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SUPPLEMENT ARTICLE

Association of Frailty, Age, and Biological Sex With Severe Acute Respiratory Syndrome Coronavirus 2 Messenger RNA Vaccine–Induced Immunity in Older Adults

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Background. Male sex and old age are risk factors for severe coronavirus disease 2019, but the intersection of sex and aging on antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines has not been characterized.

Methods. Plasma samples were collected from older adults (aged 75–98 years) before and after 3 doses of SARS-CoV-2 mRNA vaccination, and from younger adults (aged 18–74 years) post-dose 2, for comparison. Antibody binding to SARS-CoV-2 antigens (spike protein [S], S receptor-binding domain, and nucleocapsid), functional activity against S, and live-virus neutralization were measured against the vaccine virus and the Alpha, Delta, and Omicron variants of concern (VOCs).

Results. Vaccination induced greater antibody titers in older females than in older males, with both age and frailty associated with reduced antibody responses in males but not females. Responses declined significantly in the 6 months after the second dose. The third dose restored functional antibody responses and eliminated disparities caused by sex, age, and frailty in older adults. Responses to the VOCs, particularly the Omicron variant, were significantly reduced relative to the vaccine virus, with older males having lower titers to the VOCs than older females. Older adults had lower responses to the vaccine and VOC viruses than younger adults, with greater disparities in males than in females.

Conclusions. Older and frail males may be more vulnerable to breakthrough infections owing to low antibody responses before receipt of a third vaccine dose. Promoting third dose coverage in older adults, especially males, is crucial to protecting this vulnerable population.

Keywords. antibody response; ACE2; sex differences; Delta; Omicron; aging; frailty.

The disproportionate burden of coronavirus disease 2019 (COVID-19) in older adults was recognized early in the pandemic [1–3]. Phase III trials for the 2 messenger RNA (mRNA) vaccines (mRNA-1273 and BNT162b2) revealed high efficacy in older adults [4, 5], for whom immunosenescence is thought to impair vaccine-induced immune responses [6]. The clinical trials, however, failed to represent the oldest and frailest subset of the population. Accordingly, widespread use of the vaccines in long-term care facility residents revealed that old age is a risk factor for poor antibody responses [7–9].

Male sex is also a significant predictor of severe COVID-19 outcomes at older ages [10–14]. There is extensive evidence that the effects of aging on the immune system differ between the sexes, including evidence that immunosenescence occurs more slowly in females than in males [15, 16]. The implications of biological sex are evident in the response to repeated seasonal influenza vaccination in older adults, where prevaccination titers decrease with age in males but not in females, suggesting that older females enter each influenza season with greater immunity than their male counterparts [17].

In the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, however, studies have failed to provide sex-disaggregated data within each age group [18, 19], and little is known about how biological sex may modify the effects of age, and age-related factors such as frailty, on vaccine immunogenicity and the durability of protection. In the current

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study, we investigated sex differences and sex-specific effects of aging in the humoral immune response to the vaccine virus and variants of concern (VOCs) induced by 3 doses of a SARS-CoV-2 mRNA vaccine in a cohort of adults ≥75 years of age. We show that the age- and frailty-associated declines in antibody responses occur to a greater extent in males than in females.

METHODS

Cohorts

Older adults (aged 75–98 years) were recruited from the Johns Hopkins Longitudinal Influenza Immunization Study of Aging cohort ≥75 years of age [17] (Table 1). Individuals who had worsening or new onset of immune-modulating conditions (eg, rheumatoid arthritis, hematologic cancers, or other cancers) or a previous diagnosis of COVID-19 were excluded. Participants came to the Johns Hopkins Bayview Medical Center or study visits were conducted at participants' homes, as needed. At prevaccination visits (Pre), frailty status was assessed using the Fried frailty phenotype [20] and a baseline blood sample was obtained. Subsequent receipt of 2 (primary vaccination series) or 3 doses of a SARS-CoV-2 mRNA vaccine, either mRNA-1273 or BNT162b2, was confirmed by means of vaccination cards, and blood samples were collected 14–30 days (mean, ≤1 month) post-dose 1 (<1M_PD1)), 14–30 days post-dose 2 (<1M_PD2), 90 (±15) days post-dose 2 (3M_PD2), 180 (±15) days post-dose 2 (6M_PD2), and 14–60 days post-dose 3 (1M_PD3).

Younger adult healthcare workers from the Johns Hopkins Health System were also sampled as a comparison group. Recruitment of these younger adults has been reported elsewhere [21]. To be eligible for the present study, participants needed to be <75 years old, not have a history of COVID-19, and have 2 samples collected ≥90 days apart, with the first collected ≥14 days after receiving the second dose of a SARS-CoV-2 mRNA vaccine. Owing to low plasma volumes, these samples were not tested for angiotensin-converting enzyme 2 (ACE2) inhibition or virus neutralization, and antibody titration against antigens from VOCs could not be performed for some participants. Exact sample sizes are included in figure legends. For both cohorts, written informed consent was obtained from all participants, and the study protocols were approved by the Johns Hopkins School of Medicine Institutional Review Board.

Table 1. Characteristics of Older Adult Participants

Characteristic	Participants, No. (%)[a]		
	All Participants	Males	Females
Included in analysis[b]	82 (100)	34 (41)	48 (59)
Recruited, no.	86	34	52
Excluded, no.[c]	4	0	4
Age, median (IQR), y	84 (81–88)	84 (82–88)	83 (81–89)
Age category[d]			
75–82 y	32 (39)	12 (35)	20 (42)
83–87 y	28 (34)	13 (38)	15 (31)
88–98 y	22 (27)	9 (26)	13 (27)
Frailty[d]			
Robust	18 (22)	8 (24)	10 (21)
Prefrail	53 (64)	20 (59)	33 (67)
Frail	10 (12)	6 (18)	4 (8)
Missing	1 (1)	0 (0)	1 (2)
Vaccine type[d]			
mRNA-1273 (Moderna)	24 (30)	8 (24)	16 (33)
BNT162b2 (Pfizer)	58 (70)	26 (76)	32 (67)
Visit participation[d]			
Pre	82 (100)	34 (100)	48 (100)
<1M_PD1	23 (28)	11 (32)	12 (25)
<1M_PD2	69 (84)	28 (82)	41 (85)
3M_PD2	82 (100)	34 (100)	48 (100)
6M_PD2	80 (98)	33 (97)	47 (98)
1M_PD3	60 (73)	26 (76)	34 (71)

Abbreviations: IQR, interquartile range; mRNA, messenger RNA; Pre, before vaccination; <1M_PD1,<1 month post-dose 1; <1M_PD2, <1 month post-dose 2; 1M_PD3, 1 month post-dose 3; 3M_PD2, 3 months post-dose 2; 6M_PD2, 6 months-post dose 2.

[a]Data represent no (%) of participants unless otherwise specified.

[b]Subset of eligible participants without evidence of prior infection who were included in analysis.

[c]Participants with high (>1:180) nucleocapsid titers, indicating prior infection, were excluded from analysis. One additional participant was excluded owing to evidence of severe immunosuppression.

[d]Study timepoints: Pre-vaccination (Pre); 14–30 days post dose 1 (<1M_PD1); 14–30 days post dose 2 (<1M_PD2); 75–105 days post dose 1 (3M_PD2); 165–195 days post dose 1 (6M_PD2); 75–105 days post dose 1 (3M_PD2); 14–60 days post dose 3 (1M_PD3).

Laboratory Methods

Detailed enzyme-linked immunosorbent assay, ACE2 inhibition, and virus neutralization methods can be found in the Supplementary Materials. Briefly, plasmids expressing recombinant nucleocapsid (N), spike (S), or S receptor-binding domain (S-RBD) of the vaccine strain and the Alpha, Delta, and Omicron variants of SARS-CoV-2 were engineered at Johns Hopkins, as described elsewhere [22], or obtained through the National Cancer Institute's Serological Sciences Network for COVID-19 [23] (Supplementary Table 1). Recombinant proteins were used to coat plates for indirect enzyme-linked immunosorbent assay measuring plasma immunoglobulin (Ig) G against N, S, or S-RBD. Results were expressed as the $\log_{10}$-transformed area under the curve generated from ten 3-fold serial plasma dilutions, as described elsewhere [22]. The ability of plasma antibodies to inhibit ACE2 binding to S was measured using Meso Scale Diagnostics V-PLEX SARS-CoV-2 ACE2 kits, according to the manufacturer's protocol at a dilution of 1:100 [24]. Data were expressed as the $\log_{10}$-transformed concentration (in micrograms per milliliter) of ACE2-inhibiting antibodies (ACE2iAbs), which are equivalent to anti-S monoclonal antibodies. For comparison between the vaccine virus and VOCs, data were expressed as the percentage of ACE2 inhibition. Live-virus microneutralization

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assays were performed as described elsewhere, using 2-fold dilutions of plasma incubated with infectious virus and then VeroE6-TMPRSS2 cells to measure cytopathic effect [25]. Results were expressed as the $\log_{10}$-transformed neutralizing antibody (nAb) area under the curve. Because prevaccination IgG and ACE2iAb responses were low or nondetectable, live virus neutralization was performed only on postvaccination samples. IgG binding to seasonal and epidemic β-coronavirus S proteins was measured using the multiplex chemiluminescent Meso Scale Diagnostics V-PLEX COVID-19 Coronavirus Panel 3 (IgG) Kit according to the manufacturer's protocol at a dilution of 1:5000.

Statistical Methods

Longitudinal data in the older adult cohort were analyzed using mixed-effects models with random intercepts on the individual to account for repeated measures and interaction terms between the study time point (categorical) and sex (self-report), age (categorized based on terciles), and frailty status. Linear regression models, including interaction terms between sex and age or frailty, were used to investigate sex-specific effects at individual time points. To compare the older and younger cohorts, the number of days post-dose 2 was used as a continuous predictor and cubic splines were included to study nonlinear relationships [26]. Cubic spline knots were placed at 30, 100, and 160 days after vaccination, points chosen to divide the data approximately into quartiles. Mixed-effects models included an interaction term between time and cohort and were repeated separately for males and females. Differences between cohorts were tested at 3 sentinel points (14, 90, and 180, days post-dose 2). Analyses were performed using Stata 15 software (StataCorp) and differences were considered statistically signifcant at $P < .05$.

Table 2. Characteristics of Younger Adult Participants

Characteristic	All Participants	Males	Females
Included in analysis, no. (%)[a]	81 (100)	32 (40)	49 (60)
Eligible, no.[b]	84	32	52
Excluded, no.[c]	3	0	3
Age at vaccination, y, no. (%)[d]			
≤29	14 (17)	4 (12)	10 (20)
30–39	32 (40)	11 (34)	21 (43)
40–49	18 (22)	8 (25)	10 (20)
50–59	7 (9)	4 (13)	3 (6)
60–74	10 (12)	5 (16)	5 (10)
Sample 1: duration post-dose 2, d			
Mean (range)	33 (16–76)	31 (16–65)	34 (16–76)
Median (IQR)	29 (21–43)	27 (21–41)	29 (21–43)
Sample 2: duration post-dose 2, d			
Mean (range)	138 (96–190)	142 (110–190)	136 (96–183)
Median (IQR)	137 (125–150)	139 (128–156)	137 (123–147)

Abbreviation: IQR, interquartile range.

[a]Subset of eligible participants without evidence of prior infection who were included in the analysis.

[b]Eligible participants from the affiliated study were <75 years of age, had remaining serum from 2 samples collected ≥90 days apart 14–200 days after 2 doses of a messenger RNA (mRNA) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine, and did not report prior SARS-CoV-2 infection.

[c]Participants with high (> 1:180) nucleocapsid titers, indicating prior infection, were excluded from analysis.

[d]Percentages are based on the number included in analysis in each column.

RESULTS

Study Population Demographics

Eighty-six older adults were recruited from the Baltimore area, with 3 participants excluded from analysis owing to high SARS-CoV-2 N antibody titers (ie, titer >180), suggesting prior COVID-19 infection (Supplementary Figure 1). One additional participant was excluded from analysis because of evidence of severe immunosuppression, such that responses could not be accurately captured in population-level models. Characteristics of the 82 participants included in the analysis are detailed in Table 1. The population had more females (59%) than males, and a median age of 84 years. Most participants were classified as prefrail (64%) and a greater percentage of males than females were frail. All participants received 2 doses of a SARS-CoV-2 mRNA vaccine, with the majority (70%) receiving BNT162b2. Sixty participants (73%) received a third vaccine dose ≥6 months after the second dose.

Demographic information for the younger adult cohort is provided in Table 2. Of 84 eligible participants from the affiliated study [21], 3 were excluded owing to high anti-N titers (Supplementary Figure 1). In the younger population included in the analysis, there were more females than males (60% vs 40%), most participants were between 30 and 49 years of age, and a majority of samples were collected 21–43 days and 125–150 days after receipt of the second vaccine dose.

Responses to Vaccination in Older Females and Older Males

Among older adults, IgG binding to S and S-RBD of the vaccine strain increased significantly in response to the first 2 vaccine doses and then decreased significantly in the 6 months after immunization ($P < .001$ for all comparisons; Figure 1A, 1B, and 1*E*). Geometric mean titers (GMTs) decreased 11- and 12-fold for S and S-RBD, respectively, from <1M_PD2 to 6M_PD2 (Supplementary Table 2). Females mounted greater IgG responses to S and S-RBD relative to their baseline than males at all pre–dose 3 time points ($P < .02$ for all comparisons; Figure 1A, 1B, and 1*E*). Older females also had greater titers of IgG against S and S-RBD at each visit, and this difference was significant for anti-S IgG at <1M_PD1 ($P = .02$) and at 3M_PD2 ($P = .03$). Although differences appear attenuated on the log scale, GMT ratios reveal a consistent sex difference of 1.2–3-fold higher titers in females than males (Figure 1*F*). After receipt of a third vaccine dose, IgG titers increased significantly in both males and females ($P < .001$), leading to GMTs

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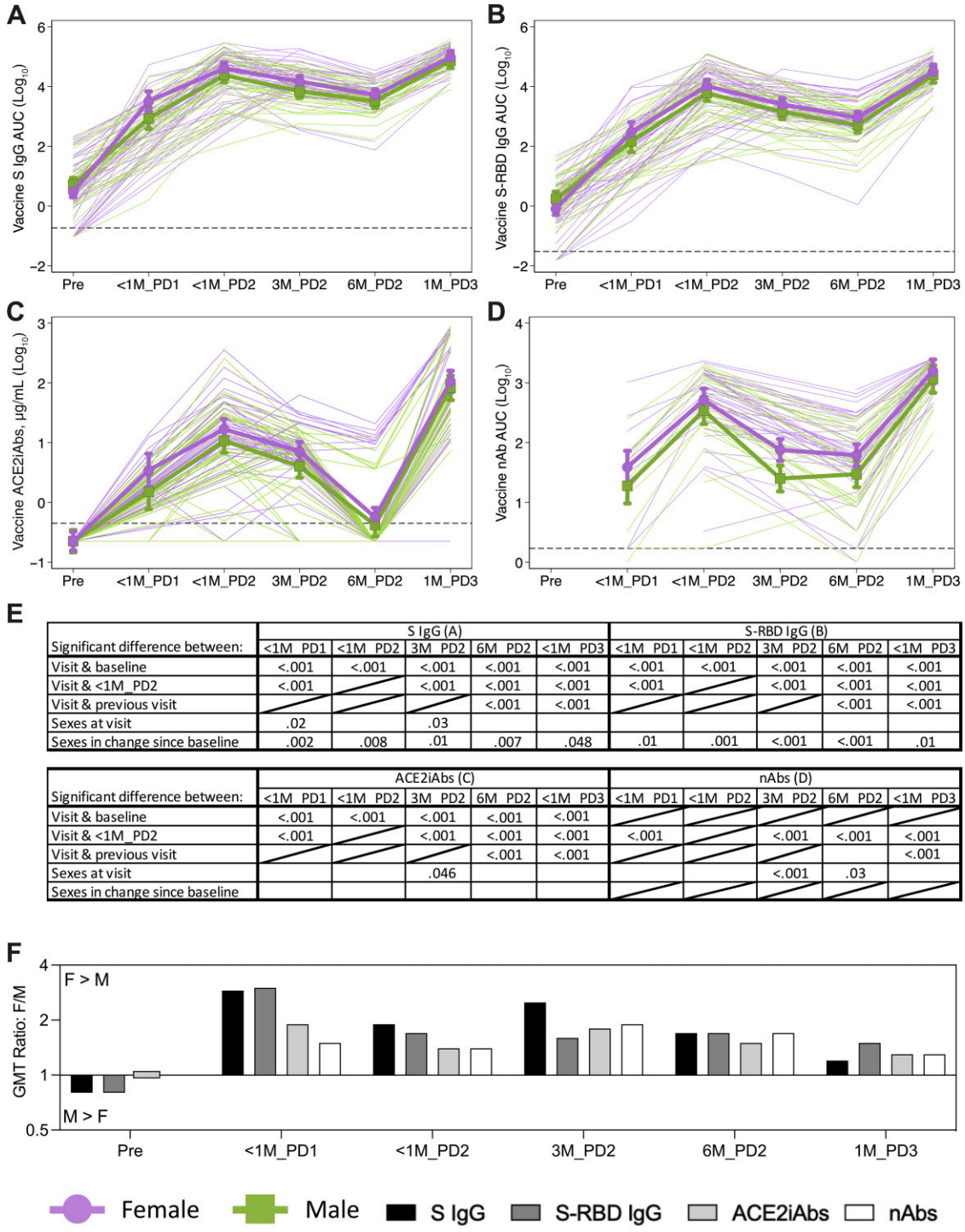

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Significant difference between:	S IgG (A)					S-RBD IgG (B)				
	<1M_PD1	<1M_PD2	3M_PD2	6M_PD2	<1M_PD3	<1M_PD1	<1M_PD2	3M_PD2	6M_PD2	<1M_PD3
Visit & baseline	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Visit & <1M_PD2	<.001		<.001	<.001	<.001	<.001		<.001	<.001	<.001
Visit & previous visit				<.001	<.001				<.001	<.001
Sexes at visit	.02		.03							
Sexes in change since baseline	.002	.008	.01	.007	.048	.01	.001	<.001	<.001	.01

Significant difference between:	ACE2iAbs (C)					nAbs (D)				
	<1M_PD1	<1M_PD2	3M_PD2	6M_PD2	<1M_PD3	<1M_PD1	<1M_PD2	3M_PD2	6M_PD2	<1M_PD3
Visit & baseline	<.001	<.001	<.001	<.001	<.001					
Visit & <1M_PD2	<.001		<.001	<.001	<.001	<.001		<.001	<.001	<.001
Visit & previous visit				<.001	<.001					<.001
Sexes at visit			.046					<.001	.03	
Sexes in change since baseline										

Figure 1. Older females mount greater humoral responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA vaccines than older males. *A–D*, Anti-spike (S) immunoglobulin (Ig) G (*A*), S receptor-binding domain (S-RBD) IgG (*B*), angiotensin-converting enzyme 2–inhibiting antibodies (ACE2iAbs) (*C*), and neutralizing antibodies (nAbs) (*D*) against the vaccine strain of SARS-CoV-2 were measured at 6 time points: before vaccination (Pre; n = 82 [48 female, 34 male]; nAbs not measured), <1 month post-dose 1 (<1M_PD1; n = 23 [12 female, 11 male]), <1 month post-dose 2 (<1M_PD2; n = 69 [41 female, 28 male]), 3 months post-dose 2 (3M_PD2; n = 82 [48 female, 34 male]), 6 months post-dose 2 (6M_PD2; n = 80 [47 female, 33 male]), and 11 month post-dose 3 (1M_PD3; n = 60 [34 female, 26 male]). Differences between time points were tested using mixed-effects models with study time point as a dummy variable and random intercepts on the individual. Sex differences were tested using an expanded mixed-effects model that included a main effect for sex and an interaction term between sex and study time point. All point estimates are shown with error bars indicating the 95% confidence interval. Dashed lines show the limits of detection. *E*, All *P* values <.05 are reported; blank cells indicate a *P* value >.05, and crossed out cells indicate that the comparison is reported elsewhere in the table or not tested. *F*, Female-to-male ratios of geometric mean titers (GMTs) for each assay and each time point are shown, with the axis on a $\log_2$ scale. Abbreviations: AUC, area under the curve; F, female, M, male.

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that were 2- and 4-fold greater than the post–dose 2 peak for S and S-RBD, respectively, and to reductions in the female-to-male GMT ratios (Figure 1*F* and Supplementary Table 2).

The functional ability of antibodies to inhibit S from binding to ACE2 followed similar kinetics as IgG in response to the primary immunization series but then decreased more rapidly in the 6 months after immunization, resulting in a 28-fold decrease in GMT from <1M_PD2 to 6M_PD2 (Figure 1*C* and Supplementary Table 2). By 6M_PD2, 79% of males and 77% of females had undetectable ACE2iAbs. Sex differences were apparent at all time points and were significant at 3M_PD2 ($P = .046$), with females mounting stronger responses than males (Figure 1*F*). Post-dose 3, all but 1 participant had detectable ACE2iAbs, and the geometric mean concentration was 7-fold higher than the post–dose 2 peak (Supplementary Table 2). Neutralizing capacity declined 6-fold in the 3 months after the second dose, and titers were then restored to 3 times the post–dose 2 peak by the third dose (Figure 1*D*). As with the other outcomes, nAb titers were consistently 1.3–1.9-fold higher for females than for males, reaching statistical significance at 3M_PD2 ($P = .001$) and 6M_PD2 ($P = .03$; Figure 1*D*–1*F*).

Despite differences in kinetics over time between the binding and functional assays, the 4 readouts of humoral immunity correlated well with each other (R > .67; Supplementary Figure 2). As expected, correlations became weaker at the lower range of the ACE2 inhibition and virus neutralization assays. Taken together, these data suggest that older females mount stronger response to SARS-CoV-2 vaccination than males and that a third vaccine dose is necessary to boost functional antibody responses in both males and females.

Effects of Age and Frailty in Males and Females

We next assessed the overall and sex-specific effects of age on the humoral response to vaccination. Among all older participants, age was significantly associated with reduced anti-S IgG, anti-S-RBD IgG, ACE2iAbs, and nAbs in the 6 months after the primary vaccination series (Figure 2*A*–2*D*). This effect was largely driven by the oldest tercile of the population (≥88 years). At 3M_PD2, nAb GMTs were 1.8-fold higher in the youngest tercile (75–82 years) compared with the oldest tercile, and the percentages of participants with undetectable ACE2iAbs by 6M_PD2 were 67% and 85% in the youngest and oldest terciles, respectively. In sex-disaggregated analyses focusing on the 3M_PD2 time point (ie, a time point when all study participants were represented), age significantly impaired responses in males but not females, leading to significant sex differences in the effect of age for anti-S IgG ($P = .02$), ACE2iAbs ($P = .001$), and nAbs ($P = .04$) (Figure 2*E*–2*H*). The trend of greater age effects in males than in females was consistent at other time points after the primary immunization series (Supplementary Figure 3*A*– 3*H*), and by 6M_PD2, 100% of males in the oldest age group, compared with 77% of females, had undetectable ACE2iABs. After receipt of a third dose, the effect of age was no longer significant in the overall population or within either sex, suggesting that a third vaccine dose eliminated sex and age disparities in vaccine-induced immunity (Figure 2*A*–2*D* and Supplementary Figure 3*I*–3*L*).

Frailty had an important overall effect, with frail participants mounting significantly weaker responses to vaccination than robust and prefrail participants (Figure 2*I*–2*L*). By 6M_PD2, 90% of frail participants had undetectable ACE2iAbs, compared with 75% of prefrail and robust participants. For the nAbs, responses in frail participants were 1.8-, 2.3- .and 1.9-fold lower than in robust participants at <1M_PD2, 3M_PD2, and 6M_PD2, respectively. As with age, the effect of frailty at 3M_PD2 was significant in males but not females for all readouts (Figure 2*M*–2*P*). No significant sex differences in the effect of frailty were observed, however, and trends were less consistent over time (Supplementary Figure 3*M*–3*X*). The effect of frailty was also attenuated by the third dose but remained significant for ACE2iAbs ($P = .005$; Figure 2*K*). From these data, we conclude that the effects of age and frailty in older adults are largely driven by males, not females.

Antibody Responses to VOCs Relative to the Vaccine Virus

The breadth of vaccine-induced immunity in older adults was assessed by measuring antibody responses to the Alpha, Delta, and Omicron variants (Supplementary Table 3). Anti-S IgG to the Alpha and Delta variants were similar to each other and were both significantly reduced relative to the vaccine virus (2–4-fold lower GMT; $P < .001$; Figure 3*A* and 3*D*). Titers to Omicron were further reduced relative to the vaccine virus (>5-fold difference in GMT) and the Alpha and Delta variants (2–4-fold lower GMT) ($P < .001$ for all comparisons; Figure 3*A* and 3*D*). Differences between anti-S IgG to the vaccine virus and the VOCs were attenuated at 1M_PD3 (fold difference in GMT, <1.5 for Alpha and Delta and <4 for Omicron) but remained significant ($P < .001$ for all comparisons).

The percentage ACE2 inhibition of the Alpha and Delta variants was also significantly lower than for the vaccine strain, and functional antibody responses to the BA.1 and BA.2 Omicron variants were undetectable until a third dose was administered (Figure 3*B* and 3*D*). nAb responses to the Alpha and Delta variants were significantly reduced relative to the vaccine virus ($P < .001$) at all time points except for Alpha at 3M_PD2, and nAb titers to the Omicron BA.1 variant were 8-fold lower than to the vaccine virus at 1M_PD3 (Figure 3*C* and 3*D*). In sex-disaggregated analyses, females had higher responses to the VOC than males, and this difference was significant for anti-Delta S IgG ($P = .04$) and anti-Alpha nAbs ($P = .048$) at 3M_PD2 (Figure 3*E*–3*G* and Supplementary Figure 4).

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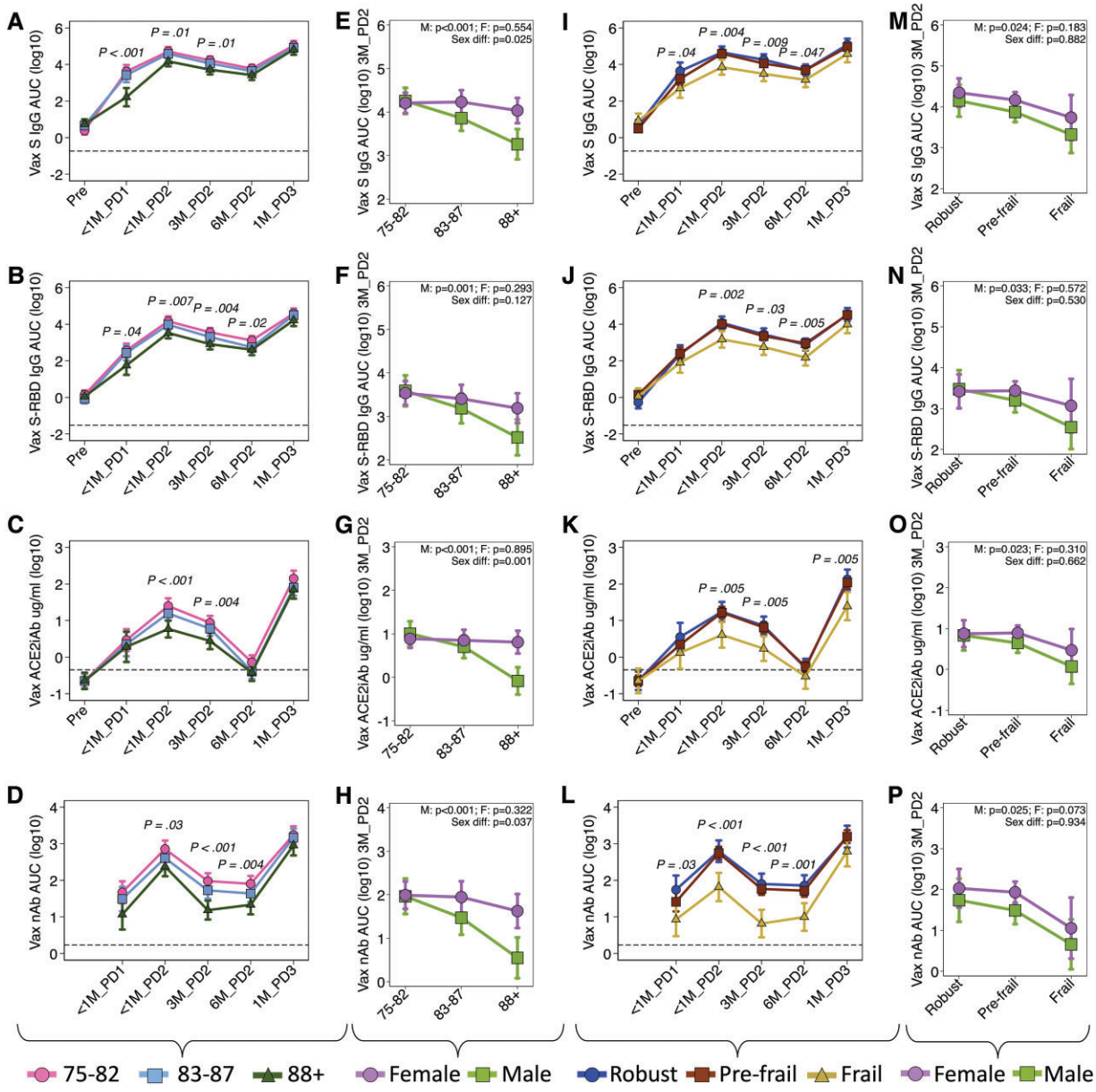

Figure 2. Age and frailty impact the antibody response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA (mRNA) vaccines in a sex-specific manner among older adults. *A–D*, Effect of age on antibody kinetics is shown for anti-spike (S) immunoglobulin (Ig) G (*A*), S receptor-binding domain (S-RBD) IgG (*B*), angiotensin-converting enzyme 2–inhibiting antibodies (ACE2iAbs) (*C*), and neutralizing antibodies (nAbs) (*D*) against the vaccine strain of SARS-CoV-2. *E–H*, Data are shown for 6 time points: before vaccination (Pre; aged 75–82, 83–87, and ≥88 years, n = 32, n = 28, and n = 22, respectively; nAbs not measured), <1 month post-dose 1 (<1M_PD1; n = 10, n = 8, and n = 5, respectively), <1 month post-dose 2 (<1M_PD2; n = 24, n = 25, and n = 20), 3 months post-dose 2 (3M_DP2; n = 32, n = 28, and n = 22), 6 months post-dose 2 (6M_PD2; n = 31, n = 28, and n = 21), and 1 month post-dose 3 (1M_PD3; n = 22, n = 21, and n = 17). Sex-specific effects of age at 3M_PD2 are shown separately for females (aged 75–82, 83–87, and ≥88 years, n = 20, n = 15, and n = 13, respectively) and males (n = 12, n = 13, and n = 9). *I–L*, The effect of frailty on antibody kinetics is shown for the 4 assays at 6 time points: Pre (robust, prefrail, and frail, n = 18, n = 53, and n = 10, respectively; nAbs not measured), <1M_PD1 (n = 6, n = 12, and n = 5), <1M_PD2 (n = 15, n = 45, and n = 9), 3M_PD2 (n = 18, n = 53, and n = 10), 6M_PD2 (n = 18, n = 52, and n = 10), and 1M_PD3 (n = 14, n = 39, and n = 7). *M–P*, Sex-specific effects of frailty are shown separately for females (robust, prefrail, and frail, n = 10, n = 33, and n = 4, respectively) and males (n = 8, n = 20, and n = 6). The overall effects of age (*A–D*) or frailty (*I–L*) at each time point were tested using mixed-effects models including a main effect for age/frailty and an interaction term between age/frailty and study time point. All *P* values <.05 are shown and dashed lines indicate the limit of detection. At 3M_PD2, the effect of age (*E–H*) or frailty (*M–P*) in males and females, and sex-differences in these effects, were tested using linear regression models with interaction terms between sex and age or frailty, and all *P* values are shown. Point estimates are shown with 95% confidence intervals. Abbreviations: AUC, area under the curve; diff, difference; F, female; M, male; Vax, vaccine strain of SARS-CoV-2 .

To investigate the cross-reactivity of the vaccine-induced humoral response, we measured IgG titers to seasonal and epidemic β-coronaviruses in the older adult cohort (Supplementary Figure 5). As reported elsewhere [27, 28], titers of IgG recognizing OC43, Middle East respiratory syndrome coronavirus, and SARS-CoV-1 increased significantly in

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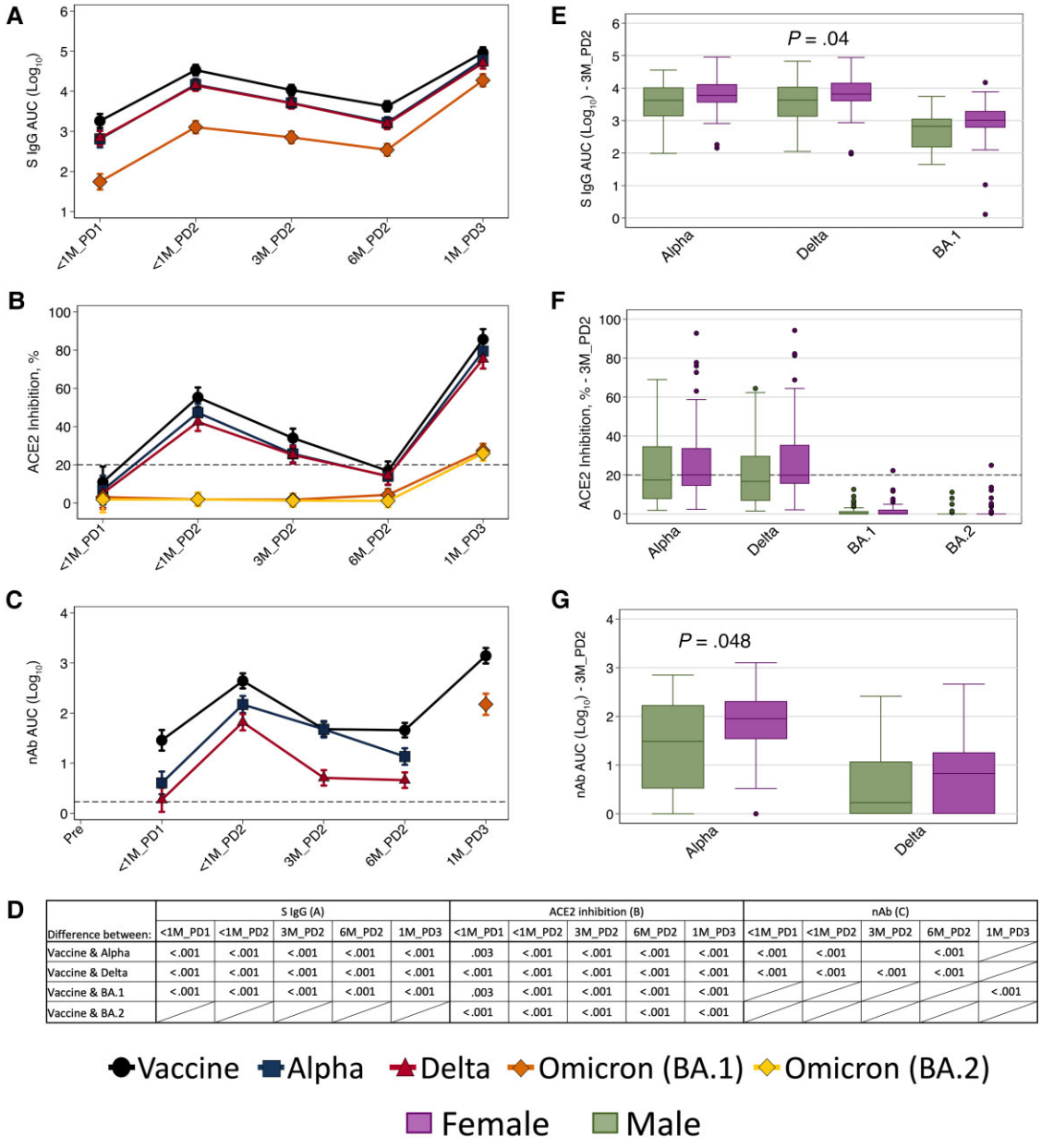

D

	S IgG (A)					ACE2 inhibition (B)					nAb (C)				
Difference between:	<1M_PD1	<1M_PD2	3M_PD2	6M_PD2	1M_PD3	<1M_PD1	<1M_PD2	3M_PD2	6M_PD2	1M_PD3	<1M_PD1	<1M_PD2	3M_PD2	6M_PD2	1M_PD3
Vaccine & Alpha	<.001	<.001	<.001	<.001	<.001	.003	<.001	<.001	<.001	<.001	<.001	<.001		<.001	
Vaccine & Delta	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	
Vaccine & BA.1	<.001	<.001	<.001	<.001	<.001	.003	<.001	<.001	<.001	<.001					<.001
Vaccine & BA.2						<.001	<.001	<.001	<.001	<.001					

Figure 3. Antibody responses to the Alpha, Delta, and Omicron variants are reduced relative to the vaccine virus in older adults. *A–C*, Anti–spike (S) (*A*), angiotensin-converting enzyme 2 (ACE2)–inhibiting (*B*), and neutralizing (*C*) antibodies against the vaccine, Alpha, Delta, and Omicron strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were measured after vaccination, with symbols indicating point estimates and error bars indicating the 95% confidence intervals. *D*, Differences in the responses between viral strains at each time point were measured using paired *t* tests, and all *P* values <.05 are shown; empty cells indicate *P* values >.05 and crossed-out cells indicate that the comparison was not tested. *E–G*, Sex-disaggregated data from the 3-month time point are shown, and significant sex differences are indicated by *P* values. Abbreviations: AUC, area under the curve; Ig, immunoglobulin; nAb, neutralizing antibody; Pre, before vaccination; <1M_PD1,<1 month post-dose 1 ; <1M_PD2, <1 month post-dose 2; 1M_PD3, 1 month post-dose 3; 3M_PD2, 3 months post-dose 2; 6M_PD2, 6 months post-dose 2.

plasma samples collected after SARS-CoV-2 vaccination and remained elevated above baseline levels for 6 months.

Effect of Male Sex on Differences Between Older and Younger Cohorts

To further investigate the sex-specific effects of aging, antibody kinetics against vaccine, Alpha, and Delta antigens were compared between the younger and older adult cohorts during the 6-month period after the primary vaccination series. Overall, anti-vaccine S IgG was significantly lower in older than in younger adults ($P < .001$ at 14 days after vaccination, $P = .004$ at 90 days, and $P = .03$ at 180 days; Figure 4*A*). In sex-disaggregated analyses, differences between the older and younger adults were significant among males at all 3 sentinel points ($P = .004$ at 14 days after vaccination, $P = .005$ at 90 days, and $P = .02$ at

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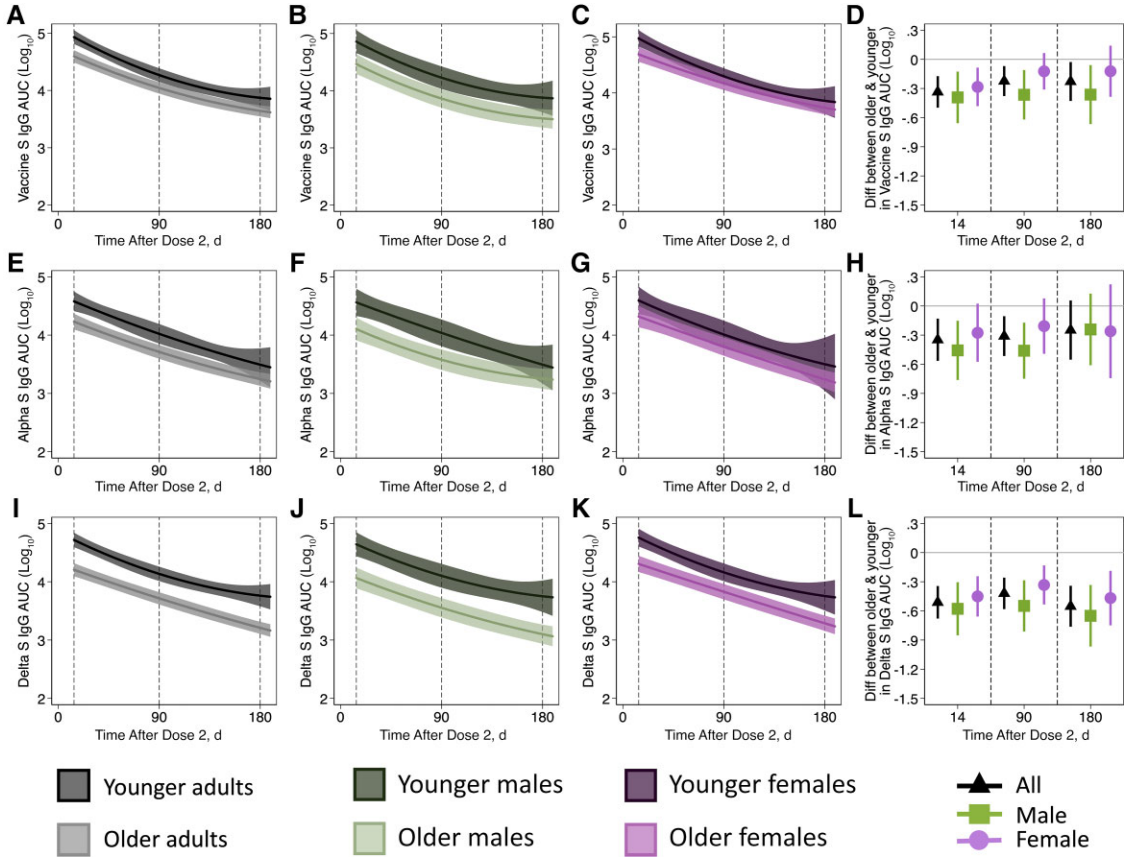

Figure 4. Differences between younger and older adults in antibody responses to the vaccine strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are sex dependent. Plasma samples were collected from older adults at 3 time points after the primary vaccination series and from younger adults at 2 postvaccination time points: 16–76 days post-dose 2 (early) and 96–190 days post-dose 2 (late). *A–D*, Differences in anti-vaccine strain S immunoglobulin (Ig) G levels over time were compared between all younger and older adults (*A*), males (younger: n = 27 early; n = 30 late) (*B*), and females (younger: n = 48 early; n = 48 late) (*C*), and summarized at 3 sentinel points (14, 90, and 180 days after vaccination) (*D*). *E–H*, Comparisons of the anti-Alpha S IgG response between the younger and older groups are shown for the whole population (*E*), males (younger: n = 27 early; n = 26 late) (*F*), and females (younger: n = 39 early; n = 34 late) (*G*), with differences summarized at 14, 90, and 180 days post-dose 2 (*H*). *I–L*, Comparisons of the anti-Delta S IgG response between the younger and older groups are shown for the whole population (*I*), males (younger: n = 27 early; n = 26 late) (*J*), and females (younger: n = 47 early; n = 42 late) (*K*), with differences summarized at 14, 90, and 180 days post-dose 2 (*L*). Kinetics were analyzed using mixed-effects models with fixed effects including days post-dose 2 as a continuous predictor and cubic B-splines (knots at 30, 100, and 160 days after vaccination). Shaded areas indicate 95% confidence intervals (*A–C, E–G, I–K*). In *D, H,* and *L*, point estimates for the difference between cohorts are shown with 95% confidence intervals, such that confidence intervals that do not span the null value of zero are statistically significant. Abbreviations; AUC, area under the curve; Diff, difference.

180 days), but only significant among females at 14-days after vaccination ($P = .004$; Figure 4*B*–4*D*). In addition, the magnitude of the difference between the mean of the older cohort and the mean of younger cohort was consistently larger for males than for females across the 3 sentinel points (Figure 4*D*). Similar results were observed for anti-Alpha and Delta S IgG (Figure 4*E*–4*L*). There were no significant differences in the rate of waning between older and younger adults, suggesting that antibody kinetics are not age dependent.

DISCUSSION

In this longitudinal study, older females mounted stronger antibody responses to SARS-CoV-2 mRNA vaccination than older males, and age and frailty were associated with reduced responses in males but not females. While the kinetics of antibody waning in the 6 months after immunization were not age dependent, older adults mounted weaker initial responses to vaccination, such that their antibody titers remained lower than those in younger adults throughout the follow-up period. A sex-specific effect of age was observed, both within the older adult cohort and when comparing younger and older adults, in which age-associated reductions in humoral immunity were greater in males than in females. In the older adult cohort, receipt of a third vaccine dose largely eliminated disparities caused by sex, age, and frailty in antibody responses, with the exception of ACE2iAbs, which remained lower in frail participants.

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The effect of age on SARS-CoV-2 vaccine responses has been studied [7–9, 29–33], but the sex differential impact of age has not been reported previously. Furthermore, studies investigating frailty have not found an effect on antibody responses [34–36] but have reported that frailty increases the risk of postvaccination breakthrough infection [37, 38], suggesting that the immunogenicity studies may have been underpowered to observe an effect of frailty, that lack of consideration of biological sex obscured the effect, or that higher levels of antibody are required to prevent infection in frail individuals than in the general population.

The inclusion of 4 measures of humoral immunity and 4 SARS-CoV-2 viruses allowed us to capture the breadth and depth of vaccine responses in this vulnerable population. In terms of responses to VOCs, the reductions in anti-S IgG to the Alpha and Delta variants observed in the older adults were similar to other reports in the general population [39]. For the Omicron variant, while reductions in live-virus neutralization in postvaccination serum samples from the general adult population have been reported and were also observed here, there were no reductions in anti-Omicron S IgG [40, 41]. Given the importance of neutralizing and nonneutralizing functions of IgG in conferring protection against SARS-CoV-2 [42, 43], the markedly lower anti-Omicron S IgG levels in older adults, which persisted after receipt of a third vaccine dose, suggests that this population may be more vulnerable to disease caused by the Omicron variant than younger adults and that reformulation of vaccines to target the Omicron variant would be beneficial.

Our study has several strengths and limitations. Some of the sex-specific effects observed were differences among males that were absent among females, without statistical evidence of a sex difference (ie, nonsignificant sex interaction terms) [44]. It is important to note that our findings were generated from post hoc analyses that were not necessarily powered to investigate sex differences, and conclusions are limited by small samples sizes in certain subgroups. Particularly for age-based analyses, however, the consistency of trends between assays and time points, coupled with statistically significant sex differences in the effect of aging at 3M_PD2, lend credibility to the conclusion that the effects of age on antiviral antibody responses are driven by males. Further supporting these findings are similar sex-specific effects of age observed after seasonal influenza vaccination in both younger and older adults [17, 45]. While it is important to not overinterpret "within-sex" differences as "between-sex" differences [46], there is considerable value in studying differences within males or females [47, 48]. This is particularly true given the uniqueness of the community-dwelling older adult cohort, which represents the "oldest" old subset, and is distinct from the population of long-term care facility residents that has been the focus of much of the SARS-CoV-2 research in older adults.

There were also missing data in the older adult cohort, particularly at the <1M_PD1 time point. These missing data, however, did not depart from the missing at random assumption, and thus multilevel models were used to account for missingness. The timing of sample collection was different in the older and younger cohorts. To account for this, analyses that compared the 2 cohorts used days after vaccination as a continuous variable. Finally, although beyond the scope of this article, future work will include measuring cellular immunity after vaccination.

In conclusion, we report that both age and frailty impair antibody responses to the primary series of SARS-CoV-2 vaccination in older males and that these disparities are largely eliminated by vaccination with the third dose. Given that male sex is an important risk factor for severe outcomes from COVID-19 [10–14], the finding that older and frail males may be vulnerable to breakthrough infections owing to low antibody responses, particularly before a third vaccine dose is administered, is of considerable public health importance. These findings emphasize that increasing third dose coverage among older males is crucial for protecting this vulnerable population from COVID-19.

Supplementary Data

Supplementary material are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the postedmaterials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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