BMJ open
accessible medical research

HIV-associated neurocognitive disorders (HAND) in a South Asian population - contextual application of the 2007 criteria

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To cite: Chan LG, Kandiah N, Chua A. HIV-associated neurocognitive disorders in a South Asian population: contextual application of the 2007 criteria. *BMJ Open* 2012;**2**:e000662. doi:10.1136/bmjopen-2011-000662

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2011-000662).

Received 22 November 2011
Accepted 11 January 2012

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ABSTRACT

Objectives: To estimate the prevalence of HIV-associated neurocognitive disorders (HAND) among HIV patients in a multiethnic South Asian population, describe the pattern of neurocognitive impairment in HAND and the factors associated with HAND.

Design: A cross-sectional survey of HIV-positive outpatients and inpatients.

Setting: The sole referral centre for HIV/AIDS treatment in Singapore.

Participants: Inclusion criteria were HIV positive, age between 21 and 80 years old and at least 3 years of education. Exclusion criteria included concomitant delirium, serious systemic disease or major psychiatric illness. 265 patients did not meet criteria or declined to participate. The final sample size was 132.

Outcome measures: The primary outcome measure was cognitive impairment based on performance on the Montreal Cognitive Assessment, International HIV Dementia Scale and Instrumental Activities of Daily Living. The secondary outcome measure was the classification of impairment based on the 2007 updated research nosology for HAND.

Results: The prevalence of HAND was 22.7% of which 70% (15.9% of total) were asymptomatic neurocognitive impairment, 23.3% (5.3% of total) were mild neurocognitive disorder and 6.7% (1.5% of total) were HIV-associated dementia. Increasing age (OR 1.104, 95% CI 1.054 to 1.155, $p<0.001$), less education (OR 0.78, 95% CI 0.69 to 0.89, $p<0.001$) and low baseline CD4 count (OR 0.15, 95% CI 0.03 to 0.74, $p=0.019$) were associated with HAND. Delayed recall, language and abstract thinking were the domains most commonly affected, but impairment in visuospatial ability (RC 3.013, 95% CI 1.954 to 4.073, $p<0.001$) and attention (RC 2.205, 95% CI 1.043 to 3.367, $p<0.001$) were most strongly associated with HAND.

Conclusion: HAND is common among HIV patients in a South Asian sample, most of whom are asymptomatic. Older patients with less education and severe illness at diagnosis are at highest risk of HAND. Delayed recall is most commonly affected, but visuospatial dysfunction is most strongly associated with prevalent HAND.

ARTICLE SUMMARY

Article focus

- What is the prevalence of HIV-associated neurocognitive disorders (HAND) in South Asia?
- What are the demographic and clinical characteristics of South Asian individuals with HAND?

Key messages

- The estimated prevalence of HAND in South Asia is high.
- Older patients with less education and more severe HIV illness at diagnosis are at highest risk for HAND.
- Early diagnosis of HIV and access to care and treatment is essential.

Strengths and limitations of this study

- The article's strengths are it is the first study on HAND in a representative multiethnic South Asian population and it used a method of detection that is applicable to local clinical practice.
- The limitations are the small sample size and non-comparability with other HAND studies due to different methods used in detection of HAND cases.
- Another major limitation is the lack of published local normative data on the tools used.

INTRODUCTION

Much research attention has been given to HIV-associated neurocognitive disorders (HAND) in recent years because this entity has taken on clinical importance now that highly active antiretroviral therapy (HAART) has achieved marked reductions in AIDS-related morbidity and mortality. Majority of the available data have emerged from Western populations citing an incidence rate of 21% and prevalence rates of up to 39%[1] with one study from the Asia-Pacific region reporting a prevalence of only 12%.[2] There is a strong body of evidence showing an adverse functional impact of HAND, with patients having difficulty with activities of daily living

and requiring more assistance to ensure adherence to medications.[3] They may even have difficulties maintaining employment, hence requiring more social assistance.[4] HAND has also been shown to be associated with low nadir CD4 counts[1] in the absence of central nervous system opportunistic infections and persists despite long-standing suppression of viraemia.[5] With evidence that HAART can improve neurocognitive functioning,[6] early initiation of antiretroviral treatment in at-risk HIV-positive individuals may prevent neurocognitive impairment.

The prevalence of known HIV cases among the Singapore resident population aged 15 years and above was 0.1% in 2009.[7] There is a cumulative total of 4845 HIV-infected Singapore residents as of end 2010. In 2010, 54% of the newly diagnosed cases already had late-stage HIV infection at the point of diagnosis, similar to the pattern in previous years.[8] Due to the country's strict drug laws, intravenous drug abuse accounts for only 2% of total cases. Previous local studies had identified older age and lower baseline CD4 counts as predictors of progression to AIDS[9] and that the commonest AIDS-defining illnesses between 1985 and 2001 did not involve the central nervous system.[10] Despite a previous study in South India that found mild-to-moderate neuropsychological deficits in a functionally normal HIV-positive group,[11] yet the total burden of HAND in Singapore and other South Asian HIV-positive populations and its clinical significance is so far unknown.

This is the first study from a multiethnic South Asian population to estimate the local prevalence of HAND and to identify the demographic and clinical characteristics of individuals with HAND. Our secondary objective is to test the use of standardised cognitive screening and clinical assessment tools for detecting HAND in our local setting.

METHODS

Study participants

This study was a cross-sectional survey conducted in the Communicable Disease Centre of Singapore, which is the country's referral centre for care and treatment of HIV/AIDS. Singapore has a multiethnic population consisting of Chinese, Malay and Indian races and represents a good reflection of the South Asian population. The study protocol had been approved by the Domain Specific Review Boards of the National Healthcare Group. The study was conducted from September 20 to October 15 of 2010 and included both inpatients and outpatients. Patients were eligible if they were HIV positive, aged between 21 and 80 years old and had at least 3 years of education. Exclusion criteria included patients with concomitant delirium, serious systemic disease or major psychiatric illness. Written informed consent was obtained from eligible patients.

Test battery

Participants were administered the Montreal Cognitive Assessment (MoCA),[12] the International HIV Dementia Scale (IHDS)[13] and the Lawton scale for Instrumental Activities of Daily Living[14] by trained members of the study team. The MoCA has been validated locally with a cut-off score of 26/27 out of 30 for the diagnosis of Mild Cognitive Impairment, but these data are currently unpublished and under peer review (Ng, A *et al*, 2011) The Instrumental Activities of Daily Living has also been validated locally and shown to be cross-culturally applicable.[15] However, the IHDS has not been validated outside of Africa but has been used in India to screen for HIV dementia in comparison with a HIV-negative group.[13 16] As presence of depression was considered to be a potential confounder, depressive symptoms were measured by administering the Patient Health Questionnaire-9 on all participants.[17 18] To avoid interviewer bias, study team members who administered the tests were blinded to the clinical details at the time of administering the cognitive tests. Patients were classified as HAND or normal based on the clinical judgement of impaired performance in at least two domains of delayed recall, executive function, visuospatial function, attention, language function, abstract thought, orientation, motor speed and psychomotor speed, in addition to scores lower than recommended cut-offs on the MoCA and IHDS, and information on functional impairment which was ascertained using the stated instruments. Hence, validated total cut-off scores on the MoCA and IHDS were not used as the sole criterion of cognitive impairment in the application of HAND criteria.[19] Demographic, relevant clinical data and laboratory data were obtained by retrospective chart review. Data included age, sex, acquisition risk for HIV, level of education, concomitant sexually transmitted infections and vascular risk factors such as hypertension, diabetes and dyslipidemia, hepatitis B and C coinfection and exposure variables of baseline CD4 cell count, current CD4 cell count, stage of illness at diagnosis, length of time since diagnosis, plasma HIV viral load and antiretroviral therapy.

Statistical analyses

Comorbid sexually transmitted infections and vascular risk factors were analysed as categorical variables. Stage of illness was defined by the United States Center for Disease Control classification. CD4 counts were analysed by three groups of severity: >500, 200−499 and <200. Five participants with newly diagnosed illness and who had only one set of laboratory results for CD4 counts had the same data recorded for both baseline and current CD4.

The prevalence of HAND and its subtypes was first computed. The Students t test and χ^2 test were used to compare continuous and categorical variables, respectively, between cognitively normal and subjects with HAND. Univariate logistic regression analysis was used to determine the variables associated with HAND. Multivariate logistic regression analysis was then performed to adjust for the effect of confounders. Subgroup analysis was not performed as the numbers in the group with the HAND outcome were insufficient for meaningful analysis.

RESULTS

During the study period, 400 patients were screened for eligibility. Two hundred and sixty-five patients either did not meet the inclusion criteria or declined to participate. Three were excluded because of concurrent delirium. A total of 132 patients gave written informed consent to participate in the study. Data from 132 participants were analysed. 90.9% of the whole sample was receiving antiretroviral treatment. Data on the eligible patients that did not participate are not available.

HAND was detected in 22.7% of the participants. Within this group, 70% (15.9% of total) had asymptomatic neurocognitive impairment, 23.3% (5.3% of total) had mild neurocognitive disorder and 6.7% (1.5% of total) had HIV-associated dementia. Table 1 shows the demographic and clinical characteristics of the two groups. HIV patients with HAND had a higher mean age (54.40 vs 43.45, p<0.001) and lower mean years of education (8.03 vs 11.45, p<0.001). Also, a larger proportion of patients with HAND had more severe stage of illness (stage C: 63.3% vs 31.4%, p=0.006) and lower baseline CD4 counts at diagnosis (CD4 <200: 80.0% vs 47.5%, p=0.002). The two groups did not differ significantly in the presence of comorbid sexually transmitted infections and vascular risk factors.

Univariate logistic regression analysis was performed for all the exposure variables and it showed that age (OR 1.104, 95% CI 1.054 to 1.155, p<0.001), education (OR 0.78, 95% CI 0.69 to 0.89, p<0.001), stage C of illness (OR 4.09, 95% CI 1.66 to 10.07, p=0.002) and baseline CD4 count between 200 and 499 (OR 10.00, 95% CI 2.23 to 44.92, p=0.003) were significantly associated with the presence of HAND (table 2). Depression as measured with the Patient Health Questionnaire-9 was found not to be associated with HAND. The OR for a history of central nervous system opportunistic infections was high at 3.67, was 1.15 for the log-transformed viral load and 1.92 for the presence of any vascular risk factor but all three were not statistically significant. Therefore, multivariate logistic regression was used to adjust for the confounders of age and education. Stage C of illness ceased to be associated with the presence of HAND, and the direction of association with a less severe baseline CD4 became more consistent with clinical reason (OR 0.15, 95% CI 0.03 to 0.74, p=0.019).

The HAND group performed consistently and significantly worse than the cognitively normal group across all domains, except for the domain of orientation (table 3).

Impairment in the domains of delayed recall, language, abstract thinking, motor speed and

Table 1 Demographic and clinical characteristics by neurocognitive status, N=132

	Normal, N=102 (77.3%)	HAND, N=30 (22.7%)	p Value
Age			
Mean (years)	43.45 (SD=10.19)	54.40 (SD=10.83)	<0.001
Education			
Mean (years)	11.45 (SD=3.97)	8.03 (SD=3.66)	<0.001
Employment (n, %)			
Professional	40 (39.2%)	3 (10%)	
Blue-collar	36 (35.3%)	13 (43.3%)	0.001
Unemployed	26 (25.5%)	14 (46.7%)	
Gender (n, %)			
Male	86 (84.3%)	28 (93.3%)	0.362
Female	16 (15.7%)	2 (6.7%)	
Race (n, %)			
Chinese	85 (83.3%)	28 (93.3%)	0.317
Malay	8 (7.8%)	0	
Indian	6 (5.9%)	2 (6.7%)	
Others	3 (2.9%)	0	
Stage of illness at diagnosis (n, %)			
A	62 (60.8%)	9 (30%)	0.006
B	8 (7.8%)	2 (6.7%)	
C	32 (31.4%)	19 (63.3%)	
Baseline CD4 (n, %)			
<200	48 (47.5%)	24 (80.0%)	
200–499	40 (39.6%)	2 (6.7%)	0.002
>500	13 (12.9%)	4 (13.3%)	
Current CD4 (n, %)			
<200	23 (22.8%)	8 (27.6%)	
200–499	53 (52.5%)	16 (55.2%)	0.670
>500	25 (24.8%)	5 (17.2%)	
Comorbid STI (n, %)	43 (42.2%)	15 (50.0%)	0.447
Comorbid vascular risk factor(s) (n, %)	38 (37.3%)	16 (53.3%)	0.115

STI, sexually transmitted infection.

Table 2 Association between listed factors and prevalent HAND

Variable	OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Age (years)	1.104 (1.054 to 1.155)	<0.001		
Education (years)	0.782 (0.687 to 0.890)	<0.001		
Years since diagnosis	1.024 (0.940 to 1.116)	0.588		
Stage at diagnosis				
A	(Reference)			
B	1.722 (0.315 to 9.427)	0.531		
C	4.090 (1.662 to 10.066)	0.002	1.333 (0.369 to 4.815)	0.661
Baseline CD4				
<200	(Reference)			
200–499	10.000 (2.226 to 44.919)	0.003	0.151 (0.031 to 0.737)	0.019
>500	0.437 (0.478 to 5.521)	0.437		
Current CD4				
<200	(Reference)			
200–499	1.152 (0.433 to 3.069)	0.777		
>500	1.739 (0.497 to 6.086)	0.387		
History of CNS OIs	3.67 (0.70 to 19.21)	0.124		
Log-transformed viral load	1.15 (0.94 to 1.40)	0.177		
Vascular risk factors	1.92 (0.85 to 4.38)	0.118		

Adjusted OR, corrected for age and education. CNS OIs, central nervous system opportunistic infections.

psychomotor speed were prevalent in at least two-thirds of the HAND group. The domains of visuospatial function, executive function and attention were affected the least frequently. However, logistic regression showed that impairment in visuospatial function, attention or language on the MoCA was most predictive for the presence of HAND (table 4).

DISCUSSION

Our study showed that one in five HIV-positive patients from a South Asian population can be expected to have HAND. The results indicate that patients with HAND tend to be older (mean 54.4 years), with fewer years of formal education (mean 8.0), and had extremely low baseline CD4 counts (CD4 <200 cells/μl). This is consistent with the previous studies.[20–22] Length of time since diagnosis and current CD4 counts did not determine the diagnosis of HAND.

Other studies have not examined directly the association between duration of illness and the presence of neurocognitive impairment but have hypothesised that central nervous system injury begins very early in the course of HIV infection.[23] Also, recovery of immunosuppression does not appear to be protective for HAND, a finding that has been recently demonstrated.[5] In our study, HAND was directly related to severely low baseline CD4 counts. The finding that nadir CD4 counts are a strong predictor for HAND has been shown in several studies.[1 20] Because our study design is cross-sectional, we are unable to assess the effect of immune recovery or comment on nadir CD4 count. We assume that because patients present with late-stage HIV infection, baseline CD4 count is an approximate surrogate for nadir CD4 cell count.

Our study failed to show any statistically meaningful relationship between HAND and sexually transmitted infections, hepatitis B and C coinfection and vascular risk factors, unlike previous studies.[24–28] This is most likely due to a small number in the HAND group. However, the effect of vascular risk factors would be an

Table 3 Comparison of scores on cognitive tests by cognitive status

Score	Normal, mean (SD)	HAND, mean (SD)	p Value
MoCA (total)	28.45 (1.45)	24.17 (3.20)	<0.001
MoCA (executive function)	3.82 (0.41)	3.03 (1.03)	<0.001
MoCA (attention)	5.95 (0.22)	5.63 (0.56)	0.004
MoCA (language)	5.71 (0.54)	4.50 (1.08)	<0.001
MoCA (abstraction)	1.61 (0.55)	1.97 (0.67)	<0.001
MoCA (recall)	4.23 (0.97)	3.23 (1.19)	<0.001
MoCA (visuospatial)	0.93 (0.25)	0.40 (0.50)	<0.001
MoCA (orientation)	5.93 (0.29)	5.73 (0.64)	0.109
IHDS (total)	10.92 (1.20)	8.65 (2.34)	<0.001
IHDS (motor speed)	3.49 (0.82)	2.60 (1.30)	0.001
IHDS (psychomotor speed)	3.59 (0.75)	2.57 (1.33)	<0.001

IHDS, International HIV Dementia Scale; MoCA, Montreal Cognitive Assessment.

Table 4 Logistic regression results showing the predictive power of domain-specific impairment, N=30

Cognitive domain	Regression coefficient	95% CI	p Value
MoCA (visuospatial)	3.013	1.954 to 4.073	<0.001
MoCA (attention)	2.205	1.043 to 3.367	<0.001
MoCA (language)	1.989	1.247 to 2.731	<0.001
MoCA (abstraction)	1.637	0.895 to 2.379	<0.001
MoCA (executive function)	1.586	0.888 to 2.283	<0.001
MoCA (total)	1.065	0.671 to 1.458	<0.001
IHDS (psychomotor speed)	0.937	0.500 to 1.373	<0.001
IHDS (total)	0.802	0.467 to 1.138	<0.001
IHDS (motor speed)	0.791	0.378 to 1.205	<0.001
MoCA (recall)	0.791	0.384 to 1.200	<0.001

IHDS, International HIV Dementia Scale; MoCA, Montreal Cognitive Assessment.

important area for future research as the baseline prevalence of metabolic diseases in Singapore is high.[29] Our study also showed that a history of central nervous system opportunistic infections is possibly an important contributing factor despite the lack of statistical significance that we attribute to the small sample size, while other studies had actively excluded such patients.[5] The viral load in plasma was traditionally thought to predict the presence of HIV-associated dementia[30] but more recent studies have shown correlation with viral loads in the cerebrospinal fluid while there is peripheral viral suppression.[5 31] Currently, it is not local practice to measure HIV RNA in the cerebrospinal fluid and great difficulties with getting consent for lumbar punctures from future research subjects are anticipated.

HAND is currently conceptualised as having a subcortical pattern[32] with an argument for bradykinesia and bradyphrenia being the cardinal features of HAND.[33] There is also general agreement that the most prevalent impairments in HIV are in the domains of Learning, Abstraction/Executive Functioning, Attention/Working Memory and Motor Functioning, whereas Verbal Functioning/Language is relatively spared.[4 32] The pattern of cognitive impairment in South Asian patients with HAND does not appear to fit into a discrete subcortical pattern as previously thought. In fact, both cortical and subcortical functions are frequently affected, and this is consistent with a recent study demonstrating both cortical and subcortical neurodegeneration.[34] It is not clear from this study whether this is due to effects of HAART, as suggested by other studies.[35] Even though it is possible to analyse the Central Nervous System Penetration Effectiveness (CPE) scores[36] of the HAART regime of the study subjects, the cross-sectional methodology limits meaningful interpretation of the results as many other confounders such as duration of treatment and the timing of treatment initiation need to be considered. Future longitudinal studies should evaluate the differences in the cognitive profile of HAND in patients with and without HAART.

An important limitation of this study is the relatively small sample size. However, previous prevalence estimates were too imprecise for an a priori sample size calculation. There was also potential response bias that was not dealt with in the study methodology. Patients who did not consent to participate in the study may have had characteristics that would skew the prevalence rate in either direction. This study is also limited by the lack of published normative data on the cognitive tools used. However, the authors have used demographically appropriate data wherever possible. Another limitation is the lack of exclusion of subjects with substance or alcohol use. However, based on the demographics of the local HIV population, substance or alcohol use is relatively uncommon.

However, we feel that this study is important as it provides the first data we have among multiethnic South Asian patients on HAND. Our centre sees the majority of HIV/AIDS patients, and thus, the study prevalence likely approximates the true prevalence of HAND in Singapore. This study adds another compelling reason for early diagnosis of HIV infection and linkage to care and treatment.

Previous studies have used specially developed neuropsychological batteries to detect and diagnose HAND.[19 37–39] To the authors' knowledge, this present study is the first to use a standardised mental status examination (an acceptable option in the updated research nosology for HAND considering resource-limited contexts)[19] in a novel way of using domain-specific performance in addition to recommended cut-off scores, as well as using a combination of standardised mental status examinations to provide for an assessment of a broad and comprehensive range of cognitive functions. In most South Asian countries, neuropsychological testing is available but mostly in non-integrated settings. Hence, even though resources are not limited, access to it is hindered by many cultural and patient factors. Making clinical diagnoses of cognitive impairment using a combination of clinical judgement and brief bedside tools is the local practice. Thus, the method of detection used in this study was chosen because of its potential clinical utility. The authors acknowledge that this methodology though novel severely limits the study's comparability with previous studies. Yet it is commendable and worth commenting that the results obtained are strikingly similar to data previously published.[1 2]

Further research is essential in order to understand the clinical importance of HAND and the profile of its longitudinal history in HIV-positive patients in South Asia. Validation of the test instruments specifically using HIV negative controls would add to the evidence base of the clinical utility of such tools. Such tools are potentially of immense use even in settings that are not resource limited.

Acknowledgements The authors would like to acknowledge Miss Tey Jing Yin, Miss Charissa Wong, Miss Muslihah Albakri, Mr Yuen Wei Lun and Miss Ho Mei Jing for their help in data collection. They would also like to thank the Clinical Research Unit of Tan Tock Seng Hospital and Miss Ivane Chew for their help in statistical analysis.

Contributors LGC contributed to the study design, data analysis and interpretation and drafting the manuscript for content; NK contributed to the study design, data interpretation and revising the manuscript for content and AC contributed to the study design and revising the manuscript for content.

Funding NK has received conference support and/or honorarium from Lundbeck, Novartis and Eisai. He also has received research funding from Singhealth Foundation and Media Development Authority of Singapore. AC reports no financial disclosures. LGC has received conference support from Abbott and research funding from National Healthcare Group.

Competing interests None.

Ethics approval Domain Specific Review Boards of National Healthcare Group.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There is no additional data available.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional 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*) Give the eligibility criteria, and the sources and methods of selection of participants
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*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
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
Outcome data	15*√	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 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 www.strobe-statement.org.