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RESEARCH ARTICLE

The relationship between mental health, sleep quality and the immunogenicity of COVID-19 vaccinations

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Summary

Sleep modulates the immune response, and sleep loss can reduce vaccine immunogenicity; vice versa, immune responses impact sleep. We aimed to investigate the influence of mental health and sleep quality on the immunogenicity of COVID-19 vaccinations and, conversely, of COVID-19 vaccinations on sleep quality. The prospective CoVacSer study monitored mental health, sleep quality and Anti-SARS-CoV-2-Spike IgG titres in a cohort of 1082 healthcare workers from 29 September 2021 to 19 December 2022. Questionnaires and blood samples were collected before, 14 days, and 3 months after the third COVID-19 vaccination, as well as in 154 participants before and 14 days after the fourth COVID-19 vaccination. Healthcare workers with psychiatric disorders had slightly lower Anti-SARS-CoV-2-Spike IgG levels before the third COVID-19 vaccination. However, this effect was mediated by higher median age and body mass index in this subgroup. Antibody titres following the third and fourth COVID-19 vaccinations ("booster vaccinations") were not significantly different between subgroups with and without psychiatric disorders. Sleep quality did not affect the humoral immunogenicity of the COVID-19 vaccinations. Moreover, the COVID-19 vaccinations did not impact self-reported sleep quality. Our data suggest that in a working population neither mental health nor sleep quality relevantly impact the immunogenicity of COVID-19 vaccinations, and that COVID-19 vaccinations do

not cause a sustained deterioration of sleep, suggesting that they are not a precipitating factor for insomnia. The findings from this large-scale real-life cohort study will inform clinical practice regarding the recommendation of COVID-19 booster vaccinations for individuals with mental health and sleep problems.

KEYWORDS
COVID-19 vaccination, immune response, psychiatric disorders, sleep function, sleep regulation, system consolidation

1 | INTRODUCTION

The immunogenicity of vaccinations is modulated by a plethora of physiological and behavioural influences (Zimmermann & Curtis, 2019). A bidirectional relationship between sleep and immune function is well established (Besedovsky et al., 2019). Sleep can modulate the cellular and humoral response to vaccinations (Lange et al., 2011); vice versa, vaccinations can impact sleep (Sharpley et al., 2016), and immune system activation might be involved in the pathophysiological hyperarousal of patients with insomnia (Riemann et al., 2010; Riemann et al., 2020).

Previous work on the impact of sleep on immunogenicity of different vaccinations has found that experimental sleep restriction and sleep deprivation as well as habitual short sleep impair the humoral immune response following influenza, hepatitis A and hepatitis B vaccinations (Rayatdoost et al., 2022). The most extensive study monitored antibody levels for 1 year over a course of three vaccinations against hepatitis A, and showed that whole night of sleep deprivation after each of the vaccinations significantly reduced antibody levels in the short and long term (Lange et al., 2011), supporting previous findings of reduced hepatitis A antibody levels 4 weeks after a single hepatitis A vaccination was followed by experimental sleep deprivation (Lange et al., 2003). However, for other vaccines the effects of sleep deprivation are less clear. Volunteers undergoing 6 days of bedtime restriction around a seasonal influenza vaccination had only half of the antibody levels at 10 days post-vaccination compared with normally sleeping volunteers, but 3–4 weeks following the sleep restriction antibody levels no longer differed between groups (Spiegel et al., 2002). Similarly, 1 night of sleep deprivation following an influenza H1N1 vaccination impacted the antibody levels only in the 5-day follow-up in males, and there was no difference to controls in females or males at later time points (Benedict et al., 2012). The relationship between short sleep and reduced vaccination response was corroborated by two studies investigating the effect of sleep habits immunogenicity of hepatitis B (Prather et al., 2012) and a tetravalent influenza vaccination (Prather et al., 2021). However, in both studies neither sleep efficiency nor sleep quality mediated antibody levels. Another study exploring the association between various psycho-behavioural factors and antibody levels in older adults who received the 2014/2015 trivalent influenza vaccination found no association with self-reported sleep duration, sleep latency and sleep efficiency (Ayling et al., 2018). Similarly, sleep disruptions due to obstructive sleep apnea did not affect antibody levels (Dopp et al., 2007). If sleep disorders impact vaccination immunogenicity also remains unclear following a study on influenza vaccination in patients with insomnia (Taylor et al., 2017). This study found lower antibody levels in patients with insomnia at baseline and after the vaccination, as well as some indications from exploratory analyses that insomnia and the Pittsburgh Sleep Quality Index (PSQI) might mediate the vaccination response (Buysse et al., 1989). However, the main analysis showed no interaction effect between the time point (before versus after vaccination) and the group (insomnia versus controls).

The COVID-19 vaccination has become a key prevention tool in the ongoing COVID-19 pandemic (Benenson et al., 2021). It has been speculated that poor sleep quality may impair the COVID-19 vaccination-derived humoral immune response (Kow & Hasan, 2021; Zhu et al., 2021), particularly in individuals with psychiatric disorders (Mazereel et al., 2021). However, data on the relationship between sleep and immunogenicity of COVID-19 vaccinations is still sparse. To our knowledge, currently the first has recently been conducted in a small cohort of Greek healthcare workers (HCWs; Athanasiou et al., 2023). Surprisingly, night shifts 2 days before or 1 day after COVID-19 vaccination did not affect antibody levels. However, the Athens Insomnia Scale (AIS; Soldatos et al., 2000) and the PSQI predicted antibody levels after the first and second vaccinations (Athanasiou et al., 2023), yet to a smaller degree than other established factors such as age and smoking. Considering that the study participants were assessed during the peak of the COVID-19 pandemic and severely sleep deprived with an average sleep duration of only 6 hr per night, it remains unclear if the effects were mediated by sleep duration, sleep quality or other factors such as mental health.

Mental health, however, is another important aspect to consider in the vaccination response (Mazereel et al., 2021). Some mental health conditions, in particular major depressive disorder, can reduce vaccine efficacy (Xiao et al., 2022). Yet, the current evidence regarding the effect of psychiatric disorders on vaccine immunogenicity is heterogenous and data on the COVID-19 vaccination are missing (Mazereel et al., 2021; Xiao et al., 2022). Considering that the COVID-19 pandemic has now been ongoing for more than 3 years (Wu et al., 2020), and that novel mRNA-based vaccines (Baden et al., 2020; Polack et al., 2020) have been administered to billions of individuals worldwide, it is surprising that the impact of sleep and mental health on the COVID-19 vaccine immunogenicity and the impact of the vaccination on sleep have not yet been studied in a large cohort.

We set out to use our large-scale real-life data of 1082 HCWs undergoing their third and fourth COVID-19 vaccinations (first and second booster vaccinations) to address this question. The sample of HCWs is particularly relevant for vaccine recommendations as this population is, on one hand, highly exposed to SARS-CoV-2 and needs the best possible vaccination protection (Gross et al., 2021; Montgomery et al., 2021) but, on the other hand, is predisposed to poor sleep and mental stress due to their daily work (Anderson et al., 2012; Chang et al., 2013; Wolkow et al., 2015). We therefore tested in this sample if mental health and sleep quality affect the immune response following COVID-19 vaccination and, vice versa, whether the COVID-19 vaccination affects sleep quality.

2 | METHODS

2.1 | Study setting

This project was part of the CoVacSer cohort study, which investigates prospectively the SARS-CoV-2 immunity, quality of life and ability to work in HCWs after COVID-19 vaccination and/or SARS-CoV-2 infection since 29 September 2021. Inclusion criteria for study enrolment were: (i) age ≥ 18 years; (ii) written consent form; (iii) 14 days minimum interval after the first polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection and/or at least one dose of COVID-19 vaccination independent of vaccination regime; (iv) employment in healthcare sector. Individuals that received vaccines without European Medicines Agency (EMA) authorisation during the data collection period were excluded from the data analysis according to the study protocol (European Medicines Agency (EMA), 2023).

Serum blood samples combined with the CoVacSer study questionnaire were collected in determined follow-up examination intervals after study inclusion: (i) 14 days; (ii) 3 months; (iii) 6 months; (iv) 12 months; and (v) 24 months after the latest event of SARS-CoV-2 infection or dose of COVID-19 vaccine with a tolerance interval of 1 month around each follow-up time point. New immunisation events lead to a restart of the follow-up cycle, that is, participants underwent the first new follow-up assessment 14 days after the new event. Infections were not assessed serologically, but participants were asked to report new SARS-CoV-2 infections and offered unrestricted and cost-free PCR testing to minimise the rate of undetected infections.

2.2 | Data collection

The data were collected between 29 September 2021 and 19 December 2022. Analysis was performed based on the vaccination status:

A. third mRNA-based COVID-19 vaccination (first booster dose);
B. fourth mRNA-based COVID-19 vaccination (second booster dose).

The following COVID-19 vaccines were used:

i. monovalent BNT162b2mRNA (Comirnaty, BioNTech/Pfizer, Mainz/Germany, New York/USA; full dose 30 µg mRNA);
ii. mRNA-1273 (Spikevax, Moderna, Cambridge/USA); half dose 50 g mRNA as booster dose following the recommendations of the German constant vaccination committee (STIKO) (Robert Koch-Institut (RKI), 2021);
iii. bivalent BNT162b2 mRNA Original/Omicron BA.1 (Comirnaty Original/Omicron BA.1, BioNTech/Pfizer, Mainz/Germany, New York/USA);
iv. bivalent BNT162b2 mRNA Original/Omicron BA.4–5 (Comirnaty Original/Omicron BA.4–5, BioNTech/Pfizer, Mainz/Germany, New York/USA).

The main analysis conducted is independent of the vaccination schedules, which are listed in Tables S3 and S4. To reduce the heterogeneity caused by different vaccine combinations, subgroup analysis for the largest subgroup of our study population, which only received homologously BNT162b2mRNA vaccine, for all vaccinations is presented in Figures S3–S5.

The study participants submitted the CoVacSer study survey with a corresponding serum blood sample at each participation date, which were defined in the study protocol:

1. pre-vaccination baseline assessment before the respective COVID-19 booster vaccine administration;
2. assessment 14–30 days after each booster vaccination, referred to as 14-days post-vaccination participation;
3. follow-up assessment 60–120 days after booster vaccination, referred to as 3-month follow-up.

Because most participants were infected in early 2022 during the rapid spread of the SARS-CoV-2 Omicron virus variant of concern in Germany, the sample size for the 6-, 12- and 24-month follow-up of uninfected individuals is insufficient for a meaningful analysis, and only the 14-day and 3-month follow-up time points were analysed. Most participants who received a fourth vaccination dose were vaccinated less than 3 months before the end date of the data collection period. Therefore, only the 14-day follow-up was analysed for the third COVID-19 vaccination.

Follow-up time points of each individual were only analysed if no further COVID-19 immunising event, that is, no SARS-CoV-2 infection or no further dose of COVID-19 vaccine, had occurred.

The CoVacSer study survey includes socio-demographic aspects and individual risk factors, containing the World Health Organisation Quality of Life (WHOQOL-BREF) questionnaire as well as the Work Ability Index (WAI; Gholami et al., 2013; Skevington, 1999; van den Berg et al., 2009). As part of this survey, the presence of a psychiatric disorder and the sleep quality were assessed by self-report.

The ability to enjoy life, the ability to concentrate, energy for everyday life, and acceptance of one's own appearance were asked in the categories: "not at all", "a little", "average", "quite" and

"extremely". Satisfaction with the ability to cope with everyday life, self-satisfaction, satisfaction with sexual life, as well as the quality of sleep were queried in the categories: "very dissatisfied", "dissatisfied", "neither satisfied nor dissatisfied", "satisfied" and "very satisfied". The frequency of occurrence of negative feelings in the frequency intervals were assessed in the categories: "never", "not often", "occasionally", "often" and "always". Participants were instructed to rate all items for the 14-day period prior to the respective assessment date.

For the analysis of the impact of mental health on vaccine immunogenicity, study participants without psychiatric disorders were compared with those who indicated to have a psychiatric disorder. To determine whether or not participants had a psychiatric disorder, the questionnaire entry 14 days after the third or fourth vaccination was used. For the analysis of the effect of sleep quality on the humoral immunogenicity of the COVID-19 vaccination, the sleep quality reported at the 14-days assessment after vaccination was used, as this refers to the time span immediately following the vaccination.

Only blood samples with a signed written consent form and a completed linked questionnaire were considered. REDCap (Research Electronic Data Capture, projectredcap.org) was used as technological platform for the questionnaire recording (Harris et al., 2009; Harris et al., 2019). In the context of pseudonymisation, blood samples were assigned to the study survey based on date of birth and dates of COVID-19 vaccination.

Most HCWs were recruited from a single tertiary hospital in Germany, the University Hospital Würzburg, along with some HCWs from surrounding hospitals and medical surgeries.

2.3 | SARS-CoV-2 IgG ELISA

The measurement of Anti-SARS-CoV-2-Spike IgG levels was performed using the SERION ELISA *agile* SARS-CoV-2 IgG (SERION diagnostics, Würzburg, Germany) as an enzyme-linked immunoassay. Detected extinction values were converted to Serion IgG units per ml (U ml^{-1}) as producer specific units in use of the software easy ANALYSE (SERION diagnostics). Consequently, the internationally established unit Binding Antibody Units per ml (BAU ml^{-1}) were calculated using the factor 2.1 in accordance with manufacturer's information. For the measurement of Anti-SARS-CoV-2-Spike-IgG levels beyond the maximum limit of 250 U ml^{-1} (> 525 BAU ml^{-1}), a dilution series containing dilution factors both 10 and 100 was conducted consistent with previous studies (Krone et al., 2021; Perkmann et al., 2021).

2.4 | Ethics statement

The study protocol was approved by the Ethics Committee of the University of Würzburg in accordance with the Declaration of Helsinki (file no. 79/21).

2.5 | Statistics

Data analysis was performed using GraphPad Prism 9.5.1 (GraphPad Software, San Diego, CA, USA). For categorical variables, the statistical significance levels were calculated using Fisher's exact tests (gender composition of the study cohort in total and separated by mental health status). For Anti-SARS-CoV-2-Spike IgG levels separated by psychiatric disorder status, the statistical significance levels were calculated using the Mann–Whitney *U*-test. The correlation of sleep quality and Anti-SARS-CoV-2-IgG levels was performed using a Spearman-Rank correlation. A multiple regression model was used to evaluate the effect of gender, age, body mass index (BMI), smoking, SARS-CoV-2 convalescence, number of individuals living within the same household, and days since the last COVID-19 immunising event at the baseline study participation on Anti-Spike-SARS-CoV-2 IgG levels. The two-tailed significance level α was set to 0.05.

3 | RESULTS

3.1 | Participant recruitment and characterisation of the study population

From 29 September 2021 to 19 December 2022, 1158 CoVacSer study participants submitted a serum blood sample along with the study questionnaire 14–30 days after their third COVID-19 vaccination. All individuals met the inclusion criteria. Seventy-six participants were excluded because they had not participated in the study prior to the third vaccination, so the third COVID-19 vaccination cohort consisted of 1082 HCWs. Of the 155 HCWs who participated 14–30 days after the fourth COVID-19 vaccination, one HCW was excluded due to missing baseline participation prior to the fourth vaccination. One-hundred and fifty-four HCWs could be eventually included for the cohort of the fourth COVID-19 vaccination (Figure 1).

For the third and fourth vaccinations, assessments before and 14 days after the COVID-19 vaccination were conducted in all participants that received the respective vaccination. The 3-month follow-up after the third vaccination could be conducted in 785 (72.6%) individuals.

The distribution of the applied COVID-19 vaccine schedules is shown in Table S3 (third vaccination) and Table S4 (fourth vaccination). All main analyses shown below were repeated in a subgroup of individuals who only received BNT162n2mRNA for all COVID-19 vaccinations, and the results are presented in the Supplementary Results and in Figures S3–S5.

In the cohort of the third COVID-19 vaccination ($n = 1082$ individuals), 86.0% (921) of participants reported no and 14.0% (161) reported at least one psychiatric disorder. Separated by underlying psychiatric disorder, there was no significant difference in terms of gender composition, yet a clear trend towards a higher prevalence of psychiatric disorders in women ($p = 0.05$, Fisher's exact test; Table 1). HCWs with psychiatric disorders were on average older and had a

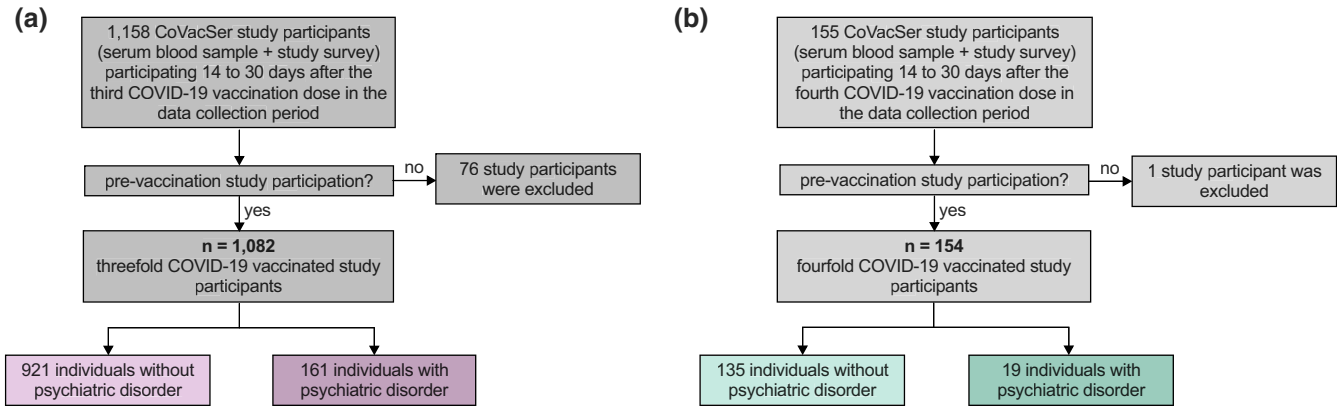

FIGURE 1 Recruitment of study participants. (a) Third COVID-19 vaccination. (b) Fourth COVID-19 vaccination

higher body weight (both $p < 0.001$, Mann–Whitney *U*-test; Table 1) compared with those without psychiatric disorders, in line with the high comorbidity rates between obesity and mental health disorders (Avila et al., 2015). They also lived with fewer people in the same household ($p = 0.02$, Mann–Whitney *U*-test). We found no significant difference in the proportion of smokers among individuals with or without psychiatric disorders ($p = 0.40$, Mann–Whitney *U*-test; Table 1). In addition, the questionnaire assessment showed that participants with psychiatric disorders are less able to enjoy their lives, less able to concentrate, have less energy for daily life, lower self-acceptance of their appearance, an impaired ability to cope with everyday life, less self-satisfaction, lower satisfaction with their sexual life, and have more often negative feelings (all $p < 0.001$, Mann–Whitney *U*-test; Table S1).

In the cohort of the fourth COVID-19 vaccination ($n = 154$ individuals), 87.7% (135) of participants reported no psychiatric disorder, 14.1% (19) reported at least one. In this much smaller cohort, we found no significant difference in any of the demographic items. However, again, individuals with psychiatric disorders tended to have a higher BMI ($p = 0.06$, Mann–Whitney *U*-test; Table 2). Consistent with their mental health status, participants with psychiatric disorders indicated that they are less able to enjoy their lives, less able to concentrate, have less energy for daily life, lower self-acceptance of their appearance, an impaired ability to cope with everyday life, less self-satisfaction, and have more often negative feelings (all $p < 0.001$, Mann–Whitney *U*-test; Table S2), as well as reduced satisfaction with their sexual life ($p = 0.0149$, Mann–Whitney *U*-test; Table S2).

3.2 | Influence of mental health on post-vaccination Anti-SARS-CoV-2 spike IgG levels

To address the question of whether mental health impacts the Anti-SARS-CoV-2 spike IgG levels following COVID-19 vaccinations, we compared those study participants that reported no psychiatric disorder with those that indicated a psychiatric disorder.

In the third COVID-19 vaccination cohort, the median Anti-SARS-CoV-2-Spike IgG levels at baseline before the third vaccination were 149 (IQR:80–259) BAU ml^{-1} for participants without, and 119 (IQR:70–228) BAU ml^{-1} for participants with a psychiatric disorder. Hence, at baseline before the third vaccination, Anti-SARS-CoV-2-Spike IgG levels were significantly lower among HCWs with underlying psychiatric disorder ($p = 0.02$, Mann–Whitney *U*-test), while there was no significant difference in Anti-SARS-CoV-2-Spike IgG levels at the time points 14 days ($p = 0.20$, Mann–Whitney *U*-test) and 3 months ($p = 0.56$, Mann–Whitney *U*-test) after the third COVID-19 vaccination (Figure 2a).

To investigate potential mediators for the significant difference in Anti-SARS-CoV-2-Spike IgG levels between participants without and with psychiatric disorders at baseline before the third COVID-19 vaccination, we performed an explorative analysis using a multiple linear regression analysis. Age ($p = 0.03$), SARS-CoV-2 infection convalescence ($p < 0.0001$), and the interval between the last COVID-19 immunising event (defined as latest administration of a COVID-19 vaccine or SARS-CoV-2 infection; $p < 0.0001$) significantly affected the Anti-SARS-CoV-2-Spike IgG levels, with higher age, absence of previous infection and longer intervals to the last immunising event predicting lower antibody titres. Importantly, an underlying psychiatric disorder did not significantly influence the humoral immune response ($p = 0.69$).

In the fourth COVID-19 vaccination cohort, there was no significant difference in antibody titres at baseline ($p = 0.59$, Mann–Whitney *U*-test) or 14 days after vaccination ($p = 0.48$, Mann–Whitney *U*-test) between participants without and with psychiatric disorders (Figure 2b).

The relative intra-individual differences in Anti-SARS-CoV-2-Spike IgG levels are shown in Figure S1. The rate of non-responders (i.e. participants showing no antibody increase after vaccination) was not different between groups at any of the time points (see Data S1 result).

3.3 | Influence of sleep quality on post-vaccination Anti-SARS-CoV-2 spike IgG levels

We investigated the effect of sleep quality on Anti-SARS-CoV-2 spike IgG levels by comparing the antibody levels stratified by self-reported sleep quality.

TABLE 1 Characterisation of the subgroups without and with psychiatric disorders undergoing a third COVID-19 vaccination

Study participants threefold COVID-19 vaccinated								
		Mentally healthy ($n = 921$)		Underlying psychiatric disorder ($n = 161$)		Total ($n = 1082$)		
		Absolute	Relative	Absolute	relative	Absolute number	Relative number	p
Gender	Female	761	82.6%	143	88.8%	904	83.5%	0.051
	Male	160	17.4%	18	11.2%	178	16.5%	
Age (years)		41 (31–52)		49 (37–58)		42 (31–54)		$p < 0.001$
BMI (kg m^{-2})		23.7 (21.5–26.6)		25.5 (22.0–30.8)		23.8 (21.6–27.2)		$p < 0.001$
Smoking individuals		323	35.1%	62	38.5%	385	35.6%	0.40
First post-vaccination participation: interval since third COVID-19 vaccination (days)		17 (15–20)		17 (15–21)		17 (15–20)		0.47
Interval of the prior COVID-19 immunising event to the baseline participation (days)		236 (203–266)		236 (207–261)		236 (203–265)		0.75
Number of SARS-CoV-2 convalescent individuals		30	3.3.%	14	8.7%	44	4.1%	0.0013
Household members (absolute number)		2 (2–3)		3 (1–3)		2 (2–3)		0.02

Note: Age, BMI, the interval since the last COVID-19 vaccination, intermission between the pre- and the initial post-vaccination participation, as well as the number of household members are reported as medians with interquartile ranges in brackets. For each sub-cohort, absolute numbers in the left, relative share in the right column.
Abbreviation: BMI, body mass index.

TABLE 2 Characterisation of the subgroups without and with psychiatric disorders undergoing a fourth COVID-19 vaccination

Study participants fourfold COVID-19 vaccinated		Mentally healthy ($n = 135$)		Underlying psychiatric disorder ($n = 19$)		Total ($n = 154$)		
		Absolute	Relative	Absolute	Relative	Absolute	Relative	*p*
Gender	Female	110	81.5%	17	89.5%	127	82.4%	0.53
	Male	25	18.5%	2	10.5%	27	17.5%	
Age (years)		51 (36–57)		53 (45–59)		51 (37–58)		0.36
BMI (kg m^{-2})		24.2 (21.6–28.0)		27.9 (21.5–33.1)		24.4 (21.6–28.3)		0.06
Smoking individuals		50	37.0%	5	26.3%	55	35.7	0.45
First post-vaccination participation: interval since fourth COVID-19 vaccination (days)		20 (17–22)		17 (15–25)		20 (17–22)		0.20
Interval of the prior COVID-19 immunising event to the baseline participation (days)		181 (116–193)		169 (96–185)		180 (112–191)		0.20
Number of SARS-CoV-2 convalescent individuals		54	40.0%	4	21.1%	58	37.7	0.13
Household members (absolute number)		2 (2–3)		2 (1–3)		2 (2–3)		0.32

Note: Age, BMI, the interval since the last COVID-19 vaccination, intermission between the pre- and the initial post-vaccination participation, as well as the number of household members are reported as medians with interquartile ranges in brackets. For each sub-cohort, absolute numbers in the left, relative share in the right column.
Abbreviation: BMI: body mass index.

In the third vaccination cohort, sleep quality and Anti-SARS-CoV-2-Spike IgG levels neither correlated pre-vaccination ($p = 0.93$, $r = 0.002$, Spearman correlation), 14-days ($p = 0.23$, $r = 0.04$, Spearman correlation) nor 3-months post-vaccination ($p = 0.73$, $r = -0.012$, Spearman correlation; Figure 3a). In the fourth COVID-19 vaccination cohort, there was also no correlation between sleep and Anti-SARS-CoV-2-Spike IgG levels pre-vaccination ($p = 0.11$, $r = -0.13$, Spearman correlation) or 14-days post-vaccination ($p = 0.44$, $r = -0.06$, Spearman correlation; Figure 3b).

The relative intra-individual differences in Anti-SARS-CoV-2-Spike IgG levels are shown in Figure S2. There was no significant difference in the rate of non-responders between subgroups (Data S1 result).

3.4 | Effect of COVID-19 vaccination on sleep quality

In order to assess whether the COVID-19 booster vaccinations had a sustained effect on sleep quality that goes beyond the established short-lasting effects of acute immune events on sleep (Besedovsky et al., 2019), we investigated the change of sleep quality across the time points before and after the third and fourth COVID-19 vaccinations.

In the third vaccination cohort, there was no significant change in sleep quality following the vaccination ($p = 0.28$) comparing the pre-vaccination sleep quality with the 14-days and $p = 0.59$ with the 3-months post-vaccination assessment, $p = 0.63$ comparing both post-vaccination participations; Mann–Whitney *U*-test (Figure 4a). Similarly, in the fourth vaccination cohort, there was no change in sleep quality in the 14 days following the vaccination ($p = 0.56$, Mann–Whitney *U*-test; Figure 4b).

4 | DISCUSSION

Mental health, sleep and immune function are interlinked, and it is of great clinical relevance to clarify if individuals with psychiatric conditions or poor sleepers are at risk of an insufficient response to COVID-19 booster vaccinations or if booster vaccinations might cause a sustained deterioration of sleep quality. To our knowledge, this is the first study investigating the relationship between mental health, sleep and immunogenicity of COVID-19 booster vaccinations. In our large sample of 1082 individuals, no effect of psychiatric disorders or sleep quality on the immunogenicity of COVID-19 booster vaccinations and no effect of the booster vaccinations on sleep quality could be obtained.

Participants with psychiatric disorders had slightly but significantly lower antibody titres before the third COVID-19 booster vaccination compared with those without psychiatric disorders. However, HCWs with a psychiatric disorder were significantly older and had a higher BMI. Based on our regression analysis, the baseline differences in the Anti-SARS-CoV-2-Spike IgG levels can be explained by these

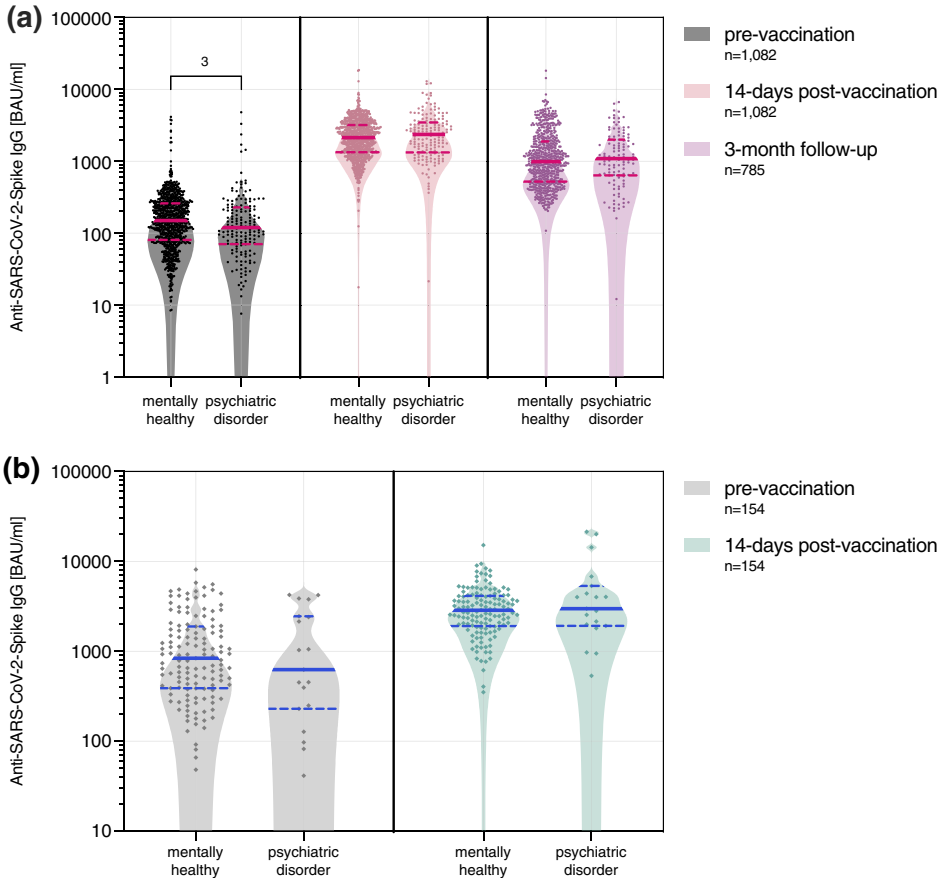

FIGURE 2 Anti-SARS-CoV-2-Spike IgG levels following COVID-19 booster vaccinations stratified by mental health status. (a) Anti-SARS-CoV-2-Spike IgG levels among healthcare workers (HCWs) before (pre-vaccination) and after (14-days and 3-months follow-up) the third COVID-19 vaccination. (b) Anti-SARS-CoV-2-Spike IgG levels among HCWs before (pre-vaccination) and after (14 days) the fourth COVID-19 vaccination. Anti-SARS-CoV-2-Spike IgG logarithmically scaled. BAU ml^{-1}, binding antibody units per millilitre. Medians are indicated as horizontal bold line, quartiles as dotted lines; *$p < 0.05$

two moderators and not by the presence of psychiatric disorders. At no other time point, Anti-SARS-CoV-2-Spike IgG levels differed between individuals with and without psychiatric conditions. This is an important finding, as it suggests that psychiatric conditions do not constitute a risk factor for an insufficient protection from COVID-19 following booster vaccinations.

Our null finding on the relationship between sleep quality and vaccine immunogenicity is in line with previous work that found an impact of sleep duration, but not of sleep quality or sleep efficiency, on the post-vaccination humoral immune response for hepatitis B and influenza vaccinations (Prather et al., 2012; Prather et al., 2021), as well as with the finding that sleep disruptions resulting from sleep apnea do not affect antibody titres following an influenza vaccination (Dopp et al., 2007). The difference between the clear effect of sleep restriction and sleep deprivation on vaccine immunogenicity (Dopp et al., 2007), at least in the short term (Benedict et al., 2012; Spiegel et al., 2002), and the absence of an impact of sleep quality or sleep efficacy might be explained by the large discrepancy between subjective and objective sleep variables, even in good sleepers (Benz et al., 2022).

Our null finding on the impact of the COVID-19 vaccinations on sleep quality provides another important result as it shows that in our large dataset there is no indication that COVID-19 vaccinations lead to a sustained deterioration of sleep, which could indicate the precipitation of insomnia.

Our study has some important limitations. This large and representative example of HCWs represents a rather young and overall healthy population with only about 20% of participants reporting dissatisfaction with their sleep, while in the adult population dissatisfactory sleep is generally more common with more than 40% reporting some insomnia symptoms before the COVID-19 pandemic and more than 50% of the population during the pandemic in 2020 (Morin et al., 2021). The insomnia prevalence of 36% and the short sleep duration of only 6 hr in the first study investigating the association of sleep variables and the immunogenicity of COVID-19 vaccines might explain why the authors found a significant impact of the AIS and PSQI scores on antibody levels at some time points after adjustment for potential confounders (Athanasiou et al., 2023). It must be considered that both clinical scores include an item on sleep duration (Buysse et al., 1989). Another important limitation of our study is that the cohort is predominantly female. This is due to the recruitment of HCWs, which are mostly female in the German healthcare system (Gesundheitsberichterstattung des Bundes, 2021). The majority of subjects received the third COVID-19 vaccination in autumn 2021. In the context of the high SARS-CoV-2 incidence phase, predominantly driven by the SARS-CoV-2 Omicron virus variant of concern in early 2022, a large proportion suffered a breakthrough infection (Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit, 2023). It should therefore be mentioned as a further limitation that we could not perform a meaningful analysis of the originally planned follow-up time points at

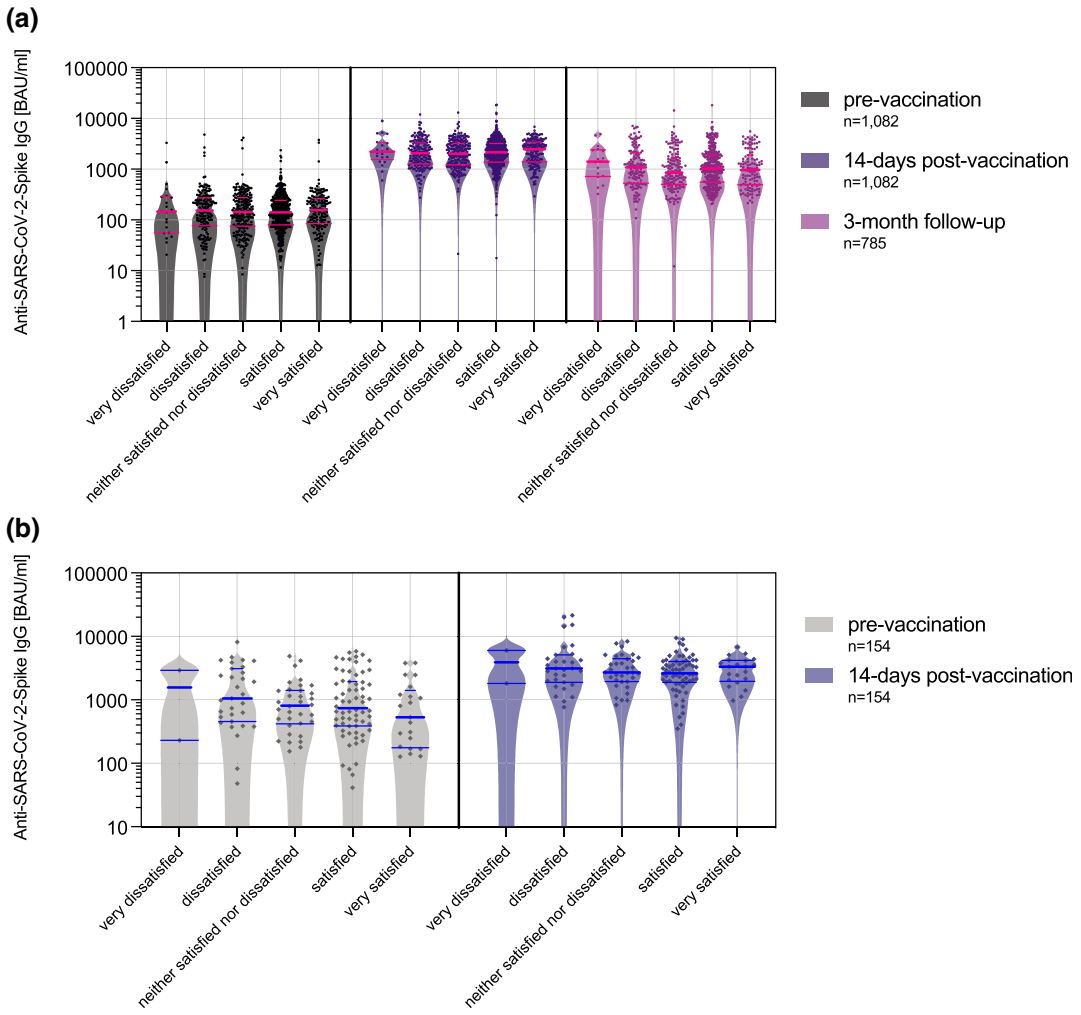

FIGURE 3 Anti-SARS-CoV-2-Spike IgG levels following COVID-19 booster vaccinations stratified by sleep quality. (a) Anti-SARS-CoV-2-Spike IgG levels among healthcare workers (HCWs) before (pre-vaccination) and after (14-days and 3-months follow-up) the third COVID-19 vaccination. (b) Anti-SARS-CoV-2-Spike IgG levels among HCWs before (pre-vaccination) and after (14 days) the fourth COVID-19 vaccination. Sleep quality is stratified in five categories (very dissatisfied to very satisfied). Anti-SARS-CoV-2-Spike IgG logarithmically scaled. BAU ml^{-1}, binding antibody units per millilitre. Medians are indicated as horizontal bold line, quartiles as dotted lines

6, 12 and 24 months after the third vaccination, as most individuals contracted a SARS-CoV-2-infection after their 3-month follow-up assessment. For the fourth COVID-19 vaccination, data could only be collected for the time of analysis 14 days after the vaccine administration, as most follow-ups at 3 months post-vaccination and beyond have not yet been collected at the end of the data collection period for this manuscript in December 2022. The cohort for the fourth vaccination is also considerably smaller, as many individuals participating in the study for the third vaccination were not eligible for a second booster following the COVID-19 vaccination recommendations for HCWs of the German Standing Committee on Vaccination (STIKO) (Robert Koch-Institut (RKI), 2021). This again is due to the fact that a relatively large proportion of the enrolled HCWs became infected with SARS-CoV-2 between the 3- and 6-months follow-ups, preventing an analysis of vaccine-induced increase of antibody titres. Regarding the study design, it should be highlighted that sleep quality was only recorded retrospectively for a 14-day time interval, and was based on the sleep quality item of the World Health Organisation Quality of Life (WHOQOL-BREF) questionnaire (Gholami et al., 2013) and not on a day-by-day self-report assessment with sleep diaries or an objective assessment with actigraphy or polysomnography. It should also be noted that due to data protection regulations, the study participants were not asked for a specific psychiatric diagnosis, and therefore it is not possible to investigate the impact of mood disorders on vaccine immunogenicity that has previously been found (Xiao et al., 2022). We considered age, convalescence from a SARS-CoV-2 infection and time interval since the last COVID-19 immunising event, as established (Reusch et al., 2023), as well as BMI and household size as possible confounders. Other potential confounders such as the amount of physical activity, having school-aged children, or living in a rural versus urban area were not recorded, but are of potential interest and should be explored in future studies. We also did not assess a potential impact of the circadian timing of the vaccine administration on the vaccine immunogenicity as our study

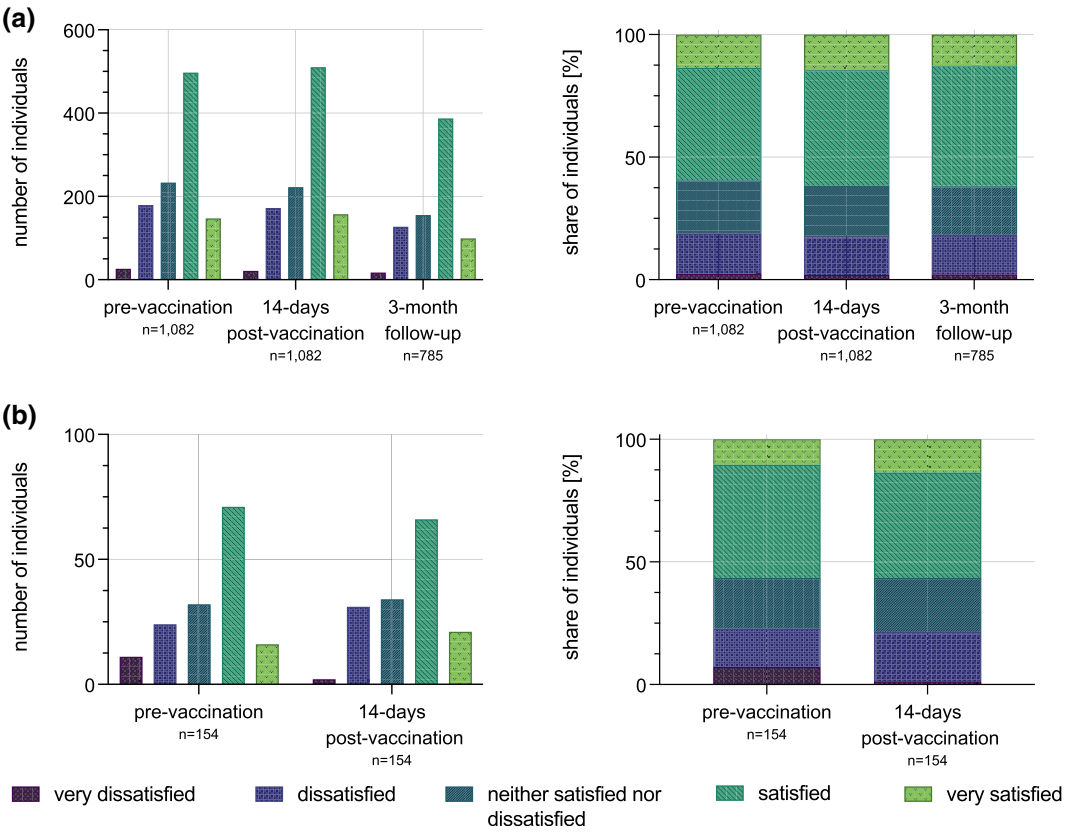

FIGURE 4 Sleep quality before and after COVID-19 booster vaccinations. (a) Sleep quality among healthcare workers (HCWs) before (pre-vaccination) and after (14-days and 3-months follow-up) the third COVID-19 vaccination (left: absolute numbers; right: relative share). (b) Sleep quality among HCWs before (pre-vaccination) and after (14 days) the fourth COVID-19 vaccination. Sleep quality is stratified in five categories (very dissatisfied to very satisfied)

design is not well suited to address this question. Experimental studies controlling for sleep–wake history and environmental factors are needed to explore this possibility.

Because of these limitations, which are mostly due to the real-life assessment in this large cohort study, our data do not exclude the possibility that severely disturbed sleep, insomnia or specific mental health conditions might impact the immunogenicity of COVID-19 booster vaccinations. However, our results suggest that low sleep quality or mental health conditions in general have no relevant impact on antibody titres following COVID-19 booster vaccinations, especially compared with established mediators of COVID-19 vaccine immunogenicity, specifically age, smoking and interval to the last immunising event (Reusch et al., 2023). While patients with insomnia generally underestimate their sleep (Benz et al., 2022), polysomnographic measurements provide evidence for an objective reduction of sleep time in insomnia cohorts (Baglioni et al., 2014). Only studies including objective and subjective sleep measurements that are currently under way will be able to disentangle the impact of sleep quality and sleep duration on COVID-19 vaccinations (Lammers-van der Holst et al., 2022).

We interpret our data as a null finding suggesting that sleep quality and mental health status do not require adjustments of vaccination schedules. Expert advice had been given that shift workers should avoid vaccinations on shift days and hospital inpatients should consider rescheduling their vaccinations due to the sleep disruptions associated with hospitalisation (Zhu et al., 2021). However, the first and only previous study investigating the effects of sleep on antibody levels following COVID-19 vaccinations found no correlation between the duration of sleep 2 days prior and 1 day after the vaccination with antibody levels (Athanasiou et al., 2023). In light of this and our data, and because COVID-19 vaccinations represent an essential disease-prevention measure (Benenson et al., 2021), COVID-19 vaccines should be applied in a timely manner.

Given the relevant impact of sleep on immune function and the hesitancy of COVID-19 booster vaccination in large segments of the population, especially among psychiatric patients, our large-cohort study provides important evidence for recommending COVID-19 booster vaccination in individuals with psychiatric disorders and sleep problems.

5 | CONCLUSION

In conclusion, our large-scale real-world study on 1082 individuals finds no effect of mental health and sleep quality on the immunogenicity of COVID-19 vaccinations, and no sustained change in sleep

quality following vaccinations. Because this study was conducted in a rather healthy and young working population, it does not contradict previous experiments, demonstrating an impact of experimental sleep deprivation or sleep restriction, and a potential influence of insomnia disorder, on vaccination immunogenicity. However, our data suggest that sleep quality does not have a major impact on Anti-SARS-CoV-2-Spike IgG levels following the COVID-19 vaccination, especially compared with other established mediators of the vaccination response, such as age, body weight and time to the last immunising event. Importantly, our data also indicate that COVID-19 vaccinations do not deteriorate sleep quality over a time span in which one would expect the precipitation of insomnia. While the role of sleep in the effectiveness of vaccinations should be investigated in greater detail, our findings can be interpreted as reassuring evidence against a major impact of mental health and sleep quality on the immunogenicity of COVID-19 vaccines or of the vaccine administration on sleep quality.

AUTHOR CONTRIBUTIONS

Isabell Wagenhäuser: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization; writing – original draft. **Julia Reusch:** Data curation; formal analysis; investigation; methodology; project administration; writing – review and editing. **Alexander Gabel:** Data curation; formal analysis; methodology; software; validation; writing – review and editing. **Juliane Mees:** Data curation; formal analysis; investigation; methodology; project administration; writing – review and editing. **Helmut Nyawale:** Investigation; project administration; writing – review and editing. **Anna Frey:** Conceptualization; supervision; writing – review and editing. **Thiên-Trí Lâm:** Conceptualization; supervision; writing – review and editing. **Alexandra Schubert-Unkmeir:** Conceptualization; resources; supervision; writing – review and editing. **Lars Dölken:** Conceptualization; supervision; writing – review and editing. **Oliver Kurzai:** Conceptualization; funding acquisition; resources; supervision; writing – review and editing. **Stefan Frantz:** Conceptualization; supervision; writing – review and editing. **Nils Petri:** Conceptualization; formal analysis; supervision; validation; writing – review and editing. **Manuel Krone:** Conceptualization; formal analysis; funding acquisition; supervision; validation; writing – review and editing. **Lukas B. Krone:** Conceptualization; formal analysis; funding acquisition; supervision; validation; visualization; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

Manuel Krone receives honoraria from GSK and Pfizer outside the submitted work. All other authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Additional data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) as well as the study protocol, statistical analysis plan, and analytic code is made available to researchers who provide a methodologically sound proposal to achieve aims in the approved proposal on request to the corresponding author.

ROLE OF FUNDING SOURCE

This study was initiated by the investigators. The sponsoring institutions had no function in study design, data collection, analysis and interpretation of data, as well as in the writing of the manuscript. All authors had unlimited access to all data. Isabell Wagenhäuser, Julia Reusch, Nils Petri, Manuel Krone and Lukas B. Krone had the final responsibility for the decision to submit for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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