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Health characteristics associated with persistence of SARS-CoV-2 antibody responses after repeated vaccinations in older persons over time: the Doetinchem cohort study

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Abstract

Background Older persons elicit heterogeneous antibody responses to vaccinations that generally are lower than those in younger, healthier individuals. As older age and certain comorbidities can influence these responses we aimed to identify health-related variables associated with antibody responses after repeated SARS-CoV-2 vaccinations and their persistence thereafter in SARS-CoV-2 infection-naïve and previously infected older persons.

Method In a large longitudinal study of older persons of the general population 50 years and over, a sub-cohort of the longitudinal Doetinchem cohort study ($n = 1374$), we measured IgG antibody concentrations in serum to SARS-CoV-2 Spike protein (S1) and Nucleoprotein (N). Samples were taken following primary vaccination with BNT162b2 or AZD1222, pre- and post-vaccination with a third and fourth BNT162b2 or mRNA-1273 (Wuhan), and up to a year after a fifth BNT162b2 bivalent (Wuhan/Omicron BA.1) vaccine. Associations between persistence of antibody concentrations over time and age, sex, health characteristics including cardiometabolic and inflammatory diseases as well as a frailty index were tested using univariable and multivariable models.

Results The booster doses substantially increased anti-SARS-CoV-2 Spike S1 (S1) antibody concentrations in older persons against both the Wuhan and Omicron strains. Older age was associated with decreased antibody persistence both after the primary vaccination series and up to 1 year after the fifth vaccine dose. In infection-naïve persons the presence of inflammatory diseases was associated with an increased antibody response to the third vaccine dose (Beta = 1.53) but was also associated with reduced persistence over the 12 months following the fifth (bivalent) vaccine dose (Beta = -1.7). The presence of cardiometabolic disease was associated with reduced antibody persistence following the primary vaccination series (Beta = -1.11), but this was no longer observed after bivalent vaccination.

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Conclusion Although older persons with comorbidities such as inflammatory and cardiometabolic diseases responded well to SARS-CoV-2 booster vaccinations, they showed a reduced persistence of these responses. This might indicate that especially these more vulnerable older persons could benefit from repeated booster vaccinations.

Keywords Ageing, Comorbidities, Inflammatory diseases, Cardiometabolic diseases, Frailty, Antibody responses, Antibody persistence, COVID-19 vaccination, Omicron

Introduction

As the global population ages, the age-related decline in immune function called immunosenescence becomes increasingly important to understand. This encompasses a multifaceted deterioration of the immune system, involving both the innate and adaptive immune responses [1]. These age-related changes in immune functioning lead to a heightened susceptibility to infections and diminished vaccine efficacy in older persons [2–4]. Older persons are also at increased risk of severe complications when infected. Factors contributing to this increased risk include the prevalence of comorbidities such as cardiometabolic or inflammatory diseases and increased overall frailty [5].

The SARS-CoV-2 pandemic has further highlighted the importance of studying the vaccine responsiveness in older persons. Given the increased vulnerability of older persons to infections, the vaccinations against SARS-CoV-2 play a crucial role in protecting older persons from severe COVID-19 illness and associated complications, as well as in reducing the risk of getting infected. From February 2021 in the Netherlands various vaccines have been offered to the general population chronologically from older to younger age groups: the mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna); and the viral-vector based vaccines AZD1222 (AstraZeneca) and ABV66.COV2.S (Janssen).

Booster vaccine doses to SARS-CoV-2 are particularly important for maintaining immunity over time, given the limited persistence of vaccine-induced protection and the continuous emergence of new virus variants. The first booster vaccination was implemented for the general Dutch population starting in December 2021 by employing mRNA vaccines. Because of the emergence of the highly transmissible Omicron variant of concern, a second booster was offered only to vulnerable older adults aged 60 and over in March 2022. A bivalent mRNA vaccine which also included Omicron specific mRNA for the first time was offered as a third booster vaccine in Autumn 2022. Altogether 3 booster vaccines have been administered to the same population in a relatively short time window.

Studying SARS-CoV-2 antibody responses upon vaccination in older adults, is essential to substantiate subsequent vaccination schedules to be able to protect this high-risk group from severe infection outcomes [6]. One such study in older persons showed that subsequent booster vaccinations had a beneficial effect on maintaining IgG antibody concentrations to SARS-CoV-2 and better prevented severe and fatal COVID-19 disease [7].

We have shown a heterogeneous antibody response after the initial primary SARS-CoV-2 vaccinations amongst older persons in which several aspects of frailty play a role [8, 9]. However, little is known about the relation between the persistence of vaccine induced antibody responses to SARS-CoV-2 and its underlying general health determinants in a general population of older persons. In the current study we assess how health characteristics such as frailty are related to the heterogeneity in antibody responses and persistence thereafter following multiple vaccinations against SARS-CoV-2, up to 1 year post fifth vaccination. Furthermore, we aim to identify determinants affecting these responses while considering the specific vaccine received, infection status, and other health related factors. Identifying potential risks for low antibody responses or decreased antibody persistence might contribute towards more targeted follow up vaccination strategies.

Methods

Study population

We used the long-running Doetinchem Cohort Study (DCS) that started in 1987 using a population-based random sample of individuals aged 20–59 who were re-examined every 5 years [10, 11]. All 3647 persons aged 50–93 years that still participated at the start of the national SARS-CoV-2 vaccination program were invited to take part in a COVID-19 vaccination study for blood sampling and questionnaires. Almost half (46%), aged 50–93 years, agreed to participate. Participants were included in the study if they planned to receive COVID-19 vaccination or had completed the primary vaccination series. This primary vaccination series was completed following either 2 AZD1222 doses or 2 BNT162b2 doses. All booster doses consisted of mRNA-based vaccination with either BNT162b2 or mRNA-1273. Bivalent vaccination booster doses consisted of a BA.1 bivalent mRNA vaccine using mRNA-1273 original and BA.1 (N=615) or BNT162b2 original and BA.1 (N=41).

A total of 1374 participants had completed their primary vaccination series and were followed over the course of the pandemic at various timepoints as seen in Fig. 1. The starting point of the study was 1 month (geometric mean 29 days ± SD: 5 days) after the second dose

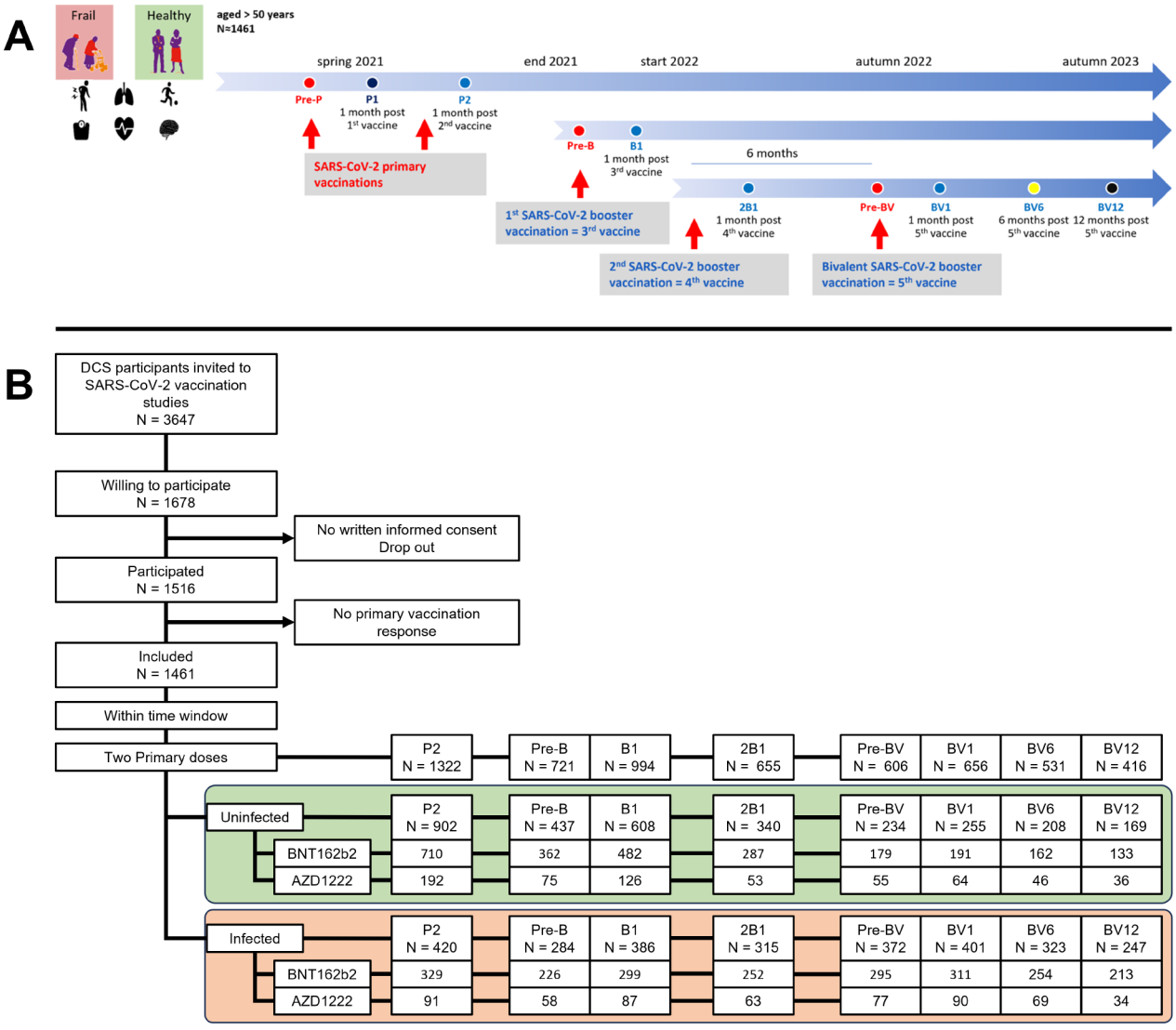

Fig. 1 **A**) Vaccination scheme of study persons and antibody measurements over time including 1 month after the second primary vaccination (P2) with either BNT162b2 or AZD1222, prior to the first mRNA booster vaccine and 1 month thereafter (Pre-B and B1) as the third vaccine, 1 month after the second mRNA booster vaccine, either the mRNA BNT162b2 or mRNA-1273, (2B1) as the fourth vaccine, prior to the bivalent mRNA booster vaccine (Pre-BV) (Wuhan/Omicron BA1) as the fifth vaccine and 1, 6, and 12 months thereafter (BV1, BV6, and BV12). **B**) Flowchart of the study cohort over time. Samples received within the defined time windows of the various timepoints post vaccination are shown. Further distinctions in sample sizes are shown between infection naïve (green block) and previously infected persons (red block) as well as booster vaccination types per timepoint

of the primary vaccination series (P2), and participants were followed up prior to the third (booster) dose (Pre-B) (geometric mean 167 days±SD: 28 days post P2), 1 month (-7, +18 days) after the third dose (B1), 1 month (-7, +21 days) after the fourth dose (2B1), up to 1 month prior to the bivalent fifth dose (Pre-BV), 1 month (-7, +18 days) following the fifth bivalent dose (BV1), and both 6 and 12 months (-1, +1 month) following the bivalent fifth dose (BV6, and BV12). During the course of the study some individuals dropped out of the study or failed to submit a sample on time explaining the decreasing cohort size towards the end of the study. In addition, following the first booster only people aged 60 years or older received a second booster and participated in the later time points (2B1 up to BV12).

Sample collection

Blood samples and questionnaires were taken at each timepoint. Questionnaires covered demographic factors, COVID-19 vaccination information (specific vaccine used and date of vaccination), and SARS-CoV-2 testing information. Finger-prick blood samples (NL76551.041.21, EudraCT 2021-001976-40 and NL74843.041.20, EudraCT 2020-003620-16) were

self-collected in microtubes and returned by mail. In addition venapunction blood samples were collected (NL76719.041.21, EudraCT 2021-002363-22). Serum was isolated from each sample by centrifugation and stored at -80 °C until sample measurement.

SARS-CoV-2 IgG antibody response measurement

Immunoglobulin G (IgG) antibody concentrations against Spike (S1) and Nucleoprotein (N) were measured simultaneously using a bead-based assay as previously described [12]. IgG concentrations were calibrated against the International Standard for human anti-SARS-CoV-2 immunoglobulin (20/136 NIBSC standard) and expressed as binding antibody units per milliliter (BAU/ml), the threshold for seropositivity was set at 14.3 BAU/ml for Nucleoprotein as described previously [8]. From the bivalent vaccination onwards (Pre-BV to BV12) Omicron BA.1 specific anti-S1 IgG antibodies were also measured in arbitrary units AU/ml by using an in house reference serum.

Table 1 Baseline health characteristics of the study population (*N* = 1374)

	Men, N = 662	Women, N = 712	P value[1]
Sociodemographic			
Age (years) (mean (SD[2])) [min – max]	69 (7.8) [50–92]	67 (7.3) [51–93]	< 0.001
Socio-Economic Status (%)			0.001
Low	28	38	
Middle	37	31	
High	35	31	
Lifestyle			
Currently smoking (%)	6.2	7.3	0.784
Drinking alcohol (%)	77.6	59.9	< 0.001
Cardiometabolic factors			
BMI (kg/m2) (mean (SD))	26.7 (3.6)	26.5 (4.8)	0.335
Waist circumference (cm) (mean (SD))	100.8 (10.2)	92.1 (12.7)	< 0.001
Systolic blood pressure (mmHg) (mean (SD))	133 (16)	130 (17)	< 0.001
Total cholesterol (mmol/L) (mean (SD))	5.1 (1.0)	5.6 (1.0)	< 0.001
HDL cholesterol (mmol/L) (mean (SD))	1.3 (0.3)	1.6 (0.4)	< 0.001
Creatinine (mmol/L) (mean (SD))	92.0 (18.3)	72.9 (11.8)	< 0.001
Glucose (mmol/L) (mean (SD))	5.9 (1.7)	5.6 (1.4)	< 0.001
Comorbidity related factors			
eGFR (mean (SD))	1.0 (0.3)	0.9 (0.2)	< 0.001
Frailty index (median [IQR[3]])	0.05 [0.02, 0.09]	0.07 [0.03, 0.12]	< 0.001
Inflammatory disease presence[4] (%)	12.4	14.0	0.409
Cardiometabolic disease presence[5] (%)	53.9	46.1	0.004

1: P values indicating sex differences were generated using a t-test or Fisher's exact test for continuous and categorical variables respectively

2: SD = standard deviation

3: IQR = interquartile range

4: Gastrointestinal diseases, Psoriasis, Osteoarthritis, Joint inflammation, Osteoporosis, Nervous system diseases

5: Diabetes, Hypertension, Stroke, Heart failure, Myocardial infarction, Bypass, Balloon dilation, Cardiac catheterization, Pacemaker, Vascular surgery

Measurement of health variables

From 1987 up to this vaccination study all participants were followed up, up to 7 times with 5 year intervals in between. During these follow-up rounds questionnaires were administered and a physical examination took place. Questionnaires included data on demographic and lifestyle factors, general health, comorbidities, and quality of life. The physical examination included measurement of blood pressure, lung function, a cognitive test battery, physical functioning, as well as taking a blood sample for measurement of total- and HDL-cholesterol, and glucose.

The frailty index was calculated, consisting of 36 'deficits' defined based on chronic conditions, cognitive, physical, and psychological functioning all of which were included in previous frailty indexes as described before [13]. Health deficits were either dichotomized or trichotomized with 0 indicating total absence, 0.5 indicating partial/mild presence, and 1 indicating total presence of a given deficit. The sum of deficits was then divided by the number of deficits included resulting in an index ranging from 0 (completely non-frail) to 1 (completely frail).

In addition to constructing the frailty index we used multiple comorbidities available in the questionnaires conducted to construct the cardiometabolic - and inflammatory disease prevalence categories as shown in Table 1. These comorbidities were either self-reported or diagnosed by a physician. Inflammatory disease presence was based on prevalence of gastrointestinal diseases, psoriasis, osteoarthritis, joint inflammation, osteoporosis, and nervous system diseases. Presence of cardiometabolic disease was based on presence of diabetes, hypertension, stroke, heart failure, heart infarct, and having received a bypass, balloon dilation, cardiac catheterization, pacemaker, and/or vascular surgery. Having at least one of these comorbidities meant inflammatory- or cardiometabolic disease presence was determined as positive whereas not having any of the afore mentioned comorbidities meant no disease presence.

Statistical analysis

The age of the study participants was determined at the sample collection date of the first primary vaccination and was used for all subsequent analyses. IgG concentrations were log-transformed prior to all analyses resulting in approximately normally distributed values. Univariable tests to determine pairwise differences in log-transformed antibody concentrations based on vaccine regimen, 10-year age groups, and sex were performed

using a Wilcoxon rank sum test and was corrected for multiple testing using the False Discovery Rate (FDR) method. The IgG kinetics post the bivalent booster (Pre-BV to BV12) were visualized using a slope fitted with a linear mixed model.

Next, we distinguished four periods between the vaccinations over time: P2 to Pre-B, Pre-B to B1, Pre-BV to BV1, and BV1 to BV12. For each of these periods we calculated the Log2 Fold-Change (LFC) as measure of the relative change in antibody concentrations between two subsequent timepoints. Multivariable linear regression analyses were used to assess the associations between the relative change in antibody LFC and: overall frailty, cardiometabolic factors such as waist circumference and HDL concentrations, and comorbidities including cardiometabolic and inflammatory diseases. Multiple separate models were used to explore the role of various groups of health characteristics on the antibody response. Out of all the cardiometabolic variables we selected HDL cholesterol concentration and waist circumference for inclusion in our regression models. Body mass index (BMI), total cholesterol, systolic blood pressure, creatinine- and glucose concentrations, and estimated glomerular filtration rate (eGFR) were excluded. This was done since these variables were correlated to HDL cholesterol and waist circumference while having more missing data.

The regression analysis was also corrected for age, sex, the specific vaccine used, and the baseline antibody concentration per period analyzed. This allowed us to assess the effect of the variables of interest on the change in antibody concentrations irrespective of their association with the antibody concentration at the start of a period. The obtained model estimates (Betas) were divided by twice the standard error per variable of interest to normalize their range resulting in the betas reported. All analyses were stratified for infection status as determined based on SARSCoV2 N-seropositivity, positive antigen test, or self-reported COVID-19 infection. All statistical analyses were performed using R version 4.3.0. Statistical significance was defined as p-value ≤ 0.05.

Results

Overview

An overview of the study and the number of older persons in the various vaccination rounds over time can be seen in Fig. 1. Based on a complete primary vaccination series as part of the inclusion criteria and the defined time window for sampling at 1 month post primary vaccination (P2), 1461 participants were included. Of these persons, 1374 had received either two doses of BNT162b2 or two doses of AZD1222 and were included in further SARS-CoV-2 antibody analyses at least at one of the timepoints in this study. Groups were divided in infection naïve and infected persons over time.

General characteristics

The baseline characteristics on demographics, lifestyle, cardiometabolic factors and comorbidities of the men and women that participated in the study are shown Table 1. We also included the frailty index, a summary measure of frailty based on 36 deficits, ranging from 0 (non-frail) to 1 (maximum frail). There were statistically significant differences between men and women for most baseline characteristics, except for current smoking behavior, body mass index (BMI), and inflammatory disease incidence. Men were on average slightly older and showed higher levels of alcohol consumption, a higher waist circumference, higher systolic blood pressure, higher creatine and glucose concentrations, a higher estimated glomerular filtration rate (eGFR) and a higher cardiometabolic disease presence, whereas in women higher total and HDL cholesterol concentrations and a higher frailty index was observed. The difference in demographic variables between Doetinchem Cohort Study participants that were not included and were included in the current study can be seen in Supplementary Table S1.

SARS-CoV-2 anti-S1 IgG antibody responses over time, stratified by infection status and sex

At 1 month after the primary vaccination series (P2) the persons vaccinated with two doses of AZD1222 showed a lower antibody concentration compared to those vaccinated with BNT162b2 (Fig. 2A). This was statistically significant for both previously infected and infection naïve individuals (Wilcoxon rank sum test P-value < 0.0001, Supplementary Table S2). After subsequent boosters this initial difference based on the primary vaccination series seemingly disappeared in infection naïve individuals following the bivalent booster vaccination. Generally, all persons, both with and without prior infection, and those vaccinated with either BNT162b2 or AZD1222 for their two primary vaccination doses, showed a similar pattern for their antibody responses over the various timepoints after the booster vaccinations (Fig. 2A, Supplementary Table S2).

After stratifying by 10-year age groups (Fig. 2B), we observed that the antibody concentrations after primary vaccination at P2 and prior to the first booster at B0 appeared lower in older age groups compared to younger ones showing significant differences between the 50–59 year old vaccinee's compared to the 80–89 year old vaccinee's ($P < 0.05$, Supplementary Table S3). In both previously infected individuals and infection naïve individuals these age related differences largely disappeared later in time after continued vaccination with either BNT162b2 or mRNA-1273 booster vaccines.

Omicron BA.1 specific anti SARS-CoV-2-S1 IgG antibody responses were measured prior to bivalent vaccination (fifth vaccine dose) (Pre-BV) and 1, 6, and 12 months

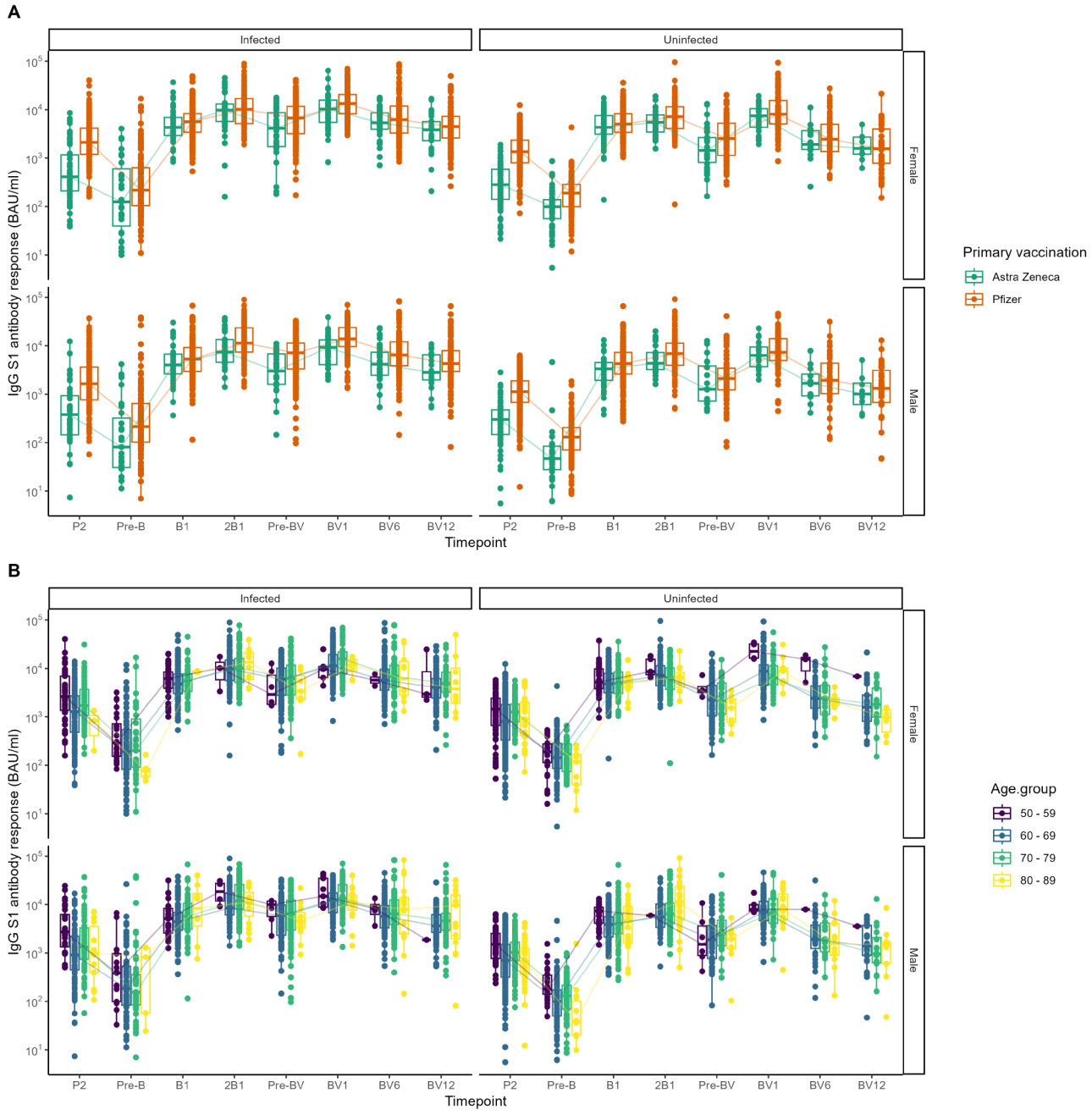

Fig. 2 Anti Wuhan strain SARS-CoV-2-S1 IgG antibody responses stratified by infection status and sex. **A**) Stratified by vaccine type. **B**) The antibody responses stratified by 10-year age groups based on age at first vaccination dose

following bivalent vaccination (BV1, BV6, BV12) (Supplementary Figure S1). There was a notable increase in Omicron specific anti-S1 IgG concentrations 1 month after bivalent vaccination (BV1). There were no differences in these antibody concentrations between males and females (Supplementary Table S4) or between various age groups (Supplementary Table S5) at any given time point.

Anti-S1 IgG antibody response and persistence of antibody levels following bivalent vaccination

In the first month following bivalent booster vaccination both infection naïve persons and those with a prior infection showed a strong increase in their Wuhan strain SARS-CoV-2 anti-S1 IgG antibody concentrations followed by a slight decline after a year post vaccination (Fig. 3A). Persons with a prior infection had a higher antibody concentration prior to vaccination and 1 month

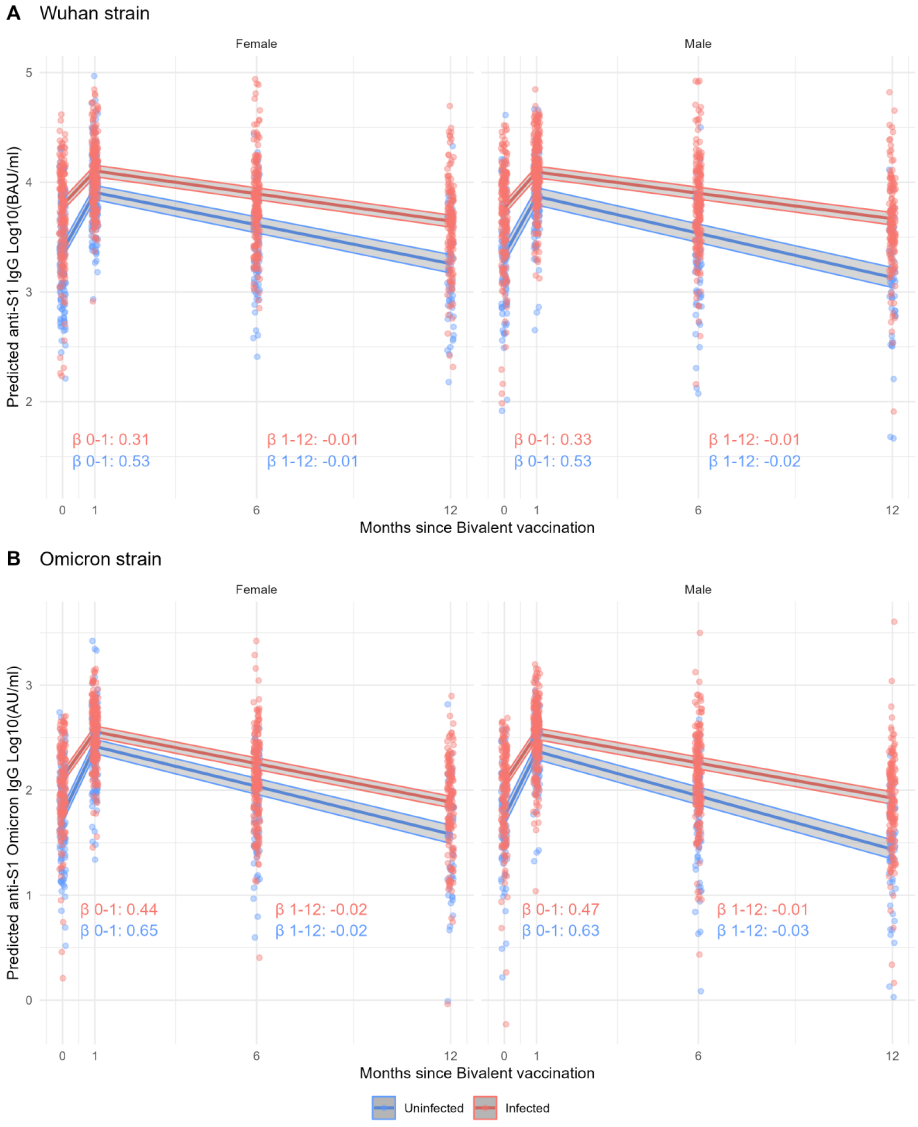

Fig. 3 Changes in Wuhan (**A**) and Omicron (**B**) specific anti-S1 IgG antibody concentrations (log10 transformed) and the respective slopes after 1 month, and from 1 to 12 months following bivalent vaccination, stratified by sex and infection status. Regression parameters are derived using a linear mixed model and shaded areas correspond to the 95% confidence bands

after vaccination. Both infection-naïve and previously infected persons experienced an increase in antibody concentrations after receiving a bivalent vaccination as indicated by the slope (Beta = 0.53 in both infection-naïve women and men, and Beta = 0.31, 0.33 in infected women and men respectively). We observed no effect of sex or infection status on the slope of the antibody persistence during the year following bivalent vaccination (Beta = -0.01, -0.02 in infection-naïve women and men respectively, and Beta = -0.01, in both infected women and men).

Omicron BA.1 specific anti-S1 IgG responses over the same period showed a similar pattern as found for the Wuhan strain anti-S1 IgG responses but with a stronger increase at 1 month post vaccination, as can be seen in Fig. 3B. We observed an increase upon vaccination for the Omicron BA.1 specific anti-S1 IgG antibodies (Beta = 0.65 and 0.63 for infection-naïve women and men respectively, and Beta = 0.44 and 0.47 for infected women and men respectively) followed by the waning of antibodies over time (Beta = -0.02 and −0.03 for infection-naïve women and men respectively, and Beta = -0.02 and −0.01 for infected women and men respectively).

Associations between age, sex, and persons health characteristics with SARS-CoV-2 IgG responses over time

Multivariable regression analysis (Fig. 4) showed a significant effect of the type of vaccine used in the primary vaccination series on the antibody persistence post second vaccination (P2 – Pre-B). Figure 4A shows

Fig. 4 Log2 fold-change (LFC) in antibody concentrations corrected for baseline concentrations and stratified by infection status. Significant associations are shown in red. The intercept shown in the figure refers to the intercept of the fitted regression model. For primary vaccination AZD1222 was taken reference, whereas for first and second booster BNT162b2 was compared with mRNA-1273 as reference. A negative Beta refers to a smaller LFC which can either refer to a weaker increase upon vaccination or a stronger (more negative) decrease thereafter. Separate multivariable linear regression results are shown for **A**) baseline characteristics, **B**) cardiometabolic markers, and **C**) comorbidities

that persons that received two BNT162b2 doses had a stronger decrease compared to those vaccinated with AZD1222 (Beta = -1.23 for infection-naïve persons and Beta = -1.71 for previously infected persons). Furthermore, within the infected group a higher frailty index was associated with a stronger decline in IgG concentrations (Beta = -1.36).

In the month following the first booster vaccination (with a third vaccine dose) (Pre-B – B1), no significant association was found between the fold increase in antibody concentrations and the type of primary vaccinations. However, both infection-naïve and previously infected persons receiving a BNT162b2 vaccine as their first booster showed a significantly lower increase in IgG concentrations compared to those who received an mRNA-1273 booster vaccine (Beta = -1.19 for infection-naïve persons and Beta = -1.13 for previously infected persons). After the subsequent booster vaccinations, no significant differences were observed in antibody responses between the received vaccine types. In the period after the fifth (bivalent) vaccination dose (BV1 – BV12) the persistence of antibodies was negatively associated with age, in just the infection-naïve persons (Beta = -1.31) (Fig. 4A).

We observed that during the month following the third vaccine dose (Pre-B – B1), HDL cholesterol concentrations were associated with a reduced increase in IgG concentrations in infection-naïve persons (Beta = -1.56) (Fig. 4B). During the one-year period following bivalent vaccination (BV1 – BV12) a positive association between HDL and antibody concentrations (Beta=1.24) was observed in these persons. This means that those with higher HDL concentrations experienced an increased antibody persistence one year post bivalent vaccination. No associations were found between waist circumference and changes in antibody concentrations during any of the periods (Fig. 4B).

Lastly, we observed that persons suffering from cardiometabolic diseases experienced a stronger decline (Beta = -1.11) in IgG concentrations following the primary vaccination series (P2 – Pre-B) (Fig. 4C). Persons suffering from inflammatory diseases experienced a stronger increase (Beta=1.53) in IgG concentrations in response to the third vaccine dose (Pre-B – B1). However, after 1 year following bivalent vaccination (BV1 – BV12), the presence of an inflammatory disease was associated with a stronger decrease in antibody levels for both infection-naïve persons (Beta = -1.7) and previously infected persons (Beta = -1.0) (Fig. 4C).

Associations between baseline health characteristics, comorbidities and Omicron specific antibody responses

Following bivalent vaccination we observed that those with a higher baseline anti-S1 IgG concentration experience a relatively smaller increase 1 month after bivalent vaccination (Pre-BV – BV1) (infection naïve Beta = -4.01; infected Beta = -3.75). Infection-naïve persons who had previously received a BNT162b2 booster vaccine as opposed to a mRNA-1273 experienced a slightly higher increase in antibody concentration upon bivalent vaccination (Beta=1.08). In addition we foundthat in previously infected persons a higher baseline anti-S1

IgG concentration was associated with a stronger decline in antibody concentration (Beta = -2.8) during the year following bivalent vaccination (BV1 – BV12) (fig. S2A). During the year following bivalent vaccination women retained higher antibody concentrations compared to men (Beta = 1.03) in infection-naïve persons (fig. S2A). During the same period HDL concentrations were also associated with a higher antibody persistence (Beta = 1.13) in infection-naïve persons (fig. S2B). Lastly, the presence of inflammatory disease was associated with a reduced persistence of antibody concentrations during this period for both infection-naïve (Beta = -1.79) and previously infected persons (Beta = -1.07) (fig. S2C).

Discussion

In this study we explored whether various health characteristics are related to the persistence of SARS-CoV-2 antibody responses of older men and women from the general population following five SARS-CoV-2 vaccinations over time. Overall the three booster mRNA vaccines over time substantially increased anti-SARS-CoV-2 Spike S1 (S1) antibody concentrations in older persons. However, ageing was associated with decreased antibody persistence both after the primary vaccination series and up to 1 year after the fifth vaccine dose. Although older persons showing comorbidities such as inflammatory diseases and cardiometabolic diseases also responded well to SARS-CoV-2 booster vaccinations, they showed a reduced persistence of these responses.

Previously we have shown that uninfected frailer persons experienced a reduced SARS-CoV-2 antibody response upon primary vaccination while those suffering from cardiometabolic diseases had an increased antibody response [9]. In contrast, in the current study we observed that infection-naïve persons with cardiometabolic disease experienced a stronger waning of their antibody concentrations. Also, in previously infected persons, frailty was associated with a stronger decrease in antibody concentrations during the same period. These results were in agreement with the positive association between antibody responses and cardiometabolic diseases followed by a faster waning of antibody concentrations afterwards reported before [14]. The relation between comorbidities and frailty in older persons and a weakened immunity has been reported extensively [15], highlighting the role of frailty in reduced antibody responses to vaccination in older persons [4]. However, our study showed that after a fifth SARS-CoV-2 vaccine dose with a bivalent vaccine the differences in antibody responses and persistence over time between frail and less frail individuals, or those with and without cardiometabolic diseases, are no longer present. We did however observe that infection-naïve persons with higher HDL cholesterol concentrations had an increased antibody persistence after bivalent vaccination. Because of the association between HDL cholesterol concentrations, and other cardiometabolic factors, the cause could be multifactorial, even related to medication use [16].

Additionally, we observed that the presence of inflammatory diseases was associated with a stronger increase of antibody response to the third vaccination. This finding is especially of interest given that previous studies in contrast have found that these patient groups experience a lower magnitude and faster waning of antibody responses upon vaccination [17]. However, these patients are often treated with anti-inflammatory therapeutics that could inhibit the antibody response by inhibiting the cytokine response or inhibiting immune cells, which could explain this association [18]. Other studies have linked a short interruption of anti-inflammatory treatment with an increased antibody response after vaccination compared to patients receiving continued treatment [19]. Based on our findings, older persons with inflammatory diseases may experience a stronger antibody response after a booster vaccination compared to relatively healthy older persons, though this group also showed a decreased antibody persistence during the 12 months following bivalent vaccination with a fifth vaccine dose. In addition, the waning of antibody concentrations over time after vaccination has been linked to increased COVID-19 mortality in frail nursing home residents [20]. This indicates that while vulnerable older people might initially induce a strong antibody response upon the first booster vaccination, there remains a need for surveillance of immunity and repeated booster vaccinations over time to maintain SARS-CoV-2 antibody levels.

Our study showed that with increasing age, antibody levels had decreased more at 6–8 months after the primary vaccinations just before the first booster. Higher antibody levels at this point were associated with a faster relative decline in antibody levels, but this is because antibody waning is a non-linear process. Increased antibody levels do not lead to a reduced antibody persistence on an absolute level. A similar association between age and antibody waning was observed during the 12 months following the fifth vaccine dose in infection-naïve participants. We also observed that women experienced a stronger increase in antibody concentrations after their first booster vaccination compared to men in infection-naïve persons that was not observed after bivalent vaccination. Sex differences have been reported before with regards to the antibody response upon SARS-CoV-2 vaccination [9, 21]. Other studies focusing on antibody persistence after just a third SARC-CoV2 vaccine dose in older persons did not observe sex differences anymore, but did find that different comorbidities affected the antibody persistence depending on sex [22]. Others like Shapiro et al. have identified sex-based differences in older

community dwelling adults and show how this difference is more pronounced in frailer populations and diminishes after the third vaccine dose [23]. The fact we do not observe these same sex differences after a fifth vaccination dose could be due to all our participants reaching similar levels of antibody responses. It could also be explained by the fact that we have a relatively healthier population of community dwelling adults or by the fact that we look at relative changes between timepoints and might not detect differences in baseline antibody concentrations if there are no relative differences. We however did observe that at least 12 months after bivalent vaccination infection-naïve women still have a higher antibody persistence for Omicron BA.1 specific anti-S1 IgG antibodies than men. This might be explained by the primary vaccine responses to the Omicron virus strain in this infection naïve group of persons.

Previous studies have shown that after infection elevated antibody concentrations can still be observed up to 9 months after recovering. Those with asymptomatic disease however showed a lower persistence of the antibody response [24]. A similar pattern based on infection severity was seen in unvaccinated hospitalized patients [25], as well as in vaccinated older persons using neutralizing antibodies [26]. We however observed a strong decline in IgG antibody concentrations approximately 6 months after the second vaccine dose in both infection-naïve and previously infected persons leading up to the first booster vaccination. This decrease in antibody concentrations following the primary vaccination series has previously also been linked to a decline in infection protection [27]. After the first booster vaccination (third vaccine dose) antibody concentrations showed a substantial increase irrespective of infection status and the vaccine used for the primary vaccination series. This substantial increase in antibody responses after the first SAR-CoV-2 booster dose has been reported by others as well even for older nursing home residents [28–31]. After vaccination with two subsequent additional booster doses we consistently observed increases in antibody concentrations 1 month after vaccination. The waning of antibody concentrations after the bivalent vaccine as the fifth vaccine dose was not as steep as seen after the primary vaccination series. This was corroborated by other longitudinal studies though these study populations included younger adults as well [32]. We observed a relatively stronger increase in Omicron BA.1 specific antibody concentrations after bivalent vaccination than those observed for Wuhan specific antibody concentrations. Although this was the first Omicron BA.1 specific immunization, antibody concentrations persisted up to one year post vaccination in infection naïve individuals, that was in contrast to the relatively fast waning of antibodies after the primary vaccination series. This might be explained by cross-reactive antibodies immunity induced by the Wuhan-strain specific vaccines and the Omicron BA.1 strain which is in accordance with other studies [33]. The ability of bivalent boosters to generate a broad and strong antibody response has been noted previously with regards to the importance to continuously adapt the SARS-CoV-2 vaccines to protect against new strains [34].

In our study about 75% of the participants received dual BNT162b2 vaccinations and 25% (aged 51–68 years) received dual AZD1222 vaccinations. Following these primary vaccination series antibody concentrations of AZD1222 vaccinee's waned significantly slower than those in persons vaccinated with BNT162b2. AZD1222 vaccinee's are reported to have a slower decay of antibody concentrations [35] while BNT162b2 vaccinee's have higher initial peak antibody response. This could explain the relatively stronger decline in antibody response after this peak that we see in BNT162b2 vaccinee's compared to AZD1222 vaccinee's. In addition, others have shown a slightly better humoral response for heterologous vaccination after the first booster dose [36]. However, we showed that after subsequent mRNA booster vaccinations in time any possible difference in antibody persistence following BNT162b2 or AZD1222 as the primary vaccination series was no longer observed.

Our study offers several key strengths. By utilizing comprehensive longitudinal data from a large, pre-existing cohort, we were able to examine the impact of various health factors, such as frailty and comorbidities, on antibody responses following SARS-CoV-2 vaccination. We developed specific health-related metrics, including a frailty index and clusters of inflammatory and cardiometabolic conditions, which provided a nuanced understanding of how these factors associate with immune responses. With a follow-up period extending over 2.5 years, we were able to explore the durability of antibody responses after multiple vaccinations, performing separate analyses for Omicron BA.1 and Wuhan strain-specific anti-S1 IgG antibodies while differentiating between infection-naïve and previously infected individuals.

However, several limitations should be acknowledged. Grouping together various self-reported inflammatory and cardiometabolic diseases allowed us to study their associations with the antibody response, however these groupings are to some extent arbitrary. Conditions like Diabetes can be viewed as both an inflammatory and a cardiometabolic disease. Furthermore, our cohort was comprised of relatively healthy, community-dwelling older adults with frailty index scores largely below 0.1. While our cohort is likely to have grown frailer during the 2.5 years follow-up period this relative fitness, combined with the fact that even people with low vaccine responsiveness such as nursing home residents responded well to the mRNA-based vaccines (Hofstee et al., submitted),

limited the generalizability of our findings regarding the impact of frailty on vaccine responses. A frailer population would be necessary for a more comprehensive evaluation. In addition, the fact that about half of the DCS participants agreed to participate in this study could have potentially led to selection bias. However, all long running cohort studies tend to select for relatively fitter participants, and while it has been shown before that this can introduce some bias with regards to estimating disease prevalences, the effects on the relations between variables were negligible [37].

Another limitation was the decreasing cohort size, this could potentially be because of frailer or sicker participants dropping out. However, after testing the differences in baseline characteristics between participants at the various timepoints we found no such trend. The low number of participants in various subgroups did limit our ability to accurately study these subgroups however. We had a relatively small number or participants that received two doses of AZD1222 during their primary vaccination series. Therefore, it was not possible to stratify our analyses based on whether participants received a classical vaccine or an mRNA-based vaccine. However, from the first booster vaccine and onwards all vaccines received were mRNA-based vaccines so instead we corrected for the specific vaccine received. Additionally, the number of infection-naïve participants diminished towards the later stages of the study, reducing the statistical power for detecting associations between comorbidities and antibody persistence in this subgroup. Furthermore, while we measured quantitative antibody levels, we did not assess neutralizing antibodies or cellular immunity, restricting the scope of our findings.

In summary, our study contributes to the surveillance of the vaccine induced antibody responses against SARS-CoV-2 over the course of the Corona virus pandemic, emphasizing the role of booster vaccination doses in older vulnerable persons for maintaining antibody concentrations. We identified that older age was associated with reduced antibody persistence but only in infection-naïve individuals. Furthermore, we identified potential risk groups within the older population such as those having inflammatory diseases and cardiometabolic diseases that have a reduced antibody response or persistence of antibody concentrations over time. These more vulnerable groups of older persons especially might benefit from further SARS-CoV-2 booster vaccinations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12979-024-00476-7.

Supplementary Material 1

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Author contributions
The study was conceptualized and designed by H.S.J.P., J.K., W.M.M.V., and A.B. Analysis was performed by Y.K. with input from by H.S.J.P., J.K., W.M.M.V., and A.B. MZB, MK and LR: data investigation, data curation and writing editing. IS. EG and RR, clinical study and data management. The manuscript was written by Y.K. with input from all authors. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted according to the principles of the World Medical Association Declaration of Helsinki and its amendments since 1964, and in accordance with the Medical Research Involving Human Subject Act (WMO). The study protocols were approved by the Medical Ethics Committee of the University Medical Center Utrecht and all informed consent was obtained from all participants. Ethical approval was for finger prick blood sampling in the majority of the DCS participants (NL76551.041.21, EudraCT 2021-001976-40) and for finger prick blood sampling as well as venapunction in a small part of the participants (NL74843.041.20, EudraCT 2020-003620-16 and NL76719.041.21, EudraCT 2021-002363-22).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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