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External validation of a Model to Determine Risk of Progression of Barrett's Oesophagus to Neoplasia

Running head: Predicting progression from Barrett's

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SUMMARY

Background: A risk prediction model containing sex, smoking history, Barrett's oesophagus length and presence of low-grade dysplasia was found to identify individuals at a higher risk of progression to oesophageal adenocarcinoma or high-grade dysplasia.

Aims: To externally validate the model predicting risk of progression from Barrett's oesophagus to neoplasia and assess the predictive utility of additional factors.

Methods: We conducted a retrospective cohort study among individuals from the population-based Northern Ireland Barrett's register with a histologically confirmed diagnosis of Barrett's oesophagus (with intestinal metaplasia) between 1993 and 2005. The association between a points based model and risk of progression to high-grade dysplasia or oesophageal adenocarcinoma until 2010 was assessed using Cox Proportional Hazards model. Model performance was assessed using area under the receiver operating characteristics curves (AUROC), sensitivity and specificity.

Results: We identified 1,198 individuals with Barrett's oesophagus of whom 54 progressed. The model discriminated reasonably well between progressors and non-progressors, with an AUROC of 0.70 (95% CI 0.63-0.78). When categorised into low, intermediate and high risk groups, the AUROC was 0.68 (95% CI 0.61-0.74). Compared to using data on dysplasia and segment length for risk stratification, the model resulted in a net reclassification improvement of 20.9%.

Conclusions: This external validation provides further evidence that a model based on sex, smoking, Barrett's segment length and baseline low-grade dysplasia may help to risk stratify patients after an initial diagnosis of Barrett's oesophagus. The model also performed better than the use of low-grade dysplasia status alone for risk-stratification.

Keywords: Barrett's oesophagus; endoscopic surveillance; risk stratification; oesophageal adenocarcinoma

INTRODUCTION

Barrett's oesophagus is an established pre-malignant condition of the oesophagus that increases risk of oesophageal adenocarcinoma and dysplasia.

Endoscopic surveillance is often recommended to aid early diagnosis and treatment for dysplasia or cancer [1,2]. Currently, the American Gastroenterology Association guidelines [1] use dysplasia status to determine recommended surveillance interval lengths or treatment, with recommended intervals of 3 to 5 years for individuals with non-dysplastic Barrett's oesophagus, and treatment with Radiofrequency ablation (RFA), Endoscopic mucosal resection (EMR) or surveillance intervals of 12 months recommended for individuals with low-grade dysplasia. The British Society of Gastroenterology (BSG) guidelines [2] are similar, but use Barrett's segment length to determine recommended surveillance interval length in patients with non-dysplastic Barrett's oesophagus, with recommended intervals of 3 to 5 years for short segment Barrett's with specialized intestinal metaplasia (<3cm), 2 to 3 years for long segment Barrett's (≥3cm) and 6 months for Barrett's with low-grade dysplasia. However, endoscopy resources are scarce and the cost-effectiveness of endoscopic surveillance for patients with non-dysplastic Barrett's oesophagus has been questioned [3]. Methods to stratify patients based on risk of progression to oesophageal adenocarcinoma or high-grade dysplasia may help to optimise use of endoscopic resources.

An alternative approach is screening using a risk prediction model. Providing clinicians with a tool that allows them to estimate a patients' risk may better aid them in deciding screening intervals and make future resource utilization even more efficient. Parasa *et al* [4] used data from 5 centres in the United States (US) and 1 Centre in the Netherlands to develop and internally validate a model to predict progression to oesophageal adenocarcinoma or high-grade dysplasia after an initial diagnosis of Barrett's oesophagus. A model including sex,

smoking history (ever versus never), Barrett's oesophagus length (cm) and low-grade dysplasia status, had reasonable discriminatory ability, with an area under the receiver operating characteristic curve of 0.76 (95% Confidence interval [CI], 0.72-0.80). However, this prediction tool needs to be validated in an independent population before its use can be recommended in clinical practice.[5] To our knowledge, no external validation has been reported to date.

Using data from the Northern Ireland Barrett's register, we aimed to externally validate the model derived by Parasa *et al* [4] (including sex, smoking history (ever versus never), Barrett's oesophagus length and low-grade dysplasia status). We also examined whether additional factors not examined in the derivation study may help to improve discriminatory performance.

METHODS

Study population

The Northern Ireland Barrett's register is a population-based register of all adults diagnosed with columnar-lined epithelium of the oesophagus in Northern Ireland since 1993. The methods of the register formation have been previously described [6]. Briefly, the register was created by reviewing pathology reports of all oesophageal biopsies (corresponding to SNOMED2 codes T62* and SNOMED3 codes T56*) logged in Northern Ireland. A standardised set of guidelines was used for creation of the register, and any pathology reports diagnosing histologically confirmed columnar epithelium of the oesophagus, or synonym terms, were deemed to be Barrett's oesophagus. Reports relating to cancer or confined to the oesophagogastric junction were excluded.

A review of hospital notes of the BE patients diagnosed between 1993 and 2005 was conducted by 1 of 3 trained data abstractors, between March 2005 and March 2010, as previously described [7,8]. A standardized electronic proforma was used to extract data on a variety of

demographic and clinical aspects, including age, sex, Barrett's segment length, body mass index, smoking status, dysplasia status, ulcerative erosion, gastroesophageal reflux symptoms, weight loss and treatment regimen, corresponding to the patient's initial (index) diagnosis of Barrett's oesophagus.

Ethical approval for the Northern Ireland Barrett's register, NICR and related research has been granted by the regional ethics committee of Northern Ireland (15/NI/0203).

Outcomes

Data from subsequent endoscopic biopsies and linkage to the Northern Ireland Cancer Registry (NICR) was conducted to identify Barrett's oesophagus patients who subsequently developed high-grade dysplasia or oesophageal cancer. The NICR contains data on all patients diagnosed with cancer in Northern Ireland since 1993. The NICR uses the International Classification of diseases V.10 (ICD10) to classify patient tumor type and location based on accompanying clinical information. ICD10 codes were used to identify patients from the NICR with adenocarcinoma or histologically unspecified tumors of the oesophagus. Histologically unspecified tumors were included to ensure complete ascertainment of tumors that may have arisen in patients with Barrett's oesophagus. For the purposes of this analysis, participants were followed up until the first diagnosis of high-grade dysplasia or oesophageal adenocarcinoma, death, or 31st December 2010.

Inclusion and exclusion

We limited the sample to individuals with Barrett's oesophagus, defined as specialized intestinal metaplasia at biopsy and visible Barrett's segment on endoscopy, who were diagnosed between 1993 and 2005 (n=3,148) and were included in our hospital case note review sample described above. Multiple endoscopies conducted within 12 months may reflect

uncertain diagnoses after the initial endoscopy, so individuals who were diagnosed with oesophageal adenocarcinoma or high-grade dysplasia within 12 months of Barrett's oesophagus diagnosis were excluded (n=58). Individuals without complete data on Barrett's segment length, smoking status and dysplasia status were excluded from the primary analyses (n=1,950, Figure 1). Therefore, a total of 1,198 individuals were eligible for inclusion and were included in the primary analysis (Figure 1).

Statistical analysis

The categorical variables were summarized as counts and percentages. The points based model developed by Parasa *et al* [4], was used to assign points to each study participant based on male sex (9 points, females: 0 points), ever smoking (5 points), Barrett's segment length (1 point per cm until 10cm) and presence of low-grade dysplasia at baseline (11 points).

Follow-up time was calculated from 12 months after index date until end of follow-up. We used Cox Proportional hazards models to assess the association between the points based model (including the assigned points on a continuous scale) and risk of progression to oesophageal adenocarcinoma or high-grade dysplasia. Model discrimination was quantified by calculating the area under the receiver operating characteristic curve (C-statistic) with 95% CI. Goodness-of-fit was assessed using Hosmer-Lemeshow tests and calibration curves. The analyses were repeated using points categories based on the Parasa *et al* [4] study (low=0-10 points; intermediate= >10-20 points; high=>20 points). The cumulative and annual risk of progression to oesophageal adenocarcinoma or high-grade dysplasia were calculated for each category.

The area under the receiver operating characteristic curve when using points categories based on the Parasa *et al* [4] study was compared to use of low-grade dysplasia only to mimic AGA guidelines, and to use of 3 categories (Short segment non-dysplastic Barrett's oesophagus; long segment non-dysplastic Barrett's oesophagus; and Barrett's oesophagus with low-grade

dysplasia) to mimic BSG guidelines. Net reclassification index (NRI), was computed as [proportion of all progressors reclassified at higher risk – proportion reclassified at lower risk] – [proportion of all non-progressors reclassified at higher risk – proportion reclassified at lower risk] [9]. The NRIs and proportions in each category, were calculated when changing from a mimic of the BSG guideline system to the points categories proposed by Parasa *et al* [4].

For comparison with the previous study, multivariate Cox proportional hazards models were used to assess the association between sex, cigarette smoking, Barrett's segment length and low-grade dysplasia status and risk of progression to oesophageal adenocarcinoma or high-grade dysplasia.

To assess potential additions to the model proposed by Parasa *et al* [4], factors previously associated with risk of progression including age, weight loss, ulceration erosion and gastrooesophageal reflux symptoms [8] were also added to the model individually. If an additional factor was associated with risk of progression ($p < 0.05$), then the C-statistic of the original model plus each additional factor was assessed.

Sensitivity analyses assessed the area under the curve: when outcomes were limited to oesophageal adenocarcinoma only; when points attributed to individual factors were excluded; when Barrett's segment length was reported as short (<3 cm; 0 points) versus long (≥ 3 cm; 5 points, chosen to reflect half the potential maximum 10 points assigned to 10cm segment lengths) rather than by centimeter; and when additionally including individuals with missing/unknown data, with missing/unknown data assigned zero points (total $n=3,090$).

Analyses were conducted using Stata/IC statistical software (version 14.1, College Station, TX, USA).

RESULTS

During 9,487 person-years of follow-up (median 7.5 years follow-up starting 12 months after diagnosis), 54 patients with Barrett's oesophagus progressed to oesophageal adenocarcinoma (n=41) or high-grade dysplasia (n=13).

Applying the point system to our study cohort, we found that the risk of progression to oesophageal adenocarcinoma or high-grade dysplasia increased by 12% per additional point (HR 1.12, 95% CI 1.08-1.16). The model discriminated reasonably well between progressors and non-progressors, with an area under the receiver operating characteristic curve of 0.70 (95% CI 0.63-0.78, Table 2). The model was well calibrated according to the calibration slope (C-slope=1.00) and the Hosmer-Lemeshow test (chi² statistic=31.55, *P*=0.54).

When categorised into three groups based on points and cut-offs described by Parasa *et al* [4], relative to the low risk group (annual risk 0.2%), risk of progression was higher in the intermediate risk group, (annual risk 0.5%; HR 2.29, 95% CI 0.94-5.59), and the highest risk group (annual risk: 1.5%; HR 7.06, 95% CI 2.87-17.34) (Figure 2 and 3). Only the latter comparison was statistically significant. Risk of progression in the high risk group was also greater, relative to the intermediate risk group (HR 3.07, 95% CI 1.75-5.43). The area under the curve for predicting risk of progression to oesophageal adenocarcinoma or high-grade dysplasia after categorisation was 0.68 (95% CI 0.61-0.74, Figure 4). This compares favourably with the area under the curve (0.70) in the original study[4], showing little evidence for overfitting or optimism. A cut-off of >20 points (high risk) predicted risk of progression with a sensitivity of 42.6% and specificity of 84.5%, with an 11.5% cumulative risk of progression in individuals above this threshold, and only 3.1% in individuals below this threshold. The intermediate cut-off point (>10) predicted risk of progression with a sensitivity of 88.9% and

specificity of 30.4%, with risk of progression of 5.7% in individuals above this threshold, and only 1.7% in individuals below this threshold.

Comparison to existing guidelines

The AUROC for predicting risk of progression to oesophageal adenocarcinoma or high-grade dysplasia using the categories proposed by Parasa *et al* [4] was improved compared with using low-grade dysplasia status only ($P<0.01$, $C=0.58$, 95% CI 0.52-0.64). There was also some evidence of improvement in discrimination when compared to using the combinations of Barrett's segment length and low-grade dysplasia status recommended by the BSG guidelines ($P=0.08$, $C=0.61$, 0.55-0.67), although the difference was not statistically significant. In comparison to use of the BSG classification, use of the Parasa *et al* [4] classification approximately doubled the proportions assigned to the low (12.3% to 29.6%) and high risk categories (8.3% to 16.7%) in our sample. The net reclassification index was positive, with 25.9% of cases and 8.4% non-cases moving up a risk category and 14.8% of cases and 26.9% of controls moving down a risk category. We observed an overall improvement in the net risk stratification of 20.9% (number of participants reclassified of overall sample was 526) for predicting neoplastic progression.

Sensitivity analyses

None of the additional factors tested changed the AUROC when added individually to the model suggested by Parasa *et al* [4] (Table 2). In secondary analyses when outcomes were limited to oesophageal adenocarcinoma only, the area under the curve was unchanged, 0.70 (95% CI 0.63-0.78, Table 2). Results were largely unchanged when conducting sensitivity analyses assessing model simplification, or inclusion of individuals with unknown/missing data (Table 2).

DISCUSSION

In an external validation of a previous risk prediction model [4], we supported previous findings that clinical factors could help to risk stratify patients with Barrett's oesophagus. The risk stratification model predicted risk of progression with an area under the curve of 0.68 (95% CI 0.61-0.74), which is in line with the results reported by Parasa *et al* (C=0.70) [4]. The model also performed better than the use of low-grade dysplasia status alone for risk-stratification, with 20.9% improvement in the NRI. This may allow tailored endoscopic surveillance and treatment decisions to be made in order to optimise use of endoscopic resources.

Multiple risk models have been derived (and some externally validated) for predicting Barrett's oesophagus [10–14] and oesophageal adenocarcinoma [15–19]. However, few models exist in the setting of risk prediction among patients with Barrett's oesophagus. A recent study used data from 5 centres in the US and 1 Centre in the Netherlands to develop and internally validate a model to predict progression to oesophageal adenocarcinoma or high-grade dysplasia after an initial diagnosis of Barrett's oesophagus [4]. A model including sex, smoking history (ever versus never), Barrett's oesophagus length (cm) and low-grade dysplasia status had reasonable discriminatory ability. The predictive ability of the model proposed by Parasa *et al* [4], was similar but slightly weaker in the current study cohort than reported previously [4], which is to be expected in external validations. One of the limitations discussed by Parasa *et al* [4], was that their data relied on patients enrolled at referral academic centres, which may represent higher risk patients. The similarity of our results when using population-based data from the Northern Ireland Barrett's register may be reassuring that the original results are generalizable to broader patient populations. Therefore, this external validation study suggests that the risk prediction model tool could be used for risk-stratification of Barrett's patients following their index endoscopic biopsy to determine surveillance intervals or treatment decisions.

Our results, using non-US based data from the Northern Ireland Barrett's register, indicate that the categories proposed by Parasa *et al* [4] may outperform the use of low-grade dysplasia status alone, as recommended by the AGA [1] for risk-stratification purposes. As inter-observer variability is high for judging the presence of low-grade dysplasia [20], the incorporation of other factors may reduce the reliance on low-grade dysplasia for risk stratification purposes. The results also give suggestive evidence that the model proposed by Parasa *et al* may also outperform the combinations of Barrett's segment length and low-grade dysplasia status recommended by the BSG [2], though the difference was not statistically significant. Whilst the statistical significance remains to be determined, adoption of the Parasa *et al* categories, could have a significant impact on clinical practice at both ends of the surveillance spectrum. The proportion of individuals assigned to the low and high risk categories both approximately doubled, which could mean more individuals in less frequent surveillance groups (E.g. 3-5 years) but more in the very frequent (6 monthly) surveillance group. Whilst some changes in risk classification were incorrect, none of the changes were major (I.e. highest to lowest or lowest to highest) and a higher proportion of both cases and controls were assigned to a more appropriate risk category. Future health economic models could consider whether the model proposed by Parasa *et al* [4] is likely to lead to improvements to the cost-effectiveness of surveillance and treatments relative to current guideline recommendations. This may complement efforts to identify biomarkers associated with risk of progression

Changes to guidelines to recommend use of the model proposed by Parasa *et al* [4] would rely on the collection of smoking data and exact Barrett's segment length, which may hinder application of the full model in some healthcare settings. However, missing data on smoking or other variables may not be problematic as exclusion of smoking or inclusion of missing data (scored as 0 points), which may reflect clinical practice, did not lead to major changes in the predictive ability. Similarly simplification of Barrett's segment length to short versus long, led

to only minor loss in predictive ability (0.68, 95% CI: 0.60-0.75). Therefore, it is possible that simpler models could be used in cases where smoking information or exact segment length are not available, without compromising the ability to predict risk of progression.

None of the additional factors tested improved risk prediction, despite being associated with the risk of progression previously [8]. Future studies, with longer follow-up time and larger sample sizes, could examine whether additional clinical factors such as age and ulcerative erosion, or biomarkers such as methylation [21,22] or somatic mutations [23–25], could be useful for predicting risk of progression.

Risk models incorporating both genetic and non-genetic factors have previously been developed for predicting risks of various cancers. However, recent studies from our working group and others have found that adding inherited genetic information to a risk model using only clinical and lifestyle factors did not improve discriminatory ability for predicting oesophageal cancer development in the general population.[18,26] Future research should assess whether or not genetic factors or somatic mutations may improve discrimination in the setting of neoplastic progression in Barrett's oesophagus patients.

The current study had several strengths. The Northern Ireland Barrett's register uses population-based data, rather than patients enrolled at referral academic centres that may represent higher risk patients. Thus, we believe our results are not overestimating the results shown. We also had data on the factors studied prior to subsequent diagnosis of oesophageal adenocarcinoma or high-grade dysplasia, so ensuring appropriate temporality of the associations studied.

Limitations of the current study included the smaller sample size than the Parasa et al study [4], particularly as missing data was common due to the use of case note reviews. It is possible that factors included in this model influenced decisions on the frequency of surveillance, which

may cause reverse causality, whereby individuals with these factors may have more opportunities to detect progression. Unfortunately, information on the number of subsequent endoscopies was not available which prevented an assessment of reverse causality.

In summary, we are the first population-based study to externally validate a risk prediction model to risk stratify patients after an initial diagnosis of Barrett's oesophagus. The model, including sex, dysplasia, smoking history and Barrett's oesophagus segment length, performed well. We also provided novel data demonstrating that this model outperformed current methods such as use of low-grade dysplasia status alone.

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Table 1. Baseline characteristics of individuals with Barrett’s oesophagus (with specialized intestinal metaplasia) according to progression status to oesophageal adenocarcinoma or high-grade dysplasia.

		Progression to oesophageal adenocarcinoma or high-grade dysplasia	
		Non-progressors (%)	Progressors (%)
Total		1,144 (100.0)	54 (100.0)
Age			
	<60	530 (46.3)	24 (44.4)
	60+	614 (53.7)	30 (55.6)
Sex			
	Male	734 (64.2)	44 (81.5)
	Female	410 (35.8)	10 (18.5)
Smoking status			
	Never	583 (51.0)	21 (38.9)
	Ever	561 (49.0)	33 (61.1)
Low-grade dysplasia			

	No	1,058 (92.5)	41 (75.9)
	Yes	86 (07.5)	13 (24.1)
Mean Barrett's segment length (cm, SD)		5.36 (2.63)	6.7 6 (2.55)
Reported reflux symptoms			
	No	487 (42.6)	16 (29.6)
	Yes	657 (57.4)	38 (70.4)
Ulcerative erosion			
	No	997 (87.2)	41 (75.9)
	Yes	147 (12.8)	13 (24.1)
Weight loss reported			
	No	1,012 (88.5)	46 (85.2)
Yes, <5kg or unknown amount		63 (05.5)	3 (05.6)
Yes, >5kg		69 (06.0)	5 (09.3)
Risk score			
	Low	348 (30.4)	6 (11.1)
	Intermediate	619 (54.1)	25 (46.3)
	High	177 (15.5)	23 (42.6)

Table 2. Area under the receiver operating characteristic curves for predicting risk of progression using points based models proposed by Parasa *et al*

	Non-progressors	Progressors	AUROC
Primary analysis	1,144	54	0.70 (0.63-0.78)
Risk categories (low, medium, high)	1,144	54	0.68 (0.61-0.74)
Coefficient based model	1,144	54	0.70 (0.64-0.78)
<u>Additional factors</u>			
Ulcerative erosion	1,144	54	0.71 (0.64-0.79)
Reflux symptoms	1,144	54	0.71 (0.64-0.78)
Weight loss	1,144	54	0.71 (0.64-0.78)
Age (<60 versus 60+)	1,144	54	0.70 (0.62-0.78)

Sensitivity analyses

Oesophageal adenocarcinoma only	1,151	41	0.70 (0.63-0.78)
Exclusion of points attributed to smoking	1,144	54	0.70 (0.63-0.77)
Exclusion of points attributed to sex	1,144	54	0.69 (0.62-0.77)
Exclusion of points attributed to low-grade dysplasia	1,144	54	0.67 (0.60-0.75)
Exclusion of points attributed to Barrett's oesophagus length	1,144	54	0.66 (0.59-0.74)
Simplification of Barrett's length			0.68 (0.60-0.75)
Inclusion of missing data as 0 points	2,976	114	0.68 (0.62-0.73)

FIGURE LEGENDS:

Figure 1. Selection of participants for primary analysis with complete data

Figure 2. Total risk of progression to oesophageal adenocarcinoma or high-grade dysplasia by risk category groups proposed by Parasa *et al.*

¹ Proportion in each risk category group progressing during a median 7.5 years of follow-up.

² Annual risk of progression in each risk category group in parentheses.

Figure 3. Cumulative incidence of progression to oesophageal adenocarcinoma or high-grade dysplasia by risk category groups proposed by Parasa *et al.*

Figure 4. Area under the receiver operating characteristic curve for predicting risk of progression to oesophageal adenocarcinoma or high-grade dysplasia when using risk category groups proposed by Parasa *et al.*

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

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	6	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	7	

		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		<i>(b) Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
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	6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	7 & Figure 1

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7-8
		(b) Describe any methods used to examine subgroups and interactions	7-8
		(c) Explain how missing data were addressed	7-8
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	7-8
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Fig 1
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	Complete case
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Table 2

		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	10
		(b) Report category boundaries when continuous variables were categorized	6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Continued on next page			

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
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	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	1