A cross-sectional analysis of over the counter codeine use amongst an Australian sample of people who regularly inject drugs

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Abstract

Aims: To examine the medical and non-medical use of over-the-counter (OTC) codeine combination drugs in a sample of people who inject drugs; and to examine risk factors associated with exceeding the recommended dose of OTC codeine, including the experience of pain.

Design and Methods: Analysis of annual survey data from a convenience sample of people who inject drugs in Australia who are interviewed for the Illicit Drug Reporting System. People who have injected drugs (n=902) on at least a monthly basis in the preceding six months across Australia were interviewed. Participants were asked about their use of OTC codeine and their experience of pain.

Results: One-third (35%) of participants had used OTC codeine in the preceding six months and 52% (95% confidence interval 48.7-55.3) of this group had exceeded the recommended dose on their last occasion of use. This clearly places them at increased risk of harms associated with toxicity from the accompanying analgesic found in combination codeine products. Multivariate analyses demonstrated that those exceeding the recommended codeine dose of OTC codeine were more likely to be experiencing moderate to very severe pain.

Discussion: There is a need to evaluate the approach to pain management in this population. Greater pharmacist involvement, real time monitoring of sales, the development of screening tools to identify those at risk of harm and further education of primary care practitioners could be beneficial in reducing the risk of harm associated with these medications for all users of OTC codeine, including people who inject drugs.

Keywords

codeine; pain; substance abuse, intravenous; opioid-related disorders; nonprescription drugs

Introduction

In Australia, low doses of codeine available over the counter (OTC) are combined with non-opioid analgesics including paracetamol and non-steroidal anti-inflammatory drugs such as ibuprofen and aspirin. In recent years there have been increasing concerns about the misuse of formulations that contain codeine, and case reports of serious harm from use of high doses of these products [1-3]. Harm associated with OTC codeine has been reported in individuals who had prior substance use disorders and those that did not have a prior history of illicit drug use [1-3]. In May 2010, regulatory changes were made in Australia, restricting supply of OTC codeine combination medicines. These medications are no longer available for self-selection on pharmacy shelves, with sales requiring a pharmacist to determine a therapeutic need. In addition, pack sizes were reduced to a maximum of 30 tablets/capsules. In the United Kingdom, regulatory changes in 2009, now require OTC codeine combination medicines to carry warning labels, and pack sizes are limited to 32 tablets/capsules [4]. In the United States, medications containing codeine are available only with a prescription.

Exceeding the recommended dose of these medications carries the risk of non-opioid toxicity from the accompanying analgesic. Prolonged use of high dose non-steroidal anti-inflammatory drugs has been associated with serious harms including gastrointestinal disease, renal failure, anaemia and hypokalaemia [1,5,6] , while paracetamol has been associated with hepatotoxicity [7]. In addition, codeine has a known dependence liability [8,9]. Prolonged use of codeine has the potential to produce tolerance, often leading to dose escalation, especially in those amongst whom pain is not well managed. These products may also be used to substitute for or to top up illicit drugs, particularly among people who regularly inject drugs [9]. In an Australian general population Internet survey of a convenience sample of 800 individuals that had recently used codeine, 20% reported using more than the recommended dose on the last occasion of use, and 17% met criteria for codeine dependence [5]. No studies examining the prevalence of dependence on or

misuse of OTC codeine in the United Kingdom were identified. Other authors have noted the lack of published literature and the need for further research in this area [10,11].

Pain relief for people who use illicit drugs is problematic. Multiple factors may contribute to use of OTC medications amongst substance users. There is a tendency for health care professionals to avoid prescribing opioid analgesics to patients self-reporting pain who also have with substance use disorders [12,13]. This avoidance is due both to concerns cited by health care professionals, including the increased risk of respiratory and central nervous system depression if opioid analgesics are prescribed in addition to opioid maintenance treatments or illicit opioid use, and a concern that the request for opioid analgesia is not for pain relief, but rather for the narcotic intoxifying effects of these substances [14]. The relationship between health care professional and patient is sometimes strained by anxious or demanding behaviour by the patient. This can often arise as a result of a general distrust of the medical community, fears of intentional mistreatment and feelings of stigmatisation [13,15].

Pain management can be complicated for some people who inject drugs (PWID), such as those that use opioids. Tolerance to opioids following repeated use often results in the need for higher doses to obtain adequate pain relief, while hyperalgesia can mean that increasing opioid doses leads to increased pain responses [16-18]. These factors, combined with the reticence to prescribe opioids for pain management among PWID may increase the likelihood of use of OTC medications among PWID. Given the potential for severe harms from OTC codeine it is important to investigate self-medication with OTC codeine amongst PWID.

The aim of this study is to examine the medical (use for analgesia) and non-medical use (use for reasons other than analgesia) of OTC codeine combination drugs in a sample of PWID. The study also aims to examine the relationship between demographic characteristics; risk behaviours; patterns of drug use; and the experience of pain in those that use OTC codeine, both within and exceeding the recommended dose.

Methods

In June 2010, 902 PWID were interviewed as part of the Illicit Drug Reporting System (IDRS). The methods for the IDRS have been described elsewhere [19].

Participants were recruited through a purposive sampling strategy that included advertisements in treatment agencies, needle and syringe programs and peer referral. Individuals wishing to participate were asked to attend study locations, where they were screened for eligibility. To be eligible to participate in the survey, participants needed to have injected at least monthly during the six months preceding the interview, and to have resided in the State/Territory capital city in which they were interviewed for at least 12 months. Eligible participants were administered the structured interview schedule which took 30-60 minutes to complete. All participants were reimbursed $40 for their time and expenses incurred.

The survey asked questions pertaining to drug use patterns, risk behaviours and health-related issues. In 2010 participants were also asked about use of OTC codeine outside of the purposes of pain relief. They were asked about frequency of use, main brands used, the reason for use, and the number of tablets/capsules used per dose. In addition participants were also asked how much pain, what type of pain and the severity of pain they had experienced recently.

Multinomial logistic regression models were used to examine the association between independent predictor variables and the use of OTC codeine in the previous six months. Comparisons were made between the baseline comparison group; (i) those who had not used OTC codeine in the six months preceding interview, and both (ii) those that had used OTC codeine within the recommended dose (2 tablets/capsules) and (iii) those that had used more than the recommended dose of OTC codeine in the six months preceding interview (‘recent use’). The independent predictor variables were demographic

characteristics and risk behaviours (including age, number of years injecting, gender, homelessness, prison history, arrest in the previous 12 months, experience of a mental health problem, Aboriginal and Torres Strait Islander status, currently in drug treatment and use of a needle after someone else), drug use history in the previous six months, severity of pain experienced and type of pain experienced. With the exception of age and number of years injecting, all demographic and risk behaviour independent variables were binary covariates.

A multivariate regression analysis was also conducted. Independent variables that were significant at a bivariate level were used in the model.

The IDRS has ethics approval from the University of New South Wales Human Research Ethics Committee and conforms to the provisions of the Declaration of Helsinki.

Results

Descriptive statistics

The mean age of the overall sample was 38 years (range 18-64) and 65% were male. Over three-quarters (81%) of the sample were currently unemployed and over half (52%) reported a previous prison history. Fourteen percent of the sample identified as being of Aboriginal or Torres Strait Islander descent. Almost half (47%) were currently in some form of drug treatment.

More than half the sample (52%, 95% confidence interval CI: 48.7-55.3, n=468) had used OTC codeine in their lifetime and 35% (n=317) had used in the six months prior to interview (Table 1). In the six months prior to interview seven percent (n=64) of participants had consumed OTC codeine for non-medical reasons. Four percent (n=34) of participants had ever injected OTC codeine.

The median number of tablets/capsules taken at one time on the last occasion of use for all reasons was three, range 1-250. The median dosage the last time they took OTC codeine was 26mg of codeine. Fifty-two percent of all recent OTC users took more than the recommended dose (2 tablets/capsules) on their last occasion of use. The median dosage the last time they took OTC codeine was 64mg of codeine. Of those reporting the use of OTC codeine for non-medical reasons, the median number of tablets/capsules taken in the session where they had the most tablets/capsules at once was six, range 1-180. In the session where they had the most tablets/capsules in the previous six months 67% of those that had used OTC codeine for non-medical reasons took more than the recommended dose (Table 2).

Those who had recently used OTC codeine for non-medical reasons were asked their reason for use. Of the 64 (7%) respondents, nine did not nominate a specific reason for doing so. Of the remaining 55 respondents the most common response (37%) was to 'substitute for heroin or illicit opioids'. Thirty-five percent of respondents used OTC codeine 'to go to sleep; 24% to 'get high/feel a buzz'; 13% to 'feel numb'; 13% to 'substitute for my pharmacotherapy dose'; and 2% to 'supplement my pharmacotherapy dose'.

Associations with OTC codeine use

Independent multinomial logistic regression analyses were conducted to estimate the strength of associations between OTC codeine use and demographic characteristics, risk behaviours, drug use history (Table 3) and recent experience of pain (Table 4). No OTC codeine use were the referent group.

Demographic and risk behaviour characteristics

Females were more likely than males to use OTC codeine either within or exceeding the recommended dose than males. Those using OTC codeine within the recommended dose were less likely to have been arrested in the past 12 months and more likely to be in

current drug treatment in comparison to those that had not used OTC codeine. Those using OTC codeine at higher than recommended doses were more likely to report mental health problems than those that had not used OTC codeine.

No significant differences were found for the other demographic and risk factors across the three codeine use groups.

Drug use history

The group using OTC codeine within the recommended dose had a higher proportion of people who had recently used methadone or other prescribed opiates than the group that had not used codeine (Table 3).

Compared to those with no recent OTC codeine use the group exceeding the recommended dose had a lower percentage of people who were primarily heroin injectors, and a higher percentage of people who had injected amphetamines in the previous six months (Table 3). Post-hoc analysis was conducted to examine the use of other drugs amongst those that had used amphetamines in the previous six months. Using chi-square tests, results indicated that those that had used amphetamines in the previous six months were significantly more likely to have recently used illicitly sourced buprenorphine (P=0.001), illicitly sourced buprenorphine-naloxone (P=0.002) or illicitly sourced oxycodone (P=0.004), than those that had not recently used amphetamines.

Experience of pain

Pain severity was significant in predicting an association with the use of OTC codeine (Table 4). Compared to those with no recent OTC codeine use both OTC codeine using groups had a significantly higher proportion of people with very mild/mild pain, moderate pain or severe/very severe pain.

In relation to type of pain experienced, in both OTC codeine-using groups, there were significantly higher proportions experiencing acute/short term pain in comparison to those

that had not used OTC codeine. Notably, compared to those with no recent OTC codeine use, both OTC codeine using groups had a lower proportion of people with chronic pain (either malignant or non-malignant in origin).

Multivariate model

Finally, Table 5 shows the results of multivariate analyses. Forcing variables that were significant at a bivariate level into the model showed that participants who had recently used OTC codeine within the recommended dose were more likely to; be receiving opiate treatment in the past six months; report moderate to severe pain; and to be female than those who had not recently used codeine. Participants who had recently exceeded the recommended dose of OTC codeine were more likely to; report moderate to severe pain and to be female; and they were less likely to report heroin as the drug injected most frequently in the past month than those who had not recently used codeine.

Discussion

To our knowledge, this is the first study examining the use of OTC codeine amongst people who regularly inject drugs. Our results show that 52% (n=156) of those who had used OTC codeine in the previous six months exceeded the recommended dose on the last occasion of use. This is considerably higher than results from an Australian web based survey designed to attract a broad range of OTC codeine users, where 20% (95% confidence interval 16.8-22.2) of participants reported using more than the recommended dose on the last occasion of use. This difference can be explained by the samples recruited. The sample from the web-based survey was more reflective of the general population, with only a minority (16%) of this community sample having ever sought treatment for any alcohol or other drug problem [5].

Understanding the risk factors associated with using higher than recommended doses of OTC codeine may assist in developing identification, prevention and treatment initiatives for this group. We found that females were more likely than males to exceed the recommended dose of OTC codeine. The issue of gender is an important one. Further research should examine in more detail why women are more likely to exceed the recommended dose.

Amongst those that had exceeded the recommended OTC codeine dose, a smaller proportion reported heroin as the drug they injected most often than amongst those that had not recently used OTC codeine, despite this group also experiencing higher levels of pain. This may be because the potency of these medications is not enough to provide pain relief in those who have continual exposure to high doses of opioids.

Compared to those with no recent codeine use, those who exceeded the recommended dose were more likely to have used amphetamines in the previous six months. Those that had recently used amphetamines were also more likely to have used illicitly sourced subutex, suboxone or oxycodone. Given this group is also more likely to exceed the recommended dose of OTC codeine, it is important to understand if this group is seeking

opioids for medical or non-medical reasons, and to determine if unmet needs for pain treatment exist. The finding of use of illicit opioid and OTC codeine use rather than prescribed opioids is consistent with previous research that suggests that amphetamine users are less likely to engage with treatment services [20]. It is also possible that amphetamine users are using illicitly source opioids to help come down from the effect of amphetamines.

In this study, taking higher than recommended doses of OTC codeine was associated with the presence of pain across a spectrum of severity, indicating that appropriate pain management is an issue in this group. In particular, results of the multivariate analyses showed that those exceeding the recommended dose of OTC codeine had higher rates of moderate, severe or very severe pain than those that had not used OTC codeine. It is clear that pain management of PWID is complicated, and that self-medication with OTC codeine products may not be effective or appropriate. Furthermore, the efficacy of OTC codeine products compared to non-opioid analgesics alone is uncertain [21] as is effectiveness of lower strength codeine products in providing effective pain relief [22,23]. The provision of alternate pathways for those in need of more specialised pain treatment available through existing points of contact with the healthcare system would be beneficial. As with all sufferers of pain, an individual approach to pain management needs to be adopted, with the development of a treatment plan based on individual needs and circumstances, including drug use histories.

Pharmacist involvement has the potential to reduce the risks associated with OTC codeine medications, especially amongst this group. Identification of those at risk of harm and real time monitoring of sales could reduce the harms associated with these medications. Real time monitoring of sales may help to prevent ‘pharmacy shopping’ where patients obtain large quantities of medication by going from pharmacy to pharmacy.

There is a need to further educate pharmacists, primary health care practitioners and patients about the potential harmful effects of these drugs. Previous research shows that patients underrate their risk of adverse drug reactions, and that there is a lack of knowledge amongst users of non-steroidal anti-inflammatory drugs regarding the potential for harm, especially gastrointestinal disease [24]. Primary health care practitioners need to be vigilant in assessing OTC medication when considering a patient's medical history. It has also been suggested that these medications carry warning labels, indicating the potential for dependence.

As a cross-sectional study of sentinel group of people who inject drugs this study has limitations. The IDRS collects data from an opportunistic sample and as such the sample may not be generalisable to all people who inject drugs. In particular, the sample was only selected from State/Territory capital cities and results may not be generalisable to those living in rural areas. Indeed, excessive OTC codeine use to manage pain may be a greater issue in rural situations where access to medical services may be more difficult. All variables recorded were subject to self-report bias. Lastly, the primary focus of the IDRS is drug use and market trends and as such there were limitations on length, structure and number of questions relating to the experience of pain that could be included. Despite these limitations, this is an important first study of OTC codeine amongst PWID.

In summary, the results of this paper indicated that there is a high rate of using OTC codeine above recommended doses amongst this sample of PWID. Given the risk of harms associated with the accompanying non-opioid analgesics in these products consideration needs to be given to ways in which the risks associated with these medications can be minimised. In particular, greater pharmacist involvement and tools to assist pharmacists to identify those at greater risk of harm would be beneficial. The data also indicates that risky use of OTC codeine is strongly associated with the experience of moderate-severe pain, drawing attention to the difficulties PWID often experience in

obtaining adequate pain management and the need to re-evaluate existing pain management practices for this group.

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Table 1: Prevalence of OTC codeine amongst injecting drug users

Codeine use	%	n
% Ever used	52	468
% Recent use	35	317
% Recent use for non-medical reasons	7	64
% Ever inject	4	34
% Recent injection OTC codeine	<1	6

Note: Recent refers to past six month use.

OTC, over the counter.

Table 2: Number of OTC codeine tablets/capsules taken by injecting drug users

Number of tablets/capsules	% of all recent OTC codeine users on their last occasion of use(n=301)	% of non-medical users on their occasion of most use in the previous 6 months (n=55)
1-2 (8-24mg codeine)	48	29
3-5 (34-60mg codeine)	35	20
6-9 (48-108mg codeine)	10	20
10 or more (>80mg codeine)	7	27

Note: Sixteen participants who reported recently using OTC codeine, did not nominate the number of tablets/capsules taken on their last occasion of use. Nine participants who reported recently using OTC codeine for non-medical purposes did not nominate the number of tablets/capsules taken on the occasion of most use in the previous six months. OTC, over the counter.

Table 3: Self-reported demographic characteristics, drug use and risk behaviours according to recent OTC codeine use

	Not recently used (n=581)	Recently used within rec. dose (<=2 tablets/capsules) (n=141)		Recently exceeded rec. dose (>2 tablets/capsules) ((n=157)	
	%	%	OR (95% CI)	%	OR (95% CI)
Demographics and risk behaviours					
Age (mean)	38.0	37.4	0.99 (0.97-1.01)	36.5	0.98 (0.96-1.00)
Years injecting (mean)	18.4	17.8	0.99 (0.97-1.01)	17.0	0.98 (0.96-1.00)
Female	30	47***	2.11 (1.44-3.07)	41**	1.62 (1.13-2.34)
Homeless past 12 months	34	32	0.94 (0.63-1.40)	37	1.16 (0.80-1.68)
Prison history	64	45	0.70 (0.49-1.02)	49	0.83 (0.58-1.18)
Arrested past 12 months	40	29*	0.62 (0.42-0.93)	43	1.15 (0.81-1.64)
Mental health problem past 6mths	46	53	1.33 (0.92-1.92)	57*	1.59 (1.11-2.27)
Aboriginal or Torres Strait Islander	13	14	1.05 (0.59-1.74)	15	1.18 (0.72-1.93)
Currently in drug tx	44	61***	2.02 (1.39-2.94)	49	1.24 (0.87-1.77)
Used a needle after someone else	10	9	0.92 (0.49-1.72)	12	1.23 0.71-2.14)
Drug use history					
Used in the previous six months					
Any opiate	92	96	1.96 (0.82-4.67)	94	1.30 (0.64-2.63)
Heroin	62	70	1.39 (0.93-2.06)	59	0.89 (0.62-1.27)
Amphetamines	58	53	0.82 (0.57-1.19)	69*	1.64 (1.13-2.40)
Morphine	44	46	1.08 (0.75-1.56)	50	1.25 (0.87-1.77)
Methadone	46	59**	1.72 (1.18-2.49)	56	1.38 (0.97-1.97)
Prescribed opiate#	57	74***	2.13 (1.41-3.21)	59	1.07 (0.75-1.53)
Drug injected most often					
Heroin	44	50	1.29 (0.89-1.86)	30**	0.55 (0.38-0.81)
Amphetamines	19	14	0.66 (0.39-1.12)	24	1.31 (0.86-2.00)
Morphine	19	16	0.79 (0.48-1.31)	21	1.10 (0.71-1.71)

*P <0.05; **P <0.01; ***P <0.001.

Prescribed opiate includes the licit use of methadone, physeptone, buprenorphine, buprenorphine-naloxone, morphine or oxycodone.

CI, confidence interval; OR, odds ratio; OTC, over the counter.

Table 4: Self-reported experience of pain according to recent OTC codeine use

	Not recently used (n=581)	Recently used within rec. dose (<=2 tablets/capsules) (n=141)		Recently exceeded rec. dose (>2 tablets/capsules) ((n=157)	
	%	%	OR (95% CI)	%	OR (95% CI)
Severity of pain					
No bodily pain	54	16***	0.16 (0.10-0.26)	20***	0.21 (0.14-0.33)
Very mild or mild pain	14	33***	3.12 (2.03-4.78)	24**	1.99 (1.28-3.10)
Moderate pain	15	25**	1.90 (1.21-2.99)	23*	1.72 (1.10-2.67)
Severe or very severe pain	17	26*	1.67 (1.07-2.60)	33***	2.34 (1.56-3.51)
Type of pain					
Acute/short-term pain	33	61***	3.14 (1.92-5.15)	58***	2.74 (1.70-4.42)
Chronic non-malignant pain	50	36*	0.56 (0.34-0.90)	32**	0.48 (0.30-0.78)
Chronic malignant pain	13	3**	0.18 (0.05-0.62)	9	0.61 (0.28-1.32)

*P <0.05; **P <0.01; ***P <0.001.

CI, confidence interval; OR, odds ratio; OTC, over the counter.

Table 5: Multivariate analyses

	Not recently used (n=581)	Recently used within rec. dose (n=141)		Recently exceeded rec. dose (n=157)	
	%	%	AOR (95% CI)	%	AOR (95% CI)
Heroin (injected most past month)	44	50	1.16 (0.79-1.72)	30**	0.56 (0.38-0.83)
Prescribed opiate (in past 6 months)	57	74**	1.87 (1.22-2.87)	59	1.02 (0.70-1.50)
Female	30	47**	1.94 (1.31-2.86)	41*	1.62 (1.11-2.37)
Moderate-very severe pain	32	51***	2.00 (1.36-2.94)	56***	2.54 (1.76-3.69)

*P <0.05;**P <0.01;***P <0.001.

AOR, adjusted odds ratio CI, confidence interval.

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Contributors
Sheena Arora conducted the literature searches, prepared the first draft of the manuscript and assisted with statistical analysis. Amanda Roxburgh conducted the statistical analysis and assisted with interpretation of data. Raimondo Bruno provided specific expertise regarding statistical analysis and assisted with interpretation of data. Suzanne Nielsen provided specific expertise regarding the subject matter and assisted with interpretation of data. Lucy Burns contributed to the study design and acquisition of data. All authors contributed to and have approved the final version of the manuscript

Conflict of Interest
All authors declare that they have no conflicts of interest.

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

	Item No	Recommendation	Checked
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y
Methods			
Study design	4	Present key elements of study design early in the paper	Y
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	N/A
		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	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	Y
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y
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	Y
Bias	9	Describe any efforts to address potential sources of bias	N/A
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	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y
		(*b*) Describe any methods used to examine subgroups and interactions	N/A

		(*c*) Explain how missing data were addressed	N/A
		(*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	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*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	Y
		(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	Y
		(b) Indicate number of participants with missing data for each variable of interest	Y
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	Y
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	Y
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*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	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Y
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	Y

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y
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	Y

*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.