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Effect of daily alcohol consumption and age over 40 years on COVID-19 vaccination antibody titers in the Delta era among hospital workers in northern Okinawa, Japan: A retrospective cohort study

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) vaccination has demonstrated efficacy in preventing infection, mitigating disease severity, and lowering the incidence of Long COVID. To enhance vaccine effectiveness, it is not only important to develop more effective vaccines but also to clarify factors, including lifestyle, that affect the immune response. The aim of this study was to investigate the impact of lifestyle factors on COVID-19 vaccination antibody titers.

Methods: Antibody titers of 354 hospital workers who received two COVID-19 vaccination doses were measured five times for more than six months. Information on medical history, demographic characteristics, and lifestyle-related items was obtained from hospital health checkups. The outcome variable (Lower-25 %) was defined as the antibody titer value below the 25th percentile of the fifth measurement. The Cox proportional hazard survival model was used to evaluate the hazard ratio for incidence of Lower-25 % according to lifestyle-related items.

Results: The crude incidence rates per 1,000 person-days for Lower-25 % among women and men were 1.35 and 1.66, respectively. The hazard ratios for Lower-25 % of those in their 40 s, 50 s, and 60 s compared with those in their 20 s were 5.82 (95 % confidence interval [CI], 2.05–16.51), 7.12 (95 % CI, 2.46–20.63), and 9.96 (95 % CI, 3.07–32.34), respectively. The hazard ratios for “daily” versus “never” drinking habits were 2.26 (95 % CI 1.17–4.34).

Conclusions: The results of this study indicate that shortening vaccination intervals for individuals over 40 years and discontinuing daily alcohol consumption are associated with the preservation of acquired antibody titers for optimizing vaccine efficacy.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a devastating impact, with over 775 million cases and over 7 million deaths worldwide (as of July 21, 2024) [1]. Although the health damage caused by COVID-19 has reduced owing to the attenuation of mutant strains, vaccination, and treatment development, COVID-19 countermeasures must continue in the future. This indicates that we have entered an era in which we will have to live with COVID-19 for a long time.

COVID-19 vaccination has demonstrated efficacy in preventing infection, mitigating disease severity, and lowering the incidence of post-acute sequelae (Long COVID) [2–12]. In addition, a cross-sectional study on "factors that worsen the severity to moderate or severe" was conducted on 1353 people extracted from 4899 COVID-19 patients who visited the hospital where the present study was conducted [13]. As a result, the adjusted odds ratio for worsening severity was 0.09 for "three or more vaccinations" compared with "zero or one vaccination," indicating an improvement of >90 %. It has become clear that vaccination will play a vital role in future COVID-19 countermeasures. To maintain

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and enhance vaccine effectiveness, it is important to develop more effective vaccines as well as clarify factors, including lifestyle, that affect the immune response.

Age, gender, and drinking habits have been reported as factors that affect immune response to COVID-19 vaccination [14–16]. However, most of these studies were cross-sectional and included limited factors. As there are several biases in the cross-sectional study, the reliability of the results regarding the multifactorial associations may be problematic. Therefore, we aimed to investigate various factors, including lifestyle, that affect antibody titers induced by vaccination and to clarify important matters for improving vaccine effectiveness in a retrospective cohort study.

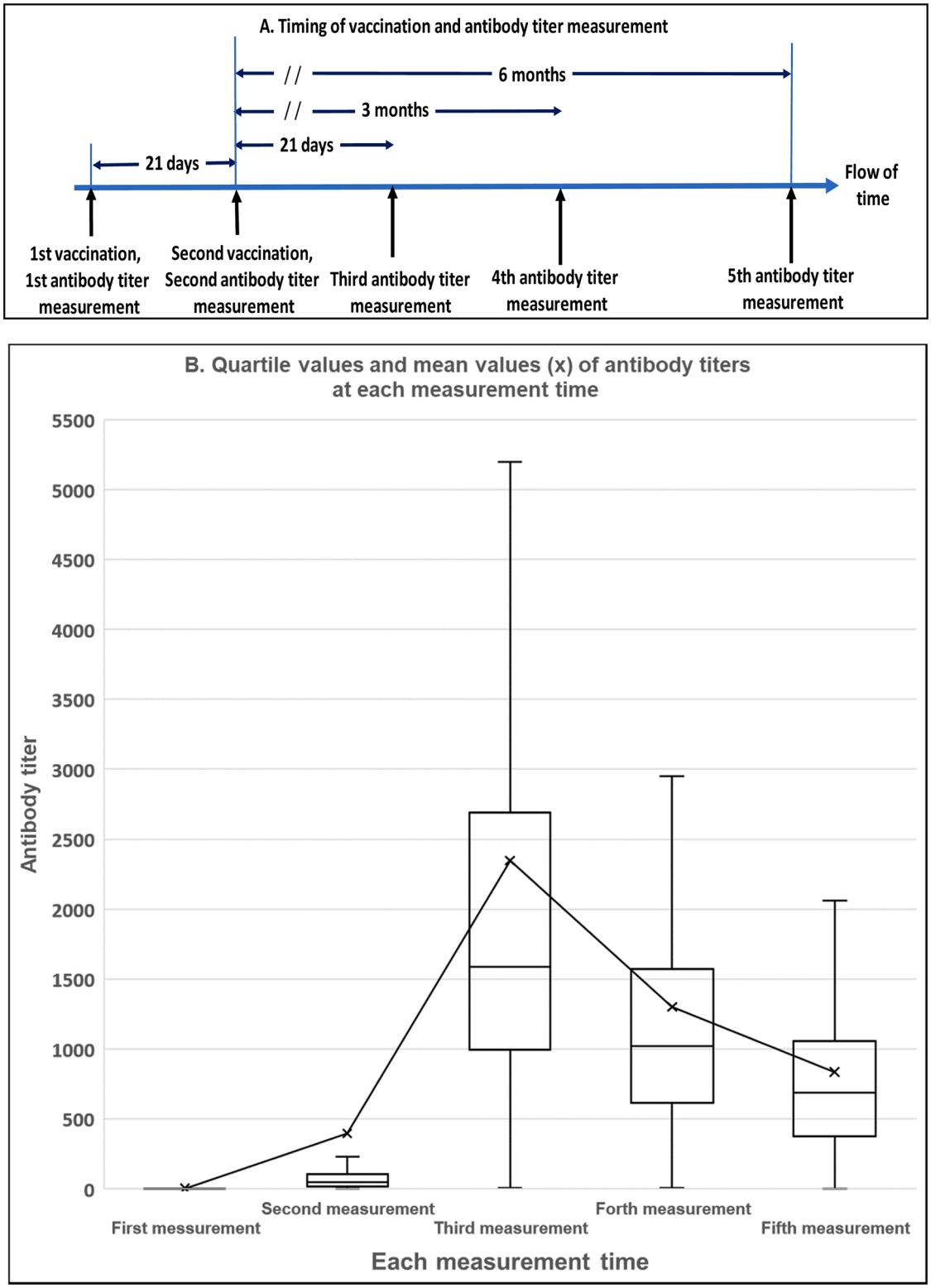

Fig. 1. Timing of vaccination and antibody titer measurement (A), Interquartile and mean values without outliers (B).

2. Materials and methods

2.1. Study design and population

This retrospective cohort study comprised 354 employees of the Okinawa North Medical Association Hospital who received two doses of the BNT162b2 mRNA COVID-19 vaccine (Pfizer/BioNTech) and underwent five antibody titrations (Fig. 1A). The two-dose vaccination was the first to be administered to healthcare workers as part of the Japanese government's policy against COVID-19. The first vaccination period ranged from March 9, 2021, to April 12, 2021, which coincided with the Delta variant predominance era. Individuals with a history of COVID-19, positive antibody titers before vaccination, and those infected with COVID-19 during the observation period (10 patients) were excluded. Total antibody titers against the SARS-CoV-2 spike antigen were measured using a commercially available electrochemiluminescence immunoassay (Elecsys® Anti-SARS-CoV-2 S RUO; Roche Diagnostics).

2.2. Outcome variable

Fig. 1A illustrates the timing of vaccination and antibody titer measurements. The outcome variable in this study (Lower-25 %) was defined as the antibody titer value obtained at either the fourth (3 months after the 2nd vaccination) or fifth (6 months after the 2nd vaccination) measurement, that fell below the 25th percentile of the fifth measurement.

2.3. Explanatory variables

The explanatory variables collected at the time of first vaccination included gender and age. Additional explanatory variables obtained from the results of the most recent health checkup before the first vaccination comprised body mass index, prevalence of metabolic syndrome, treatment for dyslipidemia, treatment for diabetes, treatment for hypertension, history of chronic renal failure, history of cardiovascular disease, history of cerebrovascular disease, and the following lifestyle-related items: (1) "having an evening meal within two hours before bedtime three days or more per week (no/yes)," (2) "eating snacks and sweet beverages other than breakfast, lunch, and dinner (no/sometimes/daily)," (3) "eating faster than others (slow/usual/fast)," (4) "skipping breakfast at least three times a week (no/yes)," (5) "walking for at least one hour/day or having equivalent physical activities (no/yes)," (6) "exercising at least two days/week at least 30 min each at an intensity that causes a slight sweat for at least one year (no/yes)," (7) "frequency of drinking (never/sometimes/daily)," (8) "regular smoker (no/yes)," and (9) "feeling refreshed after a night's sleep (no/yes)".

2.4. Adjusted variable

The adjusted variables consisted of all explanatory variables, which were incorporated into the Cox proportional hazards survival model and analyzed using forced entry and backward stepwise methods.

2.5. Statistical analysis

Explanatory variables were included in the Cox proportional hazard survival model to calculate the hazard ratio values using both forced entry and backward stepwise methods. A significance level of $\alpha = 0.05$ was used to determine the significance of both the models and variables. All statistical analyses were performed using IBM SPSS Statistics ver. 28 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Study population

This study comprised 227 women (mean age ± standard deviation: 41.4 ± 11.2 years) and 127 men (mean age: 42.2 ± 12.5 years). Baseline characteristics are detailed in Table 1. The prevalence of comorbidities was as follows: obesity (body mass index [BMI] ≥ 30) in 33 participants (9.32 %), metabolic syndrome in 31 (8.80 %), dyslipidemia in 23 (6.50 %), diabetes in 8 (2.30 %), hypertension in 36 (10.17 %), chronic renal failure in 1 (0.30 %), cardiovascular disease in 6 (1.70 %), and cerebrovascular disease in 4 (1.10 %).

3.2. Trends in the quartiles and mean values of each antibody titer across five measurements

Looking at the quartile and mean values of antibody titers at each measurement time point (Fig. 1B), the median of the antibody titers at the third antibody titer measurement (21 days after the second vaccination) increased (median: 1579 U/ml). However, the median antibody titer declined over subsequent measurements.

Table 1 shows the characteristics at baseline and the median antibody titers (quartile range) at the third, fourth, and fifth measurements. A significant relationship was observed between antibody titers and age, with the median titer decreasing with age. Additionally, a relationship was observed between the antibody titer and frequency of alcohol consumption, indicating a significant tendency for the median value to decrease with increasing frequency of alcohol consumption.

3.3. Adjusted hazard ratio for Lower-25 % of each factor by backward stepwise method

The crude incidence rates per 1000 person-days for Lower-25 % among women and men were 1.35 and 1.66, respectively (Table 2). Using the backward stepwise method, statistically significant hazard ratios for Lower-25 % were observed for individuals in their 40 s, 50 s, and 60 s compared with those in their 20 s, with values of 5.82 (95 % confidence interval [CI], 2.05–16.51), 7.12 (95 % CI, 2.46–20.63), and 9.96 (95 % CI, 3.07–32.34), respectively. Additionally, the hazard ratio value for "daily" versus "never" drinking habits was statistically significant at 2.26 (95 % CI 1.17–4.34).

4. Discussion

The aim of this retrospective cohort study was to clarify factors affecting the dynamics of the antibody titers acquired from COVID-19 vaccination. To our knowledge, this is the first retrospective cohort study to include many explanatory variables, such as various lifestyle factors, with five antibody titer measurements and an observation period of more than six months. In the present study, the antibody titers of 354 hospital workers who received two COVID-19 vaccination doses were measured five times, along with hospital health checkups. Daily drinking habits and age over 40 years were identified as significant factors that reduced COVID-19 antibody titers. These results showed that reduction of vaccination intervals in persons over 40 years of age and cessation of daily alcohol consumption led to the maintenance of acquired antibody titers, resulting in enhanced efficacy of COVID-19 vaccination.

Those in their 40 s and older showed significant hazard ratio values for Lower-25 % (Table 1). Several cross-sectional studies have shown a trend toward lower vaccine-induced antibody titers in the elderly [14,15,17]. A cross-sectional study in which antibody titers were measured twice, just before the first vaccination and 2–5 weeks after the second vaccination, and analyzed using a multivariate linear regression model revealed that age was significantly associated with decreased antibody titers acquired from vaccination [16]. This study also identified a

Table 1
Baseline characteristics of participants and median (IQR) of antibody titers by COVID-19 vaccination at the third, fourth, and fifth measurements.

Variable	Total		Antibody Titer, Median (IQR), U/ml					
	Number	%	Third Mesurement	p-Value	4th Measurement	p-Value	5th Measurement	p-Value
Gender								
Women	227	64.12	1686 (1142 – 2751)	$p = 0.014$*	1035 (651 – 1567)		702 (385 – 1010)	
Men	127	35.88	1382 (805 – 2527)		1005 (535 – 1577)		682 (359 – 1111)	
Age								
20s	66	18.64	2125 (1285 – 3619)	$p < 0.001$**	1549 (929 – 2070)	$p < 0.001$**	984 (673 – 1374)	$p < 0.001$**
30s	88	24.86	2003 (1310 – 2842)		1232 (762 – 1718)		808 (448 – 1113)	
40s	99	27.97	1354 (818 – 2110)		721 (532 – 1267)		534 (310 – 813)	
50s	77	21.75	1381 (760 – 2195)		872 (537 – 1418)		544 (340 – 848)	
60s	24	6.78	1228 (700 – 1885)		806 (365 – 1086)		499 (192 – 650)	
Body mass index (BMI)								
thin (BMI $<$ 18.5)	16	4.52	1322 (513 – 2663)		689 (544 – 1323)		455 (332 – 800)	
standard (18.5 $\leqq$ BMI $<$ 25.0)	229	64.69	1556 (991 – 2639)		999 (620 – 1539)		696 (372 – 1016)	
overweight (25.0 $\leqq$ BMI $<$ 30.0)	76	21.47	1554 (1050 – 2748)		1070 (607 – 1567)		673 (384 – 1042)	
obesity (BMI $\geqq$ 30.0)	33	9.32	1822 (1397 – 2831)		1434 (687 – 2092)		908 (430 – 1374)	
Metabolic syndrome								
not applicable	275	77.70	1582 (1002 – 2709)		1009 (624 – 1532)		688 (379 – 1003)	
reserve group	48	13.60	1713 (1108 – 2842)		1167 (628 – 1892)		717 (391 – 1333)	
applicable	31	8.80	1432 (701 – 1919)		956 (438 – 1932)		614 (234 – 1186)	
Dyslipidemia drug								
no	331	93.50	1603 (1005 – 2702)		1035 (631 – 1587)		702 (385 – 1051)	
taking internal medicine	23	6.50	1286 (745 – 2095)		637 (418 – 1430)		400 (239 – 1109)	
Antidiabetic drug								
no	346	97.70	1588 (995 – 2692)		1022 (623 – 1579)		694 (379 – 1055)	
taking internal medicine	8	2.30	1442 (669 – 2214)		576 (395 – 995)		337 (178 – 722)	
Antihypertensive drug								
no	318	89.80	1607 (1004 – 2703)		1020 (623 – 1587)		704 (381 – 1073)	
taking internal medicine	36	10.17	1371 (923 – 2000)		924 (559 – 1400)		604 (319 – 971)	
History of chronic renal failure								
no	353	99.70	1582 (991 – 2675)		1018 (616 – 1575)		688 (372 – 1052)	
yes	1	0.30	–	–			–	
History of cardiovascular disease								
no	348	98.30	1588 (986 – 2681)		1018 (614 – 1557)		687 (369 – 1040)	
yes	6	1.70	1588 (1329 – 3725)		1888 (1044 – 2090)		1115 (593 – 1211)	
History of cerebrovascular disease								
no	350	98.90	1588 (992 – 2692)		1018 (617 – 1573)		689 (372 – 1055)	
yes	4	1.10	1538.5 (974 – 2359)		1005 (596 – 1744)		661 (498 – 847)	
Having an evening meal within 2 h before bedtime 3 days or more per week								
no	255	72.00	1532 (972 – 2633)		1001 (614 – 1537)		668 (368 – 1043)	
yes	99	28.00	1686 (1043 – 2794)		1120 (626 – 1661)		770 (383 – 1113)	
Eating snacks and sweet beverages other than breakfast, lunch and dinner								
no	51	14.40	1455 (720 – 2255)		616 (437 – 1236)	$p < 0.003$**	454 (279 – 770)	
sometimes	230	65.00	1607 (1057 – 2713)		1046 (637 – 1660)		725 (407 – 1114)	
daily	73	20.60	1620 (1005 – 2649)		1111 (683 – 1523)		674 (396 – 1036)	
Eating faster than others								
slow	20	5.60	1445 (973 – 3927)		1029 (644 – 1655)		795 (441 – 1122)	
usual	221	62.40	1562 (989 – 2649)		1014 (615 – 1558)		690 (378 – 1052)	
fast	113	31.90	1665 (1099 – 2762)		1022 (604 – 1550)		678 (354 – 1050)	
Skipping breakfast at least three times a week								
no	228	64.40	1571 (1005 – 2567)		1000 (622 – 1515)		671 (369 – 930)	
yes	126	35.60	1620 (894 – 2767)		1058 (580 – 1849)		729 (381 – 1205)	
Walking for at least 1 hour/day or having equivalent physical activities								
no	186	52.50	1603 (1036 – 2713)		1073 (631 – 1562)		719 (393 – 1105)	
yes	168	47.50	1572.5 (907 – 2656)		924 (577 – 1606)		676 (351 – 1020)	
Exercising at least 2 days/week at least 30 min each at an intensity that cause a slight sweat for at least 1 year								
no	280	79.10	1581 (1002 – 2646)		1031 (622 – 1559)		699 (385 – 1051)	
yes	74	20.90	1593 (979 – 2750)		931 (595 – 1599)		596 (352 – 1110)	
Frequency of drinking								
never	87	24.60	1622 (1175 – 2669)	$p = 0.004$**	1172 (707 – 1590)	$p < 0.001$**	742 (522 – 1130)	$p < 0.001$**
sometimes	215	60.70	1665 (1005 – 2785)		1052 (645 – 1664)		718 (383 – 1122)	
daily	52	14.70	1176 (695 – 1749)		601 (434 – 1066)		420 (269 – 675)	
Regular smoker								
no	295	83.30	1613 (1017 – 2709)		1048 (627 – 1604)		692 (375 – 1092)	
yes	59	16.70	1354 (816 – 2617)		877 (533 – 1403)		688 (294 – 934)	
Feeling refreshed after a night's sleep								
no	78	22.00	1688 (1069 – 2725)		1016 (632 – 1555)		680 (355 – 907)	
yes	276	78.00	1573 (974 – 2656)		1022 (601 – 1608)		704 (380 – 1113)	

IQR: interquartile range; *: Mann-Whitney U test; **: Kurskal-Wallis test.

significant hazard ratio for Lower-25 % owing to being aged 40 years or older, but it appears that immune aging reduces response to vaccination [18]. Additionally, an increase in aging immune cells leads to decreased ability to recognize new antigens [19–21]. In any case, the timing and interval of vaccination depends on the vaccination policy of each country, but it seems important to vaccinate people over 40 years of age as soon as possible within the allotted period to shorten the vaccination interval, since they are prone to early decline in antibody titers.

Table 2
Hazard ratio values of lifestyle related items on lower-25 % by cox regression hazard survival model**.

lifestyle-related itemy	Number of participants	%	Person-days	Lower-25 %* incident cases	CIR	Hazard ratio†	95 % confidence interval	Hazard ratio‡	95 % confidence interval
Gender									
Women	227	64.12	41,606	56	1.35	1.00			
Men	127	35.88	22,326	37	1.66	0.82	0.49 – 1.37		
Age									
20s	66	18.64	12,216	4	0.33	1.00		1.00	
30s	88	24.86	16,738	15	0.90	2.88	0.91 – 9.09	2.59	0.85 – 7.92
40s	99	27.97	17,657	37	2.10	6.28	2.11 – 18.64	5.82	2.05 – 16.51
50s	77	21.75	13,442	27	2.01	7.73	2.53 – 23.67	7.12	2.46 – 20.63
60s	24	6.78	3879	10	2.58	9.89	2.79 – 35.02	9.96	3.07 – 32.34
Body mass index (BMI)									
thin (BMI $<$ 18.5)	16	4.52	3090	7	2.27	1.33	0.55 – 3.19		
standard (18.5 $\leqq$ BMI $<$ 25.0)	229	64.69	41,271	60	1.45	1.00			
overweight (25.0 $\leqq$ BMI $<$ 30.0)	76	21.47	13,843	19	1.37	0.77	0.41 – 1.42		
obesity (BMI $\geqq$ 30.0)	33	9.32	5728	7	1.22	0.94	0.34 – 2.59		
Metabolic syndrome									
not applicable	275	77.68	49,845	71	1.42	1.00			
reserve group	48	13.56	8584	11	1.28	1.19	0.53 – 2.65		
applicable	31	8.76	5314	11	2.07	1.51	0.64 – 3.57		
Dyslipidemia drug									
no	331	93.50	60,120	82	1.36	1.00			
taking internal medicine	23	6.50	3812	11	2.89	1.66	0.79 – 3.50		
Antidiabetic drug									
no	346	97.74	62,646	89	1.42				
taking internal medicine	8	2.26	1286	4	3.11				
Antihypertensive drug									
no	318	89.83	57,650	81	1.41	1.00			
taking internal medicine	36	10.17	6282	12	1.91	0.77	0.37 – 1.62		
History of chronic renal failure									
no	353	99.72	63,752	93	1.46				
yes	1	0.28	180	0	0.00				
History of cardiovascular disease									
no	348	98.31	62,816	93	1.48				
yes	6	1.69	1116	0	0.00				
History of cerebrovascular disease									
no	350	98.87	63,195	92	1.46				
yes	4	1.13	737	1	1.36				
Having an evening meal within 2 h before bedtime 3 days or more per week									
no	255	72.03	46,176	68	1.47	1.00			
yes	99	27.97	17,756	25	1.41	1.01	0.59 – 1.72		
Eating snacks and sweet beverages other than breakfast, lunch and dinner									
no	51	14.41	9003	24	2.67	1.00			
sometimes	230	64.97	41,860	52	1.24	0.73	0.42 – 1.29		
daily	73	20.62	13,069	17	1.30	0.64	0.32 – 1.31		
Eating faster than others									
slow	20	5.65	3460	4	1.16	1.00			
usual	221	62.43	40,167	57	1.42	0.65	0.22 – 1.98		
fast	113	31.92	20,305	32	1.58	0.72	0.23 – 2.23		
Skipping breakfast at least three times a week									
no	228	64.41	41,762	61	1.46	1.00			
yes	126	35.59	22,170	32	1.44	1.35	0.82 – 2.23		
Walking for at least 1 hour/day or having equivalent physical activities									
no	186	52.54	34,270	44	1.28	1.00			
yes	168	47.46	29,482	49	1.66	1.40	0.89 – 2.19		
Exercising at least 2 days/week at least 30 min each at an intensity that cause a slight sweat for at least 1 year									
no	280	79.10	50,397	70	1.39	1.00			
yes	74	20.90	12,966	23	1.77	1.20	0.70 – 2.07		
Frequency of drinking									
never	87	24.58	16,029	15	0.94	1.00		1.00	
sometimes	215	60.73	38,944	54	1.39	1.67	0.91 – 3.05	1.58	0.88 – 2.84
daily	52	14.69	8959	24	2.68	2.28	1.09 – 4.75	2.26	1.17 – 4.34
Regular smoker									
no	295	83.33	53,456	77	1.44	1.00			
yes	59	16.67	10,476	16	1.53	0.80	0.42 – 1.52		
Feeling refreshed after a night's sleep									
no	78	22.03	13,899	22	1.58	1.00			
yes	276	77.97	50,033	71	1.42	1.21	0.71 – 2.06		

Hazard ratio†: by forced entry method; Hazard ratio‡: by backward stepwise method.
Cox regression hazard servival model**: Lifestyle-related items with $<$10 were excluded from explanatory variables.
Abbrevations; Lower-25 %*: below 25th percentile of antibody titers on six months after second vaccination; CIR: crude incidence rate per 1000 person-days.

"Daily" drinking habits showed a significant hazard ratio for Lower-25 % (Table 2). A cross-sectional study revealed that alcohol consumption was significantly associated with lower antibody titers after vaccination [16]. Acute and chronic alcohol exposure can interfere with various aspects of the adaptive immune response, including antigen presentation required to activate T and B-cells [22–24]. These previously published papers suggest that excess alcohol interferes with acquired immune response and may affect antibody titers. It is unclear whether moderate drinking is an inhibitory or an enhancing factor for immune function [16,25,26]. However, further studies on this topic are required.

The limitations of this research method were examined using a target trial emulation framework [27–29] focused on four key aspects: (1) eligibility, (2) treatment assignment, (3) time zero (timing to start follow-up), and (4) causal contrasts of interest (outcome evaluation: intention-to-treat and per-protocol effects) (Fig. 2). In a target trial (an ideal randomized controlled trial), participants undergo screening based on a set of eligibility criteria, are assigned to an intervention group (treatment assignment), and are followed up (time zero), with outcomes evaluated in future studies. However, in this study, treatment assignment (presence or absence of explanatory variables) occurred in the past, while follow-up (time zero), eligibility (selection of non-infected individuals), and outcome (Lower-25 %) were evaluated.

In targeted trials, random treatment allocation can reduce the influence of unknown confounding factors. However, in this study, participants were divided based on existing factors, making it difficult to eliminate unknown confounding factors. Although the possibility of confounding bias cannot be eliminated, the fact that various lifestyle habits (adopted explanatory variables) that affect health status and immune function are influential factors may reduce the impact of confounding bias.

Information on the explanatory variables (treatment assignment) was obtained from the most recent health checkups. The duration from which the explanatory variables were maintained from the time of the health checkup to the evaluation of Lower-25 % was unclear. This indicated the impossibility of a per-protocol analysis. The explanatory variables were analyzed under the assumption that they were maintained throughout the observation period. The method used in this study appears to correspond to the intention-to-treat analysis of the target trial. Because the validity of the intention-to-treat analysis in a target trial has been confirmed, the analysis in this study appears to be valid [30].

5. Conclusions

The aim of this retrospective cohort study was to determine the impact of various factors, including lifestyle, on antibody titers conferred by the COVID-19 vaccination. Significant hazard ratio values were observed for age over 40 years and drinking frequency. The findings indicate that reduction of vaccination intervals in individuals aged over 40 years and cessation of daily alcohol consumption contributed to the maintenance of acquired antibody titers. These results underscore the importance of these factors as enhancers of COVID-19 vaccine efficacy.

Funding

Not applicable.

Data statement

The data analyzed in this study are not publicly available.

Disclosure

***Approval of the research protocol*:** This study was approved after being deliberated by the Institutional Review Board of Okinawa North Medical Association Hospital.

***Informed consent for publication*:** We obtained consent from the participants to use their anonymized personal data, such as the results of antibody titers and health checkups, for this research.

CRediT authorship contribution statement

Takuji Kishimoto: Writing – original draft, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Daisuke Tasato:** Writing – review & editing, Resources, Project administration, Conceptualization. **Yoshitaka Nagasawa:** Writing – review & editing, Resources, Conceptualization. **Akihiro Yamashiro:** Writing – review & editing, Resources. **Hayashi Shokita:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial

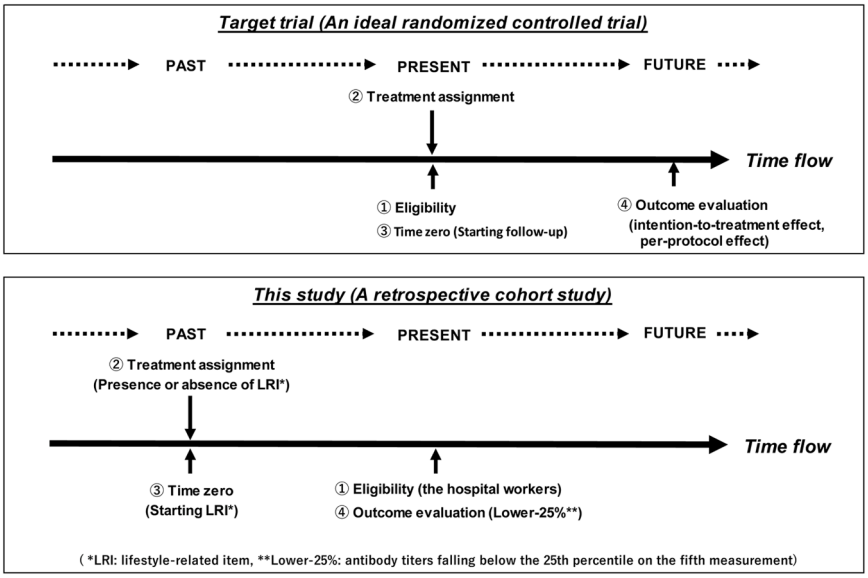

Fig. 2. Time relationship among the main items of the target trial emulation framework in this study.

interests or personal relationships that could have appeared to influence the work reported in this paper.

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