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How does comorbidity influence healthcare costs? A population-based cross-sectional study of depression, back pain and osteoarthritis

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ABSTRACT

Objectives: To analyse how comorbidity among patients with back pain, depression and osteoarthritis influences healthcare costs per patient. A special focus was made on the distribution of costs for primary healthcare compared with specialist care, hospital care and drugs.

Design: Population-based cross-sectional study.

Setting: The County of Östergötland, Sweden.

Patients: Data on diagnoses and healthcare 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 healthcare register and the national register of drug prescriptions.

Main outcome measures: The effects of comorbidity on healthcare costs were estimated as interactions in regression models that also included age, sex, number of other health conditions and education.

Results: The largest diagnosed group was back pain (11 178 patients) followed by depression (7412 patients) and osteoarthritis (5174 patients). The largest comorbidity 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). For patients having both a depression diagnosis and a back pain diagnosis, there was a significant negative interaction effect on total healthcare costs. The average healthcare costs among patients with depression and back pain was SEK 11 806 lower for a patient with both diagnoses. In this comorbidity group, there were tendencies of a positive interaction for general practitioner visits and negative interactions for all other visits and hospital days. Small or no interactions at all were seen between depression diagnoses and osteoarthritis diagnoses.

Conclusions: A small increase in primary healthcare visits in comorbid back pain and depression patients was accompanied with a substantial reduction in total healthcare costs and in hospital costs. Our results can be of value in analysing the cost effects of comorbidity and how the coordination of primary and secondary care may have an impact on healthcare costs.

ARTICLE SUMMARY

Article focus

- Comorbidity is often associated with high healthcare costs and raises questions that are of interest for the organisation of primary and secondary healthcare, for example, what is the impact on healthcare 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 healthcare contacts for single persons with many diseases?

Key messages

- The comorbidity influence on healthcare costs tended to be less—not more—than additive and among patients with back pain and depression, significantly less than additive.

Strengths and limitations of this study

- The possibility to measure total healthcare utilisation on an individual level both in primary care and hospital care was an advantage in this study.
- There are broad clinical variations in register data, for instance variations in the definition of diagnoses. An under-reporting of diagnoses in the medical records is common, especially in primary care.

INTRODUCTION

Comorbidity—the simultaneous coexistence of more than one health condition in a single individual—is common in the general population and is particularly frequent among primary care patients.[1] Polypharmacy is high among older people who often suffer from comorbidity and from having had many hospital admissions.[2 3]

Comorbidity has shown to increase with the number of chronic conditions.[4] High healthcare costs raise questions that are of interest for health services research, for example, What is the impact on healthcare 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 healthcare contacts than expected for single persons with many diseases? Little data exist how chronic health conditions cluster. The impact of combinations of chronic condition on healthcare utilisation and healthcare costs are poorly understood. There is little information about specific chronic conditions on healthcare costs.[5]

The purpose of this study was to analyse how comorbidity among patients with back pain, depression and osteoarthritis influences healthcare costs per patient.

A special focus was made on the distribution of costs for primary healthcare compared with specialist care, hospital care and drugs. It has been stated that a better coordination of care may reduce hospitalisation rated, especially for persons with multiple chronic conditions.[4] Analyses of comorbidity effects were from the perspective of healthcare professionals, that is, based on diagnoses. We have chosen the diagnoses depression, back pain and osteoarthritis because all 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.[6–10] Clinical associations between osteoarthritis 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 healthcare costs (primary care and hospital care) were made available, from these registers, for the whole population of the county. Education was used to express socioeconomic status. In a former study where we used the same data register, it was shown that education was an adequate covariate in this age interval.[11] 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 comorbidity analysis.

Healthcare utilisation and diagnoses

Healthcare contacts were collected with the help of The Care Data Warehouse in Östergötland.[12] This register consists of administrative records of all publicly financed healthcare utilisation in the county, including inpatient and outpatient care for all medical specialties (the register includes more than 95% of the healthcare utilisation in the county).

All healthcare utilisation per patient during year 2006 was extracted and expressed by the following variables: total number of hospital days, total number of visits in outpatient care including physician visits (hospital outpatient visits, general practitioner (GP) visits) and visits to paramedical staff.

Using the information registered at all healthcare 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).

To be able to adjust for the effect of other conditions besides those of interest to the study, the number of other health conditions was calculated as the number of other diagnoses registered for each individual in 2006 with a limit of one diagnosis per ICD-10 chapter (and excluding the entire F-chapter 'mental disorders' as well as the back pain and osteoarthritis subsections of the M-chapter 'musculoskeletal disorders').

Healthcare costs

The cost per patient (CPP) database of the Östergötland County Council contains data on costs for each patient utilising the healthcare system.[12] In the CPP database, clinic-specific costs are estimated for all healthcare services, for example, 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.[13]

We added drug costs from the Swedish Prescribed Drug Register.[14] 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 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 (inpatient and outpatient) and drug costs. All costs were on an individual basis and noted in SEK (2007).

Statistical methods

To examine how the different diagnoses affected healthcare costs (primary healthcare 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 comorbidity effects on costs were estimated by including all two-way interaction terms between the diagnoses (depression × osteoarthritis, depression × back pain and osteoarthritis × back pain). A positive interaction term indicates that the comorbidity 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 SEs of the regression coefficients.[15] As there were differences in age, gender, number of other health conditions and education between the diagnoses groups (table 1), all regression models also included these factors as covariates.[16]

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 diagnosed group was back pain (11 178 patients) followed by depression (7412 patients) and osteoarthritis (5174 patients). Older patients dominated in the osteoarthritis group, and the youngest patients were found in the depression group. The average number of other health conditions for the comorbidity groups was between two and three times higher compared with the total population. Total mean CPP with a depression diagnosis was SEK 36 904 (primary care SEK 5715, hospital care SEK 25 633, drugs SEK 5557). The largest comorbidity 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 healthcare costs (primary healthcare 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 healthcare costs, which indicates that the average total healthcare costs among patients 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 healthcare costs associated with depression and back pain was estimated to SEK 28 456 (22 004+6452) when these two diagnoses were not in same patient, while it was SEK 11 806 lower for a 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 comorbidity group consisting of osteoarthritis and back pain, there was a positive, not significant, interaction for drug costs.

Costs in primary care and specialist outpatient care were associated with the number of physician visits. Therefore, multiple regression models were used to

Table 1 Characteristics of the study population and diagnoses groups (2006)

	Total population	Depression	Osteoarthritis	Back pain	Dep and BP	Dep and Arth	Arth and BP
n	266 354	7712	5174	11 178	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, years							
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
No. of other conditions (mean)	1.13	1.90	2.33	2.01	2.63	3.08	3.05
Mean costs (2007)							
Primary care	1816	5715	6936	5988	9045	10 033	9481
Hospital care	7155	25 633	22 544	15 950	30 607	34 202	27 736
Drug	2020	5557	5566	4215	7257	9384	8043
Total	10 990	36 904	35 046	26 152	46 909	53 619	45 620

Per cent and mean costs (SEK 2007).

Table 2 Comorbidity effects on healthcare costs as estimated by multiple linear regression models (interactions)

	Primary HC costs	Hospital costs	Drug costs	Total costs
Intercept	20±51	−917±295**	−533±65***	−1430±326***
Gender				
Female	Ref	Ref	Ref	Ref
Male	−198±27***	1684±171***	345±51***	1830±192***
Age, years				
20–45	Ref	Ref	Ref	Ref
46–65	511±21***	742±163***	783±52***	2036±182***
66–75	1565±66***	3504±337***	1341±74	6411±373***
Education				
Primary	Ref	Ref	Ref	Ref
Secondary	−295±44***	−1549±260***	−228±56***	−2072±286***
University	−528±42***	−2111±262***	−341±59***	−2980±288***
No. of other conditions	1385±23***	6466±129***	1789±33***	9641±144***
Diagnosis				
Depression	2746±161***	16 621±1173***	2636±149***	22 004±1244***
Osteoarthritis	2849±160***	6750±830***	825±192***	10 425±940***
Back pain	2886±93***	3067±524***	499±112***	6452±581***
Interactions				
Depression and osteoarthritis	**145±1443**	**−1890±7091**	**201±897**	**−1544±7741**
Depression and back pain	**−659±609**	**−9779±3200****	**−1369±575***	**−11 806±3572*****
Osteoarthritis and back pain	**−751±558**	**−2225±3159**	**874±794**	**−2101±3616**

Regression coefficients ± SE.
*p<0.05, **p<0.01, ***p<0.001. Regression coefficients showing the comorbidity effects are highlighted using bold values.

analyse how the combination of diagnoses affected the number of visits to healthcare (table 3). The combination of depression and back pain showed a positive interaction for GP visits, but there were negative interactions for all other visits.

DISCUSSION

The total healthcare costs among patients 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.

Table 3 Comorbidity effects on healthcare visits as estimated by multiple linear regression models (interactions)

	GP	Hospital specialists	Paramedical, primary care	Paramedical hospital
Intercept	−0.68±0.010***	0.38±0.024***	0.54±0.071***	1.60±0.055***
Gender				
Female	Ref	Ref	Ref	Ref
Male	−0.23±0.006***	−0.01±0.017	−0.16±0.039***	−0.67±0.030***
Age, years				
20–45	Ref	Ref	Ref	Ref
46–65	0.07±0.006***	0.02±0.013	0.57±0.028***	−0.44±0.033***
66–75	0.18±0.011***	0.24±0.027***	2.17±0.084***	−0.65±0.050***
Education				
Primary	Ref	Ref	Ref	Ref
Secondary	−0.05±0.009***	−0.11±0.023***	−0.51±0.063***	−0.16±0.045***
University	−0.16±0.009***	−0.08±0.024**	−0.78±0.063***	−0.19±0.046***
No. of other conditions	0.33±0.003***	0.63±0.014***	0.94±0.031***	0.72±0.018***
Diagnosis				
Depression	0.57±0.029***	0.65±0.070***	1.60±0.267***	3.81±0.242***
Osteoarthritis	0.39±0.031***	0.35±0.053***	1.62±0.173***	0.69±0.144***
Back pain	0.66±0.021***	0.15±0.042***	1.12±0.104***	0.80±0.094***
Interactions				
Depression and osteoarthritis	**−0.03±0.229**	**−0.35±0.321**	**0.31±1.591**	**1.61±3.222**
Depression and back pain	**0.32±0.178**	**−0.27±0.202**	**−0.36±0.753**	**−1.45±0.645***
Osteoarthritis and back pain	**−0.14±0.116**	**0.09±0.194**	**0.24±0.585**	**0.30±0.821**

Regression coefficients ± SE.
*p<0.05, **p<0.01, ***p<0.001. Regression coefficients showing the comorbidity effects are highlighted using bold values.

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 healthcare costs. No significant interactions were found between the diagnoses, osteoarthritis and depression. However, the drug costs for patients with both osteoarthritis and back pain were higher (but non-significant) compared with 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 (266 354), the prevalence for a back pain diagnosis was 4.2% and for depression 2.9%. So by chance alone, about 330 persons (0.029×0.042×266 354) 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 as having 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.[17] There are also possible reasons for a high prevalence of comorbidity due to causal association among patients with a depression diagnosis and a back pain diagnosis. Common underlying biopsychosocial conditions might be involved. In the transition from acute to long-standing pain, the influence of psychological factors, for example, depression and anxiety, have been acknowledged.[18] Prior studies have reported a relatively large share of mental health conditions in patients with back pain.[19] Both depression diagnosis and the back pain diagnosis 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 older people.

Different kinds of associations between the three diagnoses were observed in earlier statistical analyses from the same data records used in this study.[6] 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% 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 gastrointestinal system and the musculoskeletal system, are over-represented in patients who receive antidepressant treatment.[20] A high level of drug use, especially treatment with antidepressants, has been found several years before a patient receiving a depression diagnosis.[21] It might be possible that some patients were presented with somatic complaints and a depressive health status before the depression diagnosis was made. Healthcare providers might have hesitated to record a depression diagnosis and instead used a variety of other diagnoses.[11] 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 healthcare costs, lost work productivity and an increased total healthcare utilisation.[8] 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 healthcare costs.[9] 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*[22] found, in a patient record review, that healthcare utilisation and cost in both primary and secondary care increased among patients with comorbidity. And costs increased with a higher number of chronic conditions. The comorbidity 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 healthcare costs, that is, 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 healthcare contacts and thus the healthcare costs.

In our analyses, we found that patients with a back pain diagnosis had a high share of GP visits compared with 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 of 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 healthcare 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, 7000 patients with a depression diagnosis and 5000 patients with an osteoarthritis diagnosis. Some of the subgroups of comorbidity were, however, rather small in size, and SDs were also larger. Hence, robust estimation of SEs of the regression coefficients was used. We did not include the three-way interaction term (for those with all three diagnoses) since there were only 46 patients of this kind in the population, and with these types of highly variable outcomes, the power for detecting even large effects in this group was considered too low.

A weakness of using registers is the quality of data and the broad clinical variation, for instance, variation in the definition of depression. An under-reporting of diagnoses in the medical records is common, especially in primary care. Besides, it is possible that mental health status may have been under-reported because of the existence of comorbidity. 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 healthcare, other factors should be considered. Patients with low socioeconomic status and female gender usually have a high use of healthcare resources, and it is well known that women have a high incidence and prevalence of depressive disorders.[23] However, we adjusted for these potential confounders.

Implications

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

In Sweden, there is no gatekeeping 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, gatekeeping and referral systems will influence the number of physician visits at different healthcare 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.[24] The new guidelines will probably change the distribution of healthcare 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 comorbidity. In our study, the osteoarthritis patients were largely handled by hospital specialists. Hence, for this patient group and its multimorbidities, there might have been less coordination between the disease-specific treatment and other healthcare 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 healthcare 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 multimorbidities, there might be opportunities for coordinating these healthcare processes within primary care in order to reduce costs.[25] The coordination of care among persons with multiple health conditions is also important for the quality of care and to avoid unnecessary hospitalisations. A better primary care will be essential in this coordination process.[4 26 27]

Conclusions

The comorbidity influence on healthcare costs tended to be less—not more—than additive and among patients with back pain and depression, significantly less than additive. Further studies are needed to clarify conditions for an effective healthcare for patients with comorbidity. There are different ways of organising healthcare in other countries. 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 comorbidity effects for depression and back pain on GP visits and hospital costs be replicated in other healthcare systems? The coordination between primary and secondary care and the financial responsibility for diseases within healthcare will have an impact on healthcare costs. A primary healthcare responsibility for the whole healthcare process might be one way to reduce total healthcare costs where comorbidity is involved.

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Data sharing statement There are no additional data available.

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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.