Long-term cardiovascular outcomes of COVID-19

Yan Xie1,2,3, Evan Xu1,4, Benjamin Bowe1,2 and Ziyad Al-Aly1,2,5,6,7

The cardiovascular complications of acute coronavirus disease 2019 (COVID-19) are well described, but the post-acute cardiovascular manifestations of COVID-19 have not yet been comprehensively characterized. Here we used national healthcare databases from the US Department of Veterans Affairs to build a cohort of 153,760 individuals with COVID-19, as well as two sets of control cohorts with 5,637,647 (contemporary controls) and 5,859,411 (historical controls) individuals, to estimate risks and 1-year burdens of a set of pre-specified incident cardiovascular outcomes. We show that, beyond the first 30 d after infection, individuals with COVID-19 are at increased risk of incident cardiovascular disease spanning several categories, including cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease. These risks and burdens were evident even among individuals who were not hospitalized during the acute phase of the infection and increased in a graded fashion according to the care setting during the acute phase (non-hospitalized, hospitalized and admitted to intensive care). Our results provide evidence that the risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial. Care pathways of those surviving the acute episode of COVID-19 should include attention to cardiovascular health and disease.

Post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the virus that causes coronavirus disease 2019 (COVID-19)—can involve the pulmonary and several extrapulmonary organs, including the cardiovascular system. A few studies have investigated cardiovascular outcomes in the post-acute phase of the COVID-19; however, most were limited to hospitalized individuals (who represent the minority of people with COVID-19), and all had a short duration of follow-up and a narrow selection of cardiovascular outcomes. A comprehensive assessment of post-acute COVID-19 sequelae of the cardiovascular system at 12 months is not yet available, and studies of post-acute COVID-19 sequelae across the spectrum of care settings of the acute infection (non-hospitalized, hospitalized and admitted to intensive care) are also lacking. Addressing this knowledge gap will inform post-acute COVID-19 care strategies.

In this study, we used the US Department of Veterans Affairs national healthcare databases to build a cohort of 153,760 US veterans who survived the first 30 d of COVID-19 and two control groups: a contemporary cohort consisting of 5,637,647 users of the US Veterans Health Administration (VHA) system with no evidence of SARS-CoV-2 infection and a historical cohort (pre-dating the COVID-19 pandemic) consisting of 5,859,411 non-COVID-19-infected VHA users during 2017. These cohorts were followed longitudinally to estimate the risks and 12-month burdens of pre-specified incident cardiovascular outcomes in the overall cohort and according to care setting of the acute infection (non-hospitalized, hospitalized and admitted to intensive care).

Results

There were 153,760, 5,637,647 and 5,859,411 participants in the COVID-19, contemporary control and historical control groups, respectively (Fig. 1). Median follow-up time in the COVID-19, contemporary control and historical control groups was 347 (interquartile range, 317–440), 348 (318–441) and 347 (317–440) d, respectively. The COVID-19, contemporary control and historical control groups had 159,366, 5,854,288 and 6,082,182 person-years of follow-up, respectively, altogether corresponding to 12,095,836 person-years of follow-up. The demographic and health characteristics of the COVID-19, contemporary control and historical control groups before and after weighting are presented in Supplementary Tables 1 and 2, respectively.

Incident cardiovascular diseases in COVID-19 versus contemporary control. Assessment of covariate balance after application of inverse probability weighting suggested that covariates were well balanced (Extended Data Fig. 1a).

We estimated the risks of a set of pre-specified cardiovascular outcomes in COVID-19 versus contemporary control; we also estimated the adjusted excess burden of cardiovascular outcomes due to COVID-19 per 1,000 persons at 12 months on the basis of the difference between the estimated incidence rate in individuals with COVID-19 and the contemporary control group. Risks and burdens of individual cardiovascular outcomes are provided in Fig. 2 and Supplementary Table 3 and are discussed below. Risks and burdens of the composite endpoints are provided in Fig. 3 and Supplementary Table 3.

Cerebrovascular disorders. People who survived the first 30 d of COVID-19 exhibited increased risk of stroke (hazard ratio (HR) = 1.52 (1.43, 1.62); burden 4.03 (3.32, 4.79) per 1,000 persons at 12 months; for all HRs and burdens, parenthetical ranges refer to 95% confidence intervals (CIs)) and transient ischemic attacks (TIA) (HR = 1.49 (1.37, 1.62); burden 1.84 (1.38, 2.34)). The risks and burdens of a composite of these cerebrovascular outcomes were 1.53 (1.45, 1.61) and 5.48 (4.65, 6.35).

Dysrhythmias. There were increased risks of atrial fibrillation (HR = 1.71 (1.64, 1.79); burden 10.74 (9.61, 11.91)), sinus tachycardia (HR = 1.84 (1.74, 1.95)) and sinus bradycardia (HR = 1.71 (1.64, 1.79); burden 10.74 (9.61, 11.91)).
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**Inflammatory disease of the heart or pericardium.** Inflammatory disease of the heart or pericardium included pericarditis (HR = 1.85 (1.61, 2.13)); burden 0.98 (0.70, 1.30) and myocarditis (HR = 5.38 (3.80, 7.59); burden 0.31 (0.20, 0.46)). The risks and burdens of a composite of these inflammatory diseases of the heart or pericardium were 1.69 (1.64, 1.75), and 19.86 (18.31, 21.46).

**Ischemic heart disease.** Ischemic heart disease included acute coronary disease (HR = 1.72 (1.56, 1.90); burden 5.35 (4.13, 6.70)), myocardial infarction (HR = 1.63 (1.51, 1.75); burden 2.91 (2.38, 3.49)), ischemic cardiomyopathy (HR = 1.75 (1.44, 2.13); burden 2.34 (1.37, 3.51)) and angina (HR = 1.52 (1.42, 1.64); burden 2.50 (2.00, 3.03)). The risks and burdens of a composite of these ischemic heart disease outcomes were 1.66 (1.52, 1.80) and 7.28 (5.80, 8.88).

**Other cardiovascular disorders.** Other cardiovascular disorders included heart failure (HR = 1.72 (1.65, 1.80); burden 11.61 (10.47, 12.78)), non-ischemic cardiomyopathy (HR = 1.62 (1.52, 1.73); burden 3.56 (2.97, 4.20)), cardiac arrest (HR = 2.45 (2.08, 2.89); burden

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**Fig. 1 | Flowchart of cohort construction.** Cohort construction for COVID-19 group (blue), contemporary control group (yellow) and historical control group (orange). Comparisons between groups are presented in green.
0.71 (0.53, 0.93)) and cardiogenic shock (HR = 2.43 (1.86, 3.16); burden 0.51 (0.31, 0.77)). The risks and burdens of a composite of these other cardiovascular disorders were 1.72 (1.65, 1.79) and 12.72 (11.54, 13.96).

**Thromboembolic disorders.** Thromboembolic disorders included pulmonary embolism (HR = 2.93 (2.73, 3.15); burden 5.47 (4.90, 6.08)); deep vein thrombosis (HR = 2.09 (1.94, 2.24); burden 4.18 (3.62, 4.79)) and superficial vein thrombosis (HR = 1.95 (1.80, 2.12); burden 2.61 (2.20, 3.07)). The risks and burdens of a composite of these thromboembolic disorders were 2.39 (2.27, 2.51) and 9.88 (9.05, 10.74).

**Additional composite endpoints.** We then examined the risks and burdens of two composite endpoints, including major adverse cardiovascular event (MACE)—a composite of myocardial infarction, stroke and all-cause mortality—and any cardiovascular outcome (defined as the occurrence of any incident pre-specified cardiovascular outcome included in this study). Compared to the contemporary control group, there were increased risks and burdens of MACE (HR = 1.55 (1.50, 1.60); burden 23.48 (21.54, 25.48)) and any cardiovascular outcome (HR = 1.63 (1.59, 1.68); burden 45.29 (42.22, 48.45)).

**Subgroup analyses.** We examined the risks of incident composite cardiovascular outcomes in subgroups based on age, race, sex, obesity, smoking, hypertension, diabetes, chronic kidney disease, hyperlipidemia and cardiovascular disease. The risks of incident composite cardiovascular outcomes were evident in all subgroups (Fig. 4 and Supplementary Table 4).

We examined the risks and burdens of the pre-specified outcomes in a cohort of people without any cardiovascular disease at baseline; the results were consistent with those shown in the primary analyses (Extended Data Figs. 2 and 3 and Supplementary Table 5).

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**Fig. 2 | Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes compared with the contemporary control cohort.** Outcomes were ascertained 30 d after the COVID-19-positive test until the end of follow-up. COVID-19 cohort (n = 153,760) and contemporary control cohort (n = 5,637,647). Adjusted HRs and 95% CIs are presented. The length of the bar represents the excess burden per 1,000 persons at 12 months, and associated 95% CIs are also shown.
Fig. 3 | Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes compared with the contemporary control cohort. Composite outcomes consisted of cerebrovascular disorders (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias and atrial flutter), inflammatory heart disease (pericarditis and myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction, ischemic cardiomyopathy and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis and superficial vein thrombosis), MACE (all-cause mortality, stroke and myocardial infarction) and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 d after the COVID-19-positive test until the end of follow-up. COVID-19 cohort (n = 153,760) and contemporary control cohort (n = 5,637,647). Adjusted HRs and 95% CIs are presented. The length of the bar represents the excess burden per 1,000 persons at 12 months, and associated 95% CIs are also shown.

Cardiovascular diseases before and after COVID-19. To better understand the change in the relative rates of incident cardiovascular outcomes before and after the COVID-19 exposure, we developed a difference-in-differences analysis to estimate the adjusted incident rate ratios of the cardiovascular outcomes relative to both the contemporary and historical control groups in the pre-COVID-19 and post-COVID-19 exposure periods. The results showed that the adjusted incident rate ratios of cardiovascular outcomes in the post-COVID-19 exposure period were significantly higher than those in the pre-exposure period (ratios of incident rate ratios for all cardiovascular outcomes were significantly higher than 1) and exhibited a graded increase by severity of the acute phase of the disease (Supplementary Tables 15–18).

Sensitivity analyses. We tested robustness of results in several sensitivity analyses involving the outcomes of MACE and any cardiovascular outcome (Supplementary Tables 17 and 18). The sensitivity analyses were performed in comparisons involving COVID-19 versus the contemporary control and COVID-19 versus the historical control and, additionally, COVID-19 by care setting versus both controls. (1) To test whether the inclusion of additional algorithmically selected covariates would challenge the robustness of study results, we selected and used 300 high-dimensional variables (instead of the 100 used in the primary analyses) to construct the inverse probability weighting. (2) We then also tested the results in models specified to include only pre-defined covariates (that is, without inclusion of algorithmically selected covariates) to build the inverse probability weighting. Finally, (3) we changed the analytic approach by using the doubly robust method (instead of the inverse weighting method used in primary analyses) to estimate the magnitude of the associations between COVID-19 exposure and the pre-specified outcomes. All sensitivity analyses yielded results consistent with those produced using the primary approach (Supplementary Tables 19 and 20).

Risk of myocarditis and pericarditis without COVID-19 vaccination. Because some COVID-19 vaccines might be associated with a very rare risk of myocarditis or pericarditis, and to eliminate any putative contribution of potential vaccine exposure to the outcomes of myocarditis and pericarditis in this study, we conducted two analyses. First, we censored cohort participants at the time of receiving the first dose of any COVID-19 vaccine. Second, we adjusted for vaccination as a time-varying covariate. Both analyses were conducted versus both the contemporary and historical control groups. The results suggested that COVID-19 was associated with increased risk of myocarditis and pericarditis in both analyses (Supplementary Tables 21–24).
In this study involving 153,760 people with COVID-19, 5,637,647 days was not significantly associated with any of the pre-specified cardiovascular outcomes (Supplementary Table 26).

Negative-exposure controls. To further examine the robustness of our approach, we developed and tested a pair of negative-exposure controls. We hypothesized that receipt of influenza vaccination in even-numbered (years) versus odd-numbered calendar days and the pre-specified cardiovascular outcomes examined in this analysis. We, therefore, tested the associations between receipt of influenza vaccine in even-numbered (n = 571,291) versus odd-numbered (n = 605,453) calendar days and the pre-specified cardiovascular outcomes. We used the same data sources, cohort design, analytical approach (including covariate specification and weighting method) and outcomes. The results suggest that receipt of influenza vaccination in odd-numbered calendar days versus even-numbered calendar days was not significantly associated with any of the pre-specified cardiovascular outcomes (Supplementary Table 26).

Discussion

In this study involving 153,760 people with COVID-19, 5,637,647 contemporary controls and 5,859,411 historical controls—which, altogether, correspond to 12,095,836 person-years of follow-up—we provide evidence that, beyond the first 30 d of infection, people with COVID-19 exhibited increased risks and 12-month burdens of incident cardiovascular diseases, including cerebrovascular disorders, dysrhythmias, inflammatory heart disease, ischemic heart disease, heart failure, thromboembolic disease and other cardiovascular outcomes (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 d after the COVID-19-positive test until the end of follow-up. COVID-19 cohort (n = 153,760) and contemporary control cohort (n = 5,637,647). Adjusted HRs and 95% CIs are presented.

Positive and negative outcome controls. To assess whether our data and analytic approach would reproduce known associations, we examined the association between COVID-19 and the risk of fatigue (known to be a signature sequela of post-acute COVID-19) as a positive outcome control. The results suggested that COVID-19 was associated with a higher risk of fatigue (Supplementary Table 25). We then examined the association between COVID-19 and a battery of seven negative-outcome controls where no prior knowledge suggests that an association is expected. The results yielded no significant association between COVID-19 and any of the negative-outcome controls, which were consistent with a priori expectations (Supplementary Table 25).

Negative-exposure controls. To further examine the robustness of our approach, we developed and tested a pair of negative-exposure controls. We hypothesized that receipt of influenza vaccination in odd-numbered and even-numbered calendar days between 1 March 2020 and 15 January 2021 would be associated with similar risks of the pre-specified cardiovascular outcomes examined in this analysis. We, therefore, tested the associations between receipt of influenza vaccine in even-numbered (n = 571,291) versus odd-numbered (n = 605,453) calendar days and the pre-specified cardiovascular outcomes. We used the same data sources, cohort design, analytical approach (including covariate specification and weighting method) and outcomes. The results suggest that receipt of influenza vaccination in odd-numbered calendar days versus even-numbered calendar days was not significantly associated with any of the pre-specified cardiovascular outcomes (Supplementary Table 26).

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diseases among those who survive the acute phase of COVID-19 are substantial and span several cardiovascular disorders. Care strategies of people who survived the acute episode of COVID-19 should include attention to cardiovascular health and disease.

The broader implications of these findings are clear. Cardiovascular complications have been described in the acute phase of COVID-19 (refs. 6–8). Our study shows that the risk of incident cardiovascular disease extends well beyond the acute phase of COVID-19. First, the findings emphasize the need for continued optimization of strategies for primary prevention of SARS-CoV-2 infections; that is, the best way to prevent Long COVID and its myriad complications, including the risk of serious cardiovascular sequelae, is to prevent SARS-CoV-2 infection in the first place. Second, given the large and growing number of people with COVID-19 (more than 72 million people in the United States, more than 16 million people in the United Kingdom and more than 355 million people globally), the risks and 12-month burdens of cardiovascular diseases reported here might translate into a large number of potentially affected people around the world. Governments and health systems around the world should be prepared to deal with the likely significant contribution of the COVID-19 pandemic to a rise in the burden of cardiovascular diseases. Because of the chronic nature of these conditions, they will likely have long-lasting consequences for patients and health systems and also have broad implications on economic productivity and life expectancy. Addressing the challenges posed by Long COVID will require a much-needed, but so far lacking, urgent and coordinated long-term global response strategy9,10.

Fig. 5 | Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes compared with the contemporary control cohort by care setting of the acute infection. Risks and burdens were assessed at 12 months in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (green), individuals hospitalized for COVID-19 (orange) and individuals admitted to intensive care for COVID-19 during the acute phase (first 30 d) of COVID-19 (blue). Outcomes were ascertained 30 d after the COVID-19-positive test until the end of follow-up. The contemporary control cohort served as the referent category. Within the COVID-19 cohort, non-hospitalized (n = 131,612), hospitalized (n = 16,760), admitted to intensive care (n = 5,388) and contemporary control cohort (n = 5,637,647). Adjusted HRs and 95% CIs are presented. The length of the bar represents the excess burden per 1,000 persons at 12 months, and related 95% CIs were also presented.
The mechanism or mechanisms that underlie the association between COVID-19 and development of cardiovascular diseases in the post-acute phase of the disease are not entirely clear. Putative mechanisms include lingering damage from direct viral invasion of heart tissue, complement activation and complement-mediated endotheliitis, transcriptional alteration of multiple cell types (cardiomyocytes and subsequent cell death, endothelial cell infection), and activation of TGF-β. Risk and 12-month burden of incident cardiovascular outcomes were assessed at 12 months in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (green), individuals hospitalized for COVID-19 (orange) and individuals admitted to intensive care for COVID-19 during the acute phase (first 30 d) of COVID-19 (blue). Composite outcomes consisted of cerebrovascular disorders (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias and atrial flutter), inflammatory heart disease (pericarditis and myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction, ischemic cardiomyopathy and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis and superficial vein thrombosis), MACE (all-cause mortality, stroke and myocardial infarction) and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 d after the COVID-19-positive test until the end of follow-up. The contemporary control cohort served as the referent category. Within the COVID-19 cohort, non-hospitalized (n = 131,612), hospitalized (n = 16,760), admitted to intensive care (n = 5,388) and contemporary control cohort (n = 5,637,647). Adjusted HRs and 95% CIs are presented. The length of the bar represents the excess burden per 1,000 persons at 12 months, and related 95% CIs were also presented.

In summary, using a national cohort of people with COVID-19, we show that risk and 12-month burden of incident cardiovascular disease are substantial and span several cardiovascular disease categories (ischemic and non-ischemic heart disease, dysrhythmias and others). The risks and burdens of cardiovascular disease were evident even among those whose acute COVID-19 did not necessitate hospitalization. Care pathways of people who survived the acute episode of COVID-19 should include attention to cardiovascular health and disease.
Online content
Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-022-01689-3.

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we considered both pre-defined and algorithmically selected high-dimensional covariates. To adjust for the difference in baseline characteristics between groups, we used inverse probability weighting. We then developed causal difference-in-differences analyses to estimate the adjusted incident rate ratios of all cardiovascular outcomes in the pre-COVID-19 and post-COVID-19 exposure period relative to both contemporary and historical controls. As a first step, we used multiple propensity scores to weight our analyses in a cohort without history of any cardiovascular outcomes before cohort enrollment. We then conducted multiple sensitivity analyses to test the robustness of our study results. (1) To capture additional potential confounders, we expanded our inclusion of high-dimensional variables from the top 100 to the top 300 when constructing the inverse probability weight. (2) We then modified our adjustment strategy by using only pre-defined variables when constructing the inverse probability weight (not including the 100 high-dimensional covariates used in the primary analyses). Finally, (3) we alternatively applied a doubly robust approach, where both covariates and the inverse probability weights were applied to the survival models, to estimate the associations.
COVID-19 is associated with an increased risk of fatigue in the post-acute phase of the disease, which is generally considered as a signature post-acute sequela\(^\text{9}\). To test whether our approach would reproduce known associations, we, therefore, examined the association between COVID-19 and fatigue as a positive outcome control. Reproducing this known association (using our data, cohort design and analytic strategy) would provide some measure of assurance that our approach yields result consistent with a priori expectations.

We also subjected our approach to the application of a battery of negative-outcome controls where no prior knowledge supports the existence of a causal association between the exposure and the risks of negative-outcome controls\(^{36}\). The negative-outcome controls included hypertrichosis, melanoma in situ, sickle cell trait, perforation of the tympanic membrane, malignant neoplasm of the tongue, B cell lymphoma and Hodgkin\'s lymphoma. We also developed and tested a pair of negative-exposure controls (defined as exposure to influenza vaccine in odd-numbered or even-numbered calendar days between 1 March 2020 and 15 January 2021). Our pre-test expectation was that there would be no differences in risk of any of the pre-specified cardiovascular outcomes examined in this analysis between those who received influenza vaccine in odd-numbered versus even-numbered calendar days. The successful application of negative controls might reduce concern about the presence of spurious biases related to cohort building, study design, covariate selection, analytic approaches, outcome ascertainment, residual confounding and other sources of latent biases.

Estimation of variance when weightings were applied was accomplished by using robust sandwich variance estimators. In all analyses, a 95% confidence interval that excluded unity was considered evidence of statistical significance. This study was approved by the institutional review board of the VA St. Louis Health Care System (protocol number 16063333), which granted a waiver of informed consent. Analyses were conducted using SAS Enterprise Guide version 8.2 (SAS Institute), and results were visualized using R version 4.0.4.

**Ethical approval.** This research project was reviewed and approved by the institutional review board of the VA St. Louis Health Care System (protocol number 16063333).

**Reporting Summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this article.

**Data availability**
The data that support the findings of this study are available from the US Department of Veterans Affairs. VA data are made freely available to researchers behind the VA firewall with an approved VA study protocol. For more information, visit https://www.virec.research.va.gov or contact the VA Information Resource Center at VIREC@va.gov.

**Code availability**
SAS codes are available at https://github.com/yxie618/longCVD and https://doi.org/10.5281/zenodo.5799457.

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**Author contributions**
Z.A.-A., Y.X. and E.X. contributed to the development of the study concept and design. Z.A.-A., Y.X. and E.X. contributed to data analysis and interpretation of results. Z.A.-A., Y.X. and E.X. drafted the manuscript. Z.A.-A., Y.X. and E.X. contributed to critical revision of the manuscript. Z.A.-A. provided administrative, technical and material support as well as supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors approved the final version of the report. The corresponding author attests that all the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

**Competing interests**
The authors declare no competing interests.

**Additional information**
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**Correspondence and requests for materials** should be addressed to Ziyad Al-Aly.

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Extended Data Fig. 1 | Standardized mean difference of predefined and algorithmically selected high dimensional variables. a, between COVID-19 and contemporary control cohorts; b, between COVID-19 categorized by care setting of the acute infection (non-hospitalized, hospitalized, and admitted to intensive care) and contemporary control cohorts; c, between COVID-19 and historical control cohorts; d, between COVID-19 categorized by care setting of the acute infection (non-hospitalized, hospitalized, and admitted to intensive care) and historical control cohorts. Standardized difference less than 0.15 is considered good balance.
Extended Data Fig. 2 | Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes in participants without any history of cardiovascular outcomes prior to COVID-19 exposure compared to the contemporary control cohort. Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. COVID-19 cohort without any history of cardiovascular outcomes (N = 126,575) and contemporary control cohort without any history of cardiovascular outcomes (N = 5,010,542). Adjusted hazard ratios and 95% confidence intervals are presented. Length of the bar represents the excess burden per 1000 persons at 12 months and associated 95% confidence intervals are also shown. TIA, transient ischemic attack.
Extended Data Fig. 3 | Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes in participants without any history of cardiovascular outcomes prior to COVID-19 exposure compared to the contemporary control cohort. Composite outcomes consisted of cerebrovascular (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias, and atrial flutter), inflammatory heart disease (pericarditis, myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction, ischemic cardiomyopathy, and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest, and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis), MACE (all-cause mortality, stroke, and myocardial infarction), and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. COVID-19 cohort without any history of cardiovascular outcomes (N=126,575) and contemporary control cohort without any history of cardiovascular outcomes (N=5,010,542). Adjusted hazard ratios and 95% confidence intervals are presented. Length of the bar represents the excess burden per 1000 persons at 12 months and associated 95% confidence intervals are also shown. MACE, major adverse cardiac events; TIA, transient ischemic attack.
Extended Data Fig. 4 | Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes compared to the historical control cohort. Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. COVID-19 cohort (N = 153,760) and historical control cohort (N = 5,859,411). Adjusted hazard ratios and 95% confidence intervals are presented. Length of the bar represents the excess burden per 1000 persons at 12 months and associated 95% confidence intervals are also shown. TIA, transient ischemic attack.
Extended Data Fig. 5 | Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes compared to the historical control cohort. Composite outcomes consisted of cerebrovascular (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias, and atrial flutter), inflammatory heart disease (pericarditis, myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction, ischemic cardiomyopathy, and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest, and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis), MACE (all-cause mortality, stroke, and myocardial infarction), and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. COVID-19 cohort (N = 153,760) and historical control cohort (N = 5,859,411). Adjusted hazard ratios and 95% confidence intervals are presented. Length of the bar represents the excess burden per 1000 persons at 12 months and associated 95% confidence intervals are also shown. MACE, major adverse cardiac events; TIA, transient ischemic attack.
Extended Data Fig. 6 | Subgroup analyses of the risks of incident post-acute COVID-19 composite cardiovascular outcomes compared to the historical control cohort. Composite outcomes consisted of cerebrovascular (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias, and atrial flutter), inflammatory heart disease (pericarditis, myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction, ischemic cardiomyopathy, and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest, and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis), MACE (all-cause mortality, stroke, and myocardial infarction), and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. COVID-19 cohort (N=153,760) and historical control cohort (N=5,859,411). Adjusted hazard ratios and 95% confidence intervals are presented. MACE, major adverse cardiac events; TIA, transient ischemic attack.
Extended Data Fig. 7 | Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes in participants without any history of cardiovascular outcomes prior to COVID-19 exposure compared to the historical control cohort. Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. COVID-19 cohort without any history of cardiovascular outcomes (N=126,575) and historical control cohort without any history of cardiovascular outcomes (N=5,188,992). Adjusted hazard ratios and 95% confidence intervals are presented. Length of the bar represents the excess burden per 1000 persons at 12 months and associated 95% confidence intervals are also shown. TIA, transient ischemic attack.
Extended Data Fig. 8 | Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes in participants without any history of cardiovascular outcomes prior to COVID-19 exposure compared to the historical control cohort. Composite outcomes consisted of cerebrovascular (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias, and atrial flutter), inflammatory heart disease (pericarditis, myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction, ischemic cardiomyopathy, and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest, and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis), MACE (all-cause mortality, stroke, and myocardial infarction), and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. COVID-19 cohort without any history of cardiovascular outcomes (N = 126,575) and historical control cohort without any history of cardiovascular outcomes (N = 5,188,992). Adjusted hazard ratios and 95% confidence intervals are presented. Length of the bar represents the excess burden per 1000 persons at 12 months and associated 95% confidence intervals are also shown. MACE, major adverse cardiac events; TIA, transient ischemic attack.
Extended Data Fig. 9 | Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes compared to the historical control cohort by care setting of the acute infection. Risks and burdens were assessed at 12 months in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (green), individuals hospitalized for COVID-19 (orange), and individuals admitted to intensive care for COVID-19 during the acute phase (first 30 days) of COVID-19 (blue). Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. The historical control cohort served as the referent category. Within the COVID-19 cohort, non-hospitalized (N = 131,612), hospitalized (N = 16,760); admitted to intensive care (N = 5,388); and historical control cohort (N = 5,859,411). Adjusted hazard ratios and 95% confidence intervals are presented. Length of the bar represents the excess burden per 1000 persons at 12 months and related 95% confidence intervals were also presented. TIA, transient ischemic attack.
Extended Data Fig. 10 | Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes compared to the historical control cohort by care setting of the acute infection. Risks and burdens were assessed at 12 months in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (green), individuals hospitalized for COVID-19 (orange), and individuals admitted to intensive care for COVID-19 during the acute phase (first 30 days) of COVID-19 (blue). Composite outcomes consisted of cerebrovascular (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias, and atrial flutter), inflammatory heart disease (pericarditis, myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction, ischemic cardiomyopathy, and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest, and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis), MACE (all-cause mortality, stroke, and myocardial infarction), and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 days after the COVID-19 positive test until the end of follow-up. The historical control cohort served as the referent category. Within the COVID-19 cohort, non-hospitalized (N = 131,612), hospitalized (N = 16,760); admitted to intensive care (N = 5,388); and historical control cohort (N = 5,859,411). Adjusted hazard ratios and 95% confidence intervals are presented. Length of the bar represents the excess burden per 1000 persons at 12 months and related 95% confidence intervals were also presented. MACE, major adverse cardiac events; TIA, transient ischemic attack.
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SAS Enterprise Guide version 8.2 was used to collect data for the study.

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All analyses were done using SAS Enterprise Guide version 8.2 (SAS Institute, Cary, NC). Data visualizations were performed in R 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Analytic codes are available at https://github.com/yxie618/1ongCVD

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The data that support the findings of this study are available from the US Department of Veterans Affairs. VA data are made freely available to researchers behind the VA firewall with an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center (VIRReC) at VirReC@va.gov
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Life sciences study design

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| Sample size | To achieve better precision of the study results, we enrolled all users of the US Veterans Health Administration and followed them until October 31, 2021. This cohort included 15,3,760 people with COVID-19, 5,637,647 contemporary controls and 5,859,411 historical controls. |
| Data exclusions | To examine the risk of post-acute cardiovascular outcomes beyond the first 30 days of illness, we predefined our exclusion criteria and excluded participants who did not survive the first 30 days of COVID-19 illness. |
| Replication | The finding was not replicated because no external dataset with similar features is available to us. |
| Randomization | We conducted an observational study. Exposure allocation was not random. Both predefined and algorithmically selected covariates were adjusted for through inverse probability weighting. |
| Blinding | We conducted an observational study. Blinding was not possible. |

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| Population characteristics | Study participants are users of the US Veteran Health Administration. The COVID-19 group included 153,760 people; average age was 61, 70% were of White race, 89% were males. Average eGFR was 77 ml/min/1.73m². Average systolic blood pressure was 132 mmHg. Average diastolic blood pressure was 78.32 mmHg. Average area deprivation index was 55.32. During the acute phase of COVID-19, 131,612, 36,760, and 5,388 were non-hospitalized, hospitalized, and admitted to intensive care, respectively. There were 5,637,647 contemporary controls and 5,859,411 historical controls. |
| Recruitment | Participants were recruited if they had at least 1 encounter with the US Veteran Health Administration in year 2019 within the contemporary and COVID-19 cohorts and in year 2018 within the historical cohort. Non users of the VA health care system were not included. The characteristics of the study population may be different from the general population (US or global population). Other biases due to recruitment including self-selection bias are unlikely to bias the results of this study. |
| Ethics oversight | The study was approved by the Institutional Review Board of the Veterans Affairs St. Louis Health Care System, St. Louis, MO, USA. |

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