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Short-term safety of COVID-19 mRNA vaccines with respect to all-cause mortality in the older population in Norway

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ABSTRACT

Background: There have been concerns about COVID-19 vaccination safety among frail older individuals. We investigated the relationship between COVID-19 mRNA vaccination and mortality among individuals aged ≥ 70 years and whether mortality varies across four groups of health services used.

Methods: In this nationwide cohort study, we included 688,152 individuals aged ≥ 70 years at the start of the Norwegian vaccination campaign (December 27, 2020). We collected individual-level data from the Norwegian Emergency Preparedness Register for COVID-19. Vaccinated and unvaccinated individuals were matched (1:1 ratio) on the date of vaccination based on sociodemographic and clinical characteristics. The main outcome was all-cause mortality during 21 days after first dose of COVID-19 mRNA vaccination. Kaplan-Meier survival functions were estimated for the vaccinated and unvaccinated groups. We used Cox proportional-hazards regression to estimate hazard ratios (HRs) of death between vaccinated and unvaccinated individuals, with associated 95% confidence intervals (CIs), overall and by use of health services (none, home-based, short- and long-term nursing homes) and age group.

Results: Between December 27, 2020, and March 31, 2021, 420,771 older individuals (61.1%) were vaccinated against COVID-19. The Kaplan-Meier estimates based on the matched study sample showed a small absolute risk difference in all-cause mortality between vaccinated and unvaccinated individuals, with a lower mortality in the vaccinated group (overall HR 0.28 [95% CI: 0.24–0.31]). Similar results were obtained in analyses stratified by use of health services and age group.

Conclusion: We found no evidence of increased short-term mortality among vaccinated individuals in the older population after matching on sociodemographic and clinical characteristics affecting vaccination and mortality.

1. Introduction

The Norwegian COVID-19 immunization program was established in late 2020 to plan implementation and distribution of COVID-19 vaccines. In the initial phases, there was not enough vaccine supply for all citizens, and people living in nursing homes, older people, frontline healthcare personnel and patients with certain underlying medical diseases were prioritized. Vaccination against COVID-19 started on December 27, 2020. Two weeks later, on January 14, 2021, the Norwegian Medicines Agency reported 23 deaths following vaccination of frail older people.[1] At that point, 43,740 individuals in Norway had been vaccinated with a COVID-19 mRNA vaccine. Nursing home residents in Norway are in general very frail, most residents are over 80 years of age, and many have severe underlying diseases and a relatively short life expectancy. On average, 300 nursing home residents in Norway die every week [2].

In Norway, both healthcare professionals and the public can report suspected adverse reactions following immunization to the Norwegian Medicine Agency. Monitoring of post-marketing

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vaccine safety is important to reveal rare adverse effects or adverse effects with delayed onset.[3] The clinical trials of the COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) mainly showed mild or moderate side effects passing within a few days after vaccination.[4,5] Older and frail people were underrepresented in the clinical trials.[6] Vaccine safety with respect to all-cause mortality has been studied in the clinical trials, but the reporting period has not been specified.[4].

When considering vaccine safety among frail older individuals, often living in nursing homes, it is important to account for the already increased mortality in this population group. We aimed to assess short-term safety of COVID-19 mRNA vaccination with respect to all-cause mortality in the older population in Norway.

2. Methods

2.1. Study sample

Our study population included all older residents in Norway. The original data set included 688,152 individuals aged 70 years and older when the Norwegian vaccination campaign started on December 27, 2020.

The current study follows the lines of recent studies of the effectiveness and safety of vaccines in Israel by using a rolling-cohort matching design.[7,8] In order to assess the short-term safety of COVID-19 mRNA vaccination with respect to all-cause mortality, we randomly matched newly vaccinated individuals (vaccinees) to currently unvaccinated individuals (controls) in a 1:1 ratio from December 27, 2020, to March 31, 2021. The individuals in each matched pair were matched on the day of first-dose mRNA vaccination of the vaccinee based on several baseline characteristics to obtain covariate balance between the vaccinated and unvaccinated groups. We used exact matching on the following variables: sex (male or female), age group (in five-year intervals), marital status (married/cohabiting or other), health region of residence (Northern Norway, Central Norway, Western Norway, or South-Eastern Norway), size of municipality of residence (< 50,000 residents or $\geq$ 50,000 residents), type of health services used (none, home-based, short-term stay in nursing home, or long-term stay in nursing home), influenza vaccination from September 1, 2020, to December 26, 2020 (no or yes), categorized modified Charlson comorbidity index (0, 1–2, 3–4, or 5+) (see codes in the appendix), and history of SARS-CoV-2 infection on the index day (i.e., day of first-dose mRNA vaccination of the vaccinee) (no or yes). The choice of matching variables was based on a directed acyclic graph (DAG) constructed for this study (appendix Fig. 1).

Fig. 1 displays a flow chart of the matching process. We excluded 1,609 individuals (0.2%) from the original data set due to missing data on health region of residence (n = 79) and size of municipality of residence (n = 1,601). Thus, the matching process was restricted to the 686,543 individuals (99.8%) with non-missing data on all matching variables. All vaccinated individuals were eligible to be matched as controls prior to first-dose vaccination, thereby allowing the same individual to be included twice in the matched study sample – first as a control and then as a vaccinee – in two different matched pairs. Of the 419,513 individuals vaccinated with either of the mRNA vaccines from Pfizer-BioNTech and Moderna before April 1, 2021, 414,874 individuals (98.9%) were matched: 214,344 individuals (51.7%) as vaccinees only, 105,957 individuals (25.5%) as controls only, and 94,573 individuals (22.8%) as both vaccinees and controls. Correspondingly, 108,387 individuals (40.6%) of the 267,030 individuals *not* vaccinated with an mRNA vaccine before April 1, 2021, were matched as controls. The final study sample included 308,917 matched pairs of vaccinees and controls, composed of 523,261 unique individuals (Fig. 1).

2.2. Data sources

We used data from Beredt C19, which is the national emergency preparedness register established by the Norwegian Institute of Public Health in close collaboration with the Norwegian Directorate of Health, the Norwegian Intensive Care and Pandemic Registry, and other organizations that are responsible for data sources included in the register to monitor COVID-19 infections, vaccinations, and the use of community health services in Norway during the COVID-19 pandemic.[9] Beredt C19 consists of individual-level data from various administrative databases and health registers to which reporting is mandatory, covering the entire Norwegian population (appendix Fig. 2). Data from the different registers are linked by using the unique personal identification number given to all Norwegian residents at birth or upon immigration. Beredt C19 data sources used in this study are described below. For more details about Beredt C19, see https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/.

The National Population Register includes all residents in Norway. We retrieved information on sex, marital status, county and municipality of residence, and dates of birth, emigration, and death.[10].

The Norwegian Immunisation Registry (SYSVAK) is the Norwegian national immunization register that records individuals' vaccination status.[11] We obtained information on dates of vaccination and vaccine product. The two mRNA vaccines Pfizer-BioNTech and Moderna were distributed in Norway from December 27, 2020, and January 14, 2021, respectively.

We used data from the Norwegian Patient Registry (NPR) to identify people with underlying medical diseases. The NPR covers all inpatient and outpatient care in secondary health services in Norway. Diagnoses are classified according to the International Classification of Diseases, Tenth Revision (ICD-10). We used a modified Charlson comorbidity index based on ICD-10 codes registered in the specialist health services during 2017–2020 (appendix Table 1) [12].

Use of municipal health services was obtained from the Norwegian Information System for the Nursing and Care Sector (IPLOS). We retrieved information on type of health services received at the end of 2020: no health services, home-based health services (home nursing and municipal housing for healthcare purposes), short-term stay at nursing home, and long-term stay at nursing home.

The Norwegian Surveillance System for Communicable Diseases (MSIS) provided dates of all registered laboratory-confirmed cases of SARS-CoV-2.

The Norwegian Cause of Death Registry covers deceased individuals registered as residents in Norway at the time of death. We obtained information on county of residence for all deceased individuals, as this information is not included in the National Population Register after death.

Statistics Norway provided information on the size of municipality of residence for each individual.

2.3. Study exposure and outcome

The study exposure was first dose of COVID-19 mRNA vaccine administered between December 27, 2020, and March 31, 2021. The outcome of interest was all-cause mortality during the first three weeks (21 days) after vaccination.

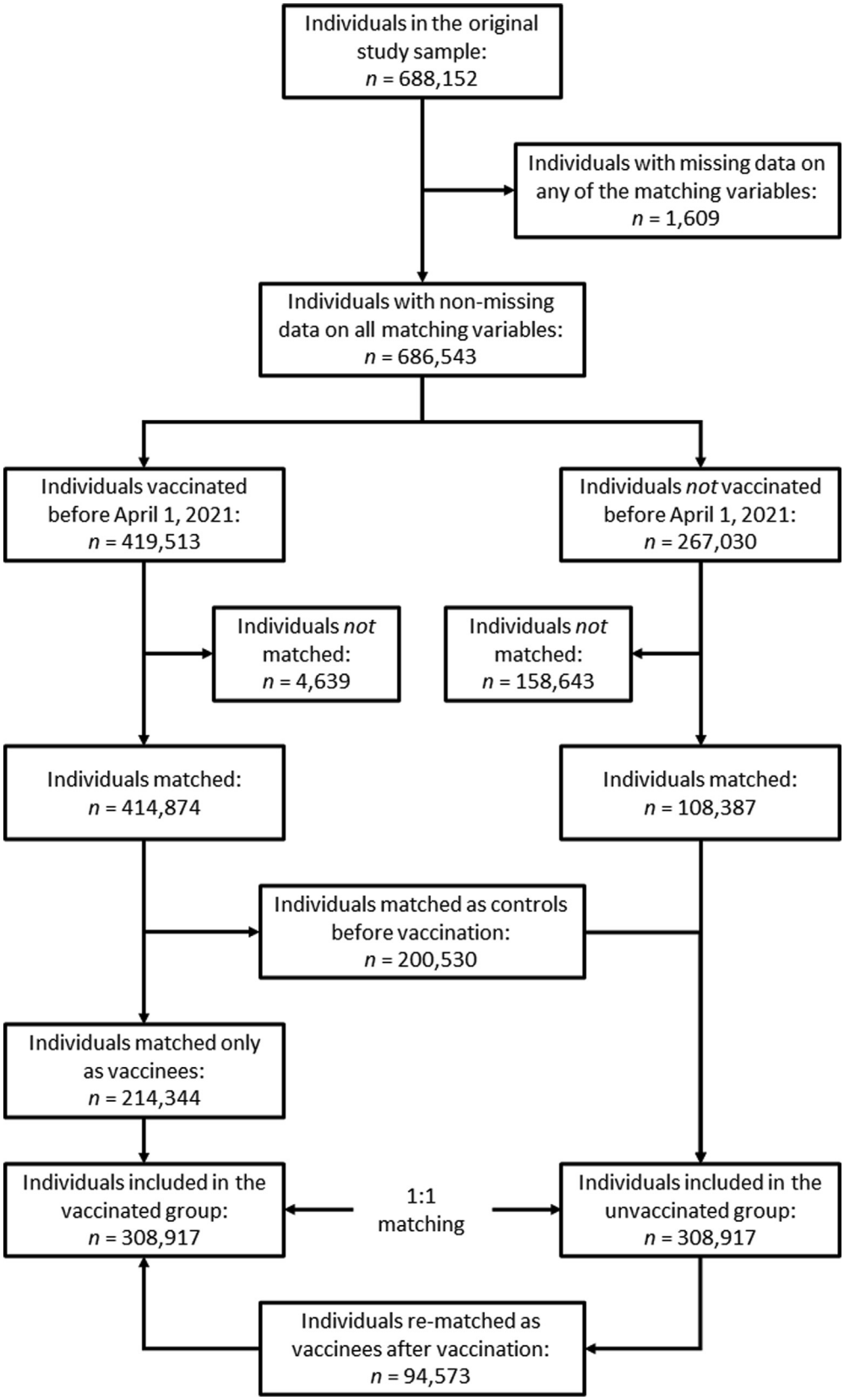

Fig. 1. Flow chart of the matching process.

2.4. Statistical analysis

The individuals in each matched pair were followed for up to three weeks from the day of the first administered mRNA vaccine dose of the vaccinee until death, emigration, first-dose vaccination of the control (censoring of both the vaccinee and the control), second-dose vaccination of the vaccinee (censoring of the vaccinee only), or end of study on April 1, 2021, whichever occurred first. The time scale was the number of days since first-dose mRNA vaccination of the vaccinee.

Kaplan-Meier survival functions were estimated for the vaccinated and unvaccinated groups by health services received at the end of 2020. In supplementary analyses, we also estimated Kaplan-Meier survival functions for the two vaccination groups within three different age groups: 70–79 years, 80–89 years, and 90+ years.

To account for the dependence in the data due to some individuals appearing as both vaccinees and controls in the matched study sample, we used the percentile bootstrap method with 750 iterations to calculate the associated 95% confidence intervals (CIs) of the Kaplan-Meier estimates. For each iteration, a bootstrap sample was created by random sampling with replacement from the original data set, restricted to individuals with observed values of all matching variables (n = 686,543). The matching process was performed separately for each bootstrap sample before calculating the Kaplan-Meier estimates. The lower and upper 95% confidence limits were defined as the 2.5 and 97.5 percentiles, respectively, of the Kaplan-Meier estimates based on the bootstrap samples.

We used Cox proportional-hazards regression to estimate crude hazard ratios (HRs) of death between vaccinated and unvaccinated individuals, overall and by use of health services and age group. Associated 95% CI were calculated by using robust variance estimates that allow for intragroup correlation within clusters of the same individual. To account for the potential dependence between the two individuals in a matched pair, we also conducted sensitivity analyses by fitting stratified Cox models that assume unique baseline hazard functions for all matched pairs.

All analyses were conducted using Stata (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC).

2.5. Ethics

The Norwegian Institute of Public Health is entitled by law to set up and use Beredt C19 to help national and international authorities handle the pandemic. The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway (REK Sør-Øst A, ref 122745) and has conformed to the principles embodied in the Declaration of Helsinki. The emergency preparedness register was established according to the Health Preparedness Act §2-4.

2.6. Public and patient involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

Table 1 displays baseline characteristics of the 688,152 individuals aged 70 years and older included in the original data set before matching. By April 1, 2021, there were 9,021 deaths, of which 46.4% were males. The estimated mortality rate for this period was 50.2 deaths per 1,000 person-years (95% CI: 49.2–51.3). From December 27, 2020, to March 31, 2021, 420,771 individuals (61.1%) were vaccinated with at least one dose of a COVID-19 vaccine. Most of all first-dose vaccinations against the coronavirus were with Pfizer-BioNTech (92.7%), followed by Moderna (7.1%), and AstraZeneca (0.1%). Administration of first-dose vaccination with Pfizer-BioNTech is shown in appendix Fig. 3. A total of 218,915 individuals (31.8%) also received a second dose within March 31, 2021.

The first-dose vaccination coverage by March 31, 2021, varied greatly by use of health services: 57.2% of individuals with no health services, 74.8% of individuals with home-based health services, 73.0% of short-term nursing-home residents, and 90.5% of long-term nursing home residents.

Baseline characteristics of the 308,917 vaccinees and 308,917 controls included in the matched study sample are displayed in Table 2. The total follow-up time for vaccinated and unvaccinated individuals was 3,567,897 and 3,575,519.5 days, respectively.

In Fig. 2, the Kaplan-Meier survival functions for the vaccinated and unvaccinated groups are plotted against time since first-dose mRNA vaccination of the vaccinees stratified by use of health services. The overall mortality was quite low in both the vaccinated and unvaccinated group during the first three weeks after vaccination. We observed a slightly lower absolute risk of all-cause mortality in the vaccinated group than in the unvaccinated group. The absolute risk difference increased with use of more extensive health services, with largest difference of survival curves observed among long-term nursing home residents (Fig. 2). Correspondingly, we observed an increase in the absolute risk difference with increasing age (Fig. 3).

In accordance with the Kaplan-Meier survival functions for the vaccinated and unvaccinated groups, the association between vaccination and all-cause mortality based on Cox proportional-hazards regression analysis showed an apparent protective effect of mRNA vaccines during the first three-week period following first-dose vaccination, with an overall HR of 0.28 (95% CI: 0.24–0.31) (Table 3). The stratified analyses by use of health services and age group showed similar results to the main analysis (Table 3).

Fitting stratified Cox models with unique baseline hazard functions for all matched pairs in sensitivity analyses gave similar results as in the main analysis (data not shown).

4. Discussion

In this nationwide register-based matched cohort study, we studied the short-term mortality following mRNA vaccination among older people in Norway. We did not find any increase in risk of death among those vaccinated compared to those unvaccinated.

The mRNA vaccines represent a new technology not used in a population-wide manner before the COVID-19 pandemic. Data on vaccine safety in the frail and older population are very limited. [13,14] Real-world studies give the possibility to monitor side effects after the vaccination has been introduced in the population (active post-marketing surveillance) and fill the knowledge gaps randomized studies did not assess.[15,16] Clinical trials and subsequent observational studies have shown that older people are less likely to experience common adverse reactions during the first days after vaccination compared to younger individuals.[17] The older will often have several other underlying conditions that make it difficult to differentiate between the common side effects of the vaccine and worsening of such conditions. During the first three months of the vaccination program in Norway, more than 90% of long-term residents in nursing homes were vaccinated, with some sporadic reports on fatal reactions after vaccination.[18] Transparency on potential adverse effects during the vaccination campaign in Norway has been a priority. Healthcare professionals

Table 1
Baseline characteristics of the original study sample by time of COVID-19 vaccination.

Characteristic	Vaccinated in December 2020[1] or January 2021 (*n* = 69,184)		Vaccinated in February 2021 (*n* = 138,945)		Vaccinated in March 2021 (*n* = 212,642)		Not vaccinated before April 1, 2021 (*n* = 267,381)		Total (*n* = 688,152)	
Sex										
Male	23,725	(34.3%)	59,493	(42.8%)	100,334	(47.2%)	129,297	(48.4%)	312,849	(45.5%)
Female	45,459	(65.7%)	79,452	(57.2%)	112,308	(52.8%)	138,084	(51.6%)	375,303	(54.5%)
Age group										
70–74 years	3,900	(5.6%)	4,084	(2.9%)	49,892	(23.5%)	203,781	(76.2%)	261,657	(38.0%)
75–79 years	5,630	(8.1%)	26,985	(19.4%)	119,990	(56.4%)	36,990	(13.8%)	189,595	(27.6%)
80–84 years	10,193	(14.7%)	58,628	(42.2%)	37,457	(17.6%)	12,893	(4.8%)	119,171	(17.3%)
85–89 years	24,966	(36.1%)	35,830	(25.8%)	3,481	(1.6%)	7,275	(2.7%)	71,552	(10.4%)
90–94 years	17,949	(25.9%)	11,320	(8.1%)	1,443	(0.7%)	4,402	(1.6%)	35,114	(5.1%)
95+ years	6,546	(9.5%)	2,098	(1.5%)	379	(0.2%)	2,040	(0.8%)	11,063	(1.6%)
Age (years)										
Mean (SD[2])	86.8	(6.4)	83.0	(4.9)	77.0	(3.5)	73.8	(4.8)	78.0	(6.5)
Median (IQR[3])	88.0	(7.0)	83.0	(6.0)	76.0	(4.0)	72.0	(3.0)	76.0	(9.0)
Marital status										
Married/cohabiting	18,291	(26.4%)	66,843	(48.1%)	126,657	(59.6%)	153,339	(57.3%)	365,130	(53.1%)
Other	50,893	(73.6%)	72,102	(51.9%)	85,985	(40.4%)	114,042	(42.7%)	323,022	(46.9%)
Health region										
Northern Norway	6,662	(9.6%)	13,729	(9.9%)	17,816	(8.4%)	31,059	(11.6%)	69,266	(10.1%)
Central Norway	8,691	(12.6%)	20,142	(14.5%)	30,020	(14.1%)	40,567	(15.2%)	99,420	(14.4%)
Western Norway	12,460	(18.0%)	26,890	(19.4%)	41,502	(19.5%)	52,154	(19.5%)	133,006	(19.3%)
South-Eastern Norway	41,354	(59.8%)	78,179	(56.3%)	123,295	(58.0%)	143,553	(53.7%)	386,381	(56.1%)
Missing	17	(0.0%)	5	(0.0%)	9	(0.0%)	48	(0.0%)	79	(0.0%)
Size of municipality[4]										
Rural	39,705	(57.4%)	81,692	(58.8%)	117,153	(55.1%)	172,207	(64.4%)	410,757	(59.7%)
Urban	29,313	(42.4%)	57,186	(41.2%)	95,428	(44.9%)	93,867	(35.1%)	275,794	(40.1%)
Missing	166	(0.2%)	67	(0.0%)	61	(0.0%)	1,307	(0.5%)	1,601	(0.2%)
Use of health services										
No health services	18,210	(26.3%)	108,117	(77.8%)	193,113	(90.8%)	239,110	(89.4%)	558,550	(81.2%)
Home-based services	23,330	(33.7%)	29,313	(21.1%)	18,687	(8.8%)	24,054	(9.0%)	95,384	(13.9%)
Nursing home, short-term stay	2,292	(3.3%)	1,088	(0.8%)	696	(0.3%)	1,511	(0.6%)	5,587	(0.8%)
Nursing home, long-term stay	25,352	(36.6%)	427	(0.3%)	146	(0.1%)	2,706	(1.0%)	28,631	(4.2%)
History of influenza vaccination[5]										
No	28,822	(41.7%)	44,406	(32.0%)	71,720	(33.7%)	131,081	(49.0%)	276,029	(40.1%)
Yes	40,362	(58.3%)	94,539	(68.0%)	140,922	(66.3%)	136,300	(51.0%)	412,123	(59.9%)
Charlson comorbidity index[6]										
0	34,751	(50.2%)	84,057	(60.5%)	139,203	(65.5%)	189,160	(70.7%)	447,171	(65.0%)
1–2	24,069	(34.8%)	39,663	(28.5%)	54,756	(25.8%)	59,322	(22.2%)	177,810	(25.8%)
3–4	7,441	(10.8%)	10,644	(7.7%)	12,789	(6.0%)	12,757	(4.8%)	43,631	(6.3%)
5+	2,923	(4.2%)	4,581	(3.3%)	5,894	(2.8%)	6,142	(2.3%)	19,540	(2.8%)
History of SARS-CoV-2 infection[7]										
No	68,822	(99.5%)	138,465	(99.7%)	211,872	(99.6%)	266,290	(99.6%)	685,449	(99.6%)
Yes	362	(0.5%)	480	(0.3%)	770	(0.4%)	1,091	(0.4%)	2,703	(0.4%)
Type of vaccine										
Pfizer-BioNTech	67,450	(97.5%)	129,798	(93.4%)	192,808	(90.7%)	0	(0.0%)	390,056	(56.7%)
Moderna	1,631	(2.4%)	8,987	(6.5%)	19,138	(9.0%)	0	(0.0%)	29,756	(4.3%)
AstraZeneca	0	(0.0%)	35	(0.0%)	458	(0.2%)	0	(0.0%)	493	(0.1%)
Unknown	103	(0.1%)	125	(0.1%)	238	(0.1%)	0	(0.0%)	466	(0.1%)
Missing	0	(0.0%)	0	(0.0%)	0	(0.0%)	267,381	(100.0%)	267,381	(38.9%)

[1] From start of the vaccination campaign on December 27, 2020.
[2] Standard deviation.
[3] Interquartile range.
[4] Based on a cut-off value of 50,000 residents in the municipality.
[5] Influenza vaccination from September 1, 2020, to December 26, 2020.
[6] Based on ICD-10 codes registered in the specialist health services during 2017–2020.
[7] History of SARS-CoV-2 infection before start of vaccination campaign on December 27, 2020.

could also tend to submit reports concerning younger people more often.

The new COVID-19 mRNA vaccines have shown high efficacy in clinical trials and observational studies from several countries. Bardenheier et al. found a reduction in mortality in a US study when they compared seven-day mortality in early vaccinated vs. late vaccinated residents in nursing homes.[19] A study from the UK showed a reduction in symptomatic COVID-19 and severe disease in older participants,[20] similar to the findings of a study from Israel.[7] A study from Spain found a reduction in mortality and hospital admissions in nursing home residents after the first COVID-19 vaccination.[14] The Centers for Disease Control and Prevention (CDC) reported no increased all-cause mortality among long-term nursing home residents one month after the COVID-19 mass vaccination started.[21] The findings of these studies are in accordance with our results.

Table 2
Baseline characteristics of the matched study sample[1] by COVID-19 vaccination status.

Characteristic	Vaccinated[2] (*n* = 308,917)		Unvaccinated[2] (*n* = 308,917)		Total[2] (*n* = 617,834)	
Sex						
Male	134,953	(43.7%)	134,953	(43.7%)	269,906	(43.7%)
Female	173,964	(56.3%)	173,964	(56.3%)	347,928	(56.3%)
Age group						
70–74 years	56,603	(18.3%)	56,603	(18.3%)	113,206	(18.3%)
75–79 years	112,693	(36.5%)	112,693	(36.5%)	225,386	(36.5%)
80–84 years	71,899	(23.3%)	71,899	(23.3%)	143,798	(23.3%)
85–89 years	41,393	(13.4%)	41,393	(13.4%)	82,786	(13.4%)
90–94 years	20,262	(6.6%)	20,262	(6.6%)	40,524	(6.6%)
95+ years	6,067	(2.0%)	6,067	(2.0%)	12,134	(2.0%)
Age (years)						
Mean (SD[3])	80.1	(6.0)	79.6	(6.3)	79.9	(6.1)
Median (IQR[4])	79.0	(8.0)	78.0	(8.0)	79.0	(9.0)
Marital status						
Married/cohabiting	155,239	(50.3%)	155,239	(50.3%)	310,478	(50.3%)
Other	153,678	(49.7%)	153,678	(49.7%)	307,356	(49.7%)
Health region						
Northern Norway	28,987	(9.4%)	28,987	(9.4%)	57,974	(9.4%)
Central Norway	41,847	(13.5%)	41,847	(13.5%)	83,694	(13.5%)
Western Norway	59,329	(19.2%)	59,329	(19.2%)	118,658	(19.2%)
South-Eastern Norway	178,754	(57.9%)	178,754	(57.9%)	357,508	(57.9%)
Size of municipality[5]						
Rural	173,865	(56.3%)	173,865	(56.3%)	347,730	(56.3%)
Urban	135,052	(43.7%)	135,052	(43.7%)	270,104	(43.7%)
Use of health services						
No health services	239,259	(77.5%)	239,259	(77.5%)	478,518	(77.5%)
Home-based services	51,793	(16.8%)	51,793	(16.8%)	103,586	(16.8%)
Nursing home, short-term stay	2,560	(0.8%)	2,560	(0.8%)	5,120	(0.8%)
Nursing home, long-term stay	15,305	(5.0%)	15,305	(5.0%)	30,610	(5.0%)
History of influenza vaccination[6]						
No	118,085	(38.2%)	118,085	(38.2%)	236,170	(38.2%)
Yes	190,832	(61.8%)	190,832	(61.8%)	381,664	(61.8%)
Charlson comorbidity index[7]						
0	192,954	(62.5%)	192,954	(62.5%)	385,908	(62.5%)
1–2	85,081	(27.5%)	85,081	(27.5%)	170,162	(27.5%)
3–4	21,550	(7.0%)	21,550	(7.0%)	43,100	(7.0%)
5+	9,332	(3.0%)	9,332	(3.0%)	18,664	(3.0%)
History of SARS-CoV-2 infection[8]						
No	307,769	(99.6%)	307,769	(99.6%)	615,538	(99.6%)
Yes	1,148	(0.4%)	1,148	(0.4%)	2,296	(0.4%)

[1] Pairs of vaccinated and unvaccinated individuals aged 70 years and older matched on sex, five-year age group, marital status, health region, size of municipality, use of health services, history of influenza vaccination, Charlson comorbidity index, and history of SARS-CoV-2 infection.
[2] Including 94,573 individuals who contributed to the matched study sample as both unvaccinated and vaccinated in two different matched pairs.
[3] Standard deviation.
[4] Interquartile range.
[5] Based on a cut-off value of 50,000 residents in the municipality.
[6] Influenza vaccination from September 1, 2020, to December 26, 2020.
[7] Based on ICD-10 codes registered in the specialist health services, including hospitals, during 2017–2020.
[8] History of SARS-CoV-2 infection before or on the day of vaccination of the vaccinee in a matched pair.

4.1. Strengths and weaknesses

The main strength of the current study was the use of individual-level data from independent, mandatory registers with nationwide coverage and high data quality. To avoid reporting bias, we did not use adverse event reports to identify deaths following vaccination. Instead, we used the immunization register and the population register, which records all vaccinations and deaths in Norway independently of each other.

We had the possibility to match for potential confounders by retrieving data on sociodemographic characteristics and risk conditions. In Norway, the vaccines were distributed among all municipalities independently of COVID-19 infection rates.

There is a risk of underreporting comorbidities among the oldest individuals, potentially leading to misclassification of the modified Charlson comorbidity index. In this study, we did not have data on the level of assistance required, access to medical journals, or data on drug use, and the use of some drugs may have had a protective or detrimental association with mortality. Information on chronic diseases is poorly registered in residents of nursing homes. About 80% of those older than 80 years living in nursing homes have dementia.[2] However, dementia and other chronic diseases among nursing home residents are poorly recorded in the data we had access to. Thus, it is likely residual confounding influenced our results. This highlights the need of better register data for older people in nursing homes.

In the current study, we observed lower mortality in the vaccinated group compared to the unvaccinated group immediately after first-dose vaccination with mRNA vaccines, which could be explained by residual confounding. The reduced mortality is most likely a healthy-vaccinee effect, as immunity against COVID-19 is not expected to develop until the end of the three-week period.

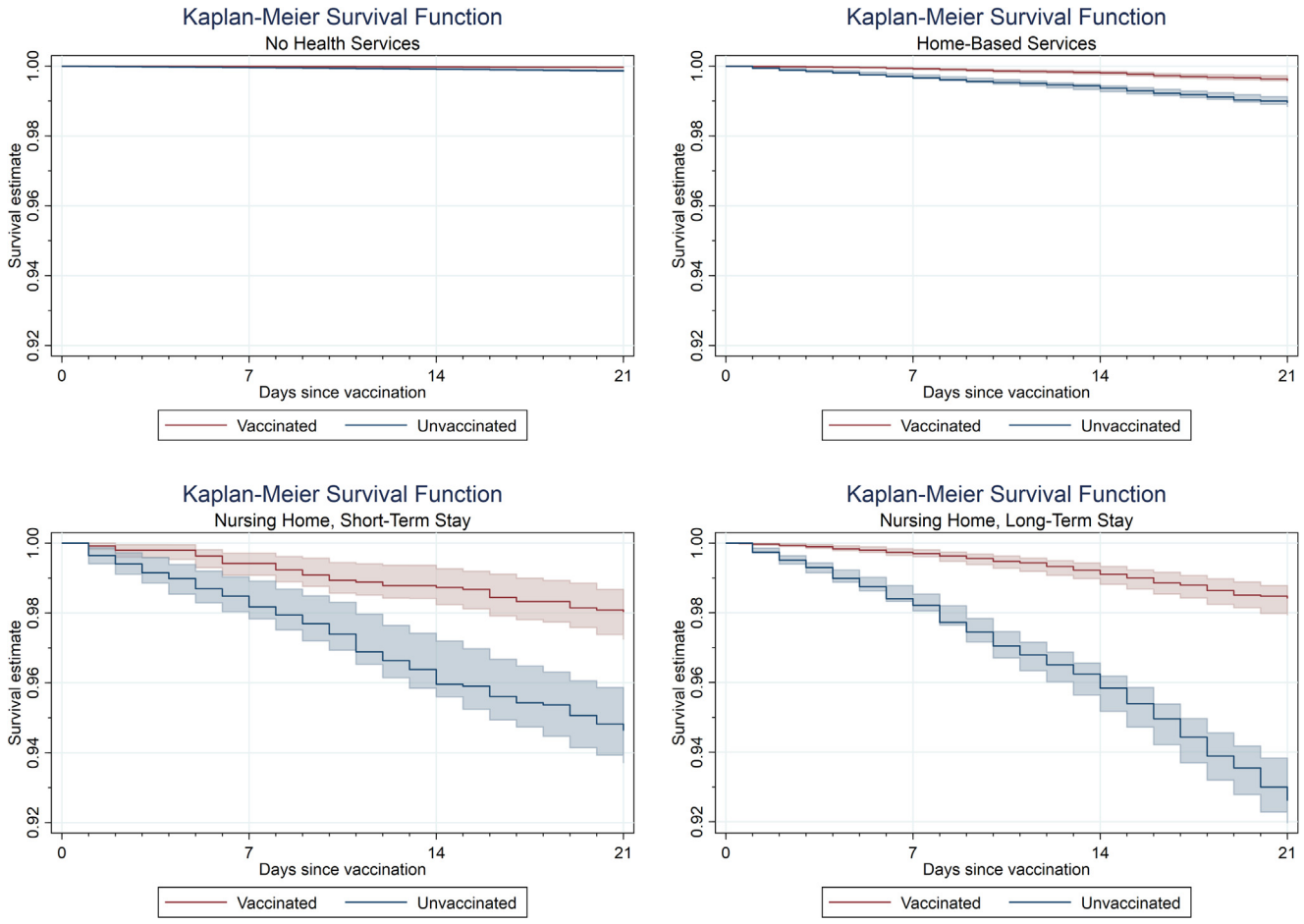

Fig. 2. Kaplan-Meier survival function by vaccination status and use of health services.

Individuals in the final stage of life are not likely to be vaccinated, and unfortunately, this kind of information was not available to us. [22] It is possible that a reduction in COVID-19-attributable deaths among vaccinated individuals could have contributed to our results. However, Norway had no excess mortality and a low proportion of deaths due to COVID-19 (2.4% of all deaths among individuals aged 70+ years) during the study period. This leads us to believe that the few deaths attributable to COVID-19 did not influence our results to a large extent.

We only studied mortality after the first vaccine dose. Some local and systemic reactions potentially associated with death in older people could be more frequent and severe after the second dose.

4.2. Interpretation of study results

During the first weeks after the vaccination campaign started in Norway, we achieved a high coverage among older individuals, especially nursing home residents. After most of the residents and health professionals were vaccinated and until the fall of 2021, COVID-19 outbreaks were less frequent. This highlights the importance of developing safe and effective COVID-19 vaccines for old and frail individuals.[23].

Population-based studies may provide information at a population level, but it is not possible to provide evidence on a specific vaccine in a specific individual.[24] Severely frail patients or patients with a short remaining life expectancy must be assessed individually whether the benefit of vaccination outweighs the risk that they may not tolerate potential adverse effects.[18,23,25] An expert review commission have investigated the medical reports of the first 100 fatal cases suspected to be related to immunization in Norwegian nursing homes and found that vaccine was considered probably linked to 10 deaths in frail older people.[18] This study was based on information from the adverse events report system, which involves a risk of reporting bias.

We believe that in some cases the frailest individuals in nursing homes were not vaccinated. Individuals in nursing homes presented with a higher proportion of all comorbidities (cardiovascular and cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, and dementia) than the general population. [26] Frailty could have led to some adverse events after vaccination.[27].

4.3. How this study could promote better decisions

Mortality in the frailest older people, like those living in nursing homes, is generally high. It is important to study whether there is an increased mortality risk from common adverse effects of vaccination, which may have accelerated the process of dying for some patients.

Better assessment of frailty, for example with the Clinical Frailty Scale, could help to individualize the decision on vaccination. However, most patients in long-term care would benefit from vaccination, not simply due to a reduction in mortality but also because infection control measures can be eased.[25] Protection of unvacci-

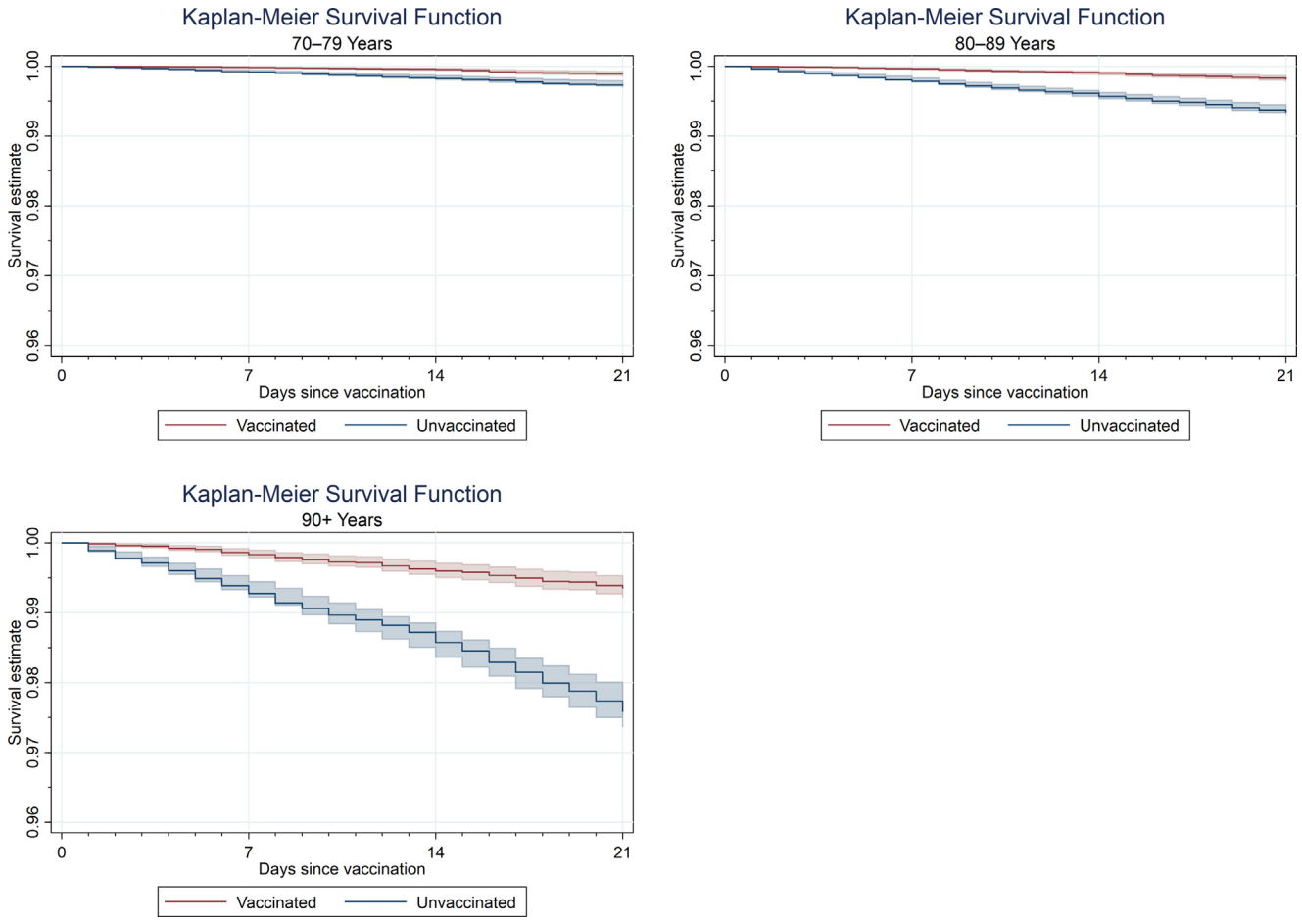

Fig. 3. Kaplan-Meier survival function by vaccination status and age group.

nated individuals will be achieved if the vaccination rates are high and other protection measures are maintained.[28].

A new study reports low immune response in nursing homes residents after vaccination,[29] and given the possibility of a periodical revaccination, more studies on safety in at-risk groups, such as the oldest and frailest, are important. Better understanding of adverse reactions to the vaccine could lead to safer vaccination practices, especially under mass vaccination campaigns.[24].

4.4. Unanswered questions and future research

In Norway, no increased excess mortality was observed during 2020,[30] nor during the study period (appendix Fig. 4). Extrapolating data from Norway to other countries should therefore be done cautiously. Daily updates received from registers to monitor adverse effects of vaccination are important to provide information and support public health measures, highlighting the importance of monitoring adverse effects and acting quickly when potential issues are detected. The oldest population has a high morbidity and mortality, so assessment of the safety and effectiveness of vaccines in this population is a public health priority.

Footnotes

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Contributors: HLG, GT, JD, JMG, and PLD designed the study. Statistical analyses were carried out by NG and PLD with help from GT and JMG. PLD and NG wrote the initial draft, and all authors participated in the discussion and interpretation of the results. Beredt C19 (NIPH) helped with administrative, technical, and material support.

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Competing interests: ØK reports participation in research projects funded by Novo Nordisk and LEO Pharma, all regulator mandated phase IV studies, all with funds paid to his institution (no personal fees) and with no relation to the work reported in this paper. HLG reports previous participation in research projects and clinical trials funded by Novo Nordisk, GSK, AstraZeneca, and Boehringer Ingelheim, all paid to her previous institution Oslo University Hospital (no personal fees) and with no relation to the work reported in this paper.

Ethical approval: The emergency preparedness register for COVID-19 has been established according to the Health Preparedness Act §2-4.

Data sharing: Data cannot be shared by the authors and are only accessible to authorized researchers after ethical approval and application to helsedata.no administered by the Directorate of eHealth.

Table 3
Crude hazard ratios (HRs) of death, with associated 95% confidence intervals (CIs), based on Cox proportional-hazards regression of the matched study sample[1] (n = 617,834), overall and by use of health services and age group.

	Vaccination status	HR (95% CI[2])	P value
Overall			
	Unvaccinated	1	
	Vaccinated	0.28 (0.24–0.31)	< 0.001
Use of health services			
No health services	Unvaccinated	1	
	Vaccinated	0.23 (0.17–0.33)	< 0.001
Home-based services	Unvaccinated	1	
	Vaccinated	0.36 (0.30–0.44)	< 0.001
Nursing home, short-term stay	Unvaccinated	1	
	Vaccinated	0.36 (0.25–0.51)	< 0.001
Nursing home, long-term stay	Unvaccinated	1	
	Vaccinated	0.19 (0.15–0.24)	< 0.001
Age group			
70–79 years	Unvaccinated	1	
	Vaccinated	0.33 (0.25–0.43)	< 0.001
80–89 years	Unvaccinated	1	
	Vaccinated	0.27 (0.22–0.32)	< 0.001
90+ years	Unvaccinated	1	
	Vaccinated	0.26 (0.21–0.33)	< 0.001

[1] Pairs of vaccinated and unvaccinated individuals aged 70 years and older matched on sex, five-year age group, marital status, health region, size of municipality, use of health services, history of influenza vaccination, Charlson comorbidity index, and history of SARS-CoV-2 infection.
[2] Clustered sandwich estimator of standard errors to allow for intragroup correlation between observations of the same individual as part of two different matched pairs – first as unvaccinated and later as vaccinated.

Data availability

The authors do not have permission to share data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.10.085.

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