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BRIEF CUTTING EDGE REPORT

Epidemiology/Genetics

Sex-associated differences between BMI and SARS-CoV-2 antibody titers following the BNT162b2 vaccine

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Abstract

Objective: This study investigated the sex-associated difference in the impact of obesity on antibody response to a COVID-19 vaccine.

Methods: This study included 2,435 health care workers who received two doses of the BioNTech, Pfizer (BNT162b2) vaccine and participated in a serological survey, during which they were tested for anti-SARS-CoV-2 spike immunoglobin G (IgG) antibodies and asked for information on height, weight, and vaccination history via a questionnaire. Multivariable linear regression analysis was used to estimate the geometric mean titers (GMT) of antibodies for each sex and BMI category.

Results: The relationship between BMI and anti-SARS-CoV-2 spike IgG titers markedly differed by sex (p value for interaction = 0.04). Spike IgG antibody titers tended to decrease with increasing BMI in men (p value for trend = 0.03); GMT (95% CI) were 6,093 (4,874-7,618) and 4,655 (3,795-5,708) for BMI < 18.5 and ≥30 kg/m^2, respectively. In contrast, spike IgG antibody titers did not significantly differ across BMI categories in women (p value for for trend = 0.62); GMT (95% CI) were 6,171 (5,714-6,665) and 5,506 (4,404-6,883) for BMI <18.5 and ≥30, respectively.

Conclusions: Higher BMI was associated with lower titers of SARS-CoV-2 spike antibodies in men, but not in women, suggesting the need for careful monitoring of vaccine efficacy in men with obesity, who are at high risk of severe COVID-19 outcomes.

INTRODUCTION

Obesity is a major risk factor for morbidity and mortality in patients with COVID-19 (1). Given the adverse effect of excess adipose tissue on the immune system (2), obesity may interfere with the production of vaccine-specific antibodies. In clinical trials on the mRNA-based vaccine against SARS-CoV-2, vaccine recipients had a markedly lower risk of COVID-19 irrespective of obesity status (3). However, a more recent observational study of 1.6 million people in Israel showed that vaccine efficacy (VE) was slightly lower among those with obesity than the total population (4).

The evidence regarding the association between BMI and vaccine-induced antibody titers is limited and inconsistent (5-7). Given the sex difference in the distribution and function of adipocytes (8), the inconsistency among previous studies could be ascribed, at least in part, to the lack of consideration of sex. Here, we investigate the sex-associated difference between BMI and SARS-CoV-2 antibodies among 2,435 health care workers who received two doses of the BioNTech, Pfizer (BNT162b2) vaccine. We hypothesize that higher BMI is associated with lower antibody titers in men only.

Study Importance

What is already known?

► Obesity can downregulate immune response, but epidemiological evidence regarding the impact of obesity on COVID-19 vaccine-induced antibody production and its gender difference is scarce.

What does this study add?

► A higher BMI was associated with lower levels of anti-SARS-CoV-2 spike immunoglobin G antibodies in male, but not female, vaccine recipients.

How might these results change the direction of research?

► Future studies on vaccine efficacy should pay attention to the sex-associated difference in the impact of obesity on the immune response to a COVID-19 vaccine.

METHODS

We launched a repeat serological survey in July 2020 to monitor the spread of SARS-CoV-2 infection among the staff of the National Center for Global Health and Medicine (NCGM; Tokyo, Japan), which has accepted a large number of COVID-19 inpatients. As of October 2021, we have completed three surveys, in each of which we measured anti-SARS-CoV-2 nucleocapsid (all surveys) and spike (from the second survey onward) protein antibodies. The details of the study design are available elsewhere (9). For the present analysis, we used the data of the third survey (June 2021), 2 months after the in-house vaccination program (COVID-19 mRNA-lipid nanoparticle BNT162b2; BioNTech, Pfizer [BioNTech SE, Mainz, Germany; Pfizer Inc., New York, New York]). Of the 3,072 workers invited, a total of 2,779 (90%) participated. Of these, we included 2,514 staff who had received two doses of the vaccine. Of these, we excluded those who attended the survey within 14 days of the second vaccination (n = 5) and those who lacked data on height or weight (n = 74), leaving 2,435 participants for analysis. Written informed consent was obtained from each participant. The study procedure was approved by the NCGM ethics committee.

Participants were asked to donate venous blood. Data on height, weight, vaccination history (confirmed against in-house records), and history of polymerase chain reaction (PCR)-confirmed COVID-19 were collected via a questionnaire. BMI was calculated as the weight in kilograms divided by the height in meters squared, and participants were grouped into five categories according to the World Health Organization (WHO) classification of BMI for Asian individuals (10): underweight (<18.5); normal weight (18.5-22.9); overweight (23-24.9); obesity I (25-29.9); and obesity II (≥30). Immunoglobulin G (IgG) against the SARS-CoV-2 spike protein was quantitatively measured (AdviseDx SARS-CoV-2 IgG II assay; Abbott ARCHITECT, Abbott Laboratories, Chicago, Illinois; positive threshold: ≥50.0 AU/mL).

We converted antibody titers into a log scale before analysis. We ran linear regression modeling to test the interaction between BMI and sex and estimate the ratio of means and the means of IgG titers for each sex and BMI category. Independent variables included BMI category, sex, the interaction term between BMI category and sex, age (continuous), days after the second vaccination (continuous), and history of COVID-19. We back-transformed the estimated values to present the ratios of means and geometric mean titers (GMT). We tested the trend of the association between BMI and antibody titers while assigning one through five to the increasing BMI categories. We repeated the analyses using other BMI classifications recommended by WHO for Asian individuals (11) and in general (12). To visualize the association between BMI and the predicted GMT of spike IgG antibodies, we ran the model while treating BMI (continuous) as a cubic polynomial (i.e., terms of BMI, BMI^2, and BMI^3). Statistical significance was set at $p < 0.05$ for trend and $p < 0.1$ for interaction tests. Statistical analyses were conducted using Stata version 17.0 (StataCorp LLC, College Station, Texas).

RESULTS

The median age was 36.6 years (interquartile range [IQR]: 27.6-47.6), 70% of participants were women, 0.5% had a history of COVID-19, and the median interval between the second vaccination and blood sampling was 64 days (range: 15-103 days). Major occupations

TABLE 1 Characteristics of study participants

	Overall (n = 2,435)	Men (n = 728)	Women (n = 1,707)
Age (y), median (IQR)	36.6 (27.6-47.6)	39.3 (30.5-49.4)	34.9 (26.5-46.8)
Age category (y), *n* (%)			
<30	791 (32.5)	161 (22.1)	630 (36.9)
30-39	597 (24.5)	212 (29.1)	385 (22.6)
40-49	558 (22.9)	179 (24.6)	379 (22.2)
≥50	489 (20.1)	176 (24.2)	313 (18.3)
Job category, *n* (%)			
Doctor	432 (17.7)	269 (37.0)	163 (9.5)
Nurse	940 (38.6)	55 (7.6)	885 (51.8)
Allied health professional	332 (13.6)	163 (22.4)	169 (9.9)
Administrative staff	230 (9.4)	58 (8.0)	172 (10.1)
Other	501 (20.6)	183 (25.1)	318 (18.6)
History of COVID-19, *n* (%)	13 (0.5)	5 (0.7)	8 (0.5)
Interval between second vaccination and blood sampling (d), median (IQR)	64 (41-69)	66 (41-70)	63 (40-69)

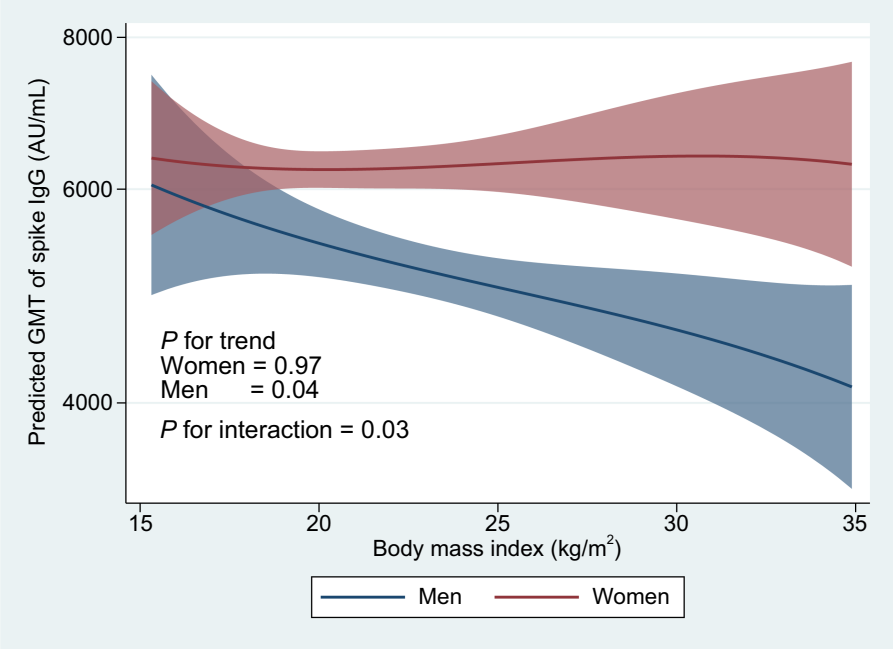

FIGURE 1 Sex-specific cubic spline curves in the association between estimated GMT of anti-SARS-CoV-2 spike IgG and BMI. Data are shown as geometric means with 95% CI predicted by linear regression model, including the following variables: a cubic polynomial of BMI (continuous); sex; an interaction term of BMI and sex; age (continuous); days after the second vaccination (continuous); and history of COVID-19. AU, arbitrary units; GMT, geometric mean titers

included nurses (38.6%), doctors (17.7%), allied health care professionals (13.6%), and administrative staff (9.4%; Table 1). All participants were positive for SARS-CoV-2 spike antibodies, with a median of 6,063 AU/mL (IQR: 3,620-9,919).

There was a significant interaction between BMI category and sex (p value for interaction = 0.04; Table 2). In men, SARS-CoV-2 spike antibody titers progressively decreased with increasing BMI (p value for trend = 0.03), and adjusted geometric means (95% CI) were 6,093 (4,874-7,618) and 4,655 (3,795-5,708) for BMI < 18.5 and ≥30, respectively. In women, antibody titers did not significantly differ across BMI categories (p value for trend = 0.62), and adjusted geometric means (95% CI) were 6,171 (5,714-6,665) and 5,506 (4,404-6,883) for BMI < 18.5 and ≥30, respectively. Men with BMI < 18.5 had antibody titers similar to that of women in the same

BMI category ($p = 0.92$), whereas men with BMI of 18.5 to 29.9 had significantly lower antibody titers than women in the corresponding BMI category ($p < 0.05$). Results were similar in analyses using other BMI classifications (Supporting Information Tables S1-S2). In cubic spline regression analysis, GMT of antibody titers decreased linearly with increasing BMI in men, whereas no association was observed in women (p value for interaction = 0.03; Figure 1).

DISCUSSION

In the present study among health care workers who received two doses of the BNT162b2 vaccine, all participants were seropositive irrespective of BMI, and most of them had high titers of SARS-CoV-2 spike IgG antibodies. As hypothesized, there was a marked sex difference in the association between BMI and SARS-CoV-2 spike IgG antibody titers, with a significant inverse association being observed in men, but not in women. To the best of our knowledge, this is the first study to associate SARS-CoV-2 vaccine-induced immune response with adiposity in a sex-specific manner.

The lower antibody titers in men with obesity may be attributed to their adipose distribution. Compared with women with obesity, men with obesity are more likely to have greater visceral adipose tissue, which dysregulates the production of adipocytokines (8). With increasing amounts of visceral adipose tissue, leptin, tumor necrosis factor α (TNF-α), and interleukin (IL)-6 are overproduced, whereas adiponectin decreases (2). Such imbalance of the adipocytokine profile can cause low-grade chronic inflammation, which can induce B cell immunosenescence and interfere with antibody production after vaccination (13).

In contrast, antibody titers did not significantly differ across BMI categories in women. Given that 82% of female participants in the present study were under the age of 50 years, this finding could be ascribed, at least in part, to the effect of estrogen and progesterone on the regulation of adipose tissue distribution, adipogenesis, and adipocyte metabolism and production (8). Owing to these hormones, women have less visceral adipose tissue, greater brown adipose tissue, and higher circulating adiponectin concentrations compared with men (8), all of which have been suggested to suppress chronic inflammation and activate the immune system (2,14).

We found that men with obesity had modestly (11%-13%) lower GMT of spike IgG antibody than those with normal weight. Although the clinical significance of such difference is unclear, this finding may give some support for those of a large observational study in Israel, which showed somewhat lower VE for infection among those with obesity compared with the total population (VE: 89.7% vs. 93.0%, respectively) (4). Further analysis stratified by sex of such large real-world data may confirm or refute the sex-associated difference in the impact of obesity on VE.

This study has some limitations. First, anti-SARS-CoV-2 spike IgG antibody does not fully characterize the humoral immune response induced by the vaccine. Nevertheless, spike IgG antibody titers measured with the assay that we employed were well correlated with

TABLE 2 Estimated GMT of SARS-CoV-2 spike IgG with 95% CI by BMI categories and sex after the second vaccination dose

	BMI categories (kg/m^2)[a]						
	Underweight (<18.5)	Normal weight (18.5-22.9)	Overweight (23-24.9)	Obesity I (25-29.9)	Obesity II (≥30)	*p* value for trend	*p* value for interaction by sex
Women, n (%)	256 (15.0)	1,111 (65.1)	174 (10.2)	136 (8.0)	30 (1.8)		**0.04**
Predicted GMT (95% CI)	6,171 (5,714-6,665)	6,265 (6,038-6,500)	5,876 (5,355-6,447)	6,966 (6,270-7,739)	5,506 (4,404-6,883)		
Ratio of means (95% CI)	0.99 (0.90-1.07)	Reference	0.94 (0.85-1.04)	1.11 (0.99-1.24)	0.88 (0.70-1.10)	0.62	
Men, n (%)	30 (4.1)	350 (48.1)	164 (22.5)	148 (20.3)	36 (4.9)		
Predicted GMT (95% CI)	6,093 (4,874-7,618)	5,331 (4,993-5,692)	4,987 (4,528-5,492)	4,740 (4,282-5,246)	4,655 (3,795-5,708)		
Ratio of means (95% CI)	1.14 (0.91-1.44)	Reference	0.94 (0.83-1.05)	0.89 (0.79-1.00)	0.87 (0.70-1.08)	**0.03**	

Note: Data are shown as GMT and the ratio of means estimated by linear regression model with adjustment for age (continuous), days after the second vaccination (continuous), and history of COVID-19.

Abbreviation: GMT, geometric mean titers

[a]World Health Organization-recommended classification for Asian individuals.

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neutralizing antibody titers in a subgroup of vaccine recipients in this cohort (Spearman $\rho = 0.91$) (Takeuchi JS et al. *MedRxiv*. doi:10.1101/2021.11.06.21265632, unpublished data). Second, we did not assess cellular immune response, another key mechanism of infection protection (15). Last, the participants were staff of a single medical facility in Japan. Caution should be exercised when generalizing the present findings to populations with different backgrounds.

CONCLUSION

In summary, higher BMI was associated with lower titers of anti-SARS-CoV-2 spike IgG antibody in male, but not female, vaccine recipients. The result suggests the need for careful monitoring of VE in men with obesity, who are at high risk of severe COVID-19 outcomes.

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CONFLICT OF INTEREST

Antibody assay reagent was provided by Abbott Japan Co., Ltd (Tokyo, Japan). The authors declared no other conflict of interest.

AUTHOR CONTRIBUTIONS

Shohei Yamamoto: conceptualization, methodology, software, formal analysis, investigation, writing (original draft), and visualization; Tetsuya Mizoue: resources, writing (review and edditing), project administration, and funding acquisition; Akihito Tanaka: investigation, project administration, and writing (review and editing); Yusuke Oshiro: investigation and writing (review and editing); Natsumi Inamura: investigation and writing (review and editing); Maki Konishi: software, validation, investigation, data curation, and writing (review and editing); Mitsuru Ozeki: resources, investigation, and writing (review and editing); Kengo Miyo: software, resources, and writing (review and editing); Wataru Sugiura: resources, supervision, and writing (review and editing); Haruhito Sugiyama: resources, supervision, and writing (review and editing); and Norio Ohmagari: conceptualization, resources, supervision, and writing (review and editing).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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