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How does multi-morbidity influence health care costs?

A population-based cross-sectional study of depression, back pain and osteoarthritis

John Carstensen[1], David Andersson[2], Malin André[2], Sven Engström[2], Henrik Magnusson[2], Lars Borgquist[2]

[1]Department of Medical and Health Sciences, Health and Society, Linköping University, Linköping, Sweden

[2] Department of Medical and Health Sciences, Family Medicine, Linköping University, SE 58183 Linköping, Sweden

Corresponding author: Lars Borgquist

e-mail: lars.borgquist@liu.se

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ABSTRACT

Objectives: To analyse how multi-morbidity influences health care costs per patient based on three diagnoses, back pain, depression and osteoarthritis. A special focus was made on the distribution of costs for primary health care compared to specialist care, hospital care and drugs.

Design*:* Population-based, cross-sectional.

Setting: All residents of the County of Östergötland, Sweden visiting primary and secondary health care during 2006

Patients: Data on diagnoses and health care costs for all 266,354 individuals between 20 and 75 years of age, who were residents of the County of Östergötland, Sweden, in the year 2006, were extracted from the local health care register and the national register of drug prescriptions.

Main outcome measures: The effects of multi-morbidity on health care costs were estimated using regression models that also included age, sex and education.

Results: The average total health care costs associated with a diagnosis of depression and a diagnosis of back pain were significantly lower when one patient had both diagnoses when compared with two patients having one diagnosis each. This decrease in costs was largely related to hospital care, while the number of GP visits showed an increase. The multi-morbidity influence on health care costs tended to be less - not more - than additive, and, for back pain and depression, significantly less than additive.

Conclusions: Our results can be of value in analysing the cost effects of multi-morbidity and how the coordination of primary and secondary care may have an impact on health care costs.

ARTICLE SUMMARY

Article focus

Multi-morbidity is often associated with high health care costs and raises questions that are of interest for the organisation of primary and secondary health care, for example: What is the impact on health care costs?

Is there an increase in costs because the complexity is high in the management of the different diseases? Or maybe there is a decline in costs due to an efficient handling and therefore a lower numbers of health care contacts for single persons with many diseases?

Key Messages

Multi-morbidity does not generally increase health care costs per diagnosis

The multi-morbidity influence on health care costs tended to be less - not more - than additive, and, for back pain and depression, significantly less than additive.

Strengths and limitations of this study

The possibility to measure total health care utilisation on an individual level both in primary care and hospital care was an advantage in this study.

There are the broad clinical variations in register data, for instance variations in the definition of diagnoses. An underreporting of diagnoses in the medical records is common, especially in primary care.

INTRODUCTION

Multi-morbidity – the simultaneous coexistence of multiple health conditions in a single individual is common in the general population and is particularly frequent among primary care patients [1]. Poly-pharmacy is high amongst elderly people who often suffer from multi-morbidity and from having had many hospital admissions [2 3].

Multi-morbidity is often associated with high health care costs and raises questions that are of interest for health services research, for example: What is the impact on health care costs? Is there an increase in costs because the complexity is high in the management of the different diseases? Or maybe there is a decline in costs due to several diseases in one patient being treated at the same consultation resulting in lower numbers of health care contacts than expected for single persons with many diseases?

The purpose of this study was to analyse how multi morbidity influences health care costs per patient based on three diagnoses, back pain, depression and osteoarthritis. A special focus was

made on the distribution of costs for primary health care compared to specialist care, hospital care and drugs. Analyses of multi-morbidity effects were from the perspective of health care professionals i.e. based on diagnoses. We have chosen the diagnoses depression, back pain and osteoarthritis because all of these health states are frequent problems both in primary care and in specialist care. Prior studies have reported a relatively large share of mental health conditions in patients with back pain [4-8]. Clinical associations between arthritis and depression have seldom been reported.

METHODS

Data sources

Statistics Sweden has created a total population register for the country. This register is mainly used as a basic register for preparation of statistics in the Swedish counties and municipalities regarding the size and composition of their populations stratified according to sex, age, educational status, etc. In this population-based study we linked the population register to different registers of the residents of the County of Östergötland, situated in south-east Sweden. Individual data on clinical diagnosis, age, gender, socioeconomic status (education), drug prescriptions, drug costs and health care costs (primary care and hospital care) were made available, from these registers, for the whole population of the county. The personal identification numbers for people living in Sweden facilitate linking information from different registers. All individuals between 20 and 75 years of age, who were residents of the County of Östergötland in year 2006, were included in the multi-morbidity analysis.

Health care utilisation and diagnoses

Health care contacts were collected with the help of The Care Data Warehouse in Östergötland [9]. This register consists of administrative records of all publicly financed health care utilisation in the county, including in-patient and out-patient care for all medical specialities (the register includes more than 95% of the health care utilisation in the county).

All health care utilisation per patient during year 2006 was extracted and expressed by the following variables; total number of hospital days, total number of visits in out-patient care

including physician visits (hospital out-patient visits, GP visits) and visits to paramedical staff.

Using the information registered at all health care contacts in the year of 2006; individuals were classified as having depression if they at least once had a diagnosis of depression (F32-F39 according to the International Classification of Diseases, 10th version (ICD-10)). In a similar way individuals were defined as having osteoarthritis (M15-M19), or back pain (M50-M54).

Health care costs

The cost per patient (CPP) database of the Östergötland County Council contains data on costs for each patient utilising the healthcare system [9]. In the CPP database, clinic-specific costs are estimated for all healthcare services, e.g. a visit to a physician, a nurse or laboratory tests Thus, it was possible, for example, to summarise the CPP for healthcare in different clinics and for each individual, over the years 2006 and 2007. Previous studies have proven its use in research [10].

We added drug costs from the Swedish Prescribed Drug Register [11]. The Drug Register contains records of all dispensed drug prescriptions and covers the whole Swedish population. Measurement units of utilisation are the number of prescriptions, Defined Daily Doses (DDDs) and expenditures. The register contains data on drugs (the prescribed and dispensed amount per item and drug costs per individual). In this study all drugs dispensed to residents in the County of Östergötland during 2006 and 2007 were included.

Three different kinds of costs were used in the analysis; primary care costs, hospital costs (in-patient and out-patient) and drug costs. All costs were on an individual basis and noted in SEK (2007).

Statistics

To examine how the different diagnoses affected health care costs (primary health care costs, hospital costs, drug costs, and total costs, respectively), multiple linear regression models were fitted with each of the diagnosis included as a dichotomous factor. The multi-morbidity

effects on costs were estimated by including all two-way interaction terms between the diagnoses (depression x osteoarthritis, depression x back pain, osteoarthritis x back pain). A positive interaction term indicates that the multi-morbidity effect on costs is more than additive and a negative term indicates a less than additive effect on costs. Since the variability in costs was higher in patient groups with higher mean costs we used robust estimation of standard errors of the regression coefficients [12]. As there were differences in age, gender and education between the diagnoses groups (table 1) all regression models also included these factors as covariates [13].

Ethics

Confidentiality was ensured by one-way encrypted ID-numbers. The study was approved by the Regional Ethical Review Board in Linköping.

RESULTS

Characteristics of the study population (266 354 persons) are summarised in table 1. The largest diagnose group was back pain (11 178 patients) followed by depression (7 412 patients) and osteoarthritis (5 174 patients). Elderly patients dominated in the osteoarthritis group and the youngest patients were found in the depression group. Total mean cost per patient with a depression diagnosis was SEK 36 904 (primary care SEK 5 715, hospital care SEK 25 633, drugs SEK 5 557). The largest multi-morbidity subgroup was the combination of back pain and depression (772 patients), followed by the combination of back pain and osteoarthritis (527 patients), and the combination of depression and osteoarthritis (206 patients).

In order to analyse how the combinations of diagnoses influence health care costs (primary health care costs, hospital costs and drug costs) multiple regression models were fitted table 2). For patients having both a depression diagnosis and a back pain diagnosis there was a significant negative interaction effect on total health care costs, which indicates that the average total health care costs associated with a depression diagnosis and a back pain diagnosis were significantly lower when one patient had both diagnoses compared with two patients having one diagnosis each. Thus, the average health care costs associated with

depression back pain was estimated to SEK 39 196 (24 763 + 14 433) when these two diagnoses are not in same patient while it was SEK 12 772 lower for the patient with both diagnoses. Significant negative interactions between depression and back pain were also observed for hospital and drug costs.

Small or no interactions at all were seen between depression diagnoses and osteoarthritis diagnoses (table 2). For the multi-morbidity group consisting of osteoarthritis and back pain there was a positive not significant, interaction for drug costs.

Costs in primary care and specialist out-patient care were associated with the number of physician visits. Therefore, multiple regression models were used to analyse how the combination of diagnoses affected the number of visits to health care (table 3). The combination of depression and back pain showed more than one strongly significant interaction. In this multi-morbidity group there was a positive interaction for GP visits, but there was a negative interaction for visits to the paramedical staff.

DISCUSSION

The total health care costs associated with a depression diagnosis and a back pain diagnosis were significantly lower when one patient had both diagnoses compared with two patients having one diagnosis each. This decrease of costs was largely related to hospital care, while the number of GP visits showed an increase. The combination of osteoarthritis and back pain had no significant reduction in health care costs. No significant interactions were found between the diagnoses, osteoarthritis and depression. However, there was a non-significant increase in the drug costs for patients with both osteoarthritis and back pain compared to the expected costs for the separate diagnoses.

Valderas et al [1] have mentioned three ways in which different diseases may be found in the same person; by chance, selection bias and by different kinds of causal association.

In our total study population (266354) the prevalence for a back pain diagnosis was 4.2 % and for depression 2.9 %. So by chance alone about 330 persons (0.029 x 0.042 x 266354) would have both depression and back pain. However, there were 772 persons with both depression and back pain. Selection bias might be an alternative explanation for this discrepancy. It is

likely that subjects already diagnosed with one disease tend to be detected in an earlier phase of another disease, since these patients will be under closer scrutiny, a phenomenon known as Berkson´s bias [14]. There are also possible reasons for a high prevalence of multi-morbidity due to causal association among patients with a depression diagnosis and a back pain diagnosis. Common underlying bio-psychosocial conditions might be involved. In the transition from acute to longstanding pain, the influence of psychological factors, as, for example, depression and anxiety, have been acknowledged [15]. Prior studies have reported a relatively large share of mental health conditions in patients with back pain [16]. Both depression diagnoses and the back pain diagnoses are based on the patients´ perceptions´ of disease and therefore the methods used in the diagnostic processes for these diagnoses differ from the more objective clinical methods used in diagnosing osteoarthritis (x-ray). Moreover, mental illness and back pain are common in middle-aged persons while osteoarthritis is more frequent in the elderly.

Different kinds of associations between the three diagnoses were observed in earlier statistical analyses from the same data records used in this study [4]. With longitudinal data we found that an episode of back pain resulted in a higher hazard rate for depression. If a person was given a back pain diagnosis he/she had a 46 percent risk of later getting a depression diagnosis. However, little association was found between osteoarthritis and depression.

From other studies it is known that many diseases, for example diagnoses in the gastro-intestinal system and the musculoskeletal system are overrepresented in patients who receive antidepressant treatment [17]. A high level of drug use, especially treatment with antidepressants, has been found several years before a patient receiving a depression diagnosis [18]. It might be possible that some patients were presented with somatic complaints and a depressive health status before the depression diagnosis was made. Health care providers might have hesitated to record a depression diagnosis and instead used a variety of other diagnoses [19]. It is well-known that chronic somatic conditions and depression are associated.

Depression alone is a cause of increased morbidity and mortality often associated with high health care costs, lost work productivity and an increased total health care utilisation [6]. Increased expenditures for other health conditions before and after an incident of back pain in the same individuals have been reported; with, as a consequence, an increase in health care

costs [7]. Clinical associations between osteoarthritis and depression have not been reported and no cost interactions were found in our analyses between these health states.

Glynn et al. [20] found, in a patient record review, that health care utilisation and cost in both primary and secondary care increased among patients with multi-morbidity. And costs increased with a higher number of chronic conditions. The multi-morbidity effect occurred independently of age, gender and socioeconomic status. However, the study did not differentiate between different kinds of diagnoses as we did in our study.

There might be some clinical reasons that interactions between diagnoses influence health care costs i.e. the costs tended to be less - not more - than additive. We found that the same kinds of drugs were used, to a very high extent, in the treatment of both back pain and depression. It is also possible that physicians could manage several different health states (diagnoses) in the same consultation. These circumstances might reduce drug utilisation and the number of health care contacts and thus the health care costs.

In our analyses we found that patients with a back pain diagnosis had a high share of GP visits compared to patients with osteoarthritis who had relatively more visits to hospital specialists. This fact might be one explanation for the higher costs in primary care for patients with depression and back pain. The high frequency in GP visits was, however, followed by lower numbers of other visits (paramedical staff and physicians in special care),which on the other hand might be a sign of less optimal paramedical care for this patient group.

Patients with back pain diagnosis and depression diagnosis, to a very high extent, received the same kind of drug treatment. Hence, the top-ten list for drugs was almost identical for the two diagnoses which could explain the decrease in expected drug costs. However, the same goes for the diagnoses back pain and osteoarthritis, where this expected reduction in drug costs was not seen.

Methodological considerations

The strengths of this study were the use of different register databases and the linkage to other registers. The possibility to follow total health care utilisation on an individual level both in primary care and hospital care was an advantage in this study. When using registers, sources of bias such as recall bias and response bias could be kept at a minimum. An additional strength was the size of the study, with more than 11 000 patients having a back pain

diagnosis, 7 000 patients with a depression diagnosis and 5 000 patients with an osteoarthritis diagnosis. Some of the subgroups of multi-morbidity were, however, rather small in size and standard deviations were also larger. Hence, robust estimation of standard errors of the regression coefficients was used.

A weakness of using registers is the quality of data and the broad clinical variation, for instance variation in the definition of depression. An underreporting of diagnoses in the medical records is common, especially in primary care. Besides, it is possible that mental health status may have been underreported because of the existence of multi-morbidity. Other health problems may have been prioritised in the recording of the diagnoses.

Although patients with a depression diagnosis are likely to be heavy users of health care, other factors should be considered. Patients with low socioeconomic status and female gender usually have a high use of health care resources, and it is well-known that women have a high incidence and prevalence of depressive disorders [21]. However, we adjusted for these potential confounders.

Implications

The management, organisational structure and coordination of diagnoses in health care will have an impact on health care costs.

In Sweden there is no gate-keeping system but still it is difficult for a patient, without a referral from a GP, to see a specialist in the hospital. A referral from a GP might facilitate contacts with a specialist if there are precise criteria for diagnosis and treatment which is the case in diagnosing osteoarthritis. Thus, gate-keeping and referral systems will influence the number of physician visits at different health care levels.

National and regional guidelines also have an impact on the localisation of care. For example the new Swedish guidelines for osteoarthritis in the knee and in the hip encourage primary care to take a greater part of the care for osteoarthritis [22]. The new guidelines will probably change the distribution of health care costs between hospital specialist care and primary care.

In hospital specialist care there is often focus on a single disease and no tradition for handling multi-morbidity. In our study the osteoarthritis patients were largely handled by hospital specialists. Hence, for this patient group and its multi-morbidities there might have been less

coordination between the disease specific treatment and other health care treatments. In the analyses we found no cost reductions in the combinations between osteoarthritis and the other two diseases.

Patients with the two diagnoses, depression and back pain, paid relatively more visits to primary care and many of the health care visits included the paramedical personnel. Therefore, depression and back pain were handled to a great extent by GPs and for these combinations significant reductions in all types of costs were seen. Hence, in the management of multi morbidities there might be opportunities for coordinating these health care processes within primary care in order to reduce costs [23].

Conclusion

The multi-morbidity influence on health care costs tended to be less - not more - than additive, and, for back pain and depression, significantly less than additive. This indicates that multi-morbidity does not generally increase health care costs per diagnosis. Further studies are needed to clarify conditions for an effective health care for patients with multi-morbidity. There are different ways of organising health care in other countries. Therefore, international comparisons with the same kind of diagnoses used in this study might be of interest in future research in order to evaluate potential additive effects. Can our finding of opposite multi-morbidity effects for depression and back pain on GP visits and hospital costs be replicated in other health care systems? The coordination between primary and secondary care and the financial responsibility for diseases within health care will have an impact on health care costs. A primary health care responsibility for the whole health care process might be one way to reduce total health care costs where multi-morbidity is involved.

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Competing interests None

Ethical approval The study was approved by the Regional Ethical Review Board in Linköping Sweden.

Contributors JC, DA and LB designed the study. LB and HM performed the acquisition of data. JC, DA and LB performed the analyses. JC, DA, MA, SE, HM and LB participated in the interpretation of data. JC, DA and LB drafted the manuscript. JC, DA, MA, SE, HM and LB revised the manuscript until its final version.

Data sharing statement There is no additional data available.

Table 1. Characteristics of the study population and diagnoses groups (2006). Percent and mean costs (SEK 2007) *

		Total population	Depression	Arthrosis	Back pain	Dep and BP	Dep and Arth	Arth and BP
	n	266354	7712	5174	11178	772	208	527
Gender								
	Male	51,0	33,1	40,0	42,6	69,8	78,8	63,9
	Female	49,0	66,9	60,0	57,4	30,2	21,2	36,1
Age								
	20-45	47,0	47,4	6,3	38,3	39,2	8,2	8,3
	46-65	39,7	41,1	54,9	47,6	48,4	58,7	59,0
	66-75	13,3	11,5	38,8	14,1	12,3	32,2	32,6
Education								
	Primary	20,9	23,7	34,4	27,9	29,0	36,5	39,1
	Secondary	49,4	50,5	44,8	53,0	52,1	40,9	45,4
	University	29,6	25,8	20,7	19,2	18,9	21,6	15,6
Mean costs	[2007]							
	Primary care	1816	5715	6936	5988	9045	10033	9481
	Hospital care	7155	25633	22544	15950	30607	34202	27736
	Drug	2020	5557	5566	4215	7257	9384	8043
	Total	10990	36904	35046	26152	46909	53619	45620

* 46 patients had all three diagnoses

Table 2. Multi-morbidity effects on health care costs as estimated by multiple linear regression models (interactions). Regression coefficients ± SE

		Primary HC costs	Hospital costs	Drug costs	Total costs
	Intercept	1627 ± 47***	6585 ± 280***	1542 ± 58***	9755 ± 312***
Gender					
	Female	REF			
	Men	-663 ± 27***	-487 ± 162**	-256 ± 47***	-1405 ± 185***
Age					
	20-45	REF			
	46-65	819 ± 22***	2178 ± 169***	1181 ± 52***	4178 ± 191***
	66-75	2683 ± 77***	8723 ± 352***	2785 ± 69***	14191 ± 397***
Education					
	Primary	REF			
	Secondary	-434 ± 45***	-2202 ± 267***	-409 ± 57***	-3045 ± 298***
	University	-840 ± 44***	-3564 ± 270***	-743 ± 60***	-5147 ± 302***
Diagnosis					
	Depression	3143 ± 162***	18472 ± 1182***	3148 ± 150***	24763 ± 1260***
	Osteoarthritis	4065 ± 160***	12426 ± 829***	2395 ± 198***	18887 ± 953***
	Back pain	4033 ± 92***	8419 ± 531***	1980 ± 109***	14433 ± 593***
Interactions					
	Depression & Osteoarthritis	**-49 ± 1483**	**-2798 ± 7262**	**-50 ± 932**	**-2897 ± 8046**
	Depression & Back pain	**-797 ± 624**	**-10426 ± 3223****	**-1548 ± 580****	**-12772 ± 3624*****
	Osteoarthritis & Back pain	**-769 ± 573**	**-2307 ± 3211**	**851 ± 821**	**-2225 ± 3731**

*=p<0.05 **=p<0.01 ***p<0.001

Table 3. Multi-morbidity effects on health care visits as estimated by multiple linear regression models (interactions). Regression coefficients ± SE

		GP	Hospital specialists	Paramedical, primary care	Paramedical hospital
	Intercept	1,07 ± 0,009***	1,11 ± 0,022***	1,64 ± 0,055***	2,45 ± 0,044***
Gender					
	Female	REF	REF	REF	REF
	Men	-0,33 ± 0,006***	-0,22 ± 0,015***	-0,46 ± 0,038***	-0,91 ± 0,030***
Age					
	20-45	REF	REF	REF	REF
	46-65	0,14 ± 0,007***	0,14 ± 0,016***	0,75 ± 0,041***	-0,31 ± 0,033***
	66-75	0,44 ± 0,010***	0,73 ± 0,024***	2,90 ± 0,059***	-0,09 ± 0,047
Education					
	Primary	REF	REF	REF	REF
	Secondary	-0,08 ± 0,008***	-0,17 ± 0,020***	-0,59 ± 0,049***	-0,23 ± 0,039***
	University	-0,23 ± 0,009***	-0,21 ± 0,022***	-0,98 ± 0,055***	-0,34 ± 0,044***
Diagnosis					
	Depression	0,67 ± 0,023***	0,84 ± 0,056***	1,87 ± 0,140***	4,02 ± 0,111***
	Osteoarthritis	0,68 ± 0,023***	0,90 ± 0,055***	2,44 ± 0,138***	1,32 ± 0,109***
	Back pain	0,93 ± 0,016***	0,66 ± 0,038***	1,88 ± 0,095***	1,39 ± 0,075***
Interactions					
	Depression & Osteoarthritis	**-0,09 ± 0,159**	**-0,46 ± 0,383**	**0,16 ± 0,957**	**1,50 ± 0,759***
	Depression & Back pain	**0,31 ± 0,087*****	**-0,30 ± 0,210**	**-0,40 ± 0,524**	**-1,48 ± 0,416*****
	Osteoarthritis & Back pain	**-0,15 ± 0,072***	**0,07 ± 0,173**	**0,22 ± 0,433**	**0,28 ± 0,343**

*=p<0.05 **=p<0.01 ***p<0.001

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
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	4-5
Bias	9	Describe any efforts to address potential sources of bias	*na*
Study size	10	Explain how the study size was arrived at	na
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	na
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	na
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	na

		included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	na
		(c) Consider use of a flow diagram	na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	na
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized	Tables (age)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
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	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
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	na

*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.