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Incidence and individual risk prediction of post-COVID-19 cardiovascular disease in the general population: a multivariable prediction model development and validation study

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Aims Previous studies suggest relatively increased cardiovascular risk after COVID-19 infection. This study assessed incidence and explored individual risk and timing of cardiovascular disease occurring post-COVID-19 in a large primary care database.

Methods and results Data were extracted from the UK's Clinical Practice Research Datalink. Incidence rates within 180 days post-infection were estimated for arterial or venous events, inflammatory heart disease, and new-onset atrial fibrillation or heart failure. Next, multivariable logistic regression models were developed on 220 751 adults with COVID-19 infection before 1 December 2020 using age, sex and traditional cardiovascular risk factors. All models were externally validated in (i) 138 034 vaccinated and (ii) 503 404 unvaccinated adults with a first COVID-19 infection after 1 December 2020. Discriminative performance and calibration were evaluated with internal and external validation. Increased incidence rates were observed up to 60 days after COVID-19 infection for venous and arterial cardiovascular events and new-onset atrial fibrillation, but not for inflammatory heart disease or heart failure, with the highest rate for venous events (13 per 1000 person-years). The best prediction models had *c*-statistics of 0.90 or higher. However, <5% of adults had a predicted 180-day outcome-specific risk larger than 1%. These rare outcomes complicated calibration.

Conclusion Risks of arterial and venous cardiovascular events and new-onset atrial fibrillation are increased within the first 60 days after COVID-19 infection in the general population. Models' *c*-statistics suggest high discrimination, but because of the very low absolute risks, they are insufficient to inform individual risk management.

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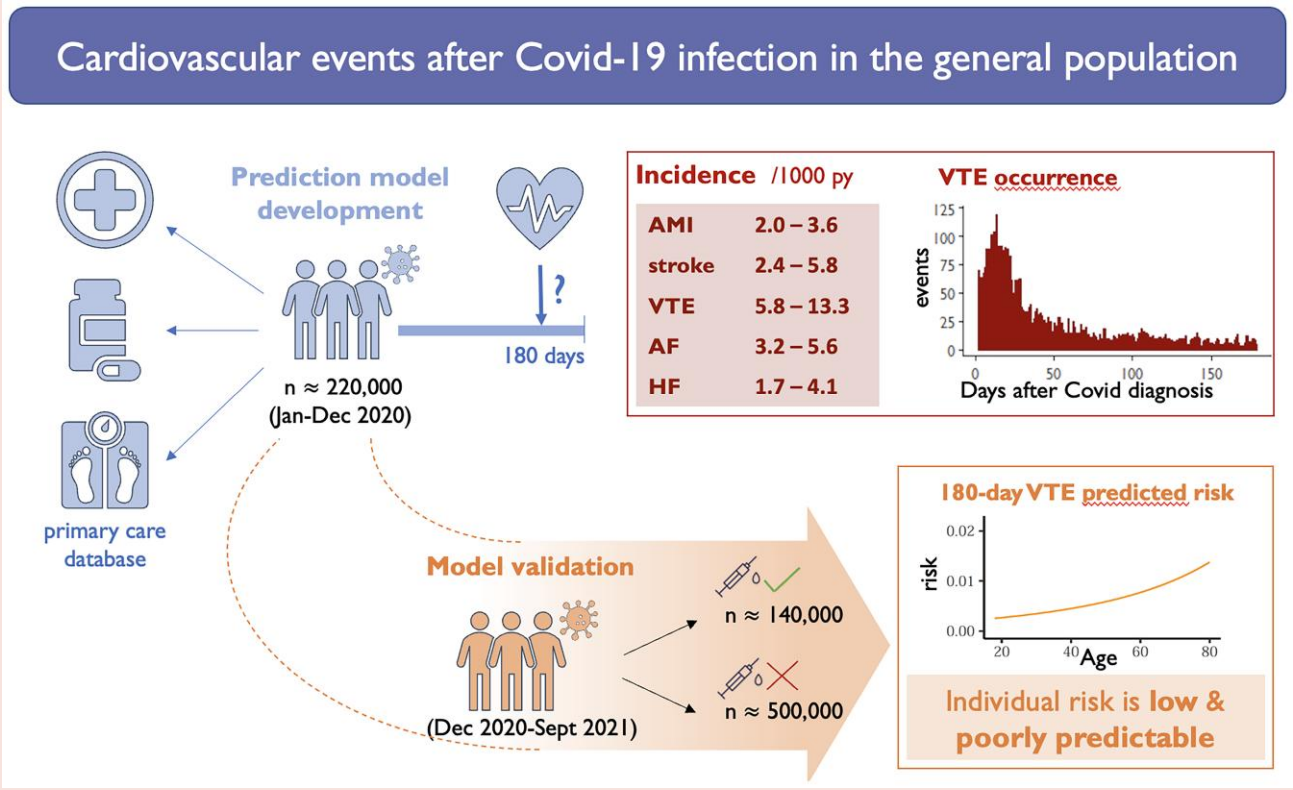
Graphical Abstract



Abbreviations: py, person-years; AMI, acute myocardial infarction; VTE, venous thrombo-embolic events; AF, new-onset atrial fibrillation; HF, new-onset heart failure

Keywords Cardiovascular disease • COVID-19 • Primary care

Introduction

Patients hospitalized with COVID-19 infection have been described to have an increased risk of cardiovascular diseases (CVD).[1] Case-control and self-controlled studies have reported associations between COVID-19 and subsequent stroke, myocardial infarction, venous thrombo-embolic events, heart failure, atrial fibrillation, pericarditis, and myocarditis.[2–8] Several pathophysiological explanations for CVD development after COVID-19 infection have been described, albeit the exact underlying mechanisms have yet to be elucidated.[2,9,10] The disease burden of post-COVID-19 CVD from a population perspective is substantial. For example, at 10% COVID-19 prevalence, England had an estimated 60 000 excess deaths due to CVD as a direct effect of COVID-19 infections.[11]

The increased risk of CVD has also been observed in COVID-19-infected individuals who did not require hospitalization.[4] Although CVD risk in non-hospitalized COVID-19 patients is lower compared with hospitalized COVID-19 patients, the potential impact of post-infection CVD in non-hospitalized COVID-19 patients may be substantial at a population level. Worldwide, even though COVID-19 hospitalizations and associated mortality rates are decreasing, infection rates are sustainably high despite global vaccination campaigns.[12] In many Western countries, COVID-19 reaches an endemic plateau phase, and as such, there will be a sustained viral burden in society.[12] Consequently, this pertained viral COVID-19 burden may continuously drive an excess in CVD rates, yet its impact will currently be unknown.

Mitigating CVD risk in a not (yet) hospitalized population with COVID-19 by means of preventive strategies may offer great opportunities for cardiovascular health. However, it requires knowledge on absolute CVD event rates in relation to the timing of COVID-19 infection, as well as preferably methods to identify individuals with a relevantly high risk. Currently, evidence for post-COVID-19 CVD risk is based upon relatively small cohorts, in selected settings such as hospitalized COVID-19 patients or elderly. Moreover, inferences from these studies have not been externally validated.[13–17] Finally, these studies had not to deal with very low incidence rates which easily hamper individual risk prediction.

Therefore, this study was performed to estimate incidence and to explore individual risk prediction of post-COVID-19 CVD in the general population. Hereto, we first estimated event rates of various post-COVID-19 CVD events and related these to the timing since infection. Secondly, we developed prediction models for all types of CVD events in individuals infected during the first and second COVID-19 waves and validated these models in later stages of the pandemic in both vaccinated and unvaccinated populations.

Methods

Design and data source

We used pseudonymized primary care data from the Clinical Practice Research Datalink (CPRD) Aurum database, released May 2022.[18] This database contains longitudinal electronic health records from more than 40

million general practice-subscribed people in the UK, from which more than 13 million are currently registered. Available data include demographics, lifestyle factors (e.g. smoking status), medical history, and medication prescriptions, including COVID-19 vaccination data. Longitudinal data until 17 March 2022 were available. The study was approved and waived from formal ethical committee review by the CPRD ISAC Committee (protocol 20_000198). The transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines for reporting prediction model development and validation studies were followed.[19]

Study population

All adults with a first diagnosis of COVID-19 in the period of 29 January 2020 (the first reported case of COVID-19 in the UK)[20] till 18 September 2021 (to enable 180 days of follow-up) were included. We defined COVID-19 diagnosis as having a CPRD Aurum COVID-19 Medcode[21] classified 'Diagnosis' or 'Diagnosis/Tested',[21] and judged to represent an actual diagnosis of acute COVID-19 infection by the researchers. That is, codes with descriptions such as 'Post-COVID-19 Syndrome' or 'Assessment using COVID-19 severity scale' were excluded. For individuals with multiple episodes of COVID-19, the diagnosis date of the first acute COVID-19 infection was taken as index date. We excluded individuals with missing or post-mortem COVID-19 diagnosis date, missing age or sex, or with <1 day of available follow-up.

Predictors

Predictors included age, sex, medical history, smoking status, body mass index (BMI), and medication prescriptions as recorded in CPRD Aurum. Baseline medical history included all diagnoses from a pre-selected list of relevant comorbidities. Diagnoses were listed into disease categories by four clinician–researchers (see Supplementary material online, File *S1*). Participants were assigned a baseline comorbidity if they had any of the listed diagnosis codes recorded before or on the index date. Smoking status was defined as the last of any historical smoking status (current smoker, former smoker, and non-smoker) known before the index date, otherwise as the first status known within 30 days after the index date, otherwise as missing. For BMI only, values between 14 and 50 were considered to prevent misclassification. The last of any historical value before the index date was taken, otherwise a value with missing date; otherwise, BMI was considered missing. Obesity was defined as a BMI of 30 or higher. Vaccination count numbers entailed all COVID-19 vaccinations of any manufacturer or vaccine type with a unique issue date of at least 14 days prior to the index date. Baseline medication use was defined as medication of interest prescribed within 45 days prior to the index date (see Supplementary material online, File *S2* for included drug product codes). Anticoagulant use included the use of direct oral anticoagulants, vitamin K antagonists, and/or heparin. Baseline diabetes included a diagnosis of diabetes type 1, diabetes type 2, gestational diabetes, and/or use of any diabetes-related medication. Baseline dyslipidaemia included a diagnosis of dyslipidaemia and/or the use of lipid-lowering medication.

Outcomes

The following CVD events occurring within 180 days after COVID-19 diagnosis were extracted from CPRD Aurum: acute myocardial infarction, instable angina pectoris, stroke, transient ischaemic accident, pulmonary embolism, deep venous thrombosis, atrial fibrillation, heart failure, pericarditis, and myocarditis. Supplementary material online, *File S1* lists the included Medcodes; recordings of codes marked with an asterisk indicating 'history of disease' were only used for baseline comorbidity encoding and not included as outcomes. Only the first occurrence of each outcome was included. For new-onset heart failure and new-onset atrial fibrillation, the outcomes were defined as a first recorded diagnosis. Participants with a previously recorded diagnosis of heart failure or atrial fibrillation were therefore excluded from the study population in the analysis for new-onset heart failure or atrial fibrillation, respectively. If the outcome of interest was encoded within 7 days after death, the outcome was considered a post-mortem–diagnosed cause of death and therefore it was recoded to the date of death. If the outcome of interest or death was encoded within 7 days after practice deregistration, registration end date was recoded to include the outcome. Initial data analysis showed a large peek in events at the day of COVID-19 diagnosis for all outcomes (see Supplementary material online, *Figure S1*), likely driven by an accidental positive COVID-19 test at the moment of hospital admission. Therefore, we decided post-hoc to only include outcomes with an event date at least 1 day after the index date to ensure that COVID-19 diagnosis preceded the outcome. For the calculation of incidence rates, individuals' follow-up times were calculated as the number of days until practice deregistration, death, last collection date for the practice, or a maximum of 180 days (whichever occurred first). The maximum follow-up period of 180 days was chosen as this is the time window in which post-COVID-19 CVD incidence rates stabilize in previous reportings.[22] Subjects were not censored in case of a second COVID-19 diagnosis during the 180 days of follow-up. Five composite CVD outcomes were defined a priori for prediction model development: atherosclerotic events (including stroke, transient ischaemic accident, and acute coronary syndrome), venous thrombo-embolism (including deep vein thrombosis and pulmonary embolism), new-onset heart failure, new-onset atrial fibrillation, and inflammatory heart disease (including pericarditis and myocarditis). Models were developed for each composite outcome separately, to predict on a binary scale whether the composite outcome occurred within 180 days or not for each individual.

Descriptives and missing data

Baseline characteristics of the study population were summarized using mean and standard deviation (SD), median and interquartile range (IQR), or counts and percentages, reporting 95% confidence intervals (95% CI). Diagnostic codes with unspecified observation date were considered baseline comorbidity; prescriptions with unspecified date were excluded. Strategies to account for missing data on BMI and smoking status were not specified a priori, but single and multiple imputation were considered depending on the characteristics of the missing data.

Incidence

The incidence rates per 1000 person-years including 95% CI were calculated for each outcome using a maximum follow-up period of 180 days per participant. For the participants who developed an outcome, the time of occurrence was plotted as days after COVID-19 diagnosis and summarized using median and IQR.

Prediction model development and internal validation

Adults with COVID-19 diagnosis during the first or second wave (up to 1 December 2020) were included in the model development cohort. The first two COVID-19 waves were chosen, because in this era the widespread COVID-19 vaccination campaigns had not started yet. Multivariable logistic regression models were used to explore the predictive performance of three sets of candidate predictors for each of the five outcomes: (i) a simple model including age, sex, and the interaction between age and sex; (ii) a general model, extending the simple model with hypertension, diabetes, smoking, dyslipidaemia, obesity, and the medical history of each of the outcomes; and (iii) an extended model, extending the general model with three to five outcome-specific predictors. Candidate predictors were selected by general practitioner–researchers based on reported prognostic factors according to clinical guidelines, existing risk scores, previous literature,[8,23] and expert knowledge. Age was modelled using a restricted cubic spline function with four knots on the percentiles 0.05, 0.35, 0.65, and 0.95, to account for possible non-linearity. Other predictors were modelled as binary variables. Models were penalized with equal parts of lasso and ridge regression (elastic net regression, alpha = 0.5) to mitigate the risk of overfitting. We used 10-fold cross-validation to estimate the tuning parameter (often described as lambda) that minimized the cross-validated deviance. Internal validation was performed with a 10-fold cross-validation on the development cohort.

External validation

Two validation cohorts were established: one cohort including all adults with a first COVID-19 diagnosis after 1 December 2020 who had not received any vaccination yet (temporal validation cohort, 'unvaccinated')

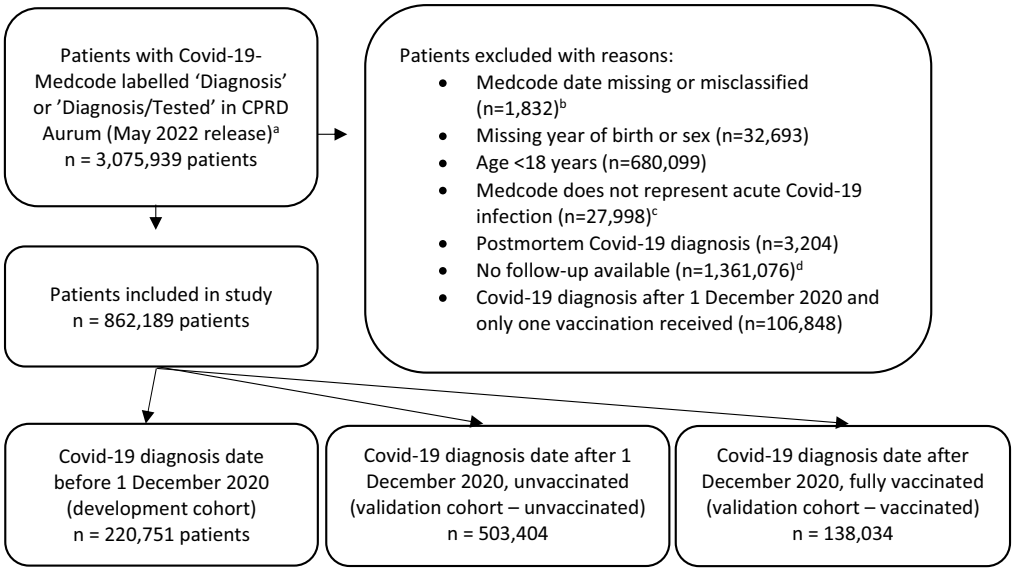


Figure 1 Flowchart of study population selection. [a]Does not include COVID-19 Medcodes labelled 'Advice', 'Possible', 'Tested' (without positive result), or 'Vaccination'. [b]COVID-19 diagnosis dates were considered misclassified if they occurred before 29 January 2020 or after 17 March 2022. [c]For example, diagnosis codes referring to history of COVID-19, post-COVID-syndrome, or severity scales. [d]Only diagnoses up to 18 September 2021 were included to enable follow-up of 180 days with the available data; patients could have <180 days of follow-up if they left the registry at an earlier point in time; however, at least 1 day of available follow-up was required for inclusion.

and another cohort including all adults with a first COVID-19 diagnosis after 1 December 2020 who had received at least two vaccinations (temporal validation cohort, 'vaccinated'). We applied all models to both validation cohorts and evaluated for each model and validation set separately the areas under the curve (AUC)/*c*-statistic, calibration intercept, calibration slope, Cox–Snell pseudo-R squared (R^2_{cs}), and Brier score.[24] R^2_{cs} and Brier score CIs were based on 0.025 and 0.975 percentile scores after bootstrapping with 1000 repetitions. We used the Delong method for *c*-statistic CIs. Calibration curves were smoothed using locally estimated scatterplot smoothing (LOESS).

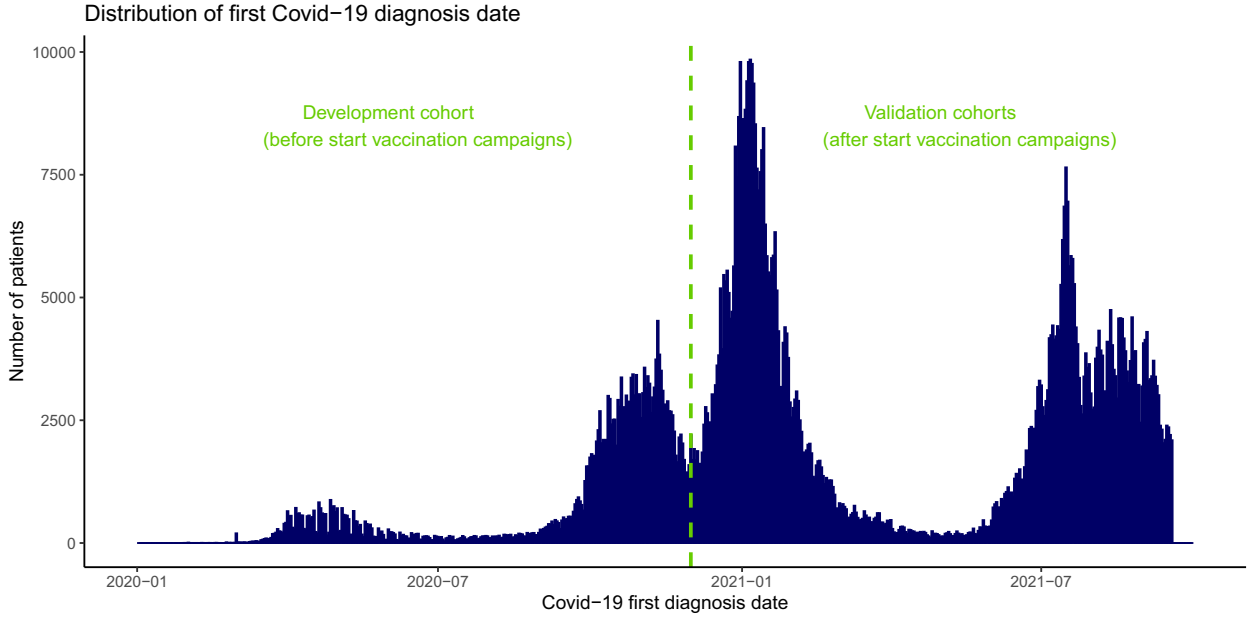


Figure 2 Distribution of first COVID-19 diagnosis date. The dashed line situated at 1 December 2020 represents the start of national vaccination campaigns in the UK.

Sample size

Cohort sizes were based on data availability. We determined the maximum number of candidate predictor parameters for each outcome by the number of events in the development cohort, using algorithms from Riley and colleagues.[25–27] Given the cohort size, event fraction, a desired shrinkage of maximal 10%, and an assumed *c*-statistic of 0.75, the models for atherosclerotic events, venous thrombo-embolic events, heart failure, atrial fibrillation, and inflammatory heart disease allowed for 122, 132, 43, 56, and 7 candidate predictor parameters, respectively. Cohort size was therefore deemed insufficient to fit models for inflammatory heart disease but sufficient to fit all other anticipated models.

Software

All data cleaning and analyses were performed in R version 4.2.2. Packages *pmsampsize*, *tableone*, *epiR*, *rms*, *glmnet*, *pROC*, *DescTools*, and *CalibrationCurves* were used.

Results

Study population

We included 862 189 adults from 34 824 unique general practitioners in the study (*Figure 1*). Of them, 220 751 with a first COVID-19

Table 1 Baseline characteristics of study population

	Development cohort	Validation cohort (unvaccinated)	Validation cohort (vaccinated)
Demographics			
Age (years), mean (SD)	44.9 (20.0)	40.4 (17.2)	48.3 (15.9)
Female, *n* (%)	123 169 (55.8)	269 312 (53.5)	76 445 (55.4)
Lifestyle factors			
Body mass index (kg/m^2), median (IQR)	26.3 (22.8, 30.7)	26.0 (22.5, 30.2)	26.9 (23.6, 31.2)
Smoker, *n* (%)	42 919 (19.4)	114 602 (22.8)	28 337 (20.5)
Medical history, n (%)			
Hypertension	42 952 (19.5)	66 188 (13.1)	27 404 (19.9)
Dyslipidaemia	31 961 (14.5)	48 743 (9.7)	20 974 (15.2)
Diabetes	21 243 (9.6)	34 845 (6.9)	13 066 (9.5)
Stroke/transient ischaemic attack	7020 (3.2)	7995 (1.6)	2816 (2.0)
Acute coronary syndrome	5305 (2.4)	6338 (1.3)	2532 (1.8)
Peripheral artery disease	1844 (0.8)	1970 (0.4)	696 (0.5)
Pulmonary embolism	2637 (1.2)	3670 (0.7)	1304 (0.9)
Deep venous thrombosis	3785 (1.7)	5561 (1.1)	2239 (1.6)
Atrial fibrillation	7835 (3.5)	8496 (1.7)	3215 (2.3)
Heart failure	4230 (1.9)	4452 (0.9)	1482 (1.1)
Pericarditis	454 (0.2)	941 (0.2)	353 (0.3)
Myocarditis	156 (0.1)	278 (0.1)	106 (0.1)
Cancer	13 644 (6.2)	18 074 (3.6)	8791 (6.4)
COPD	5909 (2.7)	6806 (1.4)	3052 (2.2)
Chronic kidney disease	15 181 (6.9)	18 698 (3.7)	7063 (5.1)
Rheumatic disease	8435 (3.8)	12 812 (2.5)	5742 (4.2)
Coagulation disorder	2377 (1.1)	4519 (0.9)	1513 (1.1)
Current medication use, n (%)			
Antiplatelet drug	10 721 (4.9)	13 495 (2.7)	5663 (4.1)
DOAC	5183 (2.3)	5842 (1.2)	2332 (1.7)
Vitamin K antagonist	1166 (0.5)	1270 (0.3)	616 (0.4)
Heparin	166 (0.1)	230 (<0.1)	56 (<0.1)
Vasodilators	3978 (1.8)	5940 (1.2)	2696 (2.0)
RAAS inhibitor	19 665 (8.9)	30 125 (6.0)	14 274 (10.3)
Calcium antagonist	15 125 (6.9)	22 998 (4.6)	10 086 (7.3)
Beta-blocker	13 487 (6.1)	19 234 (3.8)	7904 (5.7)
Number of COVID-19 vaccinations (%)			
No vaccination	220 710 (100.0)	503 404 (100.0)	—
One vaccination	21 (<0.1)	—	—
Two vaccinations	20 (<0.1)	—	137 683 (99.7)
Three or more vaccinations	0	—	351 (0.2)
Duration of follow-up			
Follow-up (days), median (IQR)	503 (483, 527)	418 (257, 438)	213 (195, 239)
180 days follow-up available, *n* (%)	203 744 (92.3)	470 455 (93.5)	130 517 (94.6)

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulants; RAAS, renin–angiotensin–aldosterone system.

diagnosis before 1 December 2020 were included in the development cohort. The other individuals were included in the validation cohorts according to their vaccination status (*Figures 1* and *2*). Baseline characteristics of the study population are shown in *Table 1*. Mean age in the development cohort was 45 years (SD = 20). Risk factors for CVD were prevalent: about 25% was obese, about 20% was current smoker, about 20% had a diagnosis of hypertension, about 15% had dyslipidaemia or currently used lipid-lowering medication, and about 10% had diabetes. Furthermore, 5.6% had a history of atherosclerotic events, 2.7% a history of venous thrombo-embolic events, and 10.2% a history of any CVD (including atherosclerotic events, peripheral artery disease, venous thrombo-embolic events, atrial fibrillation, and heart failure). On average, the vaccinated validation cohort resembled the development cohort more than the unvaccinated validation cohort. Within the validation cohorts, unvaccinated individuals were on average younger, had less comorbidities and medication use, and were more likely to smoke, compared with the vaccinated cohort (*Table 1*). Of all individuals with a COVID-19 infection before 18 September 2021 (including the development cohort, both validation cohorts, and all individuals with only one vaccination before COVID-19 infection), 84.4% had received at least one COVID-19 vaccination by 17 March 2022. Vaccinations were mainly from Pfizer (38.3%), AstraZeneca (59.6%), or Moderna (2.1%); all other manufacturers accounted for <0.1% to the administered vaccinations. Missing data on smoking status (5.9%) and BMI (10.9%) mainly concerned healthy individuals (see Supplementary material online, *Tables S1* and *S2*). We therefore imputed these values as no current smoker and non-obese for further analyses.

Incidence of cardiovascular disease

Occurrences of CVD after COVID-19 diagnosis are plotted over time in *Figure 3*. The 180-day incidence rates and the number of days after COVID-19 diagnosis until occurrence are shown in *Table 2*. Occurrences of venous thrombo-embolic events, and to a lesser extent also of atherosclerotic events and new-onset atrial fibrillation, were increased within the first 60 days after COVID-19 diagnosis. This pattern was not observed for new-onset heart failure or inflammatory heart disease, albeit absolute numbers were low for the latter outcome. Incidence rates were higher in the development cohort compared with the validation cohorts. The majority of venous thrombo-embolic events occurred within 1 month after COVID-19 diagnosis in the development cohort and unvaccinated validation cohort, whereas the other types of cardiovascular events occurred later on average, yet still within 60 days after COVID-19 diagnosis [*Table 2*, median (IQR) days after COVID-19]. When comparing both validation cohorts, events seemed to occur on average later in the vaccinated cohort. However, on average, incidence rates were similar, except for pulmonary embolism which seemed to occur less frequently in the vaccinated cohort.

Development and validation of prediction models

Twelve prediction models were fit. Models were named according to their outcome and the candidate predictors: only age, sex, and their interaction (model 1, e.g. AE1 for the outcome atherosclerotic events), adding general predictors of CVD (model 2, e.g. AE2), and additional outcome-specific predictors (model 3, e.g. AE3). Penalized logistic regression coefficients are shown in Supplementary material online, *Table S3*. Supplementary material online, *Table S4* contains all performance estimates for all models upon internal validation and in both validation cohorts. Supplementary material online, *Figures S2* and *S3* show calibration plots for the unvaccinated and vaccinated validation cohorts, respectively. Supplementary material online, *Table S5* provides the median (range), 0.95, 0.99, and 0.999 percentiles of predicted risks. Here,

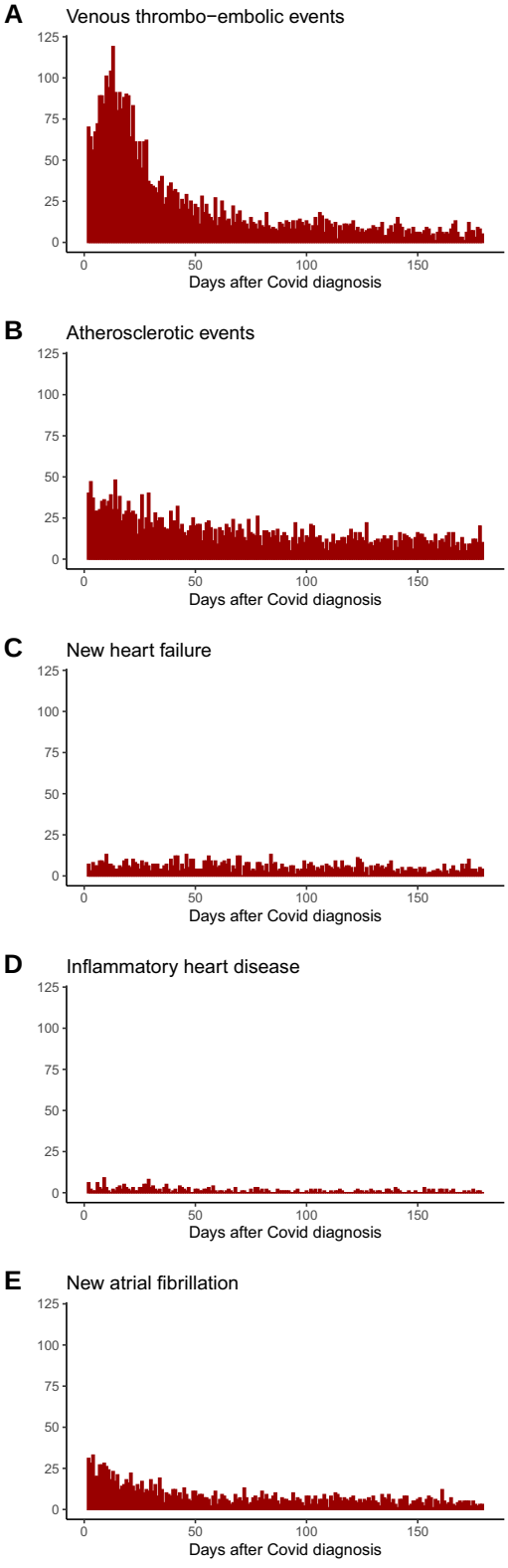


Figure 3 Occurrence of (*A*) venous thrombo-embolic events, (*B*) atherosclerotic events, (*C*) new-onset heart failure, (*D*) inflammatory heart disease, and (*E*) new-onset atrial fibrillation in days after COVID-19 diagnosis. On the vertical axis, the number of events per single day is displayed.

Table 2 Incidence of cardiovascular events within 180 days after first COVID-19 diagnosis

Cohort	Development		Validation (unvaccinated)		Validation (vaccinated)	
	Incidence (/1000 py)	Days after COVID-19, median (IQR) (*n* = events)	Incidence (/1000 py)	Days after COVID-19, median (IQR) (*n* = events)	Incidence (/1000 py)	Days after COVID-19, median (IQR) (*n* = events)
Atherosclerotic events						
AMI	3.6 (3.2, 4.0)	53 (18–102), *n* = 370	2.0 (1.9, 2.2)	61 (22–117), *n* = 488	2.3 (1.9, 2.7)	72 (31–118), *n* = 150
IAP	1.2 (1.0, 1.5)	56 (24–112), *n* = 127	0.7 (0.6, 0.8)	57 (19–112), *n* = 160	0.9 (0.7, 1.1)	65 (26–113), *n* = 57
Stroke	5.8 (5.4, 6.3)	57 (23–102), *n* = 605	2.4 (2.2, 2.6)	50 (21–106), *n* = 567	2.4 (2.0, 2.8)	81 (48–124), *n* = 157
TIA	2.0 (1.8, 2.3)	81 (35–132), *n* = 209	1.1 (1.0, 1.3)	74 (29–129), *n* = 269	1.8 (1.5, 2.2)	74 (34–130), *n* = 121
Overall	12.1 (11.4, 12.7)	57 (23–103), *n* = 1246	6.0 (5.7, 6.3)	57 (22–116), *n* = 1427	7.0 (6.3, 7.6)	73 (34–124), *n* = 460
Venous thrombo-embolic events						
PE	9.4 (8.8, 10.0)	24 (11–61), *n* = 966	7.7 (7.3, 8)	20 (11–44), *n* = 1821	3.7 (3.3, 4.2)	38 (15–96), *n* = 245
DVT	4.4 (4.0, 4.8)	45 (20–103), *n* = 453	2.7 (2.5, 2.9)	42 (21–94), *n* = 650	2.2 (1.9, 2.6)	72 (34–115), *n* = 146
Overall	13.3 (12.6, 14)	28 (13–71), *n* = 1369	10.1 (9.7, 10.5)	24 (13–55), *n* = 2394	5.8 (5.3, 6.4)	50 (19–106), *n* = 386
Heart failure[a]	4.1 (3.7, 4.5)	70 (36–120), *n* = 418	2.1 (1.9, 2.3)	76 (40–123), *n* = 497	1.7 (1.4, 2.1)	77 (38–117), *n* = 114
Atrial fibrillation[b]	5.6 (5.2, 6.1)	44 (15–101), *n* = 564	3.2 (3.0, 3.5)	43 (15–100), *n* = 757	3.2 (2.8, 3.6)	82 (38–124), *n* = 206
Inflammatory heart disease						
Pericarditis	0.5 (0.3, 0.6)	51 (18–113), *n* = 49	0.4 (0.3, 0.4)	39 (22–85), *n* = 84	0.3 (0.2, 0.4)	110 (52–150), *n* = 18
Myocarditis	0.4 (0.3, 0.5)	37 (25–81), *n* = 42	0.2 (0.2, 0.3)	48 (18–101), *n* = 58	0.1 (0.1, 0.2)	28 (14–47), *n* = 8
Overall	0.8 (0.7, 1.0)	44 (20–91), *n* = 86	0.6 (0.5, 0.7)	41 (18–94), *n* = 139	0.4 (0.3, 0.6)	76 (30–141), *n* = 26

AMI, acute myocardial infarction; IAP, instable angina pectoris; TIA, transient ischaemic accident; PE, pulmonary embolism; DVT, deep venous.
[a]Only newly diagnosed heart failure within patients with no history of heart failure.
[b]Only newly diagnosed atrial fibrillation within patients with no history of atrial fibrillation.

we further discuss the observed trends in results using illustrative examples and visualizations, rather than presenting all results for all 12 models in all 3 cohorts. However, full details can be found in the supplementary materials as referenced above.

Predictive model performance

All models but model VTE1 obtained *c*-statistics above 0.80 in internal validation (see Supplementary material online, *Table S4*). New-onset atrial fibrillation was mainly predicted by age and sex, and adding additional predictors to the model only slightly and non-significantly improved the R^2_{cs} and the *c*-statistics. For all other outcomes, adding general predictors of CVD (model 2) and outcome-specific predictors (model 3) both improved model performance compared with the simple model with age and sex (model 1), as indicated by increasing R^2_{cs} (see Supplementary material online, *Table S4*). The models with the highest R^2_{cs} per outcome and their corresponding *c*-statistics (95% CI) were AE2, 0.91 (0.90, 0.91); VTE3, 0.83 (0.82, 0.84); HF3, 0.89 (0.87, 0.90), and AF3, 0.90 (0.88, 0.91). The *c*-statistics of these models were similar in both external validation cohorts (see Supplementary material online, *Table S4*). Brier scores were below 0.0061 for all models and were stable amongst models 1, 2, and 3 for each outcome in each cohort (see Supplementary material online, *Table S4*).

Individual risk predictions

Given the low average risk, most individual risk predictions were expected to have values close to zero. We explored if we could identify individuals with a higher absolute risk that would perhaps justify prophylactic intervention, for instance, with antithrombotic medication. *Figure 4* shows how the simple models predict risk dependent on age and sex. It can be seen that in addition to age, sex is a good predictor of the (thus age-adjusted) risk of atherosclerotic events and new-onset atrial fibrillation, yet a poor predictor of age-adjusted risk of venous thrombo-embolic events or new-onset heart failure. Furthermore, the models predict absolute risks below 1% for new-onset atrial fibrillation or heart failure in individuals up to 80 years and risks below 1% for atherosclerotic or venous thrombo-embolic events for individuals up to 60 years. Extended models with additional predictors led to some increased ranges of predictions (see Supplementary material online, *Table S5*). Yet, less than one in thousand individuals in the validation cohorts had a predicted risk of >5% for new-onset atrial fibrillation or heart failure or a predicted risk >9% for atherosclerotic events or >11% for venous thrombo-embolic events, even in the most extended models. The maximum predicted risks in all cohorts were about 15%, 17%, 9%, and 14% for atherosclerotic events, venous thrombo-embolic events, new-onset heart failure, and new-onset atrial fibrillation, respectively. However, these high risks concerned only a very small proportion of the population. As an example, more than 95% of individuals in the validation cohorts had a predicted risk for atherosclerotic or venous thrombo-embolic events below 1% according to the most advanced models (see Supplementary material online, *Table S5*).

Calibration

Predicted risks tended to exceed observed risks, evidenced by all calibration intercepts having negative values in both internal and external validations. This demonstrates that the models on average tend to overestimate CVD risk, even more so in vaccinated individuals (see Supplementary material online, *Table S4*). The calibration slopes >1 in the external validation indicate that the models relatively underestimate the risk of 'high-risk' individuals and relatively overestimate the

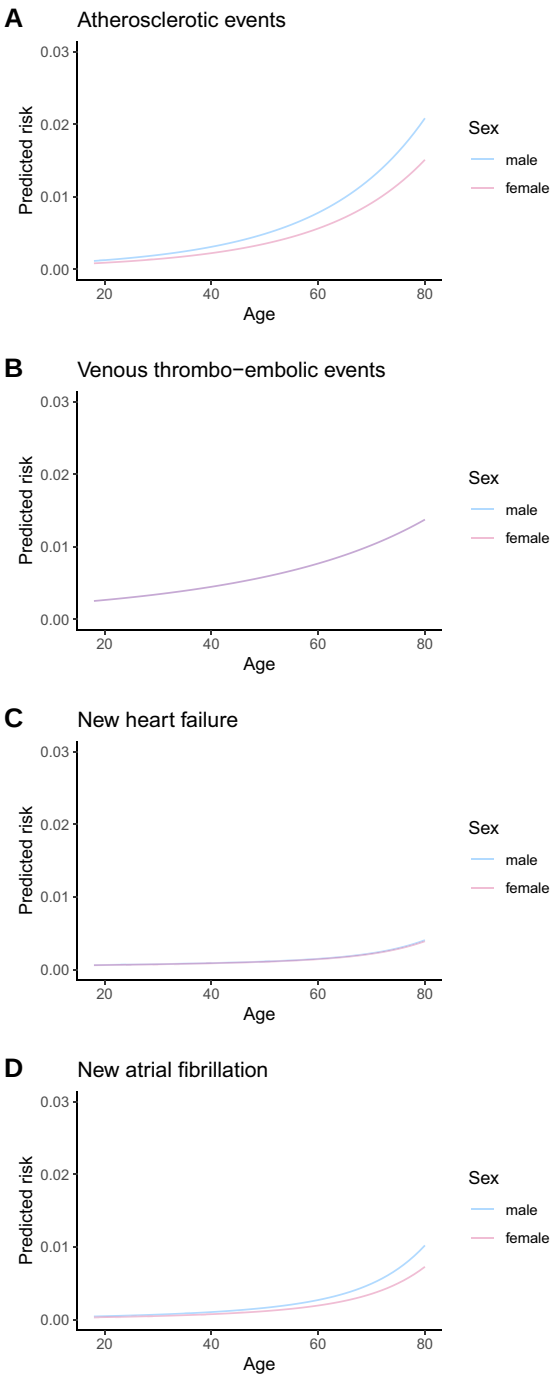


Figure 4 Individual risk predictions by models (*A*) AE1, (*B*) VTE1, (*C*) HF1, and (*D*) AF1 dependent on age and sex. Upper lines (blue) represent males, lower lines (red) represent females, and collapsed lines (purple) indicate that predicted risk from males and females overlap.

risk of 'low-risk' individuals (see Supplementary material online, *Table S4*). More details on calibration of predicted risks in the external validation cohorts can be derived from the calibration plots. These show that predicted risks align with observed proportions in the very low ranges of risks below 1%. However, they largely deviate with higher predicted risk ranges (see Supplementary material online, *Figures S2* and *S3*). As an example, *Figure 5* shows the calibration curve of model AE2 in unvaccinated and vaccinated external validation cohorts with a predicted risk between 0% and 2%, which constitutes 97% of the validation cohorts' population. Predicted risks do not completely align with the observed proportion of events in the unvaccinated cohort and align only slightly better in the vaccinated cohort. The difference in calibration between vaccinated and unvaccinated cohorts is more outspoken in model VTE3 (*Figure 6*). The miscalibration in higher ranges of predicted risk can be explained by the rare occurrence of the outcomes: if only very few individuals have a predicted risk above 5%, sparsity of observed events within higher risk intervals may draw the LOESS curve towards zero (see Supplementary material online, *Figures S2* and *S3*).

Discussion

In this study, we evaluated post-COVID-19 CVD incidences and individual risks in the general population. We found an increase in notably venous thrombo-embolic events and to a lesser extent atherosclerotic events and new-onset atrial fibrillation within the first 60 days after COVID-19 infection. We did not observe such an increase in new-onset heart failure or inflammatory heart disease following COVID-19, albeit numbers were low for the latter type of events. We developed several prediction models with high discriminative ability, yet these models are not useful to guide patient management based on individuals' predicted risks. This is due to the low incidence rates across CVD diseases; <1 in 20 individuals with COVID-19 infection had a predicted risk above 1%.

Comparison with existing literature

The incidence rates of post-COVID-19 CVD in our large population-based study seem largely in line with existing literature in primary care COVID-19 patients,[28–34] although most previous studies reported only cumulative incidence, and follow-up periods were often not specified. To what extent these incidence rates compare with those in individuals from the general population without COVID-19, however, is unknown. That is, individuals who become or do not become infected with COVID-19 may differ in baseline CVD risk, and as such, our results cannot straightforwardly be compared with the risk in uninfected individuals in the general population.[35] Several self-controlled case series have estimated the relative risk of CVD after COVID-19, but differences in study population, COVID-19 definitions, and follow-up time complicate a direct application of those results to our data in order to estimate absolute excess burdens.[22,36–40] We could postulate from *Figure 3* that the incidence rate in the period of 60 to 180 days after COVID-19 infection in our data is representative of baseline incidence of our study population (this cannot formally be concluded from our data but would be the best possible approximation of the baseline risk for conservative estimations of the excess burden). Assuming so, we would observe for venous thrombo-embolic events, atherosclerotic events, and new-onset atrial fibrillation baseline incidences of 4.0, 5.5, and 2.4 per 1000 person-years with relative risks of 5.3, 2.0, and 2.5 within the first 60 days after COVID-19 infection, respectively (these relative risks are on the conservative side of the spectrum of relative risks reported by others).[22,35–40] To put this into perspective: this implies that for each 100 000 adult cases of COVID-19 infection per year, this population would suffer from 1720 excess cases of venous thrombo-embolic events, 550 excess cases of atherosclerotic events, and 360 excess cases of new-onset atrial fibrillation. Xie and colleagues[4] have compared veteran COVID-19 survivors to non-infected controls and reported even higher excess burdens.

We decided to exclude outcomes on the same day as COVID-19 diagnosis as a potential source of selection bias based on its steep peek without visible distribution tails on the neighbouring days (see Supplementary material online, *Figure S1*). Another study used the same CPRD data as our study and reported a peek incidence of

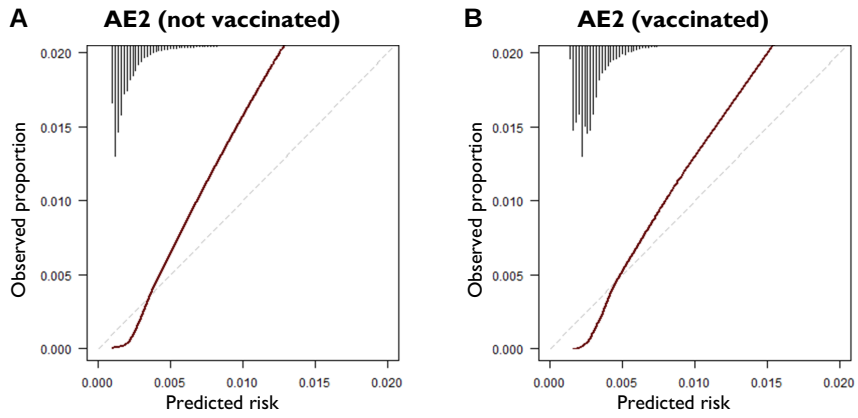


Figure 5 Calibration plots for model AE2. Calibration curves display the predicted risk of the model in the validation cohort (*x*-axis) compared with the observed proportion of events (*y*-axis). The dashed line represents perfect calibration if predictions equal observations, and the regular line represents the LOESS-smoothed non-parametric calibration curve. The range 0–0.02 is based on the range of the predicted values in the study cohort. The upper histogram represents the relative number of individuals with the corresponding predicted risk. (*A*) Model AE2 validated on a cohort of unvaccinated individuals and (*B*) model AE2 validated on a cohort of vaccinated individuals.

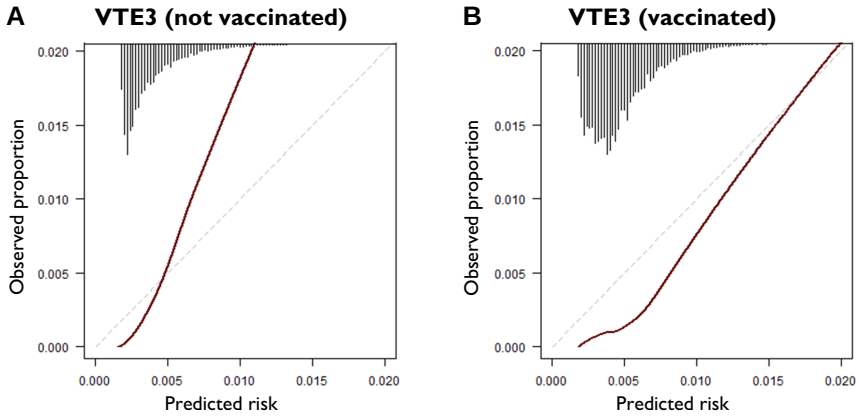


Figure 6 Calibration plots for model VTE3. Calibration curves display the predicted risk of the model in the validation cohort (*x*-axis) compared with the observed proportion of events (*y*-axis). The dashed line represents perfect calibration if predictions equal observations, and the regular line represents the LOESS-smoothed non-parametric calibration curve. The range 0–0.02 is based on the range of the predicted values in the study cohort. The upper histogram represents the relative number of individuals with the corresponding predicted risk. (*A*) Model VTE3 validated on a cohort of unvaccinated individuals and (*B*) model VTE3 validated on a cohort of vaccinated individuals.

CVD within the interval of 2 weeks before to 2 weeks after COVID-19 diagnosis, without providing numbers on daily intervals.[35] The decision whether or not to include these 'day zero' outcomes may thus highly impact results, also illustrated by a related study that reported outcomes for both scenarios.[37] In many routine care data sources, it is not possible to discriminate between diagnoses after testing for symptomatic COVID-19 and accidental findings of (asymptomatic) COVID-19 upon screening related to the outcome. Awareness is warranted about the definitions of exposure and outcomes in interpretation of post-COVID-19 CVD incidence rates.

We found low absolute risks of post-COVID-19 CVD events for individuals upon risk prediction modelling. Attempts by others to stratify absolute risk for venous thrombo-embolic events have also failed to identify high-risk subgroups with substantial risk.[41] Further exemplification on this low absolute risk comes from trials on prophylactic anticoagulation in 'high-risk' non-hospitalized adults with COVID-19 (see Supplementary material online, *Table S6* for an overview of randomized controlled trials).[42–48] Indeed, although hospitalized COVID-19 patients benefit from antithrombotic prophylaxis,[49] cardiovascular outcomes in not (yet) hospitalized adults with COVID-19 occurred in <1% of the trial populations, even if selectively patients with high cardiovascular risk were enrolled based on prognostic factors. In fact, several COVID-19 randomized clinical trials were terminated early because of low (cardiovascular) event rates. This underlines the difficulty of selecting 'high-risk' COVID-19 patients within the general population. In the same line, we also failed to identify a subpopulation

with substantially high risk on cardiovascular events, even with extensive multivariable modelling.

Strengths and limitations

Strengths of our study entail the large study population, detailed description of incidence patterns, robust modelling methods, and validation of all models in vaccinated and unvaccinated cohorts from later COVID-19 waves. Our detailed reporting of post-COVID-19 CVD incidence in different cohorts, visualized on daily intervals, provides better appreciation of the patterns in occurrence. To our knowledge, we are the first to explore post-COVID-19 CVD risk prediction in the general population.

The results from this study should also be interpreted in the light of some limitations. First, the used routine care data from CPRD may suffer from misclassification or missing data on diagnoses. Linked data from national registries and hospital databases were not yet available for our study period, which could have led to underestimation of events due to diagnosis in secondary care settings that have not been registered in primary care records or with a delayed recording date. In general, the quality of cardiovascular event registration in CPRD is well established by validation studies.[50–52] To what extent the pandemic may have impacted recordings of hospital events in primary care is unknown. Misclassification in event dates due to delayed recording may have slightly shifted the time-to-occurrence results, but impact on the prediction modelling would be less affected as the outcomes are modelled as binary rather than time-to-event and incidence was relatively low around the cut-off of 180 days. Also, misclassification is unlikely to be differential between our development and validation cohorts. We therefore do not expect major influence of data quality on our main findings. In addition, the incidence of some CVD may have been underestimated due to care avoidance during lockdowns, although this is not likely the case for severe outcomes. Underestimation of venous thrombosis events may have occurred due to low molecular weight heparin prophylaxis provided to hospitalized COVID-19 patients; however, given the primary care setting, this would concern presumably a very small proportion of our cohorts. Furthermore, even though our study population was restricted to COVID-19-infected individuals, it is not possible to directly attribute all CVD events to COVID-19 itself given other indirect effects of the pandemic (this is not a causal study). Also, we had no availability of data on COVID-19 symptoms or severity. Some included individuals may even have been asymptomatic. The results of this study are therefore representative of adults with diagnosed COVID-19 from the general population, in line with the aims and setting of our study.

Clinical and research implications

The results of this study advocate for clinical awareness of (post-)acute CVD risk after COVID-19 infection but against individual risk management in primary care. We observed a temporarily increased risk of atherosclerotic and venous thrombo-embolic events and new-onset atrial fibrillation up to 60 days after infection, with highest risk in individuals aged 60 years or older or with classical cardiovascular risk factors. Clinical awareness is thus warranted if patients present with symptoms potentially related to these events within this timeframe after a COVID-19 infection. Unfortunately, the occurrence of CVD events is hard to predict, let alone mitigate, at an early stage. Indeed, the International Society on Thrombosis and Haemostasis recently advised against initiation of anticoagulants in non-hospitalized COVID-19 patients who do not already use anticoagulants for another indication, based on the available evidence from randomized controlled trials.[49] Our findings are in line with this recommendation.

Even though the low absolute risk is beneficial from the perspective of the individual, the global total excess burden of CVD due to COVID-19 remains substantial and may continue to threaten healthcare systems now that the COVID-19 virus becomes endemic. If individual risk mitigation is unlikely to yield a solution, the question may be raised whether population-level interventions, such as COVID-19 vaccination, would be effective. Vaccinated individuals in our study had similar or lower incidence of post-COVID-19 CVD compared with unvaccinated individuals, even though they were on average older and had more comorbidities. However, it cannot be concluded from this study whether vaccination is effective in reducing cardiovascular risk. That would require proper causal inference studies that adequately account for confounders or, preferable, a randomized controlled trial. So far, one observational study using propensity score weighting showed a lower incidence of stroke and myocardial infarction after COVID-19 in vaccinated compared with unvaccinated individuals.[53] It would be interesting to compare the net incidence of CVD in vaccinated and unvaccinated individuals regardless of COVID-19 infection, because some CVD have also been reported as side-effects of particular COVID-19 vaccines[39]; however, we could not identify such literature. Further research is needed to evaluate effectiveness of COVID-19 vaccination on CVD endpoints.

Conclusions

The sustained magnitude of the COVID-19-infected population and the resulting excess burden of CVD still substantially impact society. COVID-19-infected adults are at relatively increased risk of venous thrombo-embolic and atherosclerotic events and new-onset atrial fibrillation. Clinicians should be aware of this risk within up to 60 days post-infection, especially in individuals aged 60 years or older or with cardiovascular risk factors. On the other hand, the absolute risk of experiencing such a cardiovascular event is so low that it is hard to predict in a COVID-19-infected individual from the general population at an early stage. Individualized cardiovascular risk management strategies for this population are therefore unlikely to be successful.

Lead author biography

Hannah la Roi-Teeuw, MD, MSc, is a general practitioner in vocational training and PhD candidate at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands. Her doctoral thesis focuses on the relation between respiratory infections and cardiovascular disease and prediction modelling in primary care populations.

Data availability

The data underlying this article were provided by CPRD under licence and by permission. The CPRD licence agreement does not permit data sharing. However, R scripts can be shared on request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Authors' contribution

G.-J.G. and F.H.R. acquired funding. G.-J.G., P.C.S., O.H.K., S.v.D., and F.H.R. wrote the ISAC study protocol. H.M.l.R.T., S.v.D., G.-J.G., and

M.v.S. designed the study. H.M.I.R.T., S.v.D., and P.C.S. prepared the data set. H.M.I.R.T. performed the analyses, with advice from G.-J.G., M.v.S., and S.v.D. All authors advised in interpreting the results. H.M.I.R.T. wrote the first version of the manuscript. All authors participated in revising the manuscript and approved its final version.

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