Determinants of antibody responses after vaccination against SARS-CoV-2 in older persons. The Doetinchem Cohort Study

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Abstract

Background

Immune responses to vaccination vary widely between individuals. The aim of this study was to identify health-related determinants of antibody responses to SARS-CoV-2 vaccination in older persons. We recruited participants in the long-running Doetinchem Cohort Study (DCS) who underwent vaccination as part of the national COVID-19 program, and measured antibody concentrations to SARS-CoV-2 Spike protein (S1) and Nucleoprotein (N) at baseline (T0), and a month after both the first vaccination (T1), and the second vaccination (T2). Associations between the antibody concentrations and demographic variables, including age, sex, socio-economic status (SES), comorbidities (cardiovascular diseases and immune mediated diseases), various health parameters (cardiometabolic markers, inflammation markers, kidney- and lung function) and a composite measure of frailty (‘frailty index’, ranging from 0 to 1) were tested using univariate and multivariate models.

Results

We included 1457 persons aged 50 to 92 years old. Of these persons 1257 were infection naïve after their primary vaccination series. The majority (N = 954) of these individuals were vaccinated with two doses of BNT162b2 (Pfizer) and their data were used for further analysis. A higher frailty index was associated with lower anti-S1 antibody responses at T1 and T2 for both men ($r_{T1} = -0.095$, $p_{T1} = 0.05$; $r_{T2} = -0.11$, $p_{T2} = 0.02$) and women ($r_{T1} = -0.24$, $p_{T1} < 0.01$; $r_{T2} = -0.15$, $p_{T2} < 0.01$). After correcting for age and sex the frailty index was also associated with the relative increase in anti-S1 IgG concentrations between the two vaccinations ($\beta = 1.6$, $P < 0.01$). Within the construct of frailty, history of a cardiac catheterization, diabetes, gastrointestinal disease, a cognitive speed in the lowest decile of the population distribution, and impaired lung function were associated with a lower antibody response after both vaccinations.

Conclusions

Frailty plays a key role in the primary vaccination response to the BNT162b2 vaccine within an ageing population. Frail older persons have a lower immune response after their first vaccination, and while they see a stronger increase after their second vaccination compared to healthy people, they still have a lower antibody response after their second vaccination.

Introduction

The COVID-19 pandemic was a global outbreak of disease caused by a novel coronavirus. The rapid development and implementation of SARS-CoV-2 vaccination programs helped reduce symptomatic COVID-19 and protect against severe COVID-19 in the general population (Fiolet et al., 2019) (Chen et al.,
2021). These programs included the use of two new mRNA-based vaccines, one of which was the BNT162b2 (Pfizer) vaccine which required two injections to complete the primary vaccination series.

With increasing age, physical functions decline. However, there is large heterogeneity in health at older ages (Starke et al., 2021) (Jaul E. & Barron J., 2021). This heterogeneity in health status also extends to that in the immune system (Poland et al., 2017) (Collier et al., 2021). The age-related decline in function of the immune system, called immunosenescence, affects and is affected by various autoimmune, cardiovascular, neurodegenerative, and infectious diseases as well as lifestyle and genetics (Wang et al., 2022). In an earlier study, we have seen that after the initial COVID-19 vaccinations there is much heterogeneity in antibody responses amongst older persons (van den Hoogen et al., 2022). There is, however, a lack of studies focusing on how general health influences the immune responses to vaccination against SARS-CoV-2 in the general population.

The response to SARS-CoV-2 vaccination itself has been extensively researched in the general population and in health care workers in various studies, but older persons tend to be underrepresented in such studies (Veronese et al., 2021). Further research has been done in specific patient subpopulations with diseases such as cancer, autoimmune disorders, (kidney) transplantations, and with other specific comorbidities (Haggenburg et al., 2022; Boekel et al., 2021; Tran et al., 2021; Caillard et al., 2021; Loubet et al., 2021). These studies tend to focus on patients with diseases that affect the immune system or require immune modulating medication, but do not compare these groups directly to each other or to community dwelling (more healthy) older vaccinees from the general population. Likewise, while other studies have characterized the immune response after vaccination in a healthy and frail older population they did not investigate other possible determinants in addition to frailty status, or what aspects within the construct of frailty determined the vaccine response (Vinh et al., 2022; Semelka et al., 2022).

In the current study we have used the long-running Doetinchem Cohort Study (DCS) (Verschuren et al., 2008; Picavet et al., 2017), a unique population based longitudinal cohort representative of the Dutch general population, that includes individuals now ranging from 50 to 92 years of age. In this cohort we aimed to study determinants of heterogeneity in antibody responses to the primary vaccination series with BNT162b2 (Pfizer), using an extensive set of characteristics of overall (physical and cognitive) health, including various comorbidities and other manifestations of frailty. By identifying which factors influence antibody responses upon primary vaccination we aimed to contribute towards the design of possibly more targeted vaccination strategies in the future.

Results

General characteristics

The baseline characteristics of our cohort, including all potential determinants used in this study are shown in Table 1. 1457 individuals participated in the study, 74.0% and 76.7% received the BNT162b2 vaccine for their first and second vaccination which can be seen in the flow diagram of Fig. 1. Included in
the table is a summary measure of their frailty, the frailty index which ranges from 0 (non-frail) to 1 (maximum level of frailty). A more in-depth description of the various comorbidities as well as the different parameters that make up the frailty index can be seen in table S1.
Table 1
Prevalence and mean (SD) of sociodemographic and cardiometabolic variables in the study population (N = 1457).

<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th>N = 1457</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>51.2</td>
</tr>
<tr>
<td>Age (years) (mean (SD))</td>
<td>67.4 (7.7)</td>
</tr>
<tr>
<td>Socio-Economic Status (%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>33</td>
</tr>
<tr>
<td>Middle</td>
<td>35</td>
</tr>
<tr>
<td>High</td>
<td>32</td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>6.6</td>
</tr>
<tr>
<td>Drinking alcohol (%)</td>
<td>68.0</td>
</tr>
<tr>
<td>Adherence to Dutch healthy exercise norm (NNGB) (%)</td>
<td>62.9</td>
</tr>
<tr>
<td>Cardiometabolic factors</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm) (mean (SD))</td>
<td>96.4 (12.3)</td>
</tr>
<tr>
<td>BMI (kg/m²) (mean (SD))</td>
<td>26.6 (4.2)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg) (mean (SD))</td>
<td>131 (17)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L) (mean (SD))</td>
<td>5.4 (1.0)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L) (mean (SD))</td>
<td>1.5 (0.4)</td>
</tr>
<tr>
<td>Creatinine (mmol/L) (mean (SD))</td>
<td>82.3 (19.0)</td>
</tr>
<tr>
<td>Glucose (mmol/L) (mean (SD))</td>
<td>5.7 (1.6)</td>
</tr>
<tr>
<td>GlycA (mmol/L) (mean (SD))</td>
<td>0.9 (0.1)</td>
</tr>
<tr>
<td>CRP (mmol/L) (mean (SD))</td>
<td>2.2 (4.6)</td>
</tr>
<tr>
<td>Comorbidity related variables</td>
<td></td>
</tr>
<tr>
<td>Frailty index (median (IQR))</td>
<td>0.06 (0.03–0.11)</td>
</tr>
<tr>
<td>FEV1 max (mean (SD))</td>
<td>3.1 (0.8)</td>
</tr>
<tr>
<td>FVC max (mean (SD))</td>
<td>4.2 (1.0)</td>
</tr>
<tr>
<td>FEV1/FVC ratio (mean (SD))</td>
<td>0.7 (0.1)</td>
</tr>
</tbody>
</table>
BNT162b2 induced antibody responses during the primary vaccination series

At all ages anti-S1 IgG concentrations showed an increase after vaccination. However, at both timepoints higher age was associated with a lower antibody response, as can be seen in Fig. 2A (for ten-year age categories) and 2B (for age in years). The variation in the log transformed antibody response also decreased upon the second vaccination compared to the first vaccination (IQR\_T1 = 1.46, IQR \_T2 = 1.12). Although not analyzed further due to the low number of participants, similar trends can be seen for those vaccinated with AZD1222 (AstraZeneca) in figure S1. In Fig. 3 the Pearson correlation coefficients between the anti-S1 IgG concentrations and the frailty index can be seen. Higher levels of frailty are correlated with a lower anti-S1 antibody response at both timepoints. This means that even though the anti-S1 IgG concentration increases upon the second vaccination there was still a negative correlation between the frailty index and the IgG response for both men (r\_T1 = -0.24, p\_T1 < 0.01; r\_T2 = -0.15, p\_T2 < 0.01).

Univariate analysis of BNT162b2 induced antibody responses corrected for age and sex

Univariate analysis of antibody concentrations adjusted for age and sex was performed for each potential determinant separately. Waist circumference (β = -0.013), BMI (β = -0.03), the frailty index (β =
HDL cholesterol concentrations ($\beta = 0.29$), kidney function based on estimated glomerular filtration rate, eGFR, ($\beta = -0.55$), lung function based on FEV1 ($\beta = -0.17$), a history of balloon dilatation ($\beta = -0.73$) or cardiac catheterization ($\beta = -0.36$), diabetes ($\beta = -0.69$), and lower back pain ($\beta = -0.39$) were all (with the exception of HDL cholesterol concentrations) negatively associated with the anti-S1 IgG concentrations at T1 (table S2).

Looking at changes in concentrations of anti-S1 IgG, at T2, one month post second vaccination a history of myocardial infarction ($\beta = 0.72$), lower-back pain ($\beta = -0.23$), difficulties with household activities ($\beta = -0.29$), and a cognitive flexibility score in the lowest decile of the entire study population distribution, also further referred to as an impaired cognitive flexibility ($\beta = -0.47$), were associated with the anti-S1 IgG concentrations. Of these associations only a history of myocardial infarction showed a positive relationship with the antibody responses (table S2).

In contrast, when looking at log-fold changes in anti-S1 IgG concentrations between T1 and T2, these variables showed associations in the opposite direction for the log-fold change between the two timepoints compared to their associations with the anti-S1 IgG response at T1 or T2. Waist circumference ($\beta = 0.013$), HDL cholesterol ($\beta = -0.22$), blood glucose concentrations ($\beta = 0.046$), the frailty index ($\beta = 1.6$), eGFR ($\beta = 0.58$), diabetes ($\beta = 0.73$), and BMI ($\beta = 0.034$) all showed associations with the log-fold change in antibody response that are in the opposite direction compared to their associations with that at a month after the vaccinations.

### Multivariate regression of BNT162b2 induced antibody responses

Using multivariate modelling, sex, age, and being physically active all correlated with the anti-S1 IgG concentrations upon both vaccinations, and/or the log-fold change in IgG concentration between the two timepoints. At both T1 and T2, age correlated negatively with the anti-S1 IgG concentrations as shown in Fig. 4 (T1: blue, T2: green) and table S3 ($\beta_{T1} = -0.062 [-0.11, -0.018], \beta_{T2} = -0.031 [-0.06, -0.0023]$). Both female sex and being physically active correlated positively with the log fold change in anti-S1 IgG concentrations between T1 and T2 as can be seen in Fig. 4 (red) and table S3 ($\beta_{female} = 0.6 [0.05, 1.2]; \beta_{active} = 0.44 [0.0944, 0.79]$).

Additionally, after stepwise regression analysis using additional comorbidities and all individual components of the frailty index, several statistically significant associations with the antibody response were observed as shown in Fig. 5 and table S4. At T1, age ($\beta = -0.045$), a history of cardiac catheterization ($\beta = -1.9$) and suffering from any comorbidity ($\beta = -0.66$) were associated with a lower anti-S1 IgG concentration. On the other hand, having hypertension or a history of various procedures for cardiovascular diseases ($\beta = 1.7$) were associated with a higher anti-S1 IgG concentration as shown in Fig. 5 (blue). At T2, age ($\beta = -0.03$), having an impaired cognitive speed ($\beta = -0.59$), a gastrointestinal disease ($\beta = -0.65$), and lower-back pain ($\beta = -0.41$), were all associated with lower anti-S1 IgG concentrations, whereas only BMI ($\beta = 0.31$), and osteoporosis ($\beta = 0.52$) were associated with higher anti-
S1 IgG concentrations, as shown in Fig. 5 (green). As for the log fold change between these two timepoints we only observed a statistically significant positive association between the relative increase in anti-S1 IgG concentrations and having an impaired cognitive speed, as can be seen in Fig. 5 (red).

**Discussion**

In this study we analyzed antibody responses to anti-SARS-CoV-2 vaccination in older persons, aiming to identify determinants of heterogeneity in vaccine responsiveness. We show that frailty as determined by multiple comorbidities and other health related variables had an important role in the primary vaccination response to the BNT162b2 vaccine within an ageing population. Both after the first and second vaccination the antibody response increased for all adult participants though older persons still had a lower response after the second vaccination compared to relatively younger adults.

After adjustment for age and sex, factors that were associated with the antibody responses were physical activity, waist circumference, BMI, HDL and glucose concentrations, kidney and lung function, diabetes, a history of cardiovascular procedures, lower cognitive abilities, and more physical impairments. We observed that persons with a lower antibody response after their first vaccination also tended to have lower antibody responses after their second vaccination. These persons however had a higher relative increase in antibody concentrations upon their second vaccination, resulting in a smaller IQR of the antibody concentrations at T2 compared to T1.

Multivariate analysis showed several aspects of frailty to play a role in explaining the heterogeneity in antibody responses after the primary vaccination series against a novel pathogen. Age, BMI, a history of cardiovascular procedures, gastrointestinal disease, a reduced lung function, and impaired cognitive speed were all statistically significantly associated with the antibody concentrations.

The associations of these factors separately have been shown in other longitudinal cohort studies. Specifically, that older age, male sex, diabetes, hypertension, and heart disease are associated with a lower antibody response one month after vaccination with BNT162b. This effect was reduced one month after the second vaccination (Lustig et al., 2021; Boroumand et al., 2022).

The role of physical activity in relation to immunosenescence has been studied by several researchers. In particular, remaining physically active is thought to positively affect immune function and reduce age-related comorbidities (Duggal et al., 2019). This was consistent with our findings that showed that being physically active was positively associated with the log-fold change in anti-S1 IgG response during the primary vaccination series with BNT162b.

The findings that greater cognitive speed was positively associated with anti-S1 IgG has, to our knowledge, not been reported in other studies. Studies on cognitive impairment and COVID-19 have mostly focused on either cognitive impairment as rare symptom of long-COVID or as rare side-effect of vaccination against COVID-19, i.e. not as determinant of immune responses. Other studies that did focus
on pre-pandemic cognitive impairment in relation to vaccines, have done so in the context of vaccination willingness and not IgG response upon vaccination (Batty et al., 2021).

A strength of our study was that we could employ an extensive data set on the study participants that had been collected prior to the vaccination, and that we could relate all these data to the antibody responses at regular moments after vaccination in a large and aging cohort. Furthermore, the fact that this data had been collected for all DCS participants, allowed us to make use of a frailty index that had been validated in this greater cohort.

Using an already existing cohort allowed us to create an extensive dataset with information regarding comorbidities, lifestyle, sociodemographic factors, and other measures of frailty and chronic inflammation. To determine the presence of certain diseases we used all available longitudinal data. This made it possible to identify determinants of anti-S1 IgG responses, which would have been less feasible with a newly formed cohort. Furthermore, it allowed us to evaluate markers such as the frailty index and study if these markers are indicative of the vaccine induced anti-S1 IgG response.

However, there are also limitations. Not all participants responded in time to be included at T0 or T1 and as such we had fewer samples for T1, which is where we expected to observe a larger heterogeneity in antibody responses. Additionally, we aimed to use the most recent data before vaccination for each participant separately, meaning some participants had data for as recent as early 2021 whereas for other participants data were only available for not more recent than 2013. Lastly, we also studied a relatively healthy population that was still able to participate in a study such as this one, meaning we did not capture the frailest individuals.

**Conclusions**

Various factors such as age, sex, (components of) frailty, and comorbidities were associated with the anti-S1 IgG antibody response after vaccination with BNT162b2 in our ageing population. This implied a reduced antibody concentration in older persons and those with higher frailty scores, and more specifically those with chronic comorbidities, lower cognitive speed, and greater physical impairments. Men as well as those who are physically inactive also showed a reduced increase in anti-S1 IgG response during their primary vaccination series. An increased antibody response can be seen in those who have experienced cardiac events in the past.

Among the older persons, those who were frailer and less healthy had a lower antibody response after their first vaccination yet experienced a stronger increase in their antibody response after their second vaccination compared to less frail and healthier persons. However, they still had a lower antibody response after their second vaccination compared to these less frail and healthier persons. This highlights the importance of studying the heterogeneous vaccine induced antibody responses in older individuals within the general population. This allows for the identification of potential risk groups with a weaker response to the vaccinations, and potentially adjusting their vaccination regimen. Furthermore, it enables the identification of factors such as being physically active which those with lower antibody
responses can still affect in order to positively impact their antibody response. Further studies are needed to assess the immunological mechanisms behind these potential risk factors affecting the vaccine responsiveness in older persons.

**Methods**

**Cohort selection**

We used the Doetinchem Cohort Study (Verschuren et al., 2008; Picavet et al., 2017), that started in 1987 with a population-based sample of men and women aged 20–59 years old who have been followed up every 5 years. The study collects data on lifestyle factors, biological measurements, physical and cognitive functioning, social aspects, comorbidities, and other background characteristics. From this cohort we invited all 3647 remaining participants to take part in the COVID-19 vaccination study. Participants were included in the study if they planned to receive COVID-19 vaccination or had completed the primary vaccination series within the last 28 days, as a month post second vaccination was the primary endpoint of the study.

The numbers of participants in the study are depicted in Fig. 1. In total 1457 DCS subjects were included in the vaccination study. As the study commenced after the start of the national vaccination campaign and vaccines were rolled-out per age group from old to young according to the national guidelines, some persons missed the pre-vaccination (T0) or even the T1 sampling. Thus, the number of individuals included in the study increased at subsequent timepoints. The median interval between the two vaccination doses was 35 days (interquartile range, IQR: 35–35) and did not differ between ages. At pre-vaccination (T0), 916 of the participants had a baseline antibody measurement taken, had complete cohort data, and were negative for COVID-19 infection. At one month after the first vaccination (T1) this applied to 1118 individuals and at a month after the second vaccination (T2) to 1257 individuals. Prior to receiving a vaccination 8.3% tested positive for COVID-19 and one month after completing the primary vaccination series this was 8.2%.

For further analysis, persons who had not yet been infected prior to vaccination or during our study (infection naive) were selected. 1020 individuals were sampled at both T1 and T2. In these individuals the fold increase in antibody concentration between the two vaccinations was determined. Since the majority (78% at T1 and T2) of the participants was vaccinated with BNT162b2, the main analyses were done on this group. Persons of 60–65 years of age have mainly been vaccinated with AZD1222 (20% at T1 and T2). Therefore, the antibody response across the different timepoints has been evaluated in this subset of individuals.

**Sample collection**

Blood samples and questionnaires were taken prior to COVID-19 vaccination (T0 + 7), 28 (-8 + 15) days after the first vaccination (T1), and 28 (-15 + 24 days) after the second vaccination (T2). The median interval between the two vaccination doses was 35 days (interquartile range, IQR: 35–35). Questionnaires
covered demographic factors, COVID-19 vaccination information (type and date of vaccination), and SARS-CoV-2 testing information. Finger-prick blood samples were self-collected in microtubes and returned by mail. Serum was isolated from each sample by centrifugation and stored at -20°C until sample processing.

**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 (den Hartog et al., 2020). 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) (WHO, 2020). The threshold for seropositivity was set at 10.1 BAU/ml for Spike S1 (Vos et al., 2021) and 14.3 BAU/ml for Nucleoprotein (van den Hoogen et al., 2022).

**Measurement of determinants**

Participants had filled in questionnaires relating to quality of life and general health during each 5-year follow up phase of the DCS (Round 1–7) prior to the vaccination study. Further data was collected covering various topics such as demographic and lifestyle factors, and comorbidities, both self-reported and confirmed by physicians. In addition, a physical examination was performed by trained field workers that 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. For CRP and glycA which had been measured in stored blood samples previously, the most recent measurements were used.

**Frailty index calculation**

Using the collected data a frailty index was calculated. This frailty index is a measure consisting of 36 ‘deficits’ defined based on chronic conditions, cognitive, physical, and psychological functioning as described before (Samson et al., 2019). The 36 deficits were selected based on previous inclusion in existing frailty indexes, a prevalence of greater than one percent in the entire DCS cohort, and if there was a known association with cognitive, physical, or psychological functioning. 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). This measure of frailty has been linked to various inflammatory markers and clinically relevant health related outcomes before within the DCS (Samson et al., 2022).

**Statistical analysis**

IgG concentrations were log-transformed prior to all analyses resulting in approximately normally distributed values. In all analyses the IgG response at T1, T2, and the relative increase between these two timepoints were analyzed separately. All statistical analyses were performed using R version 4.2.0. Statistical significance was defined using a p-value not greater than 0.05.
To test whether frailty and age influenced both the absolute and relative vaccine induced IgG response a Pearson correlation analysis was performed. This was done to determine which specific variables, used to construct the frailty index, to include for further analysis. Linear regression models correcting for age and sex were constructed to highlight how the different frailty-related parameters as well as other comorbidities were associated with the IgG response independent of age and sex.

A multivariable linear regression model was constructed including several preselected variables commonly associated with clinically relevant health outcomes. These variables included age, sex, socioeconomic status, physical activity, waist circumference, smoking behavior, alcohol consumption, systolic blood pressure, (HDL) cholesterol, creatinine, glucose, glycA, and CRP concentrations, as well as kidney function, lung function, frailty index, and the number of comorbidities.

Following this, a multivariate linear regression model was constructed using all frailty-related parameters and comorbidities. First, multiple stepwise regression was performed on a subset of the samples without missing data to select which variables would be included in the regression model. This was done to identify which combination of variables led to the most parsimonious model that best explained the vaccine induced IgG. The variables selected out of these frailty-related parameters and other comorbidities were used to create a multivariate linear model using all samples available in order to estimate the effects of each of these selected variables.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained through The Medical Research Ethics Committee Utrecht for finger prick blood sampling in the majority of the DCS participants (NL74843.041.21, EudraCT: 2021-001976-40 and amendment NL74843.041.20 EudraCT: 2020-003620-16) and for venapunction in a small part of the participants (NL74843.041.21, EudraCT: 2021-001976-40). All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

We welcome collaboration. For use of the available data, please contact Professor W. M. M. Verschuren or H. S. J. Picavet, PhD (doetinchemstudie@rivm.nl).

Competing interests

The authors declare no competing interests.

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**Authors’ contributions**

The study was conceptualized and designed by S. Picavet, W. M. M. Verschuren, A. Buisman, and P. Engelfriet. Analysis was performed by Y. Kuijpers with input from H. S. J. Picavet, W. M. M. Verschuren, A. Buisman, and P. Engelfriet. Y. Kuijpers wrote the manuscript with input from all authors. All authors read and approved the final manuscript.

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**References**


**Figures**
Doetinchem Cohort study participants Invited for SARS-CoV-2 vaccination studies
Invited, N = 3647

Willing to participate
N = 1678
- No written informed consent
- Drop out

Participated
N = 1516

Inclusion: Primary vaccination series response
- Missing DCS data

Included
N = 1457

- Missing samples per timepoint
- Exclusion: Infected N = 83

T0:
N = 1036
- Within time window
  N = 900
  Exclusion: Infected N = 83

T1:
N = 1304
- Within time window
  N = 1181
  Exclusion: Infected N = 113

T2:
N = 1430
- Within time window
  N = 1370

T0
916 uninfected individuals

T1: N = 1118
Pfizer: 853
AstraZeneca: 248
Moderna: 16
Other/unknown: 3

T1 & T2: N = 1020
Pfizer: 791
AstraZeneca: 206
Moderna: 16
Janssen: 31
Other/unknown: 8

Figure 1
flowchart of the study cohort. Samples were excluded in case of a missing signed informed consent, not sending samples (drop outs), or a missing sample at a month post 2nd vaccination (T2). For further data analysis, samples taken outside the time window around the predefined timepoints post vaccination were excluded, participants already infected with SARS-CoV-2 before vaccination and participants missing data on co-morbidities and other health parameters since round 6 of the Doetinchem cohort study.
Figure 2

Distribution of the SARS-CoV-2 -S1 IgG antibody concentrations in binding antibody units per milliliter (BAU/ml) at T0 (before vaccination), T1 (one month after first vaccination), and T2 (one month after second vaccination) in persons above 50 years of age per ten year age group (A) and matched antibody concentrations per individual at T1 (blue) and T2 (red) per age in years (B).

Figure 3

Correlations of anti-S1 IgG concentrations in binding antibody units per milliliter (BAU/ml) with a frailty index based on 36 deficits using univariate linear regression at a month post first vaccination (T1, blue), and a month post second vaccination (T2, red) for men (A) and women (B).
Figure 4

Multivariate associations and their respective 95% CI's in case of statistical significance of sociodemographic and cardiometabolic variables with the anti-S1 IgG concentrations at T1 (blue), T2 (green), and the log fold increase between these two timepoints (red) after mRNA BNT162b2 vaccination. Estimates have been divided by 2*SD to rescale them. Error bars are shown for variables when at least one of the three measured associations was statistically significant for that variable.
Figure 5

Multivariate associations and their respective 95% CI's in case of statistical significance of comorbidities and frailty index parameters with the anti-S1 IgG concentration at T1 (blue), T2 (green), and the log fold change between these two timepoints (red). Estimates have been divided by 2*SD to rescale them. Error bars are shown for variables when at least one of the three measured associations was statistically significant for that variable.

Supplementary Files

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