Management and clinical outcomes of Lyme disease in acute care facilities: a multicenter cohort study in two endemic regions of Quebec, Canada

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Competing interests

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ABSTRACT

Background: We describe the management and clinical evolution of patients with Lyme disease (LD) in acute care facilities in Quebec and assess adherence to the Infectious Disease Society of America (IDSA) guidelines.

Methods: We conducted a retrospective multicenter cohort study of patients with serologically confirmed LD in acute care facilities in two endemic regions of Quebec, from 2004 to 2017. Our main outcome was complete resolution of symptoms, 3 months after the initiation of treatment.

Results: Medical charts for 272 patients from 14 institutions were considered. Early disseminated LD (n=140; 51.5%) was predominant, followed by localized early (n=90; 33.1%) and late disseminated LD (n=42; 15.4%). Forty-eight patients needed hospitalization for a median of 4 days (IQR 1–7); one death unrelated to LD occurred 589 days after diagnosis. Adherence to IDSA guidelines was observed in 90% of cases and were stable over time (2004–2013: 57/64, 89.1%; 2014–2015: 64/71,90.1%; 2016–2017: 114/126, 90.5%; p=0.8). Non-adherence to guidelines was predominantly due to a treatment duration longer than recommended (16/26, 61.5%). Resolution of objective signs, 3 months after the initiation of treatment, occurred in 265/267 (99.3%) patients, while post-LD treatment syndrome (PLDTS) was observed in 27 patients (10.1%). PLDTS increased over time (2004–2013: 3/56, 4.6%; 2014–2015: 4/73, 5.5%; 2016–2017: 20/129, 15.5%; p=0.009)

Interpretation: We observed a resolution of the clinical signs of LD in most patients. Most treatments complied with the IDSA guidelines. PLDTS was found to emerge, warranting further prospective studies.

Introduction

Lyme disease (LD), a multisystem infection primarily caused by *Borrelia burgdorferi* in North America (1, 2), progresses in three phases: the early localized disease, the early and the late disseminated phases. (3). The number of LD cases reported by all Canadian provinces increased from 144 in 2009 to 992 in 2016, representing an increase from 0.4 to 2.7 per 100,000 population (4).

In Quebec, LD is a notifiable disease since November 2003 with the first locally acquired case reported in 2006 (5, 6). The number of reported cases of LD and the proportion of cases with acquired infection has increased each year. In 2019, 500 cases of LD were declared to the public health authorities, including 381 (76%) acquired in Quebec, particularly in Estrie (n= 226, 59%) and Montérégie (n=102, 27%). Despite this progression in LD cases, little is known about the management and clinical course of LD in Canada. Current evidence focuses on epidemiological surveillance, acquisition risk, and clinical case characteristics (7-9).

We describe the LD case management in acute care facilities in Quebec and the adherence to the Infectious Diseases Society of America (IDSA) guidelines (3). We assessed the clinical course of LD cases treated in Quebec and temporal changes in case severity from 2004 to 2017.

Methods

Setting, population and design

We conducted a retrospective cohort study in 14 acute care facilities in the Estrie and Montérégie regions of Quebec, Canada, with populations of 489,479 and 1,421,586 inhabitants in 2019 (10). These acute care facilities include 12 community hospitals as well as two tertiary care centers, which also get transfers from outside these two regions. The study population included all patients with serologically confirmed LD as per the two-tiered testing algorithm currently used in Canada (11) and treated (whether as inpatient and/or outpatient) in one of the 14 acute care facilities considered. The Centre intégré universitaire de santé et de services sociaux de l'Estrie-Centre hospitalier universitaire de Sherbrooke (CIUSSSE-CHUS) institutional review board approved this study (project #MP-31-2020-3251) and waived the need for individual informed consent. Data on serologic status were extracted from a database at the Laboratoire de santé publique du Québec, where all LD serology testing results are centralized for the province of Quebec.

Data collection and outcomes

Trained research assistants reviewed hospital records using a standardized questionnaire. Past medical history was collected to calculate the Charlson comorbidity index (12), along with demographic, microbiological, clinical, and therapeutic data (name of the antibiotic, dose, route of administration, and start/end dates of treatment).

Our main outcome was the proportion of patients with clinical resolution of LD at 90-days, defined as the complete disappearance of objective clinical signs. Treatment failure was considered when there was the persistence of at least one objective sign (e.g. persistent facial palsy or arthritis) 90 days after the initial treatment. Subjective symptoms, such as fatigue

or arthralgia, were not considered in the evaluation of the primary outcome. Our secondary outcome was the presence of a post-treatment Lyme disease syndrome (PTLDS), defined as the presence of any of the following symptoms : widespread musculoskeletal pain, cognitive complaints, radicular pain, paresthesias, or dysesthesias. The symptoms also had to begin within 6 months after the initial diagnosis and treatment of *B. burgdorferi* infection and had to persist for at least 6 months (3).

We formed an adjudication committee consisting of one primary care physician with expertise in LD (JBM) and two infectious diseases (SBP and AAP) fellows plus a chairperson, an infectious disease consultant (AC), to independently assess the clinical stage of each LD case, the adherence of the prescribed treatment with the IDSA guidelines, and the outcomes. IDSA guideline adherence was assessed according to the clinical stage of each patient, treatment given, and treatment duration. Reasons for guideline non-adherence were documented, namely an inadequate antibiotic, dosing or duration. In the case of disagreements between the two adjudicators, consensus meetings were set to resolve disagreements with the help of the chairperson.

To assess potential changes in Lyme disease presentation, we divided our study into three periods according to LD incidence in the province of Quebec (2004–2013: low incidence; 2014–2015: moderate incidence; 2016–2017 high incidence)(6). We used regional notifiable disease registries to assess potential changes in the proportion of serologically confirmed LD cases managed in acute care facilities.

Statistical analysis

Data were double-entered into an electronic input tool, Research Electronic Data Capture (Redcap, Vanderbilt University, Nashville, TN, USA), and analyzed using Stata 15.1 for Mac (StataCorp, College Station, TX, USA). Proportions were compared using the χ^2 test. Continuous variables were compared using the Wilcoxon's rank-sum test or Mood's median test, as appropriate. Cases with missing data were removed from the analysis. To establish risk factors for PTLDS, variables to be included in the multivariate unconditional logistic regression model were selected after univariate analysis by applying a 10% significance level. Variables were added one at a time and retained only if significant in the multivariate model according to the likelihood ratio test. The final model retained variables that significantly enhanced the fit ($p<0.05$).

Results

A flow chart detailing the study inclusion and exclusion steps is shown in figure 1. Overall, 1114 positive serologies and PCR tests were extracted from the public health laboratory database. Among these, 316 cases lived in the Estrie/Montérégie regions and were managed in acute care facilities between 2004 and 2017. Finally, 272 cases with complete medical records were analyzed.

Case characteristics

Most patients were male (169/272; 62.1%) and the median age of the patients was 51.5 years [interquartile range (IQR), 32.6–62.5]. Most cases had no comorbidities, indicated by a Charlson score of 0 for 222/272 (81.6%) of the patients. Only 19 patients (7.0%) had significant immunosuppression. To investigate potential selection bias, we compared patients included and excluded. No significant difference was found between the baseline chracateristics of the two groups.

Early disseminated LD (n=140; 51.5%) predominated in our cohort, followed by localized early (n=90; 33.1%), and late disseminated LD (n=42; 15.4%). Of the 140 early disseminated LD patients, 88 (62.9%) had multiple erythema migrans, 40 (28.6%) facial palsy, 30 (21.4%) meningitis, and 9 (6.4%) a radiculopathy. Cardiac involvement presented as carditis (8; 5.7%), first-degree atrioventricular block (4; 2.9%), second-degree atrioventricular block (3; 2.1%), and third-degree atrioventricular block (4; 2.9%). For the 42 late disseminated LD cases, apart for one case of chronic atrophic acrodermatitis (2.4%), all the remaining cases (97.6%) were suffering of arthritis.

Forty-eight patients needed hospitalization for a median duration of four days (IQR 1–7). Of these, seven patients were admitted to the intensive care units (median duration: one day, IQR 1–4). One death unrelated to LD occurred 589 days after diagnosis.

Treatment and adherence to the IDSA guidelines

Antimicrobial treatment comprised doxycycline (n=171, 62.9% of all patients), amoxicillin or amoxicillin/clavulanic acid (n=39, 14.3%), and ceftriaxone (n=46, 16.9%). The antibiotic treatment was started after the final immunoblot result was issued in 56 patients (20.6%). Assessment of guideline adherence was carried out for 261 (95.9%) patients with complete information available on antibiotic treatment. From these cases, 235 (90.0%) received a treatment supported by the IDSA guidelines. Non-adherence to the guidelines was either due to longer than recommended (16/26, 61.5%) or shorter than recommended (n=8/26; 30.8%) treatment duration, and the use of an non-supported antimicrobial (8/26; 30.8%). In patients with a longer than recommended treatment duration, the median was 28 days (IQR 27–30), as compared to 20 days in patients with the guideline-recommended treatment duration ($p<0.001$).

Outcomes assessment

The medical chart had enough data to assess primary and secondary outcomes for 267/272 patients (98.2%). We observed a complete resolution of objective signs of infection in 265/267 (99.3%) patients. The first case of treatment failure was documented in a 20-year-

old patient with late disseminated disease (Lyme arthritis) with persistent joint swelling 3 months after the initial treatment. After an additional 60 days of antibiotic therapy, he presented with persistent arthralgia but without any objective swelling 8 months after the initial treatment. The second case of treatment failure was a 55-year-old patient treated for multiple lesions of erythema migrans. Thirty days post-treatment, he developed unilateral facial palsy that persisted at three months but resolved completely after an additional 21 days of antibiotic therapy. Both patients had a complete resolution of their objective signs one year after the initial treatment.

We documented PLDTS in 27 patients (10.1%). Factors associated with PLDTS in univariate and multivariate analyses are shown in Table 1. The independent risk factors associated with PLDTS were arthralgia, tremor, and difficulty concentrating upon initial presentation as well as a diagnosis of LD in 2016–2017 compared to the 2004–2013 period.

Temporal changes in LD characteristics, treatment, and outcomes

To further investigate temporal changes in LD presentation, we compared the case characteristics diagnosed between 2004 and 2013 (low-incidence period; n=66) versus those identified in 2014–2015 (moderate-incidence period; n=74) and 2016–2017 (high-incidence period; n=132) (Table 2). The proportion of serologically confirmed LD cases decreased significantly over the study period (2004–2013: 66/122, 54.1%; 2014–2015: 74/181, 40.9%; 2016–2017: 132/358, 36.8%; p<0.001). We also observed a non-significant decrease in the proportion of hospitalizations and referral to specialist physicians over time.

IDSA guideline adherence remained stable over time. There was a significant increase in the proportion of patients who developed PLDTS over time.

Interpretation

Most LD cases treated in 14 acute care institutions of two endemic regions of Quebec who had a complete resolution of objective clinical signs following their treatment received an antimicrobial therapy according to the IDSA guidelines. As our sample includes all acute care institutions within these two regions, we have been able to assess a majority of the more severe cases encountered within these regions. These results are reassuring, in the context where concerns about LD management have recently been raised at the public and political level in Quebec (13). This is the first study assessing LD management with extensive data on antimicrobial management and long-term outcomes in Canadian LD-treated patients.

In more than 99% of cases, clinical signs completely disappeared within 3 months of the start of treatment, and all signs were completely resolved within 1 year of the first antimicrobial treatment. Our results are similar to other studies conducted in North America (14, 15). Therefore, the treatment applied seems effective in eliminating incapacitating clinical signs, such as Bell's palsy. Other studies conducted in pediatric and adult patients have found lower clinical resolution rates (16, 17). This discrepancy may be explained by the fact that these studies included mainly Lyme arthritis cases compared with our study where the proportion of arthritis was only 15%.

Although most patients in our study responded very well to treatment, 10% developed PLDTS. These results are in line with other authors' studies reporting similar proportions of PLDTS (14, 15, 18) but underline the necessity of conducting well-designed prospective basic and clinical science studies to gain a better understanding of both causes and treatment

options for patients with PLDTS, a distressing condition for affected patients (19). Our study may also provide new insights and help clinicians identify patients at a risk of developing PLDTS, as we identified initial symptoms (arthralgia and tremor) that, if present, may reflect the higher odds of developing PLDTS. These risk factors have been previously described with the European variants of LD (20, 21) but not previously in North American soil. Additionally, we documented a significant increase in the proportion of PLDTS in the recent years. We hypothesize that as both clinicians and the general public become increasingly familiar with LD, they are increasingly questioning and reporting the associated symptoms.

Our work emphasized the importance of improving turnaround time for LD diagnosis in Quebec and Canada, plateauing at almost 40 days since 2004. This is important as almost one quarter of all treatments in our cohort were initiated after the issuance of the immunoblot test results. For many years, most provincial public health or hospital laboratories have performed enzyme immunoassay testing locally, while immunoblot testing was performed at the National Microbiology Laboratory in Winnipeg. The implementation of immunoblot testing in provincial public health labs might help decrease these turnaround times and eventually decrease treatment delays for patients (22).

We observed an overall adherence of 90% to the IDSA LD guidelines, which is lower than adherence rates previously published in other contexts . Adherence rates of 100% in a small sample of patients with erythema migrans were found without mentioning the criteria for guideline adherence and treatment information was available in only 25% of reported cases. (23) Another study conducted in a hyperendemic area of Wisconsin, USA, showed treatment

adherence with IDSA recommendations in 99.9% of cases (15) but included only cases of early LD and the only criterion to compare treatment to the IDSA guidelines was the type of antimicrobial used. We considered more stringent comparison criteria as a treatment to be deemed as adequate needed to include the right molecule, at the right dosage, and for an adequate duration, which might explain the lower adherence rates. Our population was restricted to patients consulting in acute care facilities, reflecting more complex cases compared to patients seen in primary care practices. In the case of non-adherence to the IDSA guidelines, the main reason identified was a longer treatment duration. As prolonged antimicrobial therapy for the treatment of LD has not shown greater efficacy compared with shorter-duration regimens (14, 24, 25), it is important to educate clinicians about the dangers of prolonged treatment, which may bring significant risks, such as *Clostridioides difficile* colitis (26).

We found that the proportion of serologically confirmed LD cases managed in acute care facilities, a complex population, decreased significantly over time. Studies carried out in North America have found a gradual increase in the proportion of cases in the early localized phase, which consequently implies a gradual decrease in the proportion of severe LD cases (7, 27-29). Over time, clinicians become more familiar with LD and diagnose and treat the disease early, thus preventing the passage to more advanced stages.

Limitations

The main limitation of our study is its retrospective nature, which could introduce information bias. We were able to minimize this by including specialized research assistants

who ensured complete data collection. We also had limited power to significantly confirm several indicators of increasing awareness and familiarity with LD in both patients (decreasing time to the first consultation) and clinicians (decrease in time between first symptoms and treatment initiation and decrease in specialists). Finally, the guidelines in effect during the study period have not been updated since 2006. However, their validity was confirmed in 2010 (30) and the Quebec recommendations, issued in 2019, did not lead to any major changes compared to the IDSA recommendations (31).

Conclusion

In this retrospective multicenter cohort study in two endemic regions of Quebec, Canada, we found a resolution of the objective signs of LD in most patients and that most treatments complied with the IDSA guidelines. Finally, we describe the emergence of PLDTS. This finding warrants further investigation in prospective studies.

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Table and figure titles

Figure 1: Study flowchart

Table 1: Characteristics of patients with and without post-Lyme disease treatment syndrome (PLDTS)

Table 2: Characteristics of patients with Lyme disease according to study periods

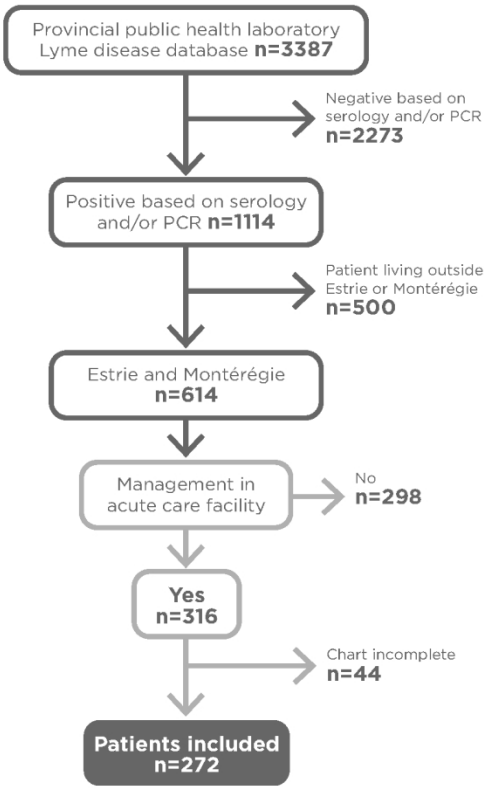

Figure 1: Study flowchart

215x279mm (200 x 200 DPI)

Table 1: Characteristics of patients with and without post-Lyme disease treatment syndrome (PLDTS)

Risk factors	PLDTS n (%) n=27	No PLDTS n (%) n=240	Crude odds ratios (95% CI)	p-value	Adjusted odds ratios (95% CI)	p-value
Sex						
Female	8 (29.6)	94 (39.2)				
Male	19 (70.4)	146 (60.8)	0.7 (0.3–1.6)	0.3		
Age category						
<18 year	2 (7.4)	37 (15.5)				
18–64 years	21 (77.8)	145 (60.7)	2.7 (0.6-11.9)	0.2		
65 years and more	4 (14.8)	57 (23.9)	1.3 (0.23-7.45)	0.8		
Symptoms upon presentation						
Arthralgia	16 (59.3)	70 (29.2)	3.5 (1.6–7.9)	0.002	2.8 (1.2–6.7)	0.02
Headache	19 (70.4)	126 (52.5)	2.2 (0.9–5.1)	0.08		
Myalgias	13 (48.2)	100 (41.7)	1.3 (0.6–2.9)	0.5		
Fatigue	19 (70.4)	138 (57.5)	1.8 (0.7–4.2)	0.2		
Insomnia	5 (18.5)	30 (12.5)	1.6 (0.6–4.5)	0.4*		
Tremor	4 (14.8)	5 (2.1)	8.2 (2.1–32.6)	0.007*	4.7 (1.1–20.0)	0.04
Paresthesias	7 (25.9)	32 (13.3)	2.3 (0.9–5.8)	0.08*		
Difficulty concentrating	4 (14.8)	8 (3.3)	5.1 (1.4–18.1)	0.02*	3.4 (0.08–14.1)	0.08
Clinical stage						
Early localized	6 (22.27)	84 (35.0)	1			

Early disseminated	15 (55.6)	121(50.4)	1.7 (0.7–7.9)	0.2		
Late disseminated	6 (22.2)	35 (14.6)	2.4 (0.6–4.7)	0.3		
Study period						
2004–2013	3 (11.1)	62 (25.8)	1		1	
2014–2015	4 (14.8)	69 (28.8)	1.2 (0.3–5.6)	0.8	1.3 (1.03–13.9)	0.7
2016–2017	20 (74.1)	109 (45.4)	3.8 (1.1 – 13.4)	0.04	3.7 (1.03–13.9)	

* Fisher's exact test

Table 2: Characteristics of patients with Lyme disease according to study periods

	2004–2013 n=66 n (%)	2014–2015 n=74 n (%)	2016–2017 n=132 n (%)	p-value
Age [years, median (IQR)]	50.0 (31.6–63.2)	47.8 (28.9–59.6)	53.3 (35.5–64.2)	0.2*
Age category				
<18	10 (15.4)	12 (16.2)	17 (12.9)	
18–64 years	41 (63.1)	50 (67.6)	80 (60.6)	
65 years and more	14 (21.5)	13 (16.2)	35 (26.5)	0.6
Sex				
Female	28 (42.4)	22 (29.7)	53 (40.2)	
Male	38(57.6)	52 (70.3)	79 (59.8)	0.2
Charlson comorbidity index				
0	55 (83.3)	60 (60.4)	107 (81.1)	
1–2	10 (15.2)	13 (17.6)	85 (11.4)	
3 and more	1 (1.5)	11 (1.4)	10 (7.6)	0.2

Lyme disease stage				
Early localized	17 (25.8)	26 (35.2)	47 (35.6)	
Early Disseminated	41 (62.1)	34 (45.9)	65 (49.2)	
Late disseminated	8 (12.1)	14 (18.9)	20 (15.2)	0.5
Adherence to IDSA recommendations	57/64 (89.1)	64/71(90.1)	114/126(90.5)	0.9
Hospitalization	15 (22,7)	16 (21,6)	17(12,9)	0.1
Time to first consultation (days, median, IQR)	7 (2–21)	4 (1–10)	3.5 (0–11)	0.3*
Time between first symptoms and treatment initiation (days, median, IQR)	18.5(9–34)	17 (4–35)	12 (4–33)	0.2*
Time between serology sampling and Western blot result (days, median, IQR)	37.5 ((29–47)	38.5 (30.5–42.5)	39 (34–43)	1.0*
Reference to specialist physican	59 (89,4)	60 (81,1)	103 (78.0)	0.06

Resolution of clinical objective signs	65/65 (100)	72/73 (98.6)	128/129(99.2)	0.7
Post-Lyme disease treatment syndrome	3/56 (4.6)	4/73 (5.5)	20/129 (15.5)	0.009

*Mood's median test of independent samples

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	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*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	5-6
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	5-6
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	7
		(*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	Fig1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
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	Tables 1 and 2
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10

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	Tables 1-2
		(*b*) Report category boundaries when continuous variables were categorized	Tables 1-2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
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	2

*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.