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Socio-demographic and other patient characteristics associated with time between colonoscopy and surgery, and choice of treatment centre for colorectal cancer: a retrospective cohort study

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ABSTRACT

Objectives: To investigate key patient clinical and demographic characteristics associated with time between colonoscopy and surgery, and choice of treatment centre for colorectal cancer (CRC) patients. This will add to the little published research examining the pathway following CRC diagnosis and prior to surgery.

Design: Retrospective cohort analysis of linked data.

Setting: A population-based sample of people diagnosed August 2004 to December 2007 in New South Wales, Australia.

Participants: 569 CRC patients, of whom 407 (72%, 95% CI 68% to 75%) had colonoscopy followed by surgery.

Primary outcome measures: Time between colonoscopy and surgery, and whether the surgery took place in a specialist cancer centre.

Results: Among the 407 eligible patients analysed, the median time from colonoscopy to surgery was 19 days (IQR 12–29 days). After adjusting for key demographic and clinical characteristics such as age and disease stage, the time was longer for rectal cancer patients and those reporting fair/poor health, although differences in medians were <5 days. 24% (95% CI 20% to 28%) had surgery in a specialist cancer centre, which was more common among people resident in metropolitan areas (37% vs 14% for others, adjusted p=0.001) and those without private health insurance (30% vs 21% for others, adjusted p=0.03).

Conclusions: There do not appear to be systemic issues affecting time from colonoscopy to surgery related to patients' socio-demographic characteristics. However, patients with private insurance and those living in rural areas may be less likely to receive optimal specialist treatment. A more systematic approach might be needed to ensure cancer patients are treated in specialist cancer centres, particularly patients requiring more specialised treatment.

ARTICLE SUMMARY

Article focus

- Investigate key patient clinical and demographic characteristics associated with time between colonoscopy and surgery, and choice of treatment centre for colorectal cancer patients in New South Wales, Australia.
- Most existing research has focused on delay prior to diagnosis, and little is known about factors associated with referral to specialist treatment following diagnosis.

Key messages

- Rectal cancer cases had slightly longer time to surgery than colon cancer cases.
- Treatment in a specialist cancer centre was associated more with patient access than disease characteristics.
- We need to ensure that those with the greatest need, such as those with rectal cancer, have access to timely and specialist treatment.

Strengths and limitations of this study

- This is one of the first studies to examine the pathway following colorectal cancer diagnosis and prior to surgery, with a relatively large population-based sample of patients.
- Surgery was the only treatment we could reliably analyse.
- Surgeon specialties were not known so specialist centres were identified as institutions with radiotherapy facilities.
- We cannot determine the exact reason for longer time to treatment and it might actually be a positive, possibly reflecting referral to a specialist surgeon or preoperative radiotherapy.

INTRODUCTION

Despite the availability of clinical guidelines,[1] many colorectal cancer (CRC) patients do not receive optimal care.[2] Two key aspects of optimal cancer care are the time between

diagnosis and treatment[3 4] and receiving treatment in a specialist cancer centre.[5–8]

A recent systematic review found a significant relationship between hospital case volume and short-term mortality for cancer patients who receive surgery.[9] However, inconsistencies in the findings mean that the relative importance of surgeon volume and hospital volume remains unclear and calls into question the usefulness of using case volume alone.[9] Nevertheless, treatment in a specialist cancer treatment centre is important for patient care, especially for rectal cancer cases.[5–8]

The time between diagnostic procedures and treatment is similarly important in terms of preventing disease progression and limiting patient psychological distress.[3 4] This may be compounded by delays in diagnosis. Patient variables such as age, sex or socioeconomic status do not seem associated with delay. However, non-recognition of symptom severity, symptom denial, having a regular general practitioner prior to receiving a cancer diagnosis, physician communication styles, receiving an initial alternate diagnosis, misdiagnosis, inadequate examination and inaccurate investigations all influence diagnostic delay.[10 11] A recent prospective study reported that 3-year mortality for CRC patients increased with diagnostic delay beyond 1 month, particularly for those presenting with serious symptoms.[12] Past studies have also reported lower levels of CRC screening in Australia among groups such as migrants and people living in remote areas,[13–15] indicating potential for further diagnostic delay for these groups. In Australia, the National Bowel Screening Program was introduced in 2006 with one-off testing for people turning 55 or 65 years, with people turning 50 years added in 2008.[16]

The aim of this study was to use linked population-based data to investigate factors associated with time between colonoscopy and surgery and choice of treatment centre for CRC cases in New South Wales (NSW), Australia.

METHODS

Data sources

Data used for the study comprised linked records from the population-based 45 and Up Study, the NSW Central Cancer Registry (CCR), the NSW Admitted Patient Data Collection (APDC) and claims for medical services from Medicare Australia.

The 45 and Up Study is a general population cohort study with over 265 000 participants in NSW aged 45 years or more, representing around 10% of the population of that age. The study methods have been described in detail elsewhere.[17] Briefly, participants were randomly selected from the Medicare Australia registration database, which covers all citizens and permanent residents of Australia. Baseline questionnaires were completed from January 2006 to April 2009, and participants gave consent to linkage to health data collections including the CCR, the APDC and Medicare claims records.

All cancers diagnosed in NSW, except for non-melanoma skin cancers, are notified to the NSW CCR. We obtained CCR records for people diagnosed with CRC between January 2001 and December 2007.

The NSW APDC contains information on all admitted hospital episodes in NSW. Hospital medical coders abstract individual patient information from medical records following the patient's discharge from hospital. Data include dates of admission and separation, procedures carried out and diagnoses relating to the hospital episode. Procedures were coded using the Medicare Benefits Schedule-Extended classification of the International Classification of Diseases 10th revision, Australian Modification (ICD-10-AM). Up to 50 procedure codes could be recorded for each episode. We used hospital separation records from July 2000 to June 2008.

Medicare data comprised claims for medical services through the Medicare Benefits Scheme (MBS) between June 2004 and January 2009. The MBS, a component of Australia's national health insurance system, provides subsidised access to medical services for Australian residents.

Record linkage

Identifying information for participants in the 45 and Up Study were linked with identifiers in the CCR, APDC hospital records and MBS claims. The linkage to the CCR and APDC was done by the Centre for Health Record Linkage[18] (CHeReL) using probabilistic matching carried out with ChoiceMaker software (ChoiceMaker Technologies Inc.). Both certain and uncertain matches were reviewed clerically, resulting in approximately 0.1% false-positive and <0.1% false-negative linkages. Linkage to MBS claims records was done by the Sax Institute using an encrypted version of the Medicare identification number. Ethical approval for the overall 45 and Up Study, this specific study and the linkage was given by the University of NSW Human Research Ethics Committee and the NSW Population and Health Services Research Ethics Committee. The provision of Medicare claims records was approved by the Department of Health and Ageing Ethics Committee.

Subjects

The group of interest comprised 45 and Up Study participants diagnosed with CRC who had a colonoscopy recorded in the APDC leading up to their diagnosis and surgical treatment after diagnosis. We restricted the sample to cases diagnosed from August 2004 to December 2007 who linked to both the APDC and MBS, so all cases had at least 2 months of treatments and consultations recorded prior to diagnosis and for at least 6 months after diagnosis.

Socio-demographic and clinical characteristics

The 45 and Up Study data included self-reported data regarding height, weight, highest education level

attained, family history of CRC, smoking status, marital status, housing type, country of birth, language spoken at home, health insurance status (private with extras, private no extras, Department of Veterans Affairs/Healthcare card, none of these), income level (Australian dollars) and health status. Body mass index was calculated as weight (kilogram) divided by the square of height (metre). The CCR provided data regarding month and year of CRC diagnosis (the date of the most definitive cancer notification, likely to be based on the pathology form for the specimen obtained via colonoscopy), age at diagnosis, disease stage (classified as localised, regional spread, distant metastases or unknown), cancer site and local government area of residence at diagnosis from which we assigned quintiles of socioeconomic disadvantage. We identified patient comorbidities from APDC diagnosis codes, including cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes and other diseases in the Charlson Comorbidity Index[19] ('other key comorbidities').

Procedures and consultations

A specialist clinical panel (MFH, IO and MB) identified relevant procedure codes and items for colonoscopies and CRC surgery in the APDC and MBS data. Surgical treatment comprised hemicolectomies, total colectomies, partial colectomies, total proctocolectomies, anterior rectal resections, Hartmann's procedure (rectosigmoidectomy), abdominoperineal resections and 'other' resections of the colon or rectum. Chemotherapy and radiotherapy are generally performed on an outpatient basis, for which data were not available, so they were not included in the analysis.

Diagnosis dates were available as month and year only, so chronology around diagnosis was based on calendar month and year only. We included surgical procedures from the month of diagnosis onwards and the last pre-surgery colonoscopy no earlier than 2 months prior to the month of diagnosis. Actual dates of colonoscopy and surgery were used in analysing time between the procedures.

Outcomes

The primary outcomes of interest were the time between diagnosis and treatment and whether or not the patient received surgery in a specialist cancer centre, as defined by an institution having radiotherapy facilities. Colonoscopy was used as the indicator for diagnosis and an appropriate surgical procedure as the treatment. Over 90% of the relevant colonoscopies and surgical procedures were identified in the APDC, with just over half of these also identified in the MBS. The remaining colonoscopies were recorded in the MBS only.

Statistical analysis

χ^2 Tests were used to compare patient groups, and unconditional multivariable logistic regression was used to identify factors associated with treatment in a specialist cancer centre. Cox's proportional hazards regression was used to investigate factors associated with time between colonoscopy and surgery. Factors of interest were patient characteristics including age, disease stage, place of residence and self-reported health status, as described in table 2. A small number of patients with missing values for variables of interest were excluded from analyses. All analyses were carried out in SAS V.9.1 (SAS Institute Inc.).

RESULTS

Baseline questionnaire data from the 45 and Up Study were received for the first 102 938 study participants, with questionnaires completed between January 2006 and May 2008. These were linked to 1023 cases of CRC in the CCR. Among these 1023 cases, 1007 (98%) linked to at least one APDC hospital record and 985 (96%) linked to at least one MBS claim in the available data. The 1023 were compared with all CRCs diagnosed in NSW between 2001 and 2007 and a greater proportion of the study sample was men (62% vs 54% overall), Australian born (76% vs 70%), diagnosed in 2007 (22% vs 16%), had localised stage of disease (42% vs 34%) or were living in rural areas (34% vs 26%) or the two least socioeconomically disadvantaged quintiles (50% vs 36%), while a lower proportion were aged 80 years or more (15% vs 23%), had distant metastases (7% vs 17%), had any of the key comorbidities (32% vs 41%) or were living in metropolitan areas (41% vs 51%).

The sample was restricted to the 569 CRC cases diagnosed from August 2004 to December 2007 who linked to both the APDC and MBS (figure 1). This represents 4% of all CRCs diagnosed in NSW between August 2004 and December 2007. We found that around 95% of surgical cases had their surgery within 3 months of diagnosis so the minimum 6 months of follow-up we have for all cases is reasonable (average follow-up: 25 months).

Of the 569 cases diagnosed from August 2004 to December 2007, 537 (94%) had a colonoscopy recorded at any time and 488 (86%) had surgery. There were 407

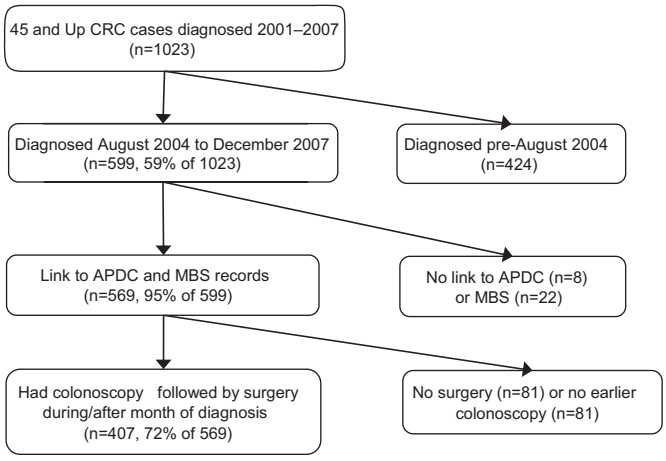

Figure 1 Sample selection process. APDC, Admitted Patient Data Collection; CRC, colorectal cancer; MBS, Medicare Benefits Scheme.

Table 1 Characteristics of colorectal cancer cases included in the study and those not included in further analyses (n=1023)

	45 and Up cases diagnosed, August 2004 to December 2007, had colonoscopy and surgery (n=407)		All other 45 and Up cases diagnosed, January 2001 to December 2007 (n=616)		p value for difference
	No. of cases	% of cases	No. of cases	% of cases	
Sex					0.72
Female	152	37	237	38	
Male	255	63	379	62	
Age at diagnosis (years)					0.08
<60	78	19	135	22	
60–69	108	27	193	31	
70–79	150	37	208	34	
80+	71	17	80	13	
Place of residence at diagnosis					0.02
Metropolitan	186	46	234	38	
Other urban	103	25	156	25	
Rural	118	29	226	37	
Self-reported health status					0.58
Good to excellent	307	75	447	73	
Fair/poor	78	19	134	22	
Unspecified	22	5	35	6	
Chronic obstructive pulmonary disorder*					0.20
Yes	29	7	32	5	
No	378	93	568	95	
Diabetes*					0.69
Yes	50	12	71	12	
No	357	88	529	88	
Cancer site					0.49
Colon	265	65	414	67	
Rectum	142	35	202	33	
Disease stage					0.003
Localised	185	45	246	40	
Regional	176	43	255	41	
Distant metastases	27	7	48	8	
Unknown	19	5	67	11	
Timing of colorectal cancer diagnosis relative to 45 and Up questionnaire					<0.001
Before (prevalent)	327	80	552	90	
After (incident)	80	20	64	10	

No differences between groups for year of diagnosis, socioeconomic status, housing type, language other than English at home, country of birth, highest education level attained, family history of colorectal cancer, body mass index, smoking status, marital status, health insurance, income level, cardiovascular disease recorded in hospital or other diseases in the Charlson Comorbidity Index.
*Excludes 16 cases not linked to Admitted Patient Data Collection who did not have comorbidity information.

cases (72%) who received surgery from the month of diagnosis onwards and had a colonoscopy beforehand (up to 2 months before the month of diagnosis). These are the cases in whom we were most interested. Table 1 shows that these 407 cases were similar to the 616 cases identified in the CCR but not included in the study, except for a higher proportion with localised disease (45% and 40%, respectively), who lived in metropolitan areas at diagnosis (46% and 38%) or who were diagnosed with CRC after completing the 45 and Up Study questionnaire (20% vs 10%).

Time between colonoscopy and surgery

The overall median time from colonoscopy to surgery was 19 days (IQR 12–29 days). After adjusting for all measured factors, the time from colonoscopy to surgery was significantly longer for cases with rectal cancer and cases reporting fair/poor health (table 2). Given the likely difference in treatment patterns for colon and rectal cancer cases, we analysed them separately. Among rectal cancer, there was shorter time to surgery for cases with COPD, Department of Veterans Affairs/Healthcare cards, good to excellent self-reported health, those living in a house (compared with flat/unit or elderly accommodation) and cases not living in rural areas (table 3). For cases with colon cancer, who should not require preoperative radiotherapy or chemotherapy, there were no major differences in the time to surgery across the subgroups compared. The period was marginally longer for cases with unknown disease stage, those with lower income and those with a comorbidity in the Charlson Index other than cardiovascular disease, COPD or

Table 2 Demographic and clinical characteristics associated with time between colonoscopy and colorectal cancer surgery for all colorectal cancer cases (n=407)

	n	Median time (days)	IQR (days)	Adjusted HR (95% CI)*	Overall p value†
Sex					0.25
Female	152	19	12–28	1.18 (0.89 to 1.58)	
Male	255	20	12–31	1.00 (ref)	
Age (years)					0.88
<60	78	17	8–29	0.96 (0.68 to 1.37)	
60–69	108	19	13–32	0.93 (0.69 to 1.26)	
70–79	150	21	12–29	1.00 (ref)	
80+	71	20	12–28	1.10 (0.77 to 1.57)	
Country of birth					0.64
Australia	320	19	13–29	1.00 (ref)	
Other	81	19	8–30	0.93 (0.67 to 1.28)	
Unknown	6	12	10–40	Not incl.	
Non-English spoken at home					0.20
Yes	30	21	10–38	1.38 (0.84 to 2.27)	
No	377	19	12–29	1.00 (ref)	
Place of residence at diagnosis					0.56
Metropolitan	186	19	11–28	1.00 (ref)	
Other urban	103	20	13–28	1.16 (0.77 to 1.74)	
Rural	118	20	11–33	0.96 (0.65 to 1.43)	
Type of housing					0.52
House	296	19	12–29	1.00 (ref)	
Flat/unit	50	19	10–29	1.10 (0.77 to 1.59)	
House on farm	28	21	12–48	0.77 (0.49 to 1.23)	
Elderly accommodation	26	22	17–42	0.85 (0.52 to 1.37)	
Other/unspecified	7	29	19–31	Not incl.	
Socioeconomic status					0.44
Least disadvantaged quintile	143	17	11–28	1.00 (ref)	
Quintile 2	64	20	12–34	0.88 (0.57 to 1.38)	
Middle quintile	126	20	8–29	1.17 (0.76 to 1.80)	
Quintile 4	58	22	14–33	0.92 (0.60 to 1.41)	
Most disadvantaged quintile	16	22	14–27	1.32 (0.66 to 2.62)	
Highest education level attained					0.59
No school certificate/other	48	20	14–31	0.99 (0.67 to 1.47)	
School/intermediate certificate	102	22	16–33	1.00 (ref)	
Higher school/leaving certificate	28	18	12–34	1.02 (0.63 to 1.65)	
Trade/apprenticeship	56	18	13–28	1.43 (0.96 to 2.13)	
Certificate/diploma	83	20	10–29	1.03 (0.74 to 1.43)	
Uni degree or higher	80	16	8–36	1.02 (0.71 to 1.48)	
Unspecified	10	13	3–22	Not incl.	
Marital status					0.18
Married/living as married	288	18	11–28	1.00 (ref)	
Single/divorced/separated	51	24	12–37	0.93 (0.64 to 1.36)	
Widowed	65	22	17–34	0.72 (0.51 to 1.02)	
Unspecified	3	20	9–21	Not incl.	
Income level					0.06
<$20K p.a.	112	21	14–31	1.00 (ref)	
$20K–<$40K p.a.	83	21	13–31	0.97 (0.67 to 1.41)	
$40K–<$70K p.a.	62	18	9–35	0.92 (0.62 to 1.36)	
$70K+ p.a.	52	13	8–29	1.59 (1.01 to 2.51)	
Unspecified	98	19	13–28	1.30 (0.93 to 1.81)	
Health insurance					0.51
Private with extras	190	18	9–28	1.00 (ref)	
Private no extras	70	17	11–28	1.13 (0.83 to 1.55)	
DVA/healthcare card	101	21	14–29	1.05 (0.77 to 1.44)	
None of these	37	28	19–41	0.76 (0.50 to 1.15)	
Missing	9	25	16–28	0.86 (0.40 to 1.86)	

Continued

Table 2 Continued

	n	Median time (days)	IQR (days)	Adjusted HR (95% CI)*	Overall p value†
Body mass index					0.15
Underweight/normal	155	18	10–28	1.00 (ref)	
Overweight	157	20	12–35	0.80 (0.61 to 1.05)	
Obese/morbidly obese	66	22	13–31	0.92 (0.65 to 1.30)	
Null/not specified	29	19	11–29	0.62 (0.38 to 0.99)	
Smoking status					0.52
Never-smoker	203	19	10–29	1.00 (ref)	
Ever-smoker	204	19	12–30	1.08 (0.85 to 1.37)	
Self-reported health status					0.02
Good to excellent	307	18	11–29	1.00 (ref)	
Fair/poor	78	21	15–40	0.69 (0.51 to 0.95)	
Unspecified	22	22	14–28	0.59 (0.35 to 1.02)	
Cardiovascular disease					0.37
Yes	47	20	9–29	0.84 (0.57 to 1.23)	
No	360	19	12–30	1.00 (ref)	
Chronic obstructive pulmonary disease					0.16
Yes	29	20	11–27	1.41 (0.87 to 2.27)	
No	378	19	12–30	1.00 (ref)	
Diabetes					0.93
Yes	50	26	14–36	1.02 (0.70 to 1.48)	
No	357	19	11–29	1.00 (ref)	
Other key comorbidity					0.25
Yes	56	20	12–29	1.22 (0.87 to 1.71)	
No	351	19	12–30	1.00 (ref)	
Family history of CRC					0.58
Yes	75	20	13–33	0.92 (0.69 to 1.23)	
No	332	19	12–29	1.00 (ref)	
Disease stage					0.18
Localised	185	19	13–29	1.00 (ref)	
Regional	176	19	10–29	1.06 (0.84 to 1.35)	
Distant metastases	27	20	12–39	0.65 (0.39 to 1.09)	
Unknown	19	35	13–48	0.70 (0.40 to 1.23)	
Cancer site					<0.001
Colon	265	18	10–27	1.00 (ref)	
Rectum	142	22	14–37	0.55 (0.43 to 0.71)	
Year of diagnosis					0.88
2004	43	19	9–26	1.10 (0.72 to 1.67)	
2005	113	19	12–29	0.98 (0.73 to 1.32)	
2006	111	21	14–32	0.92 (0.69 to 1.23)	
2007	140	18	11–32	1.00 (ref)	
Timing of CRC diagnosis relative to 45 and Up questionnaire					0.23
Before (prevalent)	327	19	11–29	1.21 (0.89 to 1.66)	
After (incident)	80	21	14–31	1.00 (ref)	

*Adjusted for all other variables in this table. HR <1 indicates longer time between colonoscopy and surgery.
†Overall p value from proportional hazards regression (ref): reference category.
CRC, colorectal cancer; DVA, Department of Veterans Affairs; Not incl., this category was not included in proportional hazards regression.

diabetes (table 3). Just over one-quarter of cases (27%) had more than 28 days between colonoscopy and surgery; this was more common for rectal cancer cases (39% vs 21% of colon cases).

Treatment in a specialist cancer centre

Ninety-nine (24%) of the 407 cases had their surgery in a specialist cancer centre. This was more frequent among those living in metropolitan areas, as well as for cases without private health insurance, those with one of the 'other' Charlson Index comorbidities and cases who were married or living with a partner (table 4). When all the factors of interest were included in the logistic regression place of residence, health insurance and other comorbidities remained significantly associated with treatment in a specialist centre.

Table 3 Demographic and clinical characteristics associated with time between colonoscopy and colorectal cancer surgery, separately for colon and rectal cancer cases

	Colon cancer (n=265)		Rectal cancer (n=142)	
	Adjusted HR* (95% CI)	Overall p value†	Adjusted HR* (95% CI)	Overall p value†
Place of residence at diagnosis		0.77		0.01
Metropolitan	1.00 (ref)		1.00 (ref)	
Other urban	1.19 (0.67 to 2.10)		1.55 (0.72 to 3.37)	
Rural	1.21 (0.71 to 2.07)		0.47 (0.21 to 1.09)	
Type of housing		0.49		0.002
House	1.00 (ref)		1.00 (ref)	
Flat/unit	1.18 (0.74 to 1.87)		0.31 (0.12 to 0.82)	
House on farm	1.65 (0.84 to 3.25)		0.43 (0.18 to 1.03)	
Elderly accommodation	1.07 (0.55 to 2.11)		0.19 (0.06 to 0.61)	
Other/unspecified	Not incl.		Not incl.	
Income level		0.04		0.06
<$20K p.a.	1.00 (ref)		1.00 (ref)	
$20K–<$40K p.a.	0.77 (0.46 to 1.29)		0.59 (0.30 to 1.17)	
$40K–<$70K p.a.	0.93 (0.55 to 1.57)		0.43 (0.18 to 0.99)	
$70K+ p.a.	1.85 (1.01 to 3.40)		0.54 (0.20 to 1.43)	
Unspecified	0.98 (0.63 to 1.52)		1.24 (0.62 to 2.46)	
Health insurance		0.12		0.02
Private with extras	1.00 (ref)		1.00 (ref)	
Private no extras	0.80 (0.52 to 1.22)		1.79 (0.93 to 3.45)	
DVA/healthcare card	0.67 (0.46 to 0.98)		3.33 (1.59 to 6.97)	
None of these	0.53 (0.29 to 0.97)		1.29 (0.58 to 2.90)	
Missing	0.42 (0.12 to 1.42)		0.99 (0.28 to 3.46)	
Self-reported health status		0.10		0.004
Good to excellent	1.00 (ref)		1.00 (ref)	
Fair/poor	0.64 (0.42 to 0.96)		0.44 (0.21 to 0.92)	
Unspecified	0.95 (0.48 to 1.89)		0.23 (0.07 to 0.76)	
Chronic obstructive pulmonary disease		0.26		0.004
Yes	1.39 (0.79 to 2.44)		6.39 (1.80 to 22.70)	
No	1.00 (ref)		1.00 (ref)	
Other key comorbidity		0.04		0.06
Yes	1.64 (1.03 to 2.59)		2.14 (0.97 to 4.75)	
No	1.00 (ref)		1.00 (ref)	
Disease stage		0.05		0.87
Localised	1.00 (ref)		1.00 (ref)	
Regional	1.08 (0.79 to 1.47)		1.03 (0.64 to 1.66)	
Distant metastases	0.53 (0.28 to 1.02)		1.39 (0.47 to 4.14)	
Unknown	0.48 (0.24 to 0.97)		0.65 (0.17 to 2.50)	

The variables not shown in the table were not associated with time to surgery for colon or rectal cancers. HR <1 indicates longer time between colonoscopy and surgery.
*Adjusted for all other variables in this table, as well as for sex, age, country of birth, language spoken at home, socioeconomic status, education level, marital status, body mass index, smoking status, cardiovascular disease, diabetes, family history of colorectal cancer, year of diagnosis and diagnosis before/after completing study questionnaire.
†Overall p value from proportional hazards regression (ref): reference category.
DVA, Department of Veterans Affairs; Not incl., this category was not included in proportional hazards regression.

There was no association with cancer site (colon/rectum).

The significant factors were similar when colon and rectal cancer cases were analysed separately, although for colon cases, there were also higher odds of treatment in a specialist centre for cases not born in Australia (39% vs 21% of Australian born) and those with distant or unknown disease stage (31% vs 24% of locoregional). Looking at all hospital records and not just episodes involving CRC surgery, 41% of cases had any admission recorded at a specialist cancer centre. Around half of all surgical procedures took place in public hospitals, and these comprised almost two-thirds of surgical procedures in specialist cancer centres.

DISCUSSION

Rectal cancer cases had slightly longer time to surgery than colon cancer cases, even after adjustment for comorbidities, disadvantage and health status, but there was no evidence that rectal cancer cases were more likely to be treated at specialist cancer centres (those with a radiotherapy unit). Treatment in a specialist cancer

Table 4 Demographic and clinical characteristics associated with receiving colorectal cancer surgery in a specialist cancer centre (n=407)

	Total (n)	Treatment in a specialist cancer centre, n (%)	Adjusted OR (95% CI)*	Overall p value†
Sex				0.71
Female	152	27 (18)	0.87 (0.43 to 1.79)	
Male	255	72 (28)	1.00 (ref)	
Age (years)				0.78
<60	78	17 (22)	0.67 (0.28 to 1.63)	
60–69	108	27 (25)	1.01 (0.48 to 2.10)	
70–79	150	33 (22)	1.00 (ref)	
80+	71	22 (31)	1.13 (0.45 to 2.85)	
Country of birth				0.14
Australia	320	68 (21)	1.00 (ref)	
Other	81	29 (36)	1.79 (0.83 to 3.90)	
Unknown	6	2 (33)	Not incl.	
Non-English spoken at home				0.25
Yes	30	10 (33)	0.50 (0.15 to 1.62)	
No	377	89 (24)	1.00 (ref)	
Place of residence at diagnosis				0.001
Metropolitan	186	68 (37)	1.00 (ref)	
Other urban	103	18 (17)	0.27 (0.10 to 0.73)	
Rural	118	13 (11)	0.14 (0.05 to 0.40)	
Type of housing				0.07
House	296	65 (22)	1.00 (ref)	
Flat/unit	50	20 (40)	2.52 (1.06 to 6.01)	
House on farm	28	7 (25)	3.08 (0.95 to 10.01)	
Elderly accommodation	26	7 (27)	1.78 (0.49 to 6.40)	
Other/unspecified	7	0	Not incl.	
Socioeconomic status				0.46
Least disadvantaged quintile	143	54 (38)	1.00 (ref)	
Quintile 2	64	9 (14)	0.78 (0.27 to 2.29)	
Middle quintile	126	26 (21)	1.23 (0.45 to 3.34)	
Quintile 4	58	9 (16)	0.52 (0.18 to 1.49)	
Most disadvantaged quintile	16	1 (6)	0.35 (0.03 to 3.88)	
Highest education level attained				0.16
No school certificate/other	48	14 (29)	3.69 (1.31 to 10.36)	
School/intermediate certificate	102	16 (16)	1.00 (ref)	
Higher school/leaving certificate	28	6 (21)	1.10 (0.29 to 4.24)	
Trade/apprenticeship	56	15 (27)	1.84 (0.69 to 4.94)	
Certificate/diploma	83	23 (28)	2.34 (0.96 to 5.68)	
Uni degree or higher	80	23 (29)	1.69 (0.64 to 4.47)	
Unspecified	10	2 (20)	Not incl.	
Marital status				0.10
Married/living as married	288	75 (26)	1.00 (ref)	
Single/divorced/separated	51	12 (24)	0.53 (0.21 to 1.35)	
Widowed	65	12 (18)	0.39 (0.15 to 1.01)	
Unspecified	3	0	Not incl.	
Income level				0.74
<$20K p.a.	112	27 (24)	1.00 (ref)	
$20K–<$40K p.a.	83	15 (18)	1.23 (0.47 to 3.24)	
$40K–<$70K p.a.	62	17 (27)	1.45 (0.54 to 3.91)	
$70K+ p.a.	52	19 (37)	2.10 (0.71 to 6.19)	
Unspecified	98	21 (21)	1.33 (0.56 to 3.16)	
Health insurance				0.03
Private with extras	190	44 (23)	1.00 (ref)	
Private no extras	70	10 (14)	0.72 (0.29 to 1.77)	
DVA/healthcare card	101	29 (29)	2.17 (0.97 to 4.89)	
None of these	37	12 (32)	2.75 (0.99 to 7.62)	
Missing	9	4 (44)	7.41 (1.17 to 47.04)	

Continued

Table 4 Continued

	Total (n)	Treatment in a specialist cancer centre, n (%)	Adjusted OR (95% CI)*	Overall p value†
Body mass index				0.78
Underweight/normal	155	41 (26)	1.00 (ref)	
Overweight	157	39 (25)	1.02 (0.53 to 1.97)	
Obese/morbidly obese	66	12 (18)	0.80 (0.33 to 1.93)	
Null/not specified	29	7 (24)	0.59 (0.18 to 1.97)	
Smoking status				0.90
Never-smoker	203	45 (22)	1.00 (ref)	
Ever-smoker	204	54 (26)	1.04 (0.57 to 1.89)	
Self-reported health status				0.19
Good to excellent	307	77 (25)	1.00 (ref)	
Fair/poor	78	17 (22)	0.55 (0.25 to 1.25)	
Unspecified	22	5 (23)	0.36 (0.08 to 1.65)	
Cardiovascular disease				0.61
Yes	47	13 (28)	0.78 (0.30 to 2.02)	
No	360	86 (24)	1.00 (ref)	
Chronic obstructive pulmonary disease				0.64
Yes	29	10 (34)	1.29 (0.44 to 3.82)	
No	378	89 (24)	1.00 (ref)	
Diabetes				0.15
Yes	50	17 (34)	1.88 (0.79 to 4.50)	
No	357	82 (23)	1.00 (ref)	
Other key comorbidity				0.04
Yes	56	19 (34)	2.43 (1.04 to 5.68)	
No	351	80 (23)	1.00 (ref)	
Family history of CRC				0.85
Yes	75	19 (25)	0.93 (0.44 to 1.96)	
No	332	80 (24)	1.00 (ref)	
Disease stage				0.55
Localised	185	41 (22)	1.00 (ref)	
Regional	176	45 (26)	1.34 (0.72 to 2.47)	
Distant metastases	27	9 (33)	2.02 (0.63 to 6.47)	
Unknown	19	4 (21)	1.89 (0.44 to 8.20)	
Cancer site				0.64
Colon	265	66 (25)	1.00 (ref)	
Rectum	142	33 (23)	1.16 (0.63 to 2.16)	
Year of diagnosis				0.11
2004	43	10 (23)	1.00 (0.36 to 2.80)	
2005	113	24 (21)	0.40 (0.19 to 0.88)	
2006	111	27 (24)	0.88 (0.43 to 1.81)	
2007	140	38 (27)	1.00 (ref)	
Timing of CRC diagnosis relative to 45 and Up questionnaire				0.98
Before (prevalent)	327	76 (23)	1.01 (0.47 to 2.19)	
After (incident)	80	23 (29)	1.00 (ref)	

*Adjusted for all other variables in this table.
†Overall p value from logistic regression (ref): reference category.
CRC, colorectal cancer; DVA, Department of Veterans Affairs; Not incl., this category was not included in the logistic regression.

centre seems associated more with patient access than disease characteristics as the only strongly significant factor was residing in a non-metropolitan area. These results add further evidence for the disadvantage suffered by rural people in terms of their access to cancer treatment and are consistent with findings from New Zealand for the Maori population.[20] Poor access may be one contributing factor to poorer cancer survival.[21 22]

The longer time from colonoscopy to surgery for rectal cancer cases compared with colon cancer cases is not necessarily a negative finding, given the additional importance of specialist treatment for rectal cancer. It may reflect referral to a CRC surgeon rather than a general surgeon, assessment by a multidisciplinary team, or the use of, or a referral for assessment for, preoperative radiotherapy for rectal cancer, each of which could lead to better patient outcomes. Furthermore, the crude difference in median time was only 4 days, which is not a clinically important difference in terms of disease progression, although it might add to

patient distress. Analysis by disease site found that while there were some statistically significant differences in time between colonoscopy and surgery, the median differences were again in the order of a few days and thus not critical to disease progression. However, we should be mindful that these small delays may compound delays in diagnosis for groups, such as migrants and people living in remote areas who have lower screening rates,[13–15] and that diagnostic delay is associated with increased mortality for patients with CRC.[12] The overall median time to surgery for all cases was 19 days and this could also be important in the context of additional delays along the total diagnostic pathway. It is also worth noting the proportion of rectal cases with more than a month between diagnosis and surgery was almost double that of colon cases. This was unrelated to issues such as private insurance but may be related to the pathway for treatment prior to surgery, including pre-surgical radiotherapy.

Treatment in a specialist cancer centre was associated with place of residence, health insurance status and the presence of comorbidities. Around one in four CRC patients had their surgery in a specialist cancer centre, while less than half were ever admitted to a specialist cancer centre. The results suggest that access plays a major role in place of treatment rather than the potentially more important disease characteristics. Rectal cancer patients in particular should be more commonly treated at specialist cancer centres[5–7] or at least be referred to a multidisciplinary team for consideration for radiotherapy even if they are not in a radiotherapy centre. Private patients may be at a disadvantage in being referred to smaller private hospitals for their surgical procedures.

The study has some limitations. Our initial plan was to link CCR, APDC and MBS records for all CRC cases diagnosed over a number of years, but MBS data could not be released without the consent of each individual and this was not feasible. Using the data from the 45 and Up Study meant that the relevant consent had already been given, but this might introduce some biases as study participants are not representative of the population due to people in rural areas being oversampled and a possible 'healthy volunteer' effect. Our sample of cancer patients represent 4% of all CRCs diagnosed in NSW and were also more likely to be men, Australian born and have localised disease. However, the study's population coverage was still reasonably broad and it has been shown that the sample profile does not substantially impact on associations within the data.[23] Some of the marginally statistically significant associations may have arisen by chance due to the large number of variables included in the analyses, but this is not likely to be an explanation for associations with small p values.

Furthermore, we did not have access to surgeon information or temporal surgeon specialty lists in the almost 100 treating institutions included in the study, so specialist cancer centres were identified as institutions with radiotherapy facilities. We believe that our findings address an important component of cancer treatment and separate analyses of the distance from the treating centre to radiotherapy facilities obtained similar results. Treatment with chemotherapy or radiotherapy was not included as the available data were not comprehensive for all people receiving these treatments. Finally, the National Bowel Screening Program commenced in August 2006, screening people aged 55 and 65 years,[16] so our results do not fully address what happens in the presence of the screening programme. However, the study is population-based, reasonably large and uses reliable surgical information[24] and is an important addition to the literature on the subject.

CONCLUSIONS

Despite considerable research on the delay between screening and colonoscopy, the study is one of the first to examine the pathway following diagnosis and prior to surgery. There do not appear to be systemic issues affecting time from colonoscopy to surgery related to patients' socio-demographic characteristics. However, a more systematic approach might be needed to ensure that cancer patients are treated in specialist cancer centres, particularly for cases requiring more specialised treatment.

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Contributors DO and MFH contributed to conception and study design, participated in its coordination, advised on the data analysis and helped to draft the manuscript. DG assisted with obtaining the data and data management, undertook the analysis and drafted the manuscript. SP, IO, MB and AS contributed to conception and study design, participated in its coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Competing interests None.

Ethics approval Ethical approval was provided by the University of New South Wales Human Research Ethics Committee and the New South Wales Population and Health Services Research Ethics Committee.

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Overall comments

The authors thank the reviewers for their comments.

Responses to comments of Reviewer 1

Comment 1: It is not clearly explained why the authors restricted the sample of patients to those with colonoscopy in the diagnostic procedure. It is not explained in the paper and it should be. Also, the reason for not being diagnosed by colonoscopy would be worth to know.

Response 1: Our aim was to investigate the period between diagnostic procedures and treatment. Colonoscopy was a common and measurable starting point for this period. Of the 569 cases with hospital and Medicare data available for analysis, 94% had a colonoscopy at any time in the study period and 89% had one up to and including in the month of diagnosis, so the cases who had a colonoscopy represent the vast majority of those for whom we have data. We have revised the following text in paragraph 11 of the Methods section to reflect this.

"The primary outcomes of interest were the time between ~~colonoscopy~~ diagnosis and ~~surgery~~ treatment, and whether or not the patient received surgery in a specialist cancer centre, as defined by an institution having radiotherapy facilities. Colonoscopy was used as the indicator for diagnosis and an appropriate surgical procedure as the treatment."

Comment 2: The fact that the data available did not include radiotherapy and chemotherapy is a severe drawback of this study. It is well known that the accepted therapeutic strategy for rectal cancer involves radiotherapy and chemotherapy preoperatively. Lack of this information did not allow us to interpret the interval between colonoscopy and surgery in a proper way. It might happen that the treatment is not appropriate and it is not possible to know with the present database. The fact that there is no association with centres with radiotherapy available and the relevance of private practice in small clinics mentioned by the authors adds relevance to this point.

Response 2: We have acknowledged that not being able to include pre-operative radiotherapy or chemotherapy is a limitation of the study in the paper. This paper provides an overview of the timing between colonoscopy and surgery, and the possible mediating factors are discussed. This includes pre-operative radiotherapy and chemotherapy (paragraphs 2 and 4 of Discussion). As described in our response to the reviewer's comment 5, we have revised paragraph 4 of the Results section as follows:

"For cases with colon cancer, who should not require pre-operative radiotherapy or chemotherapy, there were no major differences in the time to surgery across the subgroups compared. The period was marginally longer for those…"

Responses to comments of Reviewer 1 (continued)

Comment 3: The definition of a reference centre or specialized centre as the one with radiotherapy is quite unusual. It would have been better use volume of cases, which is more common as a independent variable. I would suggest a reanalysis taking volume into consideration.

Response 3: The definition of a specialist centre was debated at length by the authors. We agree that hospital volume, if accurate, would be informative. Unfortunately, we don't have patient volume data for these hospitals overall, only the number of cases in our sample. Therefore defining a high-volume centre is difficult. In our data nine centres had the highest patient volumes with 10 to a maximum of 26 surgical procedures for colorectal cancer across the three-year study period, which does not accord with the patient volumes reported in the literature. The definition of a specialist centre as one with a radiotherapy unit was a surrogate for having all cancer treatment modalities available at the one centre, thereby making it a more specialised facility, plus the importance of being able to offer radiotherapy for rectal cancer in particular.

Comment 4: Finally, I am not sure that the best definition of this study design would be retrospective cross-sectional. My proposal would have been retrospective cohort study.

Response 4: We have changed the study design to "retrospective cohort study" in the title and abstract as requested by the reviewer.

Comment 5: The research question is beyond the scope of these variables. The restriction to colonoscopy and the impossibility of having radiotherapy and chemotherapy available makes discussing of the data very difficult. A possible suggestion would be to restrict the analysis to colon cancer, although the sample will be lower.

Response 5: As described in our response to the reviewer's second comment, we are not claiming that this study provides a comprehensive assessment of all the factors influencing the time interval between diagnosis and surgery. We have described these limitations in the Discussion.

The results for colon cases (265 cases, or 65% of the sample) are given in the paper, in the paragraph 4 of the Results section and in Table 3. We have revised the following text in paragraph 4 of the Results to emphasise that the results for colon cancer are less likely to be affected by other treatment types prior to surgery.

"For cases with colon cancer, who should not require pre-operative radiotherapy or chemotherapy, there were no major differences in the time to surgery across the subgroups compared. The period was marginally longer for those…"

Responses to comments of Reviewer 1 (continued)

Comment 6: Previous evidence is quite scarce and it is not well considered in the discussion.

Response 6: As described in the paper, most existing research on this topic has focused on delays prior to diagnosis and this is one of the first studies to examine the pathway between colorectal cancer diagnosis and surgical treatment. Hence there is limited previous evidence to discuss. We have added text in paragraph 3 of the Introduction and paragraph 2 of the Discussion, referring to a recent paper by Torring et al.

Introduction: "A recent prospective study reported that 3-year mortality for CRC patients increased with diagnostic delay beyond one month, particularly for those presenting with serious symptoms."

Discussion: "However we should be mindful that these small delays may compound delays in diagnosis for groups such as migrants and people living in remote areas who have lower screening rates, and that diagnostic delay is associated with increased mortality for patients with CRC."

Reference: "Torring ML, Frydenberg M, Hansen RP, et al. Time to diagnosis and mortality in colorectal cancer: a cohort study in primary care. Br J Cancer 2011;104(6):934-940."

Responses to comments of Reviewer 2

Comment 1: The introduction summarises the literature reasonably well, although it may strengthen the paper if they were to refer to an important paper by Torring et al demonstrating associations in time to diagnosis and colorectal cancer mortality (British Journal of Cancer (2011) 104, 934 – 940).

Response 1: We have added the following underlined text to paragraph 3 of the Introduction and paragraph 2 of the Discussion, referring to the paper by Torring et al.

Introduction: "A recent prospective study reported that 3-year mortality for CRC patients increased with diagnostic delay beyond one month, particularly for those presenting with serious symptoms."

Discussion: "However we should be mindful that these small delays may compound delays in diagnosis for groups such as migrants and people living in remote areas who have lower screening rates, and that diagnostic delay is associated with increased mortality for patients with CRC."

Comment 2: The study uses data from the 45-and-Up Cohort study of approximately 10% of the total eligible NSW population, linked to health data from the Cancer Registry, hospital admissions data (APDC) and Medicare Benefit Schedule (MBS) data. It would be useful to clarify which sources of data were used to identify the date of colonoscopy (the APDC or MBS or both).

Response 2: The following line has been added to paragraph 11 of the Results section.

"Over 90% of the relevant colonoscopies and surgical procedures were identified in the APDC, with just over half of these also identified in the MBS. The remaining colonoscopies were recorded in the MBS only."

Comment 3: In the description of the datasets it should also be stated that this did not allow identification of dates of radiotherapy or chemotherapy. This is brought up in the discussion but I think it should be stated in the methods as it is an important limitation of the data available.

Response 3: We had stated the following in paragraph 9 of the Methods section.

"Chemotherapy and radiotherapy are generally performed on an outpatient basis, for which data were not available, so they were not included in the analysis."

Responses to comments of Reviewer 2 (continued)

Comment 4: On page 12 [second paragraph of Results] the description of key dates is a little confusing. There is no specific definition of the date of diagnosis, only that it was available to the nearest month. Was the date of diagnosis based on the Cancer Registry date, which will often be based on the date of the pathological specimen obtained at colonoscopy? The date of colonoscopy is defined as the last pre-surgery colonoscopy no earlier than two months prior to the month of diagnosis. Without a clear definition of date of diagnosis, this is potentially problematic.

Response 4:
Date of diagnosis used in the analysis was the date recorded by the Central Cancer Registry, supplied to us as month and year only. This is based on the information available in notifications sent to the Registry including pathology reports and hospital forms. For colorectal cancer the date of diagnosis is likely to be based on the pathology form for the specimen obtained via colonoscopy. The following line in paragraph 10 of the Methods has been revised to indicate this.

"The CCR provided data regarding month and year of colorectal cancer diagnosis (the date of the most definitive cancer notification, likely to be based on the pathology form for the specimen obtained via colonoscopy), age at diagnosis, …"

Comment 5: Under the section Sociodemographic and clinical characteristics, it should be clarified if the place of residence was at the level of postcode or collecting district, the latter giving more precise information about socioeconomic disadvantage.

Response 5: The place of residence used in the analysis was the Local Government Area of residence at the time of diagnosis, as recorded by the Central Cancer Registry. We felt this was more relevant to the diagnosis and management of colorectal cancer than the place of residence at the time that the 45 and Up Study questionnaire was completed. We have removed the latter from the list of Sociodemographic and clinical characteristics and amended the text to "~~place~~ Local Government Area of residence at diagnosis" in the description of the variables obtained from the Central Cancer Registry (paragraph 10 of the Methods).

Responses to comments of Reviewer 2 (continued)

Comment 6: While this is described as a population cohort it should be recognised that the final analysed sample actually represents less than 4% of all colorectal cancers diagnosed during the study period. Furthermore, the sample was more likely to be male, Australian-born, have localised disease, live in a rural area and be more disadvantaged socioeconomically. This probably needs to be acknowledged further as a limitation of the study.

Response 6: We have added the following sentence to the section on limitations (paragraph 4 of the Discussion) to reflect this.

"…study participants are not representative of the population due to people in rural areas being oversampled and a possible "healthy volunteer" effect. Our sample of cancer patients represent 4% of all colorectal cancers diagnosed in NSW and were also more likely to be male, Australian-born and have localised disease."

Comment 7: The results are well presented, although there is no discussion about potential problems of multiple statistical testing.

Response 7: We have added the following sentence to the section on limitations (paragraph 4 of the Discussion) to reflect this.

"Some of the marginally statistically significant associations may have arisen by chance due to the large number of variables included in the analyses, but this is not likely to be an explanation for associations with small p-values."

Comment 8: Rectal tumours had a longer pre-surgical treatment interval than colon tumours, although the crude median difference was only 4 days which is unlikely to be clinically important. However, the overall median time of 19 days could be important in the context of additional likely delays along the total diagnostic pathway.

Response 8: The following sentence has been added to paragraph 2 of the Discussion.

"The overall median time to surgery for all cases was 19 days and this could also be important in the context of additional delays along the total diagnostic pathway."

Responses to comments of Reviewer 2 (continued)

Comment 9: The interpretation of differences between rectal and colon cancer is slightly limited in having no data on radiotherapy or MDT assessment. As discussed, the longer time may represent more detailed treatment planning for rectal cancer, which is potentially more important than the duration of the pre-treatment interval. This could perhaps be discussed further.

Response 9: We have revised the following sentence in paragraph 2 of the Discussion to reflect this.

"It may reflect referral to a CRC surgeon rather than a general surgeon, assessment by a multidisciplinary team, or the use of or a referral for assessment of pre-operative radiotherapy for rectal cancer, each of which could lead to better patient outcomes. Further, the crude difference in median time was only four days…"

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort 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
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8-12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-12
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
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	8-12
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	11-12
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13-15, 29 (Figure 1)
		(b) Give reasons for non-participation at each stage	13-14, 29 (Figure 1)
		(c) Consider use of a flow diagram	29 (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14, 23-28 (Tables)
		(b) Indicate number of participants with missing data for each variable of interest	23-28 (Tables)
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	24-28 (Tables)
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	13-15, 24-28 (Tables)
		(*b*) Report category boundaries when continuous variables were categorized	23-28 (Tables)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-18
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	19

*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.