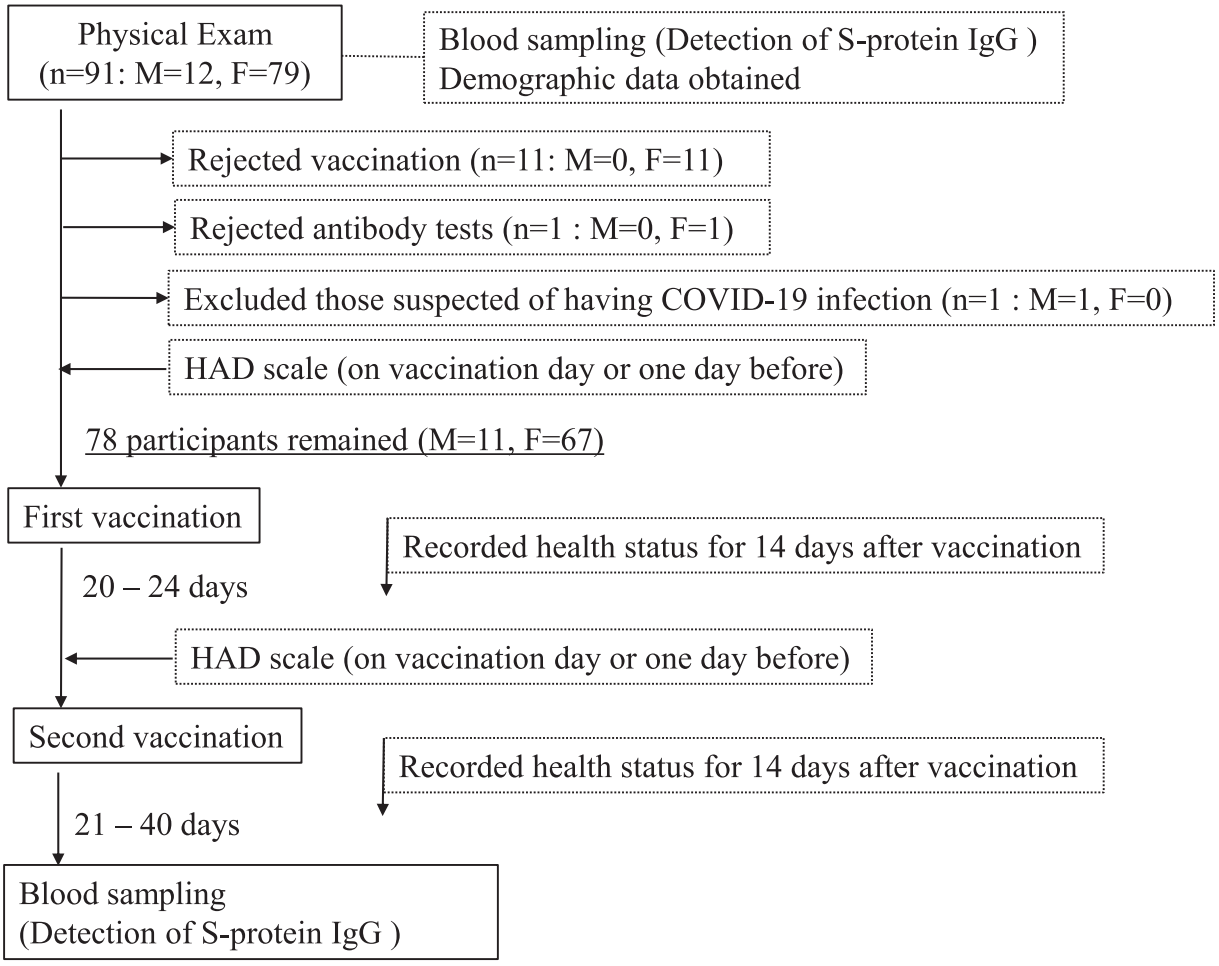

Fig. 1. A flowchart of procedures used during the present study. HAD: hospital anxiety and depression.

examined these participants' antibodies against *N*-protein (including IgG and IgM) to infer previous infection with SARS-CoV-2 (Fenwick et al., 2021). One indicated IgG(+)/IgM(–), whereas the other two showed IgG(–)/IgM(–), suggesting that the former had previously been infected with COVID-19.

The Japanese version of the IBM SPSS Statistics software package, version 26 (IBM Japan, Tokyo, Japan) was utilized for data analysis. In simple comparisons of the S-antibody titers, Pearson's correlation coefficients, the *t*-test, and analysis of variance (ANOVA) were used. Subsequently, multiple linear regression analysis was performed to identify factors associated with the S-antibody titer. Statistically significance was accepted as $p < 0.05$.

3. Results

Of the 78 participants, 7 individuals had diseases that could have affected immune reactions: ulcerative colitis (n = 1), rheumatoid arthritis (n = 1), hypothyroidism (n = 2), goiter (n = 2), and Graves' disease (n = 1). After two vaccine doses, there were no significant differences in S-antibody titers between these seven participants and the others (*t*-test: $t = 0.65$, $p = 0.52$). The mean ± S.D. of serum S-protein IgG levels following the second dose of vaccine was $12.2 \pm 7.44 \times 10^3$ AU/mL (range: 1.02–37.91). The S-antibody titers of the participants exhibited the standard curve (the Shapiro-Wilk test for normal distribution: $p < 0.0005$). Participants' characteristics are shown in Tables 1 and 2.

First, we investigated factors related to S-antibody titers following the second dose, using univariate analysis. Concerning socioeconomic status, there were no differences among occupations (ANOVA: $F(14,59) = 0.76$, $p = 0.704$) (Table 2), even though various combinations of job types were considered (data not shown). Factors significantly related to S-antibody titers included age, the duration from the second dose to blood sampling, body temperature several days after the second dose, and alcohol intake (correlation: $r = -0.24$, $p = 0.038$; $r = -0.31$, $p = 0.006$; $r = 0.46$, $p < 0.0005$; ANOVA: $F(4, 67) = 2.65$, $p = 0.041$, respectively) (Tables 1 and 2). Body temperature one day after the second dose was the factor most strongly associated with the antibody titers (Data in Brief). Anxiety at the time of the first dose and depression at the time of the second dose appeared to be associated with S-antibody titers after the second dose (correlation: $r = -0.23$, $p = 0.053$; $r = -0.21$, $p = 0.073$, respectively) (Table 1). No other factors showed any significant relationships or differences.

Next, multiple linear regression analysis was performed to predict anti-SARS-CoV-2 antibody titers following the second dose, with categorical data divided into dichotomous variables at appropriate points. Independent variables included age, sex, body mass index (BMI), alcohol consumption (sometimes vs others), health check-up results (healthy or observation or re-examination recommended vs treatment required or under treatment), days between the second dose and blood sampling, temperature one day after the second dose, and degree of depression at the second dose. Consequently, no or excessive alcohol intake, a longer period from the second dose to blood sampling, and psychological degrees of depression were found to be significantly negatively corelated with antibody titers, whereas body temperature one day after the second dose was significantly positively corelated with the antibody titers (Fig. 2).

4. Discussion

We investigated factors that affect IgG antibody titers to the SARS-CoV-2 S-protein following two doses of mRNA vaccine among hospital workers in Japan. Depressive symptoms at the time of the second dose predicted reduced IgG antibody titers, as did inappropriate alcohol intake, poor health check-up results, and duration between a second dose and blood sampling. Furthermore, body temperature one day after the second dose was a factor that was strongly associated with higher

Table 2
Characteristics of participants and the differences of serum S-protein IgG levels after the second dose of vaccine.

Variable	Item	N (men)	S-protein IgG (AU/mL) × 10^3	
			Mean (S.D.)	Range
Occupation (n=77)				
	Physician	11 (7)	8.52 ± 5.390	1.02 – 16.73
	Dentist	1 (1)	17.73	
	Pharmacist	4 (0)	17.12 ± 10.21	7.38 – 31.50
	Registered nurse	15 (0)	10.92 ± 4.90	5.07 – 19.90
	Associate nurse	5 (0)	10.97 ± 11.40	1.62 – 27.27
	Midwife	15 (0)	11.81 ± 7.07	3.09 – 26.98
	Dental hygienist	1 (0)	10.13	
	Clinical psychologist	3 (0)	12.00 ± 2.26	10.67 – 14.61
	Aromatherapist	2 (0)	7.44 ± 0.68	6.95 – 7.92
	Childcare worker	1 (0)	5.85	
	Clinical technologist	3 (0)	16.22 ± 8.75	7.91 – 25.34
	Registered dietitian	1 (0)	5.69	
	Dietitian	1 (0)	11.08	
	Cook	4 (2)	14.85 ± 5.31	7.28 – 18.69
	Medical clerk	10 (1)	15.83 ± 11.34	4.41 – 37.91
Results of health check-up (n=73)				
	Healthy	36 (1)	13.10 ± 8.18	3.09 – 37.91
	Observation or reexamination recommended	34 (7)	11.64 ± 6.41	1.02 – 31.50
	Treatment required or under treatment	3 (2)	4.80 ± 2.91	1.88 – 7.69
Diseases that may affect the immune system (n=73)				
	Yes	7 (1)	9.88 ± 6.15	1.62 – 1.64
	No	66 (8)	12.52 ± 7.58	1.02 – 3.79
Smoking (n=74)				
	Do not smoke	70 (10)	12.12 ± 7.20	1.02 – 37.91
	1–9 cigarettes per day	2 (0)	4.08 ± 1.40	3.09 – 5.07
	10–19 cigarettes per day	2 (0)	18.65 ± 12.19	10.03 – 27.27
Alcohol intake (n=74)*				
	Do not drink	24 (2)	10.21 ± 3.71	4.22 – 16.42
	Sometimes	36 (4)	14.60 ± 8.48	1.62 – 37.91
	1–2 times per week	8 (1)	10.85 ± 7.29	5.85 – 27.27
	3–4 times per week	2 (0)	6.74 ± 1.67	5.56 – 7.92
	Almost every day	4 (3)	5.93 ± 7.91	1.02 – 17.73
Breakfast intake (n=71)				
	Daily	52 (5)	11.90 ± 7.31	1.02 – 37.91
	Sometimes	15 (4)	12.80 ± 8.00	1.88 – 27.27

(*continued on next page*)

Table 2 (*continued*)

Variable	Item	N (men)	S-protein IgG (AU/mL) × 10^3	
			Mean (S. D.)	Range
	Do not eat breakfast	4 (0)	13.32 ± 10.04	7.09 – 28.26

AU: arbitrary units.
* $p < 0.05$ (analysis of variance).

antibody titers.

We found that a psychological depressive state one day before the second vaccination predicted lower antibody titers (Fig. 2). To the best of our knowledge, there have been no prior reports of the effects of depression on anti-SARS-CoV-2 antibodies levels. However, some reports have indicated an association between psychological state and humoral immune responses. For example, the IgG response against dairy proteins was suppressed in depressed patients compared with controls (Rudzki et al., 2017). It was suggested that immunosuppression could be caused by reduced B lymphocytes functions, through a high concentration of cortisol or TNFα (Rudzki et al., 2017). In an animal study using a genetic model of depression, serum levels of IgM and IgG_2 responses to inescapable shock after being immunized with the protein antigen keyhole limpet hemocyanin were lower in the depression model rats in comparison to the controls (Friedman et al., 2002). In relation to psychological stress, serum IgG, IgA, and IgM levels of *Helicobacter pylori* among soldiers significantly decreased after military training compared with their pre-training levels (Jia et al., 2016). Stress-induced upregulation of cortisol and catecholamines could lead to impaired immune function, resulting in an increased vulnerability to infection (Jia et al., 2016). Conversely, in a study that assessed a history of cytomegalovirus (CMV) infection, individuals reporting increased symptoms of depression or anxiety exhibited higher IgG antibody titers against CMV (Phillips et al., 2008). The current study investigated depressive symptoms in healthy participants, and their psychological state differed from major depression or psychological stress. However, these previous studies provided insights for interpreting the current study. Also, the study into CMV and IgG investigated the history of CMV infection, not a recent infection; the IgG levels might change over time following infection or immunization.

The intensity of fever as a side effect after the second dose of BNT162b2 significantly predicted the higher IgG titers. This result is consistent with recent reports of studies conducted among hospital healthcare workers (Kanizsai et al., 2022; Tani et al., 2022). A review article suggested that febrile temperatures boosted the effectiveness of the immune response by stimulating both the innate and adaptive arms of the immune system (Evans et al., 2015). Among demographic factors, older age has frequently been reported to be associated with reduced antibody responses following COVID-19 vaccination (Kanizsai et al., 2022; Tani et al., 2022; Terpos et al., 2021). In our study, the effect of age disappeared in the multiple regression analysis (Table 1, Fig. 2), suggesting that there were confounders between antibody responses and age. Health status might be one of the confounders, because health check-up results generally become poorer with age: as a consequence, poor health check-up results might be related to reduced antibody titers (Fig. 2). Sex difference has also been reported to associate with antibody responses (Kageyama et al., 2021; Terpos et al., 2021). Although women appeared to have a greater antibody response to the BNT162b2 vaccine in comparison with men, male population was too small to confirm the sex differences in the present study. Higher alcohol consumption has been generally reported as a negative predictor for antibody responses (Atake et al., 2022; Kageyama et al., 2021). In the current study, antibody responses among individuals who occasionally drank alcohol were significantly stronger compared with those who consumed alcohol more than one time per week and those who never consumed alcohol. In relation to the time between a second dose and the test, antibody titers were reportedly reduced (Kageyama et al., 2021). Our data confirmed the result of this previous study that demonstrated reduced antibody reactivities according to time.

The present study had some limitations. Participants only represented medical and co-medical workers, and a few males were included. Immunosuppressant intake was not assessed because no participants had

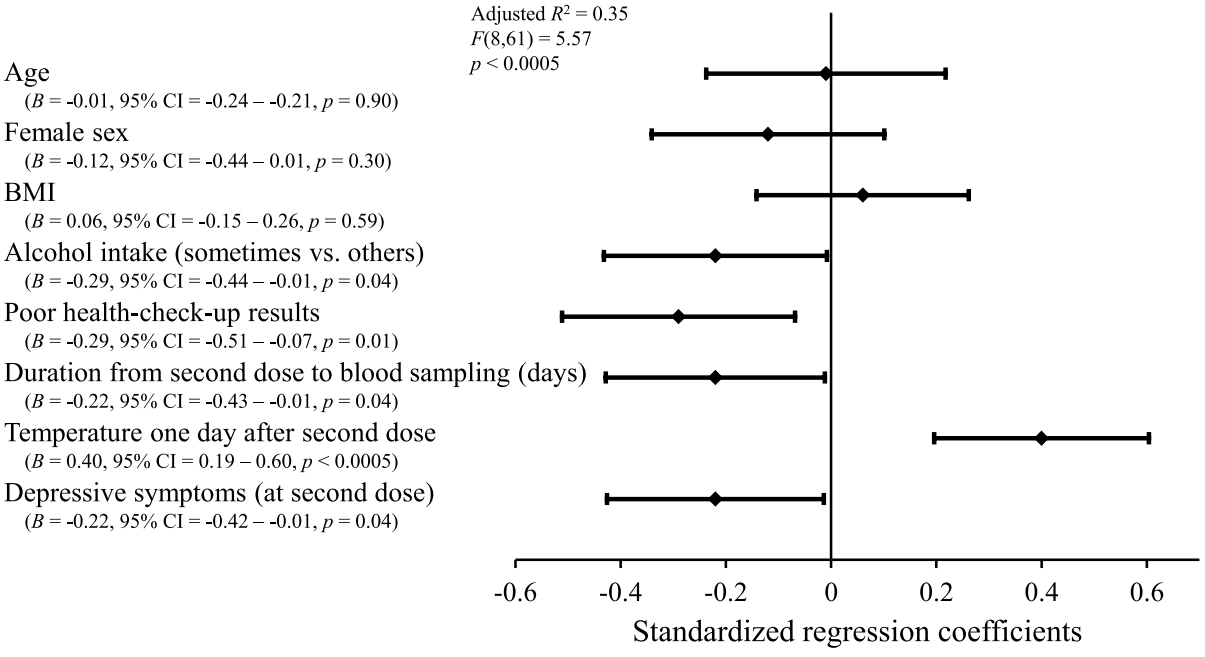

Fig. 2. Forest plot of analyzed by a multivariate linear regression model to predict anti-SARS-CoV-2 antibody titers after the second dose of vaccine. The variables retained in the multivariate model are shown. The dots and bars represent standardized regression coefficients and 95% confidence intervals for each variable, respectively. *B*: standardized regression coefficients, 95% CI: adjusted 95% confidence interval.

diseases that required immunosuppressants to be prescribed.

In conclusion, we found that a greater degree of depressive symptoms before the second dose of the COVID-19 mRNA vaccine was linked with reduced IgG antibody titers to the SARS-CoV-2 S-protein.

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.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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