Comorbid conditions delay diagnosis of colorectal cancer: a cohort study using electronic primary care records

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Background: Pre-existing non-cancer conditions may complicate and delay colorectal cancer diagnosis.

Method: Incident cases (aged ⩾40 years, 2007–2009) with colorectal cancer were identified in the Clinical Practice Research Datalink, UK. Diagnostic interval was defined as time from first symptomatic presentation of colorectal cancer to diagnosis. Comorbid conditions were classified as 'competing demands' (unrelated to colorectal cancer) or 'alternative explanations' (sharing symptoms with colorectal cancer). The association between diagnostic interval (log-transformed) and age, gender, consultation rate and number of comorbid conditions was investigated using linear regressions, reported using geometric means.

Results: Out of the 4512 patients included, 72.9% had ⩾1 competing demand and 31.3% had ⩾1 alternative explanation. In the regression model, the numbers of both types of comorbid conditions were independently associated with longer diagnostic interval: a single competing demand delayed diagnosis by 10 days, and four or more by 32 days; and a single alternative explanation by 9 days. For individual conditions, the longest delay was observed for inflammatory bowel disease (26 days; 95% CI 14–39).

Conclusions: The burden and nature of comorbidity is associated with delayed diagnosis in colorectal cancer, particularly in patients aged ⩾80 years. Effective clinical strategies are needed for shortening diagnostic interval in patients with comorbidity.

Cancer survival in England is lower than the European average, particularly for patients aged 65 years or older and in the first year after diagnosis (Coleman et al, 2011). This discrepancy is attributed in part to late diagnosis, which is generally thought to contribute to advanced stage at diagnosis, and thus to the poorer survival observed (Hamilton et al, 2016). Shortening the diagnostic interval (i.e., the time between presenting with a symptom of cancer and

ultimate diagnosis; Weller et al, 2012) was made a specific government public policy priority in *Improving Outcomes: A Strategy for Cancer* (Government, 2011).

Diagnostic intervals decreased between 2001–2002 and 2007–2008 for colorectal and five other cancer sites, and longer diagnostic intervals were associated with increasing age, being female and presenting with symptoms that did not qualify for

referral under national guidelines in place in 2005 (National Institute for Health and Clinical Excellence, 2005; Neal *et al*, 2014; Din *et al*, 2015). Consultation rates generally increase before cancer is diagnosed (Lyratzopoulos *et al*, 2012, 2013, 2015; Shephard *et al*, 2012, 2013, 2015a, b, c; Stapley *et al*, 2012, 2013). These excess consultations may represent 'missed' opportunities for expediting the diagnosis. The 2010 National Cancer Patient Experience Survey reported that the probability of three or more pre-referral consultations was greater in young compared with old patients, in women *vs* men and in those from ethnic minority groups compared with whites (Lyratzopoulos *et al*, 2012), supporting this assertion. Alternatively, the excess consultations may simply reflect an increase in the medical complexity of patients with symptomatic cancer.

Risk factors for cancer—including increasing age, social deprivation and other lifestyle factors such as smoking and obesity (Parkin *et al*, 2011; National Cancer Intelligence Network, 2014; Office for National Statistics, 2016)—are all also associated with multimorbidity, that is, the existence of two or more concurrent diagnoses (Valderas *et al*, 2009, 2015; Violán *et al*, 2014). A cohort study of 99 997 adults in England using The Clinical Practice Research Datalink (http://www.cprd.com/intro.asp) (CPRD) reported that 58 115 (58%) patients had multimorbidity, and accounted for 78% of all consultations made between 1 April 2005 and 31 March 2008 (Salisbury *et al*, 2011). Pre-existing conditions could create competing demands for clinical care (Jaen *et al*, 1994; Nutting *et al*, 2001; Ricci-Cabello *et al*, 2015b), with a higher burden of care making recognition of symptoms and signs less likely. Symptoms identified as risk markers for cancer are also features of other, more common, diseases. These conditions provide reasonable alternative explanations for the early features of cancer, encouraging the patient or clinician to misattribute them to an existing condition rather than a new one, such as cancer (Lyratzopoulos *et al*, 2015). This problem may be more severe the higher the number of conditions present, and multimorbidity may therefore obscure the diagnosis of cancer, lengthening the diagnostic interval.

There is relatively little research exploring associations between multimorbidity and cancer diagnosis. A significant event audit was conducted in 92 general practices in the North of England Cancer Network for the diagnosis of lung cancer (Mitchell *et al*, 2013). Few patients had the headline symptom of haemoptysis, whereas pre-existing chest disease was common. This comorbidity often offered a plausible alternative explanation for the symptoms, such as infection, with no further diagnostic possibilities considered initially. This delayed investigation of some of those with cancer. A prospective cohort study of patients referred for suspicion of colorectal cancer in England investigated the symptoms, clinical factors and socio-demographic factors associated with time to diagnosis of colorectal cancer, other abdominal cancer or non-cancer diagnoses. The study suggested that patients and healthcare providers may normalise persistent rectal bleeding, and that the presence of gastrointestinal comorbidities delays diagnosis, probably through misattribution of symptoms to pre-existing conditions. The same study also found that patients with self-reported anxiety or depression experienced a longer time to diagnosis (cancer or otherwise), indicating altered perception of the seriousness of physical symptoms in the presence of a mental health condition (Walter *et al*, 2016). No study has investigated the impact of increasing burden from morbidity on diagnostic interval.

We explored the associations between diagnostic interval, demographics and number of conditions in a large cohort of patients with colorectal cancer, and hypothesised that greater morbidity would increase diagnostic interval. Furthermore, we investigated the relative effects of conditions that are unrelated to colorectal cancer, but could compete for clinical attention, and of conditions providing alternative explanations for key diagnostic features of cancer.

MATERIALS AND METHODS

Data set. The Clinical Practice Research Datalink (http://www.cprd.com/intro.asp) (CPRD) is the largest database of electronic, anonymised longitudinal medical records from primary care in the world (http://www.cprd.com/intro.asp, accessed 14 Feb 2017). At the time the data for this study were recorded, the database (then known as the General Practice Research Database, GPRD) contained over 5.4 million active patient records, drawn from over 670 primary care practices within the UK, including all consultations and diagnoses. Our patient inclusion criteria were:

- A record of a primary diagnosis of incident colorectal cancer between 1st January 2007 and 31st December 2009. Cases were excluded where additional code(s) before the cancer code indicated palliative care or oncology treatment (including bowel surgery, chemotherapy or radiotherapy). In these instances, it was unclear when the diagnosis was made.
- At least 1 full year of CPRD records preceding the cancer diagnosis, with at least one consultation in that time (patients who did not consult provided no opportunity for the GP to be involved in their cancer diagnosis).
- Age at diagnosis was 40 years or older. Younger patients were excluded owing to the rarity of colorectal cancer diagnoses in this age group, in keeping with similar primary care studies (Hamilton, 2009; Neal *et al*, 2014; Din *et al*, 2015).

Symptom codes. Eleven features of colorectal cancer were selected based on previous studies in primary care (Hamilton *et al*, 2005, 2008, 2009; Hippisley-Cox and Coupland, 2012). Specific symptoms were rectal bleeding, diarrhoea, constipation, change in bowel habit, rectal mass, abdominal pain, and abdominal mass; nonspecific features were weight loss, appetite loss, fatigue and anaemia (determined from a blood test result).

Diagnostic interval. The date of diagnosis was taken as that of the first entry of a code for colorectal cancer (Hamilton, 2009; Neal *et al*, 2014). We defined a patient's diagnostic interval as the length of time (in days) between the first presentation of a symptom coded in their medical record and their date of diagnosis (Weller *et al*, 2012). We restricted analyses to symptoms occurring in the year preceding the patient's cancer diagnosis. It is possible for patients to experience symptoms more than a year before diagnosis (Corner *et al*, 2005). It is difficult, however, to establish whether these early symptoms are a result of the cancer, or of benign or incidental conditions, such as those also identified in the present study. In the CAPER studies, no symptom present more than a year before diagnosis was reliably more common in cases of colorectal cancer than in controls (Hamilton, 2009). Diagnostic intervals were therefore restricted to a maximum of 365 days to minimise the risk of misattributing a symptom as the index symptom of cancer. Patients with no identifiable symptom codes were excluded as a diagnostic interval could not be calculated for them, following the methodology of previous studies (Hamilton, 2009; Neal *et al*, 2014; Din *et al*, 2015).

Multimorbidity. To explore the effects of the two mechanisms by which multimorbidity is hypothesised to lengthen diagnostic interval, we collated two lists of conditions; designated 'competing demands' and 'alternative explanations'. While both may result in diagnostic delay of cancer, their mechanisms of action would be essentially different. The first list would place additional demands on patient care, and would thereby limit the ability of GPs to focus on key symptoms, while the latter may falsely reassure GPs that key symptoms could be reasonably attributed to pre-existing conditions, rather than to a new one.

For the 'competing demand' set of conditions, we selected 12 important chronic conditions unrelated to colorectal cancer, 11 of which are components of the Quality and Outcomes Framework (QOF); the pay-for-performance scheme in the UK. QOF conditions are well defined, and recording is likely to be reliable and comprehensive, being linked to practice payments. The 11 conditions were coronary heart disease, heart failure, hypertension, asthma, chronic obstructive pulmonary disease (COPD), dementia, depression, chronic kidney disease (CKD), epilepsy, osteoporosis and rheumatoid arthritis. Anxiety was also included as a competing demand, as previous work has linked anxiety to increased diagnostic intervals (Robertson *et al*, 2004; Walter *et al*, 2016). These conditions are defined by Read Codes (Herrett *et al*, 2010) specified by the QOF business rules, which were obtained from the code-list repository ClinicalCodes.org (https://clinicalcodes.rss.mhs.man.ac.uk/), verified by a GP (JMV), and then applied to the CPRD data to identify patients with each chronic condition. Some Read Codes for anxiety or depression included the other condition (e.g., E200300 'anxiety with depression'), and initial modelling treating these conditions separately revealed multicollinearity between the two. We therefore combined anxiety and depression into one condition-group.

We identified conditions or therapies that may provide alternative explanations for each of the following specific features of colorectal cancer: abdominal pain, rectal bleeding, irregular bowel movement (diarrhoea and/or constipation) and anaemia. Two experienced GPs and a researcher with expertise in colorectal cancer sequentially considered for each key symptom/sign the following plausible alternative explanations: frequent conditions that are part of the differential diagnosis of those symptoms/signs in Primary Care, and secondary effects of medications frequently used in the primary care. A long list of candidate conditions was iteratively reviewed until the final set of comorbid conditions was agreed by consensus. The six conditions/therapies selected were endometriosis (abdominal pain), diverticulosis or diverticulitis (rectal bleeding, irregular bowel movement and abdominal pain), haemorrhoids (rectal bleeding), irritable bowel syndrome (IBS; irregular bowel movement and abdominal pain), warfarin therapy (anaemia) and codeine therapy (irregular bowel movement). Read Codes for each of these conditions were identified by a clinical member of the research team (JMV) using a code library provided by CPRD. These Read Codes were then used to identify patients with each condition. Patients' therapy records were inspected to ascertain if they were prescribed warfarin or codeine.

We identified patients with inflammatory bowel disease (IBD), which is both an alternative explanation for symptoms (irregular bowel movement, abdominal pain and rectal bleeding) and a risk factor for colorectal cancer. Finally, we also identified patients with cancers other than colorectal, using code-lists and procedures described elsewhere (Neal *et al*, 2014).

Patients were only categorised as having a comorbidity if a code relating to the diagnosis was entered before their first cancer symptom. For each patient, we calculated their number of 'competing demand' conditions, their number of 'alternative explanation' conditions, and their total number of conditions. Both IBD and non-colorectal cancer were included in the count of total number of conditions.

Patient characteristics. We grouped patients into 5-year age bands, and combined groups that contained < 10% of the sample to facilitate subgroup analyses. We also calculated each patient's mean yearly consultation rate, averaging their number of consultations over the 1–3 years before their colorectal cancer diagnosis, as data availability permitted (each patient had at least 1 year of the data preceding diagnosis).

Data analysis. The relationships between key variables were explored graphically. The diagnostic interval had a highly skewed distribution, and therefore descriptive analyses report the median diagnostic interval and the associated interquartile range. For all regression analyses, diagnostic intervals were log transformed (0.1 was added to each patient's diagnostic interval prior to the transformation in order to retain patients with values of 0 days), and consequently are reported as geometric means with 95% confidence intervals. Unadjusted univariate linear regressions investigated the separate effect of the predictor variables of age, gender, consultation rate, the three condition counts, presence of IBD and presence of non-colorectal cancer on diagnostic interval. A regression model then included predictors significant in the univariate analyses ($P < 0.10$), unless there were indications of multicollinearity. A final model compared the effect on diagnostic interval of each condition separately, controlling for age and gender in order to identify any specific condition which may in itself pose a particular challenge in the diagnosis of cancer. All analyses were conducted in Stata\SE version 14.

RESULTS

The CPRD supplied the records of 6287 patients with colorectal cancer. Out of these, 454 (7%) were excluded as they had a treatment code, a palliative care code or a code indicating metastatic spread before their first cancer code, casting doubt on the date of diagnosis. Of the remaining 5833 cases, a further 1321 (23%) patients with no recorded features of colorectal cancer in the year preceding diagnosis were excluded, as no diagnostic interval could be calculated. The remaining 4512 patients are summarised in Table 1, showing that the total number of comorbid conditions increased sharply with age and that mean yearly consultation rates were higher for participants with a greater number of conditions. 1127/4512 (25.0%) had at least one 'competing demand' condition in addition to at least one 'alternative explanation' condition.

Figure 1 shows that diagnostic interval increased non-linearly with greater morbidity, with no clear trend up to 75–79 years of age, but with a sizeable increase in diagnostic interval thereafter. This graph appears to show a clear interaction effect between age and morbidity, such that the increase in diagnostic interval after 80 years of age only occurs in the groups reporting at least one comorbid condition, with no clear trend between age and diagnostic interval for those without comorbidities.

All variables explored as potential predictors in the unadjusted univariate analyses were significantly associated with diagnostic interval (Supplementary Table 1). There was strong multicollinearity between the count of total number of conditions and the number of 'competing demand' conditions (as expected): only the counts of 'competing demand' and 'alternative explanation' conditions entered the main model. The strong relationship between consultation rate and morbidity (Table 1) gave rise to multicollinearity with the count of 'competing demand' conditions, so consultation rate was excluded.

With the remaining predictors included (Table 2), gender was no longer significantly associated with diagnostic interval. A single 'competing demand' condition delayed diagnosis by 10 days, and a single 'alternative explanation condition' delayed diagnosis by 9 days. Patients with four or more 'competing demand' conditions had intervals over one month longer than those without comorbid conditions. Inflammatory bowel disease, which is both an alternative explanation of symptoms and a risk factor for colorectal cancer (Lukas, 2010; Kim and Chang, 2014), increased the diagnostic interval by 26 days.

A further model (Table 3) tested the interaction on diagnostic interval between age and morbidity (Figure 1). This model supports there being no clear trend in diagnostic interval across age for patients with no comorbidities, in contrast to increasing diagnostic intervals across age, especially for those aged ⩾80 years,

Table 1. Sample demography and morbidity

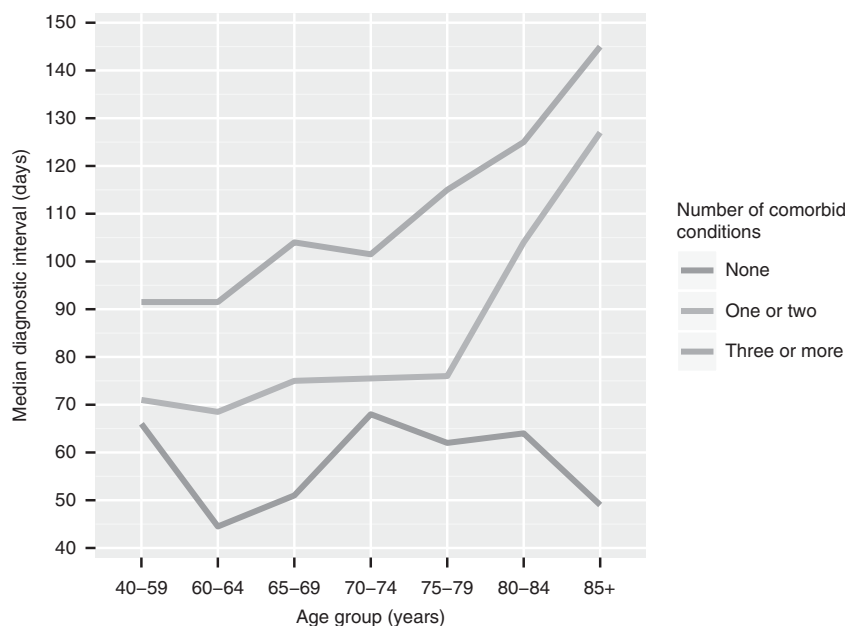|	n (%)	Median diagnostic interval (IQR)	Mean no. of conditions (s.d.)	Mean yearly consultation rate (s.d.)
Full sample	4512 (100.0)	84 (39, 192)	2.0 (1.6)	7.7 (6.4)
Men	2436 (54.0)	79 (37, 176)	1.8 (1.5)	7.5 (6.0)
Women	2076 (46.0)	89 (40, 210)	2.1 (1.7)	8.1 (6.7)
Age group (years)				
40–59	619 (13.7)	71 (35, 147)	1.1 (1.2)	5.3 (4.8)
60–64	510 (11.3)	65 (29, 130)	1.5 (1.3)	6.5 (6.1)
65–69	562 (12.5)	75.5 (38, 148)	1.8 (1.5)	7.3 (5.6)
70–74	683 (15.1)	78 (38, 178)	2.0 (1.6)	7.8 (6.1)
75–79	821 (18.2)	80 (38, 194)	2.2 (1.6)	8.5 (6.2)
80–84	685 (15.2)	109 (50, 234)	2.5 (1.8)	9.2 (7.2)
85 +	632 (14.0)	123.5 (50, 263)	2.5 (1.7)	8.8 (7.3)
Number of 'competing demand' conditions				
None	1221 (27.1)	64 (32, 143)	—	4.6 (4.0)
One	1378 (30.5)	80.5 (39, 176)	—	7.5 (5.4)
Two	990 (21.9)	89.5 (42, 206)	—	8.8 (6.0)
Three	564 (12.5)	113 (49, 241.5)	—	10.3 (7.3)
Four or more	359 (8.0)	136 (59, 258)	—	12.7 (9.2)
Number of 'alternative explanation' conditions				
None	3098 (68.7)	77 (37, 175)	—	7.0 (5.9)
One	1125 (24.9)	101 (42, 217)	—	8.7 (6.5)
Two or more	289 (6.4)	107 (50, 245)	—	11.9 (8.3)
Abbreviation: IQR = interquartile range.				

Figure 1. Median diagnostic intervals across age groups by total number of conditions.

for those with at least one comorbidity. As a sensitivity analysis, we stratified our key findings by two age categories (40–74 years, 75 + years). No notable differences were found between these models and that presented in Table 2.

Out of the 20 studied conditions and therapies, four were significantly associated with longer diagnostic intervals (Table 4). These were inflammatory bowel disease, coronary heart disease, diverticulosis or diverticulitis and anxiety/depression.

DISCUSSION

The current study is one of the first to investigate the specific impact of the burden and nature of comorbid conditions on time

to diagnosis of colorectal cancer. There was a clear association between increasing comorbidity and longer time to diagnosis in colorectal cancer, with the increase ranging from 9 to 32 days, and seen particularly in those aged 80 years or greater. This finding was observed for both genders, and little difference in effects was seen between conditions we considered to be unrelated to a colorectal cancer diagnosis (the 'competing demand' conditions) and those giving a plausible diagnostic alternative to colorectal cancer.

The observed increases in time to diagnosis reported in the present study are clinically significant. They correspond to an increase of 13% for people with a single 'competing demand' condition, and of 12% for people with a single 'alternative explanation' condition. For those with four or more 'competing demand' conditions, the increase amounts to 41%, and for the

Table 2. Regression model estimating associations between diagnostic interval and number of 'competing demand' and/or 'alternative explanation' conditions

	Coeff. (95% CI)	P-value	Exponentiated coeff. (95% CI)	Diagnostic interval change in days (95% CI)[a]
Female gender	0.02 (− 0.05, 0.09)	0.544	1.02 (0.95, 1.09)	2 (− 3, 7)
Age group (years)[b]	0.07 (0.05, 0.09)	<0.001		
40–59 (reference)	0.00	—	1.00	
60–64	− 0.13 (− 0.27, 0.02)	0.083	0.88 (0.76, 1.02)	− 9 (− 18, 1)
65–69	0.05 (− 0.09, 0.18)	0.505	1.05 (0.91, 1.20)	4 (− 7, 15)
70–74	0.06 (− 0.08, 0.19)	0.395	1.06 (0.93, 1.21)	5 (− 6, 16)
75–79	0.10 (− 0.03, 0.23)	0.132	1.11 (0.97, 1.26)	8 (− 2, 20)
80–84	0.32 (0.19, 0.45)	<0.001	1.38 (1.21, 1.57)	29 (16, 44)
85 +	0.34 (0.21, 0.48)	<0.001	1.41 (1.23, 1.62)	31 (17, 47)
No. of 'competing demand' conditions[b]	0.09 (0.06, 0.12)	<0.001		
None (reference)	0.00	—	1.00	
One	0.12 (0.03, 0.21)	0.009	1.13 (1.03, 1.24)	10 (2, 18)
Two	0.20 (0.10, 0.30)	<0.001	1.22 (1.11, 1.34)	17 (8, 26)
Three	0.30 (0.18, 0.41)	<0.001	1.34 (1.20, 1.51)	26 (15, 39)
Four or more	0.35 (0.20, 0.49)	<0.001	1.41 (1.22, 1.63)	32 (17, 49)
No. of 'alternative explanation' conditions[b]	0.09 (0.03, 0.14)	0.003		
None (reference)	0.00	—	1.00	
One	0.12 (0.04, 0.19)	0.003	1.12 (1.04, 1.21)	9 (3, 16)
Two or more	0.13 (− 0.01, 0.27)	0.061	1.14 (0.99, 1.32)	11 (0, 24)
Inflammatory bowel disease	0.29 (0.17, 0.41)	<0.001	1.34 (1.18, 1.51)	26 (14, 39)
Non-colorectal cancer	0.11 (− 0.05, 0.28)	0.173	1.12 (0.95, 1.32)	9 (− 4, 24)

Abbreviation: CI = confidence interval.
[a]Calculated using the geometric mean (as used by the log-tranformed regression model) of 76.71.
[b]Sensitivity analyses entered these covariates as ordinal variables to assess their global effects, which are reported above the effects of their separate levels.

Table 3. Interaction between age group and presence of comorbidity on diagnostic interval

	Coeff. (95% CI)	P-value	Exponentiated coeff. (95% CI)	Diagnostic interval change in days (95% CI)[a]
Age group by comorbidity				
40–59, no comorbidity (reference)	0.00	—	1.00	—
40–59, ⩾1 comorbidity	0.04 (− 0.15, 0.23)	0.655	1.04 (0.86, 1.26)	3 (− 11, 20)
60–79, no comorbidity	− 0.17 (− 0.34, 0.00)	0.053	0.84 (0.71, 1.00)	− 12 (− 22, 0)
60–79, ⩾1 comorbidity	0.20 (0.06, 0.35)	0.006	1.22 (1.06, 1.41)	17 (5, 32)
80 +, no comorbidity	0.08 (− 0.14, 0.30)	0.466	1.08 (0.87, 1.35)	6 (− 10, 27)
80 +, ⩾1 comorbidity	0.53 (0.39, 0.68)	0.000	1.71 (1.47, 1.98)	54 (36, 75)

Abbreviation: CI = confidence interval. The model controlled for gender. 40–59 year olds with no comorbidities were the reference group.
[a]Calculated using the geometric mean (as used by the log-tranformed regression model) of 76.71.

single condition of IBD the increase is 34%. In addition, it is important to note that these effects are independent and that a quarter of patients had both types of conditions.

Strengths and limitations. The main strength of this study is its primary care setting, which is the commonest starting point for cancer diagnosis. Features of possible cancer were collected before the diagnosis was established, eliminating recall bias. The study was large and generalisable, as CPRD data is representative of patients across the UK. A further key strength of this study is the modelling of both the burden and the nature of comorbidity. Our categorisation of comorbidities into 'competing demand' conditions and alternative diagnoses was based on clinical plausibility. In oo maximise reliability of coding, all the comorbid conditions in the category were part of the AQOF. These illnesses would generally impose a greater burden of care than conditions not included in the incentive scheme. Other clinicians may have generated different conditions and categories. We acknowledge that this is a novel approach to the classification of comorbidity and as such we cannot rely on or compare our methods with a gold standard methodology for the identification of alternative explanations. Further research in the area would be needed. Also, it may be too simplistic to assume from the very similar increases in

diagnostic interval for the two main groups that all comorbidities have the same effect on diagnostic interval: it remains possible they act through different mechanisms, but with similar sized effects.

The main disadvantage of using electronic records as our data source is that we were reliant upon the quality of the doctors' recording for symptoms. Cancer recording is very good in the CPRD (Dregan *et al*, 2012; Boggon *et al*, 2013). Linkage to the cancer registry was not available, and would have allowed us to check the date of diagnosis, though again discrepancies between the CPRD and cancer registry on this point are minor (Tate *et al*, 2009). Patient records have been widely used in similar cancer studies before, including the CPRD data. Symptoms may be unvoiced by the patient, not recorded by the GP, or documented solely in the text, such that the records are inaccessible to researchers: the latter appears to happen less where a symptom is known to be strongly associated with cancer (Price *et al*, 2016). Laboratory data and prescribing data are of very high quality, so the study is unlikely to have overlooked patients with anaemia, or those who have been prescribed warfarin or codeine. We only studied symptoms previously reported to be associated with colorectal cancer, including most of those in contemporaneous and current NICE guidances (NICE, 2005, 2015). Nearly a quarter of eligible patients had no apparent feature of colorectal cancer in

Table 4. Regression model estimating associations between diagnostic interval and individual conditions

	Coeff. (95% CI)	P-value	Exponentiated coeff. (95% CI)	Diagnostic interval change in days (95% CI)[a]
'Competing demand' conditions				
Anxiety/depression	**0.11 (0.03, 0.20)**	**0.007**	**1.12 (1.03, 1.22)**	**9 (3, 17)**
Asthma	0.06 (−0.05, 0.16)	0.284	1.06 (0.95, 1.18)	5 (−4, 13)
Chronic kidney disease	0.04 (−0.06, 0.13)	0.450	1.04 (0.94, 1.14)	3 (−4, 11)
COPD	0.12 (−0.01, 0.25)	0.075	1.13 (0.99, 1.28)	10 (−1, 22)
Coronary heart disease	**0.18 (0.09, 0.27)**	**<0.001**	**1.20 (1.09, 1.31)**	**15 (7, 24)**
Dementia	−0.05 (−0.34, 0.24)	0.722	0.95 (0.71, 1.27)	−4 (−22, 20)
Diabetes mellitus	0.16 (−0.07, 0.39)	0.164	1.18 (0.94, 1.48)	14 (−5, 37)
Epilepsy	0.04 (−0.07, 0.14)	0.510	1.04 (0.93, 1.15)	3 (−5, 12)
Heart failure	0.11 (−0.03, 0.26)	0.132	1.12 (0.97, 1.29)	9 (−3, 23)
Hypertension	0.04 (−0.03, 0.11)	0.254	1.04 (0.97, 1.11)	3 (−2, 9)
Osteoporosis	0.00 (−0.16, 0.17)	0.986	1.00 (0.85, 1.18)	0 (−12, 14)
Rheumatoid arthritis	0.23 (−0.02, 0.48)	0.069	1.26 (0.98, 1.62)	20 (−1, 48)
'Alternative explanation' conditions				
Codeine therapy	0.06 (−0.09, 0.22)	0.423	1.07 (0.91, 1.24)	5 (−7, 19)
Diverticulosis/diverticulitis	**0.17 (0.03, 0.30)**	**0.015**	**1.18 (1.03, 1.35)**	**14 (3, 27)**
Endometriosis	−0.31 (−0.9, 0.28)	0.299	0.73 (0.41, 1.32)	−21 (−46, 24)
Haemorrhoids	0.02 (−0.07, 0.12)	0.632	1.02 (0.93, 1.13)	2 (−5, 10)
Irritable bowel syndrome	0.11 (−0.02, 0.25)	0.103	1.12 (0.98, 1.29)	9 (−2, 22)
Warfarin therapy	0.06 (−0.09, 0.22)	0.409	1.07 (0.92, 1.24)	5 (−6, 19)
Inflammatory bowel disease	**0.29 (0.16, 0.41)**	**<0.001**	**1.33 (1.18, 1.51)**	**26 (14, 39)**
Non-colorectal cancer	0.11 (−0.05, 0.28)	0.178	1.12 (0.95, 1.32)	9 (−4, 25)

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease.
[a]Calculated using the geometric mean (as used by the log-tranformed regression model) of 76.71. This model controlled for age and gender. Conditions in bold were significantly associated with diagnostic interval.

the year before diagnosis: although some of this will represent under-recording, though some will reflect the quarter of patients who present as an emergency, often bypassing primary care (McPhail *et al*, 2013).

Comparison with previous studies. Our findings are supported by a prospective cohort study of patients referred for suspicion of colorectal cancer in two regions in England. The study reported that anxiety, depression and gastrointestinal comorbidities were associated with longer times to diagnosis of colorectal cancer, other abdominal cancers or non-cancer conditions (Walter *et al*, 2016). A pre-existing diagnosis of dementia is reported to be associated with under-diagnosis or post-mortem diagnosis of colon cancer, but the diagnostic interval was not reported (Gupta and Lamont, 2004). A small qualitative study reported weak evidence that early presentation with a possible symptom of colorectal cancer may, perversely, have contributed to diagnostic delay because the symptom was normalised by the patient and/or the GP. This may be because a symptom was falsely attributed to a benign condition, for example rectal bleeding initially attributed to existing haemorrhoids, or the patient was investigated but there were negative findings on colonoscopy (Bain *et al*, 2002). A cohort study in Scotland reported that the odds of delayed diagnosis were doubled by a past history of depression or anxiety. The authors ascribed this to the misattribution of nonspecific abdominal symptoms to benign gastrointestinal conditions, which are relatively common in patients with depression or anxiety (Robertson *et al*, 2004).

The relationship between diagnostic interval and age is inconsistent athecross cancers, though overall diagnostic intervals increase with age by an estimated 7.8 days (95% CI 6.4–9.1) per decade of age (Din *et al*, 2015). Survival from cancer worsens with age (Quaresma *et al*, 2015). The increase in multimorbidity with age has been well-characterised (Salisbury *et al*, 2011; Barnett *et al*, 2012; Violán *et al*, 2014). We hypothesised that some of the worse survival in older age groups could relate to diagnostic delay caused in turn by comorbidity, and our results support this, with the increase in diagnostic intervals considerably greater than the 5.4 days (95% CI 2.4–8.5) decrease seen in the first 5 years of 2-week

clinics for urgent investigation of suspected cancer (Neal *et al*, 2014).

Implications for practice and research. The crucial point is whether these modest, but real, delays in diagnosis matter in terms of reducing survival (or delaying treatment of symptoms). For some patients, the delay will be immaterial; for others, tumour progression or a complication may occur. It is clear from analysis of several international cohorts (Torring *et al*, 2011; Torring *et al*, 2012) that survival worsens with diagnostic delay. The co morbid patients in this study are already disadvantaged by their comorbidity; additional disadvantage—even if modest—is unhelpful.

The impact of the burden and nature comorbidity on cancer diagnosis has received little attention so far. Our observations merit replication using alternative data sources, using expanded lists of comorbid conditions and exploring the potential impact on different cancer sites. These studies should include theoretically sound models that account for the possible different mechanisms that may operate simultaneously. They include the competing demands placed by both chronic and acute conditions, the presence of known risk factors, or the potential misattribution of signs and symptoms to existing conditions, among others (Valderas, 2015; Ricci-Cabello *et al*, 2015a). Pending replication of our observations, effective interventions for minimising diagnostic delays that focus on the burden and nature of comorbid conditions would be needed, especially in patients aged over 80 years. This may necessitate creation of evidence-based guidelines for the review of patients with a possible cancer symptom who are not offered investigation (the so-called 'safety-netting'), which incorporate specific recommendations for comorbid patients.

CONCLUSIONS

This is one of the first studies to investigate the impact of the burden and nature of existing comorbid conditions on time to diagnosis of cancer. An increased time to diagnosis in colorectal cancer, ranging from 9 to 32 days, was associated with conditions

that give a plausible diagnostic alternative, or that are unrelated to colorectal cancer, yet place competing demands at the time of diagnosis. Effective clinical strategies are needed for shortening the diagnostic interval in the presence of comorbidity, which should be particularly targeted at patients aged 80 years or older.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

LM, SP, JMV and WH designed the study. SP and LM prepared the data set, and LM conducted the analyses. All authors interpreted the results, and were involved in drafting and revising the manuscript. JMV will act as guarantor.

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