Title: Prevalence, symptom patterns and management of episodic diarrhoea in the community: a population-based survey in 11 countries

Running title: Diarrhoea prevalence in the community

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Pali Hungin: interpretation of findings, analysis and final manuscript
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Kerstin Koenig: revision of the article for intellectual content
James Dalrymple: revision of the article for intellectual content
Noel Wicks: revision of the article for intellectual content
Lucy Paxman: data analysis, revising the article for intellectual content
All authors approved the final version of the article, including the authorship list
Background: The extent of episodic diarrhoea in the community is relatively unknown.

Aim: To ascertain the prevalence, symptoms and management behaviours associated with self-reported diarrhoea across 11 countries.

Methods: Community screening surveys were conducted using quota sampling of respondents to identify a nationally representative sample of individuals suffering from ‘episodic’ diarrhoea (occurring once a month or more often). Second-phase in-depth surveys provided data on epidemiology, symptoms, attributed causes and management of episodic diarrhoea.

Results: A total of 11,508 phase 1 and 6,613 phase 2 surveys were completed. The prevalence of self-reported episodic diarrhoea ranged from 16% to 23% across the 11 countries. The majority of episodic diarrhoea sufferers were female (57%) and were not diagnosed with pre-existing irritable bowel syndrome (IBS); IBS diagnosis ranged from 9% in Mexico to 44% in Italy. Diarrhoea was frequently attributed to anxiety/stress, food-related causes, gastrointestinal “sensitivity” and menstruation. Accompanying symptoms included “stomach pain/cramping” (35–62%), “stomach grumbling” (29–68%) and “wind” (18–74%). The proportion of episodic sufferers who reported treating their symptoms with remedies or medications ranged between 46% in Belgium and Canada and 90% in Mexico.
Conclusion: A substantial proportion of the population in middle- to high-income countries report episodic diarrhoea in the absence of a pre-existing diagnosis. These symptoms are likely to be associated with substantial social and economic costs and have implications on how best to configure and guide self-led, pharmacist-led and primary care management.
Introduction

Diarrhoea in adults is a common complaint and, while rarely life-threatening outside of developing countries, it continues to be an important cause of morbidity.\textsuperscript{1} Symptoms can cause distress and incapacitate sufferers,\textsuperscript{2} significantly impacting on health-related quality of life.\textsuperscript{3} The precise clinical presentation, time course and management requirements are dependent on the underlying pathological determinants. Current guidelines classify diarrhoea as either acute\textsuperscript{1,2,4} or chronic.\textsuperscript{5,6} No universally accepted definition is available, but acute diarrhoea has been described as the passage of a greater number of stools of decreased form lasting less than 14 days\textsuperscript{4} and, more recently, defined by the World Gastroenterology Organisation as three or more loose stools in the preceding 24 hours.\textsuperscript{1} Acute cases of diarrhoeal illness are usually brief and self-limiting\textsuperscript{2} and are commonly treated without consultation with a health professional.\textsuperscript{7} Thus, assessment of acute diarrhoea prevalence requires specialised community-based cohort studies or population-based surveys.\textsuperscript{7}

Previously, the rate of diarrhoeal illness (three or more loose stools in a 24-hour period causing impairment of daily activities or diarrhoea duration greater than 1 day) and/or vomiting in industrial countries has been estimated at around one episode every 18 months (0.65 episodes per person-year).\textsuperscript{7}

Chronic or persistent diarrhoea is usually defined as the abnormal passage of three or more loose stools per day lasting longer than 4 weeks.\textsuperscript{5,6} It is estimated that 3–5% of the population may have diarrhoea lasting more than 1 month in any given year.\textsuperscript{6}
The distinction between acute and chronic diarrhoea has important implications for management. Most patients with diarrhoea lasting more than 4 weeks will be found to have a non-infectious cause, whereas acute, self-limiting, uncomplicated cases of diarrhoea are generally assumed to be infectious in nature.\(^6\)

There is a paucity of data evaluating diarrhoea prevalence and causes in the community. In reality, there is likely to be a population who experience recurrent diarrhoea symptoms of limited duration, but who do not fit easily into the classically defined categories of 'acute' or 'chronic'. To further understand the impact of self-reported diarrhoea symptoms, we took a two-fold approach to investigate this in the general adult population of 11 middle-to high-income countries. Phase 1 of this study determined the prevalence of self-reported diarrhoea symptoms occurring once monthly or more often among adults, and phase 2 sought insights into symptoms and behaviours among individuals reporting episodes monthly or more often.

**Methods**

**Survey and subjects**

The results from online surveys in 11 countries administered to a total of 11,508 participants are reported here (Table 1). The surveys were originally carried out in 13 countries and, while the surveys shared a common basic theme, they were conducted on an individual basis within each country, with some national variation in questionnaire format and approaches to data
collection and analysis. Data from the UK and Russia were excluded owing to methodological differences that may have influenced survey responses. In the UK, episodic diarrhoea was defined differently (4 times in 6 months); surveys in Russia were administered by telephone interviews rather than self-administration online.

The surveys used an established research methodology for large scale data collection, with predetermined numbers in age and sex bands, to create a more representative sample than would be obtained by conventional methods such as household surveys or locally administered questionnaires. This approach has been used effectively in previous gastrointestinal research. In each of the 11 countries reported here, samples of adults from a market research panel were invited by email to complete a self-administered online survey. Market research panels are composed of pre-recruited individuals who have agreed to participate in online market research surveys. Several methodologies are used for recruitment, such as opt-in email, co-registration, electronic newsletter campaigns, and traditional banner placements. Research panels use several panel recruiting partners to build high quality panels with a varied sample population that can provide robust sample sizes. Panels measure recruitment sources on multiple metrics to track both activity and engagement by demographic group. Hundreds of profiling attributes are monitored to ensure that the panel population is representative of the national population.

Panellists, aged between either 16 or 18 and 64 years (Table 1), were randomly invited to participate in the survey. Invitations were issued blind; no information
was provided about the subject of the survey or who commissioned the research. To prevent duplication, survey links could only be used once. Quotas were applied to ensure national representativeness for age and gender and cells were filled on a first-come, first-served basis. Whilst quotas were used to achieve a representative sample, there were instances when insufficient response rates meant quota cells could not be filled. When this occurred weighting was applied to the data set to account for over- or under-representation of the demographic groups in the data set.

Any respondent who had completed a project of a similar nature in the previous 3 months or who was associated with advertising, market research, marketing, journalism, or the pharmaceutical industry, was excluded. The questionnaire was drafted in English and then translated professionally into relevant local languages. To validate questionnaire wording and routing, pilot interviews were conducted among a sample of respondents.

A specialist market research company, Incite (London, UK), was responsible for the development and undertaking of the online survey and collation of data. All surveys were conducted in accordance with the Market Research Society (MRS) guidelines.

Survey questions and application

The phase 1 survey was designed to establish demographic data and to identify individuals experiencing diarrhoea once monthly or more. The phase 2 survey
was designed to determine the perceived causes of diarrhoea, accompanying symptoms, and action taken in response to diarrhoea symptoms.

In phase 1, participants were asked how often they suffered from several problems including constipation, headache, vomiting, heartburn/indigestion and diarrhoea (“urgent, frequent, loose or watery stools”). In all countries prevalence was assessed using the following frequency of suffering question:

Q: How often do you suffer from each of the problems in the table below?

Diarrhoea (urgent, frequent, loose or watery stools)
1) Never
2) Less often
3) Once every 12 months
4) Once every 4–6 months
5) Once every 2–3 months
6) Once a month
7) 2–3 times a month
8) Once a week
9) More than once a week

Phase 2 survey links were then sent to individuals recruited from a market research panel who were targeted based on the specific demographic profile of individuals with once monthly or more often diarrhoea identified in phase 1 (in Canada, France and Italy, participants from phase 1 who selected options 6–9 were also invited to complete the phase 2 survey). In all countries, the frequency question was asked at the start of the phase 2 questionnaire to ensure all respondents experienced diarrhoea monthly or more often. A link to the survey was sent out to individuals with incentives for completion (vouchers or a prize draw).

Data analysis
All analyses were conducted using the statistical analysis software, SPSS. For quality control, data were checked for flat-liners (respondents who tended to give an average rating for all answers, suggesting that they were not really reading the question and/or answering it without much thought), and for respondents who completed the survey in a significantly faster time than would be expected or who gave inconsistent responses. These respondents were excluded according to standard research practice.
Results

Diarrhoea prevalence

A total of 11,508 phase 1 surveys were completed (Table 1); questions in this section determined if participants suffered from diarrhoea and how often. Phase 2 interviews were then completed by 6,613 individuals who reported experiencing diarrhoea once a month or more often. For the purpose of this manuscript, individuals who completed the phase 2 survey (reporting diarrhoea frequency of at least once a month) will be described as having ‘episodic’ diarrhoea.

The prevalence of self-reported episodic diarrhoea ranged from 16% to 23%. In 10 of the 11 countries, the prevalence was between 16% and 19% (Figure 1). Using data from the frequency of suffering question (see methods), the number of episodes that each phase 1 respondent would suffer in a 6-month period was calculated (assuming mid-points for ranges, e.g. once every 4–6 months = once every 5 months or 1.2 episodes in 6 months). This revealed that diarrhoea episodes experienced by the episodic diarrhoea sub-population accounted for 77% to 91% of the total self-reported episodes. In most countries, respondents with episodic diarrhoea experienced between three and four episodes per month (Figure 2). Weekly or more often symptoms were reported by 4% to 6% of phase 2 respondents in all 11 countries.

Episodic diarrhoea population

The age distribution of the sample in each country was similar for the entire survey population and those with episodic diarrhoea. However, compared with the total survey population (48%–49% female in each country), there was a trend for the
gender distribution of episodic sufferers to favour females (43.2% male, 56.8% female; Figure 3).

Episodic sufferers claiming to have been diagnosed with irritable bowel syndrome (IBS question: “Have you been diagnosed with irritable bowel syndrome by your doctor?”) ranged from 9% to 44% (Canada 21%, Belgium 35%, Australia 24%, France 38%, Germany 28%, Italy 44%, Sweden 18%, Finland 12% and Mexico 9%; question not asked in Spain and Argentina).

Symptoms and attributed causes
Participants were asked about symptoms experienced during a diarrhoea episode (question: “Which of the following problems, if any, did you suffer from at the time?”). Frequently reported symptoms accompanying diarrhoea (Table 2) included “stomach pains/cramping” (35% to 62%), “stomach grumbling” (29% to 68%) and “wind” (18% to 74%).

The precise questions relating to attributed causes of diarrhoea varied between countries. For example, most questionnaires asked, “Which of the following do you think can cause diarrhoea for you?”, while those in Canada, Australia and Belgium specified causes on the last occasion and asked, “What do you think was the cause of the problems you were suffering from on this [last] occasion?”. Although there was also some variation in the provided list of options for participants to choose from, there were some clear trends. In all countries except Mexico, “nerves, anxiety or stress” was among the three most commonly reported causes (18% to 65%). In Mexico, the top three causes were “eating certain foods”, “food
intolerance” and “excessive food”. Food-related causes were also frequently cited in the other countries. In seven countries where “eating certain foods” was an option, it was among the three most commonly reported causes, while “I have a sensitive system” was among the three most common causes in seven out of 10 countries where this was asked. Food intolerance (9% to 53%) and/or IBS (5% to 35%) were also frequently reported, while “chronic illness (such as Crohn’s disease or ulcerative colitis)” was less frequently cited (5% to 11%).

In European countries where respondents were asked about their usual cause of diarrhoea, menstruation was reported among women at rates between 24% and 43% (Germany 31%, France 24%, Italy 36%, Finland 38% and Sweden 43%), but was reported less commonly as a cause in Argentina (4%) and Mexico (18%) and countries reporting “last occasion” cause of diarrhoea: Belgium (12%), Australia (11%) and Canada (12%).

Symptom treatment
Phase 2 participants were asked about treatment of symptoms (Figure 4; example question: “In the last 6 months on the occasions when you have had diarrhoea, which of these things have you done at all”). In most countries the majority of episodic diarrhoea sufferers reported taking something to treat their symptoms during the last 6 months (list provided contained prescription, over-the-counter [OTC] and natural/non-chemical products). Belgium and Canada had the highest proportion of individuals who did not use a product to treat their symptoms (54%); Mexico exhibited the lowest proportion (10%). Among those who treated their symptoms, the proportion that used a prescription or an OTC product in the last 6
months was between 69% and 92%, with the exception of Germany (45%) and Finland (49%), which had the highest proportion of episodic diarrhoea respondents who used home remedies/natural products (Figure 5). The use of home remedies/natural products was lower in France, Mexico and Argentina compared with other countries.

In 9 countries where participants were asked, “Earlier you said you sometimes experience diarrhoea and do nothing, why is that?” there was some consistency in the most common reasons for not treating. Frequently reported reasons were “I generally avoid taking medicines” (15% to 42%), “the diarrhoea goes away quite quickly” (15% to 65%) and “I don’t get diarrhoea too severely” (25% to 62%). Although respondents did not commonly believe treatments were bad for them (0% to 10%), in many cases respondents indicated that they thought they should not interfere with the diarrhoeal process, by selecting options such as, “I prefer to let nature take its course” (31% to 44%), “purifying effect is positive” (8% to 27%) and “I don’t want to interfere with flushing out bugs and toxins” (7% to 20%).

Discussion

While diarrhoea is a common problem in developing countries, largely attributed to infection, the extent of the problem in the community of higher- and middle income countries is largely unknown. A proportion of such sufferers will have had short-lasting episodes of infectious diarrhoea, but there is also likely to be a group of sufferers who do not have a diagnosed clinical problem, such as IBS or
inflammatory bowel disease, but who are prone to diarrhoea from time to time. The gastrointestinal burden in UK primary care is approximately 10% of all consultations, around half of which are related to lower gastrointestinal problems. In addition, there exists a reservoir of people who do not consult but many of whom, nonetheless, have troublesome symptoms. Thus, quantifying the size of the potential problem is important, both to inform management strategies and to provide opportunities for effective interventions where needed.

To the best of our knowledge, the prevalence of self-reported diarrhoea symptoms occurring episodically in the community setting has not been previously ascertained. We used an established market research-based methodology to reach out to large numbers of respondents in an international setting, ensuring adequate numbers in each country, representative of the adult population to the age of 65 years. Representative surveys are ideal for assessing the prevalence of this type of symptom across whole populations, overcoming the disadvantages of smaller scale, household or locality-based surveys and providing valuable data for clinical use. Online methodology allows data to be collected across a wide geographical area, avoiding the limitations of postal services, and is less susceptible to embarrassment and interviewer bias compared with face-to-face interviews.

A weakness of this type of market research survey is that the standard age cut-off is 65 years and, thus, our results are only of relevance to the sub-65-year population. However, US surveillance reveals that adults over the age of 65 years have the lowest rates of self-reported acute diarrhoeal illness. Another limitation
to the applied survey methodology was that the respondents were not asked directly about the severity or duration of their symptoms, although the fact that in many countries the majority of sufferers reported treating their symptoms indicates that they were of sufficient severity and/or inconvenience to warrant intervention.

Previous research has confirmed that variations exist between countries in the prevalence of some gastrointestinal disorders, and that females are more likely to have been diagnosed.\textsuperscript{14} To some extent these findings may reflect national and cultural differences in consultation behavior and health care systems;\textsuperscript{15,16} our findings are likely to be associated with similar factors.

The survey confirmed that there is a large ‘hidden’ population of adult diarrhoea sufferers who report episodes of diarrhoea occurring at least once a month. The importance of this population is underlined by the fact that the overwhelming majority of all self-reported episodes of diarrhoea are experienced by adults with episodic diarrhoea. Episodic diarrhoea was reported more frequently by females and was commonly accompanied by symptoms such as “stomach cramping or grumbling” and “wind”. Those suffering from episodic diarrhoea perceived their causes to be mostly psychological and food-related rather than an underlying chronic condition. Menstruation was also a major factor, with the proportion of women reporting it as a trigger for episodic diarrhoea being relatively high in some European countries.

Diarrhoea is a major feature in IBS\textsuperscript{15} and the proportion of respondents with episodic diarrhoea claiming to have been diagnosed with IBS ranged between 9%
and 44%. However, it is not possible to predict how much of the burden of self-reported diarrhoea is related to undiagnosed functional bowel disease as many patients are likely not to have had a formal diagnosis. A previous pan-European survey reported IBS prevalence (diagnosed and undiagnosed combined) ranging from 6% to 12%, with one-fifth meeting the Rome II criteria for diarrhoea-predominant IBS and two-thirds having alternating (diarrhoea/constipation) IBS. The prevalence of episodic diarrhoea in the current survey was generally greater, ranging between 16% and 19% in most countries.

Similarities between the respondents with episodic diarrhoea in our survey and IBS populations identified in previous surveys were noted. For example, IBS is also reported to be more prevalent in women, with an international prevalence that is 67% higher than in men or an absolute difference in prevalence of around 5% between the sexes (14.0% in women compared with 8.9% in men). Furthermore, food and stress have been reported by IBS patients as major triggers for their IBS episodes. Therefore, it seems likely that IBS (and potentially other conditions such as coeliac disease and inflammatory bowel disease) may be contributing to episodic diarrhoea. However, this cannot account for the entire population with episodic diarrhoea, and it is likely that a significant proportion of these patients would not meet the criteria for diagnosis with IBS or have chronic organic conditions responsible for their symptoms. It is also likely that a proportion of patients with episodic diarrhea have either been diagnosed by their physicians as having IBS, or meet the diagnostic criteria in the absence of a formal diagnosis.

Previous infectious gastroenteritis and/or traveller’s diarrhoea [DuPont 2009] are
known risk factors for the development of so-called post-infectious-IBS, a long-term condition of altered stool form and abdominal pain. [Thabane 2007; Schwille-kiuntke 2015] It would be intriguing to determine if previous enteric infection is also a risk factor associated with episodic diarrhoea.

In most countries, the majority of those with episodic diarrhoea claim to have used some form of remedy or medication. Reported reasons for non-treatment of symptoms suggested that some sufferers with diarrhoea may benefit from more comprehensive, evidence-based advice on self-treatment. While some respondents reported that they generally avoided taking medicines or preferred to let nature take its course, responses such as, “I don’t want to interfere with flushing out bugs and toxins” indicates that some individuals may not be taking the opportunity to relieve the discomfort or the social dysfunction associated with diarrhoea because of misconceptions about diarrhoea and available treatments.²

While there is a need to avoid unnecessary medicalisation and, indeed, in many sufferers symptoms may not be sufficiently significant to warrant further investigation, health providers need to be aware of this undefined group. There are parallels in consultation behavior between episodic diarrhoea and travellers’ diarrhoea, a common and well-recognised complaint¹⁷ for which people are only likely to seek medical attention if the symptoms are persistent or severe.

Nonetheless, episodic diarrhoea symptoms are likely to represent costs in suffering, productivity loss and other economic costs such as expenditure on remedies and medications. Some will benefit from a clinical assessment and a possible diagnosis to improve their wellbeing. Thus, a better understanding of the
extent, patterns and causes of episodic diarrhoea may help to enhance self and health professional management, facilitating better strategies for this latent group. Further research to ascertain the impact on sufferers and the value of targeted management strategies is required. This should include reviewing current pharmacist-led approaches and improving awareness and education in community and primary care.
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**Statement of interests**

**Declaration of personal interests**

Pali Hungin has received travel, advisory board and/or research funding from RB, Almirall, Shire and Johnson & Johnson Ltd. and he is Chair of the Rome IV Foundation Primary Care Committee. James Walmsley and Kerstin Koenig are employees of Johnson & Johnson Ltd (UK). James Dalrymple has served as a speaker, a consultant and an advisory board member for Johnson & Johnson Ltd., Vivor and Sucampo, and is Chair of the Primary Care Society for Gastroenterology, which is funded from unrestricted educational grants from a number of pharmaceutical companies (full list is available at [www.pcsq.org](http://www.pcsq.org)). Noel Wicks has received travel and advisory board funding from GSK, Warner Chilcott, Sanofi, Johnson & Johnson Ltd. and Sucampo and is a member of the Board of the National Pharmacy Association. Lucy Paxman is an employee of Incite (UK) whose work was funded by Johnson & Johnson Ltd.

**Declaration of funding interests**

This study was supported in full by Johnson & Johnson Ltd. Initial data analyses were undertaken by Incite (UK) who received funding from Johnson & Johnson Ltd. Writing support was provided by Lisa O’Rourke of Cello Health Communications and funded by Johnson & Johnson Ltd.
Table 1. Age and gender distribution among those that completed self-administered surveys in 11 countries. Phase 1 surveys were carried out among a nationally representative sample of the population. Phase 2 surveys were carried out among individuals identified as having episodic diarrhoea.

* Included panellists from age 16. † Upper age bands represent 45–49 and 50–64 years.

Figure 1. Prevalence of self-reported diarrhoea occurring once monthly or more often. Phase 1 participants were asked, “How often do you suffer from each of the problems in the table below?” The percentage of respondents that reported experiencing “diarrhoea (urgent, frequent, loose or watery stools)” at a rate of either “once a month”, “2-3 times a month”, “once a week” or “more than once a week” are shown.

Figure 2. Average number of episodes per month among those with diarrhoea occurring once monthly or more often. Phase 1 participants were asked, “How often do you suffer from each of the problems in the table below?” The frequencies of those reporting diarrhoea (urgent, frequent, loose or watery stools) were used to estimate the number of episodes per month.

Figure 3. The gender distribution among those reporting diarrhoea once monthly or more often. Percentage of male and female respondents with episodic diarrhoea in each country.
Table 2. Self-reported symptoms secondary to diarrhoea occurring once monthly or more often. Participants with episodic diarrhoea were asked about symptoms on the last occasion they had diarrhoea, “Which of the following problems, if any, did you suffer from at the time?”. Respondents were presented with a list of possible symptoms and asked to select all those that applied. Symptoms other than diarrhoeal symptoms (diarrhoea, an urgent need to go to the toilet, loose or watery stools, slack stools/unbalanced transit) are presented here.

Question not asked in Spain or Argentina. Empty cells (—) indicate symptom was not included in the questionnaire of that country.

Figure 4. Treatment of symptoms among those with diarrhoea occurring once monthly or more often
Responses to the question, “In the last 6 months on the occasions when you have had diarrhoea, which of these things have you done at all?”. Respondents were presented with a list of options such as “Took an over-the-counter diarrhoea medication obtained directly from a pharmacy without a prescription”, “Took a non-chemical health product designed to help with diarrhoea” or “Experienced diarrhoea and did nothing”. Data is split into respondents who took something versus those who did nothing.

The Spanish survey asked about treatment over a 12-month period; all other countries were 6 months.

Figure 5. Type of treatments used among those treating diarrhoea symptoms occurring once monthly or more often.

Responses to the question, “In the last 6 months on the occasions when you have had diarrhoea, which of these things have you done at all?” Respondents were presented with a list of options such as “Took an over-the-counter diarrhoea medication obtained directly from a pharmacy without a prescription”, “Took a non-chemical health product designed to help with diarrhoea” or “Did nothing”. They were asked to select all that apply. Data are split into respondents who took prescription or over-the-counter (OTC) medication versus those that took other types of remedies.

The Spanish survey asked about treatment over a 12-month period; all other countries were 6 months.
References


STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

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<th>Item No</th>
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<td><strong>Title and abstract</strong></td>
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<td><em>(a)</em> Indicate the study’s design with a commonly used term in the title or the abstract ✓</td>
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<td><em>(b)</em> Provide in the abstract an informative and balanced summary of what was done and what was found ✓</td>
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(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

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| 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

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<td>Key results</td>
<td>18</td>
<td>Summarise key results with reference to study objectives ✓</td>
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<td>Limitations</td>
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<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ✓</td>
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<td>Interpretation</td>
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<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ✓</td>
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<td>Generalisability</td>
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<td>Discuss the generalisability (external validity) of the study results ✓</td>
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### Other information

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<td>Funding</td>
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<td>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 ✓</td>
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*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