BMJ Open Respiratory Research

Comparison of clinical characteristics and outcomes of critically ill adults with SARS-CoV-2 infection during Delta and Omicron variant predominance periods: a single-hospital retrospective cohort study

Keerthana Sankar, Neil Modi, Alexander Polyak, Michael P Directo, Lily R Johnson, Norling Kho, Sharon K Isonaka, Isabel Pedraza, Peter Chen, Matthew E Modes

To cite: Sankar K, Modi N, Polyak A, *et al*. Comparison of clinical characteristics and outcomes of critically ill adults with SARS-CoV-2 infection during Delta and Omicron variant predominance periods: a single-hospital retrospective cohort study. *BMJ Open Resp Res* 2023;**10**:e001274. doi:10.1136/bmjresp-2022-001274

NM and AP are joint first authors.

PC and MEM are joint senior authors.

Received 7 April 2022
Accepted 4 February 2023

Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA

Correspondence to
Dr Matthew E Modes; matthew.modes@cshs.org

ABSTRACT

Introduction Initial reports suggest the B.1.1.529 (Omicron) variant of SARS-CoV-2 causes less severe disease compared with the B.1.617.2 (Delta) variant, though more widespread vaccination contributed to these findings. Little is known about clinical characteristics and outcomes of patients with SARS-CoV-2 infection requiring intensive care during periods of Delta and Omicron variant predominance.

Aim To examine and compare characteristics of critically ill adults with SARS-CoV-2 infection during periods of Delta and Omicron variant predominance.

Methods We conducted a retrospective cohort study of critically ill adults with SARS-CoV-2 infection at one academic hospital in Los Angeles during Delta (15 July 2021–23 September 2021) and Omicron (21 December 2021–27 January 2022) predominance. Patient characteristics were compared between Delta-period and Omicron-period hospitalisations, overall and stratified by vaccination status.

Results 79 adults required intensive care during the Delta predominance period and 116 during the Omicron predominance period. We found similar proportions of intensive care unit admissions occurring in fully vaccinated patients between the two periods, despite Los Angeles County data revealing an almost 60% increase in the proportion of SARS-CoV-2 hospitalisations occurring in fully vaccinated persons. There was no difference in the need for invasive mechanical ventilation (IMV). Among those who required IMV, the median duration of IMV was shorter overall (Delta=18 days; Omicron=8 days; p=0.006) and among unvaccinated persons (Delta=19 days; Omicron=8.5 days; p=0.018). Among unvaccinated persons, the median intensive care unit length of stay was shorter (Delta=12 days; Omicron=5 days; p=0.037) during Omicron predominance. There was no difference in the proportion of patients who died while hospitalised.

Conclusions In this single-hospital study, critically ill patients with SARS-CoV-2 infection experienced less severe respiratory disease during Omicron predominance, likely due to reduced variant-specific virulence. Vaccination likely reduced development of critical illness in adults with SARS-CoV-2 infection during Omicron predominance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Initial reports suggest the B.1.1.529 (Omicron) variant of SARS-CoV-2 causes less severe disease in hospitalised adults compared with the B.1.617.2 (Delta) variant, though little is known about clinical characteristics and outcomes of critically ill adults during these periods.

WHAT THIS STUDY ADDS

⇒ We found similar proportions of intensive care unit admissions occurring in fully vaccinated patients between Delta and Omicron predominance periods, despite county-wide evidence of a 60% increase in the proportion of SARS-CoV-2 hospitalisations occurring in fully vaccinated persons. Among unvaccinated persons, the median intensive care unit length of stay was 7 days shorter and duration of invasive mechanical ventilation was 10.5 days shorter during Omicron predominance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Vaccination remains important, as it likely reduced development of critical illness in adults with SARS-CoV-2 infection during Omicron predominance. Adults who became critically ill with SARS-CoV-2 infection experienced less severe respiratory disease during Omicron predominance, likely due to reduced variant-specific virulence.

INTRODUCTION

The B.1.1.529 (Omicron) variant of SARS-CoV-2, the virus that causes COVID-19, overtook the B.1.617.2 (Delta) variant as the dominant strain in California in mid-December

2021.[1] Initial reports suggest the Omicron variant causes less severe illness,[2] though more widespread vaccination contributed to these findings.[3] Little is known about clinical characteristics and outcomes of patients requiring intensive care during periods of Delta and Omicron predominance. The aim of this study was to examine and compare characteristics of critically ill adults with SARS-CoV-2 infection during periods of Delta and Omicron variant predominance.

METHODS

We conducted a retrospective cohort study of adults aged >18 years with positive reverse transcription-PCR (RT-PCR) SARS-CoV-2 test results admitted to intensive care units (ICUs) at one academic hospital in Los Angeles, California, during 15 July 2021–23 September 2021 (Delta predominant period) and 21 December 2021–27 January 2022 (Omicron predominant period). Predominance periods were selected to reflect peaks in SARS-CoV-2 hospitalisations when each variant accounted for >50% of sequenced SARS-CoV-2 isolates in California.[1] A longer duration for the Delta predominant period was chosen because the incidence of COVID-19 cases and hospitalisations in Los Angeles County was substantially lower during Delta predominance as compared with Omicron predominance.[4] The hospital's internal flagging system for SARS-CoV-2 admissions was used to identify RT-PCR positive test results. This system is triggered by a laboratory report of a positive SARS-CoV-2 RT-PCR test result during hospital admission or 14 days prior to admission, or by admitting physician confirmation of RT-PCR positivity from an outside facility through patient or family interview. Adults hospitalised with a positive SARS-CoV-2 test result during the preceding 90 days were excluded unless the patient's symptoms resolved before readmission as determined by the admitting provider. Vaccination status was determined by electronic linkage from the electronic health record (EHR) to the California Immunisation Registry. Following the Centers for Disease Control and Prevention definition,[5] fully vaccinated adults were those who received the second dose of a two-dose COVID-19 vaccine series (or a third dose if immunocompromised) or a single dose of a one-dose product >14 days before receiving a positive SARS-CoV-2 test result associated with their hospitalisation. Adults without documented receipt of any COVID-19 vaccine before the SARS-CoV-2 test date were considered unvaccinated. Patient demographic, clinical characteristics and outcomes were abstracted from the EHR. Using prior published methods,[3] investigators (KS, NM and AP) conducted detailed chart review using prespecified criteria to determine whether the reason for ICU admission was likely or not likely due to COVID-19. In brief, ICU admissions were classified as likely due to COVID-19 if chart review could not clearly identify an alternative reason for ICU admission that was not plausibly linked to SARS-CoV-2 infection. Patient characteristics were compared between Delta-period and Omicron-period hospitalisations, overall and stratified by vaccination status. Categorical variables were compared with Fisher's exact tests and continuous variables with the Mann-Whitney U test. Two-sided p values <0.05 were considered statistically significant. All analyses were conducted in Stata (V.17.0).

Patient and public involvement

None.

RESULTS

There was no difference in vaccination status between the 79 adults requiring intensive care during the Delta predominant period and the 116 adults requiring intensive care during the Omicron predominant period (table 1). The median age of unvaccinated patients was older during Omicron predominance as compared with during Delta predominance (Delta=45 years; Omicron=63 years; p=0.002), while the median age of vaccinated patients was younger during Omicron predominance as compared with during Delta predominance (Delta=75 years; Omicron=68 years; p=0.037). The proportion of patients with chronic pulmonary disease was lower overall (7.6% vs 0.9%; p=0.018) and among unvaccinated persons (10.9% vs 0%; p=0.005) during Omicron predominance. Fewer patients during Omicron predominance received COVID-19 directed therapies (87.3% vs 74.1%; p=0.030). There was no difference in need for invasive mechanical ventilation (IMV). Among those who required IMV, the median duration of IMV was shorter overall (Delta=18 days; Omicron=8 days; p=0.006) and among unvaccinated persons (Delta=19 days; Omicron=8.5 days; p=0.018) during Omicron predominance. Among adults who required IMV, the proportion who received rescue therapies was lower overall (80.4% vs 49.2%; p=0.001) and among unvaccinated persons (86.5% vs 50.0%; p=0.001), and the proportion who required tracheostomy was lower among unvaccinated persons (40.5% vs 19.1%; p=0.048), during Omicron predominance. Among unvaccinated persons, the median ICU length of stay was shorter (Delta=12 days; Omicron=5 days; p=0.037) during Omicron predominance. There was no difference in the proportion of patients who died while hospitalised.

DISCUSSION

At a single hospital in California, critically ill adults with SARS-CoV-2 infection during Omicron predominance experienced fewer days in hospital as compared with during Delta predominance. This difference was driven by fewer days in the ICU among unvaccinated persons, which stemmed from fewer days of IMV among those unvaccinated persons requiring IMV. Among unvaccinated persons requiring IMV, smaller proportions received therapies used to treat refractory hypoxaemia

Table 1 Demographic characteristics, clinical characteristics and clinical outcomes among 195 adults admitted to intensive care units (ICU) with SARS-CoV-2 infection by vaccination status and period of variant predominance—one hospital, California, 15 July 2021–23 September 2021 (Delta period) and 21 December 2021–27 January 2022 (Omicron period)

	No (%)								
	Total ICU admissions (n=195)			Unvaccinated (n=129)			Fully vaccinated (n=59)		
Characteristic	Delta period	Omicron period	P value	Delta period	Omicron period	P value	Delta period	Omicron period	P value
Total	79	116	-	55	74	-	20	39	-
Vaccination status*†									
Unvaccinated	55 (69.6)	74 (63.8)	0.443	55 (100)	74 (100)	-	-	-	-
At least one dose	24 (30.4)	42 (36.2)	0.443	-	-	-	20 (100)	39 (100)	-
Fully vaccinated	20 (25.3)	39 (33.6)	0.267	-	-	-	20 (100)	39 (100)	-
Fully vaccinated and booster dose‡	-	5 (4.3)	-	-	-	-	-	5 (12.8)	-
Age, years, median (IQR)	62 (36)	65 (26)	0.116	45 (32)	63 (26)	**0.002**	75 (15)	68 (18)	**0.037**
Women	26 (32.9)	42 (36.2)	0.650	20 (36.4)	31 (41.9)	0.587	5 (25.0)	11 (28.2)	1.000
Race and ethnicity									
White, non-Hispanic	27 (34.2)	46 (39.7)	0.455	13 (23.6)	27 (36.5)	0.129	13 (65.0)	16 (41.0)	0.103
Black, non-Hispanic	19 (24.1)	18 (15.5)	0.142	14 (25.5)	11 (14.9)	0.177	3 (15.0)	7 (18.0)	1.000
Hispanic	17 (21.5)	30 (25.9)	0.609	15 (27.3)	21 (28.4)	1.000	2 (10.0)	9 (23.1)	0.302
Asian, non-Hispanic	1 (1.3)	5 (4.3)	0.404	1 (1.8)	3 (4.1)	0.636	0 (0.0)	2 (5.1)	0.544
Other, non-Hispanic§	15 (19.0)	17 (14.7)	0.437	12 (21.8)	12 (16.2)	0.495	2 (10.0)	5 (12.8)	1.000
Comorbidities									
Any	46 (58.2)	56 (48.3)	0.191	34 (61.8)	34 (46.0)	0.079	11 (55.0)	20 (51.3)	1.000
Obesity (BMI >30 kg/m^2)	29 (36.7)	41 (35.3)	0.880	18 (32.7)	30 (40.5)	0.462	10 (50.0)	11 (28.2)	0.151
Chronic pulmonary disease¶	6 (7.6)	1 (0.9)	**0.018**	6 (10.9)	0 (0.0)	**0.005**	0 (0.0)	1 (2.6)	1.000
Cardiovascular disease**	8 (10.1)	12 (10.3)	1.000	7 (12.7)	4 (5.4)	0.203	1 (5.0)	6 (15.4)	0.404
Hypertension	19 (24.1)	17 (14.7)	0.132	19 (34.6)	7 (9.5)	**0.001**	0 (0.0)	8 (20.5)	**0.042**
Diabetes Mellitus	9 (11.4)	13 (11.2)	1.000	9 (16.4)	6 (8.1)	0.172	0 (0.0)	7 (18.0)	0.083
Renal	6 (7.6)	11 (9.5)	0.798	6 (10.9)	3 (4.1)	0.169	0 (0.0)	7 (18.0)	0.083
ICU admission not likely due to COVID-19	7 (8.9)	20 (17.2)	0.138	4 (7.3)	10 (13.5)	0.392	2 (10.0)	10 (25.6)	0.192
COVID-19 therapies received									
Any	69 (87.3)	86 (74.1)	**0.030**	49 (89.1)	57 (77.0)	0.104	16 (80.0)	26 (66.7)	0.370
Dexamethasone	64 (81.0)	82 (70.7)	0.130	45 (81.8)	55 (74.3)	0.395	16 (80.0)	24 (61.5)	0.239
Remdesivir	58 (73.4)	57 (49.1)	**0.001**	41 (74.6)	37 (50.0)	**0.006**	14 (70.0)	18 (46.2)	0.103
Tocilizumab	38 (48.1)	9 (7.8)	**<0.001**	27 (49.1)	5 (6.8)	**<0.001**	9 (45.0)	4 (10.3)	**0.006**
Baricitinib	1 (1.3)	26 (22.4)	**<0.001**	0 (0.0)	20 (27.0)	**<0.001**	1 (5.0)	5 (12.8)	0.653
Casirivimab	2 (2.5)	1 (0.9)	0.567	0 (0.)	1 (1.4)	1.000	1 (5.0)	0 (0.0)	0.339
Convalescent plasma	2 (2.5)	1 (0.9)	0.567	1 (1.8)	1 (1.4)	1.000	1 (5.0)	0 (0.0)	0.339
Sequential Organ Failure Assessment (SOFA) score, median (IQR)††	9 (7)	8 (7)	0.091	9 (6)	8 (8)	0.105	8 (6.5)	8 (5)	0.506
Invasive mechanical ventilation (IMV)	46 (58.2)	61 (52.6)	0.466	37 (67.3)	42 (56.8)	0.274	8 (40.0)	15 (44.1)	1.000
IMV duration among those receiving IMV, days, median (IQR)	18 (19)	8 (21)	**0.006**	19 (22)	8.5 (21)	**0.018**	12 (7)	7 (20)	0.077
Rescue therapies received among those receiving IMV									
Any	37 (80.4)	30 (49.2)	**0.001**	32 (86.5)	21 (50.0)	**0.001**	5 (62.5)	8 (53.3)	1.000
Prone	25 (54.4)	27 (44.3)	0.333	22 (59.5)	19 (45.2)	0.261	3 (37.5)	7 (46.7)	1.000
Neuromuscular blockade	26 (56.5)	22 (36.1)	**0.049**	24 (64.9)	17 (40.5)	**0.042**	2 (25.0)	5 (33.3)	1.000
Inhale nitric oxide	21 (45.7)	20 (32.8)	0.229	18 (48.6)	16 (38.1)	0.371	3 (37.5)	4 (26.7)	0.657

Continued

Table 1 Continued

Characteristic	No (%)								
	Total ICU admissions (n=195)			Unvaccinated (n=129)			Fully vaccinated (n=59)		
	Delta period	Omicron period	P value	Delta period	Omicron period	P value	Delta period	Omicron period	P value
Extracorporeal membrane oxygenation	13 (28.3)	5 (8.2)	**0.009**	12 (32.4)	5 (11.9)	**0.032**	1 (12.5)	0 (0.0)	0.348
Tracheostomy, among those receiving IMV	15 (32.6)	12 (19.7)	0.177	15 (40.5)	8 (19.1)	**0.048**	0 (0.0)	4 (26.7)	0.257
Length of stay, days, median (IQR)	20 (17)	13 (25.5)	**0.036**	21 (30)	14.5 (26)	**0.033**	17 (15)	13.5 (31)	0.940
Length of stay in acute care, days, median (IQR)‡‡	9 (13)	7 (11)	0.538	9 (13)	6 (12)	0.535	8 (10.5)	9 (10)	0.752
Length of stay in intensive care, days, median (IQR)	9 (19)	5 (12)	0.100	12 (23)	5 (15)	**0.037**	3.5 (10.5)	5 (9)	0.678
Died in hospital	27 (34.2)	39 (33.6)	1.000	17 (30.9)	27 (36.5)	0.575	10 (50.0)	10 (29.4)	0.154

P-values <0.05 are bolded.
*Vaccination status was ascertained from the California Immunisation Registry. Booster status was unavailable for hospitalisations before 1 December 2021. Fully vaccinated persons hospitalised during Delta period were assumed not to have received a booster dose because booster doses were not recommended during the period of Delta predominance.
†Partially vaccinated adults were not included in the analyses stratified by vaccination status because of small sample size. However, they were included in overall proportions and comparisons not stratified by vaccination status; thus, the total number of patients exceeds the sum of fully vaccinated and unvaccinated patients.
‡Omicron-period patients who received a booster dose were excluded from comparisons of illness severity indicators (SOFA, IMV, rescue therapies, tracheostomy, length of stay and death while hospitalised) among fully vaccinated persons.
§Includes Native Hawaiian, other Pacific Islander, American Indian, and Alaska Native persons, and persons of unknown race or ethnicity.
¶Includes chronic obstructive pulmonary disease, pulmonary fibrosis and asthma.
**Includes coronary artery disease, congestive heart failure, arrythmias, valvular heart disease, stroke and peripheral vascular disease.
††Highest SOFA score during hospital admission is reported.
‡‡Acute care refers to hospitalisation in a lower level of care than intensive care.
BMI, body mass index.

and required tracheostomy during Omicron predominance. Taken together, our results suggest critically ill patients experienced less severe respiratory disease during Omicron predominance. That we found no difference in mortality is not incompatible with these findings, as patients requiring therapies for refractory hypoxaemia and tracheostomy may still survive after a more prolonged period of mechanical ventilation. These findings appear primarily due to lower virulence of the Omicron variant, consistent with studies demonstrating the Omicron variant has lower replication competence in lung parenchyma.[6 7]

We found that fewer patients in the Omicron predominant period received COVID-19 directed therapies. This may be due to changes in prescribing practices over time. Alternatively, lower use of COVID-19 directed therapies may reflect a higher proportion of patients perceived by providers to have incidental COVID-19 instead of direct sequalae of SARS-CoV-2 infection during Omicron predominance. Another possibility is high population-level immunity from vaccination, prior infection or both resulted in different clinical presentations of patients with COVID-19 during Omicron predominance that may have been under-recognised.

Between mid-July and mid-December 2021, the proportion of fully vaccinated adults in Los Angeles County increased by approximately 20% and the proportion of SARS-CoV-2 hospitalisations occurring in fully vaccinated persons increased almost 60%.[3 8] Despite this, we found the proportion of ICU admissions occurring in fully vaccinated persons were not substantially different between the two periods. This suggests vaccination was protective against development of severe disease during Omicron predominance.

This study has several limitations. First, sequencing data were unavailable to identify the SARS-CoV-2 variant. However, genomic surveillance data suggest each variant accounted for most sequenced isolates in its respective predominance period.[9 10] Second, small sample size limits the ability to detect differences in vaccination status, incidental COVID-19 and variant-specific outcomes. Third, we could not account for time between last dose of COVID-19 vaccine. Fourth, our analysis was confounded by differences in age and chronic pulmonary disease. However, if both variants were equally virulent then we would expect worse outcomes among unvaccinated patients during Omicron predominance given their older age and this was not observed. It is possible more chronic

pulmonary disease during Delta predominance contributed to more challenges weaning from the ventilator. Finally, these findings are from a single hospital in Los Angeles, limiting generalisability. However, the hospital captures a racially and ethnically diverse population.

In this single-hospital study, critically ill patients with SARS-CoV-2 infection experienced less severe respiratory disease during Omicron predominance, likely due to reduced variant-specific virulence. Vaccination likely reduced development of critical illness in adults with SARS-CoV-2 infection during Omicron predominance.

Acknowledgements The authors thank Haoshu Yang, PharmD, Priya Chaudhary, MBBS, Susan Bartolini, Keren Dunn and Michael Melgar, MD for their contributions.

Contributors MEM acts as guarantor and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. KS, NM, AP, IP, PC and MEM substantially contributed to the design of the study, data acquisition, data analysis, interpretation of the data, drafting and/or revising the manuscript for critically important intellectual content. Final approval was given for the version to be published. All agree to be accountable for all aspects of the work. MPD, LRJ, NK, SKI substantially contributed to the data acquisition, data analysis, revising the manuscript for critically important intellectual content. Final approval was given for the version to be published. All agreed to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was Institutional Review Board approved (Cedars-Sinai STUDY00001967).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Author note MEM is the guarantor of the content of the manuscript, including the data and analysis.

ORCID iD

Matthew E Modes http://orcid.org/0000-0002-1568-1393

REFERENCES

1 COVID-19. n.d. Available: https://covid19.ca.gov/variants
2 Iuliano AD, Brunkard JM, Boehmer TK, *et al*. Trends in disease severity and health care utilization during the early omicron variant period compared with previous SARS-cov-2 high transmission periods-United States, December 2020-january 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:146–52.
3 Modes ME, Directo MP, Melgar M, *et al*. Clinical characteristics and outcomes among adults hospitalized with laboratory-confirmed SARS-cov-2 infection during periods of B.1.617.2 (delta) and B.1.1.529 (omicron) variant predominance-one Hospital, California, July 15-september 23, 2021, and December 21, 2021-january 27, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:217–23.
4 LA county COVID-19 surveillance dashboard. n.d. Available: http://dashboard.publichealth.lacounty.gov/covid19_surveillance_dashboard
5 Frequently asked questions about COVID-19 vaccination. n.d. Available: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html
6 Hui KPY, Ho JCW, Cheung M-C, *et al*. SARS-cov-2 omicron variant replication in human bronchus and lung ex vivo. *Nature* 2022;603:715–20.
7 Halfmann PJ, Iida S, Iwatsuki-Horimoto K, *et al*. SARS-cov-2 omicron virus causes attenuated disease in mice and hamsters. *Nature* 2022;603:687–92.
8 Vaccination data. n.d. Available: https://covid19.ca.gov/vaccination-progress-data
9 Danza P, Koo TH, Haddix M, *et al*. SARS-cov-2 infection and hospitalization among adults aged ≥18 years, by vaccination status, before and during SARS-cov-2 B.1.1.529 (omicron) variant predominance-Los Angeles County, California, November 7, 2021-january 8, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:177–81.
10 Available: https://covid19.ca.gov/variants/

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-9 8-9 N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.