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RESEARCH ARTICLE

Association of sleep duration and quality with immunological response after vaccination against severe acute respiratory syndrome coronavirus-2 infection

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Summary

Growing evidence suggests that sleep could affect the immunological response after vaccination. The aim of this prospective study was to investigate possible associations between regular sleep disruption and immunity response after vaccination against coronavirus disease 2019 (COVID-19). In total, 592 healthcare workers, with no previous history of COVID-19, from eight major Greek hospitals were enrolled in

this study. All subjects underwent two Pfizer–BioNTech messenger ribonucleic acid (mRNA) COVID-19 vaccine BNT162b2 inoculations with an interval of 21 days between the doses. Furthermore, a questionnaire was completed 2 days after each vaccination and clinical characteristics, demographics, sleep duration, and habits were recorded. Blood samples were collected and anti-spike immunoglobulin G antibodies were measured at 20 ± 1 days after the first dose and 21 ± 2 days after the second dose. A total of 544 subjects (30% males), with median (interquartile range [IQR]) age of 46 (38–54) years and body mass index of 24·84 (22.6–28.51) kg/m^2 were eligible for the study. The median (IQR) habitual duration of sleep was 6 (6–7) h/night. In all, 283 participants (52%) had a short daytime nap. In 214 (39.3%) participants the Pittsburgh Sleep Quality Index score was >5, with a higher percentage in women (74·3%, $p < 0.05$). Antibody levels were associated with age ($r = -0.178$, $p < 0.001$), poor sleep quality ($r = -0.094$, $p < 0.05$), insomnia ($r = -0.098$, $p < 0.05$), and nap frequency per week ($r = -0.098$, $p < 0.05$), but after adjusting for confounders, only insomnia, gender, and age were independent determinants of antibody levels. It is important to emphasise that insomnia is associated with lower antibody levels against COVID-19 after vaccination.

KEYWORDS
COVID-19, healthcare workers, immunological response, sleep, vaccination

INTRODUCTION

Since December 2019, the world has experienced a new pandemic. A highly infectious acute respiratory syndrome, caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in Wuhan, China (Huang et al., 2020). This ribonucleic acid (RNA) betacoronavirus is responsible for the coronavirus disease 2019 (COVID-19), which has spread rapidly, causing considerable morbidity and mortality, especially among people with comorbidities (Zhou et al., 2020). Currently, many drugs are being explored against COVID-19, but with limited value. To date, the most effective management consists of infection prevention and numerous vaccines have already been developed with a high efficacy for prevention of serious illness.

Adaptive immune responses after vaccination could be influenced by several different factors, involving the environment, personal behaviour, and nutrition (Zimmermann & Curtis, 2019). These factors may have significant consequences, concerning the efficacy and the duration of vaccine protection. Adequate sleep, during the circadian night, is important for numerous of biological process. Several series of studies have proposed that sleep may facilitate immune effectiveness, and sleep deficit could make people more vulnerable to developing severe COVID-19. On the other hand, few studies have explored the role of sleep on immune response after vaccination (Benedict & Cedernaes, 2021; Sharpley et al., 2016). In these studies, it has been suggested that short sleep duration or deliberate night-time sleep deprivation close to the vaccination date was associated with lower antibody responses to hepatitis A (HAV), hepatitis B (HBV), and influenza vaccination (Benedict et al., 2012; Lange et al., 2011; Prather et al., 2012, 2021; Spiegel et al., 2002). Additionally, poor sleep quality, evaluated by the Pittsburgh Sleep Quality Index (PSQI) questionnaire, was correlated with lower immune response after influenza vaccination (Taylor et al., 2017).

In December 2020, in Greece, people with a high risk of COVID-19 infection and healthcare professionals were the first to undergo vaccination during the strict lockdown period. The messenger RNA (mRNA)-based COVID-19 vaccine Pfizer-BioNTech (BNT162b2) was one of the first to be eligible for COVID-19 immunisation in Greece (Hass et al., 2021). The mRNA vaccines contain the genetic sequence (mRNA) for protein S and after administration, the mRNA enters the cytoplasm carrying the information that is then transcripted by ribosomes. As a result, binding antibody production and active immunity development is triggered (Hass et al., 2021). Healthcare professionals who often experience a chronic circadian disruption, exhibit a markedly greater risk of COVID-19 diagnosis (Fatima et al., 2021; Rizza et al., 2021). Furthermore, there are several studies that point out the impact of COVID-19 pandemic on sleep and behaviour in healthcare professionals (Pappa et al., 2021; Trakada et al., 2020).

The main aim of this study was to conduct a novel investigation in a large sample of the Greek population, to characterise the effect of sleep quality and duration on immunisation after vaccination against SARS-CoV-2. To the best of our knowledge, this is the first study that estimates the effect of sleep on the quantity of antibody titres against SARS-CoV-2.

METHODS

Study design and participants

This is a collaborative effort of the Sleep Group of the Hellenic Thoracic Society. The participants that were voluntarily enrolled were healthcare workers, from eight General hospitals in Greece. All study participants were vaccinated with BNT162b2 vaccine against SARS-CoV2 between December 2020 and April 2021. Healthcare workers were regularly examined with nasopharyngeal swabs for a period of 6 months before vaccination. Additionally, a random sample of 360 subjects underwent a blood test, in order to confirm absence of antibodies against SARS-CoV-2. Healthcare workers who were (i) aged >18 years, (ii) without medical history of psychiatric disorders, or (iii) immunodeficiency, or (iv) active cancer, or (v) infection 2 weeks prior to vaccination were included to the study. Subjects who (i) had a serious past allergic reaction, or (ii) were pregnant or lactating, or (iii) had a positive polymerase chain reaction (PCR) test or known COVID-19 infection were excluded from the study.

All participants had two doses of the COVID-19 vaccine. The second dose was given ~21 days after the first dose (Comirnaty, Pfizer-BioNTech). In our study, the first blood sample was collected 1–2 days before the second dose and the second blood sample was collected after 19–23 days. Participants were provided with questionnaires 2 days after each vaccination.

After the completion of the study, all data regarding the time of vaccination of the participants were collected from the national registry of COVID-19 vaccination for 478 subjects, and an additional analysis was made, dividing the subjects into three groups according to the time of their vaccination (Group A, 7:00–10:59 a.m.; Group B, 11:00 a.m.–2:59 p.m.; Group C, 3:00 –9:59 p.m.). Retrospectively, a year after the completion of the two doses of vaccination, and for this period, evidence of SARS-CoV-2 infection was collected (PCR for viral RNA or anti-nucleocapsid antibody) from the national records for COVID-19 infection, in order to examine whether "good sleepers", subjects with a PSQI score of ≤5, were more protected against a COVID-19 infection.

The study complies with the Declaration of Helsinki. The study protocol was approved by each Institutional Research Ethics Committee from the eight hospitals that participated in the study, and all subjects gave their informed consent, before the first vaccination.

Assessment of SARS-CoV-2 binding antibody

Peripheral venous blood samples of 7–8 ml were obtained. Serum was separated within 4 h from blood collection and stored at −80°C until the day of measurement. Stored samples from different time points of the same subject were measured in parallel assays. Anti-spike immunoglobulin G (IgG) antibodies, which were taken at two time points, 20 ± 1 days after the first dose and 21 ± 2 days after the second dose, were determined by chemiluminescent microparticle immunoassay (Abbott Diagnostics) on an Abbott Diagnostics Architect i2000 SR analyser, according to the manufacturer s instructions. Antibodies levels were expressed in arbitrary units (AU)/ml and results >50 AU/ml were considered as positive (immune response; Bryan et al., 2020).

Questionnaires

A general questionnaire that included sociodemographic information, medical history, lifestyle, professional information, sleep habits, peri-vaccination sleep quality, as well as the Epworth Sleepiness Scale (ESS; Tsara et al., 2004), Athens Insomnia Scale (AIS; Soldatos et al., 2000), and PSQI (Kotronoulas et al., 2011), were completed by the participants. Sociodemographic variables and clinical factors included: gender, age, body mass index (BMI), medical and psychiatric history, smoking history, alcohol consumption, diet habits, caffeine consumption and recent vaccination history (influenza/*S. pneumoniae*) were also considered. Professional information included medical field-grade, work experience, working hours and days-off during the previous week, and the number of shifts during the previous month. It was also considered if the participants had a night shift in the previous 2 days before vaccination or the following day and if the answer was "yes", how many hours did they sleep. The participants were asked to report their night-time sleep duration, as well as the presence and the frequency of short afternoon naps. Habitual nappers were classified as those who reported napping at least once a week (Leong et al., 2021). Participants were informed to distinguish between a short nap and a midday sleep due to deprivation following a night shift. Furthermore, we documented the duration of sleep 2 nights prior to vaccination as well as the following night. Finally, all adverse effects from vaccination were documented by the participant. Examples of the questions: Did you have a night shift 2 nights before and/or a night after vaccination? ("Yes/No") If yes, please define, when (first night, second night, night after), please define, if you had any sleep that night, ("Yes/No") and if yes, for how long did you sleep? (scale from 0–10 h), if you slept for >10 h, please define. How many hours do you sleep, on average, every night? (scale from 0–10 h), if you slept for >10 h, please define. Do you sleep at midday? ("Yes/No") if yes, how often? (scale 1–7 days/week) and for how long? 0–15, 16–30, 31–60, 61–90, 91–120, 121–150, 151–180, 181–210, 211–240, >240 min. How many hours did you sleep during the 2 nights before your vaccination? (scale from 0–10 h), if you slept for >10 h, please define. How many hours did you sleep the night after vaccination? (scale from 0–10 h), if you slept for >10 hours, please define.

The AIS is a questionnaire developed to evaluate insomnia problems (Soldatos et al., 2000). Each item is rated from 0 (no problem at all), 1 (mild problem), and 2 (marked problem), to 3 (very serious problem). The first five items assess difficulty with sleep induction, awakenings during the night, early morning awakening, total sleep time, and overall sleep quality. The three last items assess the next-day consequences of insomnia, such as problems with one s sense of wellbeing, functioning, and daytime sleepiness. A cut-off score of >6 is used to establish the diagnosis of insomnia.

TABLE 1 Demographics and other characteristics of the study population. Subjects were divided according to gender and Pittsburgh Sleep Quality Index score

		Total, *n* (%) (*N* = 544)	Males (*N* = 163)	Females (*N* = 381)	*p*	PSQI ≤5 (*N* = 330)	PSQI >5 (*N* = 214)	*p*
Smoking	Smokers: 20 (10–305) pack-years	183 (33.6)	57 (35)	126 (33.1)	0.788	102 (30.9)	81 (37.9)	0.233
	Non-smokers	312 (57.4)	90 (55.2)	222 (58.3)		196 (59.4)	116 (54.2)	
	Ex-smokers: 6 (2–10·5) years duration of smoking termination	49 (9)	16 (9.8)	33 (8.7)		32 (9.7)	17 (7.9)	
Exercise	Everyday	106 (19.5)	38 (23.3)	68 (17.8)	0.455	66 (20)	40 (18.7)	0.563
	1–2 times/week	178 (32.7)	54 (33.1)	124 (32.5)		114 (34.5)	64 (29.9)	
	Occasionally	119 (21.9)	32 (19.6)	87 (22.8)		70 (21.2)	49 (22.9)	
	Rarely	141 (25.9)	39 (23.9)	102 (26.8)		80 (24.2)	61 (28.5)	
Alcohol	Everyday	26 (4.8)	14 (8.6)	12 (3.1)	0.001	15 (4.5)	11 (5.1)	0.634
	1–2 times/week	115 (21.1)	43 (26.4)	72 (18.9)		74 (22.4)	41 (19.2)	
	Occasionally	112 (20.6)	39 (23.9)	73 (19.2)		71 (21.5)	41 (19.2)	
	Rarely	291 (53.5)	67 (41.1)	224 (58.8)		170 (51.5)	121 (56.5)	
Caffeine	Everyday	465 (85.5)	140 (85.9)	325 (85.3)	0.943	283 (85.8)	182 (85.1)	0.781
	1–2 times/week	25 (4.6)	7 (4.3)	18 (4.7)		14 (4.2)	11 (5.1)	
	Occasionally	14 (2.6)	5 (3.1)	9 (2.4)		10 (3)	4 (1.9)	
	Rarely	40 (7.3)	11 (6.7)	29 (7.6)		23 (7)	17 (7.9)	
Diet	Free	519 (95.4)	155 (95.1)	364 (95.5)	0.825	319 (96.7)	200 (93.5)	0.081
	Special	25 (4.6)	8 (4.9)	17 (4.5)		11 (3.3)	14 (6.5)	
Occupation	Medical staff	240 (44.1)	105 (64.4)	135 (35.4)	0.000	162 (49.1)	78 (36.5)	0.014
	Nursing staff	262 (48.2)	46 (28.2)	216 (56.7)		146 (44.2)	116 (54.2)	
	Other hospital staff	42 (7.7)	12 (7.4)	30 (7.9)		22 (6.7)	20 (9.3)	
History of chronic disease		159 (29.2)	45 (27.6)	114 (30)	0.587	99 (30)	60 (28.4)	0.623
Prior vaccination (last 6 months)	Trivalent influenza	314 (57.7)	100 (61.3)	214 (56.2)	0.262	197 (59.7)	117 (54.7)	0.247
	Pneumococcus	47 (8·6)	12 (7.4)	35 (9.2)	0.488	33 (10)	14 (6.5)	0.161

Note: PSQI, Pittsburgh Sleep Quality Index.

The ESS is a widely used questionnaire for the assessment of excessive daytime sleepiness (Tsara et al., 2004). The possibility of dozing off in eight common situations is rated by the patients from 0 to 3. When the score is >10, the ESS is considered abnormal (scores between 0 and 24).

The PSQI is a widely used questionnaire. This questionnaire was used to evaluate the subjective sleep quality of the last month. The Greek version (GR-PSQI) includes 19 self-report questions in seven clinically derived domains of sleep difficulties, each answer is weighted on a 0–3 interval scale (Kotronoulas et al., 2011). A PSQI total score of >5 is associated with poor sleep quality.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS), version 10·1 (SPSS Inc., Chicago, IL, USA). Normality was tested by the Kolmogorov–Smirnov criterion. Continuous variables are expressed as mean (±SD). Skewed variables were expressed as median (interquartile range [IQR]). A comparison of continuous parameters was made by the unpaired Student s *t* test or the non-parametric Mann–Whitney *U* test for normally distributed and skewed variables, respectively. "Poor" and "good" sleepers, were categorised based on a PSQI score of >5 and PSQI ≤5, respectively. Categorical clinical variables were analysed using the chi-squared test. Correlations between continuous variables were evaluated by the Pearson s or the Spearman s correlation coefficient for parametric and non-parametric variables, respectively. Multivariable linear regression analysis was applied to evaluate the association between antibody titres after first and second dose of vaccination (dependent variables) as well as sleep factors (ESS, PSQI, AIS) as independent variables, after adjustment for potential confounders (gender, age, smoking, exercise pattern, time of day of vaccination, and antibody titres after first immunisation). Confounders were selected according to previous bibliography about factors that affect antibody levels after immunisation. Values of $p < 0{\cdot}05$ were considered statistically significant.

RESULTS

Demographic and clinical characteristics

Among the 592 participants in this study, 21 had a history of COVID-19 infection and thus were excluded. In all, 27 subjects did not complete the PSQI and AIS questionnaires, and so they were not included in the study. Finally, a total of 544 subjects (30% males), with median (IQR) age of 46 (38–54) years and BMI of 24·84 (22·6–28·51) kg/m^2 were studied. Clinical characteristics of the study population are shown in Table 1. Differences were found between males and females in alcohol consumption ($p = 0.001$) and occupation position ($p < 0.001$) (Table 1). Regarding occupation characteristics, the medical personnel worked a median (IQR) of 50 (40–60) h/week and the nursing and other hospital staff 40 (40–40) h/week. Medical personnel worked a median (IQR) of 7 (5–7) night shifts every month.

TABLE 2 Sleep data for the whole population ($N = 544$)

Variable	Value
Habitual sleep per night, h, median (IQR)	**6 (6–7)**
First night before first vaccination, h, median (IQR)	6 (6–7)
Second night before first vaccination, h, median (IQR)	6 (5.30–7)
Night after firstst vaccination, h, median (IQR)	6 (6–7)
Night shift around the day of first vaccination, *n* (%)	196 (36)
First night before second vaccination, h, median (IQR)	6 (6–7)
Second night before second vaccination, h, median (IQR)	6 (5–7)
Night after second vaccination, h, median (IQR)	6 (6–7)
Night shift around the day of second vaccination, *n* (%)	190 (35)
Short daytime naps, *n* (%)	283 (52)
Nap frequency, days/week, median (IQR)	3 (2–6)
Duration of nap, min, median (IQR)	60 (60–120)
PSQI score, median (IQR)	5 (3–7)
ESS score, median (IQR)	5 (4–9)
AIS score, median (IQR)	4 (2–7)

Note: AIS, Athens Insomnia Scale; ESS, Epworth Sleepiness Scale; IQR, interquartile range; PSQI, Pittsburg sleep quality index.

Sleep habits of participants

The median (IQR) habitual duration of sleep in all participants was 6 (6–7) h/night (Table 2). Both nurses and doctors slept for a median (IQR) of 6 (6–7) h/night. The rest of the hospital workers slept for a median (IQR) 6·25 (6–7) h/night, with no statistical differences among the three groups. In all, **283** participants (52%) habitually took short daytime naps. Males (62%) were more habitual nap sleepers than females (48%, $p < 0.01$). This group of participants had a nap a median (IQR) of 3 (2–6) days/week, for 60 (60–120) min each time. There were no differences in sleep duration between the 2 nights before and the night after vaccination. In all, 196 subjects (36%) had a night shift the 2 days before or 1 day after the first vaccination, and they slept for a median (IQR) of 5 (3–6) h that night. The median (IQR) score for the AIS, ESS and PSQI was 4 (2–7), 5 (4–9), 5 (3–7), respectively. According to the questionnaires results, 197 (36%) subjects had insomnia, 80 (14.7%) had daytime sleepiness (83.7% of them were females, $p < 0.01$). Overall, 214 (39.3%) subjects had a PSQI score of

TABLE 3 Antibody levels (AU/ml) and gender differences

	First dose	Second dose	*p*
Females	843 (423.9–1,647.5)	12,131 (7,888.5–21,913.5)	0.000
Males	626.3 (367.6–1,056.3)	11,505 (6,573–16,618.7)	0.000
p	<0.05	<0.05	

TABLE 4 Correlations (spearman coefficient, *r*) between antibody levels, after first and second vaccination dose and sleep parameters according to gender

	Females		Males	
	First dose	Second dose	First dose	Second dose
Regular night sleep	0.149, $p < 0.05$	0.112, $p < 0.05$	0.192, $p < 0.05$	0.114, $p = 0.140$
Nap frequency/week	−0.016, $p = 0.822$	−0.089, $p = 0.079$	−0.069, $p = 0.382$	−0.182, $p < 0.05$
Hours of nap sleep	0.049, $p = 0.504$	0.039, $p = 0.469$	0.006, $p = 0.944$	0.019, $p = 0.814$
AIS	−0.155, $p < 0.05$	−0.143, $p < 0.01$	−0.137, $p = 0.080$	−0.117, $p = 0.142$
ESS	−0.078, $p = 0.274$	−0.020, $p = 0.699$	−0.016, $p = 0.843$	−0.065, $p = 0.408$
PSQI	−0.200, $p < 0.01$	−0.147, $p < 0.01$	−0.139, $p = 0.076$	−0.213, $p < 0.05$

Note: AIS, Athens Insomnia Scale; ESS, Epworth Sleepiness Scale; PSQI, Pittsburg sleep quality index;.

TABLE 5 Uni- and multivariate linear regression model evaluating the association of antibodies with covariates

Univariate analysis				Multivariate analysis			
	Unstandardised coefficient	Standardised coefficient	*p*		Unstandardised coefficient	Standardised coefficient	*p*
Dependent variable: antibody titres after first dose							
AIS	−80.525	−0.091	0.033	AIS	−101.601	−0.110	0.017
				Gender	782.418	0.100	0.029
				Age	−19.630	−0.055	0.226
				Smoking	−312.670	−0.058	0.212
				Exercise	−167.781	−0.051	0.272
				Time of vaccination	111.246	0.020	0.660
PSQI	−94.500	−0.075	0.080	PSQI	−112.220	−0.086	0.052
				Gender	756.754	0.097	0.035
				Age	−21.129	−0.060	0.193
				Smoking	−292.097	−0.054	0.246
				Exercise	−182.083	−0.055	0.233
				Time of vaccination	97.870	0.018	0.700
Epworth	13.630	0.015	0.719	Epworth	3.231	0.003	0.940
				Gender	702.866	0.090	0.051
				Age	−20.623	−0.058	0.207
				Smoking	−325.772	−0.060	0.197
				Exercise	−203.264	−0.062	0.185
				Time of vaccination	91.233	0.017	0.720
Dependent variable: antibody titres after second dose							
AIS	−214.530	−0.087	0.042	AIS	−240.617	−0.097	0.037
				Gender	2456.931	0.117	0.010
				Age	−137.957	−0.146	0.001
				Smoking	−584.330	−0.040	0.379
				Exercise	201.440	0.023	0.619
				Time of vaccination	739.322	0.054	0.241
PSQI	−217.136	−0.062	0.150	PSQI	−223.233	−0.064	0.164
				Gender	2367.939	0.113	0.013
				Age	−141.867	−0.150	0.001
				Smoking	−546.151	−0.038	0.413
				Exercise	162.256	0.018	0.689
				Time of vaccination	564.748	0.041	0.365
ESS	−8.205	−0.003	0.938	ESS	3.622	0.001	0.974
				Gender	2258.518	0.108	0.018
				Age	−141.209	−0.149	0.001
				Smoking	−612.574	−0.042	0.358
				Exercise	122.147	0.014	0.764
				Time of vaccination	479.944	0.035	0.440

Note: AIS, Athens Insomnia Scale; ESS, Epworth Sleepiness Scale; PSQI, Pittsburg Sleep Quality Index.

>5, females more than males (74.3%, $p < 0.05$), and they were predominantly nursing staff (54·2%, $p < 0.05$; Table 1).

Antibody levels among participants

After the first dose of vaccination the median (IQR) antibody level was 760 (391.3–1,420) AU/ml and after the second dose was 11,998·8 (7,333–20,523) AU/ml. After the second dose, participants had significantly higher levels of antibodies compared to the levels produced after the first dose ($p < 0.001$). There were no differences between the antibody levels among medical, nursing, and other staff. Antibody levels after the first and second dose were significantly higher in females compared to males (Table 3).

Time of vaccination and relation with antibody levels

From the 478 subjects that were analysed, only 257 had both doses given at the same time of day. Subjects were divided into three groups according to the time of their vaccination (Group A, 7:00–10:59 a.m.; Group B, 11:00 a.m.–**2:59** p.m.; Group C, 3:00–9:59 p.m.). Group A comprised 146 subjects, Group B 91, and Group C 20. There were no statistically significant differences between the levels of antibody titres after the first or the second vaccination amongst the three groups. In all 478 subjects, after the first dose of the vaccination, the analysis showed that most of the subjects were in Group A ($N = 230$) and Group B ($N = 206$). Only 42 participants belonged to Group C. Comparing the levels of the antibodies after the first vaccination, there were no differences between the three groups. In addition, after dividing the sample into two groups (early in the morning $N = 230$ versus rest of the day $N = 278$) the levels of antibodies were increased when the vaccination was done later in the day and not in the early morning, showing a statistical trend $p = 0.09$, but not statistically significant.

Participants who were eventually infected after the second vaccination

In all, 80 (14.70%) subjects were infected after the two vaccinations, at a median (IQR) of 320 (282–342) days after the second vaccination. There were no significant differences between the "poor" and "good" sleepers ($p = 0.520$), neither for antibody levels after the first ($p = 0.835$) nor the second dose ($p = 0.947$) of vaccination, but firm conclusions are not possible to make because most of the healthcare workers had also a third dose of vaccine, 6 months after the second dose.

Relationship between antibody concentration and demographic characteristics and sleep

After the first vaccination, antibody levels were significantly correlated with age ($r = -0.259$, $p < 0.001$). After the second vaccination, antibody levels were associated with age ($r = -0.178$, $p < 0.001$), smoking pack-years ($r = -0.178$, $p = 0.001$), and working hours ($r = -0.085$, $p < 0.05$).

After the second vaccination, antibody levels were negatively correlated with nap frequency/week ($r = -0.098$, $p < 0.05$), AIS score ($r = -0.098$, $p < 0.05$), and GR-PSQI score ($r = -0.094$, $p < 0.05$). The relation of antibody levels to sleep was stronger in females (Table 4). The multivariate analysis showed that the levels of antibodies after the first vaccination were significantly associated with gender, AIS score, and marginally associated with the PSQI score, whereas after the second vaccination the antibody levels were significantly

TABLE 6 Multiple linear regression model evaluating the association of antibodies after the second dose with covariates

	Unstandardised coefficient	Standardised coefficient	*p*
Model 1 (dependent variable: antibody titres after second dose) adjusted $R^2 = 0.095$			
AIS	−175.93	−0.072	0.054
Gender	1734.82	0.084	0.042
Age	−124.37	−0.133	0.001
Smoking	−341.19	−0.024	0.568
Exercise	330.40	0.037	0.368
Antibodies after first dose	0.695	0.249	<0.001
Model 2 (dependent variable: antibody titres after second dose) adjusted $R^2 = 0.093$			
PSQI	−191.56	−0.055	0.188
Gender	1714.49	0.083	0.046
Age	−126.93	−0.135	0.001
Smoking	−315.61	−0.022	0.599
Exercise	304.27	0.034	0.407
Antibodies after first dose	0.702	0.252	<0.001

Note: AIS, Athens Insomnia Scale; PSQI, Pittsburg Sleep Quality Index.

associated with gender, age, and AIS score. However, when the response to the primary vaccination was included in the analysis, then the AIS was associated with antibody levels after the second vaccination ($p = 0.054$; Tables 5 and 6). There were no differences between the antibody levels in subjects who had a night shift 2 days before or a day after vaccinations, compared to subjects without any night shifts during those days.

After analysing the sum of the antibody levels after the first and the second vaccination for each subject, subjects with a PSQI score of ≤5 trended to have a higher median (IQR) antibody level at 12,367 (7,867–20,403) AU/ml compared to "poor" sleepers at 11,406·5 (6,820·5–19,552) AU/ml, but the result was marginal ($p = 0{\cdot}101$).

DISCUSSION

Even though in the last few months new therapeutic approaches have emerged, our greatest weapon against the COVID-19 pandemic and its containment is vaccination. To the best of our knowledge, this is the first study to establish a relationship between sleep quality and quantity, and immunological response after vaccination against COVID-19. This study, also, tried to summarise the observations and conclusions of other reports regarding the association between other types of vaccines and sleep.

It is of great importance to further investigate the role of sleep as a major factor of the immunological response after vaccination against the SARS-CoV-2 virus. Sleep constitutes a basic and vital need for humans as it accounts for roughly one-third of the human lifespan (Besedovsky et al., 2019). Recent studies verify that during sleep, especially in the slow-wave stage, certain information from immunity cells regarding antigen targets is transferred and encrypted, in order to produce a better immunological response against antigens (Besedovsky et al., 2019).

Although there are few studies concerning the effect of vaccination on sleep, their results seem noteworthy. Vaccination against *Salmonella typhi* in healthy volunteers raised interleukin-6 levels 2 h after administration and led to disruptions during night-time sleep and frequent awakenings, compared to those who were administered placebo (Sharpley et al., 2016). Other studies with vaccines against HAV or influenza virus H1N1 in healthy adults proved that a night of sleep deprivation after vaccination is enough to observe a reduced immunity response against HAV at 4, 8, and 16 weeks later, as well as reduced H1N1-specific antibodies 5 days after vaccination in males (Benedict & Cedernaes, 2021; Lange et al., 2011). The immunological difference between the two groups was observed even a year after vaccination (Lange et al., 2011). Another study examined the effect of reduced sleep duration (4 h) for 4 consecutive nights before and 2 nights after vaccination against influenza (Spiegel et al., 2002). This study pointed out that IgG antibody concentration 10 days after vaccination was reduced in ∼50% of the individuals who did not have an adequate sleep duration of 7·5–8 h (Spiegel et al., 2002). A recent study showed that the total antibody titre against the influenza virus at 1 and 4 months after vaccination depended on the sleep duration 2 nights before the vaccine administration (Prather et al., 2021). In our study, the duration of sleep 2 days before and a day after vaccination was not correlated with antibody levels, but it should be noted that these results were extracted from questionnaires, giving the subjective feeling of sleep of the participants. Notably, regular sleep duration in women was associated with antibody levels after the first and second vaccination. In a similar manner, a prospective study showed that a short sleep duration in actigraphy was associated with a lower antibody titre and a smaller chance of immunological protection 6 months after vaccination against HBV (Prather et al., 2012).

In our study, an increased frequency of afternoon nap sleep per week was negatively correlated with antibody levels, but this relation disappeared after adjustment for confounders. The afternoon nap is considered to be of cultural and climatic origin, and usually is more frequent in the elderly. However, it is also recognised as a factor of daytime sleepiness, indicating a possible underdiagnosed nocturnal sleep-disordered breathing (Mantua & Spencer, 2017). The afternoon nap reduces sleepiness and may have some benefit on cognitive function and emotional stability, but frequent naps have also been linked with increased risk of diabetes, hypertension, immobility, and mortality (Mantua & Spencer, 2017; Fang et al., 2013; Cao et al., 2014). Recent evidence supports the notion that inflammation could act as a mediator between frequent naps and unfavourable outcomes (Mantua & Spencer, 2017).

A previous study presented that, patients who had insomnia, developed lower antibody titres against the influenza virus compared to healthy individuals (Taylor et al., 2017). Also, poor sleep quality evaluated with the PSQI questionnaire was correlated with a lower immune response to vaccination regardless of the presence of insomnia (Taylor et al., 2017). Similar findings were observed in the present study, poor sleep quality, and the presence of insomnia, according to the PSQI and AIS questionnaire, respectively, was negatively associated with antibody levels against COVID-19. The association of the AIS score with antibody titres remained even after adjusting for confounding factors. Interestingly, this relationship between antibody levels and sleep was stronger in females. Previous studies have shown gender differences in sleep questionnaires (Pataka et al., 2020). Especially for insomnia, the AIS questionnaire seems to be more sensitive in females with obstructive sleep apnea than in males. Evidence suggests that self-reported sleep quality also differs between men and women. Studies have also shown that the association between disrupted sleep and markers of inflammation are stronger in women than in men (Irwin et al., 2010; Miller et al., 2009). In our present study, levels of antibodies were significantly more elevated in females than in males. Similar results were obtained in various studies (Kontou et al., 2021; Terpos et al., 2021). Likewise, previous studies, concerning the influenza vaccine, showed higher antibody titres in women who were vaccinated with the trivalent inactivated seasonal influenza vaccine (TIV) in comparison to men (Voigt et al., 2019), and serum testosterone levels were inversely associated with the TIV antibody titres (Furman et al., 2014).

Innate immunity and adaptive immune mechanisms are known to be affected by cigarette consumption (Qiu et al., 2017). Previous studies have shown reduced IgG concentration in smokers (Gonzalez-Quintela et al., 2008; McMillan et al., 1997). As stated previously, there was a negative correlation between the total antibody count after vaccination and smoking in the present study. A recent study, by Watanabe et al. (2021) showed similarly that smokers had a lower antibody titre after Pfizer-BioNTech vaccination against COVID-19.

Our immune system follows a circadian pattern (Druzd et al., 2017) and healthcare professionals who often experience a chronic circadian disruption exhibit a markedly greater risk of COVID-19 diagnosis (Rizza et al., 2021). Furthermore, there are several studies that point out the effect of COVID-19 pandemic as well as the consequent lockdown on sleep in healthcare professionals (Trakada et al. 2020; Pappa et al., 2021). In this study, the amount of night shifts/month was not associated with the immune response against COVID-19. There was no association between antibodies and the presence of night shifts before vaccination. This could be explained by the fact that the percentage of medical personnel that had a night shift before vaccination was small, therefore no firm conclusions can be drawn. According to the AIS results, 197 (36%) subjects had insomnia in this study, this percentage is higher than the estimated proportion of insomnia in the Greek population (Paparrigopoulos et al., 2010). However, our results are in accordance with previous work, concerning the percentage of insomnia in medical personnel (Győrffy et al., 2016). Particularly, female medical staff seemed to be more vulnerable on presenting with insomnia because of work overload (Győrffy et al., 2016). In this study, increased working hours were associated with lower antibody titres.

The time of vaccination is highlighted as an important factor affecting the immune response. Previous studies have shown conflicting evidence. A study (Wang et al., 2022) found that anti-Spike responses were higher in those who were vaccinated later in the day after a single dose of vaccination, but another study (Zhang et al., 2021) presented the opposite results. Specifically, the study showed an increase of anti-Spike antibodies in participants vaccinated in the morning. In the Zhang et al. (2021) research, antibodies were examined after the first and after the second dose of vaccine, and those doses were given at the same time of a day. These two studies have many methodological differences, and it is difficult to compare them. In our study, the two doses in many subjects were not given at the same time of the day, so it would be difficult to extrapolate firm conclusions. It would be better to examine the results after the first dose of vaccination, like Wang et al. (2022) did. In that analysis, dividing the participants into two groups (early in the morning $N = 230$ versus rest of the day $N = 278$) there was a statistical trend $p = 0.09$, but not significant.

There are limitations that need to be acknowledged. Currently, there is no adequate evidence linking the increased levels of antibodies against COVID-19 with greater intensity and duration of protection or reduced risk of transmission after infection. These matters should be further investigated. Another limitation is the age of the participants. As the participants were all healthcare workers, elderly people were excluded from this study. Further studies should target the elderly, as older adults are more vulnerable to COVID-19 infection, and they manifest more frequently with sleep difficulties.

CONCLUSIONS

In conclusion, insomnia was associated with lower levels of vaccine-induced anti-S protein IgG antibodies against COVID-19. Given the high importance of preserving an adequate immune response against COVID-19, the findings of the present study have important implications. The primary role of adequate sleep should be emphasised in order to obtain a satisfactory immune response against COVID-19. Moreover, our study observations pave the way for further studies investigating the impact of sleep on long-term vaccine effectiveness in protecting from SARS-CoV2 infection.

AUTHOR CONTRIBUTIONS

All authors contributed in a meaningful way to this manuscript. Conceptualisation, Katerina Baou, Nikolaos Athanasiou and Emmanouil Vagiakis; methodology, Nikolaos Athanasiou and Katerina Baou; formal analysis, Katerina Baou and Nikolaos Athanasiou; investigation, Nikolaos Athanasiou, Katerina Baou, Eleni Papandreou, Georgia Varsou, Anastasia Amfilochiou, Elisavet Kontou, Athanasia Pataka, Konstantinos Porpodis, Ioanna Tsiouprou, Evangelos Kaimakamis, Serafeim-Chrysovalantis Kotoulas, Evgenia Katsibourlia, Christina Alexopoulou Izolde Bouloukaki, Meropi Panagiotarakou, Aspasia Dermitzaki, Nikolaos Charokopos, Kyriakh Pagdatoglou, Kallirroi Lamprou, Sofia Pouriki, Foteini Chatzivasiloglou, Zoi Nouvaki, Alexandra Tsirogianni, Ioannis Kalomenidis, Paraskevi Katsaounou, Emmanouil Vagiakis; writing – original draft preparation, Nikolaos Athanasiou and Katerina Baou; writing – review and editing, Nikolaos Athanasiou, Katerina Baou, Emmanouil Vagiakis, Athanasia Pataka, Ioannis Kalomenidis, Nikolaos Charokopos and Lamprou Kallirroi; supervision, Emmanouil Vagiakis, Nikolaos Athanasiou, Katerina Baou, Athanasia Pataka, Alexopoulou Christina and Amfilochiou Anastasia; project administration, Nikolaos Athanasiou, Katerina Baou and Emmanouil Vagiakis. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

Benedict, C., Brytting, M., Markström, A., Broman, J. E., & Schiöth, H. B. (2012). Acute sleep deprivation has no lasting effects on the human antibody titer response following a novel influenza a H1N1 virus vaccination. *BMC Immunology*, *13(1)*, *1-5*. https://doi.org/10.1186/1471-2172-13-1

Benedict, C., & Cedernaes, J. (2021). Could a good night's sleep improve COVID-19 vaccine efficacy? *The Lancet Respiratory Medicine*, *9*(5), 447–448. https://doi.org/10.1016/S2213-2600(21)00126-0

Besedovsky, L., Lange, T., & Haack, M. (2019). The sleep-immune crosstalk in health and disease. *Physiological Reviews*, *99*(3), 1325–1380. https://doi.org/10.1152/PHYSREV.00010.2018

Bryan, A., Pepper, G., Wener, M. H., Fink, S. L., Morishima, C., Chaudhary, A., Jerome, K. R., Mathias, P. C., & Greninger, A. L. (2020). Performance characteristics of the Abbott architect SARS-CoV-2 IgG assay and Seroprevalence in Boise, Idaho. *Journal of Clinical Microbiology*, *58*(8), e00941-e00920. https://doi.org/10.1128/JCM.00941-20

Cao, Z., Shen, L., Wu, J., Yang, H., Fang, W., Chen, W., Yuan, J., Wang, Y., Liang, Y., & Wu, T. (2014). The effects of midday nap duration on the risk of hypertension in a middle-aged and older Chinese population: A preliminary evidence from the Tongji-Dongfeng cohort study, China. *Journal of Hypertension*, *32*(10), 1993–1998. https://doi.org/10.1097/HJH.0000000000000291

Druzd, D., Matveeva, O., Ince, L., Harrison, U., He, W., Schmal, C., Herzel, H., Tsang, A. H., Kawakami, N., Leliavski, A., Uhl, O., Yao, L., Sander, L. E., Chen, C. S., Kraus, K., Juam, de, A., Hergenhan, S. M., Ehlers, M., Koletzko, B., … Scheiermann, C. (2017). Lymphocyte circadian clocks control lymph node trafficking and adaptive immune responses. *Immunity*, *46*(1), 120–132. https://doi.org/10.1016/J.IMMUNI.2016.12.011

Fang, W., Li, Z., Wu, L. L., Cao, Z., Liang, Y., Yang, H., Wang, Y., & Wu, T. (2013). Longer habitual afternoon napping is associated with a higher risk for impaired fasting plasma glucose and diabetes mellitus in older adults: Results from the Dongfeng-Tongji cohort of retired workers. *Sleep Medicine*, *14*(10), 950–954. https://doi.org/10.1016/J.SLEEP.2013.04.015

Fatima, Y., Bucks, R. S., Mamun, A. A., Skinner, I., Rosenzweig, I., Leschziner, G., & Skinner, T. C. (2021). Shift work is associated with increased risk of COVID-19: Findings from the UKbiobank cohort. *Journal of Sleep Research*, *30*(5), e13326. https://doi.org/10.1111/JSR.13326

Furman, D., Hejblum, B. P., Simon, N., Jojic, V., Dekker, C. L., Thiébaut, R., Tibshirani, R. J., & Davis, M. M. (2014). Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(2), 869–874. https://doi.org/10.1073/PNAS.1321060111

Gonzalez-Quintela, A., Alende, R., Gude, F., Campos, J., Rey, J., Meijide, L. M., Fernandez-Merino, C., & Vidal, C. (2008). Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities. *Clinical and Experimental Immunology*, *151*(1), 42–50. https://doi.org/10.1111/J.1365-2249.2007.03545.X

Győrffy, Z., Dweik, D., & Girasek, E. (2016). Workload, mental health and burnout indicators among female physicians. *Human Resources for Health*, *14*(1), 12. https://doi.org/10.1186/S12960-016-0108-9

Hass, E. J., Angulo, F. J., McLaughlin, J. M., Anis, E., Singer, S. R., Khan, F., Brooks, N., Smaja, M., Mircus, G., Pan, K., Southern, J., Swerdlow, D. L., Jodar, L., Levy, Y., & Alroy-Preis, S. (2021). Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: An observational study using national surveillance data. *Lancet (London, England)*, *397*(10287), 1819–1829. https://doi.org/10.1016/S0140-6736(21)00947-8

Huang, R., Zhuid, L., Xue, L., Liu, L., Yan, X., Wang, J., Zhang, B., Xu, T., Ji, F., Zhao, Y., Cheng, J., Wang, Y., Shao, H., Hong, S., Cao, Q., Li, C., Zhao, X. A., Zou, L., Sang, D., … Wu, C. (2020). Clinical findings of patients with coronavirus disease 2019 in Jiangsu Province, China: A retrospective, multi-center study. *PLoS Neglected Tropical Diseases*, *14*(5), 1–14. https://doi.org/10.1371/JOURNAL.PNTD.0008280

Irwin, M. R., Carrillo, C., & Olmstead, R. (2010). Sleep loss activates cellular markers of inflammation: Sex differences. *Brain, Behavior, and Immunity*, *24*(1), 54–57. https://doi.org/10.1016/J.BBI.2009.06.001

Kontou, E., Ranellou, K., Zoulas, D., Bletsa, A., Rompola, E., Piperaki, E. T., Athanasiou, N., Ampelakiotou, K., Patikaki, M., Stergioloulou, C., Argyropoulou, A., Alevra, A., Megalou, A., & Tsirogianni, A. (2021). Antibody response following a two-dose mRNA vaccination regimen, in health Care Workers of a Tertiary Hospital in Athens, Greece. *Journal of. Personalized Medicine*, *11*(6), 576. https://doi.org/10.3390/JPM11060576

Kotronoulas, G. C., Papadopoulou, C. N., Papapetrou, A., & Patiraki, E. (2011). Psychometric evaluation and feasibility of the Greek Pittsburgh sleep quality index (GR-PSQI) in patients with cancer receiving chemotherapy. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *19*(11), 1831–1840. https://doi.org/10.1007/S00520-010-1025-4

Lange, T., Dimitrov, S., Bollinger, T., Diekelmann, S., & Born, J. (2011). Sleep after vaccination boosts immunological memory. *Journal of Immunology (Baltimore, Md.: 1950)*, *187*(1), 283–290. https://doi.org/10.4049/JIMMUNOL.1100015

Leong, R. L. F., Yu, N., Ong, J. L., Ng, A. S. C., Jamaluddin, S. A., Cousins, J. N., Chee, N. I. Y. N., & Chee, M. W. L. (2021). Memory performance following napping in habitual and non-habitual nappers. *Sleep*, *44*(6), 1–11. https://doi.org/10.1093/SLEEP/ZSAA277

Mantua, J., & Spencer, R. M. C. (2017). Exploring the nap paradox: Are mid-day sleep bouts a friend or foe? *Sleep Medicine*, *37*, 88–97. https://doi.org/10.1016/J.SLEEP.2017.01.019

McMillan, S. A., Douglas, J. P., Archbold, G. P., McCrum, E. E., & Evans, A. E. (1997). Effect of low to moderate levels of smoking and alcohol consumption on serum immunoglobulin concentrations. *Journal of Clinical Pathology*, *50*(10), 819–822. https://doi.org/10.1136/JCP.50.10.819

Miller, M. A., Kandala, N.-B., Kivimaki, M., Kumari, M., Brunner, E. J., Lowe, G. D. O., Marmot, M. G., & Cappuccio, F. P. (2009). Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: Whitehall II study. *Sleep*, *32*(7), 857 /pmc/articles/PMC2706900/.

Paparrigopoulos, T., Tzavara, C., Theleritis, C., Psarros, C., Soldatos, C., & Tountas, Y. (2010). Insomnia and its correlates in a representative sample of the Greek population. *BMC Public Health*, *10*(1), 1–7. https://doi.org/10.1186/1471-2458-10-531

Pappa, S., Athanasiou, N., Sakkas, N., Patrinos, S., Sakka, E., Barmparessou, Z., Tsikrika, S., Adraktas, A., Pataka, A., Migdalis, I., Gida, S., & Katsaounou, P. (2021). From recession to depression? Prevalence and correlates of depression, anxiety, traumatic stress and burnout in healthcare workers during the COVID-19 pandemic in Greece: A multi-center, cross-sectional study. *International Journal of Environmental Research and Public Health*, *18*(5), 1–16. https://doi.org/10.3390/IJERPH18052390

Pataka, A., Kotoulas, S., Kalamaras, G., Schiza, S., Sapalidis, K., Giannakidis, D., Michalopoulos, N., Koulouris, C., Aidoni, Z., Amaniti, A., Bouloukaki, I., Chatzopoulos, E., Romanidis, K., Oikonomou, P., Steiropoulos, P., Trakada, G., Vagionas, A., Ioannidis, A., Katsios, I. N., … Kosmidis, C. (2020). Gender differences in obstructive sleep apnea: The value of sleep questionnaires with a

separate analysis of cardiovascular patients. *Journal of Clinical Medicine*, *9*(1), 130. https://doi.org/10.3390/JCM9010130

Prather, A. A., Hall, M., Furry, J. M., Ross, D. C., Muldoon, M. F., Cohen, S., & Marsland, A. L. (2012). Sleep and antibody response to hepatitis B vaccination. *Sleep*, *35*(8), 1063–1069. https://doi.org/10.5665/SLEEP.1990

Prather, A. A., Pressman, S. D., Miller, G. E., & Cohen, S. (2021). Temporal links between self-reported sleep and antibody responses to the influenza vaccine. *International Journal of Behavioral Medicine*, *28*(1), 151–158. https://doi.org/10.1007/S12529-020-09879-4

Qiu, F., Liang, C. L., Liu, H., Zeng, Y. Q., Hou, S., Huang, S., Lai, X., & Dai, Z. (2017). Impacts of cigarette smoking on immune responsiveness: Up and down or upside down? *Oncotarget*, *8*(1), 268–284. https://doi.org/10.18632/ONCOTARGET.13613

Sharpley, A. L., Cooper, C. M., Williams, C., Godlewska, B. R., & Cowen, P. J. (2016). Effects of typhoid vaccine on inflammation and sleep in healthy participants: A double-blind, placebo-controlled, crossover study. *Psychopharmacology*, *233*(18), 3429–3435. https://doi.org/10.1007/S00213-016-4381-Z

Soldatos, C. R., Dikeos, D. G., & Paparrigopoulos, T. J. (2000). Athens insomnia scale: Validation of an instrument based on ICD-10 criteria. *Journal of Psychosomatic Research*, *48*(6), 555–560. https://doi.org/10.1016/S0022-3999(00)00095-7

Spiegel, K., Sheridan, J. F., & Van Cauter, E. (2002). Effect of sleep deprivation on response to immunization. *JAMA*, *288*(12), 1471-a-1472. https://doi.org/10.1001/JAMA.288.12.1471-A

Rizza, S., Coppeta, L., Grelli, S., Ferrazza, G., Chiocchi, M., Vanni, G., Bonomo, O. C., Bellia, A., Andreoni, M., Magrini, A., & Federici, M. (2021). High body mass index and night shift work are associated with COVID-19 in health care workers. *Journal of Endocrinological Investigation*, *44*(5), 1097–1101. https://doi.org/10.1007/S40618-020-01397-0

Taylor, D. J., Kelly, K., Kohut, M. L., & Song, K. S. (2017). Is insomnia a risk factor for decreased influenza vaccine response? *Behavioral Sleep Medicine*, *15*(4), 270–287. https://doi.org/10.1080/15402002.2015.1126596

Terpos, E., Trougakos, I. P., Apostolakou, F., Charitaki, I., Sklirou, A. D., Mavrianou, N., Papanagnou, E. D., Liacos, C. I., Gumeni, S., Rentziou, G., Korompoki, E., Papassotiriou, I., & Dimopoulos, M. A. (2021). Age-dependent and gender-dependent antibody responses against SARS-CoV-2 in health workers and octogenarians after vaccination with the BNT162b2 mRNA vaccine. *American Journal of Hematology*, *96*(7), E257–E259. https://doi.org/10.1002/AJH.26185

Trakada, A., Nikolaidis, P. T., Andrade, M. D. S., Puccinelli, P. J., Economou, N. T., Steiropoulos, P., Knechtle, B., & Trakada, G. (2020). Sleep during "lockdown" in the COVID-19 pandemic. *International Journal of Environmental Research and Public Health*, *17*(23), 1–10. https://doi.org/10.3390/IJERPH17239094

Tsara, V., Serasli, E., Amfilochiou, A., Constantinidis, T., & Christaki, P. (2004). Greek version of the Epworth sleepiness scale. *Sleep & Breathing = Schlaf & Atmung*, *8*(2), 91–95. https://doi.org/10.1007/S11325-004-0091-6

Voigt, E. A., Ovsyannikova, I. G., Kennedy, R. B., Grill, D. E., Goergen, K. M., Schaid, D. J., & Poland, G. A. (2019). Sex differences in older Adults' immune responses to seasonal influenza vaccination. *Frontiers in Immunology*, *10*, 180. https://doi.org/10.3389/FIMMU.2019.00180

Wang, W., Balfe, P., Eyre, D. W., Lumley, S. F., O'Donnell, D., Warren, F., Crook, D. W., Jeffery, K., Matthews, P. C., Klerman, E. B., & McKeating, J. A. (2022). Time of day of vaccination affects SARS-CoV-2 antibody responses in an observational study of health care workers. *Journal of Biological Rhythms*, *37*(1), 124–129. https://doi.org/10.1177/07487304211059315

Watanabe, M., Balena, A., Tuccinardi, D., Tozzi, R., Risi, R., Masi, D., Caputi, A., Rossetti, R., Spoltore, M. E., Filippi, V., Gangitano, E., Manfrini, S., Mariani, S., Lubrano, C., Lenzi, A., Mastroianni, C., & Gnessi, L. (2021). Central obesity, smoking habit, and hypertension are associated with lower antibody titres in response to COVID-19 mRNA vaccine. *Diabetes/Metabolism Research and Reviews.*, *38*(1), e3465. https://doi.org/10.1002/DMRR.3465

Zhang, H., Liu, Y., Liu, D., Zeng, Q., Li, L., Zhou, Q., Li, M., Mei, J., Yang, N., Mo, S., Liu, Q., Liu, M., Peng, S., & Xiao, H. (2021). Time of day influences immune response to an inactivated vaccine against SARS-CoV-2. *Cell Research*, *31*(11), 1215–1217. https://doi.org/10.1038/S41422-021-00541-6

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet (London, England)*, *395*(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zimmermann, P., & Curtis, N. (2019). Factors that influence the immune response to vaccination. *Clinical Microbiology Reviews*, *32*(2), 1-50. https://doi.org/10.1128/CMR.00084-18

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