SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study

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ABSTRACT

OBJECTIVE

To investigate the association between SARS-CoV-2 vaccination and myocarditis or myopericarditis.

DESIGN

Population based cohort study.

SETTING

Denmark.

PARTICIPANTS

4 931 775 individuals aged 12 years or older, followed from 1 October 2020 to 5 October 2021.

MAIN OUTCOME MEASURES

The primary outcome, myocarditis or myopericarditis, was defined as a combination of a hospital diagnosis of myocarditis or pericarditis, increased troponin levels, and a hospital stay lasting more than 24 hours. Follow-up time before vaccination was compared with follow-up time 0-28 days from the day of vaccination for both first and second doses, using Cox proportional hazards regression with age as an underlying timescale to estimate hazard ratios adjusted for sex, comorbidities, and other potential confounders.

RESULTS

During follow-up, 269 participants developed myocarditis or myopericarditis, of whom 108 (40%) were 12-39 years old and 196 (73%) were male. Of 3 482 295 individuals vaccinated with BNT162b2 (Pfizer-BioNTech), 48 developed myocarditis or myopericarditis within 28 days from the vaccination date compared with unvaccinated individuals (adjusted hazard ratio 1.34 (95% confidence interval 0.90 to 2.00); absolute rate 1.4 per 100 000 vaccinated individuals within 28 days of vaccination (95% confidence interval 1.0 to 1.8)). Adjusted hazard ratios among female participants only and male participants only were 3.73 (1.82 to 7.65) and 0.82 (0.50 to 1.34), respectively, with corresponding absolute rates of 1.3 (0.8 to 1.9) and 1.5 (1.0 to 2.2) per 100 000 vaccinated individuals within 28 days of vaccination, respectively. The adjusted hazard ratio among 12-39 year olds was 1.48 (0.74 to 2.98) and the absolute rate was 1.6 (1.0 to 2.6) per 100 000 vaccinated individuals within 28 days of vaccination. Among 498 814 individuals vaccinated with mRNA-1273 (Moderna), 21 developed myocarditis or myopericarditis within 28 days from vaccination date (adjusted hazard ratio 3.92 (2.30 to 6.68); absolute rate 4.2 per 100 000 vaccinated individuals within 28 days of vaccination (2.6 to 6.4)). Adjusted hazard ratios among women only and men only were 6.33 (2.11 to 18.96) and 3.22 (1.75 to 5.93), respectively, with corresponding absolute rates of 2.0 (0.7 to 4.8) and 6.3 (3.6 to 10.2) per 100 000 vaccinated individuals within 28 days of vaccination, respectively. The adjusted hazard ratio among 12-39 year olds was 5.24 (2.47 to 11.12) and the absolute rate was 5.7 (3.3 to 9.3) per 100 000 vaccinated individuals within 28 days of vaccination.

CONCLUSIONS

Vaccination with mRNA-1273 was associated with a significantly increased risk of myocarditis or myopericarditis in the Danish population, primarily driven by an increased risk among individuals aged 12-39 years, while BNT162b2 vaccination was only associated with a significantly increased risk among women. However, the absolute rate of myocarditis or myopericarditis after SARS-CoV-2 mRNA vaccination was low, even in younger age groups. The benefits of SARS-CoV-2 mRNA vaccination should be taken into account when interpreting these findings. Larger multinational studies are needed to further investigate the risks of myocarditis or myopericarditis after vaccination within smaller subgroups.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Recent pharmacovigilance reports and studies within healthcare systems have suggested an increased risk of myocarditis or myopericarditis after vaccination with SARS-CoV-2 mRNA vaccines

No cohort study has investigated the association using information from a complete population

WHAT THIS STUDY ADDS

Vaccination with mRNA-1273 (Moderna) was associated with a significantly increased rate of myocarditis or myopericarditis, especially among individuals aged 12-39 years (adjusted hazard ratio 5.24 (95% confidence interval 2.47 to 11.12); absolute rate 5.7 (3.3 to 9.3) per 100 000 individuals aged 12-39 years within 28 days of vaccination)

Vaccination with BNT162b2 (Pfizer-BioNTech) was associated with a significantly increased rate of myocarditis or myopericarditis among women only; in the 12-39 year age group, the absolute rate was 1.6 (95% confidence interval 1.0 to 2.6) per 100 000 individuals aged 12-39 years within 28 days of vaccination

Clinical outcomes of myocarditis or myopericarditis were predominantly mild and generally similar between vaccinated and unvaccinated individuals, although precision in describing clinical outcomes was limited owing to few myocarditis or myopericarditis events

Introduction

Pharmacovigilance reports, health system surveillance studies, and case series suggest an association between SARS-CoV-2 vaccination and myocarditis and myopericarditis.[1-9] This association is thought to occur particularly after the second booster dose

of mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). In their most severe forms, myocarditis and myopericarditis can result in chronic heart failure or death, and are important safety concerns. The biological mechanism is not clear, but the same adverse events have been attributed to use of the smallpox vaccine in adults.[10] Both the US Centers for Disease Control and Prevention and the European Medicines Agency have ongoing investigations into the association using surveillance data,[11 12] but to our knowledge, no publicly available controlled cohort studies have examined the association within a complete population.

Denmark has nationwide, population based registers containing data on vaccinations, hospital admissions, and results of laboratory assays of blood samples. By taking advantage of these registers, we explored the association between vaccination with SARS-CoV-2 vaccines and a predefined endpoint consisting of a hospital diagnosis of myocarditis or pericarditis, a blood measurement showing increased troponin levels, and a hospital stay lasting more than 24 hours.

Methods

Materials

Using individual level information on vaccinations from the Danish Vaccination Register, hospital based diagnoses from the Danish National Patient Register, and the unique personal identifier issued by the Danish Civil Registration System,[13] we created a full population cohort with information on vaccination status of all individuals in Denmark.[14] The unique identifier ensures completeness concerning linkage to registered medical incidents because it is used for registration of all contacts within the Danish healthcare system. We accessed the Register of Laboratory Results for Research to obtain biochemical measurements of blood samples analysed at Danish hospitals. This register allowed characterisation of myocarditis or myopericarditis beyond a hospital diagnosis, based on blood sample measurements of troponin levels.[15] Additionally, we accessed information on SARS-CoV-2 polymerase chain reaction (PCR) test results from the Danish Microbiology Database.[16] SARS-CoV-2 PCR tests were widely available during the study period, regardless of symptom status and without the need for referral by a medical professional. Furthermore, patients were regularly tested for SARS-CoV-2 on emergency hospital admission.

Study cohort

All Danish residents were followed from 1 October 2020 or from their 12th birthday (whichever occurred later), until emigration, death, an event, or 5 October 2021. To avoid misclassification, individuals were included only if they were registered as residents of Denmark between 1 January 2017 and 1 October 2020. We excluded individuals who received a hospital based diagnosis of myocarditis or pericarditis between 1 January 2017 and 30 September 2020. Furthermore, individuals who received two different types of vaccines were censored on receipt of their second dose. Finally, we censored individuals with a positive SARS-CoV-2 test result, to avoid associating outcomes of SARS-CoV-2 infection with outcomes of SARS-CoV-2 vaccination.

Vaccination

Vaccinated individuals in the cohort received a vaccine against SARS-CoV-2 in Denmark (approved by the European Medicines Agency) and were followed up from the date of vaccination with the first dose (with BNT162b2, mRNA-1273, ChAdOx1 nCoV-19 (AstraZeneca), or Ad26.COV2.S (Johnson and Johnson)). Only estimates for individuals vaccinated with BNT162b2 or mRNA-1273 are presented in the main analysis. Estimates for individuals vaccinated with ChAdOx1 nCoV-19 or Ad26.COV2.S are presented in the supplemental materials, because these vaccines were withdrawn from the national mass vaccination programme and rarely used. The main risk window of interest was the 28 days after vaccination, which included day 0, the day of vaccination. If study participants received a second dose, they re-entered a 28 day risk window.

Study covariates

Study covariates were age, sex, vaccine priority group, and clinical comorbidities (that is, asthma, chronic pulmonary disease (including chronic obstructive pulmonary disease), ischaemic heart disease, heart failure, atrial fibrillation or flutter, diabetes mellitus, inflammatory bowel disease, malignancy, and renal failure), as defined by hospital registered ICD-10 codes (international classification of diseases, 10th revision; see table S1 for definitions of covariates). Comorbidities were categorised as binary variables (present or not present) and ascertained at baseline (1 October 2020).

Outcomes

We defined the primary study outcome of myocarditis or myopericarditis as a hospital diagnosis code of myocarditis or pericarditis (ICD-10 codes listed in table S1) and co-occurrence of increased troponin levels (that is, a troponin T or a troponin I measurement above the assay specific upper normal limit), in addition to a hospital stay lasting more than 24 hours. The criterion of increased troponin levels in the outcome definition was chosen to focus on events characterised by biochemically verifiable myocardial damage. Troponin measurements occurring within 48 hours before or after diagnosis was considered as co-occurring. The event date for co-occurring diagnosis and troponin measurement was defined as the latest date of diagnosis or measurement (see flowchart in fig S1 for classification of outcomes). Myocarditis and pericarditis diagnosis codes were combined into one outcome owing to the large overlap in pathology, clinical findings, and symptoms of these two disease entities. As an additional secondary outcome, we estimated the association between SARS-CoV-2 vaccination and

the combined endpoint of cardiac arrest or death. This outcome was included to investigate any association between SARS-CoV-2 vaccination and the most severe manifestations of myocarditis or myopericarditis. Finally, among participants with myocarditis or myopericarditis, we assessed Kaplan-Meier estimates of hospital admission lasting more than 72 hours; readmission within 28 days of discharge; heart failure within 28 days of outcome; and death within 28 days of outcome, by vaccination status, sex, and age group.

Statistical analysis

Study cohort, covariates, main outcomes, and statistical analysis design were prespecified in our statistical analysis protocol and revisions suggested by editors and reviewers are described in our revised statistical analysis protocol (supplementary material). We followed the cohort from 1 October 2020 to 5 October 2021. Our main analysis compared follow-up time within a 28 day risk window after vaccination with unvaccinated follow-up time using Cox proportional hazards to estimate hazard ratios by vaccination status, with age as the underlying timescale (see fig S2 for illustration of follow-up time). Hazard ratios were adjusted for sex, vaccination priority group, season (1 October 2020 to 31 December 2020, 1 January 2021 to 31 March 2021, 1 April 2021 to 30 June 2021, and 1 July 2021 to 5 October 2021), and comorbidities. Vaccine priority group was assessed on 22 February 2021 and treated as a time invariant variable, except that individuals were coded as belonging to a separate group before 1 January 2021. The proportional hazards assumption was evaluated by testing for interaction between the time windows of main interest (within 28 days of BNT162b2 and mRNA-1273 vaccination) and the underlying timescale (age) treated as a linear variable. We found no indication that the proportional hazards assumption was violated. To evaluate study period effects, we varied the start of follow-up in sensitivity analyses. The significance level was set at $P<0.05$.

Within our cohort we also created a nested self-controlled case series study, consisting of only people with a diagnosis of myocarditis or myopericarditis during follow-up. The self-controlled case series design compares periods of follow-up time according to vaccination status within individuals, who also act as their own controls. As a consequence, time invariant characteristics (eg, sex, ethnic origin, or socioeconomic status) are implicitly taken into account. In addition, the self-controlled case series analysis is adjusted for season, as defined in the cohort analysis. The study also had a 28 day risk window after vaccination with BNT162b2 or mRNA-1273 and used the same study period and exclusion or censoring criteria (except that experiencing an outcome did not censor follow-up for an individual). The unvaccinated period was considered the reference period. We designated a 14 day pre-risk period before vaccination with both the first and second dose; follow-up during this period was not included in the unvaccinated period or in the 28 day risk period if they overlapped. The reason for this is that individuals are unlikely to be vaccinated shortly after diagnosis, leading to an upwardly biased risk period effect and underestimation of risk in the pre-risk period. The assumption of the self-controlled case series approach was that the probability of vaccination does not depend on having had a study outcome. We evaluated this assumption by visual inspection of plots showing the temporal timing of myocarditis or myopericarditis events in relation to vaccination (fig S3). We also applied Firth's method for bias reduction to evaluate the effect of sparse events.

Additionally, we calculated the absolute number of people with myocarditis or myopericarditis within 28 days of vaccination per 100 000 vaccinated individuals (individuals vaccinated at least once) and presented the cumulative incidences after first and second vaccine dose. To weigh the benefits of SARS-CoV-2 vaccination against SARS-CoV-2 infection, we also investigated the analogous risk of myocarditis or myopericarditis after infection with SARS-CoV-2. We used the same cohort but instead measured a first positive PCR test for SARS-CoV-2 and censored individuals who received a SARS-CoV-2 vaccination. In this analysis, we also used a 28 day risk period after infection as the main time period of interest.

Patient and public involvement

Due to the urgency of the study question, no patients were formally involved in the design, analysis, or interpretation of the study.

Results

Our population cohort included 4 931 775 individuals, who were followed until 5 October 2021, yielding 4 717 464 person years (1.0 years on average). Among cohort members, 4 155 361 were vaccinated with a SARS-CoV-2 vaccine during follow-up, with 3 482 295 (83.8%) individuals vaccinated with BNT162b2 (Pfizer-BioNTech) and 498 814 (12.0%) individuals vaccinated with mRNA-1273 (Moderna), while the remaining vaccinated individuals were vaccinated with ChAdOx1 nCoV-19 or Ad26.COV2.S (Johnson and Johnson). Of the vaccinated cohort, 3 417 744 individuals vaccinated with BNT162b2 (98.1%) and 483 270 individuals vaccinated with mRNA-1273 (96.9%) had received both vaccine doses. The median time between administration of the first and second dose was 35 days (interquartile range 24-36 days) for BNT162b2 and 31 days (28-35) for mRNA-1273. Additional characteristics of the population cohort are presented in table 1.

SARS-CoV-2 mRNA vaccination and myocarditis or myopericarditis in cohort analysis

During follow-up, 269 individuals had myocarditis or myopericarditis, of whom 108 (40%) were 12-39 years old and 196 (73%) were male. Among individuals vaccinated with BNT162b2 and mRNA-1273, 48 and 21 individuals had myocarditis or myopericarditis within 28 days of vaccination, respectively (fig 1).

Table 1 | Risk time characteristics of Danish nationwide population cohort, based on follow-up from 1 October 2020.* Data are number (%) of person years

Characteristics	Unvaccinated risk time	BNT162b2 (Pfizer-BioNTech) vaccinated risk time†	mRNA-1273 (Moderna) vaccinated risk time†
Total No of person years†	3 213 951 (100)	1 305 870 (100)	153 982 (100)
Age (years)			
12-39	1420 687 (44.2)	271 263 (20.8)	61 278 (39.8)
40-59	985 432 (30.7)	406 184 (31.1)	29 087 (18.9)
≥60	807 832 (25.1)	628 424 (48.1)	63 617 (41.3)
Sex			
Female	1 585 356 (49.3)	681 838 (52.2)	76 771 (49.9)
Male	1 628 595 (50.7)	624 032 (47.8)	77 211 (50.1)
Vaccination status			
Vaccinated with first dose	—	301 675 (23.1)	44 780 (29.1)
Vaccinated with both doses	—	1 004 195 (76.9)	109 202 (70.9)
Vaccine priority group‡			
Vulnerable individuals§	10 166 (0.3)	59030 (4.5)	837 (0.5)
Patients with increased risk of severe disease¶	18 000 (0.6)	51551 (3.9)	2186 (1.4)
Healthcare workers or similar activity**	95 185 (3.0)	104800 (8.0)	6041 (3.9)
Individuals prioritised by age criteria alone	1 874 027 (58.3)	1090233 (83.5)	144 917 (94.1)
Follow-up time up to 31 December 2020	1 216 573 (37.9)	257 (0.0)	0 (0.0)
Comorbidities			
Any comorbidity listed below	462 660 (14.4)	312 806 (24.0)	30 326 (19.7)
Asthma	88 902 (2.8)	41 186 (3.2)	4040 (2.6)
Chronic pulmonary disease	57 931 (1.8)	47 880 (3.7)	4357 (2.8)
Ischaemic heart disease	80 173 (2.5)	59 991 (4.6)	5725 (3.7)
Heart failure	33 433 (1.0)	29 162 (2.2)	2578 (1.7)
Atrial fibrillation or flutter	76 690 (2.4)	66 507 (5.1)	6806 (4.4)
Diabetes mellitus	90 096 (2.8)	64 016 (4.9)	5658 (3.7)
Inflammatory bowel disease	32 506 (1.0)	17 389 (1.3)	1683 (1.1)
Malignancy	118 298 (3.7)	93 102 (7.1)	9264 (6.0)
Moderate to severe renal disease	32 489 (1.0)	26 044 (2.0)	2223 (1.4)

*Information on vaccines currently used outside the national mass vaccination programme (ChAdOx1 nCoV-19 (AstraZeneca) and Ad27.COV2.S (Johnson and Johnson)) is provided in table S8.
†Follow-up time of vaccinated individuals covers both the initial 0-28 day time windows after vaccinations and any later follow-up time.
‡Person years by vaccine priority group from 1 January 2021 were assessed on 22 February 2021. By 1 January 2021, data on vaccine priority group was missing for 1744 individuals (corresponding to 0.036% of the cohort); by mode imputation, these individuals were assigned to the largest vaccine priority group (that is, "Individuals prioritised by age criteria alone").
§Individuals living in care homes or similar facilities, or aged 65 years or older and receiving home assistance with activities of daily life.
¶Individuals clinically determined to be at increased risk of severe disease from SARS-CoV-2 infection.
**Individuals working in the healthcare and social care sectors, and relatives in close contact with individuals at increased risk of severe disease.

Overall, individuals vaccinated with BNT162b2 had a non-significantly increased rate of myocarditis or myopericarditis in the 28 days after vaccination compared with unvaccinated follow-up (adjusted hazard ratio 1.34, 95% confidence interval 0.90 to 2.00), after adjustment for age, sex, vaccine priority group, season, and clinical comorbidities. Among individuals aged 12-39 years, we also found a non-significantly increased rate in the 28 days after vaccination compared with unvaccinated follow-up (1.48, 0.74 to 2.98). Individuals vaccinated with mRNA-1273 had a significantly increased rate of myocarditis or myopericarditis compared with unvaccinated follow-up (3.92, 2.30 to 6.68). Among individuals aged 12-39 years, we also found a significantly increased rate of myocarditis or myopericarditis compared with unvaccinated follow-up (5.24, 2.47 to 11.12). Additionally, we found that both BNT162b2 and mRNA-1273 were associated with a markedly reduced hazard ratio of cardiac arrest or death (0.51 (0.49 to 0.53) and 0.41 (0.37 to 0.46), respectively) compared with unvaccinated follow-up. The tests for proportional hazards for the adjusted analyses yielded P=0.47 for BNT162b2 and P=0.14 for mRNA-1273.

SARS-CoV-2 mRNA vaccination and myocarditis or myopericarditis in self-controlled case series analysis

The self-controlled case series corroborated our main analysis, showing a significantly increased risk of myocarditis or myopericarditis by vaccination with mRNA-1273, while vaccination with BNT162b2 was associated with a non-significantly increased risk of myocarditis or myopericarditis (fig 2).

Absolute rates of myocarditis or myopericarditis after vaccination

The overall absolute rate of myocarditis or myopericarditis within 28 days of any SARS-CoV-2 mRNA vaccination was 1.7 (95% confidence interval 1.3 to 2.2) per 100 000 vaccinated individuals. The rates for BNT162b2 or mRNA-1273 vaccinations separately were 1.4 (1.0 to 1.8) and 4.2 (2.6 to 6.4) per 100 000 individuals within 28 days of vaccination, respectively. Among women, the corresponding rates for BNT162b2 or mRNA-1273 vaccinations were 1.3 (0.8 to 1.9) and 2.0 (0.7 to 4.8), respectively. Among men, the corresponding rates for BNT162b2 or mRNA-1273 vaccinations were 1.5 (1.0 to 2.2) and 6.3 (3.6

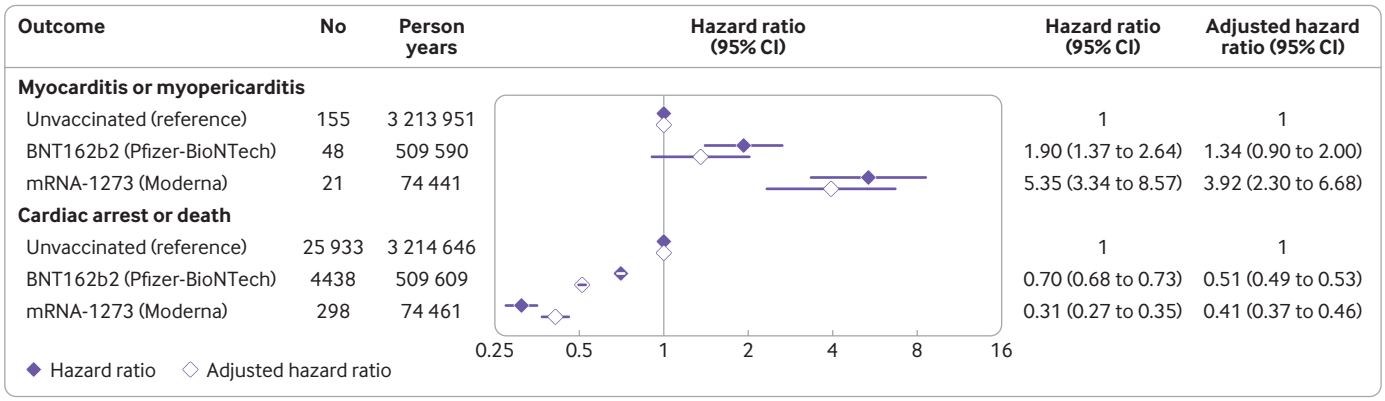

Fig 1 | Hazard ratios of primary and secondary study outcomes within 28 days after vaccination in the cohort study, by vaccine type, with follow-up until 5 October 2021. Hazard ratios are adjusted for age and sex; adjusted hazard ratios are adjusted for age, sex, vaccine priority group, season, and clinical comorbidities

to 10.2) per 100 000 individuals within 28 days of vaccination, respectively. Among individuals aged 12-39 years, the corresponding rates of myocarditis or myopericarditis for BNT162b2 or mRNA-1273 vaccinations were 1.6 (1.0 to 2.6) and 5.7 (3.3 to 9.3) per 100 000 individuals within 28 days of vaccination, respectively. Among individuals aged 12-17 years, the rate was 1.0 (0.2 to 3.0) per 100 000 individuals within 28 days of BNT162b2 vaccination; myocarditis or myopericarditis was not recorded in this age group among individuals vaccinated with mRNA-1273, but only 831 individuals in the cohort had been vaccinated with mRNA-1273 in this age group during follow-up. To further illustrate the proportion of myocarditis or myopericarditis events by time since vaccination, figure 3 presents the cumulative incidence of events by vaccine type and dose number.

Sensitivity analyses

In sensitivity analyses, BNT162b2 vaccination was not associated with an increased hazard ratio of myocarditis or myopericarditis for any of our predefined age groups (12-39, 40-59, and ≥60 years) within the first 28 days after vaccination compared with unvaccinated follow-up (table S2). Stratifying by sex, we found that both BNT162b2 and mRNA-1273 vaccinations were significantly associated with myocarditis or myopericarditis events among female participants (adjusted hazard ratio 3.73 (95% confidence interval 1.82 to 7.65) and 6.33 (2.11 to 18.96), respectively). By contrast, only vaccination with mRNA-1273 was significantly associated with myocarditis or myopericarditis among male participants (3.22 (1.75 to 5.93) for mRNA-1273 *v* 0.82 (0.50 to 1.34) for BNT162b2; table S3). Investigating effects by vaccine dose number, we did not observe a significant association overall between BNT162b2 vaccination and myocarditis or myopericarditis, for either the first or the second dose (table S4). For mRNA-1273, only vaccination with a second dose was significantly associated with myocarditis or myopericarditis (table S4).

We also investigated potential long term effects of SARS-CoV-2 vaccination, different periods of follow-up, and association by vaccine technology. Using both a cohort design and a self-controlled case series design, we found a significantly decreased rate of myocarditis or myopericarditis occurring 29 days or more after vaccination with BNT162b2 vaccination, but not with mRNA-1273 vaccination (table S5). Changing the study period, we found no difference in the association between SARS-CoV-2 vaccination and the occurrence of myocarditis or myopericarditis compared with our main analysis (table S6). Combining information by vaccine technology, we found a significantly increased hazard ratio of myocarditis or myopericarditis occurring after vaccination with any SARS-CoV-2 mRNA vaccine, but our cohort had too few individuals to reliably assess the association after vaccination with any SARS-CoV-2 viral vector vaccine (table S7).

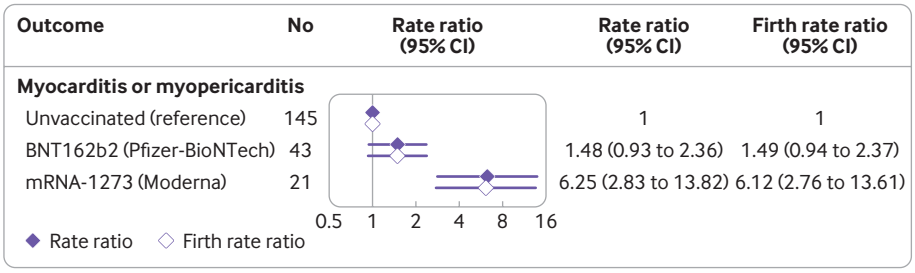

Fig 2 | Rate ratios of myocarditis or myopericarditis within 28 days after vaccination in the self-controlled case series, by vaccine type. Analyses use a 14 day pre-risk period for each dose and are adjusted for season. Rate ratios are given without and with Firth's correction

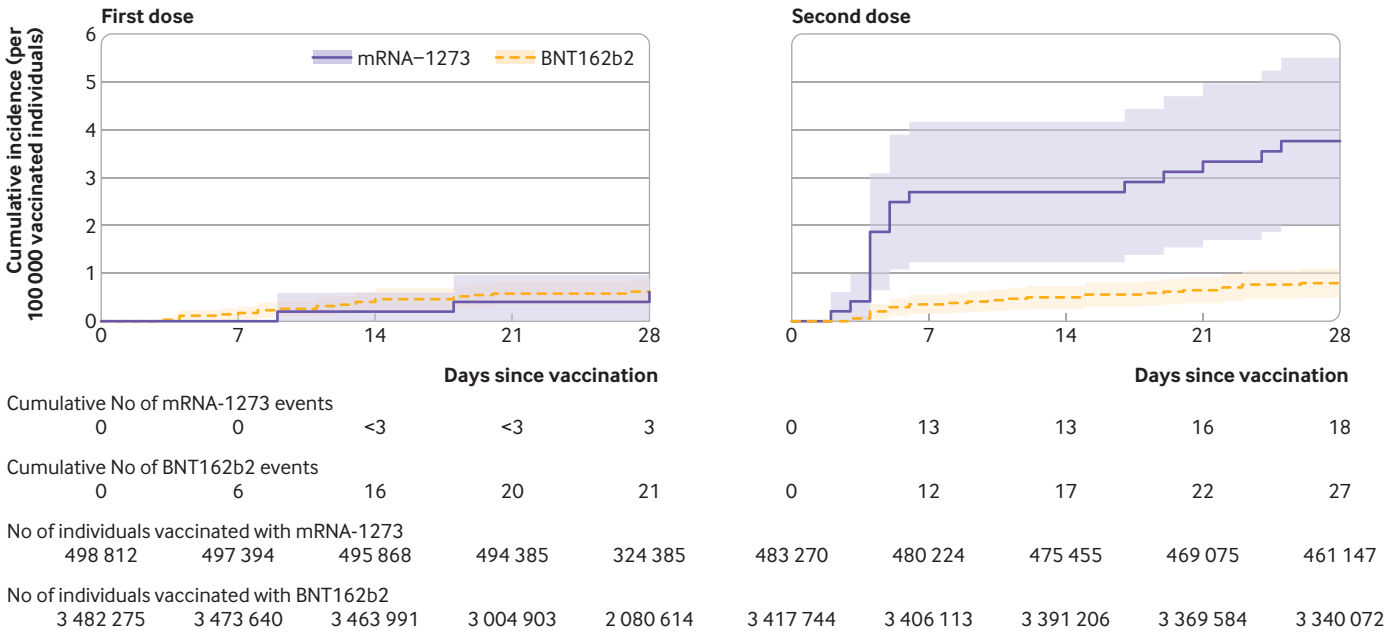

Fig 3 | Cumulative incidence of myocarditis or myopericarditis events after vaccination, by vaccine type and dose number

In post hoc analyses, we estimated the adjusted hazard ratio of myocarditis or myopericarditis among young men (aged 12-39 years) after their second dose of a SARS-CoV-2 vaccine (1.54 (95% confidence interval 0.62 to 3.81) for BNT162b2 and 9.80 (4.20 to 22.84) for mRNA-1273). The corresponding rates per 100 000 vaccinated individuals within 28 days of vaccination were 1.8 (0.8 to 3.4) for BNT162b2 and 9.4 (5.0 to 16.0) for mRNA-1273.

Clinical outcomes among vaccinated individuals with myocarditis or myopericarditis

Vaccination status did not appear to be associated with the clinical outcome of participants who had myocarditis or myopericarditis, although our precision is limited because our cohort had only a few individuals with severe outcomes. Among 155 unvaccinated individuals who had myocarditis or myopericarditis, it was estimated that 47.7% (95% confidence interval 39.7% to 55.3%) were still in hospital 72 hours after admission, 4.5% (2.2% to 9.2%) were diagnosed with heart failure, and 1.9% (0.6% to 5.9%) died within 28 days of the myocarditis or myopericarditis event (table S8). Corresponding rates for the 48 individuals who had myocarditis or myopericarditis within 28 days of BNT162b2 vaccination were 58.3% (43.2% to 70.8%), 2.1% (0.3% to 13.9%), and 2.1% (0.3% to 13.9%), respectively. For the 21 individuals who had myocarditis or myopericarditis within 28 days of mRNA-1273 vaccination, 40.0% (19.3% to 60.0%) were in hospital 72 hours after admission, while none was diagnosed with heart failure or died within 28 days of outcome.

Additional analyses of other vaccine types, different statistical adjustment, different censoring, different time windows, and troponin levels are presented in tables S9-S16 and figure S4. We found no events of myocarditis or myopericarditis in the 28 days after SARS-CoV-2 mRNA vaccination among individuals who had a diagnosis of either myocarditis or pericarditis between 1 January 2017 and 30 September 2020 (table S12). In addition, we found BNT162b2 to be significantly associated with myocarditis or myopericarditis event when using a narrowed 14 day time window (adjusted hazard ratio 1.89 (95% confidence interval 1.23 to 2.90); table S14).

Myocarditis or myopericarditis after SARS-CoV-2 infection

In comparative analyses of outcomes within 28 days of a positive SARS-CoV-2 test (tables S17-S19 and fig S5), SARS-CoV-2 infection was associated with an adjusted hazard ratio of 2.09 (95% confidence interval 0.52 to 8.47) for myocarditis or myopericarditis, but our statistical precision was limited. Nevertheless, SARS-CoV-2 infection was associated with a 14-fold increased risk of cardiac arrest or death in the 28 days after a positive SARS-CoV-2 test compared with uninfected follow-up.

Discussion

Principal findings

Using healthcare data covering the entire Danish population, we did observe a strong association between vaccination with mRNA-1273 and myocarditis or myopericarditis, defined as the combined outcome of a hospital diagnosis of myocarditis or pericarditis, increased troponin levels, and a hospital stay lasting more than 24 hours. Vaccination with BNT162b2 was only associated with an overall increased rate of myocarditis or myopericarditis among female participants. In general, the rate of myocarditis or myopericarditis was about threefold to fourfold higher for mRNA-1273 vaccination than that for

BNT162b2 vaccination. Nevertheless, the absolute number of events were low. Even in the youngest age group (12-39 years), the absolute rates of myocarditis or myopericarditis were 1.6 (95% confidence interval 1.0 to 2.6) and 5.7 (3.3 to 9.3) per 100 000 individuals within 28 days of BNT162b2 vaccination and mRNA-1273 vaccination, respectively. Clinical outcomes among vaccinated people with myocarditis or myopericarditis were predominantly mild. We observed no readmissions, diagnoses of heart failure, or deaths among people with myocarditis or myopericarditis occurring within 28 days of mRNA-1273 vaccination.

Comparison with other countries

Previous reports have also suggested an increased risk of myocarditis in Israel and the United States after vaccination with SARS-CoV-2 mRNA vaccines, indicating similar adverse effects in diverse populations.[1 3 4 8 9] We did not observe similarly clear overall findings for the general Danish population with regards to vaccination with BNT162b2. When stratifying by vaccine dose number, we also did not find the second vaccine dose of BNT162b2 to be associated with a markedly higher rate of myocarditis or myopericarditis. In contrast to previous reports, we found that BNT162b2 was associated with an increased hazard ratio of myocarditis or myopericarditis among female participants, but not in male participants. This finding went against our previous beliefs about the potential association. Our sensitivity analysis with a narrowed time window of 14 days suggested an overall 1.89-fold increased risk of myocarditis or myopericarditis after BNT162b2 vaccination, although the magnitude of risk was about threefold larger for mRNA-1273 than for BNT162b2.

One potential reason for the discrepancies between our findings for Denmark compared with those for Israel and the US could be that the vaccinated population in Denmark was older. However, our age stratified analysis did not suggest a strong increased risk among younger individuals in Denmark vaccinated with BNT162b2. Furthermore, in our post hoc analysis of male participants aged 12-39 years vaccinated after a second dose of BNT162b2, we did not find a significantly increased rate of myocarditis or myopericarditis and an absolute rate of only 1.8 (95% confidence interval 0.8 to 3.4) per 100 000 vaccinated individuals within 28 days of vaccination. Another explanation could be that the median time interval between first and second doses was longer in Denmark (median interval of five weeks for BNT162b2) than in Israel and the US (three week schedule).[17] The longer interval between vaccinations in Denmark could dampen an immediate vaccine immune response. Finally, fewer Danish residents have tested positive for SARS-CoV-2 than residents in the other two countries,[18] which might have led to fewer immune reactions, including myocarditis or pericarditis, owing to pre-existing immunity against SARS-CoV-2 (as described previously).[19]

Strengths and limitations

Compared with previous reports, our study had the advantage of using prospectively collected information on vaccination and hospital admissions for a complete population, virtually eliminating recall and selection bias. In addition, use of two different study designs (the cohort study and self-controlled case series) allowed us to examine effects of different methodological approaches. Overall, we did not find a discrepancy between our results in the two study analyses. This suggested no strong confounding effects from ethnic origin or socioeconomic status, which were not adjusted for in the cohort analysis, but were automatically controlled for in the self-controlled case series analysis. Furthermore, use of registry data ensured a systematic evaluation of exposures, covariates, and outcomes. However, we were not able to obtain valid information concerning electrocardiography or cardiac imaging. In addition, hospital diagnoses of myocarditis and pericarditis in the Danish National Patient Registry do not provide complete certainty that these diseases actually occurred.[20] Nevertheless, the newly amended Register of Laboratory Results for Research (which covers all biochemical assays of patient blood samples analysed at hospitals in Denmark from October 2020 onwards) allowed us to confirm suspected myocarditis or myopericarditis by confirming concurrent increased troponin levels as a specific marker of myocardial damage.

A potential bias in our observational study is that the decision to become vaccinated is an active personal choice, which could confound the association between SARS-CoV-2 mRNA vaccination and myocarditis or myopericarditis. Nevertheless, myocarditis or myopericarditis is a rare event. Most people with the conditions have no known predisposing factors other than sex and age, for which our analyses are adjusted. We thus have little reason to believe that vaccinated individuals have an inherently higher risk of the outcome. However, one could argue that individuals who choose vaccination are more health conscious, leading to healthcare seeking bias, which would overestimate the risk of myocarditis or myopericarditis after vaccination if people with mild disease are more likely to be ascertained among vaccinated individuals. Furthermore, increased public awareness of potential side effects of vaccines (eg, risk of myopericarditis) could also introduce detection bias in the vaccinated population and detection of myopericarditis that otherwise would not have been diagnosed. However, such bias is probably minimal in our study, because biochemically verified increases in troponin levels and 24 hour hospital admission were criteria for the outcome.

Potential confounding by SARS-CoV-2 exposure could occur if recent exposure to the virus (eg, from infected friends or family members) leads an individual to be vaccinated during a potential incubation period for the infection. Hypothetically, this bias also could introduce a spurious association between SARS-CoV-2 mRNA vaccination and myocarditis or myopericarditis,

because SARS-CoV-2 infection also appears to be a cause of this outcome. However, an infected individual who tested positive for SARS-CoV-2, up to or at hospital admission, would have been censored in our study design. The exclusion of these individuals is likely given the high rates of SARS-CoV-2 testing (of both individuals with or without symptoms) during follow-up and routine testing for SARS-CoV-2 on hospital admission in Denmark. Furthermore, for recent SARS-CoV-2 exposure to be a confounding factor, the vaccination decision would have to be linked strongly to recent SARS-CoV-2 exposure, but this association is not indicated by the high and stable vaccine uptake in Denmark. SARS-CoV-2 incidence would also have to be high, given the relative rarity of myocarditis or myopericarditis after this viral infection, but this was not the case during most of the study period. Taken together, these circumstances suggest that confounding by recent SARS-CoV-2 exposure is not an important factor in this study.

Another possible limitation of our study was potential surveillance bias, whereby an increased risk of myocarditis or pericarditis arises from closer scrutiny for signs of the diseases among recently vaccinated individuals. However, the different findings for BNT162b2 compared with mRNA-1273 suggest that surveillance bias is not prominent. Finally, the fact that SARS-CoV-2 vaccines are rarely given to people with an acute or terminal illness is a likely explanation for the low 28 day risk of cardiac arrest or death in our study.

We found a decreased rate of myocarditis of myopericarditis 29 days after vaccination with BNT162b2 compared with unvaccinated follow-up. This finding could suggest that we underestimated the effect within 28 days of vaccination if the follow-up of unvaccinated people (who are mainly those being vaccinated later in the study period) has a higher baseline rate than the follow-up of vaccinated people. However, this pattern was not consistent with regards to mRNA-1273, suggesting that the result could be a spurious finding and not a systematic bias.

Policy implications

Uncertainty regarding the incidence and severity of myocarditis and pericarditis after SARS-CoV-2 vaccination was a contributing factor for the Joint Committee on Vaccination and Immunisation to defer recommending full vaccination of children and young people aged 12-17 years with SARS-CoV-2 mRNA vaccines in the United Kingdom.[21] Our population based findings do not support a threefold or higher overall increased risk of myocarditis or myopericarditis for the youngest age group (12-39 years) when vaccinated with BNT162b2. Among this age group, the absolute rate of myocarditis or myopericarditis was only 1.6 (95% confidence interval 1.0 to 2.6) per 100 000 individuals aged 12-39 years within 28 days of BNT162b2 vaccination. The rate in the youngest age group (12-17 years) was only 1.0 (0.2 to 3.0) per 100 000 individuals aged 12-17 years within 28 days of BNT162b2 vaccination. By comparison, the estimated occurrence of multisystem inflammatory syndrome in individuals aged 12-17 years is 27 per 100 000 individuals with serologically determined SARS-CoV-2 infection.[22]

Given the worldwide spread of the highly contagious SARS-CoV-2 delta and omicron variants, future infection is the undesirable alternative to vaccination against SARS-CoV-2. Taken together with the potential long term sequelae of even mild SARS-CoV-2 infection,[23] and with the risk of multisystem inflammatory syndrome among adolescents (which is associated with severe morbidity),[24] our finding of a low absolute risk of myocarditis or myopericarditis with BNT162b2 or mRNA-1273 vaccination supports the overall benefits of such vaccination on an individual, societal, and global level.

Conclusions

We found that mRNA-1273 vaccination was associated with an increased rate of myocarditis or myopericarditis compared with unvaccinated individuals overall, while BNT162b2 vaccination was associated with an increased rate of myocarditis or myopericarditis among female individuals. However, the absolute rate of myocarditis or myopericarditis cases after SARS-CoV-2 mRNA vaccination was low overall, among female participants, and among younger age groups. In addition, the clinical outcomes after myocarditis or myopericarditis events were predominantly mild, providing evidence to support the overall safety of SARS-CoV-2 mRNA vaccines. Nevertheless, larger multinational studies and meta-analyses are needed to specify risks within smaller subgroups and the risk of myocarditis or myopericarditis after SARS-CoV-2 infection versus vaccination.

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Contributors: All the authors designed the study. AHu, JVH, EMT, and AHv processed the data. AHu and AHv directed the analyses, which were carried out by JVH and EMT. All authors participated in the discussion and interpretation of the results. AHu and AHv wrote the initial draft. All authors critically revised the manuscript for intellectual content, approved the final version, and meet the ICMJE criteria for authorship. AHu and AHv are guarantors of the study. The

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Ethical approval: The study was conducted using administrative register data. According to Danish law, ethical approval is not required for such research.

Data sharing: The datasets analysed in the study are stored in the Danish national covid-19 surveillance system database at Statens Serum Institute. The data will be made available for research on reasonable request and with permission from the Danish Data Protection Agency and Danish Health and Medicines Authority.

The lead author (AHu) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of the study will be disseminated through social media postings, press releases, and interviews explaining the result to news media and general public.

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Web appendix: Supplemental material