LESSONS FROM THE COVID-19 THIRD WAVE IN CANADA: THE IMPACT OF VARIANTS OF CONCERN AND SHIFTING DEMOGRAPHICS

Finlay A. McAlister,[1,2,3] MD MSc; Majid Nabipoor,[2] PhD; Anna Chu,[4,5] MHSc; Douglas S. Lee, [4,5,6] MD PhD; Lynora Saxinger,[1] MD; Jeffrey A. Bakal,[1,2] PhD on behalf of the CORONA Collaboration

From:
[1]The Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[2]The Alberta Strategy for Patient Oriented Research Support Unit, Canada
[3]The Canadian VIGOUR Centre, University of Alberta, Edmonton, Canada
[4] ICES (formerly Institute for Clinical Evaluative Sciences), Toronto, Canada
[5] University of Toronto, Toronto, Canada
[6] University Health Network, Toronto, Canada,

Correspondence: Dr. F. McAlister, 5-134C Clinical Sciences Building
11350 83 Avenue
Edmonton, Alberta, Canada T6G 2G3
Tele: (780) 492-7387 Fax: (780) 492-7277
e-mail: Finlay.McAlister@ualberta.ca

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ABSTRACT

Background: We examined 30-day outcomes in Canadians with COVID-19 during the first 3 waves of the pandemic.

Methods: Retrospective cohort study using linked healthcare datasets in Alberta and Ontario to identify all-cause hospitalizations or deaths within 30 days after a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction test from March 1, 2020 until June 30, 2021, with genomic confirmation of variants of concern (VOC).

Results: Compared to the 372,070 individuals with SARS-CoV-2 infection between March 2020 and January 2021 (first 2 waves in Canada), there was a shift in transmission towards younger patients in the 359,079 COVID-19 wave three cases. Third wave patients were more likely to be hospitalized (aOR 1.57 [95%CI 1.46-1.70]), but had shorter lengths of stay (median 6 vs. 7 days, p<0.001) and lower 30 day mortality (aOR 0.73 [0.65-0.81]). The 217,892 third wave patients infected with VOC (83.5% confirmed Alpha, 1.7% confirmed Delta) exhibited higher risks of death (aOR 1.42 [1.05-1.91]) and hospitalization (aOR 1.67 [1.33-2.10]) than those with wild type infections. Specifically, those with Delta variant infections exhibited higher 30-day risks of death (aOR 2.10 [1.53–2.89]) and hospitalization (aOR 2.21 [1.34 – 3.64]) than those with non-VOC infections in wave 3.

Interpretation: There has been a shift towards younger patients, more hospitalizations, shorter lengths of stay, and lower mortality risk during the third wave compared to the first 10 months of the pandemic in Canada. However, in spite of advances in COVID-19 care, infection with a VOC is associated with substantially higher risks of hospitalization or death than the original wild-type SARS-CoV-2.

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Since December 2020, the World Health Organization has recognized 4 variants of concern (VOC) for SARS-CoV-2 as they are more transmissible.[1,2] While preliminary reports from the United Kingdom and Europe suggested VOC infections are more severe, there is a paucity of North American evidence.[3,4] The third wave of COVID-19 in Canada occurred between February and June 2021 and was driven by VOC, particularly Alpha (B.1.1.7) and emerging Delta (B.1.617) variants, with Gamma (P1) and Beta (B.1.351) largely seen only in returning travellers. The Alpha variant has been associated with higher risks of mortality (approximately 64% in a UK case-control study and 59% in a UK cohort study)[5,6] and hospitalization (52% in a UK cohort study[6] and approximately 70% in the European Surveillance System data)[7]. However, the UK studies[5,6] relied solely on community tests, omitting as many as 70% of COVID-19 deaths occurring in patients diagnosed after hospital admission, and in the European study[7] less than 1% of SARS-CoV-2-positive specimens were sequenced for variants. A pre-print from Denmark also reported higher hospitalization rates with the Alpha variant, but was based on only 128 (of 1235 total) hospitalizations and the difference was only detected in adjusted analyses.[8] Thus, questions remain about disease severity and trajectories (i.e., timing of hospitalizations or death) with VOC compared to the original SARS-CoV-2 clade in North America, crucial information for health system planners. In particular, given emerging evidence that the Delta variant replicates faster and Delta-infected individuals have much higher viral loads (over 1,200 fold compared to the original wild-type)[9], there is an urgent need to define the

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phenotype of Delta variant infections since it will rapidly become the most common circulating strain.

To address this gap in the literature, we examined 30-day outcomes in Canadians infected with SARS-CoV-2 in the first 15 months of the pandemic and to compare event rates in those with VOC versus wild-type infection.

METHODS

Subjects and Setting

We conducted a retrospective cohort study in two of Canada's most populous provinces - Alberta and Ontario. Canadian healthcare is a government funded single-payer system with free universal access to hospital, emergency department (ED), laboratory, and physician services and each province is the legal custodian of the health data for its citizens. Ethical approval for this study was granted by the University of Alberta Health Ethics Research Board (Pro00101096), with waiver of individual patient signed informed consent for Alberta data as we analyzed de-identified healthcare administrative data. The use of Ontario data is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board. We linked SARS-CoV-2 reverse transcriptase Polymerase Chain Reaction (RT-PCR) testing data from the Alberta and Ontario provincial laboratories with administrative health databases in each province which capture all ED visits (the National Ambulatory Care Reporting System), hospitalizations and ICU admissions (the Discharge Abstract Database), and demographics, geographic locale, and deaths (the Health Care Insurance Registry files of each province).

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Definition of Cases, Index Date, and Outcomes

The study population included all individuals (outpatients and inpatients) with a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab from March 1, 2020 until June 30, 2021, with genomic confirmation of all VOC screen-positive tests after February 7, 2021. For patients tested multiple times during our study, we only examined the data related to their first positive SARS-CoV-2 test. Index date was the date of the first positive RT-PCR test and outcomes examined included ED visits, hospitalizations, ICU admissions, and/or deaths in the first 30 days after the positive RT-PCR test.

Covariates

We identified comorbidities for each patient (and generated their Charlson Comorbidity Scores) using standardized ICD-9 and ICD-10-CA case definitions (previously validated in Alberta and Ontario)[10] based on all hospitalizations in the 2 years prior to and including the index date for each individual.

Statistical Analyses

We present summary statistics stratified according to the timing of the positive SARS-CoV-2 swab and, for those detected after February 1, 2021 whether they had VOC or wild-type SARS-CoV-2 detected. We compared outcome risks after adjusting for age, sex, and Charlson Comorbidity Score (which includes the most important of the QCOVID risk score factors [https://qcovid.org/] such as diabetes, pulmonary disease, kidney disease, heart failure, neurologic disease, and cancer). All analyses were conducted using SAS 9.4 [Cary, NC, USA] within each province separately. We then pooled the aOR for each province using meta-analysis. Although both Alberta and

Ontario used a common protocol and common case definitions for comorbidities, there

are still several potential sources of heterogeneity between the provinces (such as

differences in populations, drug formulary restrictions, data capture, and SARS-CoV-2

testing priorities). Therefore, as per the convention of the Canadian Network for

Observational Drug Effect Studies (https://www.cnodes.ca/), we conducted a random

effect meta-analysis using package 'metafor' in R package version 1.4-0

(http://CRAN.R-project.org/package=metafor). We used the restricted maximum

likelihood estimator to estimate the population heterogeneity due to its high efficiency

compared to other estimators when number of effect sizes is small.

Data Disclosure

To comply with each province's Health Information Protection Act, the dataset

used for this study cannot be made publicly available but requests to access the dataset

from qualified researchers trained in human subject confidentiality protocols may be

sent to the corresponding author (Dr. Finlay McAlister).

RESULTS

Compared to the 372,070 individuals with SARS-CoV-2 positive samples

between March 2020 and January 2021 (the Canadian first and second waves), there

was a leftward shift in age distribution for the 359, 079 COVID-19 cases identified in the

third wave in Alberta and Ontario (Table). The percentage of test samples positive for

SARS-CoV-2 was similar in all 3 waves (5.2% overall). Hospitalization rates within 30

days were higher in the third wave (5.6% vs. 5.4%, $p<0.001$), a difference which

remained statistically significant after adjusting for the differences in demographics and

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comorbidity burdens (aOR 1.51 [95%CI 1.44-1.58] in Alberta, aOR 1.63 [1.59-1.67] in

Ontario, and pooled aOR 1.57 [1.46-1.70] for third wave patients vs. earlier waves).

However, hospital lengths of stay were shorter in the third wave (median 5 vs. 7 days in

Alberta and 6 vs. 7 days in Ontario, both p<0.001) than in the first and second waves.

Patients with COVID-19 during the third wave were also less likely to die within 30 days

(0.9% vs. 2.2%, p<0.0001) than those in the first and second waves, even after

adjusting for their younger age and lower comorbidity burdens (aOR 0.68 [0.61-0.76] in

Alberta, aOR 0.76 [0.72-0.80] in Ontario, and pooled aOR 0.73 [0.65-0.81]).

Examining third wave data only, of the 359,079 patients with SARS-CoV-2

positive samples between February and June 2021, 310,319 (86%) were screened for

VOC, of which 217,892 (70.2%) were confirmed VOC positive, 182,020 (83.5%) were

the Alpha variant and 3,708 (1.7%) Delta. After adjusting for age, sex and

comorbidities, VOC-infected patients exhibited higher 30-day risks of death (aOR 1.67

[1.36-2.05] in Alberta, aOR 1.23 [1.09-1.39] in Ontario, and pooled aOR 1.42 [1.05-1.91])

and hospitalization (aOR 1.88 [1.74-2.02] in Alberta, aOR 1.49 [1.42-1.57] in Ontario,

and pooled aOR 1.67 [1.33-2.10]) than those with non-VOC infections in the same

timeframe. Those with Delta variant infections exhibited higher 30-day risks of death

(aOR 5.44 [2.65 - 11.17] in Alberta, aOR 1.67 [1.17-2.38] in Ontario, and pooled aOR

2.10 [1.53–2.89]) and hospitalization (aOR 2.94 [2.08 - 4.14] in Alberta, aOR 1.76 [1.52-

2.04] in Ontario, and pooled aOR 2.21 [1.34-3.64]) than those with non-VOC infections

during the third wave. However, length of hospital stays and times between positive

swab and death were similar among patients with VOC versus wild-type infections in the

third wave.

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DISCUSSION

Our data provides a description of disease severity phenotypes for SARS-CoV-2 VOC in Canada, which is important for public health messaging and for health system planners. Our finding of a 42% higher mortality risk with predominantly Alpha VOC infections in Canada is consistent with effect estimates from the UK and Europe.[4,5,7] However, given that the third wave in Canada affected younger patients more than the first two waves (at least partially due to vaccination eligibility criteria in early 2021) and the increasing use of proven efficacious therapies like corticosteroids, we also found that the case fatality rate was 27% lower in the third wave compared to the earlier waves, even though hospitalization risk increased by 57% in the third wave.

Our finding that individuals infected with a VOC were more likely to require hospitalization than those with wild type SARS-CoV-2 is consistent with reports from UK and Europe of a higher hospitalization risk with the VOC (over 80% of which were Alpha in those studies).[6-8] Our finding of even higher event rates in individuals infected with the Delta variant confirms reports from Scotland (85% higher hospitalization risk with Delta variant infections compared to those with the Alpha variant)[11] and England (aHR for hospitalization with the Delta variant of 2.26 compared to Alpha).[12] Indeed, a preprint from Ontario has also reported a markedly higher risk of hospitalization and death in patients infected with the Delta variant (with aOR of 2.08 and 2.32 respectively).[13] These findings suggest that communities with high Delta transmission could experience major potential impacts on health system capacity compared to previous waves. In particular, the 8% hospitalization risk in individuals infected with the

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Delta variant during the third wave in Alberta and Ontario is concerning as Delta continues to spread and becomes the dominant strain in Canada. Of note, although we did not have access to vaccination data in individually linkable form for analysis, it is worth noting that the vast majority of hospitalizations occur in unvaccinated or partially vaccinated individuals: for example, 91% in Alberta since January 1, 2021 and 83% of currently hospitalized patients on August 31, 2021 (https://www.alberta.ca/stats/covid-19-alberta-statistics.htm#vaccine-outcomes last accessed August 31, 2021).

A major strength of our study is that the majority of SARS-CoV-2-positive specimens during the Alberta and Ontario third wave were screened for VOC with subsequent genomic confirmation of screen positives, compared with very low proportions in other studies describing VOC disease severity (for example, only 0.7% in the recent report from the European Surveillance System[7]). A limitation of our analysis is that it is largely based on Alpha variant infections, although we do have 30 day outcome data from over 3700 Delta variant infected individuals.[3,6,7] As with other studies comparing VOC and non-VOC infections, our sampling frame may result in overestimates of absolute risks since minimally symptomatic or asymptomatic patients are less likely to be tested.[14] However, we examined all positive community cases, which is less biased than studying only hospitalized cases (which prior studies have done) and sample positivity rates were similar in all 3 waves (approximately 5%). To the extent that Alpha or Delta variants infections may have been circulating in Alberta and Ontario before VOC screening began, our results may underestimate the impact of VOC on outcomes since events in undiagnosed VOC infections would be included in our wild-type controls (although the Public Health Agency of Canada update from

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February 19, 2021 suggested there were few VOC cases nationally even 10 days after

widespread screening had started in Alberta and Ontario:

https://www.canada.ca/content/dam/phac-aspc/documents/services/diseases-

maladies/coronavirus-disease-covid-19/epidemiological-economic-research-

data/update-covid-19-canada-epidemiology-modelling-20210219-en.pdf).

Unfortunately, the duration of the pre-symptomatic stage (and the frequency of

asymptomatic cases) with different SARS-CoV-2 clades are not yet described and

cannot be assessed using our dataset. Moreover, as we do not have access to in-

hospital treatments, we cannot adjust for the impact of therapies proven beneficial in the

treatment of COVID (such as corticosteroids) when examining trends in mortality rates.

Finally, although we do not have data on vaccination status in our dataset, initial

vaccine roll-out in Canada focused on long term care residents, the very elderly,

indigenous adults, and front line health care workers only and it was not until mid-March

that vaccination eligibility criteria expanded to include other groups in both

provinces.[15,16] The Ontario pre-print mentioned earlier was able to adjust for

vaccination status and reported very similar aOR as we did for hospitalizations and all-

cause mortality with the Delta and Alpha variants.[13] In addition, preliminary data from

England has also shown that the elevated hazard ratio (HR) for hospitalization among

vaccinated individuals who contract Delta variant infections is not significantly different

than the HR for unvaccinated or partially vaccinated individuals (p=0.82). Of course, it

deserves emphasizing that the absolute risks for hospitalization or poor outcomes is

substantially lower in vaccinated individuals than in those who are unvaccinated or

partially vaccinated, even with the Delta variant.[11,13,17]

While genomic monitoring for the evolution of SARS-CoV-2 VOCs is crucial,[18] we believe it is equally important to describe disease expression and outcomes among patients infected with VOC to fully understand both the disease phenotype and the anticipated burdens for the healthcare system. Although preliminary data regarding the effectiveness of current full vaccination schedules against hospitalization and death from the VOC remain encouraging,[19-21] continued assessment of disease severity phenotypes in different jurisdictions in vaccinated and unvaccinated individuals and as VOCs evolve is important.

For health system planners, the COVID-19 pandemic has shifted towards younger age groups and more hospitalizations but shorter lengths of stay and lower mortality risk in the third wave than seen in the first 10 months of the pandemic. However, high community transmission rates for the Delta variant could result in substantial increases in hospital admissions and affect healthcare capacity again – the pandemic is definitely not waning. Our demonstration that the VOC are associated with substantially higher risk of hospitalization or death than infections with the original wild-type strain in Canada is also important for individual patient counselling to address vaccine hesitancy and public information campaigns reinforcing the need for continued risk reduction measures such as social distancing and masking.

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Table: Demographics and outcomes for individuals with SARS-CoV2 infection from March 1 2020 to June 30 2021 in Alberta and Ontario, Canada

	Mar20 to Jan21 (waves 1 & 2)	Feb21-Jun21 (wave 3)						TOTAL	p-value (waves 1/2 vs 3)
		Nonvariant	Alpha variant	Delta variants	Other variants	Not tested/ Indeterminate	Sum for wave 3		
Number with a positive SARS-CoV2 test	372,070	92,427	182,020	3,708	32,164	48,760	359,079	731,149	-
< 18 years old, n (%)	46641 (12.5%)	19884 (21.5%)	31875 (17.5%)	702 (18.9%)	5439 (16.9%)	8449 (17.3%)	66349 (18.5%)	112990 (15.5%)	<.0001
18-39 years old, n (%)	132339 (35.6%)	31017 (33.6%)	69101 (38%)	1409 (38%)	12440 (38.7%)	18944 (38.9%)	132911 (37%)	265250 (36.3%)	<.0001
40-65 years old, n (%)	141474 (38%)	34832 (37.7%)	67697 (37.2%)	1290 (34.8%)	11652 (36.2%)	16551 (33.9%)	132022 (36.8%)	273496 (37.4%)	<.0001
65+ years old, n (%)	51616 (13.9%)	6694 (7.2%)	13347 (7.3%)	307 (8.3%)	2633 (8.2%)	4816 (9.9%)	27797 (7.7%)	79413 (10.9%)	<.0001
Age, median (IQR) Alberta	36 (23-52)	32 (18-47)	33 (20-47)	32 (20-45)	35 (22-48)	Not applicable	33 (19-47)	35 (21-49)	<.0001
Age, median (IQR) Ontario	41 (26-58)	36 (23-54)	36 (23-52)	35 (22-52)	36 (22-52)	36 (22-53)	36 (23-52)	38 (24-55)	<.0001
Male, n (%)	181852 (48.9%)	47217 (51.1%)	92315 (50.7%)	1898 (51.2%)	16700 (51.9%)	24492 (50.2%)	182622 (50.9%)	364474 (49.8%)	<.0001
Death									
Death within 30d*	8223 (2.2%)	532 (0.6%)	1384 (0.8%)	52 (1.4%)	325 (1%)	346 (0.7%)	2639 (0.7%)	10862 (1.5%)	<.0001
Age, median (IQR) Alberta	85 (76, 91)	75 (63, 86)	74 (65, 85)	72 (69, 80)	66 (56, 73)	Not applicable	74 (63, 85)	84 (73, 90)	<.0001
Age, median (IQR) Ontario	85 (77-91)	79 (70-87)	75 (65-84)	73 (60-86)	74 (65-84)	78 (66-86)	76 (66-85)	83 (73-90)	<.0001
Male, n (%)	4083 (49.7%)	302 (56.8%)	822 (59.4%)	30 (57.7%)	202 (62.2%)	192 (55.5%)	1548 (58.7%)	5631 (51.8%)	<.0001
Days to death, median (IQR) in Alberta	8 (4, 13)	8 (3, 14)	9 (4, 17)	12 (4, 18)	9 (3, 14)	Not applicable	9 (4, 15)	8 (4, 13)	0.12
Days to death, median (IQR) in Ontario	10 (6-16)	11 (6-17)	12 (7-19)	16 (11-21)	13 (6-20)	10 (4-16)	12 (6-19)	11 (6-17)	<.0001
All-cause hospitalization									
Hospital admission within 30d*	20061 (5.4%)	3470 (3.8%)	11552 (6.3%)	295 (8%)	2321 (7.2%)	2618 (5.4%)	20256 (5.6%)	40317 (5.5%)	<.0001
Age, median (IQR) Alberta	65 (48, 79)	55 (38, 69)	54 (41, 66)	57 (39, 69)	53 (40, 62)	Not applicable	54 (40, 67)	59 (44, 74)	<.0001
Age, median (IQR) Ontario	69 (55-82)	63 (48-77)	59 (46-71)	57 (43-70)	60 (48-72)	61 (41-75)	60 (46-73)	64 (50-77)	<.0001
Male, n (%)	10714 (53.4%)	1878 (54.1%)	6284 (54.4%)	169 (57.3%)	1335 (57.5%)	1381 (52.8%)	11047 (54.5%)	21761 (54%)	0.02
Median length of stay, day (IQR) Alberta	7 (3, 13)	5 (3, 10)	5 (3, 10)	6 (3, 10)	6 (3, 10)	Not applicable	5 (3, 10)	6 (3, 11)	<.0001
Median length of stay, day (IQR) Ontario	7 (3-16)	6 (3-11)	6 (3-11)	6 (3-11)	7 (3-12)	6 (2-11)	6 (3-12)	7 (3-13)	<.0001

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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	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
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	4, 5
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*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	6
		(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	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	30 days
Outcome data	15*	Report numbers of outcome events or summary measures over time	7 and Table 1

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	7 and Table 1
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7 and Table 1
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
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	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
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	1 and 12

*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.