Association of COVID-19 vaccination with risks of hospitalization and mortality due to cardiovascular and other diseases: A study of the UK Biobank

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Abstract

Background Vaccines for COVID-19 represent a breakthrough in the fight against the pandemic. However, worries about adverse effects have led to vaccine hesitancy in some people. On the other hand, as COVID-19 may be associated with a range of sequelae, it is possible that vaccines may protect against hospitalization and mortality of various diseases.

Methods We leveraged a large prospective cohort, the UK-Biobank (UKBB), and studied associations of at least one dose of COVID-19 vaccination (BioNTech BNT162b2 or Oxford-AstraZeneca ChAdOx1 nCoV-19) with hospitalization and mortalities from cardiovascular and other diseases (*N*=180,727). Multivariable Cox and Poisson regression was conducted controlling for main confounders. For hospitalizations, we also conducted separate analysis for new-onset and recurrent cases. All-cause and cardiovascular mortality were also included as outcome.

Results We observed that COVID-19 vaccination (at least one dose) was associated with lower risks of hospitalizations from stroke (hazard ratio [HR]=0.371, 95% CI: 0.254-0.543, p=3.36e-7), venous thromboembolism (VTE) (HR=0.485, 95% CI: 0.292-0.804, p=4.99e-3), dementia (HR=0.207, 95% CI 0.091-0.470; p=1.66e-4) and non-COVID-19 pneumonia (HR=0.482, 95% CI 0.313-0.742; p=9.18e-4). Regarding mortality, an association with lower all-cause and cardiovascular mortality was observed, as well as lower mortality from several diseases including stroke, coronary artery disease(CAD), and chronic obstructive pulmonary disease (COPD) and dementia. There is no evidence that vaccination was associated with increased hospitalization/fatality from any specific disorders.

Conclusions Taken together, this study provides further support to the safety and benefits of COVID-19 vaccination, and such benefits may extend beyond reduction of infection risk or severity per se. As an observational study, causal relationship cannot be concluded and further replications are required to verify the findings.

Introduction

More than 196 million confirmed cases of COVID-19 and >4 million fatalities have been reported as at 3 Aug 2021. Vaccines for COVID-19 have been developed at an unprecedented speed, and offer hope to reduce the burden of this pandemic. Nevertheless, vaccine hesitancy has been a major hurdle, and some may worry about adverse effects or exacerbation of existing diseases[1,2]. There have been case reports of fatalities after vaccination[3,4], which has led to concerns about the safety of the vaccine among some people. However, so far there has been no direct evidence that COVID-19 vaccination is causally linked to increased risks of mortality in general.

On the other hand, as COVID-19 may be associated with a range of complications such as cardiovascular/cerebrovascular events, thromboembolism, renal failure etc. [5,6], it is reasonable to hypothesize that COVID-19 vaccination may reduce the risks of these complications. Of note, it has been shown in many reports and meta-analysis that influenza vaccination is associated with reduced cardiovascular risks. For example, a recent meta-analysis of both randomized controlled trials and observational studies[7] showed that flu vaccination was associated with a lower risk of all-cause and cardiovascular mortality, as well as major cardiovascular events compared to controls. Other meta-analysis also reported similar findings of reduced cardiovascular and stroke risks[8-10]. Although reduction of flu infection is a possible mechanism, it has also been reported that flu vaccines may promote plaque stabilization via its interaction with the immune system[11,12]. Other mechanism such as increased nitric oxide production has been proposed[13]. In view of these findings, it is possible that COVID-19 vaccination may also reduce cardiovascular risks.

Here we conducted a study to investigate the association of COVID-19 vaccination with hospitalization and mortalities from cardiovascular and other diseases. Cardiovascular diseases (CVD; including stroke) are chosen for analysis as they are leading cause of mortalities worldwide, and the protective effects of flu vaccines against CVD lead us to hypothesize that similar effects may also be observed for COVID-19 vaccines. Besides CVD, we also included in our analyses several other diseases that are likely linked to COVID-19 as complications/sequelae. For example, renal dysfunction is a common complication of the infection[14]. COPD exacerbations are common after viral infections[15] and may also be relevant complications. Venous thromboembolism (VTE) is also one of the major complications of COVID-19[16]. In addition, both the infection and vaccination involve complex interplay with the immune system, and therefore related disorders such as autoimmune diseases may be associated with the infection and/or vaccination[17]. As for neurological sequelae, a recent study revealed that across all neuropsychiatric disorders, the risks of mortality from dementia appeared to be particularly elevated[18]. In this work, the association of COVID-19 vaccination with hospitalization and mortality from the above diseases were investigated.

Methods

UK Biobank sample

The UK Biobank (UKBB) is a large-scale prospective cohort comprising ~500,000 subjects aged 40–69 years when they were recruited in 2006–2010. The current age of subjects included in our analyses ranged from 50 to 87 years. For details of the UK Biobank cohort please also refer to[19]. As vaccination records were only available from the subjects with general

practitioner (GP) records under the TPP system, our analysis was restricted to these subjects (sample size, *N*=180,727). The present analysis was conducted under the project number 28732.

Outcome definition

Hospitalization records were extracted from the Hospital Episode Statistics (HES) of UKBB. Detailed descriptions of the HES can be found in https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/HospitalEpisodeStatistics.pdf. The inpatient core and diagnoses datasets were updated to 31 Mar 2021 (accessed 20 June 2021). The diagnosis codes and corresponding dates were summarized based on each participant's inpatient record. All the diagnosis codes were converted to 3-character ICD-10 codes. We followed the mapping strategy as described in https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/first_occurrences_outcomes.pdf . The mortality records contain the date and cause of death (ICD10 coded) and are linked to national death registries (please refer to https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/DeathLinkage.pdf). Mortality data were updated to 8 Apr 2021 (accessed 20 June 2021).

The ICD codes for defining each disease outcome were listed in Table S1. The disease outcomes (hospitalization and mortality) studied included coronary artery disease (CAD), chronic kidney disease (CKD), atrial fibrillation (AF), heart failure (HF), hypertension (HTN), stroke, renal failure (RF), type 2 diabetes mellitus (T2DM), venous thromboembolism (VTE), immunodeficiencies, systemic and organ-specific autoimmune diseases, chronic obstructive pulmonary disease (COPD), non-COVID-19 pneumonia (NCP) and dementia.

Only primary causes of admission or mortality were considered. All diagnosis given before the date of first vaccination were regarded as medical history of comorbidities; diagnoses given after the date of first vaccination were treated as new hospitalization/mortality. For better statistical power, we primarily present the results from any hospitalization or mortality from specific diseases. However, we also conducted further stratified analysis on new-onset (subjects with no prior history) and recurrent/relapse diseases (subjects with known history of the disease).

Covariates

We performed multivariable regression analysis with adjustment for covariates including basic demographic variables (age, sex, ethnic group), comorbidities (CAD, stroke, T2DM, HTN, AF, COPD, dementia, history of cancer, chronic kidney disease[CKD], history of pneumonia), risk factors of cardiometabolic disorders (lipids, glucose levels, HbA1c), disorders of the immune system (autoimmune diseases, immunodeficiency, drug history of immunosuppressants), indicators of general health (number of medications prescribed by GP in the past year, number of hospitalizations in the past year, number of non-cancer illnesses), anthropometric measures (body mass index [BMI], waist circumference), socioeconomic status (Townsend Deprivation index) and lifestyle risk factor (smoking status). For disease traits, we included information from Primary care data, Hospital inpatient data, ICD-10 diagnoses (code 41270), and self-reported illnesses (code 20002) and incorporated data from all waves of follow-ups. The strategy of integrating all the diagnosis records were based on information provided by UKBB (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/first_occurrences_outcomes.pdf). Subjects with no records of the relevant disease from any data source were regarded as having no history of the disease.

Covariates were selected based on potential relevance to COVID-19 and/or its complications, based on literature evidence. The full list of covariates is listed in Table S2.

Missing covariate data

Missing values of remaining features were imputed with the R package missRanger. The program is based on missForest, which is an iterative imputation approach based on random forest. It has been widely used and has been shown to produce low imputation errors and good performance in predictive models [20]. The missing rate of each covariate and the OOB (out-of-bag error) of the one-time imputation were listed in Table S3.

COVID-19 infection status

COVID-19 testing data were downloaded from the UKBB data portal. Information regarding COVID-19 data in the UKBB was given at https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=COVID19. Briefly, the latest COVID test results were downloaded on 23 July 2021 (last update 21 Jul 2021). Diagnosis of COVID-19 (ICD code: U071) from hospital inpatient or mortality records were also extracted. Subjects with any positive testing results, diagnosis of COVID-19 (U071) from health records or the "Y2a3b" code within TPP clinical records (https://biobank.ndph.ox.ac.uk/showcase/coding.cgi?id=8708&nl=1) during the follow-up period were regarded as having a history of COVID-19 infection. Untested subjects or subjects without any positive results during the whole follow-up period were treated as uninfected.

Vaccination status definition

Vaccination status was extracted from the TPP General Practice clinical records. Since the type of vaccine was not recorded for most subjects, we did not stratify our analysis based on vaccine type. During the period of study, all subjects received either the BioNTech BNT162b2 or Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine. Also, since only very few events/fatalities were observed within fully vaccinated (i.e., vaccinated with two doses) subjects, we consider vaccination with at least one dose of COVID-19 vaccine as the main exposure.

Statistical analysis

Two types of statistical approaches were employed, namely Cox and Poisson regression. Cox regression models time to development of event, while Poisson regression models the incidence rate (with consideration of follow-up time). Briefly, the time to hospitalization or mortality from the studied diseases was treated as outcome in Cox regression, controlling for other covariates. For Poisson regression, presence/absence of the event of interest was considered as outcome, with 'offset' specified (=number of days of follow-up) to account for the differences in duration of follow-up for each subject. For vaccinated subjects, the start-date was set at the date of first vaccination; for unvaccinated subjects, the start-date was set at 8 Dec 2020, the date COVID-19 vaccines were first deployed in the UK. The end of follow-up was set at 31 Mar 2021 for outcomes related to hospitalization and 8 Apr 2021 for mortality outcomes, as UKBB records were updated up to these dates at the time of analysis. All statistical analysis were performed by R (version number 3.6.1).

Different sets of analysis to check for robustness of findings

We performed a variety of different analyses to verify the robustness of our findings under different modeling strategies and assumptions: (1) While we primarily focused on all hospitalizations/fatalities regardless of past history of the disease, we also conduct stratified analysis for new-onset and recurrent diseases, as described above; (2) for counting the 'start-date', we primarily consider day 0 as the day of vaccination, as it is possible that some side-effects can occur early. However, we also performed another set of analysis with start-date set at 14 days after the 1st vaccination, since the protective effects of vaccines may only be apparent ~2 weeks later; (3) to study whether the associations with CVD and other diseases were affected by infection status, we repeated our analysis controlling for prior infections, and also repeated the analyses limited to those with no recorded history of infection all along. Note that as the subjects were not routinely screened for infection, a substantial proportion of asymptomatic and mild infections might not be captured.

Results

We will primarily our findings with at least one dose of vaccination, and results from Cox regression with start-date defined as the day of (first) vaccination. We first present the results without adjustment for infection status, then those with corresponding adjustment. As described below and in supplementary information, the main findings are mostly robust to different modeling strategies. The results from Cox and Poisson regression models were also very similar. The full results of all analyses are listed in Tables S4 to S13.

Association of hospitalization with COVID-19 vaccination status (at least one dose of vaccine)

The main results are listed in Table 1 and full results in Tables S4 to S5. Considering all hospitalizations (regardless of history of the studied disease), COVID-19 vaccination was significantly associated with reduced hazards of hospitalization due to stroke (hazard ratio [HR]=0.371, 95% CI: 0.254-0.543, p=3.36e-7), VTE (HR=0.485, 95% CI: 0.292-0.804, p=4.99e-3), dementia (HR=0.207, 95% CI 0.091-0.470; p=1.66e-4) and non-COVID-19 pneumonia (NCP) (HR=0.482, 95% CI 0.313-0.742; p=9.18e-4). Lower rates of hospitalizations were also observed for COPD (HR=0.521, 95% CI 0.263-1.032), but the result fell short of statistical significance with a marginal p=0.061.

Restricting the outcome to hospitalizations due to *new-onset* diseases (i.e. without prior history), we observed that vaccination was associated with reduced hazards of hospitalizations from stroke (HR=0.400, CI: 0.255-0.627; p=6.35e-5), renal failure (HR=0.165, CI: 0.051-0.533; p=2.61e-3) and NCP (HR=0.387, CI 0.223-0.670; p=6.98e-4). Note that the number of events was too small for further analyses for some diseases. On the other hand, if we consider hospitalizations due to *recurrent* disease (i.e. those with known history of the disease) as outcome, vaccination was associated with decreased hospitalization hazards due to stroke (HR=0.314, CI:0.150-0.655; p=2.04e-3), VTE (HR=0.284, CI:0.121-0.664, p=3.68e-3) and dementia (HR=0.149, CI:0.061-0.368; p=3.54e-5). In general, the protective associations were more prominent in recurrent cases when compared to all hospitalizations without consideration of past history.

We also repeated the analysis using Poisson regression which models the incidence rate of hospitalization. The results were similar to those from Cox regression, with similar significant associations observed (Table S4-5).

With consideration of infection status

Restricted to subjects with no known history of COVID-19

We repeated the analysis, limiting the subjects to those with no known history of COVID-19 infection all along (Table S6-7). Considering all hospitalizations, vaccination was associated with reduced hospitalization hazards for stroke (HR=0.434, CI:0.288-0.655; p=6.96e-5), NCP (HR=0.533, CI:0.336-0.843, p=7.23e-3) and VTE (HR=0.554, CI:0.330-0.932; p=2.6e-2); however, the previous associations with reduced risks of dementia were no longer significant (p>0.05). The effect sizes were attenuated compared to previous estimates and the level of statistical significance were generally weaker.

Considering hospitalizations from new-onset diseases, vaccination was associated with reduced hazards for stroke (HR=0.431, CI:0.269-0.693; p=5.01e-4), NCP (HR=0.441, CI:0.241-0.806; p=7.74e-3) and renal failure (HR=0.232, CI:0.062-0.869; p=3.01e-2). Considering hospitalizations within patients with known history of the disease, we observed associations of vaccination with lower hazards of VTE (HR=0.267, CI:0.109-0.652; p=3.74e-3) and dementia (HR=0.277, CI:0.093-0.825; p=2.11e-2). Again, results from Poisson models are largely similar.

Adjusting for infection status in regression model

The results adjusted for infection status were similar to the above (Tables S8-9). For all hospitalizations, reduced hazards for stroke, VTE, NCP and dementia were observed. The same pattern of association was also seen for hospitalizations from recurrent disease. For hospitalizations from new-onset diseases, we observed reduced hazards for stroke, renal failure and NCP.

Association of cause-specific and all-cause mortality with COVID-19 vaccination status

Cause-specific mortality

The main results are shown in Table 2 and full results in Tables S10-13. We primarily considered mortality regardless of history of the studied diseases, since there are very few events among those without prior history. We observed that vaccination was associated with significantly reduced hazards of mortality with CAD (HR=0.190, CI:0.093-0.389; p=5.25e-6), COPD (HR=0.065, CI:0.017-0.250; p=7.02e-5), stroke (HR=0.161, CI:0.061-0.430; p=2.63e-4) and dementia (HR=0.140, CI:0.073-0.269; p=3.24e-9). Significant associations with the same set of diseases were observed with Poisson regression. We observed similar results when prior infection status was controlled for (Table S12) or limiting the analysis to those with no known record of COVID-19 infection (Table S11).

For example, if we restrict the analysis to subjects with no known history of infection (Tables S11), we observed significantly lower hazards with CAD (HR=0.174, CI:0.083-0.367; p=4.37e-6), COPD (HR=0.080, CI:0.020-0.316; p=3.24e-4), stroke (HR=0.167, CI:0.060-0.459; p=5.37e-4) and dementia (HR=0.174, CI:0.077-0.394; p=2.69e-5). Similar results were observed if infection status was controlled for.

CVD mortality and all-cause mortality

We then considered mortality specific to cardiovascular diseases (ICD-10 code I00–I99) (Table S13). Vaccination was associated with significantly lower CVD mortalities (HR=0.092, CI:0.070-0.122; p=1.89e-62). The result was similar when

the analysis was restricted to subjects with no infection history or conducted with adjustment for infection status. Of note, known history of infection was associated with significantly higher CVD-specific mortality (HR=7.39, CI:5.559-9.827; p=4.18e-43), after controlling other covariates.

For all-cause mortality, vaccination was associated with significantly reduced all-cause mortality (HR=0.090, CI:0.074-0.108; p=2.27e-124), with similar estimates when adjusted for infection status.

We also repeated all analysis with the start date set at 14 days after (first) vaccination, as the vaccine may take longer to exert protective effects for COVID-19 infection. The results are largely similar and are shown in the supplementary tables.

Discussions

Overview of main findings

Overall, we observed that COVID-19 vaccinations (at least one dose) was associated with lower risks of hospitalizations and mortality from several diseases in short-term follow-up. In particular, reduced hospitalizations for stroke, VTE, NCP and dementia were consistently observed across different analyses. Regarding mortalities, an association with lower all-cause and CVD-specific mortality was observed, as well as lower mortality from several diseases including stroke, CAD, COPD and dementia. In general, there is no evidence that vaccination was associated with increased hospitalization or fatality from any specific disorders, providing further support for the safety of the vaccines.

Interpretation of findings and comparison to previous studies

There is unequivocal evidence that both the BioNTech and Oxford-AstraZeneca vaccines were effective in reducing the risks of COVID-19 infection and severe disease, and partially vaccinated individuals are also protected, especially against severe disease[21,22]. There has also been mounting evidence that COVID-19 is associated a range of sequelae[23,24]. For instance, there is strong evidence that COVID-19 is associated with elevated risks of stroke[25,26] and VTE[16], and a recent study also suggested particularly elevated risks of mortality due to dementia, among all possible neuropsychiatric sequelae[18]. COVID-19 is also associated with higher cardiovascular and all-cause mortality, up to 6 months after the infection[24]. Taken together, COVID-19 vaccines might protect against hospitalization/mortality from the above disorders, possibly via reduction of the risks of infection and severe disease.

Analogy may be drawn with influenza vaccinations. As also described in the introduction section, a number of studies have shown that flu vaccination was associated with reduced cardiovascular risks and mortality, as well as all-cause mortality.

Interestingly, we observed that the protective associations for several diseases (including stroke, VTE and NCP) remained after adjustment for infection status, or restriction to subjects with no known history of infection (although the effect sizes were generally attenuated). We speculate one possible explanation is that people with mild or moderate infections may not get tested, but such infections can still be associated with elevated risks of complications compared to the non-infected population[24]. COVID-19 vaccination also protects against mild and even asymptomatic infections[22,27] and hence may also protect against the corresponding complications. An alternative possibility is that the vaccine may also provide beneficial

effects via other mechanisms beyond protection from infection. For flu vaccines, pre-clinical studies have shown that flu vaccines may stabilize atherosclerotic plaques and lead to increased nitric oxide production[12]. However, the exact mechanisms still require further investigations.

Strengths and limitations

This study is based on a relatively large sample with detailed phenotypic information and health records. We have conducted a comprehensive analysis covering a range of cardiovascular and other relevant diseases. We have also conducted analyses with different statistical models to evaluate if the findings are robust to different modeling strategies. To our knowledge, this is the first comprehensive study to investigate the association of COVID-19 vaccination with hospitalization/mortality for a wide range of diseases.

There are several imitations of the present study. First and foremost, this is a real-world observational study without randomization of vaccination. As such, residual confounding cannot be excluded, and our results should not be regarded as confirmatory evidence of causal relationships between vaccination and the diseases under study. We have controlled for a wide range of covariates such as general health and comorbidities, but residual confounding is still likely present. For example, some subjects may not be vaccinated due to frailty or worry about their underlying conditions, but on the other hand underlying medical conditions may also motivate vaccinations in view of higher risks from COVID-19 complications. The effect size estimates may also be affected by residual confounding. For example, in this analysis, vaccination was associated with a relatively large reduction in cause-specific or all-cause mortality However, we caution that the effect sizes could be over-estimated due to residual confounding. Other possible confounders may include differences in health consciousness or other health-seeking behaviors between the vaccinated and non-vaccinated groups. Nevertheless, a reassuring finding is that we did not observe unanimously significant effects of vaccination for all diseases; the associations appeared to be consistent and specific to a few diseases. Yet another point to note is that this study focused on events occurring in Dec 2020 - Mar 2021, which coincide with a period of high COVID-19 incidence in the UK. The reduction in hospitalization/mortality is likely to be larger during periods of higher infection rate.

Another limitation is that while other total sample size is large, the number of events is still small in view of short period of follow-up. The effect size estimates (especially for mortality) generally had relatively wide confidence intervals and should be interpreted with care. Also due to relatively short follow-ups, longer-term effects of vaccinations cannot be addressed in this study. A related limitation is that few events were observed in fully vaccinated individuals, and therefore we decided to focus on the effects of at least one dose of vaccine. In addition, we could not retrieve the type of vaccine (BioNTech or Oxford-AstraZeneca) for most subjects; practically, stratified analysis may also further reduce statistical power due to limited number of events. The emergence of viral variants, such as the delta variant, may also affect the efficacy of vaccines[28] but variant information is currently unavailable in the UKBB. We note that the delta-variant was not the mainstream variant during the follow-up period in our analyses. Finally, the UKBB may not be representative of the entire UK population, as participants are generally healthier and of higher socioeconomic status than non-participants[29]. Also, the generalizability of the findings to other types of COVID-19 vaccines and other populations (e.g. different age groups and ethnicities) remains to be studied.

Conclusions

In conclusion, the current study suggests that COVID-19 vaccination may protect against hospitalization and mortality from several diseases, such as stroke, VTE, NCP, COPD and dementia. There is tentative evidence of an association between vaccination and reduction in CVD-related and all-cause mortality. We observe no evidence of increased risks of hospitalization/mortality for the diseases under study. Taken together, this study provides further support to the safety and benefits of COVID-19 vaccination, and such benefits may be beyond reduction of infection risk or disease severity per se. As an observational study, causal relationship cannot be concluded and further replications are required to verify the findings.

Author Contributions

Conception and design: HCS (lead), with input from YX and YF. Study supervision: HCS. Funding acquisition: HCS. Methodology: HCS (lead), YX. Data curation: YX (lead), YF, JQ. Data analysis: YX (lead), YF, JQ. Data interpretation: HCS, YX, YF. Preparation of first draft of manuscript: HCS (lead), YX, with input from YF and JQ.

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Supplementary Information

All supplementary Tables and notes are available at the journal's website and at https://drive.google.com/drive/folders/1IlhuvKJf1JdjLYUojoOo2alpnDIV4-mL?usp=sharing

Conflicts of interest

The authors declare no conflict of interest.

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