OBSERVATIONS: BRIEF RESEARCH REPORTS

Sickle Cell Disorders and Severe COVID-19 Outcomes: A Cohort Study

Background: Sickle cell disease is a collection of compound heterozygote hemoglobinopathies, including sickle cell anemia (1). The heterozygote hemoglobinopathies are characterized by erythrocyte deformation with hemolysis; immune and coagulation dysfunction; and chronic complications, including pulmonary hypertension and cardiac failure (1, 2). Sickle cell trait is a carrier status for sickle cell disease. Given the established susceptibility to other viral infections and the ethnic "patterning" of sickle cell disorders, affected persons may have increased risks for severe COVID-19. Evidence about COVID-19 risks in sickle cell disorders mostly derives from studies of hospitalized persons or selective registries (3–5). Robust quantification of risks in sickle cell disorders at a population level may be informative for public health strategies.

Objective: To evaluate the risks for COVID-19–related hospitalization and death in children and adults with sickle cell disorders (disease and trait, separately) using a population-level database of linked electronic health care records.

Methods and Findings: A cohort study of 12.28 million persons aged 0 to 100 years was done using QResearch, a primary care database covering approximately 18% of the English population. The cohort comprised 1317 general practices with individual-level linkage to SARS-CoV-2 test results from Public Health England, hospital admissions data, and the Office for National Statistics death register. Follow-up was from 24 January 2020 to 30 September 2020 (hospitalization) and 18 January 2021 (death). Cause-specific Cox regression models stratified by individual general practice were used to estimate hazard ratios (HRs) with 95% CIs for COVID-19–related hospitalization and COVID-19–related death associated with sickle cell disease (genotypes SC, SD, or SE; sickle cell anemia; thalassemia with hemoglobin S; sickle thalassemia; or not otherwise specified) and sickle cell trait. Models were adjusted for age, sex, and ethnicity. Hospitalization related to COVID-19 was defined as confirmed or suspected COVID-19 as reason for admission (International Classification of Diseases, 10th Revision, code U07.1 or U07.2) or admission within 14 days of a positive SARS-CoV-2 test result. Death related to COVID-19 was defined as confirmed or suspected COVID-19 on the death certificate (International Classification of Diseases, 10th Revision, code U07.1 or U07.2) or death of any cause within 28 days of confirmed SARS-CoV-2 infection. Missing ethnicity data were handled using multiple imputation (10 imputed data sets); the imputation model included end points and all variables in the **Table**. Analyses used Stata, version 16 (StataCorp).

The **Table** describes the study cohort. There were 5059 (0.04%) persons with sickle cell disease and 25 682 (0.21%) persons with sickle cell trait. During the study, there were 23 699 COVID-19–related hospitalizations, 19 068 COVID-19–related deaths, and 104 499 deaths from any cause.

There were fewer than 5 COVID-19–related hospitalizations in children with sickle cell disorders but no COVID-19–related deaths. Adults with sickle cell disease had 40 (0.79%) hospitalizations and 10 (0.20%) deaths. In the cohort, sickle cell disease was associated with increased risks for COVID-19–related hospitalization (HR, 4.11 [95% CI, 2.98 to 5.66]) and death (HR, 2.55 [CI, 1.36 to 4.75]) (**Figure**). E-values for HRs for COVID-19–related hospitalization and death were 7.69 (lower limit of the CI, 5.41) and 4.54 (lower limit of the CI, 2.06), respectively, suggesting robustness to residual confounding.

Persons with sickle cell trait had 98 (0.38%) hospitalizations and 50 (0.19%) deaths. In the cohort, sickle cell trait was also associated with higher risks for COVID-19–related hospitalization (HR, 1.38 [CI, 1.12 to 1.70]) and death (HR, 1.51 [CI, 1.13 to 2.00]). E-values for COVID-19–related hospitalization and death were 2.1 (lower limit of the CI, 1.49) and 2.39 (lower limit of the CI, 1.51), respectively.

Discussion: Our analysis estimated a 4-fold increased risk for COVID-19–related hospitalization and a 2.6-fold increased risk for COVID-19–related death for sickle cell disease. Sickle cell trait was also associated with increased risks for both outcomes, albeit to a lesser extent. Several aspects of sickle cell phenotypes overlap with the pathophysiology of severe COVID-19 (1, 2), which could be relevant mechanisms worthy of further study, as should the directionality of infection and sickle crisis.

Study limitations include the potential underdiagnosis of sickle cell trait in the population, the rarity of outcomes limiting extended adjustments and sickle subtype–specific or age- or sex-specific analyses, the lack of information on symptoms or presentation, and that the HRs do not possess a direct causal interpretation.

Given that sickle cell disease affects approximately 15 000 persons in the United Kingdom, 100 000 persons in the United States, and 8 million to 12 million persons globally, we believe our results are relevant to policymakers and decision making about vaccination prioritization for potentially high-risk groups.

Ashley Kieran Clift, MBBS
University of Oxford, Oxford, United Kingdom

Defne Saatci, MBChir
University of Oxford, Oxford, United Kingdom

Carol A.C. Coupland, PhD
University of Nottingham, Nottingham, United Kingdom

Hajira Dambha-Miller, PhD
University of Southampton, Southampton, United Kingdom

Julia Hippisley-Cox, MD
University of Oxford, Oxford, United Kingdom

*on behalf of the International Investigator Group for Ethnicity and COVID-19**

* For members of the International Investigator Group for Ethnicity and COVID-19, see the **Appendix**, available at Annals.org.

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Table. Characteristics of the Study Cohort*

Parameter	Persons Without Sickle Cell Disorders, *n* (*column* %)	Persons With Sickle Cell Disease, *n* (*column* %)	Persons With Sickle Cell Trait, *n* (*column* %)
Total	12 247 445	5059	25 682
Positive SARS-CoV-2 test result	541 460 (4.42)	287 (5.67)	1346 (5.24)
COVID-19–related hospitalization	23 561 (0.19)	40 (0.79)	98 (0.38)
COVID-19–related death	19 008 (0.16)	10 (0.20)	50 (0.19)
Death from any cause	104 320 (0.85)	32 (0.63)	147 (0.57)
Sex			
Female	6 112 770 (49.91)	2723 (53.82)	15 787 (61.47)
Male	6 134 675 (50.09)	2336 (46.18)	9895 (38.53)
Age			
0–17 y	2 440 907 (19.93)	1513 (29.91)	5455 (21.24)
18–29 y	1 983 686 (16.20)	973 (19.23)	3545 (13.80)
30–39 y	1 902 466 (15.53)	820 (16.21)	4090 (15.93)
40–49 y	1 615 287 (13.19)	641 (12.67)	4340 (16.90)
50–59 y	1 597 322 (13.04)	647 (12.79)	4639 (18.06)
60–69 y	1 194 049 (9.75)	291 (5.75)	2112 (8.22)
70–79 y	921 254 (7.52)	98 (1.94)	846 (3.29)
80–89 y	470 535 (3.84)	67 (1.32)	565 (2.20)
90–100 y	121 939 (1.00)	<10	90 (0.35)
Ethnicity†			
White	7 518 553 (61.39)	541 (10.69)	2862 (11.14)
South Asian	760 873 (6.21)	139 (2.75)	414 (1.61)
Black	417 131 (3.41)	2626 (51.91)	13 750 (53.54)
Other ethnic group	837 051 (6.83)	1025 (20.26)	5867 (22.84)
Not recorded	2 713 837 (22.16)	728 (14.39)	2789 (10.86)
Body mass index			
<18.5 kg/m^2	465 679 (3.80)	531 (10.50)	925 (3.60)
18.5–24.9 kg/m^2	3 341 248 (27.28)	1522 (30.08)	5528 (21.52)
25–29.9 kg/m^2	2 729 268 (22.28)	905 (17.89)	6322 (24.62)
30–34.9 kg/m^2	1 265 436 (10.33)	377 (7.45)	3867 (15.06)
35–39.9 kg/m^2	479 112 (3.91)	135 (2.67)	1744 (6.79)
≥40 kg/m^2	240 316 (1.96)	76 (1.50)	928 (3.61)
Not recorded	3 726 386 (30.43)	1513 (29.91)	6368 (24.80)
Townsend Deprivation Index score group‡			
1 (most affluent)	2 713 808 (22.16)	306 (6.05)	1259 (4.90)
2	2 660 696 (21.72)	450 (8.90)	2150 (8.37)
3	2 453 767 (20.03)	801 (15.83)	3879 (15.10)
4	2 270 862 (18.54)	1224 (24.19)	6320 (24.61)
5 (least affluent)	2 072 253 (16.92)	2240 (44.28)	11 875 (46.24)
Not recorded	76 059 (0.62)	38 (0.75)	199 (0.77)
Household size			
1 person	3 829 899 (31.27)	1682 (33.25)	8018 (31.22)
2 persons	2 893 184 (23.62)	921 (18.21)	4969 (19.35)
3–5 persons	4 734 341 (38.66)	2017 (39.87)	10 565 (41.14)
6–9 persons	619 718 (5.06)	391 (7.73)	1903 (7.41)
≥10 persons	170 303 (1.39)	48 (0.95)	227 (0.88)
Smoking status			
Nonsmoker	5 940 323 (48.50)	2887 (57.07)	15 751 (61.33)
Former smoker	2 064 366 (16.86)	365 (7.21)	2323 (9.05)
Light smoker (1–9 per day)	1 263 178 (10.31)	373 (7.37)	2088 (8.13)
Moderate smoker (10–19 per day)	256 936 (2.10)	38 (0.75)	229 (0.89)
Heavy smoker (≥20 per day)	117 709 (0.96)	11 (0.22)	95 (0.37)
Not recorded	2 604 933 (21.27)	1385 (27.38)	5196 (20.23)
Congestive heart failure	113 804 (0.93)	59 (1.17)	221 (0.86)
Hypertension	1 639 984 (13.39)	577 (11.41)	5004 (19.48)
Atrial fibrillation	234 951 (1.92)	44 (0.87)	188 (0.73)
Peripheral vascular disease	71 825 (0.59)	17 (0.34)	81 (0.32)
Venous thromboembolism	169 056 (1.38)	208 (4.11)	518 (2.02)
Chronic kidney disease			
Stage 3	344 496 (2.81)	107 (2.12)	981 (3.82)
Stage 4	19 925 (0.16)	<10	63 (0.25)
Stage 5	21 076 (0.17)	39 (0.77)	134 (0.52)
Chronic liver disease	19 586 (0.16)	<10	35 (0.14)
Pulmonary hypertension	9230 (0.08)	62 (1.23)	31 (0.12)
Asthma	1 503 920 (12.28)	549 (10.85)	3224 (12.55)
Chronic obstructive pulmonary disease	225 066 (1.84)	23 (0.45)	137 (0.53)
Bronchiectasis	48 894 (0.40)	29 (0.57)	68 (0.26)
Stroke	208 990 (1.71)	178 (3.52)	378 (1.47)

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Table–Continued

Parameter	Persons Without Sickle Cell Disorders, *n* (*column* %)	Persons With Sickle Cell Disease, *n* (*column* %)	Persons With Sickle Cell Trait, *n* (*column* %)
Type 2 diabetes mellitus	622 357 (5.08)	241 (4.76)	2356 (9.17)
Type 1 diabetes mellitus	50 975 (0.42)	18 (0.36)	186 (0.72)
Dementia	98 963 (0.81)	27 (0.53)	159 (0.62)
Epilepsy	141 726 (1.16)	48 (0.95)	270 (1.05)
Severe mental illness	1 092 363 (8.92)	333 (6.58)	2227 (8.67)
Blood cancer	50 440 (0.41)	23 (0.45)	101 (0.39)
Lung cancer	12 606 (0.10)	0	<10
Rheumatoid arthritis/systemic lupus erythematosus	97 439 (0.80)	61 (1.21)	250 (0.97)

* All of the parameters were used in the multiple imputation model to impute missing data for ethnicity. (Age was handled using a restricted cubic spline with 5 knots in the models but is presented here as a categorical variable for descriptive purposes.) A sex imbalance is noted in those with sickle cell disorders, which suggests differential diagnosis or recording of hemoglobin status between males and females in the United Kingdom.
† Ethnicity refers to self-reported ethnic group in primary care records (Black = Black African, Black Caribbean, or Black other; South Asian = Bangladeshi, Indian, or Pakistani; other = multiracial, Chinese, other Asian, Arab, or other ethnic group).
‡ Five groups, cut at quintiles.

Episode Statistics data and civil registration data used in this analysis are reused by permission from NHS Digital, which retains the copyright. This study was undertaken as part of a larger project, which is detailed at www.qresearch.org/research/approved-research-programs-and-projects/quantifying-the-association-between-covid-19-ethnicity-and-mortality-a-cohort-study-across-three-uk-national-databases.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-1375.

Reproducible Research Statement: *Study protocol:* Available at www.qresearch.org/research/approved-research-programs-and-projects/quantifying-the-association-between-covid-19-ethnicity-and-mortality-a-cohort-study-across-three-uk-national-databases. *Statistical code:* Available on request to Dr. Clift (e-mail, ashley.clift@phc.ox.ac.uk). Code groups used by the researchers are available at www.qresearch.org/qcode-group-library. *Data set:* Access to the anonymized health care data in the QResearch database is on application to the QResearch Scientific Committee by bona fide researchers employed at U.K. academic institutions according to information onwww.qresearch.org.

Corresponding Author: Ashley Kieran Clift, MBBS, Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 4GG, United Kingdom; e-mail, ashley.clift@phc.ox.ac.uk.

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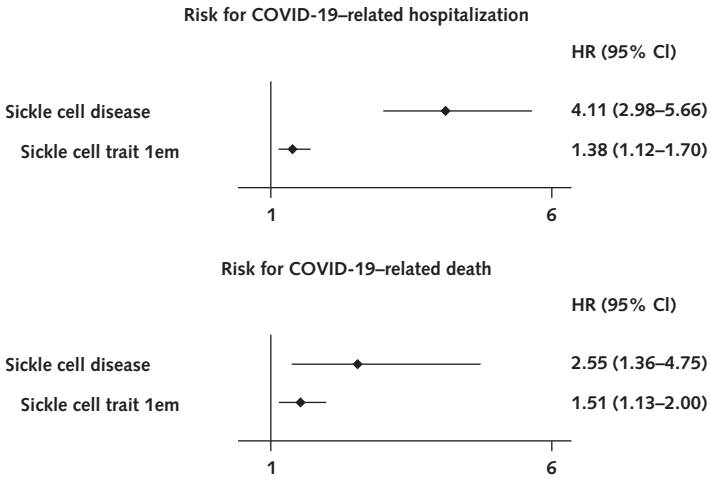
Figure. Adjusted HRs with 95% CIs for the observed associations between sickle cell disease and sickle cell trait with COVID-19–related hospitalization and COVID-19–related death; the reference group is persons without any sickle cell disorder.



Cause-specific Cox regression models were stratified by individual general practice and adjusted for age (restricted cubic spline with 5 knots), sex, and self-reported ethnicity (White, South Asian, Black, and other [including Chinese, multiracial, and Arab]). We did post hoc analyses restricted to those with sickle cell disorders. For COVID-19–related hospitalization, compared with persons with sickle cell trait, those with sickle cell disease had an adjusted HR of 3.00 (95% CI, 1.99 to 4.52). For COVID-19–related death, persons with sickle cell disease had an adjusted HR of 1.37 (CI, 0.62 to 3.02) compared with those with sickle cell trait. HR = hazard ratio.