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Prevalence of distressing symptoms at the end of life in an acute care hospital

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Abstract:	Background There is currently debate over the benefits and harms of physician-assisted death. One of the factors influencing this debate is concern about distressing symptoms in the days prior to death. The objective of this study was to describe the frequency of symptoms prior to death and determine patient characteristics associated with these symptoms. Methods We reviewed the medical record of every patient who died at a multi-site academic teaching hospital over a 3-month period. We determined the number of episodes of pain, dyspnea, agitation and nausea during the final 48 hours of life and assessed the patient and encounter characteristics associated with 2 or more episodes of distressing symptoms. Results 480 patients died during the study period. 29% (140/480) had 2 or more distressing symptoms in the final 48 hours of life. Higher Elixhauser comorbidity scores (RR 1.35, 95% CI 1.23 – 1.49), having a family doctor (RR 2.33, 95% CI 1.02 – 5.38), being admitted to the medical oncology service (RR 1.51, 95% CI 1.11 – 2.05), and having a documented order for no resuscitation written early in the hospitalization (RR 1.38, 95% CI 1.01 – 1.89) were independently associated with distressing symptoms. Admission to intensive care was associated with fewer distressing symptoms (RR 0.39, CI 95% 0.19 – 0.80). Interpretation

	Distressing symptoms are common in the final 48 hours of life, especially in patients with multi-morbidity who want limitations on the aggressiveness of their care. An integrated palliative approach is needed for select at-risk patients.

Prevalence of distressing symptoms at the end of life in an acute care hospital

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Abstract

Background

There is currently debate over the benefits and harms of physician-assisted death. One of the factors influencing this debate is concern about distressing symptoms in the days prior to death. The objective of this study was to describe the frequency of symptoms prior to death and determine patient characteristics associated with these symptoms.

Methods

We reviewed the medical record of every patient who died at a multi-site academic teaching hospital over a 3-month period. We determined the number of episodes of pain, dyspnea, agitation and nausea during the final 48 hours of life and assessed the patient and encounter characteristics associated with 2 or more episodes of distressing symptoms.

Results

480 patients died during the study period. 29% (140/480) had 2 or more distressing symptoms in the final 48 hours of life. Higher Elixhauser comorbidity scores (RR 1.35, 95% CI 1.23 – 1.49), having a family doctor (RR 2.33, 95% CI 1.02 – 5.38), being admitted to the medical oncology service (RR 1.51, 95% CI 1.11 – 2.05), and having a documented order for no resuscitation written early in the hospitalization (RR 1.38, 95% CI 1.01 – 1.89) were independently associated with distressing symptoms. Admission to intensive care was associated with fewer distressing symptoms (RR 0.39, CI 95% 0.19 – 0.80).

Interpretation

Distressing symptoms are common in the final 48 hours of life, especially in patients with multi-morbidity who want limitations on the aggressiveness of their care. An integrated palliative approach is needed for select at-risk patients.

Introduction

The care of terminally ill patients has become a significant issue facing providers and policy makers. Heightening this attention is the evolving perspectives on physician-assisted death by various patient advocacy groups and the general public. It is likely these views are driven in part by recognition that many patients experience distressing symptoms at the time of death. Avoiding distressing symptoms is very important to patients at the end of life and is likely a primary motivation for physician assisted death[1-3].

Our knowledge of terminal patients' experiences is limited. In Canada, as in many other developing countries, the majority of deaths occur in acute care hospitals [4,5]. This may not be the most appropriate location to provide end-of-life care[6]; but it does create an opportunity to evaluate symptoms in a large proportion of dying patients. Prior research is dated or has focused on disease specific cohorts [7-11]. These prior studies, while limited in focus, do suggest that a significant proportion of patients have poor symptom control at the time of death [12-14].

We performed this study to describe the epidemiology of distressing symptoms prior to death for patients in a multi-site academic health sciences center. This information will guide better service delivery by instructing providers on the extent of any potential care gap between patient desires and outcomes. More importantly, it will help define target populations to maximize the impact of any interventions, such as enhanced palliative care services and physician assisted death.

Methods

Study Design and Population

We conducted this study at The Ottawa Hospital - an academic health sciences center with three campuses, 1065 beds, and a catchment area of approximately 1 million people. We included all adult inpatients that died in hospital between September 5th and December 16th 2013. We excluded people who died in the emergency department prior to admission.

Data Sources

Data was extracted from two main sources, the Ottawa Hospital Data Warehouse (OHDW), and from direct review of the patient's medical record by a clinician. The OHDW is a relational database that contains clinical and administrative information for each patient hospitalized and treated at The Ottawa Hospital.

Study Variables

Using a standardized chart extraction form, a clinician reviewed the medical record from the final hospitalization of each patient. The form was initially piloted on 10 charts, prior to use on the full cohort. Information on patient decision-making about resuscitation was collected in order to understand the wishes of people with more symptoms at the end of life. In addition, early documentation of patient preferences is a quality indicator for end of life care [15,16]. The variables extracted from the patient's medical record included: the patient's wishes for cardiopulmonary resuscitation (CPR) and mechanical ventilation as documented in the first 24 hours of admission, any order

to withhold CPR and mechanical ventilation written before the time of death, the number of days prior to death the resuscitation orders were written, whether family was present at any point in the final 24 hours of life, and symptoms of pain, dyspnea, agitation or nausea occurring in the final 48 hours of life.

Using the OHDW we extracted information regarding patient demographics, previous inpatient encounters, total length of hospital stay prior to death, whether the patient had a family physician, hospital service on admission and at the time of death, Elixhauser comorbidity score, and baseline risk of death at time of admission. The Elixhauser comorbidity score uses 30 different conditions identified through administrative data to create a score that summarizes disease burden and is correlated with the risk of in-hospital mortality [17,18]. The estimated baseline risk of death in hospital was calculated using a validated risk score that uses laboratory test values, patient demographics, and comorbidities [19].

Outcomes

The primary outcome was the incidence of distressing symptoms during the final 48 hours of life, as documented in the patient chart. We defined distressing symptoms as pain (≥5/10) on a scale anchored at 0 – no pain and 10 – worst possible pain [20], dyspnea, nausea, or agitation. These symptoms were selected because they are common at the end of life and cause significant distress for many patients [1,21]. We used a threshold of 5 or more out of 10 for pain scores in order to capture pain that was likely causing distress and not simply a nuisance. During the study period our hospital had an

hourly rounding policy that required nurses to assess each patient every hour. There was however no standardized treatment pathway to deal with distressing symptoms.

Analysis

We described the frequency of each distressing symptom in the final 48 hours of life. We used means (± standard deviation), medians (inter-quartile range), and proportions as appropriate to describe the characteristics of patients who died during the study period. We compared characteristics of patients who had 2 or more episodes of distressing symptoms in the final 48 hours of life versus to those who had less than 2 episodes of distressing symptoms in the final 48 hours of life. Chi-squared test or 2-sample t-test was used as appropriate for the bivariate analysis.

We developed multivariable log binomial regression models to identify patient and hospitalization characteristics associated with the presence of distressing symptoms in the final 48 hours of life. We chose log binomial regression because of the intuitive interpretation of relative risks and the divergence of odds ratios and relative risks when an outcome is common [22,23]. A stepwise model building approach was selected using relative risks (RR) with corresponding 95% confidence intervals (CI) as the common measure of association. All patient and hospitalization characteristics that had p-values ≤ 0.10 in the bivariate analysis were used for multivariate analysis. Specifically, we tested patient characteristics (age, sex, Elixhauser comorbidity score at admission (modeled as a continuous variable), and presence of a family physician), hospital admission characteristics (admitting service, number of prior admissions in past 6

months, and involvement of a palliative care physician), and patient wishes regarding resuscitation and mechanical ventilation at time of admission. Variables that had a potential for reverse causation given their timing related to the outcome of interest were not included in multivariate analysis. This included patient's wishes for resuscitation recorded at the time of death and presence of family during the final 24 hours of life. We then used backwards elimination techniques (with an alpha level of 0.05) to develop reduced models. All analyses were completed using SAS 9.3 statistical software (SAS Institute Inc., Cary, NC). This study was approved by the Ottawa Health Science Network Research Ethics Board.

To further describe patients who died with distressing symptoms we selected several representative cases to describe in narrative format. These cases were pseudonymised to maintain confidentiality.

Results

During the study period there were 14,266 patients admitted, the mean age (SD) was 48.9 years (27.3 years), 56.5% were female and the median length of stay (IQR) was 3 days (2-7 days). There were 480 deaths during the study period (3.4% mortality rate). The mean age (SD) of the decedents was 73.7 years (16.1 years), 47.5% were female, and median length of stay (IQR) was 7 days (3-17 days). The medical record of one patient could not be located and was therefore excluded from further analysis.

Among the 479 patients who died and had complete records, 207 (43.2%) had at least one distressing symptom documented in the final 48 hours of life, while 140

(29.2%) had at least two. Pain and dyspnea were the most common symptoms while nausea was the least common (**Table 1).**

Table 2 contains the characteristics of patients with 2 or more episodes of distressing symptoms in the final 48 hours of life compared to those with less than 2 episodes. Patients with 2 or more episodes of distressing symptoms in the final 48 hours of life had significantly more inpatient encounters in the last 6 months, more inpatient days in the last year, longer length of stay, and higher Elixhauser comorbidity scores compared to patients who had less than 2 distressing symptoms **(Table 2).**

Patients with 2 or more episodes of distressing symptoms were also more likely to have a family physician, more likely to be admitted to an oncology service and less likely to be admitted to the intensive care unit (ICU). Interestingly, patients with 2 or more episodes of distressing symptoms were more likely to have a documented wish for no resuscitation and no ICU admission within 24 hours of admission (47.1% versus 34.4% p=0.01), compared to those with less than 2 distressing symptoms. Patients with distressing symptoms prior to death were more likely to have a no resuscitation order documented in the chart at the time of death (90.7% versus 71.1%), were less likely to have this order written within 24 hours of death (12.9% versus 23.9%) and were more likely to be seen by a palliative care physician prior to death (45.0% versus 23.8%). It is notable that there were no differences in age or the predicted risk of death on admission for patients with or without distressing symptoms prior to death.

Within our fully adjusted multivariable regression model, we found that higher Elixhauser score (RR 1.35, 95% CI 1.23 – 1.49), having a family doctor (RR 2.33, 95% CI

1.02 – 5.38), being admitted to medical oncology (RR 1.51, 95% CI 1.11 – 2.05) and having a documented wish for no CPR and no intubation during the first 24 hours in hospital (RR 1.38, 95% CI 1.01 – 1.89) were all associated with distressing symptoms at the end of life. Being admitted to intensive care was associated with fewer distressing symptoms at the end of life (RR 0.39, 95% CI 0.19 – 0.80) (**Figure 2**). **Box 1** contains 3 representative case vignettes of patients who died with more than 2 episodes of distressing symptoms.

Discussion

We found that almost 1 in 3 people who died in hospital had two or more episodes of distressing symptoms in the final 48 hours of life. People with distressing symptoms prior to death had higher comorbidity burden, were more likely to have a family doctor, more likely to be admitted to medical oncology and more likely to have an order for no resuscitation written in the chart within 24 hours of admission.

Consistent with previous research we found that many patients experience distressing symptoms prior to death [21,24,25]. While some patients may choose less aggressive treatment of symptoms in favor of being more lucid, patients need to be counseled about the frequency and severity of symptoms at the end of life so they can make educated choices. Patients consistently state that freedom from distressing symptoms is one of the most important elements of quality end-of-life care [1,3]. This is in contrast to the reality that many patients do experience distressing symptoms at the end of life. If patients knew they were likely to experience distressing symptoms at the

end of life some may choose more aggressive symptomatic treatment or physician assisted death.

In our study comorbidity burden had the strongest association with symptoms prior to death. This finding is likely because patients with multiple comorbidities experience more symptoms at all times, not just in the days prior to death [13,26,27]. As other research has suggested, care for multimorbid patients is often inappropriately focused on disease modifying treatments instead of a palliative approach that prioritizes treatment of symptoms along with disease modifying treatments [28-31]. Further reinforcing the importance of a palliative approach, we found that patients with more symptoms at the end of life wanted limitations on the aggressiveness of care they received. Part of the challenge in implementing a palliative approach to care is the perception that palliative care is only for those who have predictably terminal illnesses such as incurable cancer [32,33]. For patients with chronic progressive diseases with frequent exacerbations, a recovery from the current episode is often possible; therefore focusing on prolonging life may seem appropriate. This is in contrast to the World Health Organization's model for palliative care that recommends therapy to alleviate suffering be initiated early in the disease course along with disease modifying therapy [34].

We found several other interesting associations. Patients who were admitted to medical oncology had more symptoms prior to death than those admitted to other specialties. This finding differs from prior studies showing that there is no difference in the symptom burden of patients who die from cancer versus non-cancer causes [8,14,35]. This is likely because only very symptomatic oncology patients are admitted for end of

life care while those with fewer symptoms remain at home. Lastly we found that patients admitted to the intensive care unit experience fewer symptoms prior to death. This likely occurred because they are usually sedated and therefore unable to report symptoms. Also the one-to-one nursing ratio likely facilitates rapid assessment and treatment of any symptoms.

Strengths and Limitations

We performed this study in a multi-facility hospital that provides a significant proportion of the acute care health services in a large Canadian urban center. This suggests the study is generalizable. Although our chart assessments were retrospective, significant effort at the Ottawa Hospital has been made to standardize hourly nursing assessments and documentation. This may mitigate some concerns over our primary outcome assessment. We believe that if anything our outcome ascertainment method will underestimate the prevalence of distressing symptoms as staff will not document symptoms that are not present but may, at times, miss symptoms.

Conclusions

In a group of unselected patients who died in hospital, almost 1 in 3 experienced distressing symptoms in the last 48 hours of life. The high incidence of distressing symptoms in highly comorbid patients, who have asked for less aggressive care, suggests that further work is needed to integrate a palliative approach into chronic disease care. Future work should seek to understand symptoms experienced at the end

of life by people who receive ideal care. Knowledge translation work is needed to determine how accurate expectations about end of life symptoms influence patient's decisions about palliative care and physician-assisted death.

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Author Contributions

DK and AF conceived of the study, performed data collection, analysis and wrote the manuscript. PR DM and SM contributed to analysis and interpretation of results. They critically revised the manuscript and gave final approval of the manuscript for publication.

Conflicts of Interest

None

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Figure 1. Patient and Encounter level characteristics associated with presence of 2 or more distressing symptoms in the last 48 hours of life

*For patient's wishes for resuscitation as documented in the chart 24 hours after admission, the reference category was "not documented".

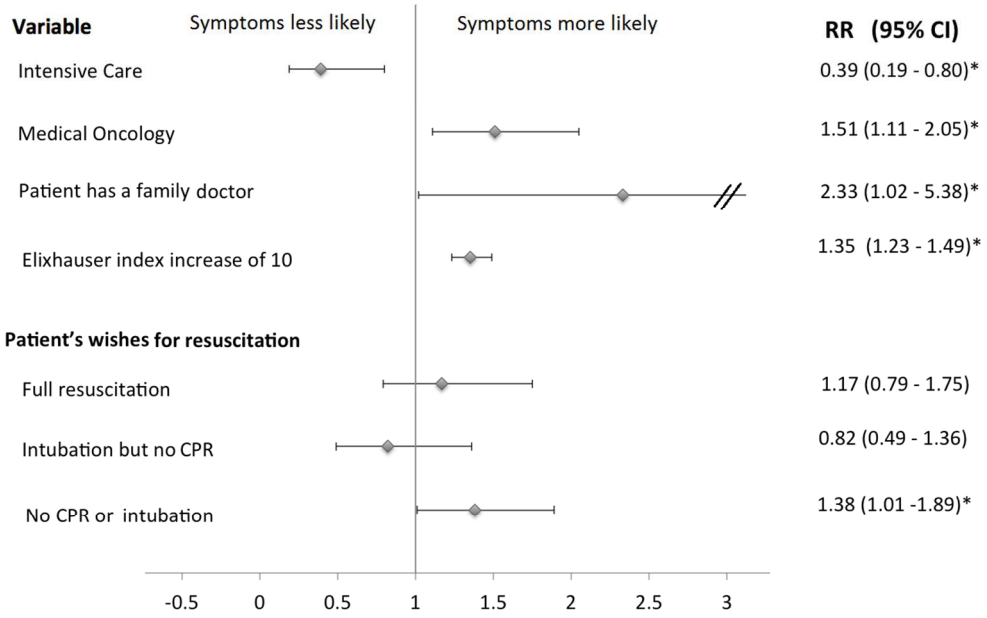

Figure 1. Patient and Encounter level characteristics associated with presence of 2 or more distressing symptoms in the last 48 hours of life
*For patient's wishes for resuscitation as documented in the chart 24 hours after admission, the reference category was "not documented".

Table 1: Distressing symptoms documented in the medical record during the final 48 hours of life, N=479

	Number of patients with each symptom N=479 (%)				
Frequency of symptom	**Pain**	**Dyspnea**	**Agitation**	**Nausea**	**TOTAL Symptoms**
0	376 (78.5)	373 (77.9)	402 (83.9)	459 (95.8)	272 (56.8)
1	49 (10.2)	54 (11.3)	45 (9.4)	12 (2.5)	67 (14.0)
2	27 (5.6)	32 (6.7)	14 (2.9)	6 (2.5)	45 (9.4)
3	15 (3.1)	13 (2.7)	10 (2.1)	1 (1.3)	44 (9.2)
4	8 (1.7)	4 (0.8)	5 (1.0)	0 (0)	18 (3.8)
≥ 5	4 (0.8)	3 (0.6)	3 (0.6)	1 (0.6)	33 (6.9)

Table 2: Characteristics of patients with and with out 2 or more documented episodes of distressing symptoms in the final 48 hours of life.

	≥ 2 episodes of distressing symptoms prior to death n=140 (29.2%)	**< 2 episodes of distressing symptoms 48 hours prior to death n=339 (70.8%)**	**p-value**
Mean age (±SD)	74.8 (13.4)	73.6 (17.1)	P=0.40
Gender - Female	76 (54.3)	155 (45.6)	P=0.09
Hospital Service at time of death (top 10)			
Intensive Care	15 (10.7)	111 (32.7)	P<0.001
General Medicine	49 (35.0)	87 (25.6)	P=0.05
Cardiology	9 (6.4)	33 (6.9)	P=0.29
Oncology	22 (15.7)	14 (4.1)	P<0.001
Neurology	2 (1.4)	12 (3.5)	P=0.37
Malignant hematology	6 (4.3)	6 (1.8)	P=0.12
General Surgery	5 (3.6)	7 (2.1)	P=0.35
Radiation Oncology	7 (5.0)	5 (1.5)	P=0.15
Family Medicine	2 (1.4)	8 (2.4)	P=0.73
Gynecologic Oncology	5 (3.6)	4 (1.2)	P=0.13
Number of inpatient encounters in the last 6 months			
0	76 (54.3)	231 (67.9)	P=0.005
1	36 (25.7)	63 (18.5)	P=0.08
2	15 (10.7)	24 (7.1)	P=0.20
3	5 (3.6)	17 (5.0)	P=0.63
≥ 4	8 (5.7)	5 (1.5)	P=0.007
In-Patient days in the last year	14.4 (27.1)	10.1 (24.1)	P=0.09
Patient has a family physician	135 (96.4)	299 (87.9)	P = 0.04
Median Total LOS (IQR)	17.6 (31.6)	13.2 (19.8)	P=0.05
Predicted Mortality	0.29 (0.19)	0.31 (0.20)	P=0.31
Elixhauser comorbidity score (SD)	15.5 (9.3)	11.2(8.5)	P<0.001
Q1 -3 - 5	27 (19.3)	103 (30.5)	
Q2 6 -12	25 (17.9)	100 (29.6)	
Q3 12 - 19	39 (27.9)	83 (24.6)	
Q4 19 - 48	49 (35.0)	52 (15.4)	
Patient wishes for resuscitation documented			

within 24 hours of admission			
Not documented	36 (25.7)	100 (29.7)	P=0.44
Full resuscitation including CPR	27 (19.3)	71 (20.9)	P=0.71
Resuscitation but no CPR	11 (7.9)	51 (15.0)	P=0.04
No resuscitation	66 (47.1)	117 (34.4)	P=0.01
Family Present in the last 24 hours of life	106 (75.7)	272 (80.0)	P=0.27
Patient wishes for no resuscitation documented in chart at time of death	127 (90.7)	241 (71.1)	P<0.001
Patient wishes for no resuscitation documented ≤ 24 hours before death	18 (12.9)	81 (23.9)	P<0.001
Palliative Care consulted	63 (45.0)	81 (23.8)	P <0.05

*Abbreviations: CPR: Cardiopulmonary Resuscitation; SD: Standard Deviation

Box 1: Representative cases of patients who experienced multiple episodes of distressing symptoms in the final 48 hours of life.

Symptom				Case description
Pain	**Dyspnea**	**Agitation**	**Nausea**	
4	0	0	0	65 yo female with metastatic squamous cell carcinoma of the nasopharynx admitted because of dysphagia. The patient received a percutaneous endoscopic gastrostomy tube for feeding. They experienced worsening episodic chest pain and dyspnea that worsened over the next 5 weeks that was treated with narcotics as needed and then continuous narcotics. The chart documents that the patient appeared in distress on numerous occasions but because of a language barrier it was difficult to know what symptoms they were experiencing. The patient died after a period of agitation and apparent distress that was treated with more narcotics.
2	5	0	0	84 year old male with metastatic renal cell carcinoma was admitted with delirium secondary to hypercalcemia. He was treated with intravenous fluids. The patient began experiencing flank pain and dyspnea. Initially every recorded episode was treated with narcotics but the following assessment documents that the patient is still complaining of pain. The patient was getting frustrated with the poor pain control. The patient had increasing dyspnea that was treated with benzodiazepines. He died after 3 hours of increasing dyspnea.
3	0	4	0	62 year old female with metastatic esophageal cancer presented to hospital with diabetic ketoacidosis (DKA), acute kidney injury and malignant ascites. The DKA was treated and the kidney injury resolved. The patient was waiting to go to hospice but developed worsening abdominal pain and severe agitation that was treated with phenobarbital. The phenobarbital was titrated up until the patient was obtunded but calm. The patient passed away shortly after.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ✓
Objectives	3	State specific objectives, including any prespecified hypotheses ✓
Methods		
Study design	4	Present key elements of study design early in the paper ✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ✓
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ✓ *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ✓
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 ✓
Bias	9	Describe any efforts to address potential sources of bias ✓
Study size	10	Explain how the study size was arrived at ✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ✓
		(*b*) Describe any methods used to examine subgroups and interactions ✓
		(*c*) Explain how missing data were addressed ✓
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed N/A *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses N/A

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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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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