Vascular and inflammatory diseases after COVID-19 infection and vaccination in children and young people in England: a retrospective, population-based cohort study using linked electronic health records

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Summary

Background The rarity of severe diseases following COVID-19 infection balanced against rare COVID-19 vaccination-related adverse effects is an important consideration for vaccination policies. We aimed to assess the short-term and long-term risks of vascular and inflammatory diseases following first COVID-19 diagnosis and vaccination in children and young people.

Methods In this retrospective, population-based cohort study, we analysed whole-population linked electronic health records for all individuals in England aged younger than 18 years, registered with a general practitioner, and with known age, sex, and region of residence, between Jan 1, 2020, and Dec 31, 2022. Outcomes were arterial thrombotic events, venous thrombotic events, thrombocytopenia, myocarditis or pericarditis, and inflammatory conditions. COVID-19 diagnosis was defined as the earliest record of a positive SARS-CoV-2 PCR or antigen test, or a COVID-19 diagnosis code in primary-care or secondary-care records; COVID-19 vaccination was defined as the earliest documented receipt of the BNT162b2 vaccine (the predominant vaccine during the study period). Adjusted hazard ratios (aHRs) for all outcomes were estimated by time since a first COVID-19 diagnosis during Jan 1, 2020–March 31, 2022 and by time since a first COVID-19 vaccination during Aug 6, 2021–Dec 31, 2022, adjusting for age, sex, ethnicity, region, deprivation, general practitioner contact frequency, and medication use.

Findings Of 13 896 125 individuals younger than 18 years (6 784 260 [48·8%] female and 7 111 865 [51·2%] male; 9 979 420 [71·7%] White), 3 903 410 (28·1%) had a COVID-19 diagnosis. COVID-19 diagnosis (compared with no or before diagnosis) was associated with higher risk of arterial thromboembolism (aHR 2·33 [95% CI 1·20–4·51]), venous thromboembolism (4·90 [3·66–6·55]), thrombocytopenia (3·64 [2·21–6·00]), myocarditis or pericarditis (3·46 [2·06–5·80]), and inflammatory conditions (14·84 [11·01–19·99]) in the first week after diagnosis. Incidence declined in weeks 2–4, but remained elevated to beyond 12 months for venous thromboembolism (1·39 [1·14–1·69]), thrombocytopenia (1·42 [1·01–2·00]), and myocarditis or pericarditis (1·42 [1·05–1·91]). Among 9 245 395 individuals aged between 5 and younger than 18 years who were eligible for vaccination (4 510 490 [48·8%] female and 4 734 905 [51·2%] male; 6 684 140 [72·3%] White), 3 407 560 (36·9%) received a first vaccine. COVID-19 vaccination (compared with no or before vaccination) was associated with elevated risk of myocarditis or pericarditis within the first 4 weeks after vaccination (1·84 [1·25–2·72]). The 6-month absolute excess risks for myocarditis or pericarditis were 2·24 (1·11–3·80) per 100 000 individuals after diagnosis versus before diagnosis or undiagnosed, and 0·85 (0·07–1·91) after vaccination versus before vaccination or unvaccinated.

Interpretation Children and young people have higher risks of rare vascular and inflammatory diseases up to 12 months after a first COVID-19 diagnosis and higher risk of rare myocarditis or pericarditis up to 4 weeks after a first BNT162b2 vaccine, although the risk following vaccination is substantially lower than the risk following infection. These findings are of great importance for national policy makers and caregivers considering vaccination consent for children, and support the public health strategy of COVID-19 vaccination in children and young people to mitigate the more frequent and persistent risks associated with SARS-CoV-2 infection.

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Research in context

Evidence before this study

We searched Embase and Web of Science on Aug 4, 2025, for studies published between Jan 1, 2019, and Aug 4, 2025, using the terms: ("coronavirus" OR "SARS-CoV-2" OR "COVID") AND ("vaccine" OR "vaccination") AND ("child" OR "children" OR "adolescent" OR "paediatric" OR "pediatric" OR "under 18") AND ("arterial thrombotic event" OR "arterial thrombosis" OR "arterial thromboembolism" OR "ATE" OR "venous thrombotic event" OR "VTE" OR "thrombocytopenia" OR "myocarditis" OR "pericarditis" OR "inflammatory disease" OR "MIS-C" OR "PIMS") AND ("prospective" OR "population"). 350 studies were identified.

Previous studies show that COVID-19 infection in children and young people is associated with higher risks of adverse health outcomes, particularly rare occurrences of myocarditis, pericarditis, and thrombocytopenia. Some studies also reported increased risks of myocarditis shortly after COVID-19 vaccination, especially with mRNA vaccines. However, most studies focused on short-term outcomes and did not compare long-term vascular and inflammatory risks between infection and vaccination and in a large paediatric population.

Added value of this study

Using comprehensive nationwide linked health records in England from Jan 1, 2020, to Dec 31, 2022, this study assessed cardiovascular and inflammatory outcomes following first COVID-19 infection and vaccination in children and young people. Our large cohorts (13·9 million in the analytical cohort to evaluate COVID-19 infection and 9·2 million in the analytical cohort to evaluate COVID-19 vaccination) and the breadth of data sources (including primary care, secondary care, emergency care, and mortality data) allowed detailed subgroup analyses by age, sex, ethnicity, and deprivation. Incidence rates and hazard ratios for cardiovascular and inflammatory outcomes were estimated separately following first COVID-19 infection or first COVID-19 vaccination, enabling a robust assessment of short-term and long-term risks, with follow-up of up to 15 months after exposure. This approach allowed comparison of the severity and duration of risks associated with infection versus vaccination.

Implications of all the available evidence

COVID-19 infection in children and young people was associated with elevated risks of rare vascular and inflammatory conditions—including venous thromboembolism, thrombocytopenia, myocarditis, and pericarditis—particularly in the first month after diagnosis, with some risks remaining elevated up to 12 months after diagnosis. These findings show the importance of monitoring long-term outcomes following infection. By contrast, COVID-19 vaccination was associated with a short-term increased risk of myocarditis or pericarditis, mainly within the first 4 weeks. However, no increased risk was observed beyond that period, and there was no evidence of long-term myocarditis signal after vaccination. In summary, first COVID-19 infection was associated with rare but serious health risks that persisted for many months, whereas the elevated risks observed after first vaccination were confined to the early post-vaccination period and were substantially lower than the risks following COVID-19 infection. These contrasting findings support continued vaccination in children and young people as an effective public health strategy to mitigate the more frequent and persistent risks associated with SARS-CoV-2 infection. Policy makers and health-care providers can use these results to support informed discussions with caregivers regarding the relative safety profiles of infection and vaccination.

Introduction

Children and young people experience similar or higher rates of SARS-CoV-2 infection compared with adults, and their clinical manifestations are often asymptomatic or milder.[1–3] However, some children and young people develop serious disease.[4] In England, the Joint Committee on Vaccination and Immunisation has defined severe childhood SARS-CoV-2 infection as cases requiring intensive care unit admission or those involving the severe complication known as paediatric inflammatory multisystem syndrome (PIMS; also known as multisystem inflammatory syndrome in children [MIS-C]).[5,6] In England, between the first three variant waves of COVID-19 (original, alpha, and delta) and the omicron era up to August, 2023, among children with hospital admissions associated with COVID-19 the number with PIMS decreased from 1575 (11·2%) of 14020 to 270 (0·8%) of 31905; the corresponding proportion of intensive care unit admissions decreased from 1175 (8·4%) to 1390 (4·4%).[7] PIMS can lead to severe outcomes such as coronary artery aneurysms, cardiac dysfunction, multiorgan inflammation, and thromboembolism.[8–11] Similarly, SARS-CoV-2 infection in adults is associated with higher risks of arterial thrombotic events (ATEs) and venous thrombotic events (VTEs) up to 49 weeks after infection.[12,13]

The UK COVID-19 vaccine rollout began on Dec 8, 2020, and prioritised groups based on age, clinical vulnerability, and occupation, as advised by the Joint Committee on Vaccination and Immunisation. Multiple studies have shown that COVID-19 vaccines in children reduce severe infection and hospitalisation.[14–16] However, COVID-19 vaccines have been linked to rare cases of myocarditis or pericarditis in young people, especially among males.[17,18] The short-term risk of myocarditis or pericarditis after vaccination balanced against the risk of severe diseases after SARS-CoV-2 infection in children and young people is an important consideration in vaccination policies.[19]

To inform public health policies, we aimed to assess, in a whole-population study of England, the risks of vascular

and inflammatory complications linked to both first SARS-CoV-2 infection and first COVID-19 vaccination in children and young people. These complications included ATEs, VTEs, thrombocytopenia, myocarditis or pericarditis, and systemic inflammatory conditions leading to hospitalisation or death. Using longitudinal linked primary-care and secondary-care data, we quantified associations between these complications and both first recorded COVID-19 diagnosis (compared with no or before diagnosis) and first COVID-19 vaccination (compared with no or before vaccination).

Methods

Study design and participants

In this retrospective, population-based cohort study in England, data were accessed and analysed in the UK National Health Service (NHS) England Secure Data Environment, via the British Heart Foundation Data Science Centre's[20] CVD-COVID-UK/COVID-IMPACT Consortium.[21] Primary-care data (General Practitioner Data for Pandemic Planning and Research) were available for 98% of the general practices in England, and were linked to secondary-care data (NHS hospital admissions and Hospital Episode Statistics Admitted Patient Care and Secondary Uses Service data), COVID-19 laboratory testing data (Pillar 1 and Pillar 2),[22] national community drug dispensing data (NHS Business Services Authority Dispensed Medicines), the Emergency Care Data Set, and death records from UK Office of National Statistics death registrations. Data from these sources were deterministically linked using unique NHS identifiers at the individual level, as described by Wood and colleagues,[21] providing a nationally representative and longitudinal dataset of more than 58 million individuals in England. Our study followed the RECORD and STROBE guidelines for observational studies using routinely collected health data. No individuals with lived experience were involved in the research or writing process.

We defined an infection cohort following individuals' outcomes associated with COVID-19 diagnosis from Jan 1, 2020 (study start date), to March 31, 2022 (study end date aligning with the end of community testing recording and free mass testing in England), and a vaccination cohort following individuals' outcomes associated with vaccination from Aug 6, 2021 (study start date, when vaccination rollout started for children in England), to Dec 31, 2022 (study end date). Both cohorts comprised children and young people younger than 18 years, registered with a general practitioner in England, with known sex, age, and region, and who were alive on the study start date. In the infection cohort, children born during the follow-up period were included, with their date of birth defined as the study start date, and those with a COVID-19 diagnosis before Jan 1, 2020, were excluded. In the vaccination cohort, children younger than 5 years were excluded because they were not offered COVID-19 vaccination in England during the study period investigated.

The North East—Newcastle and North Tyneside 2 Research Ethics Committee provided ethical approval for the CVD-COVID-UK/COVID-IMPACT research programme (20/NE/0161) to access, within secure trusted research environments, unconsented, whole-population, de-identified data from electronic health records collected as part of patients' routine health care. This analysis followed a prespecified plan, with variable definitions and code available online. Analyses used Spark SQL, Python, and R (version 4.1.3).

Exposures

COVID-19 diagnosis was defined at the earliest recorded date of a positive COVID-19 PCR or antigen test, or a confirmed COVID-19 diagnosis in primary-care or secondary-care hospital admission records, as defined in previous analyses.[13] Individuals who were hospitalised with a first COVID-19 primary diagnosis within 4 weeks of a confirmed SARS-CoV-2 infection (RT-PCR or antigen test) were categorised as hospitalised COVID-19 diagnosis; otherwise, they were categorised as non-hospitalised COVID-19 diagnosis.

COVID-19 vaccination was defined as a record of the first dose of the BNT162b2 mRNA (Pfizer–BioNTech) vaccine. In the UK, the Pfizer–BioNTech vaccine was initially authorised for children aged 16 years and older on Dec 2, 2020. This authorisation was extended to those aged 12–15 years from June 4, 2021, and to those aged 5–11 years from Dec 22, 2021. Individuals receiving other vaccine types were excluded.

The infection cohorts comprised children with or without a COVID-19 diagnosis, and the vaccination cohort comprised children with or without COVID-19 vaccination. These two cohorts are not mutually exclusive. To allow for independent estimation of risks following each exposure, follow-up time was not censored by the other exposure.

Outcomes

Outcomes (appendix p 1) were identified from hospitalisation and death records using ICD-10, and from Emergency Care Data Set data using clinically verified Systematized Nomenclature of Medicine Clinical Terms for the following conditions: ATEs (acute myocardial infarction or ischaemic stroke [ischaemic or unclassified stroke, spinal stroke, or retinal infarction]); VTEs (pulmonary embolism, lower limb deep venous thrombosis, other deep vein thrombosis, intracranial venous thrombosis, portal vein thrombosis, or other vein thromboses); any thrombocytopenia (idiopathic, primary, secondary, or unspecified); myocarditis or pericarditis; and systemic inflammatory conditions (including mucocutaneous lymph node syndrome [Kawasaki disease], systemic inflammatory response syndrome, and PIMS or

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For more on the **study analysis variable definitions and code** see https://github.com/BHFDSC/CCU002_07

See **Online** for appendix

MIS-C). Conditions were grouped together due to their rarity in children younger than 18 years.

We prespecified the following covariates as potential confounders of adverse outcomes following COVID-19 diagnosis and vaccination: sex (female or male), age (years), ethnicity (White, Mixed, Asian or South Asian, Black, Other, or Missing), region (East of England, East Midlands, London, North East, North West, South East, South West, West Midlands, or Yorkshire and Humber), area level deprivation (quintiles from 1—most deprived to 5—least deprived), number of general practitioner contacts in the 12 months before study start, and number of prescribed medications in the previous 3 months (British National Formulary coded). Covariates were identified from primary-care and secondary-care records using the latest records available up to the study start date for each individual. All covariates were complete (ie, had no missing values) by design.

	Analytic cohort to evaluate COVID-19 diagnoses (Jan 1, 2020–March 31, 2022)		Analytic cohort to evaluate COVID-19 vaccinations (Aug 6, 2021–Dec 31, 2022)	
	Participants (n=13 896 125)	First COVID-19 diagnoses (n=3 903 410)	Participants (n=9 245 395)	First BNT162b2 COVID-19 vaccines (n=3 407 560)
Sex				
Female	6 784 260 (48·8%)	1 979 450 (50·7%)	4 510 490 (48·8%)	1 683 420 (49·4%)
Male	7 111 865 (51·2%)	1 923 960 (49·3%)	4 734 905 (51·2%)	1 724 140 (50·6%)
Age, years				
0 to 4	4 683 300 (33·7%)	684 995 (17·5%)	..	..
5 to 11	5 060 030 (36·4%)	1 780 045 (45·6%)	5 042 900 (54·5%)	812 400 (23·8%)
12 to 15	2 772 430 (20·0%)	996 000 (25·5%)	2 842 105 (30·7%)	1 678 055 (49·2%)
16 to <18	1 380 365 (9·9%)	442 365 (11·3%)	1 360 385 (14·7%)	917 105 (26·9%)
Ethnicity				
White	9 979 420 (71·7%)	3 177 570 (81·4%)	6 684 140 (72·3%)	2 666 195 (78·2%)
Black	747 645 (5·4%)	106 440 (2·7%)	504 400 (5·5%)	97 465 (2·9%)
Mixed	646 245 (4·7%)	154 415 (4·0%)	403 295 (4·4%)	113 255 (3·3%)
South Asian	1 679 950 (12·1%)	330 195 (8·5%)	1 099 905 (11·9%)	392 130 (11·5%)
Other	578 820 (4·2%)	99 705 (2·7%)	378 730 (4·1%)	98 315 (2·9%)
Missing	264 045 (1·9%)	35 085 (0·9%)	174 915 (1·9%)	40 225 (1·2%)
Index of multiple deprivation quintile				
1: Most deprived	3 427 280 (24·7%)	767 175 (19·7%)	2 272 250 (24·6%)	590 830 (17·3%)
2	2 912 535 (21·0%)	731 365 (18·7%)	1 900 980 (20·6%)	608 240 (17·8%)
3	2 610 495 (18·8%)	754 060 (19·3%)	1 718 840 (18·6%)	659 030 (19·3%)
4	2 459 600 (17·7%)	782 375 (20·0%)	1 643 415 (17·8%)	712 750 (20·9%)
5: Least deprived	2 486 220 (17·9%)	868 435 (22·2%)	1 709 910 (18·5%)	836 710 (24·7%)
Region				
East of England	1 532 585 (11·0%)	474 510 (12·2%)	1 021 200 (11·0%)	403 080 (11·8%)
East Midlands	1 154 830 (8·3%)	340 705 (8·7%)	773 155 (8·4%)	304 995 (9·0%)
London	2 418 520 (17·4%)	506 745 (13·0%)	1 562 510 (16·9%)	450 965 (13·2%)
North East	607 675 (4·4%)	185 510 (4·8%)	406 160 (4·4%)	150 625 (4·4%)
North West	1 821 990 (13·1%)	493 480 (12·6%)	1 216 270 (13·2%)	412 600 (12·1%)
South East	2 249 605 (16·2%)	708 720 (18·2%)	1 517 520 (16·4%)	652 175 (19·1%)
South West	1 252 440 (9·0%)	404 130 (10·4%)	841 985 (9·1%)	363 250 (10·7%)
West Midlands	1 508 090 (10·9%)	421 180 (10·8%)	1 006 365 (10·9%)	346 395 (10·2%)
Yorkshire and Humber	1 350 395 (9·7%)	368 430 (9·4%)	900 225 (9·7%)	323 480 (9·5%)
Number of general practitioner contacts in the 12 months before study start				
0	6 047 705 (43·5%)	1 417 175 (36·3%)	3 042 225 (32·9%)	890 420 (26·1%)
1–6	7 062 085 (50·8%)	2 244 670 (57·5%)	5 681 800 (61·5%)	2 259 260 (66·3%)
≥7	786 330 (5·7%)	241 565 (6·2%)	521 365 (5·6%)	257 875 (7·6%)
Number of medications in the previous 3 months				
0	11 208 785 (80·7%)	3 009 595 (77·1%)	7 482 110 (80·9%)	2 613 675 (76·7%)
1–2	2 309 515 (16·6%)	771 580 (19·8%)	1 510 975 (16·3%)	677 045 (19·9%)
≥3	377 820 (2·7%)	122 240 (3·1%)	252 305 (2·7%)	116 840 (3·4%)

Data are n (%). In line with NHS England disclosure rules, counts of less than 10 were reported as less than 10, and other numbers rounded to the nearest 5. Percentages were calculated from rounded counts.

Table 1: **Cohort characteristics**

Statistical analysis

We described baseline characteristics by cohort and exposure status. Outcome events and person-years were reported overall and by exposure, with crude incidence rates per 100 000 person-years. In line with NHS England disclosure rules, counts of less than 10 were reported as less than 10, and other numbers rounded to the nearest 5. Percentages and incidence rates were calculated from rounded counts; incidence rates based on fewer than 10 events should be interpreted as upper bounds.

We analysed the time from COVID-19 diagnosis to the first event for each outcome by fitting Cox models with a calendar time scale (to account for secular changes in absolute risk), starting from Jan 1, 2020. We estimated adjusted hazard ratios (aHRs) and 95% CIs by comparing the risk of each outcome after COVID-19 diagnosis with the risk before or without COVID-19 diagnosis for the following time intervals: day 0, week 1, weeks 2–4, weeks 5–26, weeks 27–52, and more than 52 weeks since COVID-19 diagnosis. A substantial proportion of outcome events were recorded on the day of COVID-19 diagnosis (day 0), which might have resulted from additional investigations performed during hospital admissions or health-care visits in patients with COVID-19 concomitant symptoms. To minimise the potential of reverse causality, we separated day 0 in all analyses.

We analysed the time from COVID-19 vaccination to the first event for each outcome by fitting Cox models with a calendar timescale (to account for secular changes in absolute risk), starting from Aug 6, 2021. We estimated aHRs and corresponding 95% CIs by comparing the risk of each outcome after COVID-19 vaccination with the risk before or without COVID-19 vaccination for the following time intervals: 1 week, 2–4 weeks, 5–26 weeks, and more than 26 weeks since COVID-19 vaccination.

When both exposure (COVID-19 diagnosis or vaccination) and the outcome occurred on the same day, we enumerated these occurrences and assumed that exposure happened first. Individuals in both cohorts were followed up to whichever was earliest out of death, outcome event of interest, or the study end date. Follow-up duration varied by individual depending on their index exposure date and censoring.

To improve computational efficiency, for each analysis we included all children and young people with the outcome of interest (cases), along with a random sample of other children and young people at a 20:1 ratio relative to the number of cases. We applied inverse probability weights to account for this sampling, and robust variances were used to calculate CIs. For each outcome we estimated hazard ratios (HRs) adjusting for age and sex (minimally adjusted) and for all measured confounders (maximally adjusted).[12,13,23] We treated age, age squared, number of general practitioner–patient contacts, and medications as continuous confounders, and others as binary or categorical.

We did subgroup analyses for all outcomes by age group, sex, ethnic group, area deprivation quintile, and COVID-19 hospitalisation status (for the infection cohort only). Sensitivity analyses were performed as follows: using hospitalisation and death records (excluding Emergency Care Data Set data); treating PIMS or MIS-C as a separate outcome; and stratifying the analysis for COVID-19 diagnosis by period (January, 2020–May, 2021 *vs* June, 2021–March, 2022) with censoring by vaccination in the second period.

We calculated the absolute excess risk (AER) for each exposure and outcome using a life-table approach. AER for the infection cohort was also calculated for individuals aged between 5 and younger than 18 years for direct comparison with the vaccination cohort. The life table was populated with the estimated average daily incidence rate of each outcome in the unexposed population (q) for each follow-up day, from which we derived the daily survival and cumulative survival rates for the unexposed population. We then derived the daily incidence rate and 95% CIs for the exposed group by multiplying q by the corresponding estimated aHR for each follow-up period. From this calculation, we derived the daily survival rate and cumulative survival rate and their 95% CIs for the exposed population. Finally, we generated the AER as the difference in cumulative survival rates between the unexposed and exposed populations at 180 days, providing the excess number of events per 100 000 children or young people after infection or vaccination.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

There were 13 896 125 children and young people included in the infection analytic cohort. 6 784 260 (48·8%) participants were female and 7 111 865 (51·2%) male; 4 683 300 (33·7%) were aged 0–4 years, 5 060 030 (36·4%) were aged 5–11 years, and 4 152 795 (29·9%) were aged 12 to younger than 18 years; and 9 979 420 (71·7%) were White, 1 679 950 (12·1%) South Asian, 747 645 (5·4%) Black,

	Analytic cohort to evaluate COVID-19 diagnoses (Jan 1, 2020–March 31, 2022)			Analytic cohort to evaluate COVID-19 vaccinations (Aug 6, 2021–Dec 31, 2022)		
	n	Person-years	Incidence rate, per 100 000 person-years	n	Person-years	Incidence rate, per 100 000 person-years
Arterial thrombotic events	1565	29 747 116	5·26 (5·00–5·53)	680	12 967 636	5·24 (4·86–5·65)
Acute myocardial infarction	120	29 748 490	0·39 (0·32–0·46)	40	12 968 046	0·31 (0·22–0·42)
Stroke	1375	29 747 280	4·72 (4·48–4·98)	1030	12 967 667	7·94 (7·47–8·44)
Other arterial embolism	40	29 748 561	0·13 (0·10–0·18)	10	12 968 062	0·08 (0·04–0·14)
Venous thrombotic events	3165	29 745 981	10·64 (10·27–11·02)	1725	12 966 957	13·30 (12·68–13·95)
Pulmonary embolism	1920	29 747 073	6·71 (6·42–7·01)	1080	12 967 395	8·33 (7·83–8·86)
Deep vein thrombosis	900	29 747 796	3·06 (2·86–3·26)	520	12 967 718	4·01 (3·67–4·38)
Intracranial venous thrombosis	145	29 748 458	0·50 (0·43–0·59)	65	12 968 027	0·50 (0·39–0·64)
Portal vein thrombosis	50	29 748 555	0·17 (0·12–0·22)	25	12 968 046	0·19 (0·12–0·29)
Other deep vein thrombosis	900	29 748 465	0·47 (0·40 –0·56)	70	12 968 026	0·54 (0·42–0·69)
Thrombocytopenia	2500	29 746 363	8·40 (8·08–8·74)	1030	12 967 324	7·94 (7·47–8·44)
Myocarditis or pericarditis	1330	29 747 597	4·47 (4·23–4·72)	900	12 967 435	6·94 (6·49–7·41)
Myocarditis	520	29 748 250	1·75 (1·60–1·90)	335	12 967 824	2·58 (2·31–2·88)
Pericarditis	870	29 747 910	2·91 (2·72–3·11)	605	12 967 659	4·67 (4·30–5·05)
Inflammatory conditions	2395	29 746 577	8·05 (7·73–8·38)	895	12 967 193	6·90 (6·46–7·37)
Kawasaki disease	1315	29 747 253	4·54 (4·30–4·79)	270	12 967 860	2·08 (1·84–2·35)
Systemic inflammatory response syndrome	<10	29 748 605	..	<10	12 968 069	..
PIMS or MIS-C	1135	29 747 867	3·82 (3·60–4·04)	650	12 967 368	5·01 (4·63–5·41)

Data are n or incidence rate (95% CI). In line with NHS England disclosure rules, counts of less than 10 were reported as less than 10, and other numbers rounded to the nearest 5. Incidence rates were calculated from rounded counts; incidence rates based on fewer than 10 events should be interpreted as upper bounds. PIMS=paediatric inflammatory multisystem syndrome. MIS-C=multisystem inflammatory syndrome in children.

Table 2: **Arterial thrombotic, venous thrombotic, other vascular, and inflammatory events in the overall infection cohort and vaccination cohort**

646 245 (4·7%) Mixed, 578 820 (4·2%) from other ethnic groups, and 264 045 (1·9%) with missing ethnicity data. 3 427 280 (24·7%) participants lived in the most deprived area quintile (table 1).

During 15 months of follow-up, we identified 3 903 410 individuals with a first COVID-19 diagnosis. Those with a recorded COVID-19 diagnosis were more likely to be female, older, of White ethnicity, from less deprived areas, and have more frequent general practitioner contacts than the general population. Among those in the infection cohort there were 1565 incident ATEs (incidence rate 5·26 per 100 000 person-years [95% CI 5·00–5·53]), 3165 VTEs (10·64 per 100 000 person-years [10·27–11·02]), 2500 thrombocytopenia events (8·40 per 100 000 person-years [8·08–8·74]), 1330 myocarditis or pericarditis events (4·47 per 100 000 person-years [4·23–4·72]), and 2395 systemic inflammatory conditions (8·05 per 100 000 person-years [7·73–8·38]; table 2). Crude incidence rates were higher for those with a recorded COVID-19 diagnosis, compared with those without or before diagnosis (appendix p 2).

For all outcomes, HRs were highest on the day of COVID-19 diagnosis (day 0), particularly among individuals hospitalised with COVID-19 (appendix p 3). Across all outcomes and time periods after COVID-19 diagnosis, maximally adjusted HRs were modestly lower than age-adjusted and sex-adjusted HRs (figure 1). The highest rise in risk was observed for systemic inflammatory conditions (aHR 14·84 [95% CI 11·01–19·99]) in week 1 after COVID-19 diagnosis, followed by VTEs (4·90 [3·66–6·55]), thrombocytopenia (3·64 [2·21–6·00]),

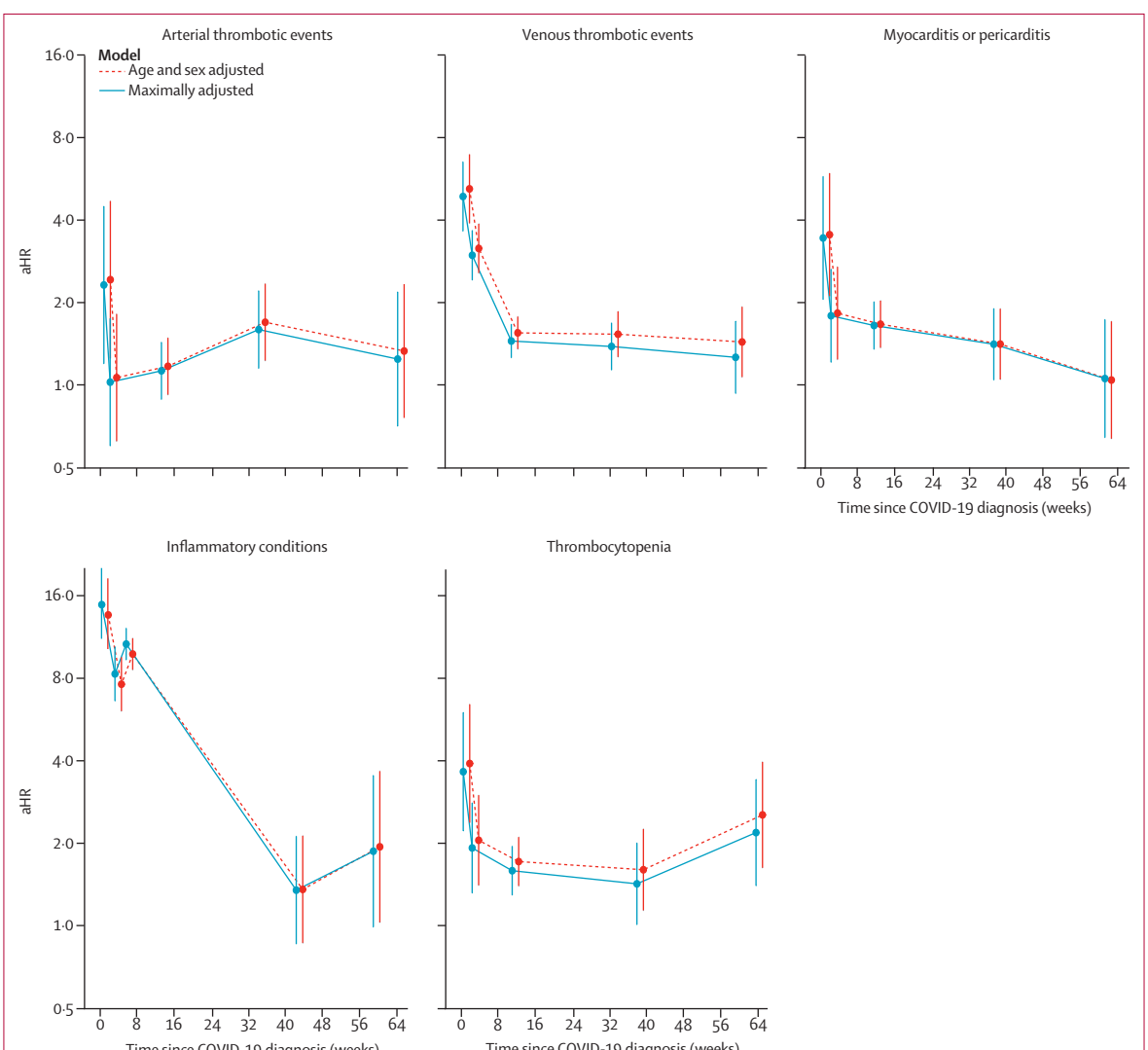

Figure 1: **aHRs comparing the incidence of cardiovascular and inflammatory outcomes in children after versus before COVID-19 diagnosis**
Bars represent 95% CIs. All fully adjusted estimates are plotted at the median time of the outcome event within each follow-up period (in weeks 1, 2–4, 5–26, 27–52, and >52); estimates for the age-adjusted and sex-adjusted model are slightly offset to the right to ensure visual clarity. Events on the day of COVID-19 diagnosis (day 0) were excluded. Numerical values of aHRs and 95% CIs are in the appendix (p 3). aHR=adjusted hazard ratio.

myocarditis or pericarditis (3·46 [2·06–5·80]), and ATEs (2·33 [1·20–4·51]). The risk of each outcome generally declined rapidly after the first week but remained elevated in the interval beyond 26 weeks up to 52 weeks after COVID-19 diagnosis for VTEs (1·39 [1·14–1·69]), thrombocytopenia (1·42 [1·01–2·00]), and myocarditis or pericarditis (1·42 [1·05–1·91]), and ATEs (1·60 [1·15–2·22]). In subgroup analyses, week 1 aHRs for ATEs were greater in those with higher index of deprivation (most deprived) and remained elevated after the first week since COVID-19 diagnosis (appendix pp 4–7, 21–25). aHRs for ATEs, VTEs, thrombocytopenia, and inflammatory conditions were substantially higher during weeks 1–4 after hospitalised than non-hospitalised COVID-19. There were no consistent differences in aHRs between age groups, sex, and ethnicity. In sensitivity analyses restricted to records extracted from hospitalisation and death records (appendix pp 8–9, 26), aHRs for PIMS or MIS-C were higher than those for all inflammatory conditions during weeks 1–26 (appendix p 11). In analyses stratified by calendar period, the aHRs were generally lower in the later versus earlier period of the COVID-19 pandemic (appendix pp 12–13, 16).

There were 9 245 395 children and young people aged between 5 and younger than 18 years included in the vaccination analytic cohort; characteristics were similar to those in the cohort used for the COVID-19 diagnosis analysis (table 1). During 17 months of follow-up, we identified 3 407 560 recipients of their first COVID-19 vaccine dose (table 1). Those vaccinated were more likely to be from less deprived areas (836 710 [24·7%] from the least deprived area quintile, and 590 830 [17·3%] from the most deprived area quintile), to have had more general practitioner contacts, and to have received more medications than the general population.

Among those in the vaccination cohort, there were 680 incident ATEs (incidence rate 5·24 [95% CI

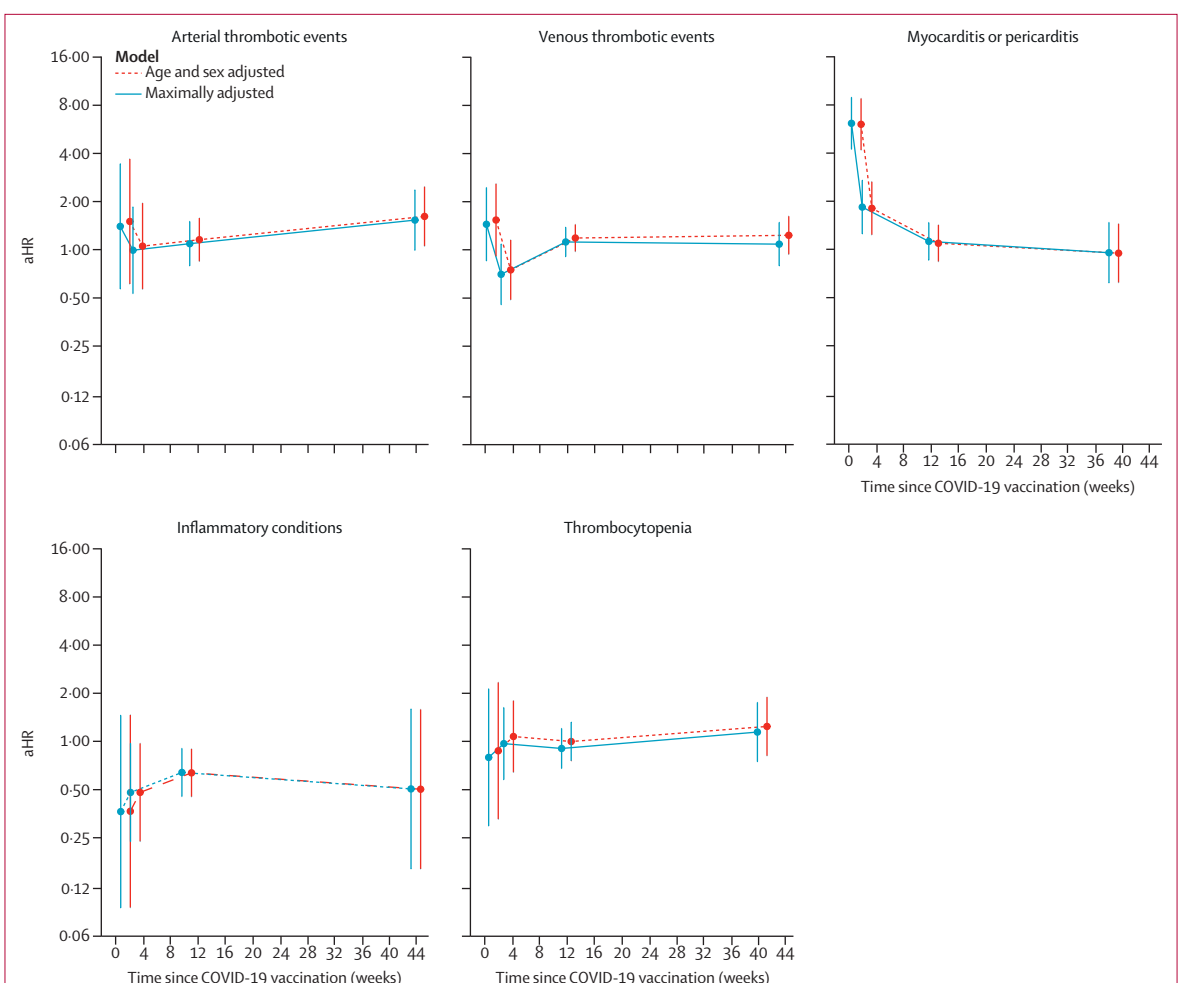

Figure 2: **aHRs comparing the incidence of cardiovascular and inflammatory outcomes in children after versus before a BNT162b2 vaccination against COVID-19**

Bars represent 95% CIs. All fully adjusted estimates are plotted at the median time of the outcome event within each follow-up period (in weeks 1, 2–4, 5–26, and >26); estimates for the age-adjusted and sex-adjusted model are slightly offset to the right to ensure visual clarity. Numerical values of aHRs and 95% CIs are in the appendix (p 15). aHR=adjusted hazard ratio.

4·86–5·65]), 1725 VTEs (13·30 [12·68–13·95]), 1030 thrombocytopenia events (7·94 [7·47–8·44]), 900 myocarditis or pericarditis events (6·94 [6·49–7·41]), and 895 inflammatory conditions (6·90 [6·46–7·37]; table 2). Crude incidence rates for all outcomes, with the exception of myocarditis or pericarditis, were generally lower for those who were vaccinated than unvaccinated (appendix p 14).

Across all outcomes and time periods after COVID-19 vaccination, maximally adjusted HRs were similar to age-adjusted and sex-adjusted HRs (figure 2, appendix p 15). The risk of myocarditis or pericarditis was elevated in the first 4 weeks after vaccination, with the aHR declining from 6·17 (95% CI 4·24–8·96) in week 1 to 1·84 (1·25–2·72) in weeks 2–4 since vaccination. aHRs for inflammatory conditions were lower than other outcomes in the first 6 months after vaccination than for all other outcomes: 0·36 (0·09–1·44) for week 1, 0·47 (0·23–0·96) for weeks 2–4, 0·63 (0·45–0·89) for weeks 5–26, and 0·50 (0·16–1·58) for after week 26. There were no consistent trends in associations between time since COVID-19 vaccination and ATEs, VTEs, or thrombo cytopenia.

In subgroup analyses, aHRs for myocarditis or pericarditis were higher in younger children aged 5–11 years, with the highest risk 11·27 (95% CI 3·29–38·60) observed during week 1 after vaccination (appendix pp 16–17, 27–31). There were no consistent differences between age groups, sex, ethnicity, or index of deprivation. Similar results were found in sensitivity analyses restricted to records extracted from hospitalisation and death records (appendix pp 8, 30). In sensitivity analyses, findings remained consistent when PIMS or MIS-C was examined as a separate outcome (appendix p 11).

We also estimated AERs of each outcome following first COVID-19 diagnosis or vaccination among individuals aged 5–18 years (figure 3, appendix p 19). The estimated AER of ATEs in the 6 months following a COVID-19 diagnosis was 0·88 per 100 000 (95% CI –0·08 to 2·28) in individuals diagnosed with COVID-19 between the ages of 5 and 18 years. Corresponding AERs were 5·58 per 100 000 (3·65–7·92) for VTEs, 2·28 per 100 000 (1·12–3·85) for thrombocytopenia, 2·24 per 100 000 (1·11–3·80) for myocarditis or pericarditis, and 17·43 per 100 000 (14·67–20·71) for inflammatory conditions in children and young people diagnosed with COVID-19. AERs were higher in the first versus second period of the COVID-19 pandemic for all outcomes except for inflammatory conditions (appendix p 34). In comparison, AERs were 0·85 per 100 000 (0·07 to 1·91) for myocarditis or pericarditis and –1·61 per 100 000 (–2·41 to –0·31) for inflammatory conditions during the 6 months following first COVID-19 vaccination in individuals aged 5–18 years. AERs for all other outcomes assessed were negligible.

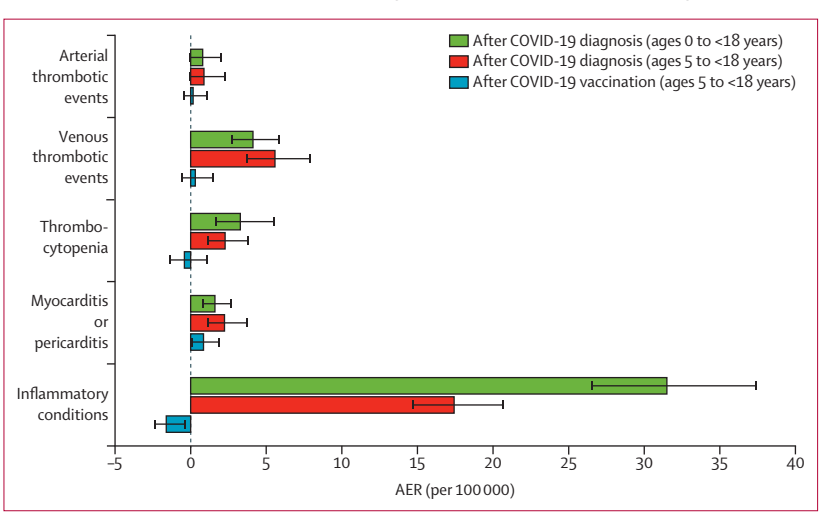

***Figure 3*: Estimated AER (per 100 000) of cardiovascular and inflammatory outcomes after 6 months of COVID-19 diagnosis or vaccination**

Bars represent AER point estimates, and whiskers represent 95% CIs. Numerical values of AERs and 95% CIs are in the appendix (pp 19–20). AER=absolute excess risk.

Discussion

Our study shows that children and young people are at higher risk of rare vascular and inflammatory conditions persisting beyond 12 months following a first COVID-19 diagnosis compared with no COVID-19 diagnosis or before COVID-19 diagnosis. Following first COVID-19 vaccination, although the presentation of myocarditis or pericarditis was rare, we found an elevated risk of myocarditis or pericarditis in the first 4 weeks after COVID-19 vaccination compared with no vaccination or before vaccination. The risk following vaccination was found to be much lower than the risk following COVID-19 infection. These findings are crucial for policy makers and caregivers in making informed decisions regarding vaccination consent for children and young people.

Like other studies of vascular disease risk after COVID-19 diagnosis in children and young people,[24,25] we found that the incidence of VTEs, thrombocytopenia, and myocarditis or pericarditis was markedly elevated in the first month after infection, but persisted for longer than previously reported, remaining elevated beyond 12 months. This prolonged risk might be related to a sustained post-infectious inflammatory response, potentially linked to syndromes such as MIS-C, and appears to primarily affect the venous rather than arterial circulation. However, it remains unclear whether this effect is primarily driven by endothelial, leukocyte, or other inflammatory components.[13]

Our findings are consistent with reports of MIS-C following SARS-CoV-2 infection, supporting further research into the mechanisms underlying these outcomes and potential therapeutic strategies to mitigate them. Our study also indicates that, although there is an initial elevated risk of ATEs in children and young people after COVID-19 diagnosis, this risk declines more rapidly compared with in adults. Knight and colleagues[13] found that adults had a more sustained and higher risk of ATEs

after SARS-CoV-2 infection, suggesting age-related differences in the vascular response to COVID-19. This comparison adds valuable context to understanding how COVID-19 affected cardiovascular health differently across age groups, emphasising the need for age-specific health-care strategies in managing post-COVID-19 outcomes. Furthermore, our results suggest a temporal weakening in the association between first COVID-19 diagnosis and subsequent inflammatory and vascular disease risk, probably reflecting shifts in the epidemiology and pathogenicity of circulating SARS-CoV-2 variants, which could continue to fluctuate over time.

Our findings indicate a complex temporal effect of COVID-19 vaccination on vascular and inflammatory diseases. Short-term higher risks of rare events of myocarditis or pericarditis should be considered alongside lower risks of less rare inflammatory conditions. Our findings are consistent with other publications that showed a higher risk of myocarditis or pericarditis following mRNA vaccines, especially among male individuals aged 12–29 years.[26–28] In adults, especially those aged 70 years and older, vaccination with ChAdOx1 and BNT162b2 was linked to a reduced risk of major ATEs and VTEs compared with unvaccinated individuals.[23] However, our study did not observe a similar reduction in the post-vaccination risk of these thromboembolic events. This difference could be due to several factors: children are rarely affected by thrombotic events, and the baseline risk of vascular diseases is substantially lower in children compared with adults. Differences in immune and inflammatory responses to the vaccine might differ between these age groups, potentially influencing the outcomes observed.

Our findings should not be misinterpreted as evidence to challenge the safety and efficacy of mRNA COVID-19 vaccines in children and young people. Although we observed a short-term higher risk of myocarditis or pericarditis following first vaccination, these events were very rare and not sustained,[29] whereas SARS-CoV-2 infection was associated with rare but more frequent and longer-lasting vascular and inflammatory outcomes.[30] Taken together with extensive evidence that vaccination markedly reduces the risk of severe COVID-19, hospitalisation, and related complications,[31,32] our results reinforce that the benefits of mRNA COVID-19 vaccination clearly outweigh its small risks and that these vaccines have played a critical role in protecting this population.

The strengths of our study include its comprehensive analysis of whole-population electronic health records covering 98% of England's population—reflecting national geographic, socioeconomic, and ethnic diversity—making it, to our knowledge, the largest study to date to investigate the association of COVID-19 with vascular and inflammatory diseases in children and young people, and providing sufficient power to detect differences for rare events. To ensure transparent and comparable measures of the impact of both first COVID-19 diagnosis and vaccination in younger populations, we used consistent cohort study designs in all analyses. We also described the impact of both COVID-19 diagnosis and vaccination in younger populations. The unique scale and linkage of our study across primary, secondary, and emergency care records enabled robust outcome ascertainment and facilitated the investigations and subgroup analyses of rare outcomes, such as VTEs, myocarditis or pericarditis, and MIS-C associated with COVID-19. To minimise confounding, we adjusted for several potential confounders, including non-linear relationships between age and the outcomes.

There are potential limitations to our study. First, the identification of exposures, outcomes, and covariates relies on the accuracy of electronic health records. Associations with COVID-19 diagnosis might have been underestimated due to unrecorded infections early in the COVID-19 pandemic (2020), low levels of testing, and undetected asymptomatic infections, especially in children aged 0–4 years.[33] Additional laboratory and imaging data could have improved outcome ascertainment, particularly for thrombocytopenia and myocarditis. Differential ascertainment across age groups could have occurred due to varying thresholds and protocols for testing. Second, differences in vaccine uptake and dosing scheduling might have influenced the results. Third, we separated events recorded on the day of COVID-19 diagnosis (day 0) from those in weeks 1–4, as many events occurred on day 0. The distinct aHRs across these periods suggest that reverse causality was unlikely to explain the elevated risks. Fourth, earlier vaccination among immunocompromised individuals might have diluted vaccine effectiveness estimates.[25] Fifth, we did not account for subsequent or combined exposures, whether reported or unreported. Relative risks following a COVID-19 diagnosis might be higher[12] or potentially lower among unvaccinated individuals. Sixth, only first COVID-19 diagnosis and vaccination were considered, and not repeated exposures. Findings among adults suggest a lowering of risks of adverse effects for repeated vaccination.[34]

In summary, this large, national cohort study shows that children and young people face higher risks of rare vascular and inflammatory diseases up to 12 months after first COVID-19 diagnosis and higher risk of rare myocarditis or pericarditis up to 4 weeks after a first BNT162b2 vaccine, although the risk following vaccination is substantially lower than the risk following infection. These findings are of great importance for national policy makers and caregivers considering vaccination consent for children, and support the public health strategy of COVID-19 vaccination in children and young people to mitigate the more frequent and persistent risks associated with SARS-CoV-2 infection.

Contributors
AS, WS, KLB, JACS, WNW, GC, and AMW contributed to conceptualisation. AS, WS, WNW, GC, and AMW contributed to the

methodology. AS and WS contributed to formal analysis and visualisation. AS, TB, GC, and AMW contributed to investigation. AS, WS, TB, and GC contributed to data curation. AS and AMW wrote the original draft. GC and AMW supervised the study. All authors made substantial contributions to the interpretation of the data, reviewed and edited the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests

KK reports grants, contracts, consulting fees, or honoraria from Amgen, Applied Therapeutics, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, Sanofi, Servier, Oramed Pharmaceuticals, Pfizer, Roche, Daiichi-Sankyo, Embecta, and Nestle Health Science; and membership of and chairing the ethnicity subgroup of the UK Scientific Advisory Group for Emergencies. All other authors declare no competing interests.

Data sharing

The data used in this study are available in NHS England's Secure Data Environment (SDE) service for England, but as restrictions apply, they are not publicly available (https://digital.nhs.uk/services/secure-data-environment-service). The CVD-COVID-UK/COVID-IMPACT programme led by the British Heart Foundation (BHF) Data Science Centre (https://bhfdatasciencecentre.org/) received approval to access data in NHS England's SDE service for England from the Independent Group Advising on the Release of Data (https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/independent-group-advising-on-the-release-of-data) via an application made in the Data Access Request Service Online system (DARS-NIC-381078-Y9C5K; https://digital.nhs.uk/services/data-access-request-service-dars/dars-products-and-services). The CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board (https://bhfdatasciencecentre.org/areas/cvd-covid-uk-covid-impact/) subsequently granted approval to this project to access the data within NHS England's SDE service for England. The de-identified data used in this study were made available to accredited researchers only. Those wishing to gain access to the data should contact bhfdsc@hdruk.ac.uk in the first instance.

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