Socioeconomic inequalities in

colorectal cancer survival

in England and Japan

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Declaration

I, Mari Saito, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date:

09 May 2019

Abstract

Large improvements in cancer survival have been seen in the last two decades due to improvement in early diagnosis and treatment. However, inequalities in cancer survival remain, not only between but also within countries; survival varies by gender, age, ethnicity and socioeconomic status. Notably, socioeconomic inequalities in cancer survival were observed in England and part of Japan, despite healthcare systems based on universal health coverage. Particularly, colorectal cancer (CRC) has a wide range of variability in its survival by deprivation. For example, 3 to 10% difference in 1-year net survival for CRC between the least and the most deprived has been reported in both countries. However, the mechanisms of socioeconomic inequalities in cancer survival are still not fully understood.

I examined whether socioeconomic inequalities in CRC treatment and survival existed in current data, and explored factors associated with the inequalities by investigating data from whole England and Osaka University Hospital in Japan.

Firstly, I examined socioeconomic disparities in receipt of major surgery for the primary lesion and the postoperative mortality. Secondly, I examined the socioeconomic gap in CRC survival using flexible parametric models. Lastly, I proceeded to mediation analysis, a novel technique, to investigate the mechanism of survival inequalities.

In England, socioeconomic inequalities in survival existed for both colon and rectal cancer in the stages of potential for cure. There were socioeconomic inequalities in receipt of surgery for rectal cancer, and in postoperative mortality for colon cancer in England. In Japan, no socioeconomic inequalities existed in receipt of major surgery and survival.

Results of mediation analyses revealed that, in England, reducing emergency presentation for both colon and rectal cancer and improving postoperative care for colon cancer may reduce the survival inequalities. In Japan, further investigation with a larger population is needed to determine the survival inequalities and understand its mechanism.

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Numbers	
5-FU	Fluorouracil
95% CI	95% confidence interval
A	
ADI	Area Deprivation Index (Japan)
ADL	Activities of daily living (Japan)
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
APER	Abdominoperineal excision of the rectum
AR	Anterior resection
ASA grade	American Society of Anesthesiologists grade
C	
CRC	Colorectal cancer
CRT	Chemoradiotherapy
CT	Computed tomography
D	
DAG	Directed acyclic graph
DCH	Designated Cancer Hospital (Japan)
df	Degrees of freedom
DPC	Diagnosis Procedure Combination (Japan)
E	
EGFR	Epidermal Growth Factor Receptor
EHR	Excess hazard ratio
EMR	Endoscopic mucosal resection
ERUS	Endorectal ultrasound
ESD	Endoscopic submucosal dissection
F	
FFS	Fee-for-service
FIT (iFOBT)	Faecal immunochemical test (immunochemical faecal occult blood test)
FOBT	Faecal occult blood test
FOLFOX	Folinic acid, 5-FU and oxaliplatin
FPM	Flexible parametric model
G	
gFOBT	Guaiac-based faecal occult blood test
H	
HES	Hospital Episode Statistics (England)
HR	Hazard ratio
I	
ICD-10	International Classification of Diseases tenth version
ICU	Intensive care unit
IMD	Index of Multiple Deprivation (England)

L	
LSHTM	London School of Hygiene & Tropical Medicine
M	
MAR	Missing at random
MDT	Multidisciplinary team
MHLW	Ministry of Health, Labour and Welfare (Japan)
MRI	Magnetic resonance imaging
N	
NBOCA	National Bowel Cancer Audit (England)
NOS	Newcastle-Ottawa Scale
NICE	National Institute for Health and Care Excellence (England)
NIE	Natural indirect effect
NHS	National Health Service (England)
O	
OECD	Organisation for Economic Co-operation and Development
OPCS-4	Office of Population Censuses and Surveys fourth version
OR	Odds ratio
OUH	Osaka University Hospital
P	
P4P	Pay for performance
PM	Proportion mediated
S	
SCPRT	Short-course preoperative radiotherapy
SES	Socioeconomic status
T	
TCE	Total causal effect
TEM	Transanal endoscopic microsurgery
TME	Total mesorectal excision
TVC	Time-varying covariate
TVE	Time-varying effect
U	
UHC	Universal health coverage
UICC	Union for International Cancer Control
UK	United Kingdom
W	
WHO	World Health Organization

Chapter 1: Introduction

1.1 Global burden of cancer

Worldwide, cancer is a leading cause of death; in 2018, new cancer cases were estimated to be 18.1 million [1]. The disease has accounted for an estimated 9.5 million deaths in 2018, with the most common cancer sites of the deaths being lung, colorectal, stomach, liver and breast [1]. Significant improvements in cancer survival have been seen in the last two decades. This has been due to improvements in early diagnosis and treatment. However, inequalities in cancer survival remain, not only between but also within countries; survival varies by gender, age, ethnicity and socioeconomic status (SES). Notably, socioeconomic inequalities in cancer survival have been observed in England and a part of Japan, despite the national healthcare systems based on universal health coverage (UHC). In particular, colorectal cancer (CRC) has a wide range of variability in its survival by SES. For example, 3 to 10% difference in the one-year net survival for CRC has been reported between the least and the most deprived groups in both countries [2, 3].

Determinants of cancer survival include tumour (stage), patient (age, comorbidities and awareness [4]) and healthcare system factors (prompt access to specialist investigations, diagnostic assessment and stage-appropriate treatment) [5]. Previous research has examined factors such as perceived barriers to timely presentation [6] and the role of primary care in ensuring timely access to diagnosis [7]. However, the mechanism of how cancer care affects inequalities in cancer survival is not fully understood.

In this thesis, I examine whether the socioeconomic inequalities in survival exist in the current data and explore which factors could explain these inequalities by investigating data from England and Japan. Both countries have well-established UHCs, but England has a history of investigating socioeconomic inequalities, while Japan has only begun to examine them. I use the example of CRC since it is one of the five most common cancers affecting males and females in both countries.

1.2 Socioeconomic inequalities in cancer survival in countries with universal health coverage

1.2.1 Universal health coverage

Universal health coverage aims to offer quality healthcare services to all people according to their need, removing both financial and non-financial barriers as far as possible [8]. Non-financial barriers can mean acceptable healthcare services, for example in terms of quality of care delivered or distance to these services [8, 9].

Universal health coverage has three dimensions: the breadth, depth and height of coverage. The breadth means the proportion of the population covered, the depth the range of quality services covered, and the height the proportion of healthcare costs covered [10].

Although the extent of each dimension covered is different by UHC countries, basically, UHC should ensure financial protection and equity of access to healthcare. However, even in countries achieving UHC, socioeconomic inequalities in cancer care have been reported [11].

1.2.2 Socioeconomic inequalities and terminology

Kawachi *et al.* (2002) defined SES as an individual's social and economic position related to others and consists of education, income and occupation [12]. Deprivation can be defined in two ways: absolute and relative [12-14]. Absolute deprivation is the inability to satisfy basic human needs (food and shelter) [12]. Relative deprivation is the deprivation relative to the standards in a society [12]. Socioeconomic inequalities in health partly reflect the consequence of relative deprivation [12].

Strictly speaking, the term socioeconomic 'inequalities' in survival means variations in survival among patients with different socioeconomic backgrounds. Inequalities do not involve any moral judgement [12]. On the other hand, 'inequity' implies inequalities which are unfair, unnecessary, systematic and socially produced, so avoidable (amenable) [9, 12, 15].

Equity in healthcare can be seen in two ways. Firstly, horizontal equity is 'equal treatment for equal need'. The principle is that people with the same level of need should be assured of equal access, use or expenditure [9]. Secondly, vertical equity means ‘unequal treatment for unequal need’.

In this thesis, I defined that the need is the ‘capacity to benefit from treatment’. Thus, the CRC patients, at the same stage and the same general condition should be offered equal treatment, irrespective of their socioeconomic circumstances. I assess how much of the effect of SES on survival could be explained by socioeconomic inequalities in healthcare access.

1.2.3 Study rationale: why focusing on healthcare system to tackle health inequalities?

Inequalities in health can result from various causes. The Lalonde Report in 1974 suggested a conceptual model for the determinants of health [16]. In the 'health field' concept, health is determined by genetic predispositions, behaviour and lifestyle, environment, and healthcare systems. Subsequently, Whitehead and Dahlgren reported a framework for broader health determinants. Solving health inequalities not only requires improving access to essential facilities and services (i.e. healthcare systems), strengthening individuals and communities (to be able to make healthier choices) and encouraging macroeconomic and cultural changes, but it also requires equal distribution of these factors [17]. Healthcare systems are considered as 'down-stream factors', and other factors are considered as 'up-stream factors'. For cancer, as shown in Figure 1.1, other than healthcare system factors, a patient's health-seeking behaviour may have an impact on the timeliness of diagnosis. Lifestyle (e.g. smoking, obesity), age, comorbidities and genetic predispositions can also be potentially associated with survival inequalities.

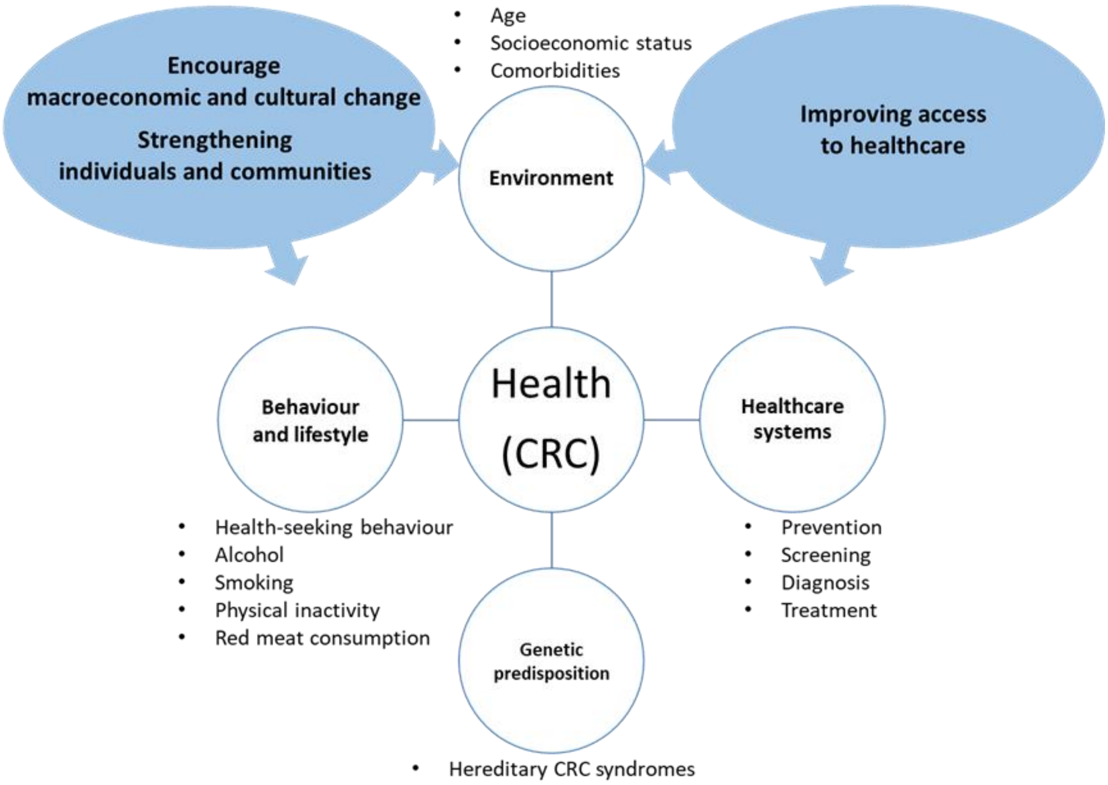

Figure 1.1 Health field concept for colorectal cancer

Bullet points indicate examples in CRC. Modification from source: Lalonde, Whitehead and Dahlgren [16, 17].

When we consider an association between SES and cancer care, socioeconomic differences in access to cancer care can be influenced by multiple factors. As shown in Figure 1.2, SES is primarily defined by education, occupation and income, but is also influenced by country affluence. A country's affluence influences capacity in healthcare resources and the primary and secondary prevention of CRC, such as lifestyle change and screening [18]. Insufficient healthcare resources can be one reason for people from different SES groups compete to receive cancer care. The competition may force patients to take responsibility for receiving a timely and appropriate diagnosis by themselves. The corresponding capacity to deal with this situation depends more on up-stream factors such as the ability to perceive, seek and engage [19]. Worse stage distribution may be observed in deprived groups as a consequence, and the competition may continue for receiving treatment. Accordingly, the final outcome, cancer survival can result in an unequal manner.

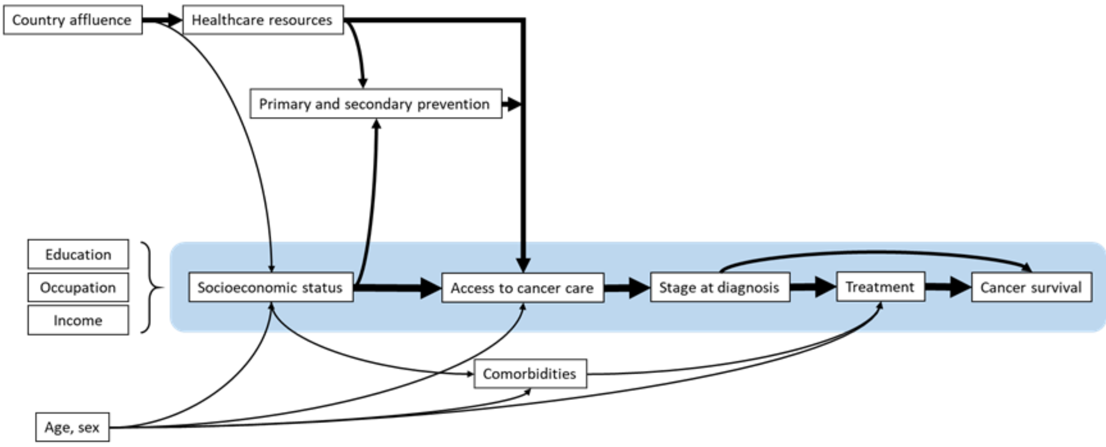

Figure 1.2 Association between socioeconomic status, access to cancer care and survival

Modification from source: Alberto, 2013 [20].

Concentration index and Lorenz curve are used to show the existence and distribution of equity in healthcare access or health outcomes. However, these indices neither show how inequity in healthcare access is translated into a final health outcome nor the mechanism of how inequities in a health outcome is generated. Nolte and McKee (2004) suggested the concept of ‘amenable mortality’ as an indicator assessing healthcare quality [21, 22]. Some studies have explored the association between inputs (health expenditure) and mortality [5, 23]. However, the relationship is difficult to interpret because of reverse causality [24].

Debates have raged on whether healthcare impacts on health outcomes [22]. So far, studies exploring mechanisms on how socioeconomic inequalities impact on cancer survival are sparse [25]. Cancer care requires high resource inputs and sophisticated coordination of care by multiple levels of healthcare factors [5, 26]. Survival is one of the key measures to assess the quality of cancer care in a country, and it reflects the progress of how people are treated [5]. Thus, evaluating the role of treatment on the effects of SES on survival is essential to tackle inequalities [26].

1.3 Colorectal cancer in England and Japan

I describe here the epidemiology of CRC, as well as the characteristics of the population and healthcare system in England and Japan. Next, I detail the diagnosis, treatment and patient pathway for CRC patients to highlight where socioeconomic inequalities in CRC survival may arise in each country.

1.3.1 Epidemiology

Colorectal cancer was estimated to be the third commonest diagnosed cancer in the world in 2018 [1]. Of cancer deaths worldwide, CRC accounted for 9.2%, with approximately 880,792 estimated deaths in 2018 [1]. CRC is also a growing public health burden in both England and Japan. England had 34,952 new CRC cases (age-standardised incidence rate 84.4 in males and 55.4 in females per 100,000 population), which made it the fourth most prevalent cancer in 2016 [27]. The total number of deaths from CRC in England was 13,417 in 2016, which accounted for 10% of all cancer deaths [28]. Japan had 158,127 new CRC cases (excluding carcinoma *in situ*, age-standardised incidence rate 77.5 in males and 47.3 in females per 100,000 population) in 2016, which was the third commonest cancer diagnosed in male and the second in female [29]. The total number of CRC deaths in Japan was 50,681 in Japan in 2017, which was the second largest cause of cancer deaths of all neoplasms [30].

Both countries have suffered socioeconomic inequalities in CRC survival. In England in 2006, the deprivation gap (i.e. a simple difference in survival estimates between the most and the least deprived groups) in one-year survival from colon and rectal cancer was approximately 7% in males and 10.6% in females [3]. In Osaka Prefecture, Japan in 2001–2004, the deprivation gap in one-year net survival from CRC was 6.3% in males and 2.9% in females [2].

1.3.2 Population characteristics

England has an estimated population of 55.6 million (84% of the total population, 66.0 million in the United Kingdom [UK]), with 18% aged 65 years and over [31]. In 2016, life expectancy at birth in the UK was 81.0 [32]. The large gap in life expectancy between different local areas in England has been reported continuously [33, 34]. The Gini coefficient (income inequality) was 0.35 in the UK in 2016 [35]. The poverty rate (a ratio of the number of people whose income is under poverty line: defined as half the median of the household income in the total population) was 0.11 in 2016 [36]. In 2017, cancer was the most common cause of death at 28%, followed by cardiovascular diseases (heart diseases and strokes at 25%) in England and Wales [37]. Expenditure spent on cancer was £6.7 billion (United States [US]$ 9.6 billion) in 2012–2013 [38].

Japan has an estimated population of 126.8 million in 2017, with 27% aged 65 years and over. Japan's life expectancy at birth was 84.0 years in 2016 [32]. Cancer was the leading cause of death at 30%, followed by heart disease (16%) and cerebrovascular disease (11%) in 2010 [39]. Of the total health expenditure at ¥ (Japanese Yen) 42 trillion (US$ 383 billion), 10.1% was spent on cancer care in 2016 [40]. The Osaka Prefecture, which is the site of this study in Japan, sits on the west side of the main island. The prefecture had an estimated population of 8.8 million in 2017, being the third most populated prefecture in Japan [41]. Japan has a relatively homogenous ethnic composition; however, health inequalities have begun to be reported, alongside a rising relative poverty rate since the economic recession in the 1990s [42, 43]. The Gini coefficient was 0.34 [35], and the poverty rate was 0.16 in 2015 [36]. The number of people in Osaka Prefecture, who receive public assistance because of their income falling below the minimum living standard, is by far the highest among the 47 prefectures in Japan. Approximately 54‰ (permil, per 1,000 inhabitants) and 33‰ of the population in Osaka City and Osaka Prefecture, respectively, received the assistance, whereas at the national level, this figure was 16.9‰ in 2016 [44]. Population characteristics and cancer risk factors in England and Japan are shown in Table 1.1.

Table 1.1 Population characteristics and cancer risk factors in England and Japan

	England	Japan
Land area (km²)	242 thousand (UK)	337.9 thousand (Japan)
	132.9 thousand (England)	1899 (Osaka Prefecture)
Estimated total population (2017)	66.0 million (UK)	126.8 million (Japan)
	55.6 million (England)	8.8 million (Osaka Prefecture)
Aged 65 or more (2017)	18.2%*	27.0%
Country of birth different from the country of residence (2017)	14%*	2.0%
Poverty rate ratio	0.111 (2016)*	0.157 (2015)
Life expectancy at birth (years, 2016)	81.0*	84.0
Total health expenditure (% GDP, 2015)	9.9*	10.9
Health spending per capita (US $, 2016)	3833*	4513
Expenditure spent on cancer service (US $)	£6.7 billion (US $9.6 billion) (England, 2012–2013)	¥4.2 billion (US $38.3 billion) (2016)
Gini coefficient	0.35 (2016)*	0.34 (2015)
Smoking prevalence (2016)	22.3%*	22.1%
Obesity in adults (measured, 2016)	26.2%*	4.2%
Total alcohol consumption (litters per capita, 2016)	11.5*	8.0

Abbreviations: GDP, Gross domestic product; UK, United Kingdom; US $, United States dollars. *Figures of the UK. All figures for Japan are of Japan as a country but not of Osaka Prefecture unless stated.
Data source: Ministry of Health, Labour and Welfare (Japan), National Audit Office (UK), OECD data (Japan, UK), Office for National Statistics (UK), Osaka Prefectural Government (Japan) and The World Bank Data (Japan, UK).

1.3.3 Governance of healthcare system and cancer policy

The healthcare in both countries is publicly funded (tax-based in England and social health insurance in Japan); however, provision of care is public-based in England and private-based in Japan with more of self-regulation by providers. The National Health Service (NHS) in England maintains a free-of-charge principle in the public healthcare system; thus, patients have equal access to cancer care in terms of direct costs. On the other hand, irrespective of public or private care, patients in Japan pay co-payment depending on their insurance plans, but it is at a relatively low cost at 10–30% of their total health expenditure. To save catastrophic payment, a threshold of monthly co-payment is set, depending on age and income. For extremely poor households, a public assistance system exists with exemption from co-payment [45].

In England, cancer care is provided within networks of hospitals, each organised as what are termed Trusts, semi-autonomous organisations within the NHS. While this system enables the care of some rare cancers to be centralised, common cancers such as CRC are managed in most general hospitals, where care is based on the national guidelines and subject to a variety of national regulators that monitor aspects of care such as quality. All hospitals providing cancer care should have multidisciplinary teams (MDTs), bringing together an appropriate combination of specialists. However, despite this framework, which should facilitate equitable treatment in theory, inequities persist [46].

In Japan, the Ministry of Health, Labour and Welfare (MHLW) initiated an accreditation system for what it termed Designated Cancer Hospitals (DCHs) in 2001; however, CRC is also treated in non-DCHs [47]. In 2016, 80% of all CRC cases in Osaka Prefecture were treated in DCHs in Osaka (data not shown). Hospitals are so designated if they fulfil certain requirements, including the presence of MDTs, sufficient volumes of cancer surgery or chemotherapy, and the employment of specialists in a range of aspects of cancer care. In 2019, there are 392 DCHs in Japan, and Osaka Prefecture had one prefectural and 16 regional DCHs in 2018 [48, 49]. However, even in DCHs, wide variations in surgical volumes and the use of chemotherapy or radiotherapy have been reported [50, 51].

1.3.4 Provider reimbursement and incentives

In both countries, individual doctors, who work in secondary care are paid by salary, whereas doctors working at the primary care level are paid by different systems. Eighty percent of primary care doctors, so-called general practitioners (GPs) in England, are paid mainly by capitation, but also with a combination of fee-for-service (FFS) and pay-for-performance (P4P) [52]. P4P incentives are used in primary care to achieve targeted performances set by the Quality and Outcomes Framework (e.g. immunisation uptake) [52, 53]. Regarding cancer, P4P incentives are used for the uptake of cervical cancer screening [54], but not for the early detection of CRC.

In Japan, historically, there is little distinction between doctors working in primary care and hospitals. Japan does not have physicians that correspond precisely with the GPs in England [55]. The speciality of ‘general internal medicine’ is relatively minor in Japan, and most doctors have another sub-speciality, such as gastroenterology. There are no performance or waiting time targets set for the doctors working at the primary care level; we may call them primary care physicians (PCPs), and they are paid by FFS for the outpatient services. The benefit for cancer diagnosis is that there is no disincentive for doctors to conduct diagnostic tests. Rather, PCPs profit more if they test more, making the overall system vulnerable to market failure (supplier-induced demand).

Since the function of primary and secondary care duplicates in the general healthcare system in Japan, MHLW promotes distinct role-sharing and coordination in cancer care. For DCHs in Japan, the government provides subsidies for hospitals to achieve requirements for the accreditation. Both clinics and DCHs are incentivised when they provide coordinated cancer care (e.g. referrals from and follow-up at PCPs). An additional fee is set for patients who are treated in these accredited DCHs.

1.3.5 Resources and workforce

While resources are controlled by the government in England, they are not centrally controlled in Japan. England has a higher density of doctors per population; however, the proportion of CRC specialists is assumed to be higher in Japan due to the nature of speciality composition.

Regarding medical technology resources, the total number of CT scans in Japan was by far the highest among all the Organisation for Economic Co-operation and Development (OECD) countries (107 per 1,000,000 inhabitants in Japan, 9 per 1,000,000 inhabitants in the UK in 2014) [56]. In Japan, colonoscopy is widely available at both the primary and secondary healthcare levels [57] (Table 1.2). Geographical variations (by prefectures or medical area) in terms of density of medical resources or number of colonoscopies conducted have not been studied and are not known.

In England, the NHS Cancer Plan (2000) and the NHS Improvement Plan (2004) proposed the increases in equipment procurement [58, 59]. The Plan in 2000 also stated to increase the number of specialists (e.g. gastroenterologists and radiotherapists). A significant increase in the cancer workforce was reported in the Cancer Reform Strategy in 2007 [60]. However, the density in secondary care facilities, such as medical devices and hospital beds, is still much lower than that of Japan and other European countries (MRI with 51.7 per 1,000,000 inhabitants in Japan, 7.2 per 1,000,000 inhabitants in the UK in 2014, hospital beds with 13.1 per 1,000 inhabitants in Japan, 3.6 per 1,000 inhabitants in the UK in 2016) [56, 61, 62] (Table 1.2).

In Japan, the problem of quality differences among DCHs is compounded by the geographical maldistribution of doctors [63]. Inequalities in overall healthcare access have not been solved in Japan; persistent shortages of doctors occur in rural areas where doctors have no additional monetary incentives.

Table 1.2 Medical resources by England and Japan

	UK	Japan
Number of doctors per 1,000‡ (2016)	2.78	2.43
Number of nurses per 1,000‡ (2016)	7.88	11.34
Hospital beds per 1,000‡ (2017)	2.5	13.1
Length of hospital stay‡ (acute care in days, 2017)	5.9	16.2
Number of hospitals (2017)	1,920 (estimate)‡ 7,361 (GP practices in England) [64]	8,412 (hospitals)‡ 101,471(clinics)§
Number of hospitals per 1,000,000‡ (2017)	29.06 (estimate)	66.39
Adult ICU beds per 100,000 (2005)	3.5 [65]	4.3 [65-67]
Number of institutions with colonoscopy Upper: hospitals (number of beds≥20), lower: clinics (number of beds<20) (Japan)§	484 [68]	4,091 6,647
Total number of colonoscopies conducted/month‖ Upper: hospitals, lower: clinics (Japan)§	119,000 [68]†	258,000 137,000
Number of CT scans per 1,000,000‡ (2014)	9	107
Number of MRI per 1,000,000‡ (2014)	7.2	51.7

Source: ‡ OECD data [56, 61, 62, 69], § Ministry of Health, Labour and Welfare (Japan) [57]. ‖ Rounded to the nearest 1000. # MDCT (multi-detector CT); ## other CT (single-detector CT. Excluding PET CT). † Derived by dividing the annual figure in the reference by 12 (months).

1.3.6 Screening, diagnosis and treatment

Change in bowel habit, blood in faeces and abdominal pain are the main three symptoms in CRC. These symptoms are very common and non-specific, making a decision to provide diagnostic tests for CRC sometimes challenging especially at early stages.

Diagnostic tests used are faecal occult blood testing (FOBT), barium enema and endoscopy (flexible sigmoidoscopy and colonoscopy). National screening programmes for CRC are available in both England and Japan. FOBT, flexible sigmoidoscopy, colonoscopy, computed tomography (CT) colonography and barium enemas are the main tests used for the screening worldwide. The choice of screening tests varies by countries [70], depending on sensitivity, specificity and cost-effectiveness. For symptomatic patients, endoscopy is the initial diagnostic procedure.

In England, biannual Guaiac-based FOBT (gFOBT) was introduced as a population-based screening programme in 2006, i.e. before the study period covered in this thesis in England (2010 to 2013). The screening is performed at approximately 100 local screening centres for the eligible population (age 60–74, from 2010 onwards) [71]. Participants with an abnormal test result are arranged to attend specialist screening practitioner (SPP) clinics for colonoscopy [71]. In 1993, a pilot study commenced using flexible sigmoidoscopy; this procedure was only introduced in 2013 for screening in aged 55, in addition to gFOBT [72], and therefore cannot affect the analysis and results of the present study in England. In 2012–2015, the screening uptake was 57.9% among the target population in England [73, 74].

In Japan, annual iFOBT (immunochemical faecal occult blood test, same as FIT: faecal immunochemical test) has been performed on 40 years old and over (no upper limit for the eligible age), since 1992, i.e. covering the study period in Japan (2012 to 2015) in this thesis. Apart from the population screening, opportunistic screening (iFOBT, barium or flexible sigmoidoscopy) is also offered to applicants. Among the population aged 40 to 69 in Japan, the screening uptake (including opportunistic screening) was 29.8% in 2013 [75].

Histopathological assessment by endoscopic biopsy is needed for the definitive diagnosis of the primary tumour. Metastasis to other organs (particularly liver and lungs for CRC) are assessed by imaging (CT scan). Although sensitivity is around 60 to 70% depending on the type of CT [76], lymph node metastasis is also assessed by the routine use of multi-detector CT (MDCT) in Japan [77]. Endorectal ultrasound (ERUS) for early T stage or MRI (magnetic resonance imaging) for intermediate/advanced T stage is used to identify the depth of invasion in rectal cancer, which has a higher local recurrence risk than colon cancer.

Treatment decisions depend mostly on the clinical stage, but age, comorbidities and performance status are also taken into consideration. In Japan, for purely localised tumours (cTis and carcinoma with slight submucosal invasion), endoscopic resection, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) without node dissection, is the first choice of treatment [78-81].

Tumour resection, by major surgery, is performed with curative intent for CRC clinically diagnosed as T1 (submucosal cancer) and over. In the past, APER (abdominoperineal excision of rectum) with permanent stoma was performed for rectal cancer. Although APER is the only option for rectal cancer which is located very close to the anal canal, as surgical techniques improve, APER became less preferable compared with anterior resection (AR) combined with anastomosis (connection of the intestine by staplers). In emergency or aged cases, Hartmann's operation is performed; the operation resects cancer without removing the distal rectal stump; thus, it is less invasive.

For stage II (high risk) and III patients, adjuvant (postoperative) chemotherapy is added to the R0 (no residual) resection. Combination chemotherapy of FOLFOX (folinic acid, 5-FU and oxaliplatin) or capecitabine monotherapy are the recommended options in England [82]. In Japan, in addition to these regimens, the use of 5-FU plus folinic acid, UFT (tegafur-uracil) plus folinic acid, capecitabine plus oxaliplatin, or S-1 (tegafur gimeracil oteracil) are covered by insurance; the chemotherapy is recommended to start within four to eight weeks after curative resection, with in principle a duration of six months in Japan [80, 81]. Chemotherapy may also be performed for stage IV patients with unresectable tumour aiming to prolong their survival if the patient has a good performance status, or for some cases, even aiming cure. If a patient with stage IV shows a substantial tumour size reduction after 12 to 16 weeks of the chemotherapy, an operation could be offered (called ‘conversion therapy’) [83, 84]. Biologic targeted agents (e.g. bevacizumab, panitumumab, cetuximab and regorafenib) have been developed in recent years; however, the indication of the use is only for stage IV patients, depending on individual’s molecular pathological types.

Radiotherapy is performed for either curative or palliative intent. In European countries, neoadjuvant (preoperative) radiotherapy, either chemoradiotherapy (CRT) or short-course preoperative radiotherapy (SCPRT), is recommended for the locally advanced rectal cancer (>cT3b) to reduce recurrence at the local site [85-87]. In Japan, neoadjuvant radiotherapy is rarely used. Instead, aiming an improvement in overall survival and a reduction in local recurrence, lateral lymph node dissection is performed for lower rectal cancer of which the lower margin locates below the peritoneal reflection [78-80]. Pathologically proven T3 (pT3 invading deeper than subserosa or more) or node extension (N positive) are the indications for adjuvant radiotherapy [80]. Although local recurrence is decreased by adjuvant radiotherapy, there is no evidence that this therapy improves survival [88].

1.3.7 Patient pathways for CRC patients

Patient pathway is mapped in Figure 1.3 to outline provision of cancer care in England and Japan. The map identifies steps in the care that might influence survival in each context, from the recognition of symptoms to the end of the initial definitive treatment. Screening was removed from the patient pathway map because, for the study period, it is considered as secondary preventative measure: less than 10% of all CRC cases were detected through screening in England [89], while in Japan, this proportion was likely to be low too because of the relatively small screening uptake [90].

Ten principal events were identified in the care process (in the centre) that are common to the pathways in both countries, starting from consultation with a primary care doctor through the end of the first definitive treatment. Each event is connected by a path, drawn as an arrow A to J in the centre of the figure. The left-hand side of the figure describes those elements and processes that are specific to England, while the right-hand side describes those specific to Japan. In the following sections, I describe the CRC patient journey from the steps of presentation, diagnosis to treatment.

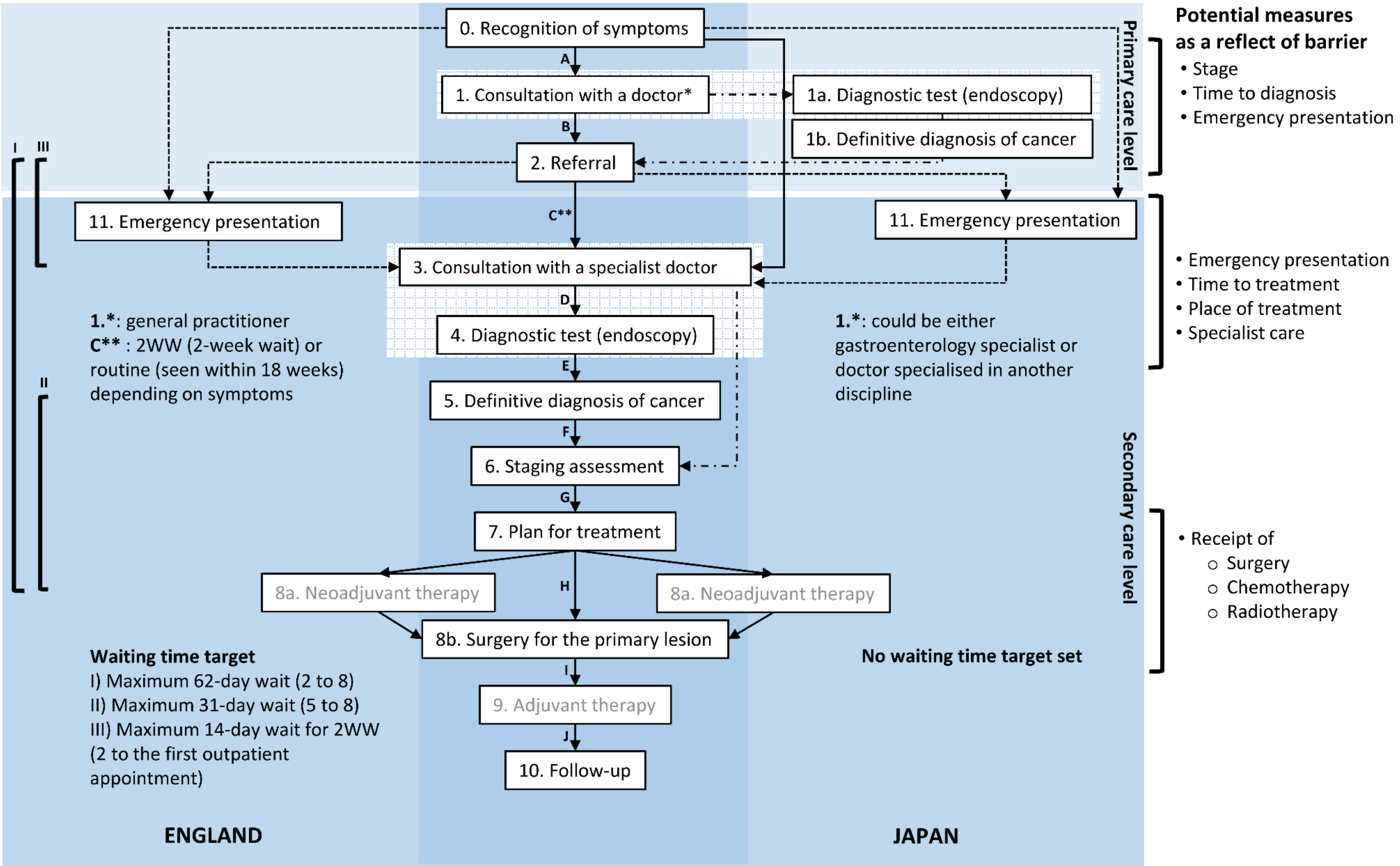

Figure 1.3 Patient pathways for colorectal cancer patients in England and Japan

Presentation

In the NHS, patients with symptoms typically consult their GP first before they can access more specialised services (Figure 1.3, box 1). The only exceptions are emergencies, such as intestinal bleeding or obstruction, when patients access the hospital emergency department directly (box 0 to box 11 on the left side). In England, 85% of all-site cancer cases are diagnosed with symptoms, and 26% of the CRC cases are diagnosed after an emergency admission [7, 89, 91]. The GP will assess the patient's history and physical signs and, possibly, undertake basic blood tests such as a full blood count. Then the GP decides whether to refer the patient on for further diagnostic tests (e.g. endoscopy) and specialist consultations. Those with suspected cancer should have a consultation of a cancer specialist with a maximum two-week-wait (2WW) from the GP's referral ('fast-track' or urgent referral) if they have certain red flag symptoms or signs (Figure 1.3, path C).

Borderless access and free movement among any medical institutions are the essential characteristics of the healthcare system in Japan [55]. Patients can directly access a specialist either in a clinic at primary care level (Figure 1.3 path A) or most hospitals. The majority of patients use a clinic as the first contact.

Diagnosis

In England, all colonoscopies are conducted at the secondary care level in principle. There is evidence of variations in the use of colonoscopy and flexible sigmoidoscopy across CCGs [46].

In Japan, there is evidence of socioeconomic differences in the utilisation of outpatient services, and delays in obtaining care among older people due to co-payment (barrier at Figure 1.3, path A) [42, 92-94]. However, the horizontal inequity and delays in the elderly population did not differentiate the speciality of healthcare (PCP or specialist service); thus, it is not known whether those figures influence the rates of emergency presentation (Figure 1.3, box 0 to box 11 on the right side), timeliness of diagnosis, or the place for cancer treatment.

Although co-payment is necessary, patients have access to diagnostic tests including endoscopy performed by gastroenterology specialists at both primary and secondary care levels (box 1 to box 1a on the right side and box 4, two grid pattern areas in Figure 1.3). However, the capacity of colonoscopies is not investigated nationwide [95].

Treatment

In England, at the planning phase (Figure 1.3, box 7), NICE (National Institute for Health and Care Excellence) (2004) used to recommend all newly diagnosed CRC patients to be cared by MDT [96, 97].

In Japan, MDT meetings are not necessary for all cases but are usually held only for the patients who are out of indication for treatment recommended in the guidelines. In DCHs, radiotherapy is available at the same institution where surgical treatment is provided. A specialised colorectal surgeon would contact a radiotherapist directly when radiotherapy is needed. For lower rectal cancer in Japan, neoadjuvant radiotherapy is rarely used; the first definitive treatment for most of the advanced cases is surgical resection with lateral lymph node dissection (Figure 1.3, path H) [78-80, 98]. Usually, in contrast to England, the CRC specialist surgeon who operated (box 8b) is fully responsible for the postoperative care (including urgent re-operation), planning of the adjuvant therapy and follow-up (path I and J).

1.3.8 Potential steps on the patient pathway where inequalities may rise

Potential measures that may reflect barriers in the pathway are listed to the right of Figure 1.3. Apart from patients' health-seeking behaviour or preferences, late-stage presentation, delays in diagnosis or emergency presentation may partly originate from barriers in primary care. Delays in treatment, differences in place of treatment (e.g. reference cancer care centre or non-cancer hospitals, high-volume hospital or low-volume hospital, hospital with specialist or non-specialist) or receipt of treatment may mean barriers in secondary care.

1.3.9 Receipt of treatment as a measure of healthcare access

Over the last decades, various indicators have been developed to assess cancer care. What elements 'quality of care' consists of depends firstly on the cancer site. In the specific context of CRC, early detection, accurate diagnosis and staging, prompt and stage-appropriate treatment, management of complications after surgery, regular follow-up by specialist and palliative care may imply good quality of care [5]; however, it does not necessarily mean that all these elements contribute to better survival.

According to Donabedian model, quality indicators can be categorised into three groups: structure, process and outcome measures [99]. Achieving a longer survival is a self-explanatory outcome goal, and receipt of treatment (i.e. process measure), particularly surgical treatment, remains a crucial step to survive for CRC patients. Receipt of surgical treatment can also be a composite measure of accessibility of care, as shown in the patient pathway.

Additional measures have also been suggested for assessing the quality of the provided care or postoperative management [100]. Regarding quality of surgery, one example of quality indicators is the number of lymph nodes yield [100, 101]. For postoperative management, some indicators incorporate postoperative complications such as anastomotic leakage [102], reoperation [103], failure to rescue [104, 105] and short-term postoperative mortality [106-108]. Postoperative complications and failure to rescue can be challenging to capture within population-level datasets because of, for example, inaccuracy of coding and missing data [109, 110], whereas data on postoperative mortality are generally more reliable, as individual vital status is usually available at national level.

My focus here is to gather evidence on the differential access to care by SES and how such inequalities in access to care may influence the survival of CRC. In this thesis, I employ receipt of surgery for the primary lesion as a measure of access to CRC care, and postoperative 30-day mortality as the quality indicator of surgery as well as the short-term outcome measure. Because the detailed information is not available in the population-level database as described above, building indicators to assess the quality of care is beyond the aim of this thesis.

1.4 Aims and objectives

Based on the patient pathway presented in Figure 1.3, this thesis focuses on the receipt of treatment (intermediate outcome) to explain inequalities in survival.

1.4.1 Aims

This study aims to understand the mechanisms by which the socioeconomic inequalities in CRC survival can be explained by patient, tumour and treatment factors.

1.4.2 Objectives

1. To examine whether socioeconomic inequalities in CRC care exist in each country of England and Japan, in recent years (England: 2010–2013, Japan: 2012–2015).
2. To examine whether socioeconomic inequalities in CRC survival exist in each country of England and Japan, in recent years (England: 2010–2013, Japan: 2012–2015).
3. To estimate how much of the socioeconomic inequalities in CRC survival are affected by socioeconomic inequalities in receipt of treatment.

1.5 Thesis structure

Chapter 2 reviews the literature on inequalities in receipt of treatment in UHC countries.

Chapter 3 explains the data materials used in Chapters 4 and 5, and the methodology used in **Chapter 4.5**.

Chapter 4 and **Chapter 5** explore the socioeconomic inequalities in CRC care and survival in England and Osaka, Japan.

Chapter 6 concludes the thesis with implications for future research.

Chapter 2: Literature review

2.1 Inequalities in receipt of treatment in UHC countries

2.1.1 Introduction and methods

This literature review aims to explore evidence on the socioeconomic inequalities in access or utilisation of CRC care, especially focusing on the receipt of treatment in UHC countries.

Socioeconomic inequalities in cancer survival can be caused by patient, tumour (stage) or healthcare system factors [111]. Reports have suggested evidence for socioeconomic inequalities in survival in countries with UHC [3, 112, 113]; however, how cancer care is accessed or utilised by different SES groups, the consequences of the differential treatment in relation to the survival inequalities, are poorly understood. As described in **Chapter 1.2.1**, in theory, in countries with UHC, equity of access to the acceptable quality of care should be ensured. Therefore, differential cancer care should not be observed by SES.

OECD high-income countries with public health coverage were defined as UHC countries and included in the review [114, 115]; therefore, the United States, where private health coverage has been dominant (54%), was excluded from this review.

In this thesis, I defined that cancer care refers to diagnosis and treatment but not the first and second prevention measures such as screening. Of the cancer care defined and the potential care measures identified in Figure 1.3, I further confined this review to the receipt of treatment (surgery, chemotherapy or radiotherapy) or type of treatment to explore evidence on the socioeconomic inequalities in access or utilisation of cancer care at the secondary care level. Measures of treatment receipt that do not necessarily affect survival (e.g. receipt of palliative care, stoma reversal, use of outpatient service or length of hospitalisation) were excluded.

'Socioeconomic status' contains complex concepts; for this review, I defined disadvantaged groups as those with low incomes, in low occupation classes, or categorised as deprived groups defined by a multiple index. Reports defining disparities by age, sex, ethnicity, race, educational years, marital status, insurance status, geographical distance or rurality were therefore excluded.

Epidemiological research papers published between 1st January 2000 and 31st June 2019 were reviewed in PubMed, Ovid system (Embase, Global Health, Econlit, Social Policy and Practice) and Web of Science. Research papers, which were identified in the references of the original articles reviewed, were also manually assessed and added. Reports published in the 1990s or earlier were excluded as CRC treatment had changed dramatically since the 1990s. Non-English documents, non-Japanese documents, conference abstracts, review papers (e.g. literature review and meta-analysis), letters and qualitative reports were also excluded. Search strategies comprised the follows and are further detailed in Table 2.1.

The aim of this review is to assess differential receipt of treatment; therefore, regarding socioeconomic variations in mode of presentation and outcomes (both postoperative mortality and survival from diagnosis), the articles that do not report disparities in treatment receipt, were excluded from this review, even if variations in presentation or mortality/survival are used as final outcomes.

1. (bowel OR colon* OR rectum or rectal OR colorectal) AND (adenocarcinoma OR cancer) (as title)
2. socioeconomic OR socio-economic OR deprivation OR income (as keyword)
3. inequalit* OR inequit* OR differen* OR variation OR disparit* (as title)
4. inequalit* OR inequit* OR disparit* (as keyword)
5. treatment OR management OR care OR operation OR surgery OR resection OR specialty OR specialist OR time OR delay OR therapy OR chemotherapy OR radiotherapy OR chemoradiotherapy (as keyword)

Table 2.1 Search strategies in three search engines

Pubmed	((bowel[Title] OR colon*[Title] OR rectum[Title] OR rectal[Title] OR colorectal[Title]) AND (adenocarcinoma[Title] OR cancer[Title])) AND ((inequalit*[Title] OR inequit*[Title] OR differen*[Title] OR variation[Title] OR disparit*[Title]) OR (inequalit*[Abstract] OR inequit*[Abstract] OR disparit*[Abstract])) AND (socioeconomic OR socio-economic OR deprivation OR income) AND (treatment OR management OR care OR operation OR surgery OR resection OR specialty OR specialist OR time OR delay OR therapy OR chemotherapy OR radiotherapy OR chemoradiotherapy)
Ovid system Embase Global Health Econlit Social Policy and Practice	1 (bowel or colon* or rectum or rectal or colorectal).m_titl. 2 (adenocarcinoma or cancer).m_titl. 3 1 and 2 4 (socioeconomic or socio-economic or deprivation or income).mp. [mp=ab, ti, ot, bt, hw, id, cc, tx, ct, sh, tn, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy, pt] 5 (inequalit* or inequit* or differen* or variation or disparit*).m_titl. 6 (inequalit* or inequit* or disparit*).mp. [mp=ab, ti, ot, bt, hw, id, cc, tx, ct, sh, tn, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy, pt] 7 (treatment or management or care or operation or surgery or resection or specialty or specialist or time or delay or therapy or chemotherapy or radiotherapy or chemoradiotherapy).mp. [mp=ab, ti, ot, bt, hw, id, cc, tx, ct, sh, tn, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy, pt] 8 5 or 6 9 3 and 4 and 8 and 7 10 limit 9 to yr="2000 -Current" 11 remove duplicates from 10 12 (America* or United States or USA).m_titl. 13 11 not 12
Web of Science	#1 TI=(bowel OR colon* OR rectum OR rectal OR colorectal) AND TI=(adenocarcinoma OR cancer) #2 ALL=(inequalit* OR inequit* OR disparit*) #3 TI=(inequalit* OR inequit* OR differen* OR variation OR disparit*) #4 ALL=(socioeconomic OR socio-economic OR deprivation OR income) #5 ALL=(treatment OR management OR care OR operation OR surgery OR resection OR specialty OR specialist OR time OR delay OR therapy OR chemotherapy OR radiotherapy OR chemoradiotherapy) #6 #1 AND (#2 OR #3) AND #4 AND #5

The quality of studies was then assessed by using Newcastle-Ottawa Scale (NOS) for non-randomized studies (cohort or case-control studies) (Table 2.2) [116]. The scale assesses three main components: for cohort studies, (i) selection, (ii) comparability of cohorts and (iii) assessment of outcome: for case-control studies, (i) selection, (ii) comparability of cases and controls and (iii) ascertainment of exposure. Each outcome in a study was assessed and allotted a star if the study design or description fulfils a requirement in each of the nine questions. The maximum total a study can obtain is nine stars. Regarding the comparability, I assigned one star if a study outcome is derived controlling for stage. I also allotted an additional star if a study outcome is derived controlling for comorbidities or ASA (American Society of Anesthesiologists) grade.

The aim of this literature review is to summarise the available evidence on socioeconomic inequalities in access to cancer care for my analyses in the later chapters, but not to develop or assess quality indicators for cancer care. As the definitions and measurement of outcomes vary among studies, the outcomes were not pooled and this review is thus descriptive.

Table 2.2 Newcastle-Ottawa Scale for cohort or case-control studies

Cohort studies	
Selection (4 stars)	1. Representativeness of cohort members: truly or somewhat representative of the community 2. Selection of non-exposed cohort members: coming from the same community as the exposed members 3. Ascertainment of exposure: secure record (e.g. surgical records) or structured interview 4. Demonstration that outcome was not known at the start of study: yes or no
Comparability (2 stars)	1. a) Outcome controlled for stage b) Outcome controlled for comorbidities or ASA grade
Outcome (3 stars)	1. Assessment of outcome: independent blind assessment or record linkage 2. Adequate length of follow-up for observing outcome to occur: yes or no 3. Adequacy of follow-up: complete follow-up or small proportion of lost to follow-up (less than 30%) or description of the lost to follow-up
Total 9 stars	
Case-control studies	
Selection (4 stars)	1. Adequacy of case definition: yes (ICD codes, record linkage, self-reports) or no (no description) 2. Representativeness of cases: obviously representative 3. Selection of controls: community controls 4. Definition of controls: no history of endpoint/disease
Comparability (2 stars)	1. a) Outcome controlled for stage b) Outcome controlled for comorbidities or ASA grade
Exposure (3 stars)	1. Ascertainment of exposure: secure record or structured interview (blind to case or control status) 2. Same method of ascertainment for case and control: yes or no 3. Non-response rate: same rate for both groups
Total 9 stars	

2.1.2 Results

PubMed identified 427 articles. Ovid system (Embase, Global Health, Econlit, Social Policy and Practice) and Web of Science identified 922 and 477 articles, respectively. After removing duplications and irrelevant studies by screening titles and abstracts, 101 full-text articles were assessed for the eligibility. From the initially identified articles, further 28 articles were deemed as relevant (Figure 2.1).

A total of 60 articles from seven UHC countries were identified as having descriptions on socioeconomic variations in receipt of treatment. The UK reported the most, followed by France. From other European countries, the Netherlands and Sweden reported some socioeconomic variations in cancer care. From Asia, one article from Korea reported socioeconomic variations. There was no article reporting disparities in receipt of treatment from Japan.

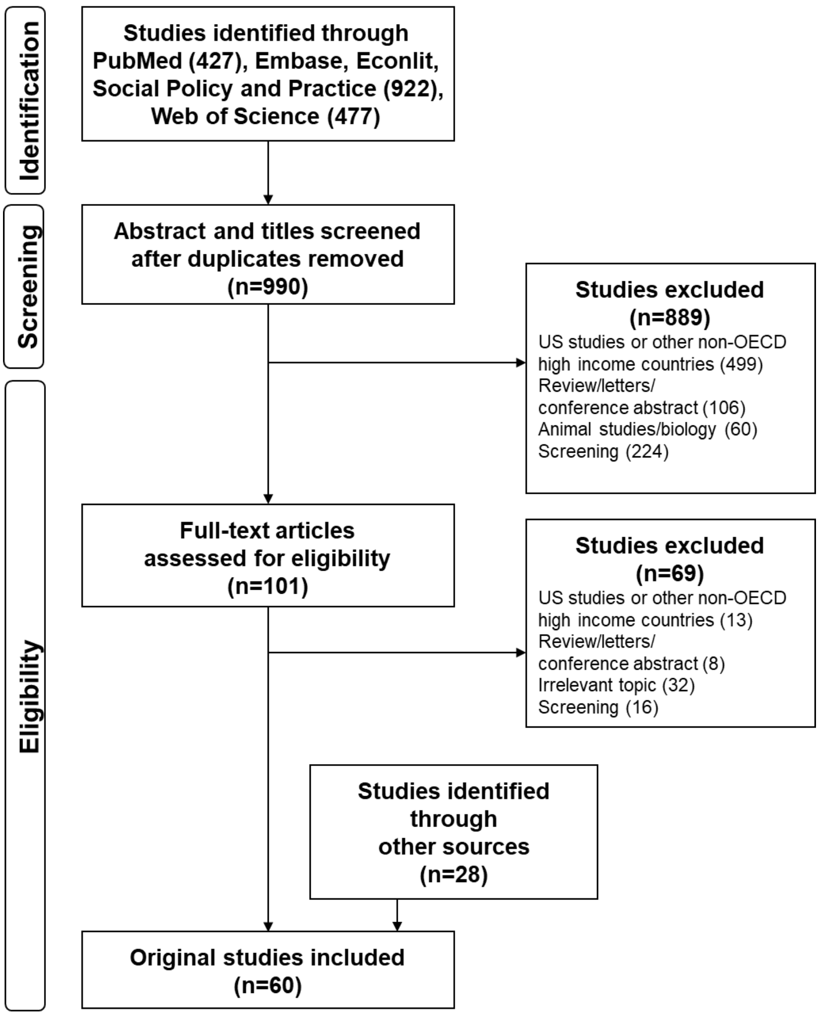

Figure 2.1 Flow diagram for literature review

Description on variations in receipt of treatment was categorised into eight groups: socioeconomic variations in mode of presentation, place of treatment, time to treatment, receipt of any treatment, receipt of surgical treatment, type of surgical treatment, receipt of chemotherapy and receipt of radiotherapy. The identified studies are listed by group in Table 2.3.

Of the 60 studies, nine studies had reported socioeconomic differences in mode of presentations, and 26 had assessed the postoperative mortality or long-term survival, in addition to the report of differential receipt of treatment. Eight studies assessed differences in places of treatment (e.g. referral cancer care centres or not, high-volume or low-volume hospitals). Fifteen studies reported time to treatment by SES. Six studies reported on receipt of any treatment, 14 on receipt of surgery, 18 on type of surgery, 20 on receipt of chemotherapy, and ten on receipt of radiotherapy.

Treatment and survival can be determined by stage, comorbidities, urgency of presentation or operation and speciality/volume of surgeon or hospital [111, 117]. Thus, I extracted information on whether an analysis was adjusted for those factors. For all outcomes, important factors, which were adjusted in each multivariable model, are shown in italics after adjusted odds ratios (ORs) or hazard ratios (HRs).

Results of the quality assessment of the studies by NOS for cohort or case-control studies are shown in Table 2.14.

Mode of presentation or surgery

In addition to the variations in receipt of treatment, nine studies reported socioeconomic disparities in mode of presentations (Table 2.4). In most studies, the unadjusted odds of emergency presentation were higher in the most deprived group than the least deprived group. Because mode of presentation was not the final outcome in the reviewed studies, all studies except two [118, 119] did not control for stage and comorbidities (Table 2.4 and Table 2.14). For these two studies, the adjusted odds of emergency presentation did not differ by SES. The definition of emergency presentation varied also by country. All three studies, which reported urgency of treatment, was from England, comparing elective *versus* emergency surgery [120-122]. The OR of receiving emergency treatment in the most deprived group varied between 1.15 and 1.30 in these three studies.

Place and time to treatment

In the eight studies on place of treatment, the OR of the most deprived group being treated in a reference cancer care centre or a high-volume hospital ranged from 0.32 to 1.22 (Table 2.5). Regarding the time to treatment, although there were 15 studies, there was mixed evidence for deprived groups with longer time to treatment. Not only the definitions for starting dates, but outcomes varied among the studies (Table 2.6).

Regarding the quality of the studies, studies reporting place of treatment pointed generally higher than seven stars in NOS. On the contrary, two studies on time to treatment [123, 124] were poor in the description of selection of the study population (Table 2.14).

Receipt of any treatment, surgery and type of surgery

Of the six studies on the receipt of any treatment, two studies from England [125, 126] found that deprived groups were less likely to receive treatment than the least deprived group (Table 2.7). In other studies, socioeconomic trends favouring affluent patients were less clear.

Receipt of surgery was reported to be generally low in deprived patients. The OR of receiving surgery in the most deprived group varied between 0.52 and 1.13 (Table 2.8). In most studies reporting the receipt of surgery, disease stage was controlled. Three studies adjusted for the mode of presentation [118, 127, 128] and one study adjusted for the urgency of operation [120]. Four studies assessed socioeconomic variation in receipt of liver resection for stage IV CRC. Three studies specified liver-limited metastasis to synchronous cancer [128-130], whereas one [131] did not.

Of the 18 studies on the type of surgery, there were two studies on curative *vs* palliative surgery, one on total *vs* partial pelvic exenteration, nine on non-restorative surgery, two on laparoscopic surgery, six on the number of lymph node yields and two on the speciality of a surgeon (Table 2.9). Generally, deprived patients were likely to receive non-restorative surgery, such as APER, rather than restorative surgery such as AR. Laparoscopic surgery was also less received by the deprived group. Lymph node yield 12 or more was relatively equally achieved among different SES groups. Access to a specialised surgeon was also consistent among the SES groups.

Almost all studies scored eight or nine stars in quality assessment by NOS regarding receipt of surgery. When type of surgery was the outcome, some studies scored seven or lower stars because not controlling for stage or comorbidities (Table 2.14).

Receipt of chemotherapy

Of the 20 studies, four studies specified the study population to patients with stage IV [125, 132-134] (Table 2.10). Other studies, except for one [135], specified the use to adjuvant therapy or controlled stage information. One study evaluated access to KRAS testing [132]. Access to adjuvant chemotherapy was generally low for the deprived groups; the OR of receiving chemotherapy in the most deprived group ranged from 0.31 to 0.99.

Regarding the quality of the studies, most studies scored seven or higher stars in NOS; however, some studies were unclear in terms of follow-up period to observe receipt of chemotherapy (Table 2.14, no star for the question Outcome 2. for cohort studies).

Receipt of radiotherapy

Ten studies on the receipt of radiotherapy mostly focused on neoadjuvant therapy use for rectal cancer patients (Table 2.11). The OR in receiving radiotherapy varied between 0.62 and 1.39. One study from Sweden reported strong evidence for socioeconomic inequalities in the use of radiotherapy, even stratified by several factors [136]. All studies scored seven or higher stars in NOS (Table 2.14).

Postoperative mortality and long-term survival

Table 2.12 represents those studies which reported postoperative mortality or survival. Table 2.13 shows survival reports of which the entry is the diagnosis. Nine studies measured postoperative short-term mortality (Table 2.12). Eight studies extended the analysis to overall (i.e. all-cause) survival, of which the end point was more than one year from the entry. Three studies [137-139] assessed cancer-specific survival, one [140] assessed relative survival, and two [120, 141] assessed net survival. Most studies adjusted disease stage or showed results by stratified stage. ASA grades were adjusted in two studies [120, 122]. Comorbidities were adjusted in four studies [138, 139, 142, 143], and the urgency of presentation or surgery (emergency or elective) were adjusted in six studies [120, 122, 137, 141-143]. In all studies, the odds of postoperative short-term death in the most deprived group exceeded one.

Eleven studies measured long-term survival since diagnosis (Table 2.13). Even after adjusting for the effects of stage and treatment factors, the hazard of death in the most deprived group was generally higher than that of the least deprived group; the HR ranged between 0.83 and 1.54.

Quality of study was high (8 or 9 stars in NOS) in all studies except one [121] (Table 2.14).

Table 2.3 Literature identified for variations in cancer care by socioeconomic status

Cancer care	Australia	Canada	France	Netherlands	Sweden	UK	Korea
Emergency presentation		Helewa, 2013 [119]	Rollet, 2018 [118]			Raine (E), 2010 [144] Borowski (E), 2016 [145] Hole (S), 2002 [137] Oliphant (S), 2013 [141] Bharathan (E), 2011 [120] Harris (E), 2009 [121] Smith (E), 2006 [122]	
Place of treatment	Kelsall, 2008 [146] Field, 2015 [147]		Blais, 2006 [148] Dejardin, 2005 [149]			Pitchforth (S), 2002 [150] Vallance (E), 2017 [151] Borowski (E), 2016 [145]	Kim, 2010 [152]
Time to treatment	Jorgensen[a], 2014 [142]	Porter, 2005 [124] Bardell, 2006 [153] Lima, 2011 [139] Rayson, 2012 [154] Maddison, 2012 [155] Johnston, 2004 [156] Helewa, 2013 [119]	Moriceau, 2015 [157]	van der Geest, 2013 [158]		Neal (E), 2005 [123] Campbell (S), 2002 [159] Chamberlain (E), 2015 [133] Lejeune (E), 2010 [126] Redaniel (E), 2014 [140]	
Any treatment	Jorgensen[a], 2014 [142] Beckman, 2014 [160]	Maddison, 2012 [155]	Rollet, 2018 [118]			Crawford (E), 2012 [125] Lejeune (E), 2010 [126]	
Surgical treatment	Beckman, 2014 [160] Hall, 2005 [127]		Rollet, 2018 [118]	t Lam-Boer, 2015 [129]	Olsson, 2010 [161] Noren, 2016 [130]	Campbell (S), 2002 [159] Hayes (E), 2019 [162] Jones (E), 2008 [163] Paterson (S), 2014 [135] Harris (E), 2009 [121] Bharathan (E), 2011 [120] Morris (E), 2010 [131] Vallance (E), 2018 [128]	
Type of surgical treatment, others		Del Paggio, 2017 [138]	Dolet, 2019 [164] Lamy, 2018 [132] Rollet, 2018 [118]	Dik, 2014 [143]	Olsson, 2010 [161]	Hole (S), 2002 [137] Oliphant (S), 2013 [141] Harris (E), 2009 [121] Paterson (S), 2014 [135] Morris (E), 2008 [165] Raine (E), 2010 [144] Smith (E), 2006 [122] Tilney (E), 2008 [166] Tilney (E), 2009 [167] Byrne (E), 2018 [168] Radwan (W), 2016 [169] Wrigley (E), 2003 [170]	

Table 2.3 continued

Cancer care	Australia	Canada	France	Netherlands	Sweden	UK
Chemotherapy	Jorgensen[b], 2014 [171] Kelsall, 2008 [146] Beckman, 2014 [160]	Lima, 2011 [139] Rayson, 2012 [154]	Dejardin, 2008 [172] Lamy, 2018 [132] Rollet, 2018 [118]	van der Geest, 2013 [158] Lemmens, 2005 [173] Meulenbeld, 2008 [134] van Steenbergen, 2010 [174]		Campbell (S), 2002 [159] Hayes (E), 2019 [162] Hole (S), 2002 [137] Jones (E), 2008 [163] Paterson (S), 2014 [135] Pitchforth (S), 2002 [150] Chamberlain (E), 2015 [133] Crawford (E),2012 [125]
Radiotherapy	Jorgensen[b], 2014 [171] Kelsall, 2008 [146] Beckman, 2014 [160]	Maddison, 2012 [155]		Vulto, 2007 [175]	Olsson, 2011 [136]	Campbell (S), 2002 [159] Jones (E), 2008 [163] Paterson (S), 2014 [135] Radwan (W), 2016 [169]
Perioperative death	Jorgensen[a], 2014 [142]	Lima, 2011 [139] Del Paggio, 2017 [138]		Dik, 2014 [143]	Noren, 2016 [130]	Oliphant (S), 2013 [141] Harris (E), 2009 [121] Hole (S), 2002 [137] Bharathan (E), 2011 [120] Smith (E), 2006 [122] Tilney (E), 2008 [166] Tilney (E), 2009 [167] Radwan (W), 2016 [169] Redaniel (E), 2014 [140]
Survival	Kelsall, 2008 [146] Hall, 2005 [127] Field, 2015 [147]	Helewa, 1013 [119]	Dejardin, 2008 [172]	Meulenbeld, 2008 [134] Lemmens, 2005 [173] t Lam-Boer, 2015 [129]		Harris (E), 2009 [121] Wrigley (E), 2003 [170] Lejeune (E), 2010 [126] Vallance (E), 2018 [128]

Abbreviations: E, England; S, Scotland; UK, United Kingdom; W, Wales.

Table 2.4 Description of socioeconomic variations in mode of presentation

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios or days (95% CI) in the most deprived group unless specified (reference: least deprived group)
Rollet [118] (France, 2018)	European Deprivation Index (EDI)	C, stage II, III, IV, 2005–2010	Emergency admission (with occlusion, sub-occlusion or perforation)	Adjusted OR 1.22 (0.92, 1.61) *#St, Cm*
Raine [144] (England, 2010)	Index of Multiple Deprivation (IMD)	CR, no stage information, 1999–2006	Emergency admission (vs elective)	Adjusted OR 1.52 (1.47, 1.56)
Helewa* [119] (Canada, 2013)	Income	CR, AJCC stage I–IV, 2004–2006	Urgent presentation (presented to emergency department and had surgeon consultation within 2 weeks of major surgery date)	Adjusted OR 0.83 (0.52, 1.30) *#St, Cm*
Borowski [145] (England, 2016)	IMD	CR, stage I–IV, 2009–2014	Emergency presentation (vs other referral routes)	OR 1.70 (p=0.048, chi square test for trend)
Hole* [137] (Scotland, 2002)	Carstairs index	CR, Duke's stage A–D, 1991–1994	Emergency presentation (vs elective)	OR 0.99 (p=0.80, chi square test for trend)
Oliphant* [141] (Scotland, 2013)	Scottish Index of Multiple Deprivation (SIMD) score	CR who underwent surgery, Duke's stage A–D, 2001–2004	Emergency presentation (vs elective)	OR 1.21 (p=0.033, chi square test for trend)
Bharathan [120] (England, 2011)	IMD	CR, Duke's stage A–D, 1998–2002	Urgency of treatment (non-elective)	OR 1.15 (p=0.014, chi square test for trend)
Harris* [121] (England, 2009)	IMD	R, stage I–IV, 2001–2004	Emergency surgery	OR 1.30 (p=1.00, Fisher's exact test)
Smith [122] (England, 2006)	Townsend score	CR who underwent surgery, Duke's stage A–D, 2001–2002	Emergency surgery (vs elective)	OR 1.24 (p=0.003, chi square test for trend)

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; C, colon cancer; CR, colorectal cancer; OR, odds ratio; SES, socioeconomic status.
* has analysis on mortality or survival. *# shows important factors adjusted in each multivariable model. Cm, comorbidities; St, stage.*

Table 2.5 Description of socioeconomic variations in place of treatment

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios or days (95% CI) in the most deprived group unless specified (reference: least deprived group)
Blais [148] (France, 2006)	Annual income	CR, Duke's stage A–D, 1981–2000	Care centre type for surgery (treatment in reference care centre)	1981–1990: adjusted OR 1.22 (0.87, 1.69), 1991–2000: adjusted OR 1.00 (0.75, 1.33) *#St, Sx*
Dejardin [149] (France, 2005)	Occupation	CR, Duke's stage A–D, 1995	Management in reference cancer site	Social class not associated with management in reference cancer site (social class not included in the multivariable model)
Kelsall* [146] (Australia, 2008)	Socio-Economic Indexes for Areas (SEIFA)	CR, AJCC stage I–IV, 1990–1994	Use of high-volume hospital	OR 0.68
Kim [152] (Korea, 2010)	Income	C, no stage information, 2002–2005	Colectomy at high-volume hospitals	High-volume hospital use: adjusted OR 0.59 (0.53, 0.66), low-volume hospital use: adjusted OR 1.54 (1.38, 1.72) *#Cm, EmPr*
Pitchforth [150] (Scotland,2002)	Carstairs index	CR, Duke's stage C who were admitted to a non-cancer hospital, 1992–1996	Referral on to the next cancer hospitals	OR 0.60 (p=0.014)
Field* [147]	Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) score	CR, AJCC stage IV, 2009–2014	Use of private or public hospital	OR 0.32 (p<0.001, chi square test for trend)
Vallance [151] (England, 2017)	IMD	CR, stage IV who had liver only metastasis at diagnosis and underwent bowel resection, 2010–2013	Use of spoke or hub hospital	Hub hospital use: OR 0.60 (p<0.001, chi square test for trend)
Borowski [145] (England, 2016)	IMD	CR, stage I–IV, 2009–2014	Volume of hospital referred from emergency referral	High-volume hospital use: OR 1.05, low-volume hospital use: OR 1.08 (p=0.95, chi square test for trend)

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; C, colon cancer; CR, colorectal cancer; OR, odds ratio; R, rectal cancer; SES, socioeconomic status. * has analysis on mortality or survival. *# shows important factors adjusted in each multivariable model. Cm, comorbidities; EmPr, mode of presentation/admission (emergency or not); St, stage; Sx, use/type of surgery*.

Table 2.6 Description of socioeconomic variations in time to treatment

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios or days (95% CI) in the most deprived group unless specified (reference: least deprived group)
Maddison [155] (Canada, 2012)	Income	C (stage III), R (stage II or III), 2001–2005	Waiting time within clinical benchmark (14 days from radiation oncology referral to consultation in rectal cancer)	Adjusted OR 0.78 (0.38, 1.61) *#Cm*
Moriceau [157] (France, 2016)	EDI	CR, all TNM stage, 2013	Time to diagnosis	Adjusted HR 0.97 (0.50, 1.90) *#St*
			Time to treatment	Adjusted HR 1.17 (0.60, 2.29) *#St*
Neal [123] (England, 2005)	Occupation	CR, no stage information, 2002	Total delay	Social class not associated with the outcome (social class not included in the multivariable model)
			Patient and primary care delays (pre-hospital delay)	Social class not associated with the outcome (social class not included in the multivariable model)
			Referral delays	Social class not associated with the outcome (social class not included in the multivariable model)
			Secondary care delay	F(7)=2.247, p=0.028 in generalised linear model
Porter [124] (Canada, 2005)	Annual income	CR, stage I–IV, 2001	Time from symptoms to first medical doctor (days)	Median days (IQR): 36 (11, 72) in the most deprived group, 20 (9, 61) in the least deprived group (p=0.34)
			Time from first medical doctor to diagnosis (days)	Median days (IQR): 87 (40, 177) in the most deprived group, 60 (30, 155) in the least deprived group (p=0.20)
			Time from diagnosis to surgery (days)	Median days (IQR): 24 (14, 46) in the most deprived group, 15 (9, 40) in the least deprived group (p=0.25)
Bardell [153] (Canada, 2006)	Median household income	CR, no stage information, 1984–2000	Waiting time from diagnosis to admission for surgery (days)	Adjusted mean waiting time 28.2 (27.2, 29.3) days in the least deprived group, 28.8 (27.7, 30.0) days in the most deprived group *#Sp*
			Surgery within 2 weeks of diagnosis	Adjusted OR 1.09 (1.00, 1.18) *#Sp*
Campbell [159] (Scotland, 2002)	Carstairs index	CR, Duke's stage A–D, 1995–1996	Time from first referral to first treatment (surgery, chemotherapy or radiotherapy)	Adjusted HR 1.24 (0.93, 1.67) *#St, EmPr*
Chamberlain [133] (England, 2015)	IMD	CR, stage IV, 2011–2013	Time to treatment	Adjusted HR 1.20 (0.92, 1.59)
Jorgensen [a]* [142] (Australia, 2014)	SEIFA	CR, all stages who underwent surgery, 2007–2008	Treatment within 31 days of decision	SES not associated with the outcome (SES not included in the multivariable model) *#St, Cm (C), St (R)*
			Treatment within 62 days of referral	SES not associated with the outcome (SES not included in the multivariable model) *#St, EmPr (C), St (R)*

Table 2.6 continued

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios or days (95% CI) in the most deprived group unless specified (reference: least deprived group)
Paterson [135] (Scotland, 2014)	SIMD	CR, Duke's stage A–D, 2003–2009	62-day target met	OR 1.02 (p=0.18, chi square test for trend)
Lejeune* [126] (England, 2010)	Townsend index	CR, AJCC stage I–IV, 1997–2000	Time to treatment (treatment within first week)	Adjusted OR 0.78 (0.72, 0.84) *#St*
			Time to treatment (treatment within first month)	Adjusted OR 0.84 (0.78, 0.90) *#St*
			Time to treatment (treatment within 2-3 months)	Adjusted OR 0.91 (0.85, 0.98) *#St*
			Time to treatment (treatment within4-6 months)	Adjusted OR 1.07 (0.96, 1.18) *#St*
Johnston [156] (Canada, 2004)	Median household income	CR, all stages who received radiotherapy within 1 year of diagnosis, 1992–2000	Time from diagnosis to first consult with radiation oncologist (T1)	Adjusted HR 1.06 (0.98, 1.13) per $10000 increase in median household income (continuous) *#St*
			Time from first consult with radiation oncologist to first radiotherapy (T2)	Adjusted HR 0.99 (0.92, 1.06) per $10000 increase in median household income (continuous) *#St*
			Time from diagnosis to first radiotherapy (T1+T2)	Adjusted HR 1.04 (0.97, 1.12) per $10000 increase in median household income (continuous) *#St*
Lima* [139] (Canada, 2011)	Median annual household income	C, stage III, 2000–2005	Adjuvant chemotherapy within 12 weeks from surgery	OR 0.65
van der Geest [158] (Netherlands, 2013)	SES based on the Netherlands Institute for Social Research	C, stage III, 2006–2008	Delay of adjuvant chemotherapy	Adjusted OR 0.32 (0.13, 0.76) *#EmSx*

Table 2.6 continued

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios or days (95% CI) in the most deprived group unless specified (reference: least deprived group)
Maddison [155] (Canada, 2012)	Income	C (stage III) and R (stage II or III), 2001–2005	Waiting time within clinical benchmark (14-day from radiation oncology referral to consultation in rectal cancer)	Adjusted OR 0.78 (0.38, 1.61) *#Cm*
Rayson [154] (Canada, 2012)	Quebec Model (social and material deprivation index)	C (stage IIB or III) and R (stage II and III), 2000–2005	Chemotherapy receipt within 12 weeks of curative-intent surgery	CR: adjusted OR 0.4 (0.18, 0.91), C: no variable associated with delay, R: adjusted OR 0.31 (0.10, 0.91)
Helewa* [119] (Canada, 2013)	Income	CR, AJCC stage I–IV, 2004–2006	Higher total waiting time quartiles for non-urgent presentation	Adjusted OR 1.06 (0.74, 1.52) *#St, Cm*
Redaniel* [140] (England, 2014)	IMD	CR, Duke's stage A–B, 1996–2009	Time from diagnosis to major surgical resection	Coefficient 0.21 (-0.55, 0.98) *#St, Cm*

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; C, colon cancer; CR, colorectal cancer; EDI, European Deprivation Index; HR, hazard ratio; IMD, Index of Multiple Deprivation; IQR, interquartile range; OR, odds ratio; R, rectal cancer; SEIFA, Socio-Economic Indexes for Areas; SES, socioeconomic status; SIMD, Scottish Index of Multiple Deprivation score. * has analysis on mortality or survival. *# shows important factors adjusted in each multivariable model. Cm, comorbidities; EmPr, mode of presentation/admission (emergency or not); EmSx, urgency of surgery (elective or emergency); Sp, speciality/type of surgeon/hospital or surgical/hospital volume; St, stage.*

Table 2.7 Description of socioeconomic variations in receipt of any treatment

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) in the most deprived group unless specified (reference: least deprived group)
Crawford [125] (England, 2012)	IMD	CR, stage I–IV, 1994–2002	Any treatment	C: adjusted OR 0.54 (0.39, 0.76), R: adjusted OR 0.54 (0.34, 0.84) *#St*
Lejeune* [126] (England, 2010)	Townsend index	CR, AJCC stage I–IV, 1997–2000	Any treatment within 6 months after first contact within the NHS	Adjusted OR 0.87 (0.82, 0.92) *#St*
Maddison [155] (Canada, 2012)	Income	C (stage III) and R (stage II or III), 2001–2005	Receipt of clinically recommended care (chemotherapy for colon cancer, chemotherapy and radiotherapy in rectal cancer)	Adjusted OR 0.69 (0.43, 1.10) *#Cm*
Jorgensen[a]* [142] (Australia, 2014)	SEIFA	CR, all stages who underwent surgery, 2007–2008	Discussed at MDT meeting	SES not associated with the outcome (SES not included in the multivariable model) *#St, Sp*
Rollet [118] (France, 2018)	EDI	C, stage I–IV, 2005–2010	Assessment of extension (metastasis)	Adjusted OR 1.02 (0.76, 1.36) *#St, Cm, EmPr*
Beckman [160] (Australia, 2014)	SEIFA	CR, Duke's stage D, 2003–2008	Receipt of treatment	Adjusted OR 0.99 (0.93, 1.07) *#Cm*
		CR, Duke's stage A–D, 2003–2008	Treatment differing from guidelines	Adjusted prevalence ratio 0.94 (0.82, 1.09) *#St, Cm*

Abbreviations: 95% CI, 95% confidence interval; C, colon cancer; CR, colorectal cancer; EDI, European Deprivation Index; HR, hazard ratio; IMD, Index of Multiple Deprivation; MDT, multidisciplinary team; NHS, National Health Service; OR, odds ratio; R, rectal cancer; SEIFA, Socio-Economic Indexes for Areas; SES, socioeconomic status. * has analysis on mortality or survival. *# shows important factors adjusted in each multivariable model. Cm, comorbidities; EmPr, mode of presentation/admission (emergency or not); Sp, speciality/type of surgeon/hospital or surgical/hospital volume; St, stage.*

Table 2.8 Description of socioeconomic variations in receipt of surgery

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) in the most deprived group unless specified (reference: least deprived group)
Campbell [159] (Scotland, 2002)	Carstairs index	CR, Duke's stage A–D, 1995–1996	Surgery	Adjusted OR 0.52 (0.14, 1.87) *#St*
Hayes [162] (England, 2019)	IMD	C, all stages, 1999–2010	Surgery	Adjusted OR 0.62 (0.55, 0.70) *#St, Cm*
Beckman [160] (Australia, 2014)	SEIFA	CR, Duke's stage A–C, 2003–2008	Surgery	Adjusted OR 1.00 (0.98, 1.02) *#St, Cm*
Hall [127] (Australia, 2005)	Index of relative socioeconomic disadvantage (IRDS)	CR, no stage information, 1982–2001	Surgery	1982–2001: adjusted OR 1.02 (0.80, 1.30), 1991–2001: adjusted OR 1.13 (0.88, 1.45) *#Cm, EmPr*
Jones [163] (England, 2008)	IMD	CR, stage I–IV, 1994–2002	Surgery	C: adjusted OR 0.99 (0.99, 1.0), R: adjusted OR 0.99 (0.98, 0.99) for one increment in the deprivation score (ranging from 0: least deprived to 80: most deprived) *#St*
Rollet [118] (France, 2018)	EDI	C, stage I–IV, 2005–2010	Surgical approach in intention to treat	Adjusted OR 1.01 (0.77, 1.33) *#St, Cm, EmPr*
Paterson [135] (Scotland, 2014)	SIMD score	CR, Duke's stage A–D, 2003–2009	Resection for primary tumour	Adjusted OR 0.81 (0.63, 1.04) *#St*
Harris* [121] (England, 2009)	IMD	R, stage I–IV, 2001–2004	Operative procedure	OR 0.84 (p=0.003, Fisher's exact test)
			Resectional procedure	OR 0.85 (p=0.005, Fisher's exact test)
Bharathan* [120] (England, 2011)	IMD	CR, Duke's stage A–D, 1998–2002	Operative treatment	OR 0.97 (p=0.18, chi square test for trend)
			Curative resection	Adjusted OR 0.81 (0.66, 0.99) *#ASA, EmSx*
Olsson [161] (Sweden, 2010)	Income	R, stage I–IV, 1995–2005	Any surgical treatment	Adjusted OR 0.81 (0.63, 1.03) *#St, Sp*
			Any resection	Adjusted OR 0.76 (0.63, 0.91) *#St, Sp*

Table 2.8 continued

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) in the most deprived group unless specified (reference: least deprived group)
Morris [131] (England, 2010)	IMD	CR, all AJCC stages who underwent major resection for CRC (both synchronous and metachronous), 1998–2004	Liver resection	Adjusted OR 0.70 (0.61, 0.80) *#St, Cm, CR*
Vallance* [128] (England, 2018)	IMD	CR, stage IV (synchronous liver-limited metastases), 2010–2016	Liver resection	Adjusted OR 0.70 (0.59, 0.85) *#EmPr, CR, Sp*
t Lam-Boer* [129] (Netherlands, 2015)	Income	CR, stage IV (synchronous liver-only metastasis), 2004–2012	Liver resection	Adjusted OR 0.52 (0.31, 0.88) *#CR, Cm*
Noren* [130] (Sweden, 2016)	Income	CR, stage IV (synchronous liver-only metastasis), 2007–2011	Resection of synchronous liver metastasis	Adjusted OR 1.05 (0.75, 1.48) *#ASA, CR, Sp*

Abbreviations: 95% CI, 95% confidence interval; C, colon cancer; CR, colorectal cancer; EDI, European Deprivation Index; HR, hazard ratio; IMD, Index of Multiple Deprivation; OR, odds ratio; R, rectal cancer; SIMD, Scottish Index of Multiple Deprivation; SES, socioeconomic status.* has analysis on mortality or survival. *# shows important factors adjusted in each multivariable model ASA, ASA (American Society of Anesthesiologists) grade; CR, site (right/left-sided colon or rectum); Cm, comorbidities; EmPr, mode of presentation/admission (emergency or not); EmSx, urgency of surgery (elective or emergency); Sp, speciality/type of surgeon/hospital or surgical/hospital volume; St, stage.*

Table 2.9 Description of socioeconomic variations in type of surgery and others

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) in the most deprived group unless specified (reference: least deprived group)
Hole* [137] (Scotland, 2002)	Carstairs index	CR, Duke's stage A–D who underwent resection, 1991–1994	Type of resection (curative or palliative)	Curative resection: OR 1.04 (p=0.52, chi square test for trend)
Oliphant* [141] (Scotland, 2013)	SIMD score	CR, Duke's stage A–D who underwent surgery, 2001–2004	Intent of curative resection (*vs* palliative resection, no resection)	Curative resection: OR 0.89 (p <0.001, chi square test for trend)
Radwan* [169] (Wales, 2016)	Welsh Index of Multiple Deprivation (WIMD)	R, all TNM stage who underwent pelvic exenteration, 2006–2014	Type of exenteration (total or partial)	Total pelvic exenteration: OR 1.40 (p=0.69, chi square test for overall)
Dolet [164] (France, 2019)	EDI	R, stage I–IV who underwent curative surgery, 1997–2015	Non-restorative surgery	Adjusted OR 1.28 (0.89, 1.83) in the deprived groups (1: least deprived as reference vs 2+3+4+5) *#St*
Harris* [121] (England, 2009)	IMD	R, 2001–2004	Permanent stoma	OR 1.36 (p=0.11, Fisher's exact test)
Paterson [135] (Scotland, 2014)	SIMD score	CR, Duke's stage A–D, 2003–2009	Permanent stoma	C: OR 1.32, (p=0.25, chi square test for trend), R: OR 1.03 (p=0.16, chi square test for trend)
Morris [165] (England, 2008)	IMD	R, Duke's stage A–D who underwent surgery, 1998–2004	APER	Adjusted OR 1.37 (1.24, 1.50) *#St, EmPr, Sp*
Olsson [161] (Sweden, 2010)	Income	R, stage I–IV, 1995–2005	APER	Adjusted OR 1.14 (0.94, 1.39) *#St, Sp*
			AR	Adjusted OR 0.80 (0.69, 0.94) *#St, Sp*
			AR by stratified age groups	≤65 years: adjusted OR 0.79 (0.60, 1.04), 66–79 years: adjusted OR 0.91 (0.71, 1.16), ≥80 years: adjusted OR 0.62 (0.43, 0.91) *#St, Sp*
			AR by stratified by sex	Men: 0.84 (0.68, 1.04), women: OR 0.74 (0.56, 0.97) *#St, Sp*
			AR by stratified period	1995–2000: no difference in OR by income (SES not included in the multivariable model), 2001–2005: adjusted OR 0.75 (0.61, 0.92) *#St, Sp*
Raine [144] (England, 2010)	IMD	R, no stage information, 1999–2006	AR	Adjusted OR 0.75 (0.68, 0.82) *#EmPr*

Table 2.9 continued

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) in the most deprived group unless specified (reference: least deprived group)
Smith* [122] (England, 2006)	Townsend score	CR, Duke's stage A–D who underwent surgery, 2001–2002	Surgery procedure (AR, APER, others)	AR: OR 0.78, APER: OR 1.09 (p<0.001, chi square test for trend)
Tilney* [166] (England, 2008)	IMD	CR who underwent APER or AR, no stage information, 1996–2004	APER (vs AR)	Adjusted OR 1.58 (1.45, 1.74) *#EmPr*
Tilney* [167] (England, 2009)	IMD	R, Duke's stage A–C who underwent APER or AR, 2000–2005	APER (vs AR)	Adjusted OR 1.64 (1.36, 1.97) *#NATx*
Byrne [168] (England, 2018)	IMD deciles	CR, adults undergoing elective surgery, 2002–2012	Laparoscopic surgery (vs open)	Lower level of deprivation (more affluent) by 0.16 deciles (0.12-0.20)
Dik* [143] (Netherlands, 2014)	Mean household income and postcodes	CR, stage I–III who underwent surgery, 2005–2010	Laparoscopy	C: adjusted OR 0.72 (0.56, 0.93), R: adjusted OR 0.75 (0.50, 1.14) *#St, Cm*
			Laparoscopy converted to laparotomy (C)	Adjusted OR 1.89 (1.09, 3.22) *#St, Cm*
			Resection of primary tumour (R)	Adjusted OR 0.69 (0.41, 1.19) *#St, Cm*
			Endoscopic/TEM followed by surgery (R)	Adjusted OR 1.61 (0.63, 4.17) *#St, Cm*
			Lymph node yield at least 12	OR 0.93 (p=0.025, chi square test)
Del Paggio* [138] (Canada, 2017)	SES based on Canadian census	C, stage II or III, 2002–2008	Lymph node yield at least 12	Adjusted OR 0.90 (0.85, 0.94) *#St, Cm, Sx, Sp*
Lamy [132] (France, 2018)	EDI	CR, stage II, 2010	Lymph node yield at least 12	Adjusted OR 1.02 (0.38, 2.73) *#St, Cm, Sp*
Oliphant* [141] (Scotland, 2013)	SIMD score	CR, Duke's stage A–D who underwent surgery, 2001–2004	Lymph node yield at least 12	OR 0.92 (p=0.016, chi square test for trend)
Rollet [118] (France, 2018)	EDI	C, stage I– IV, 2005–2010	Lymph node yield at least 12	Adjusted OR 0.82 (0.64, 1.05) *#St, Cm, Sx, EmPr*
Tilney* [167] (England, 2009)	IMD	R, Duke's stage A–C who underwent APER or AR, 2000–2005	Lymph node yield at least 12	AR: OR 0.95 (p=0.07, chi square test for trend), APER: OR 1.12 (p=0.78, chi square test for trend)
Oliphant* [141] (Scotland, 2013)	SIMD score	CR, Duke's stage A–D who underwent surgery, 2001–2004	Speciality of surgeon	Specialist: OR 1.06 (p=0.001, chi square test for trend)
Wrigley* [170] (England, 2003)	Townsend score	CR, Duke's stage A–D, 1991–1995	Specialist treatment	OR 1.01 (p=0.51, chi square test for trend)

Abbreviations: 95% CI, 95% confidence interval; APER, abdominoperineal excision of rectum; AR, anterior resection; C, colon cancer; CR, colorectal cancer; EDI, European Deprivation Index; HR, hazard ratio; IMD, Index of Multiple Deprivation; OR, odds ratio; R, rectal cancer; SIMD, Scottish Index of Multiple Deprivation; SES, socioeconomic status; TEM, transanal endoscopic microsurgery. * has analysis on mortality or survival. *# shows important factors adjusted in each multivariable model. Cm, comorbidities; EmPr, mode of presentation/admission (emergency or not); NATx, use of neoadjuvant therapy; Sp, speciality/type of surgeon/hospital or surgical/hospital volume; St, stage; Sx, use/type of surgery.*

Table 2.10 Description of socioeconomic variations in receipt of chemotherapy

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) in the most deprived group unless specified (reference: least deprived group)
Campbell [159] (Scotland, 2002)	Carstairs index	CR, Duke's stage A–D, 1995–1996	Chemotherapy	Adjusted OR 0.49 (0.22, 1.10) *#St, EmPr*
Beckman [160] (Australia, 2014)	SEIFA	CR, Duke’s stage C, 2003–2008	Chemotherapy	Adjusted OR 0.94 (0.83, 1.96) *#Cm*
Jones [163] (England, 2008)	IMD	CR, stage I–IV, 1994–2002	Chemotherapy	C: adjusted OR 0.99 (0.98, 0.99), R: adjusted OR 0.99 (0.99, 1.0) for one increment in the deprivation score (ranging from 0: least deprived to 80: most deprived) *#St*
Dejardin* [172] (France, 2008)	Carstairs index	C, positive lymph nodes, metastasis, 1997–2000	No receipt of chemotherapy	Adjusted OR 1.31 (0.77, 1.86)
van der Geest [158] (Netherlands, 2013)	SES based on the Netherlands Institute for Social Research	C, stage III, 2006–2008	Adjuvant chemotherapy	SES not associated with chemotherapy receipt (SES not included in the multivariable model). *#St, Cm, EmSx*
			Discontinuation of adjuvant chemotherapy	SES not associated with discontinuation (SES not included in the multivariable model).
Hayes [162] (England, 2019)	IMD	C, all stages, 1999–2010	Adjuvant chemotherapy in surgical patients	Adjusted OR 0.72 (0.65, 0.80) *#St, Cm*
			Chemotherapy in non-surgical patients	Adjusted OR 0.44 (0.36, 0.55) *#St, Cm*
Hole* [137] (Scotland, 2002)	Carstairs index	CR who underwent resection, Duke's stage A–D, 1991–1994	Adjuvant therapy	OR 0.31 (p=0.01, chi square test for trend)
Jorgensen[b] [171] (Australia, 2014)	SEIFA	C (lymph node positive) and R (high-risk), 2007–2008	Adjuvant chemotherapy for node-positive colon cancer	Adjusted OR 0.97 (0.41, 2.29) *#Cm, EmPr*
Kelsall* [146] (Australia, 2008)	SEIFA	CR, AJCC stage I–IV, 1990–1994	Adjuvant chemotherapy	OR 0.79
van Steenbergen [174] (Netherlands, 2010)	Income	C, stage III, 2001–2007	Adjuvant chemotherapy	Adjusted OR 0.67 (0.50, 0.91) *#St (stage IIIA–IIIC), Cm*
Lamy [132] (France, 2018)	EDI	CR, stage III, 2010	Adjuvant chemotherapy	Adjusted OR 0.45 (0.16, 1.24) *#Cm, Sp*
		CR, stage IV, 2010	Access to KRAS testing	Adjusted OR 1.42 (0.61, 3.32) *#Cm, Sp*

Table 2.10 continued

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) in the most deprived group unless specified (reference: least deprived group)
Lemmens* [173] (Netherlands, 2005)	Mean household income and postcodes	C, stage III, 1995–2001	Adjuvant chemotherapy	Adjusted OR 0.5 (p=0.02) *#St, Cm*
Lima* [139] (Canada, 2011)	Median annual household income	C, stage III, 2000–2005	No receipt of adjuvant chemotherapy	OR 2.00
Paterson [135] (Scotland, 2014)	SIMD score	CR, Duke's stage A–D, 2003–2009	Any chemotherapy (palliative or adjuvant)	Adjusted OR 0.68 (0.55, 0.86)
Pitchforth [150] (Scotland, 2002)	Carstairs index	CR, Duke's stage C, 1992–1996	Chemotherapy	1990–94: adjusted OR 0.73 (0.55, 0.96), 1992–1996: adjusted OR 0.55 (0.20, 0.90) *#EmPr, Sp*
Rayson [154] (Canada, 2012)	Quebec Model (social and material deprivation index)	C (stage IIB or III) and R (stage II and III), 2000–2005	Chemotherapy	SES not associated with the outcome (SES not included in the multivariable model). *#St*
			Adjuvant chemotherapy	C: OR 0.94, R: OR 0.93
Rollet [118] (France, 2018)	EDI	C, stage II, III, IV, 2005–2010	Chemotherapy	Adjusted OR 0.89 (0.58, 1.35) *#St, Cm, Sx*
Maddison [155] (Canada,2012)	Income	C (stage III) and R (stage II or III), 2001–2005	Clinically recommended care (chemotherapy for colon cancer)	Adjusted OR 0.69 (0.43, 1.10) *#Cm*
Chamberlain [133] (England, 2015)	IMD	CR, stage IV, 2011–2013	Access to cancer drug fund	OR 0.43 (p=0.001, chi square test for trend)
Crawford [125] (England, 2012)	IMD	CR, stage I–IV, 1994–2002	Chemotherapy for stage IV	C: adjusted OR 0.45 (0.27, 0.77), R: adjusted OR 0.73 (0.36, 1.50)
Meulenbeld* [134] (Netherlands, 2008)	SES (not mentioned)	C, stage IV, 1990–2004	Chemotherapy	1990–94: OR 0.50, 1995-95: OR 0.41, 2000–02: OR 0.57, 2003–04: OR 0.94

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; C, colon cancer; CR, colorectal cancer; EDI, European Deprivation Index; HR, hazard ratio; IMD, Index of Multiple Deprivation; OR, odds ratio; R, rectal cancer; SIMD, Scottish Index of Multiple Deprivation; SEIFA, Socio-Economic Indexes for Areas; SES, socioeconomic status.* has analysis on mortality or survival. *# shows important factors adjusted in each multivariable model. Cm, comorbidities; EmPr, mode of presentation/admission (emergency or not); EmSx, urgency of surgery (elective or emergency); Sp, speciality/type of surgeon/hospital or surgical/hospital volume; St, stage; Sx, use/type of surgery.*

Table 2.11 Description of socioeconomic variations in receipt of radiotherapy

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) in the most deprived group unless specified (reference: least deprived group)
Campbell [159] (Scotland, 2002)	Carstairs index	CR, Duke's stage A–D, 1995–1996	Radiotherapy	Adjusted OR 0.85 (0.38, 1.91) *#St*
Jones [163] (England, 2008)	IMD	CR, stage I–IV, 1994–2002	Radiotherapy	C: adjusted OR 0.99 (0.99, 1.0), R: adjusted OR 0.99 (0.99, 1.0) for one increment in the deprivation score (ranging from 0: least deprived to 80: most deprived) *#St*
Beckman [160] (Australia, 2014)	SEIFA	R, Duke's stage B–C, 2003–2008	Radiotherapy	Adjusted OR 1.38 (1.05, 1.81) *#St, Cm*
Jorgensen[b] [171] (Australia, 2014)	SEIFA	C (lymph node positive) and R (high-risk), 2007–2008	Adjuvant radiotherapy for high-risk rectal cancer	SES not associated with the outcome (SES not included in the multivariable model) *#St, Cm, Sx*
Kelsall* [146] (Australia, 2008)	SEIFA	CR, AJCC stage I–IV, 1990–1994	Adjuvant radiotherapy	OR 1.39
Maddison [155] (Canada, 2012)	Income	C (stage III) and R (stage II or III), 2001–2005	Clinically recommended care (chemotherapy and radiotherapy in rectal cancer)	Adjusted OR 0.69 (0.43, 1.10) *#Cm*
Vulto [175] (Netherlands, 2007)	Mean household income	R, stage I–IV, 1996–2000	Secondary radiotherapy	Adjusted OR 1.11 (0.77, 1.67) *#St, Cm*
Olsson [136] (Sweden, 2011)	Income	R, stage I– IV, 1995–2005	Neoadjuvant radiotherapy	Adjusted OR 0.76 (0.67, 0.86) *#St, Sp*
			Neoadjuvant radiotherapy by age groups	–65 years: adjusted OR 0.62 (0.49, 0.77), 66–79 years: adjusted OR 0.78 (0.65, 0.93), 80–years: adjusted OR 0.70 (0.49, 1.02) *#St, Sp*
			Neoadjuvant radiotherapy by sublocalisation (distance from anal verge)	0–5 cm: adjusted OR 0.72 (0.57, 0.91), 6–10 cm: adjusted OR 0.81 (0.67, 0.98), 11–15 cm: adjusted OR 0.72 (0.58, 0.91) *#St, Sp*
			Neoadjuvant radiotherapy by sex	Men: adjusted OR 0.78 (0.66, 0.93), women: adjusted OR 0.68 (0.55, 0.83) *#St, Sp*
Paterson [135] (Scotland, 2014)	SIMD score	R, Duke's stage A–D, 2003–2009	Neoadjuvant radiotherapy	OR 1.09 (p=0.75, chi square test for trend)
Radwan* [169] (Wales, 2016)	WIMD	R, all TNM stage who underwent pelvic exenteration, 2006–2014	Neoadjuvant therapy	OR 1.00 (p=0.69, chi square test for overall)

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; C, colon cancer; CR, colorectal cancer; EDI, European Deprivation Index; HR, hazard ratio; IMD, Index of Multiple Deprivation; OR, odds ratio; R, rectal cancer; SIMD, Scottish Index of Multiple Deprivation; SEIFA, Socio-Economic Indexes for Areas; SES, socioeconomic status; WIMD, Welsh Index of Multiple Deprivation.* has analysis on mortality or survival. *# shows important factors adjusted in each multivariable model. Cm, comorbidities; Sp, speciality/type of surgeon/hospital or surgical/hospital volume; St, stage; Sx, use/type of surgery.*

Table 2.12 Description of socioeconomic differences in postoperative mortality or survival

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) or survival in the most deprived group unless specified (reference: least deprived group)
Bharathan [120] (England, 2011)	IMD	CR, Duke's stage A–D who underwent surgery, 1998–2002	Postoperative 30-day mortality	Adjusted OR 1.39 (0.51, 2.08) #*St, ASA, EmSx, Sx*
			5-year overall survival (entry: start of Sx)	Adjusted HR 1.20 (1.05, 1.37) #*St, ASA, EmSx, Sx*
			5-year net survival (entry: start of Sx)	Adjusted EHR 1.35 (1.05, 1.72) #*St, ASA, EmSx, Sx*
Jorgensen[a] [142] (Australia, 2014)	SEIFA	CR, all stage who underwent surgery, 2007–2008	30-day all-cause mortality	SES not associated with the outcome (SES not included in the multivariable model) #*St, Cm, EmPr*
			1-year overall mortality (entry: Sx)	SES not associated with the outcome (SES not included in the multivariable model) #*St, Cm, EmPr*
Dik [143] (Netherlands, 2014)	Mean household income and postcodes	CR, stage I–III who underwent surgery, 2005–2010	30-day postoperative mortality	C: adjusted OR 1.11 (0.64, 1.96) *St, Cm, EmSx*, R: adjusted OR 1.67 (0.56, 4.76) #*St, Cm*
Harris [121] (England, 2009)	IMD	R, stage I–IV, 2001–2004	Perioperative death	OR 1.40 (p=1.00, Fisher's exact test)
			Survival after resectional surgery (3-year, 5-year)	3-year: 85.0% in the least deprived, 74.6% in the most deprived, 5-year: 72% in the least deprived, 49.9% in the most deprived (p=0.03, log-rank test)
Hole [137] (Scotland, 2002)	Carstairs index	CR, Duke's stage A–D who underwent resection, 1991–1994	Postoperative 30-day mortality for patients who underwent curative resection	OR 1.24 (p=0.41, chi square test for trend)
			Postoperative 30-day mortality for patients who underwent palliative resection	OR 1.18 (p=0.98, chi square test for trend)
			5-year overall survival for patients who underwent curative resection	Adjusted HR 1.36 (1.09, 1.69) #*St, EmPr*
			5-year cancer-specific survival who underwent curative resection	Adjusted HR: 1.26 (0.95, 1.67) #*St, EmPr*

Table 2.12 continued

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) or survival in the most deprived group unless specified (reference: least deprived group)
Oliphant [141] (Scotland, 2013)	SIMD score	CR, Duke's stage A–D who underwent surgery, 2001–2004	Postoperative 30-day mortality from any cause	Adjusted OR 2.26 (1.45, 3.53) #*St, EmPr, Sx, Sp*
			5-year net survival (entry: Sx)	Adjusted relative excess risk 1.25 (1.03, 1.51) #*St, EmPr, Sx, Sp*
Smith [122] (England, 2006)	Townsend score	CR, Duke's stage A–D who underwent surgery, 2001–2002	Postoperative mortality	Adjusted OR 1.02 (p=0.14) per unit increase in SES *#St, ASA, EmSx, Sx*
Tilney [166] (England, 2008)	IMD	CR who underwent APER or SR, no information on stage, 1996–2004	Postoperative 30-day mortality	AR: OR 1.21 (p=0.004, chi square for trend), APER: 1.31 (p=0.058, chi square test for trend)
Tilney [167] (England, 2009)	IMD	R, Duke's stage A–C who underwent APER or AR, 2000–2005	Postoperative 30-day mortality	AR: OR 1.53 (p=0.058, chi square test for trend), APER: OR 1.04 (p=0.90, chi square test for trend)
Del Paggio [138] (Canada, 2017)	SES based on Canadian census	C, stage II or III, 2002–2008	Overall survival (entry: Sx)	Stage II: adjusted HR 1.11 (0.89, 1.39) #*St, Cm, Sx, ATx, Sp*, stage III: adjusted HR 0.99 (0.84, 1.17) #*St, Cm, Sx, ATx, Sp*
			Cancer-specific survival (entry: Sx)	Stage II: adjusted HR 0.98 (0.73, 1.32) #*St, Cm, Sx, ATx, Sp*, stage III: adjusted HR 1.00 (0.82, 1.21) #*St, Cm, Sx, ATx, Sp*
Lima [139] (Canada, 2011)	Median annual household income	C, stage III, 2000–2005	Overall survival (entry: 16 weeks after Sx)	Adjusted HR 1.14 (0.77, 1.68) #*Cm, TmCTx*
			Cancer-specific survival (entry: 16 weeks after Sx)	Adjusted HR 0.98 (0.63, 1.54) #*Cm, TmCTx*
Radwan [169] (Wales, 2016)	WIMD	R, all TNM stage who underwent pelvic exenteration, 2006–2014	5-year survival (entry: Sx)	73% in the least deprived, 53% in the most deprived (p=0.015, log-rank test)
Noren [130] (Sweden, 2016)	Income	CR, stage IV (synchronous liver-only metastasis), 2007–2011	5-year overall survival (entry: Sx for primary lesion)	Adjusted HR 1.02 (0.90, 1.16) *#ASA, Cm, Sx (liver resection), Sp*
Redaniel [140] (England, 2014)	IMD	CR who underwent major resection, Duke's stage A–B, 1996–2009	Postoperative 5-year relative survival (entry: Sx)	Adjusted EHR 1.29 (1.13, 1.46) *#St, TmSx*

Abbreviations: 95% CI, 95% confidence interval; APER, abdominoperineal excision of rectum; AR, anterior resection; C, colon cancer; CR, colorectal cancer; EDI, European Deprivation Index; HER, excess hazard ratio; HR, hazard ratio; IMD, Index of Multiple Deprivation; OR, odds ratio; R, rectal cancer; SIMD, Scottish Index of Multiple Deprivation; SEIFA, Socio-Economic Indexes for Areas; SES, socioeconomic status; Sx, surgery; WIMD, Welsh Index of Multiple Deprivation. *# shows important factors adjusted in each multivariable model. ASA, ASA (American Society of Anesthesiologists) grade; ATx, use of adjuvant therapy; Cm, comorbidities; EmPr, mode of presentation/admission (emergency or not); EmSx, urgency of surgery (elective or emergency); Sp, speciality/type of surgeon/hospital or surgical/hospital volume; St, stage; Sx, use/type of surgery; TmCTx, time to chemotherapy; TmSx, time to major resection.*

Table 2.13 Description of socioeconomic differences in survival

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) or survival in the most deprived group unless specified (reference: least deprived group)
Meulenbeld [134] (Netherlands, 2008)	SES (not mentioned)	C, stage IV, 1990–2004	Overall survival	Adjusted HR 1.02 (0.91, 1.15) #*Cm, CTx*
Lemmens [173] (Netherlands, 2005)	Mean household income and postcodes	C, stage III, 1995–2001	Overall survival	Adjusted HR 1.00 (p=0.9) #*St, Cm, CTx*
Dejardin [172] (France, 2008)	Carstairs index	C, positive lymph nodes, metastasis, 1997–2000	Overall survival	Adjusted relative risk 0.99 (0.72, 1.26) #*CTx*
Kelsall [146] (Australia, 2008)	SEIFA	CR, AJCC stage I–IV, 1990–1994	Overall survival	Adjusted HR 1.37 (1.00, 1.89) #*St, ATx*
			Cancer-specific survival	Adjusted HR 1.25 (0.89, 1.75) #*St, ATx*
Harris [121] (England, 2009)	IMD	R, stage I–IV, 2001–2004	Overall survival (3-year, 5-year)	3-year:80.7% in the least deprived, 46.6% in the most deprived, 5-year: 64.0% in the least deprived, 32.8% in the most deprived (p<0.001, log-rank test)
Wrigley [170] (England, 2003)	Townsend score	CR, Duke's stage A–D, 1991–1995	Overall survival	Adjusted HR 1.15 (1.04, 1.27) #*St, Cm, EmSx, Sp*
			Cancer-specific survival	Adjusted HR 1.11 (0.99, 1.25) #*St, Cm, EmSx, Sp*
Lejeune [126] (England, 2010)	Townsend index	CR, AJCC stage I–IV, 1997–2000	Excess hazard of death≤3years	All patients: adjusted EHR 1.12 (1.07, 1.17), treatment within 1 weeks: adjusted EHR 1.05 (0.96, 1.14), treatment within 1 month: adjusted EHR 1.04 (0.95, 1.15), treatment within 2–3 months: adjusted EHR 1.20 (1.09, 1.31), treatment within 4–6 months: adjusted EHR 1.14 (0.93, 1.39), no treatment: adjusted EHR 1.15 (1.08, 1.24) # *St, TmTx*
Hall [127] (Australia, 2005)	IRDS	CR, no stage information,1982–2001	5-year overall survival	1982–2001: adjusted HR 1.13 (0.98,1.31), 1991–2001: adjusted HR 1.13 (0.98, 1.31) #*Cm, EmPr*
Helewa [119] (Canada, 2013)	Income	CR, AJCC stage I–IV, 2004–2006	5-year overall survival	Adjusted HR 1.54 (1.14, 2.08) #*St, Cm, EmPr, CTx, Tm (total waiting time: from index contact to first treatment)*

Table 2.13 continued

First author (country, year)	SES	Site, stage, year of study	Cancer care outcome	Description of ratios (95% CI) or survival in the most deprived group unless specified (reference: least deprived group)
Field*[147]	Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) score	CR, AJCC stage IV, 2009–2014	5-year overall survival	Adjusted HR 1.04 (0.85, 1.28) for four deprived groups (reference: one least deprived group) *#Sp, Cm, CR, PS, Nm, Pre*
Vallance [128] (England, 2018)	IMD	CR, stage IV (synchronous liver-limited metastases), 2010–2016	3-year overall survival	Adjusted HR 0.83 (0.77, 0.90) #*St, Cm, CR, EmPr, Sp*
			3-year overall survival for patients who underwent liver resection	Adjusted HR 1.03 (0.81, 1.32) #*St, Cm, CR, EmPr, Sp*
			3-year overall survival for patients without liver resection	Adjusted HR 0.86 (0.79, 0.93) #*St, Cm, CR, EmPr, Sp*
t Lam-Boer [129] (Netherlands, 2015)	Income	CR, stage IV (synchronous liver-only metastasis), 2004–2012	5-year overall survival	Adjusted HR 1.08 (0.87, 1.33) *#Cm, CR, Sx (liver resection), Tx*

Abbreviations: 95% CI, 95% confidence interval; C, colon cancer; CR, colorectal cancer; EDI, European Deprivation Index; EHR, excess hazard ratio; HR, hazard ratio; IMD, Index of Multiple Deprivation; IRDS, Index of Relative Socioeconomic Disadvantage; OR, odds ratio; R, rectal cancer; SEIFA, Socio-Economic Indexes for Areas; SES, socioeconomic status. *# shows important adjusted factors in multivariable model. ATx, use of adjuvant therapy; Cm, comorbidities; CR, site (right/left-sided colon or rectum); CTx, use of chemotherapy; EmPr, mode of presentation/admission (emergency or not); EmSx, urgency of surgery (elective or emergency);Nm, number of metastatic sites; Pre, clinical or other presentation; PS, performance status; Sp, speciality/type of surgeon/hospital or surgical/hospital volume; St, stage; Sx, use of surgery; Tx, use of systemic treatment; TmTx, time to treatment.*

Table 2.14 Summary of quality of studies by Newcastle-Ottawa Scale (NOS) for case-control and cohort studies

Study	**Selection**				**Comparability**		**Outcome/Exposure**			**Total score**
Question	**1**	**2**	**3**	**4**	**1 a)**	**1 b)**	**1**	**2**	**3**	
Mode of presentation										
Rollet [118] (France, 2018)	*	*	*	*	*	*	*		*	8
Raine [144] (England, 2010)	*	*	*	*			*	*	*	7
Helewa* [119] (Canada, 2013)	*	*	*	*	*	*	*	*	*	9
Borowski [145] (England, 2016)	*	*	*	*			*	*	*	7
Hole* [137] (Scotland, 2002)	*	*	*	*			*	*	*	7
Oliphant* [141] (Scotland, 2002)	*	*	*	*			*	*	*	7
Bharathan [120] (England, 2011)	*	*	*	*			*	*	*	7
Harris* [121] (England, 2009)	*	*	*	*				*	*	6
Smith [122] (England, 2006)	*	*	*	*			*	*	*	7
Place of treatment										
Blais [148] (France, 2006)	*	*	*	*	*	*	*	*	*	9
Dejardin [149] (France, 2005)	*	*	*	*	*		*	*	*	8
Kelsall* [146] (Australia, 2008)	*	*	*	*			*		*	6
Kim [152] (Korea, 2010)	*	*	*	*		*	*	*	*	8
Pitchforth [150] (Scotland,2002)	*	*	*	*			*	*	*	7
Field [147] (Australia, 2015)	*	*	*	*			*	*	*	7
Vallance [151] (England, 2017)	*	*	*	*			*	*	*	7
Borowski [145] (England, 2016)	*	*	*	*			*	*	*	7

Table 2.14 continued

	Selection				Comparability		Outcome/Exposure			Total score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Time to treatment										
Maddison [155] (Canada, 2012)	*	*	*	*	*	*	*	*	*	9
Moriceau [157] (France, 2016)	*	*	*	*	*	*	*	*	*	9
Neal [123] (England, 2005)		*	*	*				*		4
Porter [124] (Canada, 2005)				*				*		2
Bardell [153] (Canada, 2006)	*	*	*	*			*	*	*	7
Campbell [159](Scotland, 2002)	*	*	*	*	*		*	*	*	8
Chamberlain [133] (England, 2015)	*	*	*	*	*		*	*		7
Jorgensen [a]* [142] (Australia, 2014)	*	*	*	*	*	*	*	*	*	9
Paterson [135] (Scotland, 2014)	*	*	*	*	*		*	*	*	8
Lejeune* [126] (England, 2010)	*	*	*	*	*		*	*	*	8
Johnston [156] (Canada, 2004)	*	*	*	*	*		*	*	*	8
Lima* [139] (Canada, 2011)	*	*	*	*	*	*	*	*	*	9
van der Geest [158] (Netherlands, 2013)	*	*	*	*	*	*	*	*	*	9
Maddison [155] (Canada, 2012)	*	*	*	*	*	*	*	*	*	9
Rayson [154] (Canada, 2012)	*	*	*	*	*	*	*	*	*	9
Helewa* [119] (Canada, 2013)	*	*	*	*	*	*	*	*	*	9
Redaniel* [140] (England, 2014)	*	*	*	*	*		*	*	*	8

Table 2.14 continued

	Selection				Comparability		Outcome/Exposure			Total score
	1	2	3	4	5	6	7	8	9	
Any treatment										
Crawford [125] (England, 2012)	*	*	*	*	*		*	*	*	8
Lejeune* [126] (England, 2010)	*	*	*	*	*		*	*	*	8
Maddison [155] (Canada, 2012)	*	*	*	*	*	*	*	*	*	9
Jorgensen[a]* [142] (Australia, 2014)	*	*	*	*	*	*	*	*	*	9
Rollet [118] (France, 2018)	*	*	*	*	*	*	*		*	8
Beckman [160] (Australia, 2014)	*	*	*	*	*	*	*	*	*	9
Surgical treatment										
Campbell [159] (Scotland, 2002)	*	*	*	*	*		*	*	*	8
Hayes [162] (England, 2019)	*	*	*	*	*	*	*	*	*	9
Beckman [160] (Australia, 2014)	*	*	*	*	*	*	*	*	*	9
Hall [127] (Australia, 2005)	*	*	*	*		*	*	*	*	8
Jones [163] (England, 2008)	*	*	*	*	*		*	*	*	8
Rollet [118] (France, 2018)	*	*	*	*	*	*	*	*	*	9
Paterson [135] (Scotland, 2014)	*	*	*	*	*		*	*	*	8
Harris* [121] (England, 2009)	*	*	*	*				*	*	6
Bharathan* [120] (England, 2011)	*	*	*	*	*	*	*	*	*	9
Olsson [161] (Sweden, 2010)	*	*	*	*	*		*	*	*	8
Morris [131] (England, 2010)	*	*	*	*	*	*	*	*	*	9
Vallance* [128] (England, 2018)	*	*	*	*	*	*	*	*	*	9
t Lam-Boer* [129] (Netherlands, 2015)	*	*	*	*	*	*	*	*	*	9
Noren [130] (Sweden, 2016)	*	*	*	*	*	*	*	*	*	9

Table 2.14 continued

	Selection				Comparability		Outcome/Exposure			Total score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Type of surgery										
Hole* [137] (Scotland, 2002)	*	*	*	*			*	*	*	7
Oliphant* [141] (Scotland, 2013)	*	*	*	*			*	*	*	7
Radwan* [169] (Wales, 2016)	*	*	*	*			*	*	*	7
Dolet [164] (France, 2019)	*	*	*	*	*		*	*	*	8
Harris* [121] (England, 2009)	*	*	*	*				*	*	6
Paterson [135] (Scotland, 2014)	*	*	*	*	*		*	*	*	8
Morris [165] (England, 2008)	*	*	*	*	*	*	*	*	*	9
Olsson [161] (Sweden, 2010)	*	*	*	*	*		*	*	*	8
Raine [144] (England, 2010)	*	*	*	*	*		*	*	*	8
Smith* [122] (England, 2006)	*	*	*	*			*	*	*	7
Tilney* [166] (England, 2008)	*	*	*	*			*	*	*	7
Tilney* [167] (England, 2009)	*	*	*	*			*	*	*	7
Byrne [168] (England, 2018)	*	*	*	*			*	*	*	7
Dik* [143] (Netherlands, 2014)	*	*	*	*	*	*	*	*	*	9
Del Paggio* [138] (Canada, 2017)	*	*	*	*	*	*	*	*	*	9
Lamy [132] (France, 2018)	*	*	*	*	*	*	*	*	*	9
Rollet [118] (France, 2018)	*	*	*	*	*	*	*		*	8
Wrigley* [170] (England, 2003)	*	*	*	*			*	*	*	7

Table 2.14 continued

	Selection				Comparability		Outcome/Exposure			Total score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Receipt of chemotherapy										
Campbell [159] (Scotland, 2002)	*	*	*	*	*		*	*	*	8
Beckman [160] (Australia, 2014)	*	*	*	*	*	*	*	*	*	9
Jones [163] (England, 2008)	*	*	*	*	*		*		*	7
Dejardin* [172] (France, 2008)	*	*	*	*			*		*	6
van der Geest [158] (Netherlands, 2013)	*	*	*	*	*	*	*	*	*	9
Hayes [162] (England, 2019)	*	*	*	*	*	*	*	*	*	9
Hole* [137] (Scotland, 2002)	*	*	*	*			*	*	*	7
Jorgensen[b] [171] (Australia, 2014)	*	*	*	*	*	*	*		*	8
Kelsall* [146] (Australia, 2008)	*	*	*	*			*		*	6
van Steenbergen [174] (Netherlands, 2010)	*	*	*	*	*	*	*		*	8
Lamy [132] (France, 2018)	*	*	*	*	*	*	*		*	8
Lemmens* [173] (Netherlands, 2005)	*	*	*	*	*	*	*	*	*	9
Lima* [139] (Canada, 2011)	*	*	*	*	*	*	*	*	*	9
Paterson [135] (Scotland, 2014)	*	*	*	*	*		*		*	7
Pitchforth [150] (Scotland, 2002)	*	*	*	*	*		*	*	*	8
Rayson [154] (Canada, 2012)	*	*	*	*	*	*	*	*	*	9
Rollet [118] (France, 2018)	*	*	*	*	*	*	*		*	8
Maddison [155] (Canada,2012)	*	*	*	*	*	*	*	*	*	9
Chamberlain [133] (England, 2015)	*	*	*	*	*		*	*		7
Crawford [125] (England, 2012)	*	*	*	*	*		*	*	*	8
Meulenbeld* [134] (Netherlands, 2008)	*	*	*	*			*		*	6

Table 2.14 continued

	Selection				Comparability		Outcome/Exposure			Total score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Receipt of radiotherapy										
Campbell [159] (Scotland, 2002)	*	*	*	*	*		*	*	*	8
Jones [163] (England, 2008)	*	*	*	*	*		*		*	7
Beckman [160] (Australia, 2014)	*	*	*	*	*	*	*	*	*	9
Jorgensen[b] [171] (Australia, 2014)	*	*	*	*	*	*	*		*	8
Kelsall* [146] (Australia, 2008)	*	*	*	*			*		*	6
Maddison [155] (Canada, 2012)	*	*	*	*	*	*	*	*	*	9
Vulto [175] (Netherlands, 2007)	*	*	*	*	*	*	*	*	*	9
Olsson [136] (Sweden, 2011)	*	*	*	*	*		*	*	*	8
Paterson [135] (Scotland, 2014)	*	*	*	*	*		*		*	7
Radwan* [169] (Wales, 2016)	*	*	*	*			*	*	*	7
Postoperative mortality or survival										
Bharathan [120] (England, 2011)	*	*	*	*	*	*	*	*	*	9
Jorgensen[a] [142] (Australia, 2014)	*	*	*	*	*	*	*	*	*	9
Dik [143] (Netherlands, 2014)	*	*	*	*	*	*	*	*	*	9
Harris [121] (England, 2009)	*	*	*	*				*	*	6
Hole [137] (Scotland, 2002)	*	*	*	*	*		*	*	*	8
Oliphant [141] (Scotland, 2013)	*	*	*	*	*		*	*	*	8
Smith [122] (England, 2006)	*	*	*	*	*	*	*	*	*	9
Tilney [166] (England, 2008)	*	*	*	*			*	*	*	7
Tilney [167] (England, 2009)	*	*	*	*			*	*	*	7
Del Paggio [138] (Canada, 2017)	*	*	*	*	*	*	*	*	*	9
Lima [139] (Canada, 2011)	*	*	*	*	*	*	*	*	*	9
Radwan [169] (Wales, 2016)	*	*	*	*			*	*	*	7
Noren [130] (Sweden, 2016)	*	*	*	*	*	*	*	*	*	9
Redaniel [140] (England, 2014)	*	*	*	*	*		*	*	*	8

Table 2.14 continued

	Selection				Comparability		Outcome/Exposure			Total score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Survival										
Meulenbeld [134] (Netherlands, 2008)	*	*	*	*	*	*	*	*	*	9
Lemmens [173] (Netherlands, 2005)	*	*	*	*	*	*	*	*	*	9
Dejardin [172] (France, 2008)	*	*	*	*	*		*	*	*	8
Kelsall [146] (Australia, 2008)	*	*	*	*	*		*	*	*	8
Harris [121] (England, 2009)	*	*	*	*				*	*	6
Wrigley [170] (England, 2003)	*	*	*	*	*	*	*	*	*	9
Lejeune [126] (England, 2010)	*	*	*	*	*		*	*	*	8
Hall [127] (Australia, 2005)	*	*	*	*		*	*	*	*	8
Helewa [119] (Canada, 2013)	*	*	*	*	*	*	*	*	*	9
Field [147] (Australia, 2015)	*	*	*	*	*	*	*	*	*	9
Vallance [128] (England, 2018)	*	*	*	*	*	*	*	*	*	9
t Lam-Boer [129] (Netherlands, 2015)	*	*	*	*	*	*	*	*	*	9

2.1.3 Discussion

Socioeconomic variations in access to treatment were observed widely. This review revealed that treatment receipt was generally lower in the deprived groups in terms of surgery, chemotherapy and radiotherapy. Also, emergency presentation was likely to be more frequent among the deprived groups. Although definitions of SES and categorisation varied by countries and over time, persistent inequalities in access to treatment were found. As in line with previous reviews on time to treatment [176, 177], this review found a wide diversity in the definition of 'delay'. The reported outcome also differed by studies (e.g. days, HRs, ORs at a cut-off time); therefore, the studies were not easily comparable and pooling (i.e. meta-analysis) was not possible.

The relationship between time interval (expressed as 'delay') to diagnosis or treatment and survival was explored in a recent meta-analysis, concluding that the delay was not associated with survival [176]. However, in quality assessment by NOS, some studies included in that meta-analysis were low quality (with less than 7 stars). There is no clear definition of 'delay'. Although meta-analysis was not conducted in this thesis, evidence for the association between diagnostic or therapeutic 'delay' and survival is inconclusive.

After 2010, socioeconomic inequalities in receipt of liver resection for stage IV CRC have begun to be reported. Indications for liver resection started to change in the 1990s [178, 179] and currently, candidates for liver resection include some complicated cases (e.g. patients with extrahepatic disease or multiple liver metastases) [180]. However, some of these complications are continuously reported to be associated with for poorer survival. The known clinical prognostic factors include tumour grade, number of liver metastases and tumour size [178, 179, 181]. Synchronous over metachronous liver metastasis is also related to worse outcome [182, 183]. In Japan, involvement of hepatic hilar lymph nodes is considered to be associated with worse survival [184]. In the literature, only three (out of five articles) confined the study population to synchronous liver metastasis, but no studies controlled for the positivity of the hepatic hilar lymph nodes. Considering that the studies are population-based data, it might be difficult to obtain detailed clinical factors.

Most studies used population-based data. Therefore, regarding quality of study assessed by NOS, selection of the study population and definition of the outcome were clearly stated in general. Mostly, missingness in the vital status was low (<10%), which reflects the characteristic of the population-based data. Follow-up period to observe an outcome was less articulated in receipt of chemotherapy. Stage and comorbidities are essential information for receipt of treatment, and majority studies controlled for these variables.

Because the aim of this review is to assess differential receipt of treatment by SES, some important reports were excluded. One study reported postoperative 30-day morality by SES, but not reporting variations in receipt of treatment by SES, thus excluded [107]. One study reported failure-to-rescue by laparoscopic *vs* open surgery [168] but not by SES, thus not included. Pooling of the results was not done; meta-analysis carries risks of comparing studies that are not comparable, and random effects may disregard the problem of heterogeneity (for example between countries) [185].

Evidence of socioeconomic inequalities in postoperative mortality suggests that the quality of care/hospital may differ among SES groups [106, 107, 186]. Even after being adjusted for stage and treatment factors, inequalities in long-term survival remained. This fact implies that there may be other unmeasured factors, which confound the effect of SES on survival. Of the reviewed studies, one study on survival controlled for three treatment factors (receipt/type of surgery, adjuvant chemotherapy and hospital volume) [138]. The study provided evidence that the hazard of the deprived groups is not inferior to that of the affluent group if patient factors (age, comorbidities), tumour factors (site and stage) and all potential treatment factors (receipt of surgery, adjuvant therapy and hospital volume) were controlled. A report on survival comparing England and France also showed that the survival difference between the two countries was nullified when all treatment receipt (surgery, chemotherapy and radiotherapy use) were controlled [187]. From the fact that inequalities in access to cancer care were observed in all treatment steps, other studies on survival found in this review may have marked weaker socioeconomic gradient if the other unmeasured treatment factors were adjusted.

Treatment is influenced by tumour and patient factors such as stage and comorbidities; nevertheless, the findings of this review represented differential access in important steps of treatment through the CRC care. The effect of one differential treatment giving on survival inequalities may amplify as a patient goes through neoadjuvant therapy, surgery and adjuvant therapy.

Chapter 3: Data materials and methods

3.1 Data acquisition and ethics approval

For this thesis, I use population-based cancer registry data from England, held by the Cancer Survival Group (CSG) at the London School of Hygiene & Tropical Medicine (LSHTM). All ethics and statutory approvals, for data access and analyses in England, have been obtained by the CSG (LSHTM Ethics Reference 11984).

I use hospital-based cancer registry data and administrative data from Japan, held by Osaka University Hospital (OUH). Ethics approval was obtained by Dr Yuri Kitamura at OUH (OUH Ethics Reference 18127), and by the author of this thesis at the LSHTM (LSHTM Ethics Reference 16219). Letters of the ethics approvals are attached in Appendix 2.

3.2 Study settings

3.2.1 England

Study population

Residents in England, who were diagnosed with a primary colon or rectal cancer between January 2010 and March 2013 and followed up until the end of 2014, were included. Inclusion criteria were CRC (coded by the International Classification of Diseases tenth version: ICD-10 with C18, C19 and C20) of any histological type and age at diagnosis younger than 100 years old. Tis (carcinoma *in situ*) was excluded from the analysis. Vital status, socioeconomic status, date of birth, date of death, sex, tumour site (coded by ICD-10) and stage at diagnosis were obtained from the national cancer registry (Office for National Statistics: ONS) in England. These data were linked to Cancer Analysis System (CAS) data, National Bowel Cancer Audit (NBOCA) data and Hospital Episode Statistics (HES) data. CAS data provide information on pathology (histology and tumour grade). Histology and tumour grade recorded on CAS were included in analysis to explore any biological variations among different SES groups, since tumour grade independently affects survival from stage. NBOCA data record information on clinical diagnosis (date), referral (routes to diagnosis and date), screen-detected cancer or not, clinical staging, treatment and pathology (histology and tumour grade). HES provides information on referral (routes to diagnosis and date), treatment (date and type of procedures coded by the Office of Population Censuses and Surveys fourth version: OPCS-4, Classification of Interventions and Procedures) and comorbidities.

Stage information (the fifth edition of UICC TNM Classification [188]) was finally derived by a restrictive approach using both national cancer registry data and NBOCA data [189]. Histology and tumour grade were derived from CAS data and categorised into three and two groups, respectively (Appendix 3 shows histology categorisation). Emergency presentation before the first definitive treatment (i.e. emergency presentation recorded at the time of diagnosis or the time of the first major surgery for the primary lesion) was derived from routes to diagnosis recorded in NBOCA data and supplemented by HES data. Information on the first major surgery for the primary lesion (dates and type of surgery procedure) was also derived from NBOCA data and supplemented by HES data. Appendix 4 and Appendix 5 shows the type of surgery defined as major surgery for the primary lesion in this thesis. Surgery information was extracted from 30 days before to 180 days after the diagnosis date. Hospital record has a maximum of 20 diagnostic fields; thus, 17 comorbidities defined in Charlson Index and obesity were extracted from HES based on an algorithm [190, 191].

Income domain of the Index of Multiple Deprivation (IMD 2010) was used for deriving information on deprivation level of patients, according to their residence at the time of cancer diagnosis. The Index is an ecological measure defined at lower-layer super output area (LSOA) level (1,500 inhabitants on average) [192].

Comorbidities

When measuring the quality of cancer care and outcomes, comorbidities are one of the most important factors which may relate to both cancer care outcomes and survival. Comorbidities can be defined as important medical conditions not related to the main cause of hospitalisation (in this thesis, CRC), but may lead to a poorer outcome [193]. I extracted the comorbidities that were recorded from five to zero years before the diagnosis of CRC.

Comorbidities, which appeared on HES at least once between 0.5 and five years before diagnosis, were categorised as chronic comorbidities. Comorbidities, which were recorded for the first time, between the date of diagnosis and 0.5 years before diagnosis, were categorised as acute comorbidities. Unlike the Charlson Index, comorbidities were not assigned weight but were just counted.

Of the 17 comorbidities, I further selected ten and 14 comorbidities for the chronic and acute comorbidities, respectively, based on its clinical relevance to CRC treatment [191, 193] (Appendix 6).

Comorbidities not directly related to CRC but which imply irreversible conditions of vital organs (brain, heart, lung, liver, kidney, immune system or vascular system), which may affect the timeline of or selection of CRC treatment (e.g. invasive or less invasive treatment, curative or palliative treatment), were chosen as chronic comorbidities. Obesity was included independently in acute phase only (0 to 0.5 years before CRC diagnosis) since body mass index (BMI) is a time-varying variable (i.e. reversible condition) and may confound with stage at diagnosis (e.g. patients with advanced stage may have suddenly lost weight just before the diagnosis and record low BMI).

3.2.2 Japan

Study population

Residents in Osaka Prefecture, who were diagnosed with colon or rectal cancer at Osaka University Hospital (OUH) between January 2012 and December 2015 and followed up until the end of July 2018, were included in the analysis. The OUH is one of the DCHs, which sits in the north of Osaka Prefecture. The OUH has approximately 1,000 beds in total, with around 100 beds for the gastrointestinal surgery unit and 29 beds for the intensive care unit (ICU).

Inclusion criteria were primary CRC of any histological type and age at diagnosis younger than 100 years old. Tis (carcinoma *in situ*) was excluded from the analysis. Vital status, date of birth, date of death, sex, tumour site (coded by ICD-10) were obtained from the hospital-based cancer registry in OUH. Hospital-based cancer registry data also provide information on pathology (histology and tumour grade), information on clinical diagnosis (date of diagnosis, place of diagnosis), referral route, clinical staging, treatment (open or laparoscopic surgery, chemotherapy and radiotherapy at OUH, coded by yes/no) at the institution. Date of diagnosis is defined as the date of the first diagnostic test (endoscopy) conducted. If a patient received a diagnostic test in other clinics or hospitals before consultation at OUH, the date of the diagnostic test in the other clinics is recorded. The UICC TNM staging is not used in clinical settings in Japan. Instead, Japanese Classification of Colorectal Carcinoma seventh edition [194] (eighth edition for the cases diagnosed after July 2013 [195]) is used. The Japanese Classification was converted to UICC TNM stages (seventh edition [196]) first, then to four stages (localised, positive regional lymph nodes, invasion to adjacent organs and distant metastasis). The dataset was linked to Diagnostic Procedure Combination (DPC) data at OUH. DPC data were missing for 24.1% of CRC patients who were registered in the hospital-based cancer registry. DPC data provide detailed information on treatment (date and types of procedures coded by medical fee points), emergency admission, use of ICU, height and weight, activities of daily living (ADL), Brinkman index and comorbidities present at admission. Operation codes, extracted as major surgery for the primary lesion, are listed in Appendix 7. Information on treatment was not restricted to procedures for CRC but extracted also for any other co-existing diseases. Nor was the period of the extraction of treatment information restricted from 30 days before diagnosis to 180 days after diagnosis, as in England.

The relative measure of SES, the area deprivation index (ADI) in Osaka Prefecture divided into quintiles, was linked to the hospital-based cancer registry data. A national census is performed every five years and contains data for income, education and employment status. Ecological deprivation information was constructed using the national census and Japanese General Social Survey (JGSS) data, defined at ‘Cho-Aza’ level (3,000 inhabitants on average) [197].

Comorbidities

Comorbidities were coded by ICD-10 for up to four concurrent diseases in the DPC data. As was done for data in England, 14 acute comorbidities were selected based on the Charlson Index and Elixhauser’s comorbidity scoring system [191, 193, 198], and the number of the comorbidities was counted. Information on chronic comorbidities (i.e. coded five years to six months before CRC diagnosis) was not used since no such data is available in Japan. In addition to the acute comorbidities, Brinkman index (number of cigarettes per day times number of years of smoking), BMI and ADL were analysed.

3.3 Statistical analysis

Stata 14 (StataCorp, College Station, TX, US) was used for all analyses. Details of the statistical methods are described in each chapter. An extended analysis, called mediation analysis, is used in **Chapter 4.5** under the causal inference framework.

Mediation analysis is useful when one wants to not only measure the magnitude of the causal effect of an exposure variable on an outcome but also isolate the causal effect(s) passing via mediator(s). For instance, in this thesis, I aim to measure the magnitude of the effect of an exposure variable, SES, on an outcome (survival status), mediated by a patient factor (comorbidities), a tumour factor (stage) and a healthcare system factor (receipt of treatment). The simplified example is shown in a directed acyclic graph (DAG) (Figure 3.1).

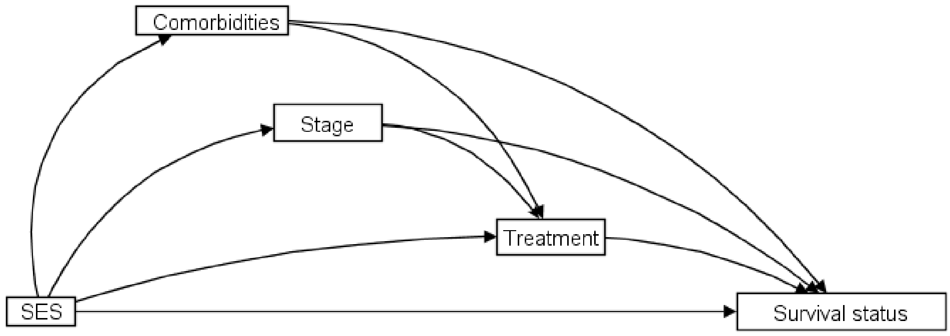

Figure 3.1 Example of DAG in mediation analysis

The stage at diagnosis and comorbidities could be affected by SES, and act as exposure-induced mediator-outcome confounders. Treatment could act as a mediator between SES and survival status, affected by SES, comorbidities and stage. Age at diagnosis, sex, year of diagnosis are the baseline confounders (not shown in Figure 3.1). I applied g-computation for the mediation analysis, initially developed by Robins to address the issue of a mediator being affected by exposure [199, 200]. The final models in **Chapter 4.5** have multiple mediators. When multiple mediators exist, the effect of the mediators will be measured jointly [201, 202].

3.3.1 Mediation analysis under the causal inference framework

Evaluation of causal effects needs to compare factual and counterfactuals. Factual refers to the fact outcomes that actually happened, and counterfactuals refer to potential outcomes that people would have experienced if they had taken a different path. I present definitions with examples.

Total causal effect

The total causal effect (TCE) of SES on survival variation at a population level can be decomposed in natural direct and indirect effect.

Y(X) stands for the outcome: survival status Y, when SES is set at X. If we denote X=1 as the SES set as the most deprived, and X=0 as the least deprived, individual causal effect of the SES is defined as Y(1)-Y(0).

The average causal effect in the population is defined as E{Y(1)-Y(0)} and it represents TCE of SES on survival status.

Natural direct effect

Natural direct effect (NDE) is defined as an effect of SES (X) on survival status (Y), when mediators (denoted as M, treatment: e.g. receipt of major surgery for the primary lesion) set as a natural value of M(x*) under X=x*. The NDE is the effect unmediated by M, thus, in a simple example, the NDE is the effect of SES on survival status unmediated by healthcare system factors.

$$NDE=E\{Y(x, M(x^*))\}-E\{Y(x^*, M(x^*))\}$$

Natural indirect effect

Natural indirect effect (NIE) is defined as an effect of SES (X) on survival status (Y) mediated by M (healthcare system factors). We compare two hypothetical worlds with the reference condition of X set as x and compare M(x) and M(x*).

$$NIE=E\{Y(x, M(x))\}-E\{Y(x, M(x^*))\}$$

Proportion mediated

The proportion of the total effect which healthcare system factors mediate, are measured by proportion mediated (PM).

PM=NIE/TCE

The PM quantifies how much of the total causal effect (effect of SES on survival status) is due to the effect of the mediated pathway (effect of SES on the mediator: treatment) [203].

Assumptions

There are several assumptions for mediation analysis.

- Conditional exchangeability: conditional on the observed confounders (e.g. same age group), the allocation to SES is random in the age group. Once patients are stratified by SES and age group, their allocation to mediators (e.g. receipt of major surgery) is random within these strata.
- Positivity: each level of mediator(s) can be observed at every level of the confounders.
- No unmeasured confounding between mediators and outcome in order to identify the path-specific effects.
- No interference between patients: a patient's mediator level is not affected by the mediator level of other patients. A patient's mediator level does not affect the outcome of other patients. For example, the option in receipt of surgery by a patient does not influence the outcome (survival status) of another.
- Consistency: the observed (factual) outcome of a patient receiving treatment is equal to the potential (counterfactual) outcome of a patient assigned to the same treatment [204, 205].
- Correct model specification of outcome or mediators.

Detailed models of the mediation analysis are explained in **Chapter 4.5** with DAGs.

Chapter 4: Colorectal cancer in England

Chapter 4 explored socioeconomic inequalities in both care and survival of CRC patients in England. In **Chapter 4.1**, I examined socioeconomic variations in receipt of major surgery. In **Chapter 4.2**, I confined the study population to the patients who received major surgery and explored whether there was a difference by SES in postoperative 30-day mortality. **Chapter 4.3** explored general patterns of mortality rate and survival by five SES groups not controlling for other factors. In **Chapter 4.4**, I examined socioeconomic disparities in survival incorporating receipt of major surgery. Finally, in **Chapter 4.5**, I investigated the potential magnitude of the effects of inequalities in cancer care on socioeconomic inequalities in survival.

4.1. Factors associated with receipt of major surgery and socioeconomic inequalities in receipt of surgery

The objective of this analysis was twofold. The first analysis explored potential factors associated with receipt of major surgery for the primary lesion and examined whether there was a difference by SES group in the receipt of major surgery. The second analysis explored factors associated with time to treatment and examined whether it varied by SES.

4.1.1 Methods

Study population

Patients with colon or rectal cancer, who resided in England and diagnosed between January 2010 and March 2013 and followed up until the end of December 2014, were included. Patients with Tis (carcinoma *in situ*) and those above 100 years old at the time of diagnosis were excluded from the analysis.

Outcome measure

In the first analysis, whether a patient received major surgery for the primary lesion (0 yes, 1 no) was set as a surrogate outcome to measure appropriate cancer care. Other potential surrogate outcomes could include the percentage of patients who received major surgery for curative intent, the number of lymph nodes yielded or complications of surgery. However, due to the large proportion of missing data, those measures were not used as the outcome measure. Type of surgery (e.g. APER or AR for rectal cancer) could also be an outcome; however, this was not used because the type of operation in rectal cancer largely depends on the sublocalisation of the tumour (i.e. height from the anal verge), for which data were again largely missing [84, 206, 207].

Regarding the extraction of the date and type of operation procedure of the first major surgery, I defined the NBOCA data as the priority. Information on operation procedure and date of the first major surgery was extracted from HES if NBOCA data had no information. A major operation for the primary lesion was extracted from 30 days before diagnosis to 180 days after diagnosis. NBOCA data covered 82.0% and 80.3% of the total information on the first major surgery for the primary lesion in colon and rectal cancers, respectively. Operation procedure codes identified as major surgery are displayed in Appendix 4 for colon cancer and Appendix 5 for rectal cancer.

The first analysis was extended to the second analysis to examine whether timely cancer care was provided equally to the different SES groups. The outcome of the second analysis was the number of days from diagnosis to surgical treatment (major surgery for the primary lesion).

For colon cancer, sites were categorised into three groups: right-sided colon (ascending colon, hepatic flexure, caecum and appendix), transverse colon (transverse colon and splenic flexure) and left-sided colon (descending colon and sigmoid colon). A sub-group analysis was conducted for the left-sided colon, by analysing descending and sigmoid colon separately.

Analysis strategy

For the first analysis, I applied logistic regression. To examine the length of the time from diagnosis to treatment in the second analysis, I applied linear regression.

In both analyses, *a priori* exposure was SES, and an interaction term between SES and stage was added as the main interest. Since important information (stage, tumour grade and emergency presentation) was missing, I conducted analyses with multiply imputed data and with complete cases (i.e. without imputations) as sensitivity analyses. The stage was missing at

31.1% and 27.3%, and tumour grade was missing at 24.3% and 22.3%, respectively, for colon and rectal cancers. Emergency presentation (i.e. routes to diagnosis or to the first major surgery for the primary lesion) was missing at 10% for colon and 6.7% for rectal cancer. Those three variables and histology (missing at less than 3% for each cancer) were imputed 30 times by multiple imputation with chained equations after the mechanisms of missingness in all three variables were examined to have missingness at random (MAR) dependent on covariates and outcome. Missingness of all three variables was associated with age group, cancer site, number of chronic or acute comorbidities, receipt of major surgery for the primary lesion, vital status (dead or alive) at the end of follow-up and government office region. Socioeconomic status was not associated with the missingness of stage but was associated with the missingness of tumour grade and emergency presentation in both cancers. Sex was associated with the missingness of stage in both cancers, but not with the missingness of tumour grade in either cancer or with emergency presentation in colon cancer. Year of diagnosis was not associated with the missingness of tumour grade in rectal cancer or the missingness of emergency presentation in colon cancer. Therefore, for the imputation, I used the following variables: sex, age group, cancer site, number of chronic and acute comorbidities, receipt of major surgery, vital status, Nelson-Aalen estimator and government office region. The distributions of the imputed stage, histology, tumour grade and emergency presentation are illustrated in Appendix 8.

In the second analysis, patients who received surgery within seven days of the date of diagnosis were defined as having received an 'urgent operation' and were thus excluded from the analysis; undergoing an urgent operation could mean that the patient did not receive an adequate assessment of cancer stage and comorbidities. As the distribution of the days from the diagnosis to treatment was right-skewed, the outcome in days was log-transformed. After the log-transformation, the distribution of the outcome became normally distributed only for colon cancer. The distribution of the days from diagnosis to treatment for rectal cancer patients was bi-modal with a truncation at 180 days. The distribution did not become normally distributed even after a log-transformation; therefore, I did not conduct the second analysis for rectal cancer. The distribution of the number of days for rectal cancer patients is illustrated in Appendix 9.

In both analyses using logistic and linear regression, I conducted bivariable analyses with *a priori* interest variable SES, to assess the changes in the association between SES and the outcome (i.e. the confounding effect of each variable). Each variable was also retained in the multivariable analysis based on the Wald test (p-value< 0.05) of the bivariable analysis. The Wald test was unifiedly used rather than likelihood ratio test for both imputed and completed data (i.e. data of complete cases) to account for the uncertainty in imputed data [208]. Variables were finally selected by backward elimination. A removed variable was added to the multivariable model again as a confounder if a model with the variable changed the effect of SES (OR of the most deprived in the first analysis) by more than 10%. Age group and sex were added as *a priori* confounders.

4.1.2 Results

There were 69,766 patients with colon cancer and 38,267 patients with rectal cancer. Baseline characteristics of the patients with colon and rectal cancer are displayed separately in Table 4.1 and Table 4.2. For both cancers, over half of the patients were male (53% for colon, 63% for rectal cancer). While the median age for both cancers was over 70 years old, the median age of the patients with rectal cancer was three years smaller than that of patients with colon cancer.

Noticeable socioeconomic gradients were observed in emergency presentation and number of chronic and acute comorbidities, which all showed better figures for the least deprived group. Mortalities at the end of the follow-up and postoperative 30-day mortality were also better among the less deprived groups in both cancers. Worse stage distribution among the deprived groups was only observed in rectal cancer. Stage information was missing at approximately 30% in both colon and rectal cancer. Socioeconomic gradient in histology and tumour grade was unclear. However, there was higher missingness in tumour grade in more deprived groups. Screen-detected cancer was approximately 5% in both cancers with smaller percentages in more deprived groups. However, in both cancers, missingness of data on screen-detected cancer exceeded 65% equally across all SES groups.

Table 4.1 Baseline characteristics of patients with colon cancer, England

		SES				
	Total number	**1st (least deprived)**	**2nd**	**3rd**	**4th**	**5th (most deprived)**
Total number	69766	15257	15472	14676	13720	10641
(%)	100	21.9	22.2	21.0	19.7	15.3
Median age at diagnosis	73.9	73.4	74.2	74.2	74.1	73.2
IQR	64.8–81.4	65.0–81.0	65.2–81.6	65.3–81.7	64.7–81.6	63.5–80.9
Female (%)	33081 (47.4)	7077 (46.4)	7241 (46.8)	7047 (48.0)	6648 (48.5)	5068 (47.6)
Death at the end of follow up (%)	32140 (46.1)	6392 (41.9)	6886 (44.5)	6781 (46.2)	6715 (48.9)	5366 (50.4)
Year of diagnosis (%)						
2010	21010 (30.1)	4484 (29.4)	4721 (30.5)	4515 (30.8)	4097 (29.9)	3193 (30.0)
2011	21692 (31.1)	4811 (31.5)	4799 (31.0)	4570 (31.1)	4265 (31.1)	3247 (30.5)
2012	21804 (31.3)	4761 (31.2)	4792 (31.0)	4508 (30.7)	4318 (31.5)	3425 (32.2)
2013	5260 (7.5)	1201 (7.9)	1160 (7.5)	1083 (7.4)	1040 (7.6)	776 (7.3)
Cancer site (%)						
Right-sided colon (ascending colon, hepatic flexure, caecum, appendix)	29213 (41.9)	6444 (42.2)	6414 (41.5)	6161 (42.0)	5750 (41.9)	4444 (41.8)
Transverse colon (transverse colon, splenic flexure)	7984 (11.4)	1752 (11.5)	1776 (11.5)	1707 (11.6)	1590 (11.6)	1159 (10.9)
Left-sided colon (descending colon, sigmoid colon)	26887 (38.5)	5923 (38.8)	5995 (38.8)	5679 (38.7)	5246 (38.2)	4044 (38.0)
Descending colon	3235 (4.6)	701 (4.6)	713 (4.6)	643 (4.4)	642 (4.7)	536 (5.0)
Sigmoid colon	23652 (33.9)	5222 (34.2)	5282 (34.1)	5036 (34.3)	4604 (33.6)	3508 (33.0)
Overlapping site or unspecified	5682 (8.1)	1138 (7.5)	1287 (8.3)	1129 (7.7)	1134 (8.3)	994 (9.3)
Stage at diagnosis (%)						
I	6002 (8.6)	1401 (9.2)	1308 (8.5)	1282 (8.7)	1129 (8.2)	882 (8.3)
II	13655 (19.6)	3021 (19.8)	3100 (20.0)	2836 (19.3)	2607 (19.0)	2091 (19.7)
III	12673 (18.2)	2812 (18.4)	2827 (18.3)	2615 (17.8)	2459 (17.9)	1960 (18.4)
IV	15722 (22.5)	3349 (22.0)	3410 (22.0)	3304 (22.5)	3232 (23.6)	2427 (22.8)
Missing	21714 (31.1)	4674 (30.6)	4827 (31.2)	4639 (31.6)	4293 (31.3)	3281 (30.8)

Table 4.1 continued

		SES				
	Total number	1st (least deprived)	2nd	3rd	4th	5th (most deprived)
Histology (%)						
Adenocarcinoma	66650 (95.5)	14554 (95.4)	14790 (95.6)	13998 (95.4)	13145 (95.8)	10163 (95.5)
Adenosquamous cell, squamous cell carcinoma	272 (0.4)	48 (0.3)	63 (0.4)	64 (0.4)	52 (0.4)	45 (0.4)
Non-epithelial tumours	1207 (1.8)	256 (1.7)	252 (1.6)	239 (1.6)	240 (1.8)	220 (2.1)
Missing	1636 (2.3)	399 (2.6)	366 (2.4)	375 (2.6)	283 (2.1)	213 (2.0)
Tumour grade (%)						
Well/moderately differentiated (G1/G2)	42944 (61.6)	9679 (63.4)	9656 (62.4)	8949 (61.0)	8279 (60.3)	6381 (60.0)
Poorly differentiated/undifferentiated (G3/G4)	9829 (14.1)	2254 (14.8)	2186 (14.1)	2115 (14.4)	1846 (13.5)	1428 (13.4)
Missing (GX)	16993 (24.4)	3324 (21.8)	3630 (23.5)	3612 (24.6)	3595 (26.2)	2832 (26.6)
Screening-detected cancer (%)	3743 (5.4)	946 (6.2)	885 (5.7)	756 (5.2)	673 (4.9)	483 (4.5)
Emergency presentation (%)						
No	45794 (65.6)	10398 (68.2)	10322 (66.7)	9787 (66.7)	8796 (64.1)	6491 (61.0)
Yes	17105 (24.5)	3325 (21.8)	3581 (23.2)	3538 (24.1)	3580 (26.1)	3081 (29.0)
Missing	6867 (9.8)	1534 (10.1)	1569 (10.1)	1351 (9.2)	1344 (9.8)	1069 (10.0)
Number of chronic comorbidities (%)						
0	59779 (85.7)	13480 (88.4)	13417 (86.7)	12634 (86.1)	11560 (84.3)	8688 (81.7)
1	7976 (11.4)	1479 (9.7)	1656 (10.7)	1627 (11.1)	1708 (12.5)	1506 (14.2)
2	1640 (2.4)	254 (1.7)	340 (2.2)	328 (2.2)	366 (2.7)	352 (3.3)
3+	367 (0.5)	42 (0.3)	59 (0.4)	87 (0.6)	84 (0.6)	95 (0.9)
Number of acute comorbidities (%)						
0	57964 (83.1)	13077 (85.7)	13048 (84.3)	12213 (83.2)	11197 (81.6)	8429 (79.2)
1	9712 (13.9)	1819 (11.9)	2036 (13.2)	2049 (14.0)	2047 (14.9)	1761 (16.6)
2	1705 (2.4)	294 (1.9)	329 (2.1)	333 (2.3)	380 (2.8)	369 (3.5)
3+	381 (0.6)	65 (0.4)	59 (0.4)	81 (0.6)	94 (0.7)	82 (0.8)
Obesity at diagnosis (BMI>30) (%)	1004 (1.4)	144 (0.9)	191 (1.2)	237 (1.6)	236 (1.7)	196 (1.8)
Received major surgery for primary lesion (%)	45907 (65.8)	10258 (67.2)	10322 (66.7)	9655 (65.8)	8845 (64.5)	6827 (64.2)
Postoperative 30-day mortality (%)*	1855 (4.0)	308 (3.0)	384 (3.7)	397 (4.1)	407 (4.6)	359 (5.3)

Abbreviations: BMI, body mass index; G, grade; IQR, interquartile range; SES, socioeconomic status. * Denominator is the number of patients who received major surgery (n=45907).

Table 4.2 Baseline characteristics of patients with rectal cancer, England

		SES				
	Total number	**1st (least deprived)**	**2nd**	**3rd**	**4th**	**5th (most deprived)**
Total number	38267	7977	8363	8057	7649	6221
(%)	100	20.9	21.9	21.1	20.0	16.3
Median age at diagnosis	70.8	70.8	70.8	70.9	71.2	70.1
IQR	62.2–79.1	62.3–78.8	62.4–79.1	62.5–79.2	62.3–79.5	60.7–78.6
Female (%)	14238 (37.2)	2982 (37.4)	3130 (37.4)	2967 (36.8)	2917 (38.1)	2242 (36.0)
Mortality at the end of follow up (%)	15668 (40.9)	2913 (36.5)	3205 (38.3)	3287 (40.8)	3328 (43.5)	2935 (47.2)
Year of diagnosis (%)						
2010	11621 (30.4)	2417 (30.3)	2575 (30.8)	2413 (30.0)	2299 (30.1)	1917 (30.8)
2011	11793 (30.8)	2475 (31.0)	2567 (30.7)	2478 (30.8)	2344 (30.6)	1929 (31.0)
2012	12019 (31.4)	2504 (31.4)	2605 (31.2)	2560 (31.8)	2457 (32.1)	1893 (30.4)
2013	2834 (7.4)	581 (7.3)	616 (7.4)	606 (7.5)	549 (7.2)	482 (7.8)
Cancer site (%)						
Rectosigmoid junction	7247 (18.9)	1489 (18.7)	1591 (19.0)	1489 (18.5)	1437 (18.8)	1241 (20.0)
Rectum	30771 (80.4)	6446 (80.8)	6733 (80.5)	6511 (80.8)	6153 (80.4)	4928 (79.2)
Overlapping site or unspecified	249 (0.7)	42 (0.5)	39 (0.5)	57 (0.7)	59 (0.8)	52 (0.8)
Stage at diagnosis (%)						
I	6355 (16.6)	1417 (17.8)	1408 (16.8)	1379 (17.1)	1220 (16.0)	931 (15.0)
II	5866 (15.3)	1229 (15.4)	1300 (15.5)	1223 (15.2)	1195 (15.6)	919 (14.8)
III	8312 (21.7)	1720 (21.6)	1842 (22.0)	1764 (21.9)	1635 (21.4)	1351 (21.7)
IV	7286 (19.0)	1426 (17.9)	1566 (18.7)	1518 (18.8)	1497 (19.6)	1279 (20.6)
Missing	10448 (27.3)	2185 (27.4)	2247 (26.9)	2173 (27.0)	2102 (27.5)	1741 (28.0)

Table 4.2 continued

		SES				
	Total number	**1st (least deprived)**	**2nd**	**3rd**	**4th**	**5th (most deprived)**
Histology (%)						
Adenocarcinoma	36240 (94.7)	7581 (95.0)	7956 (95.1)	7621 (94.6)	7229 (94.5)	5853 (94.1)
Adenosquamous cell, squamous cell carcinoma	486 (1.3)	81 (1.0)	95 (1.1)	111 (1.4)	110 (1.4)	89 (1.4)
Non-epithelial tumours	539 (1.4)	111 (1.4)	87 (1.0)	104 (1.3)	108 (1.4)	129 (2.1)
Missing	1002 (2.6)	204 (2.6)	225 (2.7)	221 (2.7)	202 (2.6)	150 (2.4)
Tumour grade (%)						
Well/moderately differentiated (G1/G2)	25919 (67.7)	5550 (69.6)	5759 (68.9)	5426 (67.4)	5098 (66.7)	4086 (65.7)
Poorly differentiated/undifferentiated (G3/G4)	3831 (10.0)	807 (10.1)	807 (9.7)	843 (10.5)	763 (10.0)	611 (9.8)
Missing (GX)	8517 (22.3)	1620 (20.3)	1797 (21.5)	1788 (22.2)	1788 (23.4)	1524 (24.5)
Screen-detected cancer (%)	2195 (5.7)	490 (6.1)	524 (6.3)	434 (5.4)	424 (5.5)	323 (5.2)
Emergency presentation (%)						
No	31507 (82.3)	6675 (83.7)	6977 (83.4)	6689 (83.0)	6277 (82.1)	4889 (78.6)
Yes	4210 (11.0)	685 (8.6)	795 (9.5)	869 (10.8)	924 (12.1)	937 (15.1)
Missing	2550 (6.7)	617 (7.7)	591 (7.1)	499 (6.2)	448 (5.9)	395 (6.4)
Number of chronic comorbidities (%)						
0	33858 (88.5)	7228 (90.6)	7539 (90. 2)	7128 (88.5)	6716 (87.8)	5247 (84.3)
1	3611 (9.4)	628 (7.9)	672 (8.0)	769 (9.5)	767 (10.0)	775 (12.5)
2	647 (1.7)	106 (1.3)	114 (1.4)	133 (1.7)	136 (1.8)	158 (2.5)
3+	151 (0.4)	15 (0.2)	38 (0.5)	27 (0.3)	30 (0.4)	41 (0.7)
Number of acute comorbidities (%)						
0	33942 (88.7)	7295 (91.5)	7540 (90.2)	7148 (88.7)	6665 (87.1)	5294 (85.1)
1	3643 (9.5)	578 (7.3)	685 (8.2)	764 (9.5)	832 (10.9)	784 (12.6)
2	575 (1.5)	92 (1.2)	116 (1.4)	117 (1.5)	126 (1.7)	124 (2.0)
3+	107 (0.3)	12 (0.2)	22 (0.3)	28 (0.4)	26 (0.3)	19 (0.3)
Obesity at diagnosis (BMI>30) (%)	422 (1.1)	63 (0.8)	81 (1.0)	79 (1.0)	104 (1.4)	95 (1.5)
Received major surgery for primary lesion (%)	19703 (51.5)	4333 (54.3)	4452 (53.2)	4205 (52.2)	3871 (50.6)	2842 (45.7)
Postoperative 30-day mortality (%)*	487 (2.5)	86 (2.0)	85 (1.9)	126 (3.0)	99 (2.6)	91 (3.2)

Abbreviations: BMI, body mass index; G, grade; IQR, interquartile range; SES, socioeconomic status. * Denominator is the number of patients who received major surgery (n=19703).

First analysis (logistic regression for receipt of major surgery and odds ratios by SES)

Multivariable logistic regression included 69,762 colon and 37,265 rectal cancer patients in imputed data. Sensitivity analyses using completed data included 38,624 colon (55.4% of total) and 22,630 rectal (59.1% of total) cancer patients. For colon cancer, 45,907 (65.8% of total) patients received major surgery. For rectal cancer, 19,703 (51.5% of total) received major surgery (Table 4.1 and Table 4.2). Table 4.3 and Table 4.4 illustrate the results of the bivariable and multivariable logistic regression analyses. To show the overall change in the effect of SES, the adjusted ORs of SES in those tables were based on a model without interaction between SES and stage. For the rest, adjusted ORs were based on the multivariable model with interaction between SES and stage (final model). The sub-group analysis of changing the category of site (left-sided colon separated to descending and sigmoid colon) did not affect the results of other variables in multivariable analyses in an important amount. Therefore, the results of the adjusted ORs for the other variables in the sub-group analyses were omitted.

Factors associated with receipt of major surgery

All examined factors except obesity were associated with receipt of major surgery in both cancers. With imputed data, age of 80+ with colon or rectal cancer had approximately three times the odds of not receiving surgery after adjusting for other factors, compared with the patients aged under 65 years. Patients with an emergency presentation had lower adjusted odds of not receiving surgery than the patients without an emergency presentation in colon cancer but had higher adjusted odds in rectal cancer. In both cancers, patients with an increased number of chronic and acute comorbidities had higher adjusted odds of not receiving surgery than patients without comorbidities.

In a bivariable analysis for colon cancer, patients with an emergency presentation had 1.2 times the odds of not receiving surgery compared with the patients without an emergency presentation (Table 4.3). However, the effect of emergency presentation on the receipt of surgery was reduced by stage, making the ORs of emergency presentation less than 1 in the multivariable analysis.

Receipt of major surgery by SES

Although deprived groups were more likely not to receive a major surgery in the bivariable analysis, after controlling for all potential confounders, the trend weakened to almost null in both imputed and completed data only for colon cancer (adjusted ORs of SES in Table 4.3 and Table 4.4).

In bivariable analyses, no factors cancelled the socioeconomic gradient favouring the least deprived in the receipt of major surgery. For both cancers, the gradient was slightly weakened when stage was adjusted in the bivariable analysis. Chronic and acute comorbidities also weakened the gradient, but age worsened the gradient in both cancers. The reduction of the gradient made by acute comorbidities was smaller than that made by chronic comorbidities. The effects of site and emergency presentation reduced the effect of SES on non-receipt of surgery for colon cancer but increased the effect of SES for rectal cancer.

The multivariable analyses stratified on stage showed that, among rectal cancer patients using imputed data, the most deprived group, compared with the least deprived, had higher adjusted odds of not receiving surgery at a significant level for stage II, III, and IV (Table 4.5). A similar trend was observed for colon cancer patients with stage III, but this did not reach a statistical significance. In other stages and sites (stage I, II and IV in colon cancer, stage I in rectal cancer), the socioeconomic gradient was weak.

In the sensitivity analyses using completed data, socioeconomic trends of the stage-specific ORs confirmed similar results with the analyses using imputed data. Deprived groups had increased odds of not receiving surgery among stage II, III and IV in rectal cancer patients (Table 4.5).

Table 4.3 Odds ratios of not receiving major surgery for primary lesion using logistic regression for colon cancer, England

Variable	Bivariable analysis			Multivariable analysis Multiple imputation (n=69762)			Multivariable sensitivity analysis Complete cases (n=38624)		
	OR*	95% CI	p-value[†]	OR**	95% CI	p-value[†]	OR**	95% CI	p-value[†]
SES									
1 (least deprived)	1.00			1.00			1.00		
2	1.02	(0.98, 1.07)		0.99	(0.93, 1.05)		0.96	(0.88, 1.06)	
3	1.07	(1.02, 1.12)	<0.001[‡]	1.00	(0.94, 1.06)	0.05[‡]	1.00	(0.91, 1.10)	0.51[‡]
4	1.13	(1.08, 1.19)		1.03	(0.97, 1.09)		0.96	(0.87, 1.06)	
5 (most deprived)	1.15	(1.09, 1.21)		1.06	(0.99, 1.13)		0.96	(0.87, 1.07)	
Sex									
Male	1.00			1.00			1.00		
Female	1.02	(0.99, 1.06)	0.15	0.96	(0.92, 1.00)	0.08	0.86	(0.81, 0.92)	<0.001
Age									
<65	1.00			1.00			1.00		
65–79	0.89	(0.86, 0.93)	<0.001[‡]	0.99	(0.94, 1.05)	<0.001[‡]	0.91	(0.84, 0.98)	<0.001[‡]
80–99	2.13	(2.04, 2.22)		2.82	(2.66, 2.99)		1.36	(1.24, 1.49)	
Year of diagnosis									
2010	1.00			1.00			1.00		
2011	1.06	(1.01, 1.10)	0.009	1.18	(1.12, 1.25)	<0.001	1.15	(1.05, 1.26)	0.002
2012	1.08	(1.03, 1.12)	<0.001	1.29	(1.22, 1.36)	<0.001	1.41	(1.30, 1.54)	<0.001
2013	1.17	(1.10, 1.25)	<0.001	1.42	(1.31, 1.54)	<0.001	1.44	(1.28, 1.64)	<0.001
Cancer site									
Right-sided colon[#]	1.00			1.00			1.00		
Transverse colon[#]	0.90	(0.86, 0.96)	<0.001	1.03	(0.96, 1.11)	0.37	1.13	(1.01, 1.26)	0.04
Left-sided colon[#]	1.27	(1.22, 1.31)	<0.001	1.72	(1.64, 1.80)	<0.001	2.11	(1.97, 2.27)	<0.001
Descending colon	1.11	(1.02, 1.20)	<0.001	1.56	(1.41, 1.73)	<0.001	1.96	(1.68, 2.28)	<0.001
Sigmoid colon	1.29	(1.24, 1.34)	<0.001	1.74	(1.66, 1.83)	<0.001	2.13	(1.98, 2.30)	<0.001
Overlapping site or unspecified	4.98	(4.68, 5.29)	<0.001	4.27	(3.95, 4.63)	<0.001	3.48	(3.02, 4.02)	<0.001

Table 4.3 continued

Variable	Bivariable analysis			Multivariable analysis Multiple imputation (n=69762)			Multivariable sensitivity analysis Complete cases (n=38624)		
	OR*	95% CI	p-value†	OR**	95% CI	p-value†	OR**	95%CI	p-value†
Stage at diagnosis									
I	1.00		<0.001‡				1.00		<0.001‡
II	0.25	(0.23, 0.27)					0.19	(0.15, 0.24)	
III	0.35	(0.32, 0.38)					0.23	(0.18, 0.29)	
IV	4.62	(4.32, 4.93)					3.34	(2.82, 3.97)	
Stage at diagnosis§									
I	1.00		<0.001‡	1.00		<0.001‡			
II	0.24	(0.22, 0.26)		0.23	(0.19, 0.27)				
III	0.32	(0.30, 0.35)		0.31	(0.26, 0.36)				
IV	3.79	(3.56, 4.02)		4.15	(3.64, 4.72)				
Histology									
Adenocarcinoma	1.00			1.00			1.00		
Adenosquamous and squamous cell carcinoma	1.63	(1.29, 2.08)	<0.001	4.28	(3.11, 5.90)	<0.001	3.28	(1.94, 5.56)	<0.001
Non-epithelial tumours	3.66	(3.25, 4.13)	<0.001	7.81	(6.68, 9.13)	<0.001	7.66	(6.11, 9.58)	<0.001
Tumour grade									
Well/moderately differentiated	1.00						1.00		
Poorly/undifferentiated	1.11	(1.05, 1.17)	<0.001				1.08	(1.00, 1.17)	0.06
Tumour grade§									
Well/moderately differentiated	1.00			1.00					
Poorly/undifferentiated	1.47	(1.39, 1.55)	<0.001	1.14	(1.07, 1.22)	<0.001			

Table 4.3 continued

Variable	Bivariable analysis			Multivariable analysis			Multivariable sensitivity analysis		
				Multiple imputation (n=69762)			Complete cases (n=38624)		
	OR*	95% CI	p-value†	OR**	95% CI	p-value†	OR**	95%CI	p-value†
Emergency presentation									
No	1.00						1.00		
Yes	1.10	(1.05, 1.14)	<0.001				0.65	(0.60, 0.70)	<0.001
Emergency presentation§									
No	1.00			1.00					
Yes	1.20	(1.16, 1.25)	<0.001	0.72	(0.68, 0.76)	<0.001			
Number of chronic comorbidities									
0	1.00		<0.001‡	1.00		<0.001‡	1.00		<0.001‡
1	1.51	(1.44, 1.58)		1.55	(1.45, 1.65)		1.32	(1.20, 1.47)	
2	2.90	(2.62, 3.20)		3.42	(2.99, 3.92)		2.84	(2.29, 3.53)	
3+	4.10	(3.30, 5.10)		4.89	(3.66, 6.55)		4.05	(2.59, 6.34)	
Number of acute comorbidities									
0	1.00		<0.001‡	1.00		<0.001‡	1.00		<0.001‡
1	1.27	(1.21, 1.32)		1.23	(1.16, 1.30)		1.11	(1.01, 1.22)	
2	1.93	(1.75, 2.13)		1.82	(1.60, 2.06)		1.52	(1.22, 1.90)	
3+	2.20	(1.80, 2.69)		2.37	(1.80, 3.13)		1.67	(1.04, 2.70)	
Obesity at diagnosis									
No	1.00			1.00					
Yes	0.69	(0.60, 0.79)	<0.001	0.74	(0.62, 0.88)	0.002			

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SES, socioeconomic status. * Adjusted for SES in all variables. Results of bivariable analysis on histology with imputed data and completed data did not differ in an important amount. Thus, results with only imputed data are shown. ** All variables are mutually adjusted. For SES only, adjusted ORs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. # Right-sided colon includes ascending colon, hepatic flexure, caecum and appendix. Transverse colon includes transverse colon and splenic flexure. Left-sided colon includes descending colon and sigmoid colon. † P-value of Wald test. ‡ P-value of Wald test for trend. § Multiply imputed.

Table 4.4 Odds ratios of not receiving major surgery for primary lesion using logistic regression for rectal cancer, England

Variable	Bivariable analysis			Multivariable analysis Multiple imputation (n=37265)			Multivariable sensitivity analysis Complete cases (n=22630)		
	OR*	95% CI	p-value†	OR**	95% CI	p-value†	OR**	95%CI	p-value†
SES									
1 (least deprived)	1.00			1.00			1.00		
2	1.04	(0.98, 1.11)		1.02	(0.95, 1.09)		1.06	(0.97, 1.17)	
3	1.09	(1.02, 1.16)	<0.001‡	1.02	(0.95, 1.10)	<0.001‡	1.07	(0.98, 1.18)	<0.001‡
4	1.16	(1.09, 1.24)		1.05	(0.98, 1.13)		1.11	(1.01, 1.22)	
5 (most deprived)	1.41	(1.32, 1.51)		1.29	(1.19, 1.39)		1.35	(1.22, 1.49)	
Sex									
Male	1.00			1.00			1.00		
Female	1.16	(1.11, 1.21)	<0.001	1.05	(1.00, 1.11)	0.04	1.00	(0.94, 1.06)	0.92
Age									
<65	1.00			1.00			1.00		
65–79	1.05	(1.00, 1.10)	<0.001‡	1.12	(1.06, 1.18)	<0.001‡	1.10	(1.02, 1.18)	<0.001‡
80–99	2.79	(2.63, 2.95)		2.84	(2.65, 3.04)		2.16	(1.98, 2.36)	
Year of diagnosis									
2010	1.00			1.00			1.00		
2011	1.03	(0.98, 1.09)	0.24	1.12	(1.06, 1.20)	<0.001	1.11	(1.02, 1.21)	0.01
2012	1.06	(1.01, 1.12)	0.02	1.19	(1.12, 1.27)	<0.001	1.20	(1.10, 1.29)	<0.001
2013	1.08	(0.99, 1.17)	0.08	1.23	(1.12, 1.35)	<0.001	1.22	(1.08, 1.38)	0.001
Cancer site									
Rectosigmoid junction	1.00			1.00			1.00		
Rectum	1.52	(1.44, 1.60)	<0.001	2.21	(2.07, 2.36)	<0.001	2.95	(2.69, 3.22)	<0.001
Overlapping site or unspecified	9.69	(6.70, 14.02)	<0.001	6.60	(4.24, 10.28)	<0.001	14.09	(6.94, 28.63)	<0.001
Stage at diagnosis									
I	1.00						1.00		
II	0.72	(0.67, 0.78)	<0.001‡				0.54	(0.44, 0.66)	<0.001‡
III	1.04	(0.98, 1.12)					0.86	(0.72, 1.02)	
IV	6.33	(5.87, 6.82)					5.79	(4.80, 6.98)	
Stage at diagnosis§									
I	1.00			1.00					
II	0.72	(0.66, 0.78)	<0.001‡	0.59	(0.50, 0.70)	<0.001‡			
III	1.03	(0.96, 1.11)		0.96	(0.82, 1.12)				
IV	6.16	(5.72, 6.63)		6.33	(5.32, 7.54)				

Table 4.4 continued

Variable	Bivariable analysis			Multivariable analysis			Multivariable sensitivity analysis		
				Multiple imputation (n=37265)			Complete cases (n=22630)		
	OR*	95% CI	p-value†	OR**	95% CI	p-value†	OR**	95%CI	p-value†
Histology									
Adenocarcinoma	1.00			1.00			1.00		
Adenosquamous and squamous cell carcinoma	20.48	(13.70, 30.61)	<0.001	22.71	(14.56, 33.36)	<0.001	20.65	(12.23, 34.87)	<0.001
Non-epithelial tumours	7.87	(6.07, 10.20)	<0.001	8.48	(6.83, 11.83)	<0.001	3.59	(2.46, 5.42)	<0.001
Tumour grade									
Well/moderately differentiated	1.00						1.00		
Poorly/undifferentiated	1.63	(1.53, 1.75)	<0.001				1.13	(1.03, 1.24)	0.009
Tumour grade§									
Well/moderately differentiated	1.00			1.00					
Poorly/undifferentiated	1.72	(1.60, 1.84)	<0.001	1.14	(1.05, 1.24)	<0.001			
Emergency presentation									
No	1.00						1.00		
Yes	2.40	(2.24, 2.56)	<0.001				1.44	(1.30, 1.60)	<0.001
Emergency presentation§									
No	1.00			1.00					
Yes	2.57	(2.40, 2.74)	<0.001	1.61	(1.48, 1.75)	<0.001			
Number of chronic comorbidities									
0	1.00			1.00			1.00		
1	1.65	(1.54, 1.77)	<0.001‡	1.58	(1.46, 1.72)	<0.001‡	1.44	(1.29, 1.60)	<0.001‡
2	2.80	(2.36, 3.33)		2.46	(2.02, 2.99)		1.94	(1.50, 2.52)	
3+	5.57	(3.63, 8.57)		4.50	(2.82, 7.22)		2.08	(1.10, 3.87)	
Number of acute comorbidities									
0	1.00			1.00			1.00		
1	1.50	(1.40, 1.60)	<0.001‡	1.25	(1.15, 1.36)	<0.001‡	1.23	(1.11, 1.37)	<0.001‡
2	2.79	(2.33, 3.35)		2.16	(1.75, 2.68)		1.94	(1.46, 2.60)	
3+	3.13	(2.03, 4.82)		2.14	(1.31, 3.50)		1.48	(0.77, 2.98)	
Obesity at diagnosis									
No	1.00								
Yes	0.84	(0.69, 1.02)	0.07						

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SES, socioeconomic status. * Adjusted for SES in all variables. Results of bivariable analysis on histology with imputed data and completed data did not differ in an important amount. Thus, results with only imputed data are shown. ** All variables are mutually adjusted. For SES only, adjusted ORs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. † P-value of Wald test. ‡ P-value of Wald test for trend. § Multiply imputed.

Table 4.5 Stage-specific odds ratios of not receiving major surgery for primary lesion using multivariable logistic regression with interaction between SES and stage for colon and rectal cancer, England

	Colon						Rectum					
	Multiple imputation[a]			Complete cases[b]			Multiple imputation[c]			Complete cases[d]		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Stage I												
SES												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	0.89	(0.76, 1.04)		0.89	(0.72, 1.09)		0.93	(0.80, 1.09)		0.99	(0.83, 1.19)	
3	0.99	(0.84, 1.15)	0.38	1.03	(0.84, 1.27)	0.24	0.96	(0.82, 1.12)	0.68	0.97	(0.81, 1.16)	0.49
4	1.04	(0.89, 1.22)		1.08	(0.88, 1.34)		0.99	(0.85, 1.15)		1.06	(0.88, 1.27)	
5 (most deprived)	1.00	(0.84, 1.19)		1.05	(0.84, 1.32)		1.02	(0.86, 1.21)		1.05	(0.86, 1.28)	
Stage II												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	0.96	(0.81, 1.14)		1.03	(0.79, 1.34)		1.16	(0.98, 1.38)		1.28	(1.03, 1.58)	
3	0.98	(0.83, 1.16)	0.29	0.99	(0.75, 1.30)	0.51	1.14	(0.95, 1.36)	0.004	1.32	(1.06, 1.63)	0.004
4	1.03	(0.87, 1.23)		1.00	(0.76, 1.33)		1.08	(0.91, 1.29)		1.18	(0.95, 1.47)	
5 (most deprived)	1.10	(0.92, 1.30)		0.89	(0.65, 1.21)		1.44	(1.19, 1.75)		1.53	(1.22, 1.93)	
Stage III												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.03	(0.88, 1.20)		0.99	(0.77, 1.29)		0.99	(0.86, 1.14)		1.06	(0.90, 1.26)	
3	1.02	(0.87, 1.19)	0.15	0.94	(0.72, 1.23)	0.25	1.01	(0.88, 1.16)	<0.001	1.09	(0.92, 1.29)	<0.001
4	1.13	(0.97, 1.32)		1.09	(0.83, 1.42)		1.12	(0.98, 1.28)		1.23	(1.04, 1.46)	
5 (most deprived)	1.14	(0.96, 1.36)		1.16	(0.88, 1.53)		1.33	(1.16, 1.53)		1.47	(1.23, 1.75)	
Stage IV												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.02	(0.93, 1.12)		0.97	(0.85, 1.11)		1.03	(0.88, 1.22)		1.00	(0.83, 1.22)	
3	1.01	(0.92, 1.11)	0.58	1.00	(0.87, 1.14)	0.06	1.03	(0.87, 1.22)	0.002	1.01	(0.84, 1.23)	0.01
4	1.00	(0.91, 1.10)		0.88	(0.77, 1.01)		1.02	(0.86, 1.21)		0.97	(0.80, 1.18)	
5 (most deprived)	1.05	(0.95, 1.16)		0.90	(0.78, 1.04)		1.42	(1.19, 1.70)		1.43	(1.16, 1.77)	

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SES, socioeconomic status. All p-values are of Wald test for trend. Model a: adjusted for sex, age, year of diagnosis, site, histology[§], tumour grade[§], emergency presentation[§], chronic and acute comorbidities, obesity (§: multiply imputed). Model b: adjusted for sex, age, year of diagnosis, site, histology, tumour grade, emergency presentation, chronic and acute comorbidities. Model c: adjusted for sex, age, year of diagnosis, site, histology[§], tumour grade[§], emergency presentation[§], chronic and acute comorbidities. Model d: adjusted for sex, age, year of diagnosis, site, histology, tumour grade, emergency presentation, chronic and acute comorbidities.

Second analysis (linear regression for days from diagnosis to treatment and its difference by SES)

Among the 45,907 patients (65.8% of total) with colon cancer who received major surgery, 2,755 patients underwent surgery before the diagnosis (30 days to 1 day before the diagnosis), and 14,477 patients underwent surgery within seven days of the date of diagnosis; those patients (a total of 17,232, 37.5% of the patients who received major surgery) were removed from the analysis. Among the 19,703 patients (51.5% of total) with rectal cancer who received major surgery, 432 patients underwent surgery before the diagnosis, and 1,926 patients underwent surgery within seven days of the date of diagnosis; in total, 2,358 patients (12.0% of the patients who received major surgery) received major surgery emergently.

Among only colon cancer patients, the deprived groups tended to receive major surgery emergently compared with the least deprived group (Table 4.6). An additional analysis revealed that the socioeconomic gradient in the receipt of emergency surgery for colon cancer was largely confounded by emergency presentation. Of the patients who had an emergency presentation, 4,665 (27.2%) and 1,221 (29.0%) had stage IV in colon and rectal cancer, respectively.

Table 4.6 Percentage of patients who received major surgery for the primary lesion as elective or emergency (colon and rectal cancer), England

		SES					
	Total (%)	**1 (least deprived)**	**2**	**3**	**4**	**5 (most deprived)**	**p-value**
Colon cancer							
Elective	28675 (62.5)	6594 (64.3)	6620 (64.1)	6018 (62.3)	5361 (60.6)	4082 (59.8)	<0.001
Emergency	17232 (37.5)	3664 (35.7)	3702 (35.9)	3637 (37.7)	3484 (39.4)	2745 (40.2)	
Rectal cancer							
Elective	17345 (88.0)	3804 (87.8)	3948 (88.7)	3731 (88.7)	3370 (87.1)	2492 (87.7)	0.29
Emergency	2358 (12.0)	529 (12.2)	504 (11.3)	474 (11.3)	501 (12.9)	350 (12.3)	

Abbreviations: SES, socioeconomic status. P-value of chi square test for trend.

For rectal cancer patients, the distribution of the days from diagnosis to treatment was bi-modal with a dip at around 100 days. The second peak may be composed of two different patient groups: those who had surgery after neoadjuvant therapy and those who had delayed surgery without neoadjuvant therapy. Since there was no information available on who had neoadjuvant therapy, an interpretation of whether it is a delay is problematical; hence, I did not conduct a linear regression analysis for rectal cancer patients.

Factors associated with time to treatment

Histological type, emergency presentation and the number of comorbidities mostly influenced the time to treatment. Table 4.7 displays the results of the linear regression analysis on the number of days from diagnosis to treatment for colon cancer patients.

When adjusted for all other variables, females had a 3% reduction in time from diagnosis to treatment compared with males. In the bivariable analysis, age was associated with time to treatment in a quadratic term, but in the multivariable analysis, the association was linear rather than quadratic (p=0.93, likelihood ratio test comparing quadratic and linear terms) or categorised group. For every 10-year increase in age from the mean age of 72.2, the number of the days increased by 2% (β as a coefficient, e^{β} 1.02 in multivariable regression). A histological type of non-adenocarcinoma had a significant longer time to treatment, at more than a 30% increase in days compared with adenocarcinoma. Other factors, such as cancer site, stage and tumour grade were associated with slightly longer time interval to surgery; increase in the time to treatment was no more than 15% depending on the differences in those factors. Sub-group analysis separating the descending and sigmoid colon, showed sigmoid colon cancer had more than 10% longer time to surgery when compared with the right-sided colon cancer, whereas time to treatment was almost the same in right-sided, transverse and descending colon cancer . With an emergency presentation, time from diagnosis to treatment was shortened by approximately 10% despite the exclusion of patients receiving surgery within seven days of diagnosis. The presence of comorbidities also contributed to longer time interval to treatment. Notably, patients with three or more acute comorbidities experienced a greater than 20% increase in time to treatment.

Sensitivity analysis with completed data revealed a similar trend with the same covariates included in the multivariable model with imputed data. Obesity was not associated with time to treatment in multivariable linear regressions.

Table 4.7 Reference number of days from diagnosis to major surgery for primary lesion and ratios using linear regression for colon cancer, England

Variable	Bivariable analysis			Multivariable analysis			Multivariable sensitivity analysis		
				Multiple imputation (n=28675)			Complete cases (n=20825)		
	Days	95% CI		Days**	95% CI		Days**	95% CI	
Reference (geometric mean) days in SES 1	36.4	(35.9, 36.9)		38.5	(37.6, 39.4)		38.3	(37.3, 39.4)	
	e^{β}*	95% CI	p-value†	e^{β}**	95% CI	p-value†	e^{β}**	95% CI	p-value†
SES									
1 (least deprived)	1.00			1.00			1.00		
2	1.01	(0.99, 1.03)		1.00	(0.99, 1.02)		1.00	(0.98, 1.02)	
3	1.01	(0.99, 1.03)	0.94‡	1.01	(0.99, 1.03)	0.59‡	1.01	(0.99, 1.03)	0.83‡
4	1.02	(1.00, 1.04)		1.02	(1.00, 1.04)		1.02	(1.00, 1.05)	
5 (most deprived)	0.99	(0.97, 1.01)		0.99	(0.97, 1.02)		0.99	(0.96, 1.01)	
Sex									
Male	1.00			1.00			1.00		
Female	0.96	(0.95, 0.97)	<0.001	0.97	(0.96, 0.98)	<0.001	0.97	(0.95, 0.98)	<0.001
Age									
Mean age at diagnosis	72.2	SD 12.6							
Age as linear term (e^{β} by 10-year increase)	1.01	(1.01, 1.02)	<0.001	1.02	(1.01, 1.03)	<0.001	1.02	(1.02, 1.03)	<0.001
Age as quadratic term††	††		0.04††	††		NA	††		0.93††
Year of diagnosis									
2010	1.00								
2011	1.01	(1.00, 1.03)	0.13						
2012	1.00	(0.98, 1.02)	0.99						
2013	1.01	(0.98, 1.04)	0.50						
Cancer site									
Right-sided colon#	1.00			1.00			1.00		
Transverse colon#	0.99	(0.97, 1.01)	0.23	0.99	(0.97, 1.02)	0.57	1.00	(0.98, 1.03)	0.90
Left-sided colon#	1.12	(1.11, 1.14)	<0.001	1.12	(1.10, 1.13)	<0.001	1.12	(1.10, 1.14)	<0.001
Descending colon	1.04	(1.01, 1.08)	<0.001	1.05	(1.01, 1.08)	<0.001	1.06	(1.02, 1.10)	<0.001
Sigmoid colon	1.13	(1.12, 1.15)	<0.001	1.13	(1.11, 1.14)	<0.001	1.13	(1.11, 1.15)	<0.001
Overlapping site or unspecified	1.08	(1.04, 1.12)	<0.001	1.08	(1.04, 1.12)	<0.001	1.11	(1.05, 1.16)	<0.001

Table 4.7 continued

	Bivariable analysis			Multivariable analysis Multiple imputation (n=28675)			Multivariable sensitivity analysis Complete cases (n=20825)		
	e^{β}*	95% CI	p-value†	e^{β}**	95% CI	p-value†	e^{β}**	95% CI	p-value†
Stage									
I	1.00						1.00		
II	0.85	(0.83, 0.86)	<0.001‡				0.87	(0.83, 0.91)	<0.001‡
III	0.86	(0.84, 0.87)					0.90	(0.86, 0.94)	
IV	0.87	(0.85, 0.90)					0.92	(0.87, 0.98)	
Stage§									
I	1.00			1.00					
II	0.87	(0.85, 0.89)	<0.001‡	0.88	(0.85, 0.93)	<0.001‡			
III	0.88	(0.86, 0.90)		0.91	(0.87, 0.95)				
IV	0.89	(0.87, 0.91)		0.93	(0.88, 0.98)				
Histology									
Adenocarcinoma	1.00			1.00			1.00		
Adenosquamous and squamous cell carcinoma	1.58	(1.39, 1.79)	<0.001	1.77	(1.56, 2.00)	<0.001	1.33	(1.13, 1.58)	0.001
Non-epithelial tumours	1.27	(1.17, 1.39)	<0.001	1.37	(1.26, 1.49)	<0.001	1.27	(1.14, 1.41)	<0.001
Tumour grade									
Well/moderately differentiated	1.00						1.00		
Poorly/undifferentiated	0.93	(0.91, 0.95)	<0.001				0.97	(0.95, 0.99)	0.001
Tumour grade§									
Well/moderately differentiated	1.00			1.00					
Poorly/undifferentiated	0.94	(0.92, 0.95)	<0.001	0.96	(0.94, 0.98)	<0.001			
Emergency presentation									
No	1.00						1.00		
Yes	0.89	(0.87, 0.91)	<0.001				0.90	(0.88, 0.92)	<0.001
Emergency presentation§									
No	1.00			1.00					
Yes	0.89	(0.87, 0.91)	<0.001	0.89	(0.87, 0.91)	<0.001			

Table 4.7 continued

Variable	Bivariable analysis			Multivariable analysis Multiple imputation (n=28675)			Multivariable sensitivity analysis Complete cases (n=20825)		
	e^{β}*	95% CI	p-value†	e^{β}**	95% CI	p-value†	e^{β}**	95% CI	p-value†
Number of chronic comorbidities									
0	1.00		<0.001‡	1.00		<0.001‡	1.00		<0.001‡
1	1.06	(1.04, 1.08)		1.06	(1.04, 1.09)		1.07	(1.05, 1.10)	
2	1.13	(1.07, 1.20)		1.14	(1.08, 1.21)		1.16	(1.08, 1.24)	
3+	1.08	(0.95, 1.23)		1.11	(0.97, 1.26)		1.10	(0.95, 1.27)	
Number of acute comorbidities									
0	1.00		<0.001‡	1.00		<0.001‡	1.00		<0.001‡
1	1.03	(1.00, 1.05)		1.04	(1.02, 1.06)		1.05	(1.02, 1.08)	
2	1.10	(1.04, 1.17)		1.14	(1.07, 1.21)		1.17	(1.10, 1.26)	
3+	1.14	(0.97, 1.34)		1.21	(1.03, 1.42)		1.36	(1.12, 1.63)	
Obesity at diagnosis									
No	1.00								
Yes	1.07	(1.00, 1.14)	0.04						

Abbreviations: 95% CI, 95% confidence interval; NA, not applicable; SD, standard deviation; SES, socioeconomic status. * Adjusted for SES in all variables. Results of bivariable analysis on histology with imputed data and completed data did not differ in an important amount. Thus, results with only imputed data are shown. ** All variables are mutually adjusted. For SES only, days and adjusted ratios are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. # Right-sided colon includes ascending colon, hepatic flexure, caecum and appendix. Transverse colon includes transverse colon and splenic flexure. Left-sided colon includes descending colon and sigmoid colon. † P-value of the null hypothesis that the coefficient (β) is 0 (e^{β}=1) when all other variables were set at the reference group. ‡ P-value of Wald test for trend. †† When age is put as a quadratic term, in bivariable analysis, log(days) is derived from α(constant) + β_1(0 in SES=1) + β_2(age−mean age) + β_3(age−mean age)^2. § Multiply imputed.

Time to treatment by SES

In the bivariable analysis, there was no evidence that the number of days from diagnosis to treatment differed by SES. The mean days from diagnosis to treatment was 36.4 (95% CI 35.9, 36.9) in the least deprived as a reference group (geometric mean of days, reference meaning 'intercept' days in bivariable analysis, Table 4.7). No factors influenced the socioeconomic difference in time to treatment by an important amount.

Stage-specific ratios of time to treatment by SES group are displayed in Table 4.8. Mean number of days from diagnosis to treatment in the reference group (the least deprived group) are also shown by each stage, which were derived by multivariable models with interaction between SES and stage. The mean days from diagnosis to treatment in the reference group ranged from 34.0 in stage II to 38.5 in stage I after adjusting for all other factors, but the number of days did not differ by SES in all stages. There was no evidence of a socioeconomic trend in time to treatment in sensitivity analyses with completed data.

Table 4.8 Stage-specific ratios and reference number of days from diagnosis to major surgery for primary lesion using multivariable linear regression with interaction between SES and stage for colon cancer, England

	Multiple imputation[a]			Complete cases[b]		
	e^{β}	95% CI	p-value	e^{β}	95% CI	p-value
Stage I						
SES						
Reference (days) in SES 1	38.5	(37.0, 40.0)		38.0	(36.5, 39.5)	
1 (least deprived)	1.00			1.00		
2	0.99	(0.94, 1.05)		1.02	(0.99, 1.06)	
3	1.01	(0.96, 1.07)	0.25	1.03	(1.00, 1.07)	0.12
4	1.01	(0.95, 1.06)		1.05	(1.01, 1.09)	
5 (most deprived)	1.03	(0.98, 1.10)		0.98	(0.94, 1.02)	
Stage II						
Reference (days) in SES 1	34.0	(33.1, 34.9)		34.1	(33.0, 35.1)	
1 (least deprived)	1.00			1.00		
2	1.02	(0.99, 1.06)		1.02	(0.99, 1.06)	
3	1.03	(1.00, 1.07)	0.64	1.03	(1.00, 1.07)	0.70
4	1.04	(1.00, 1.08)		1.05	(1.01, 1.09)	
5 (most deprived)	0.99	(0.95, 1.03)		0.98	(0.94, 1.02)	
Stage III						
Reference (days) in SES 1	35.0	(34.0, 36.0)		35.1	(33.6, 36.7)	
1 (least deprived)	1.00			1.00		
2	0.98	(0.95, 1.02)		0.97	(0.94, 1.01)	
3	1.00	(0.96, 1.04)	0.63	1.00	(0.96, 1.04)	0.84
4	1.01	(0.97, 1.04)		0.99	(0.96, 1.04)	
5 (most deprived)	1.00	(0.96, 1.04)		0.99	(0.95, 1.04)	
Stage IV						
Reference (days) in SES 1	35.8	(34.3, 37.3)		37.4	(35.8, 39.1)	
1 (least deprived)	1.00			1.00		
2	1.02	(0.97, 1.08)		1.02	(0.96, 1.09)	
3	0.99	(0.93, 1.05)	0.18	0.97	(0.91, 1.03)	0.05
4	1.02	(0.96, 1.08)		1.02	(0.96, 1.08)	
5 (most deprived)	0.95	(0.89, 1.01)		0.92	(0.86, 0.98)	

Abbreviations: 95% CI, 95% confidence interval; SES, socioeconomic status. All p-values are of Wald test for trend. Model a: adjusted for sex, age, site, histology§, tumour grade§, emergency presentation§, chronic and acute comorbidities (§: multiply imputed). Model b: adjusted for sex, age, site, histology, tumour grade, emergency presentation, chronic and acute comorbidities.

4.1.3 Summary of findings

The first analysis demonstrated a socioeconomic difference in receipt of major surgery for the primary lesion. A socioeconomic trend favouring the affluent patients was observed for colon cancer patients in stage III and rectal cancer patients in stages II to IV. Stage and number of chronic comorbidities contributed to a reduction in the socioeconomic gap, but the inequalities in receipt of surgery were not completely cancelled.

The mean time to surgical treatment was approximately 38 days for colon cancer patients. No socioeconomic disparities were observed for the time to treatment. Patients with non-adenocarcinoma, having 3+ acute comorbidities experienced a longer time to treatment than patients with adenocarcinoma or those with no acute comorbidities. For rectal cancer patients, a group of patients received surgery within 100 days of diagnosis, but there was also a considerable number of patients who received surgery after 100 days.

4.2 Postoperative 30-day mortality by socioeconomic status

Chapter 4.1 explored characteristics of patients who were not likely to receive major surgery, and whether there were socioeconomic differences in surgery receipt. In **Chapter 4.2**, I restricted the study population to the patients who received surgery to examine whether the quality of care varied by SES. Postoperative 30-day mortality is one of the quality measures for CRC care [107]. Here, I explored factors associated with postoperative 30-day mortality and investigated socioeconomic differences in the mortality.

4.2.1 Methods

The analysed population also included cases with urgent operations who had seven days or less from the diagnosis to major surgery. Vital status (0 alive, 1 dead) at thirty days from the date of major surgery for the primary lesion was set as the outcome.

I fitted logistic regression with imputed and completed data. An interaction term between SES and stage was added as the main interest. Stage, tumour grade and emergency presentation were multiply imputed 30 times under the MAR assumption (see **Chapter 4.1**). As sensitivity analyses, multivariable models with completed data were compared with the models with imputed data.

I started with bivariable analyses, adjusting *a priori* interest variable, SES, for all other variables to assess the changes in the association between SES and the outcome. Each variable was also retained in the multivariable analysis based on the Wald test (p-value< 0.05) of the bivariable analysis. The Wald test was unifiedly used, rather than likelihood ratio test, for both imputed and completed data to account for the uncertainty in imputed data [208]. Finally, variables were selected by backward elimination. A removed variable was added to the multivariable model again as a confounder if a model with the variable changed the effect of SES (OR of the most deprived) by more than 10%. Age group and sex were added as *a priori* confounders.
As same as **Chapter 4.1**, for colon cancer, sites were categorised into three groups and sub-group analysis of the left-sided colon was also conducted.

4.2.2 Results

Of all patients, 45,907 (65.8% of total) with colon cancer and 19,703 (51.5% of total) with rectal cancer who received major surgery for the primary lesion were analysed separately. Overall, postoperative 30-day mortality was 4.0% for colon cancer and 2.5% for rectal cancer with socioeconomic gradients towards higher mortalities in the deprived groups (Table 4.1 and Table 4.2).

Table 4.9 and Table 4.10 display the results of the potential associated factors for postoperative death in the bivariable and multivariable logistic regression analyses. To show the overall change in the effect of SES, the adjusted ORs of SES in those tables were based on a model without interaction between SES and stage. For the rest, adjusted ORs were based on the multivariable model with interaction between SES and stage (final model). For the same reason in **Chapter 4.1**, in the sub-group analysis regarding left-sided colon cancer, results of variables other than site in the multivariable analyses were omitted.

Factors associated with postoperative 30-day mortality

Worse deprivation, increased age, worse tumour grade, emergency presentation and presence of acute/chronic comorbidities were associated with postoperative death for both cancers. Site of cancer and obesity were associated with a worse outcome only for colon cancer (Table 4.9 and Table 4.10).

Clear socioeconomic trends towards worsening odds in the deprived groups were observed in both cancers. Patients aged 80+ had 5 to 7 times higher adjusted odds of postoperative death compared with patients under 65. Patients with worse tumour grade had approximately 1.4 times adjusted odds of postoperative death, and the patients with an emergency presentation had a two to threefold increase in adjusted odds compared with the patients in the reference groups. For both cancers, the presence of chronic comorbidities increased the adjusted odds of death by 1.59 to 3.93 times, and acute comorbidities increased the adjusted odds by 1.44 to 7.11 times. Transverse colon cancer had 1.3 times higher adjusted odds of death compared with the patients with right-sided colon cancer. Both descending and sigmoid colon cancer had similar adjusted odds of death with right-sided colon cancer. Site was not associated with the postoperative mortality in rectal cancer. Obesity increased the adjusted odds of death by 1.5 times for colon cancer.

The results of the sensitivity analyses with completed data largely agreed. Among rectal cancer patients, tumour grade was not associated with the odds of death.

Odds ratios of postoperative death by SES

Table 4.11 displays the results of stage-specific ORs of postoperative death among SES groups in each stage when all potential factors were adjusted and an interaction term between SES and stage was added in the multivariable logistic regression model.

The stage-specific ORs provided evidence that the deprived groups had higher odds of death than the least deprived group among colon cancer patients with stage II, III and IV and rectal cancer patients with stage I. In colon cancer with stage I and rectal cancer with stage II to IV, there were similar socioeconomic gradients, but the p-values did not reach a statistical significance. All trends of the stage-specific ORs in sensitivity analyses were comparable to those of the main analyses using imputed data.

Bivariable analyses revealed that the socioeconomic gradient towards higher odds of death in the deprived groups lessened by around 5 to 10% when stage, emergency presentation or number of acute comorbidities were adjusted one at a time; however, no variable cancelled the trend completely.

Table 4.9 Odds ratios of postoperative death within 30 days using logistic regression for colon cancer, England

Variable	Bivariable analysis			Multivariable analysis Multiple imputation (n=45907)			Multivariable sensitivity analysis Complete cases (n=32903)		
	OR*	95% CI	p-value[†]	OR**	95% CI	p-value[†]	OR**	95% CI	p-value[†]
SES									
1 (least deprived)	1.00			1.00			1.00		
2	1.25	(1.07, 1.45)		1.21	(1.03, 1.42)		1.25	(1.02, 1.53)	
3	1.39	(1.19, 1.61)	<0.001[‡]	1.31	(1.12, 1.53)	<0.001[‡]	1.30	(1.06, 1.59)	<0.001[‡]
4	1.56	(1.34, 1.81)		1.42	(1.21, 1.66)		1.51	(1.24, 1.84)	
5 (most deprived)	1.79	(1.53, 2.09)		1.63	(1.38, 1.91)		1.57	(1.28, 1.94)	
Sex									
Male	1.00			1.00			1.00		
Female	0.95	(0.87, 1.04)	0.29	0.84	(0.76, 0.93)	0.001	0.87	(0.77, 0.99)	0.04
Age									
<65	1.00			1.00			1.00		
65–79	2.99	(2.51, 3.56)	<0.001[‡]	3.04	(2.54, 3.64)	<0.001[‡]	2.68	(2.14, 3.35)	<0.001[‡]
80–99	7.67	(6.44, 9.13)		6.96	(5.81, 8.34)		6.19	(4.94, 7.75)	
Year of diagnosis									
2010	1.00			1.00			1.00		
2011	0.83	(0.74, 0.93)	0.001	0.85	(0.75, 0.96)	0.008	0.81	(0.68, 0.96)	0.02
2012	0.79	(0.70, 0.89)	<0.001	0.83	(0.73, 0.94)	0.003	0.88	(0.75, 1.03)	0.11
2013	0.91	(0.75, 1.09)	0.31	0.99	(0.81, 1.20)	0.89	1.00	(0.79, 1.27)	0.98
Cancer site									
Right-sided colon[#]	1.00			1.00			1.00		
Transverse colon[#]	1.28	(1.12, 1.46)	<0.001	1.30	(1.13, 1.50)	<0.001	1.36	(1.15, 1.63)	0.001
Left-sided colon[#]	0.79	(0.71, 0.88)	<0.001	1.09	(0.97, 1.23)	0.14	1.09	(0.94, 1.26)	0.25
Descending colon	0.95	(0.76, 1.19)	<0.001	1.12	(0.88, 1.42)	0.35	1.28	(0.96, 1.71)	0.09
Sigmoid colon	0.76	(0.68, 0.86)	<0.001	1.08	(0.96, 1.22)	0.91	1.06	(0.91, 1.23)	0.47
Overlapping site or unspecified	1.94	(1.62, 2.34)	<0.001	2.06	(1.69, 2.51)	<0.001	1.84	(1.38, 2.47)	<0.001

Table 4.9 continued

Variable	Bivariable analysis			Multivariable analysis Multiple imputation (n=45907)			Multivariable sensitivity analysis Complete cases (n=32903)		
	OR*	**95% CI**	**p-value[†]**	**OR****	**95% CI**	**p-value[†]**	**OR****	**95% CI**	**p-value[†]**
Stage									
I	1.00						1.00		
II	2.31	(1.78, 3.00)	<0.001[‡]				1.59	(0.83, 3.03)	0.05[‡]
III	2.09	(1.60, 2.72)					1.30	(0.67, 2.53)	
IV	4.03	(3.09, 5.25)					2.22	(1.13, 4.36)	
Stage[§]									
I	1.00			1.00					
II	1.00	(0.74, 1.26)	<0.001[‡]	1.67	(0.92, 3.01)	<0.001[‡]			
III	1.02	(0.76, 1.28)		1.61	(0.88, 2.93)				
IV	1.98	(1.72, 2.23)		4.11	(2.25, 7.50)				
Histology									
Adenocarcinoma	1.00								
Adenosquamous/squamous cell carcinoma	1.50	(0.76, 2.94)	0.24						
Non-epithelial tumours	0.74	(0.42, 1.28)	0.28						
Tumour grade									
Well/moderately differentiated	1.00						1.00		
Poorly/undifferentiated	1.69	(1.51, 1.89)	<0.001				1.39	(1.20, 1.61)	<0.001
Tumour grade[§]									
Well/moderately differentiated	1.00			1.00					
Poorly/undifferentiated	0.60	(0.49, 0.71)	<0.001	1.39	(1.23, 1.57)	<0.001			

Table 4.9 continued

Variable	Bivariable analysis			Multivariable analysis			Multivariable sensitivity analysis		
				Multiple imputation (n=45907)			Complete cases (n=32903)		
	OR*	95% CI	p-value†	OR**	95% CI	p-value†	OR**	95% CI	p-value†
Emergency presentation									
No	1.00						1.00		
Yes	3.99	(3.63, 4.39)	<0.001				2.63	(2.32, 2.99)	<0.001
Emergency presentation§									
No	1.00			1.00					
Yes	1.38	(1.29, 1.48)	<0.001	2.70	(2.44, 2.99)	<0.001			
Number of chronic comorbidities									
0	1.00			1.00			1.00		
1	1.90	(1.67, 2.15)	<0.001‡	1.59	(1.39, 1.82)	<0.001‡	1.75	(1.48, 2.06)	<0.001‡
2	3.34	(2.62, 4.25)		2.61	(2.01, 3.38)		2.89	(2.12, 3.93)	
3+	3.00	(1.68, 5.35)		1.88	(1.01, 3.51)		2.27	(1.05, 4.89)	
Number of acute comorbidities									
0	1.00			1.00			1.00		
1	2.56	(2.29, 2.86)	<0.001‡	1.92	(1.71, 2.16)	<0.001‡	1.75	(1.50, 2.03)	<0.001‡
2	5.09	(4.18, 6.20)		3.01	(2.43, 3.72)		2.83	(2.16, 3.70)	
3+	11.05	(7.92, 15.42)		5.98	(4.16, 8.58)		5.30	(3.37, 8.42)	
Obesity at diagnosis									
No	1.00			1.00					
Yes	1.50	(1.10, 2.03)	0.010	1.49	(1.08, 2.06)	0.02			

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SES, socioeconomic status. * Adjusted for SES in all variables. Results of bivariable analysis on histology with imputed data and completed data did not differ in an important amount. Thus, result with only imputed data are shown. ** All variables are mutually adjusted. For SES only, adjusted ORs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. # Right-sided colon includes ascending colon, hepatic flexure, caecum and appendix. Transverse colon includes transverse colon and splenic flexure. Left-sided colon includes descending colon and sigmoid colon. † P-value of Wald test. ‡ P-value of Wald test for trend. § Multiply imputed.

Table 4.10 Odds ratios of postoperative death within 30 days using logistic regression for rectal cancer, England

Variable	Bivariable analysis			Multivariable analysis			Multivariable sensitivity analysis		
				Multiple imputation (n=19703)			Complete cases (n=15401)		
	OR*	95% CI	p-value†	OR**	95% CI	p-value†	OR**	95% CI	p-value†
SES									
1 (least deprived)	1.00			1.00			1.00		
2	0.96	(0.71, 1.30)		0.94	(0.69, 1.29)		0.85	(0.57, 1.25)	
3	1.53	(1.16, 2.01)	<0.001‡	1.48	(1.11, 1.97)	0.003‡	1.41	(1.00, 1.99)	0.003‡
4	1.30	(0.97, 1.74)		1.18	(0.87, 1.60)		1.20	(0.83, 1.72)	
5 (most deprived)	1.63	(1.21, 2.20)		1.53	(1.12, 2.09)		1.61	(1.11, 2.33)	
Sex									
Male	1.00			1.00			1.00		
Female	0.66	(0.53, 0.80)	<0.001	0.61	(0.49, 0.75)	<0.001	0.56	(0.43, 0.73)	<0.001
Age									
<65	1.00			1.00			1.00		
65–79	2.72	(2.06, 3.58)	<0.001‡	2.55	(1.93, 3.38)	<0.001‡	2.23	(1.61, 3.10)	<0.001‡
80–99	8.16	(6.14, 10.85)		6.82	(5.07, 9.16)		5.56	(3.93, 7.87)	
Year of diagnosis									
2010	1.00			1.00					
2011	0.72	(0.58, 0.91)	0.006	0.76	(0.60, 0.96)	0.02			
2012	0.82	(0.66, 1.03)	0.09	0.87	(0.69, 1.09)	0.22			
2013	0.86	(0.60, 1.24)	0.43	0.98	(0.67, 1.42)	0.91			
Cancer site									
Rectosigmoid colon	1.00								
Rectum	0.71	(0.58, 0.87)	<0.001						
Overlapping site or unspecified	0.99	(0.13, 7.33)	1.00						
Stage									
I	1.00						1.00		
II	2.47	(1.75, 3.49)	<0.001‡				2.58	(1.09, 6.11)	0.05‡
III	1.86	(1.31, 2.63)					1.94	(0.80, 4.69)	
IV	3.09	(2.08, 4.58)					3.47	(1.31, 9.16)	
Stage§									
I	1.00			1.00					
II	2.64	(1.89, 3.68)	<0.001‡	2.30	(1.03, 5.17)	0.002‡			
III	2.16	(1.52, 3.06)		1.91	(0.84, 4.32)				
IV	5.88	(4.15, 8.34)		4.73	(2.01, 11.11)				

Table 4.10 continued

Variable	Bivariable analysis			Multivariable analysis Multiple imputation (n=19703)			Multivariable sensitivity analysis Complete cases (n=15401)		
	OR*	95% CI	p-value†	OR**	95% CI	p-value†	OR**	95% CI	p-value†
Histology									
Adenocarcinoma	1.00								
Adenosquamous/squamous cell carcinoma	1.00		empty						
Non-epithelial tumours	0.60	(0.08, 4.30)	0.61						
Tumour grade									
Well/moderately differentiated	1.00								
Poorly/undifferentiated	1.51	(1.15, 1.98)	0.003						
Tumour grade§									
Well/moderately differentiated	1.00			1.00					
Poorly/undifferentiated	1.71	(1.32, 2.21)	<0.001	1.41	(1.07, 1.85)	0.01			
Emergency presentation									
No	1.00						1.00		
Yes	4.98	(4.05, 6.13)	<0.001				2.85	(2.14, 3.79)	<0.001
Emergency presentation§									
No	1.00			1.00					
Yes	4.95	(4.03, 6.09)	<0.001	3.11	(2.49, 3.90)	<0.001			
Number of chronic comorbidities									
0	1.00			1.00			1.00		
1	2.03	(1.55, 2.65)	<0.001‡	1.72	(1.30, 2.28)	<0.001‡	1.84	(1.33, 2.56)	<0.001‡
2	4.31	(2.59, 7.18)		3.36	(1.95, 5.79)		3.93	(2.13, 7.24)	
3+	5.41	(1.61, 18.22)		2.22	(0.61, 8.15)		2.38	(0.51, 11.11)	
Number of acute comorbidities									
0	1.00			1.00			1.00		
1	2.42	(1.89, 3.10)	<0.001‡	1.62	(1.24, 2.10)	<0.001‡	1.44	(1.03, 2.02)	<0.001‡
2	4.14	(2.37, 7.23)		2.29	(1.26, 4.18)		3.20	(1.63, 6.28)	
3+	13.93	(5.87, 33.08)		6.47	(2.46, 17.00)		7.11	(2.36, 21.46)	
Obesity at diagnosis									
No	1.00								
Yes	1.73	(0.91, 3.29)	0.09						

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SES, socioeconomic status. * Adjusted for SES in all variables. Results of bivariable analysis on histology with imputed data and completed data did not differ in an important amount. Thus, result with only imputed data are shown. ** All variables are mutually adjusted. For SES only, adjusted ORs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. † P-value of Wald test. ‡ P-value of Wald test for trend. § Multiply imputed.

Table 4.11 Stage-specific odds ratios of postoperative death within 30 days using multivariable logistic regression with interaction between SES and stage for colon and rectal cancer, England

	Colon						Rectum					
	Multiple imputation[a]			Complete cases[b]			Multiple imputation[c]			Complete cases[d]		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Stage I												
SES												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.20	(0.58, 2.50)		1.42	(0.65, 3.09)		0.59	(0.19, 1.88)		0.54	(0.16, 1.86)	
3	1.20	(0.56, 2.56)	0.27	1.05	(0.45, 2.46)	0.30	1.27	(0.51, 3.15)	0.04	1.42	(0.54, 3.72)	0.007
4	0.64	(0.25, 1.65)		0.69	(0.25, 1.90)		1.65	(0.68, 3.98)		2.01	(0.78, 5.16)	
5 (most deprived)	2.00	(0.97, 4.14)		2.09	(0.95, 4.58)		1.93	(0.77, 4.81)		2.45	(0.94, 6.39)	
Stage II												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.06	(0.78, 1.46)		1.00	(0.72, 1.40)		0.91	(0.50, 1.64)		0.81	(0.42, 1.55)	
3	1.12	(0.82, 1.53)	<0.001	1.10	(0.78, 1.53)	<0.001	1.21	(0.69, 2.13)	0.09	1.16	(0.64, 2.10)	0.05
4	1.49	(1.11, 2.00)		1.61	(1.17, 2.20)		1.07	(0.60, 1.92)		1.04	(0.57, 1.89)	
5 (most deprived)	1.59	(1.16, 2.18)		1.56	(1.12, 2.18)		1.67	(0.94, 2.96)		1.79	(0.99, 3.22)	
Stage III												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.25	(0.91, 1.73)		1.29	(0.89, 1.86)		0.97	(0.52, 1.81)		0.94	(0.49, 1.81)	
3	1.46	(1.05, 2.02)	0.006	1.54	(1.08, 2.21)	0.03	1.85	(1.08, 3.16)	0.35	1.88	(1.05, 3.37)	0.42
4	1.35	(0.95, 1.91)		1.36	(0.94, 1.98)		1.14	(0.63, 2.08)		1.19	(0.62, 2.27)	
5 (most deprived)	1.62	(1.17, 2.26)		1.54	(1.05, 2.26)		1.23	(0.65, 2.32)		1.16	(0.57, 2.33)	
Stage IV												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.33	(0.98, 1.79)		1.58	(1.07, 2.34)		1.12	(0.56, 2.21)		1.01	(0.43, 2.41)	
3	1.39	(1.03, 1.87)	0.001	1.41	(0.95, 2.10)	0.05	1.46	(0.75, 2.84)	0.26	1.09	(0.47, 2.57)	0.46
4	1.52	(1.13, 2.02)		1.73	(1.18, 2.53)		1.17	(0.61, 2.23)		1.03	(0.43, 2.47)	
5 (most deprived)	1.61	(1.18, 2.19)		1.50	(0.98, 2.29)		1.55	(0.74, 3.23)		1.50	(0.61, 3.68)	

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SES, socioeconomic status. All p-values are of Wald test for trend. Model a: adjusted for sex, age, year of diagnosis, site, tumour grade[§], emergency presentation[§], chronic and acute comorbidities, obesity (§: multiply imputed). Model b: adjusted for sex, age, year of diagnosis, site, tumour grade, emergency presentation, chronic and acute comorbidities. Model c: adjusted for sex, age, year of diagnosis, tumour grade[§], emergency presentation[§], chronic and acute comorbidities. Model d: adjusted for sex, age, emergency presentation, chronic and acute comorbidities.

4.2.3 Summary of findings

Increased age, transverse colon cancer, worse tumour grade, emergency presentation and presence of comorbidities were associated with poorer postoperative mortality.

Among colon cancer patients with stage II to IV and rectal cancer patients with stage I, there was evidence that the more deprived groups had higher postoperative mortality than the least deprived group when all potential factors were adjusted. A similar socioeconomic gradient was also observed among colon cancer patients with stage I and rectal cancer patients with stage II to IV, but p-values for trend were high.

The socioeconomic gradient was reduced but not completely nullified when stage and presence of acute comorbidities were taken into account.

4.3 Survival by socioeconomic status

In **Chapters 4.1** and **4.2**, I explored factors associated with receipt of cancer care and the patterns of care by SES. In **Chapter 4.3**, I investigated general patterns of survival and mortality rates by SES without controlling for any other factors. In **Chapter 4.4**, I explored factors associated with survival and displayed socioeconomic differences in survival after the potential factors were controlled.

4.3.1 Methods

Mortality rates, three-year survival since diagnosis and difference in those figures among SES groups were set as the outcomes. I analysed both overall and net survival.

For net survival, excess hazard ratios (EHRs) of death from CRC can be estimated. Excess hazard ratios of death by CRC were derived by comparing the observed overall survival of the CRC patients with the expected survival of a similar population (i.e. same sex, age, deprivation group and government regions), using lifetables of the background population. Since there are no lifetables for 2012 and 2013, the lifetable of 2011 was used to derive net survival for those years.

I used the Royston-Parmar flexible parametric survival model (FPM), which models the basic cumulative hazard by restricted cubic spline functions [209]. Advantages of using the FPM over a semi-parametric or non-parametric model, such as the Cox regression model or the Kaplan-Meier method, are that the FPM allows an estimation of the baseline survival function, and the FPM enables us to observe the 'difference' in hazard and survival graphically [210].

Firstly, to apply the restricted cubic splines for the FPM, I modelled the number and positions of internal knots for the baseline hazard without any covariates using `stpm2`. The positions of these internal knots were chosen at 90 days, six months and one year since diagnosis based on clinical relevance and were compared with the default knots, which were varied from 2 to 5 degrees of freedom (df). The models were evaluated based on the Akaike information criterion (AIC). A model with a smaller AIC is preferred when choosing the number of knots [210].

After selecting a model with a plausible number and positions of knots in the null model, I fitted an FPM with a variable SES only. The cumulative hazards were assumed here to be proportional among the SES groups (i.e. proportional hazard model [PH] model). Further, I assessed the proportional hazard assumption by AIC. I compared the AIC of two models: a model with SES acting proportionally and a model with SES treated as a time-varying effect (TVE) (i.e. SES interacts with time). For the TVE, the number of internal knots was reduced to two [210], positioning at six months and one year since diagnosis.

The survival curves in the final FPM were graphically compared with survival curves derived by the Kaplan-Meier method. The log-cumulative hazard for overall survival was displayed. The differences in mortality rate and survival between the least and the most deprived groups (subtracting mortality rate/survival of the least deprived from the mortality rate/survival of the most deprived) were also estimated by the final FPM for both overall and net survival.

4.3.2 Results

Number and positions of knots in null FPM

A total of 69,766 colon cancer and 38,267 rectal cancer patients were included. Figure 4.1 and Figure 4.2 illustrate the baseline mortality rate and excess mortality rate per 1,000 person-years (PYs) for colon cancer. Table 4.12 displays the AIC by number and position of internal knots. As shown in the graphs of mortality rate in Figure 4.1 and Figure 4.2, all models with different numbers and positions of the knots were similar in both overall and net survival. When comparing the AIC of the models, the model with three internal knots positioning at 90 days, six months and one year since diagnosis and the model with df 5 (four internal knots positioning at 20, 40, 60 and 80 centiles of the distribution of uncensored log event-times) showed a relatively small AIC. Considering that a smaller number of df is sufficient to understand how data behave [211], the model with three internal knots (internal knots positioning at 90 days, six months and one year) was chosen for colon cancer.

The mortality rates and excess mortality rates for rectal cancer displayed in Figure 4.3 and Figure 4.4 also showed that all models were similar; however, it was clearer than in the figures for colon cancer that the models with df 4 and df 5 show signs of overfitting (curves fluctuating at the period of one to two years since diagnosis). From the overfitting figures and AIC (Table 4.13), the model with three internal knots (internal knots positioning at 90 days, six months and one year) was chosen for rectal cancer.

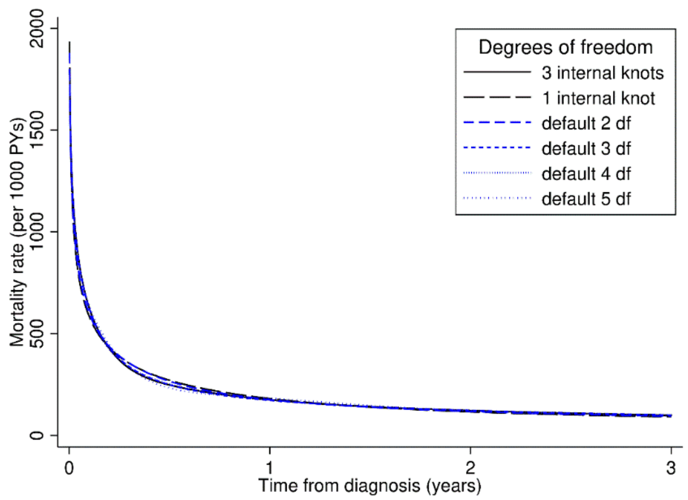

Figure 4.1 Mortality rate curves by different degrees of freedom for colon cancer, England

Abbreviations: 1000 PYs, 1000 person-years; df, degrees of freedom.

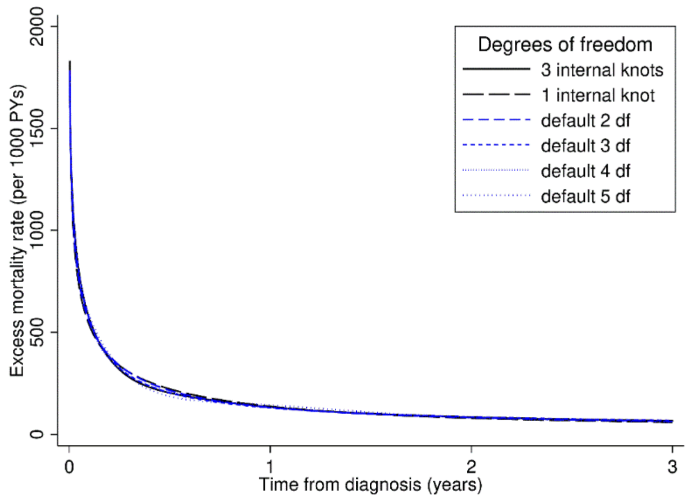

Figure 4.2 Excess mortality rate curves by different degrees of freedom for colon cancer, England

Abbreviations: 1000 PYs, 1000 person-years; df, degrees of freedom.

Table 4.12 AIC by number and position of knots for colon cancer, England

Number and position of knots	**AIC**	
	Overall survival	**Net survival**
3 internal knots (at 90 days, 6 months, 1 year)	198576.0	121658.6
1 internal knot (at 1.5 years)	198710.5	121748.9
Default 2df (1 internal knot: 50 centiles)	198654.6	121706.2
Default 3df (2 internal knots: 33, 67 centiles)	198581.5	121667.0
Default 4df (3 internal knots: 25, 50, 75 centiles)	198593.3	121672.7
Default 5df (4 internal knots: 20, 40, 60, 80 centiles)	198539.5	121600.5

Abbreviations: AIC, Akaike information criterion; df, degrees of freedom. The positions of the knots sit on the noted centiles of the distribution of uncensored log event-times.

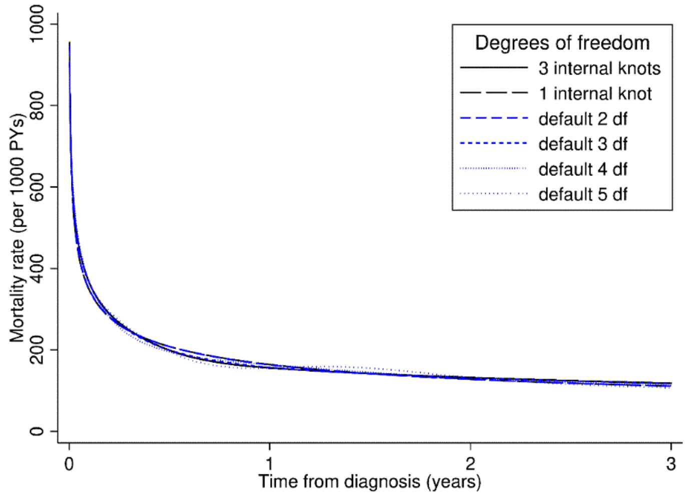

Figure 4.3 Mortality rate curves by different degrees of freedom for rectal cancer, England

Abbreviations: 1000 PYs, 1000 person-years; df, degrees of freedom.

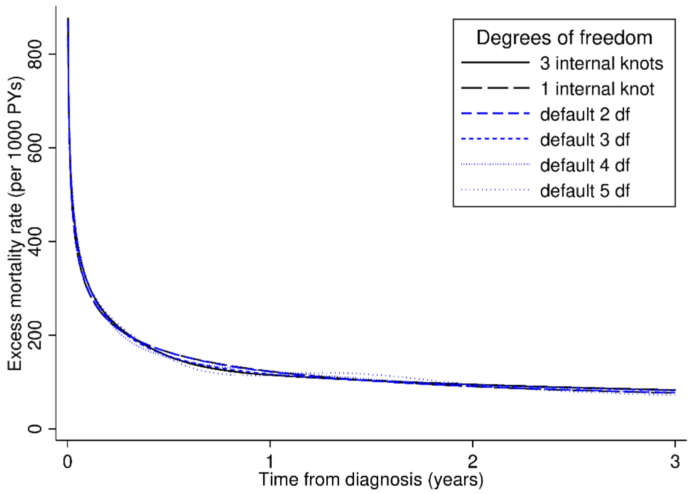

Figure 4.4 Excess mortality rate curves by different degrees of freedom for rectal cancer, England

Abbreviations: 1000 PYs, 1000 person-years; df, degrees of freedom.

Table 4.13 AIC by number and position of knots for rectal cancer, England

Number and position of knots	**AIC**	
	Overall survival	**Net survival**
3 internal knots (at 90 days, 6 months, 1year)	93769.2	68131.5
1 internal knot (at 1.5 year)	93791.7	68150.8
Default 2df (1 internal knot: 50 centiles)	93789.9	68148.6
Default 3df (2 internal knots: 33, 67 centiles)	93771.5	68133.8
Default 4df (3 internal knots: 25, 50, 75 centiles)	93769.4	68131.8
Default 5df (4 internal knots: 20, 40, 60, 80 centiles)	93742.0	68101.4

Abbreviations: AIC, Akaike information criterion; df, degrees of freedom. The positions of the knots sit on the noted centiles of the distribution of uncensored log event-times.

Survival curves and difference in mortality rate, survival by SES

I added SES to the null model and examined whether HRs among SES groups stayed proportional or varied over time. The AIC in Table 4.14 indicates that the model with SES treated as a TVE was better in colon cancer, and the model with SES acting proportional was better in rectal cancer for both overall and net survival.

Table 4.14 AIC of FPMs with SES (proportional or TVE), England

Model	AIC			
	Colon cancer		Rectal cancer	
	Overall survival	Net survival	Overall survival	Net survival
SES (proportional)	198539.5	121458.5	93553.9	67968.3
SES (TVE)	198261.9	121422.1	93560.8	67976.5

Abbreviations: AIC, Akaike information criterion; SES, socioeconomic status; TVE, time-varying effect.

Figure 4.5 displays the overall survival curves for colon cancer of five SES groups: (a) being modelled by FPM with SES treated as TVE and (b) being derived by the Kaplan-Meier method. The survival curves modelled by FPM showed a gradient by SES, which did not conflict with the curves derived by the Kaplan-Meier method, but rather with smoother lines. There was a clear worsening gradient among SES groups from the least deprived to the most deprived in both graphs. Since SES interacts with time for colon cancer, the gaps among SES groups in terms of (c) log-cumulative hazards and (d) mortality rates narrowed over time. Net survival also demonstrated a clear socioeconomic gradient, as shown in Figure 4.6 (a), under a model with SES treated as TVE. The gaps among SES groups in excess mortality rates gradually diminished.

Figure 4.7 displays the overall survival curves of five SES groups for rectal cancer. As SES acts proportional, the gaps among SES groups in (c) log-cumulative hazards and (d) mortality rates were not reduced. Net survival curves and excess mortality rates in Figure 4.8 showed similar patterns as for overall survival.

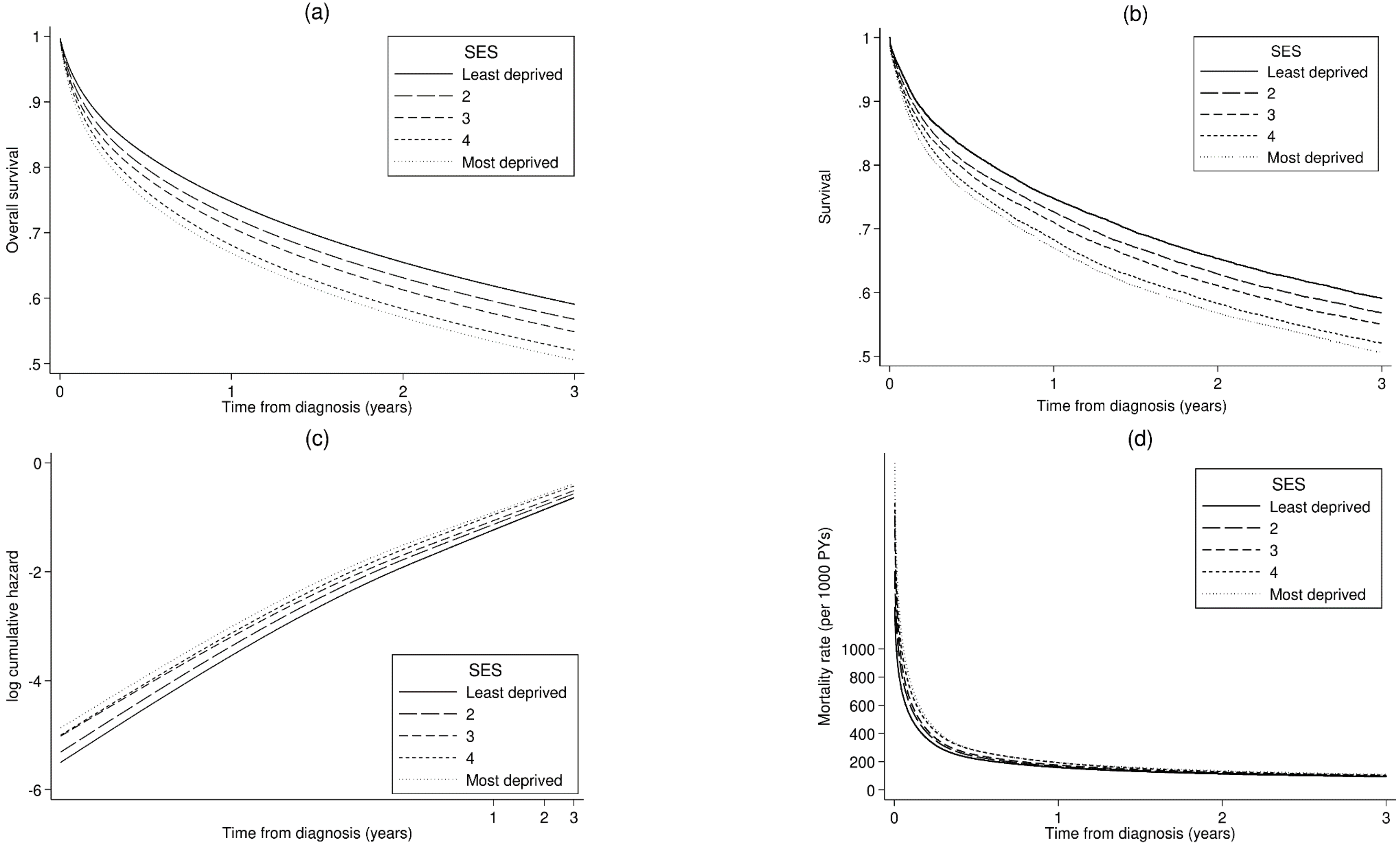

Figure 4.5 (a) Overall survival curves by FPM (b) survival curves by Kaplan-Meier method (c) log-cumulative hazards (d) mortality rates by SES group for colon cancer, England (SES set as time-varying effect)

Abbreviations: 1000 PYs, 1000 person-years; FPM, flexible parametric model; SES, socioeconomic status.

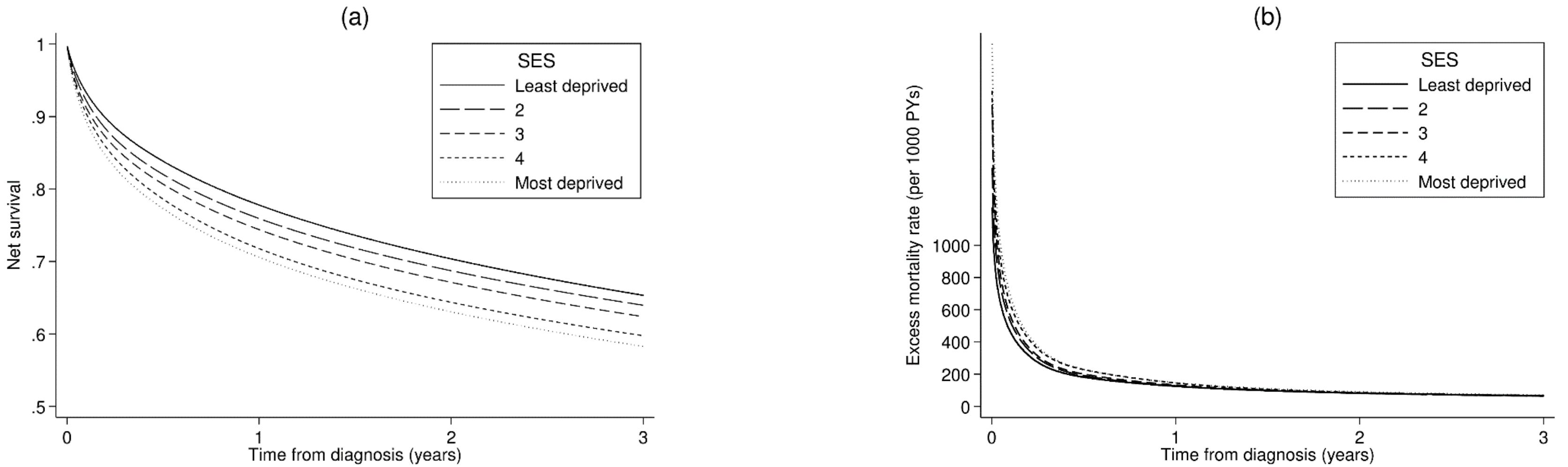

Figure 4.6 (a) Net survival curves by FPM (b) excess mortality rates by SES group for colon cancer, England (SES set as time-varying effect)

Abbreviations: 1000 PYs, 1000 person-years; FPM, flexible parametric model; SES, socioeconomic status.

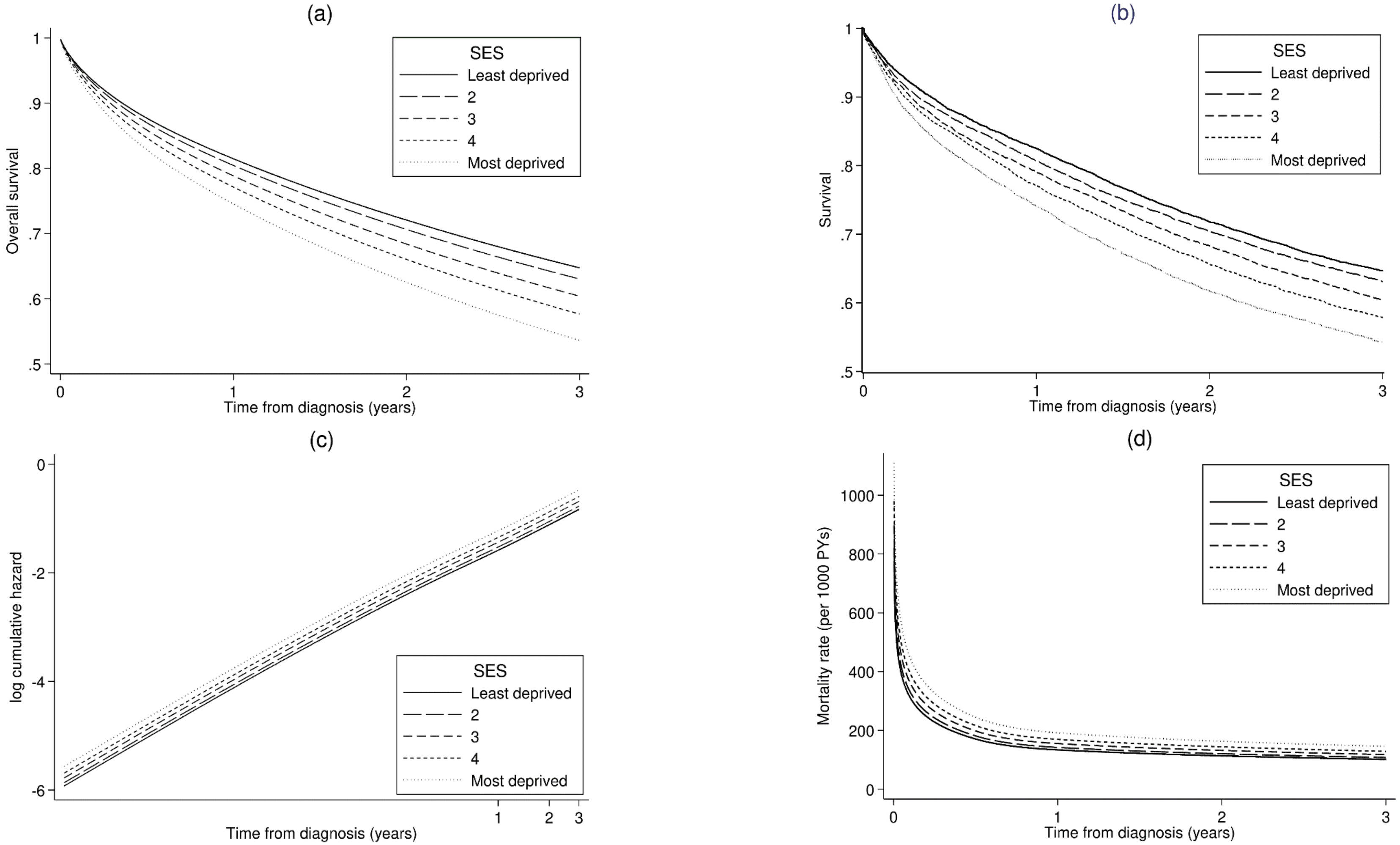

Figure 4.7 (a) Overall survival curves by FPM (b) survival curves by Kaplan-Meier method (c) log-cumulative hazards (d) mortality rates by SES group for rectal cancer, England (SES set as no time-varying effect)

Abbreviations: 1000 PYs, 1000 person-years; FPM, flexible parametric model; SES, socioeconomic status.

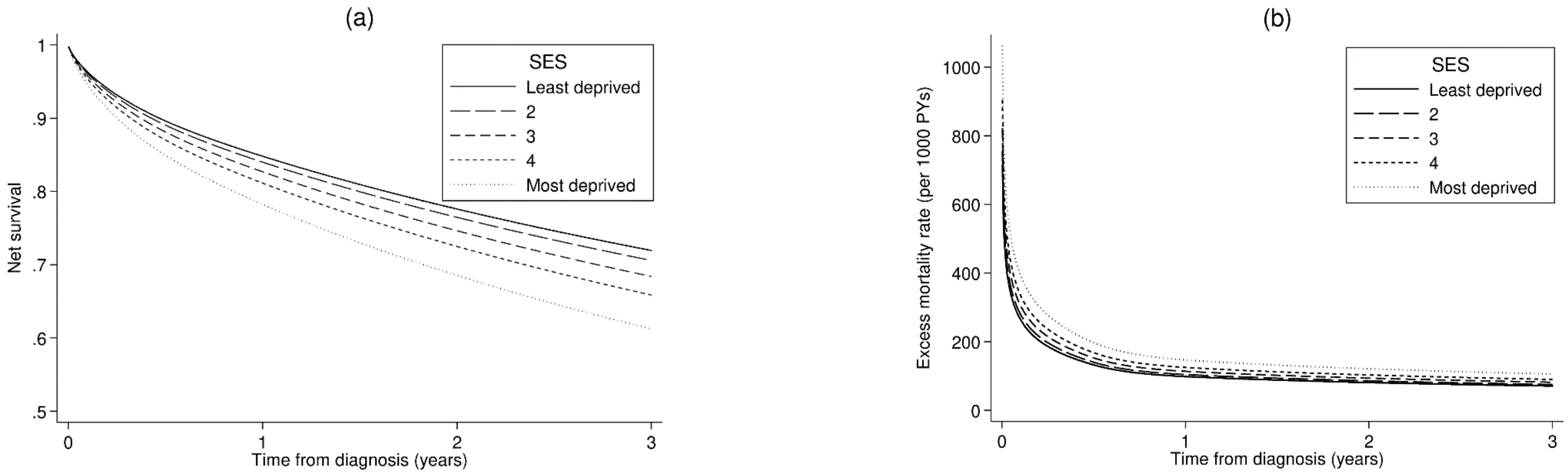

Figure 4.8 (a) Net survival curves by FPM (b) excess mortality rates by SES group for rectal cancer, England (SES set as no time-varying effect)

Abbreviations: 1000 PYs, 1000 person-years; FPM, flexible parametric model; SES, socioeconomic status.

Figure 4.9 graphically demonstrates (a) the HR of the most deprived group when the least deprived group is the reference for colon cancer in both overall and net survival, and three measures of difference between the least and the most deprived groups derived by the FPM with SES treated as TVE. Figure 4.9 (b) displays the difference in the mortality rates per 1,000 PYs, (c) survival curves and (d) difference in survival. When no other covariates were adjusted, the graphs confirm that both overall and net survival were better in the least deprived group by more than 5% at the 3-year point since diagnosis, even with the HR of the most deprived approaching 1 (i.e. difference in mortality rate approaching 0) over time.

For rectal cancer, since the hazard of SES kept proportional throughout, the survival gap between the least and the most deprived groups reached more than 10% at the 3-year point since diagnosis, as illustrated in Figure 4.10.

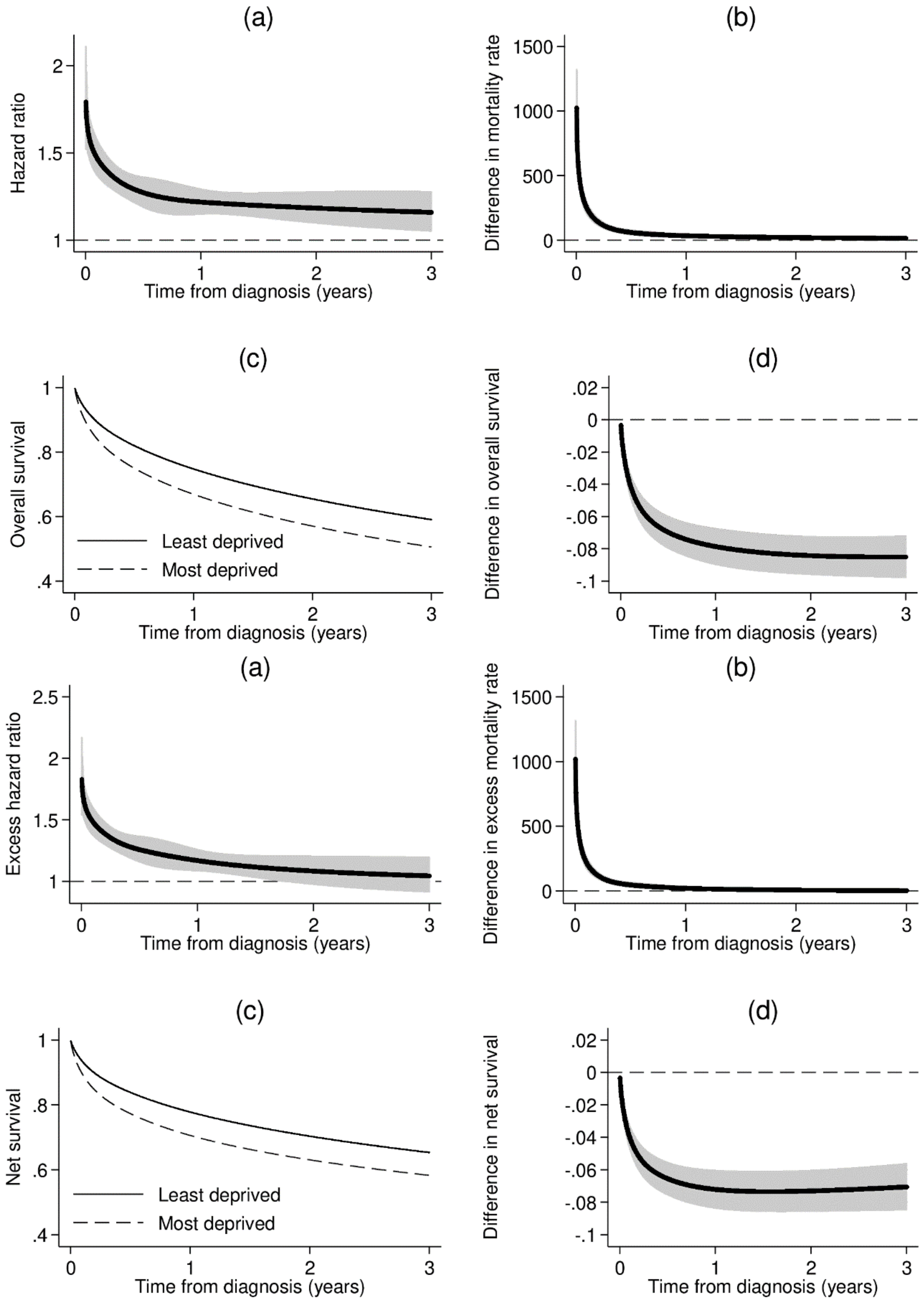

Figure 4.9 Upper graphs: overall survival, lower graphs: net survival for colon cancer, England. (a) Hazard ratio of SES 5 (b) difference in (excess) mortality rate per 1000 PYs (c) (overall/net) survival (%) in the most and least deprived groups (d) difference in (overall/net) survival (%) between the most and the least deprived groups

Abbreviations: 1000 PYs, 1000 person-years; SES, socioeconomic status. (a) Reference is SES 1 (least deprived group). (b) A positive value means that the mortality is larger in SES 5 (the most deprived group). (d) A negative value means that the survival is worse in SES 5.

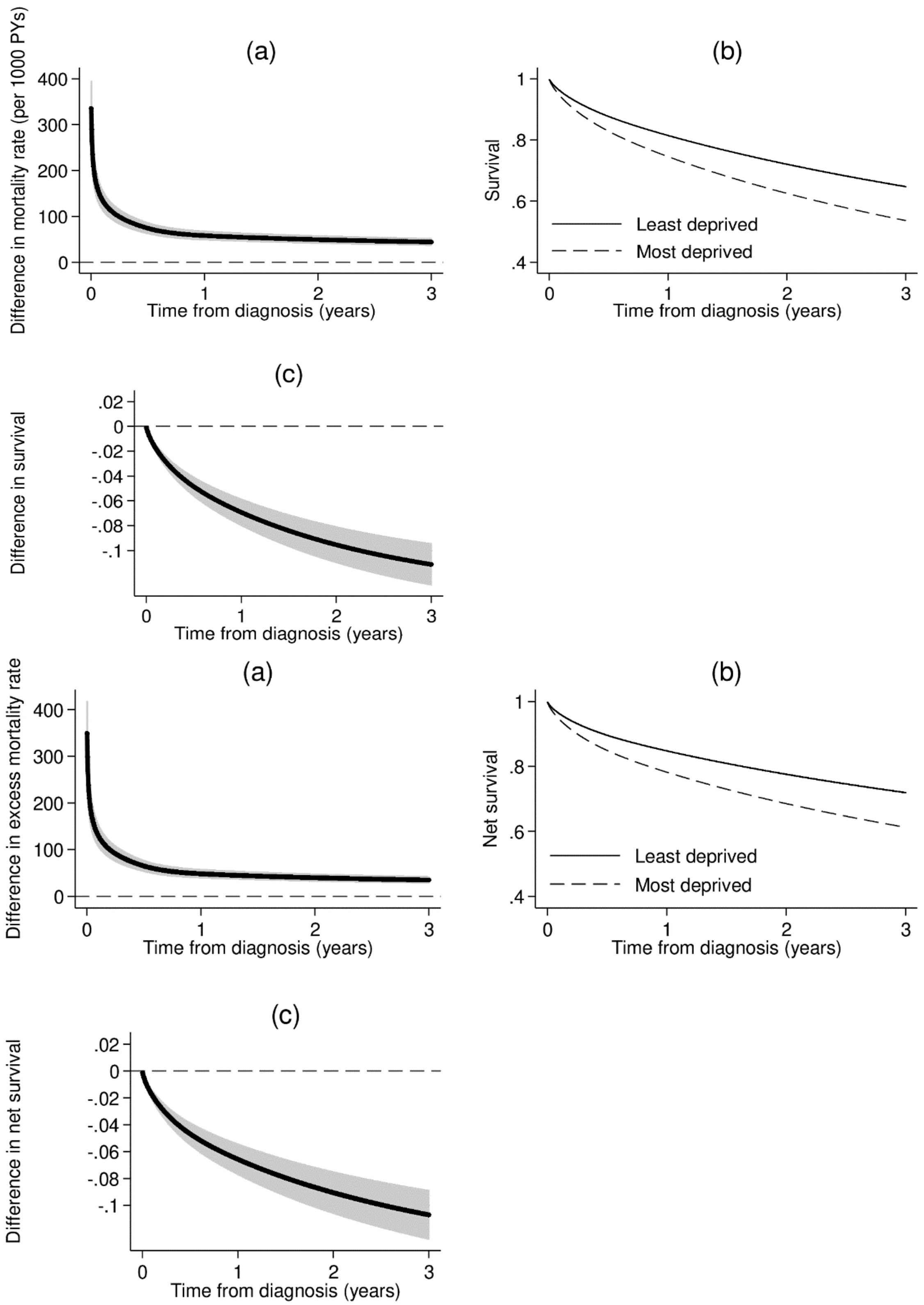

Figure 4.10 Upper graphs: overall survival, lower graphs: net survival for rectal cancer, England. (a) Difference in (excess) mortality rate per 1000 PYs (b) (overall/net) survival (%) in the most and least deprived groups (c) difference in (overall/net) survival (%) between the most and the least deprived groups

Abbreviations: 1000 PYs, 1000 person-years; SES, socioeconomic status. (a) A positive value means that the mortality is larger in SES 5 (the most deprived group). (c) A negative value means that the survival is worse in SES 5.

4.3.3 Summary of findings

The use of an FPM seemed appropriate, and the number and position of the internal knots clinically defined demonstrated a good statistical fit. The graphs estimated by FPMs showed that the differences in mortality rates between the least and the most deprived groups in England were largest shortly after diagnosis. The mortality rates and excess mortality rates peaked before 90 days since diagnosis and declined to less than 200 per 1,000 PYs after one year for both colon and rectal cancer patients. When not adjusted for any other conditions, the most deprived group had lower survival than the least deprived group. The differences in both overall and net survival reached approximately 8% for colon cancer and 10% for rectal cancer at the 3-year point since diagnosis.

4.4 Factors associated with survival and socioeconomic inequalities in survival

Previous sub-chapter (**Chapter 4.3**) illustrated general patterns of survival by SES, not controlling for any other factors. In this sub-chapter, I explored potential factors associated with survival and examined whether survival differed by SES after adjusted for the associated factors.

4.4.1 Methods

Outcome measure

I conducted three analyses in this sub-chapter. In the first and second analyses, I explored potential factors associated with survival and mortality rate ratios (i.e. HR of death) by SES. The entry for all survival analyses was the date of diagnosis. In the third analysis, as in **Chapter 4.3**, in addition to the mortality rate 'ratios', 'difference' measures by SES group were graphically explored, after adjusting for all potential factors. Three graphical measures were presented for each stage for overall and net survival: difference in mortality rates (excess mortality rates for net survival) between the least deprived group (SES 1) and the most deprived group (SES 5), survival curves of SES 1 and SES 5 and survival difference between the two SES groups.

Analysis strategy

For deriving factors associated with survival and HRs of SES in the first analysis, I employed Cox regression with both imputed and completed data for overall survival. Important variables (stage, tumour grade, emergency presentation and histology) were multiply imputed 30 times under the MAR assumption (see **Chapter 4.1**). I conducted bivariable analyses with the main effect (SES) for all other variables one at a time, to assess and the confounding effect of each variable. Each variable that had strong evidence for association ($p<0.05$ in the Wald test) with the outcome was retained in the multivariable model. Instead of likelihood ratio test, the Wald test was unifiedly used for both imputed and completed data to account for the uncertainty in imputed data [208]. Variables were further removed by backward elimination. Finally, excluded variables were added back into the model one at a time, and were included in the final multivariable model as confounders if the effect of SES in the HR (HR of the most deprived group) changed by more than 10%. An interaction term between SES and stage was also added as the main interest. Age at diagnosis and sex were included as *a priori* confounders.

In the second analysis, I applied the FPM using `stpm2`. In addition to the advantage of visuality in survival differences between groups, the other advantage of using the FPM over a semi-parametric model, such as the Cox regression model, is that the FPM easily enables us to deal with time-varying effects when the proportional hazard assumption does not hold in the Cox regression model. Variable selection of the potential factors associated with survival in the FPM was based on multivariable Cox regression analyses in the first analysis [212]. After the variable selection, I checked the proportional hazard assumption using Schoenfeld residuals for each variable. The identified variables that did not hold the proportional hazard assumption were changed to time-varying covariates (TVCs) in the FPM model. When fitting the FPM, from the results of **Chapter 4.3**, positions of the internal knots for the non-TVCs were set at three points at 90 days, six months and one year from the date of diagnosis. For the TVCs, the number of internal knots was reduced from three (baseline hazard) to two [210]: time points at six months and one year from the date of diagnosis. Since imputed data are not technically supported in estimations of hazard and survival difference by FPM, the model was built with completed data only. Therefore, in this chapter, analyses using imputed data in the first analysis were considered sensitivity analyses. After building the FPMs with TVCs for overall survival, I adopted the same models for net survival.

In the third analysis, differences in mortality rates and survival were displayed in figures using the results of FPMs in the second analysis for both overall and net survival.

As in **Chapter 4.1** and **4.2**, in all analyses in **Chapter 4.4**, site of colon cancer was categorised in three groups, but sub-group analysis (site categorised in four groups: right-sided, transverse, descending and sigmoid colon) were also conducted.

4.4.2 Results

First analysis (Cox regression for overall survival and hazard ratios by SES)

Factors associated with overall survival

The first analysis using Cox regression included 38,624 colon cancer (55.4% of total) and 22,630 rectal cancer patients (59.1% of total) with completed data. The sensitivity analysis using imputed data included 69,762 colon cancer and 38,267 rectal cancer patients.

Table 4.15 and Table 4.16 illustrate the results of bivariable and multivariable analyses of Cox regression for overall survival. To show the overall change in the effect of SES, the adjusted HRs of SES in those tables were based on a model without interaction between SES and stage. For the rest, adjusted HRs were based on the multivariable model with interaction between SES and stage (final model). As in **Chapter 4.1** and **4.2**, for the sub-group analysis, results of variables except site in the multivariable analyses were omitted.

All factors except obesity were associated with survival. Adjusted HRs of SES on Table 4.15 and Table 4.16 confirmed that the socioeconomic gradient in survival remained even after controlling for the associated factors. For both colon and rectal cancer patients in completed data, there was strong evidence for the association between increased age, increased number of comorbidities and higher mortality rates. Patients with worse tumour grades (poorly differentiated or undifferentiated tumours) or emergency presentation had a 70 to 80% increase in mortality rates compared with the patients with better tumour grades (well or moderately differentiated tumours) or those without emergency presentation. Patients who did not receive major surgery had a threefold increase in mortality rate compared with the patients who received surgery when adjusting for all other variables. Patients with left-sided colon cancer (both descending and sigmoid colon cancer) had slightly lower mortality rates than patients with right or transverse colon cancer. Mortality rates were lower among patients with rectal cancer than patients with rectosigmoid cancer.

Hazard ratios of death by SES

Table 4.17 compares the stage-specific HRs among SES groups in each stage derived by the multivariable Cox regression models with interaction between SES and stage using imputed and completed data.

Analyses of completed data suggested a clear socioeconomic gradient towards higher HRs in deprived groups for colon cancer with stages II and III, and for rectal cancer at stages I and II, even after adjusting for all other factors (Table 4.17). A weak socioeconomic trend was also observed for colon cancer at stage I and rectal cancer at stages III and IV. The trend was more evident in the sensitivity analyses using imputed data in all stages for both cancers.

Bivariable analyses implied that stage and emergency presentation confounded the effect of SES on survival. The HR of the most deprived group was reduced when those factors were adjusted one at a time, but only by less than 10%. Other factors influenced the socioeconomic inequalities in survival in a negligible amount in bivariable analyses.

Table 4.15 Hazard ratios of death using Cox regression for colon cancer, England

Variable	Bivariable analysis			Multivariable sensitivity analysis Multiple imputation (n=69762)			Multivariable analysis Complete cases (n=38624)		
	HR*	95% CI	p-value†	HR**	95% CI	p-value†	HR**	95% CI	p-value†
SES									
1 (least deprived)	1.00			1.00			1.00		
2	1.08	(1.05, 1.12)		1.04	(1.01, 1.08)		1.03	(0.97, 1.08)	
3	1.15	(1.11, 1.20)	<0.001‡	1.10	(1.06, 1.14)	<0.001‡	1.05	(0.99, 1.10)	<0.001‡
4	1.26	(1.22, 1.31)		1.17	(1.12, 1.21)		1.13	(1.07, 1.19)	
5 (most deprived)	1.32	(1.27, 1.37)		1.25	(1.20, 1.30)		1.16	(1.09, 1.22)	
Sex									
Male	1.00			1.00			1.00		
Female	1.07	(1.05, 1.10)	<0.001	0.98	(0.96, 1.01)	0.24	0.93	(0.90, 0.97)	<0.001
Age									
<65	1.00			1.00			1.00		
65–79	1.37	(1.33, 1.42)	<0.001‡	1.57	(1.51, 1.63)	<0.001‡	1.46	(1.39, 1.53)	<0.001‡
80–99	3.00	(2.90, 3.09)		2.54	(2.45, 2.64)		2.37	(2.26, 2.50)	
Year of diagnosis									
2010	1.00			1.00			1.00		
2011	0.99	(0.96, 1.02)	0.40	1.06	(1.03, 1.10)	<0.001	0.96	(0.92, 1.01)	0.13
2012	0.96	(0.94, 0.99)	0.02	1.09	(1.05, 1.12)	<0.001	0.94	(0.90, 0.98)	0.006
2013	1.01	(0.96, 1.06)	0.63	1.11	(1.06, 1.18)	<0.001	0.94	(0.87, 1.01)	0.08
Cancer site									
Right-sided colon#	1.00			1.00			1.00		
Transverse colon#	1.03	(0.99, 1.06)	0.17	1.03	(0.99, 1.08)	0.13	1.04	(0.98, 1.09)	0.20
Left-sided colon#	0.77	(0.75, 0.79)	<0.001	0.83	(0.81, 0.86)	<0.001	0.82	(0.79, 0.85)	<0.001
Descending colon	0.83	(0.78, 0.88)	<0.001	0.86	(0.80, 0.91)	<0.001	0.85	(0.78, 0.93)	<0.001
Sigmoid colon	0.76	(0.74, 0.78)	<0.001	0.83	(0.80, 0.85)	<0.001	0.81	(0.78, 0.85)	<0.001
Overlapping site or unspecified	2.21	(2.13, 2.29)	<0.001	1.23	(1.18, 1.29)	<0.001	1.12	(1.03, 1.21)	0.007

Table 4.15 continued

Variable	Bivariable analysis			Multivariable sensitivity analysis Multiple imputation (n=69762)			Multivariable analysis Complete cases (n=38624)		
	HR*	95% CI	p-value†	HR**	95% CI	p-value†	HR**	95% CI	p-value†
Stage									
I	1.00						1.00		
II	1.85	(1.70, 2.02)	<0.001‡				1.70	(1.36, 2.12)	<0.001‡
III	3.53	(3.25, 3.84)					3.39	(2.74, 4.18)	
IV	15.28	(14.10, 16.56)					11.22	(9.16, 13.75)	
Stage§									
I	1.00			1.00					
II	1.91	(1.75, 2.08)	<0.001‡	2.04	(1.69, 2.46)	<0.001‡			
III	3.50	(3.22, 3.80)		3.75	(3.12, 4.50)				
IV	14.82	(13.65, 16.09)		11.00	(9.26, 13.07)				
Histology									
Adenocarcinoma	1.00			1.00			1.00		
Adenosquamous and squamous cell carcinoma	0.77	(0.63, 0.93)	0.008	0.49	(0.39, 0.63)	<0.001	0.83	(0.62, 1.12)	0.23
Non-epithelial tumours	0.47	(0.42, 0.53)	<0.001	0.35	(0.31, 0.40)	<0.001	0.68	(0.57, 0.81)	<0.001
Tumour grade									
Well/moderately differentiated	1.00						1.00		
Poorly/undifferentiated	2.23	(2.16, 2.31)	<0.001				1.76	(1.69, 1.83)	<0.001
Tumour grade§									
Well/moderately differentiated	1.00			1.00					
Poorly/undifferentiated	2.19	(2.11, 2.26)	<0.001	1.60	(1.55,1.66)	<0.001			

Table 4.15 continued

Variable		Bivariable analysis			Multivariable sensitivity analysis			Multivariable analysis	
					Multiple imputation (n=69762)			Complete cases (n=38624)	
	HR*	95% CI	p-value†	HR**	95% CI	p-value†	HR**	95% CI	p-value†
Emergency presentation									
No	1.00						1.00		
Yes	2.06	(2.01, 2.12)	<0.001				1.85	(1.78, 1.92)	<0.001
Emergency presentation§									
No	1.00			1.00					
Yes	2.19	(2.11, 2.26)	<0.001	1.69	(1.64, 1.73)	<0.001			
Major surgery for primary lesion									
Received	1.00			1.00			1.00		
Not received	4.91	(4.79 ,5.02)	<0.001	2.89	(2.80, 2.98)	<0.001	2.92	(2.79, 3.05)	<0.001
Number of chronic comorbidities									
0	1.00			1.00			1.00		
1	1.50	(1.45, 1.55)	<0.001‡	1.21	(1.17, 1.26)	<0.001‡	1.22	(1.15, 1.28)	<0.001‡
2	2.22	(2.09, 2.35)		1.40	(1.30, 1.50)		1.70	(1.53, 1.90)	
3+	2.65	(2.35, 2.98)		1.53	(1.32, 1.79)		1.51	(1.19, 1.91)	
Number of acute comorbidities									
0	1.00			1.00			1.00		
1	1.57	(1.52, 1.62)	<0.001‡	1.27	(1.22, 1.31)	<0.001‡	1.24	(1.18, 1.30)	<0.001‡
2	2.39	(2.25 ,2.53)		1.45	(1.36, 1.55)		1.56	(1.41, 1.72)	
3+	3.07	(2.74, 3.45)		1.73	(1.49, 2.00)		2.41	(1.98, 2.93)	
Obesity at diagnosis									
No	1.00								
Yes	0.93	(0.85, 1.03)	0.16						

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; SES, socioeconomic status. * Adjusted for SES in all variables. Results of bivariable analysis on histology with imputed data and completed data did not differ in an important amount. Thus, results with only completed data are shown. ** All variables are mutually adjusted. For SES only, adjusted HRs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. # Right-sided colon includes ascending colon, hepatic flexure, caecum and appendix. Transverse colon includes transverse colon and splenic flexure. Left-sided colon includes descending colon and sigmoid colon. † P-value of Wald test. ‡ P-value of Wald test for trend.

Table 4.16 Hazard ratios of death using Cox regression for rectal cancer, England

Variable	Bivariable analysis			Multivariable sensitivity analysis			Multivariable analysis		
				Multiple imputation (n=38267)			Complete cases (n=22630)		
	HR*	95% CI	p-value†	HR**	95% CI	p-value†	HR**	95% CI	p-value†
SES									
1 (least deprived)	1.00		<0.001‡	1.00		<0.001‡	1.00		<0.001‡
2	1.06	(1.01, 1.12)		1.01	(0.96, 1.07)		0.97	(0.90, 1.04)	
3	1.16	(1.10, 1.22)		1.09	(1.03, 1.15)		1.05	(0.97, 1.13)	
4	1.27	(1.20, 1.33)		1.14	(1.07, 1.20)		1.04	(0.96, 1.12)	
5 (most deprived)	1.43	(1.36, 1.51)		1.23	(1.16, 1.30)		1.16	(1.08, 1.26)	
Sex									
Male	1.00			1.00			1.00		
Female	1.06	(1.03, 1.10)	0.001	0.98	(0.94, 1.01)	0.23	0.91	(0.87, 0.96)	<0.001
Age									
<65	1.00		<0.001‡	1.00		<0.001‡	1.00		<0.001‡
65–79	1.49	(1.43, 1.56)		1.63	(1.56, 1.71)		1.60	(1.51, 1.70)	
80–99	3.73	(3.57, 3.90)		2.99	(2.84, 3.14)		2.96	(2.77, 3.17)	
Year of diagnosis									
2010	1.00			1.00			1.00		
2011	0.94	(0.90, 0.98)	0.002	1.02	(0.98, 1.07)	0.33	0.97	(0.91, 1.03)	0.26
2012	0.87	(0.84, 0.91)	<0.001	0.97	(0.93, 1.01)	0.16	0.89	(0.84, 0.95)	<0.001
2013	0.89	(0.83, 0.96)	0.002	1.06	(0.98, 1.15)	0.12	0.93	(0.83, 1.03)	0.15
Cancer site									
Rectosigmoid junction	1.00			1.00			1.00		
Rectum	0.78	(0.75, 0.81)	<0.001	0.81	(0.78, 0.85)	<0.001	0.89	(0.84, 0.95)	<0.001
Overlapping site or unspecified	0.93	(0.76, 1.12)	0.43	0.85	(0.67, 1.08)	0.19	0.79	(0.53, 1.20)	0.27

Table 4.16 continued

Variable	Bivariable analysis			Multivariable sensitivity analysis Multiple imputation (n=38267)			Multivariable analysis Complete cases (n=22630)		
	HR*	95% CI	p-value[†]	HR**	95% CI	p-value[†]	HR**	95% CI	p-value[†]
Stage									
I	1.00						1.00		
II	2.13	(1.94, 2.34)	<0.001[‡]				2.38	(1.87, 3.04)	<0.001[‡]
III	2.89	(2.66, 3.15)					3.27	(2.62, 4.09)	
IV	12.34	(11.40, 13.36)					10.10	(8.18, 12.48)	
Stage[§]									
I	1.00			1.00					
II	2.17	(1.99, 2.38)	<0.001[‡]	2.25	(1.83, 2.77)	<0.001[‡]			
III	2.83	(2.61, 3.08)		2.88	(2.39, 3.48)				
IV	11.87	(11.00, 12.81)		8.96	(7.50, 10.70)				
Histology									
Adenocarcinoma	1.00			1.00			1.00		
Adenosquamous and squamous cell carcinoma	0.85	(0.72, 0.99)	0.03	0.60	(0.50, 0.71)	<0.001	0.77	(0.61, 0.98)	0.03
Non-epithelial tumours	0.98	(0.86, 1.13)	0.83	0.77	(0.64, 0.94)	0.01	1.58	(1.27, 1.97)	<0.001
Tumour grade									
Well/moderately differentiated	1.00						1.00		
Poorly/undifferentiated	2.15	(2.05, 2.26)	<0.001				1.79	(1.69, 1.90)	<0.001
Tumour grade[§]									
Well/moderately differentiated	1.00			1.00					
Poorly/undifferentiated	2.09	(1.99, 2.20)	<0.001	1.70	(1.61, 1.79)	<0.001			

Table 4.16 continued

Variable	Bivariable analysis			Multivariable sensitivity analysis Multiple imputation (n=38267)			Multivariable analysis Complete cases (n=22630)		
	HR*	95% CI	p-value†	HR**	95% CI	p-value†	HR**	95% CI	p-value†
Emergency presentation									
No	1.00						1.00		
Yes	3.30	(3.16, 3.44)	<0.001				1.81	(1.70, 1.93)	<0.001
Emergency presentation§									
No	1.00			1.00					
Yes	3.38	(3.24, 3.52)	<0.001	1.93	(1.84, 2.02)	<0.001			
Major surgery for primary lesion									
Received	1.00			1.00			1.00		
Not received	4.82	(4.64, 5.01)	<0.001	2.89	(2.77, 3.02)	<0.001	2.90	(2.74, 3.06)	<0.001
Number of chronic comorbidities									
0	1.00		<0.001‡	1.00		<0.001‡	1.00		<0.001‡
1	1.62	(1.55, 1.71)		1.31	(1.23, 1.38)		1.38	(1.28, 1.48)	
2	2.46	(2.23, 2.70)		1.58	(1.42, 1.76)		1.87	(1.59, 2.20)	
3+	3.05	(2.53, 3.66)		1.82	(1.40, 2.37)		2.76	(1.98, 3.84)	
Number of acute comorbidities									
0	1.00		<0.001‡	1.00		<0.001‡	1.00		<0.001‡
1	1.81	(1.73, 1.90)		1.35	(1.28, 1.42)		1.32	(1.22, 1.42)	
2	2.72	(2.46, 3.01)		1.57	(1.39, 1.77)		1.69	(1.42, 2.00)	
3+	3.60	(2.89, 4.48)		1.93	(1.50, 2.48)		2.12	(1.46, 3.08)	
Obesity at diagnosis									
No	1.00								
Yes	0.92	(0.79, 1.08)	0.30						

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; SES, socioeconomic status. * Adjusted for SES in all variables. Results of bivariable analysis on histology with imputed data and completed data did not differ in an important amount. Thus, results with only completed data are shown. ** All variables are mutually adjusted. For SES only, adjusted ORs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. ‡ P-value of Wald test for trend.

Table 4.17 Stage-specific hazard ratios of death using multivariable Cox regression with interaction between SES and stage for colon and rectal cancer, England

	Colon						Rectum					
	Multiple imputation[a]			Complete cases[b]			Multiple imputation[c]			Complete cases[d]		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Stage I												
SES												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.15	(0.91, 1.44)		1.03	(0.78, 1.36)		1.07	(0.86, 1.34)		1.01	(0.77, 1.33)	
3	1.16	(0.93, 1.46)	0.002	1.00	(0.75, 1.32)	0.42	1.09	(0.86, 1.37)	0.007	1.10	(0.84, 1.44)	0.01
4	1.27	(1.01, 1.59)		1.03	(0.77, 1.37)		1.21	(0.97, 1.51)		1.13	(0.86, 1.49)	
5 (most deprived)	1.47	(1.15, 1.88)		1.16	(0.86, 1.55)		1.36	(1.07, 1.72)		1.43	(1.08, 1.88)	
Stage II												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.07	(0.96, 1.20)		1.01	(0.88, 1.16)		1.00	(0.85, 1.19)		0.98	(0.80, 1.20)	
3	1.17	(1.04, 1.31)	<0.001	1.11	(0.97, 1.27)	<0.001	1.18	(1.00, 1.40)	<0.001	1.15	(0.94, 1.40)	0.002
4	1.38	(1.23, 1.56)		1.38	(1.21, 1.59)		1.23	(1.04, 1.47)		1.14	(0.93, 1.39)	
5 (most deprived)	1.46	(1.30, 1.64)		1.45	(1.26, 1.67)		1.34	(1.13, 1.59)		1.32	(1.08, 1.63)	
Stage III												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.14	(1.04, 1.25)		1.17	(1.05, 1.30)		1.02	(0.91, 1.16)		0.98	(0.85, 1.13)	
3	1.14	(1.04, 1.25)	<0.001	1.11	(0.99, 1.23)	<0.001	1.15	(1.03, 1.29)	<0.001	1.07	(0.93, 1.24)	0.09
4	1.21	(1.10, 1.33)		1.18	(1.06, 1.32)		1.23	(1.09, 1.39)		1.12	(0.97, 1.29)	
5 (most deprived)	1.37	(1.25, 1.51)		1.32	(1.19, 1.48)		1.20	(1.07, 1.36)		1.07	(0.92, 1.25)	
Stage IV												
1 (least deprived)	1.00			1.00			1.00			1.00		
2	1.01	(0.96, 1.06)		0.97	(0.90, 1.04)		1.00	(0.92, 1.08)		0.95	(0.85, 1.05)	
3	1.08	(1.02, 1.13)	<0.001	1.01	(0.94, 1.08)	0.29	1.04	(0.96, 1.13)	<0.001	1.00	(0.90, 1.11)	0.05
4	1.11	(1.06, 1.17)		1.04	(0.97, 1.12)		1.07	(0.99, 1.16)		0.95	(0.86, 1.06)	
5 (most deprived)	1.17	(1.10, 1.24)		1.00	(0.93, 1.09)		1.20	(1.10, 1.31)		1.13	(1.02, 1.26)	

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; SES, socioeconomic status. All p-values are of Wald test for trend. Model a, b, c, d: adjusted for sex, age, site, year of diagnosis, histology[§], tumour grade[§], emergency presentation[§], receipt of major surgery, number of chronic and acute comorbidities (§: multiply imputed in Model a, c).

Second analysis (Flexible parametric model for overall/net survival and hazard ratios/excess hazard ratios by SES)

The variables in the first analysis using Cox regression were applied to the FPM in the second analysis for overall and net survival to address variables violating the proportional hazard assumption.

To identify TVCs, I checked the proportional hazard assumption in each variable of the multivariable Cox regression models derived in the first analysis. In both cancers, the proportional hazard assumption was held among SES groups after adjusting for covariates in the Cox regression models. In colon cancer, the assumption was violated for nine variables: sex, age at diagnosis, site, stage, histology, tumour grade, emergency presentation, receipt of major surgery and number of acute comorbidities. Those nine variables were included as TVCs in the FPM for overall survival. Histology was changed to non-TVC for net survival since the FPM did not converge if histology was treated as a TVC.

In rectal cancer, the proportional hazard assumption was violated for five variables: age at diagnosis, site, histology, tumour grade and emergency presentation. Those five variables were included as TVCs in the FPM for both overall and net survival.

Factors associated with survival

Hazard ratios of the non-TVCs in the FPM for overall survival showed close agreement with HRs in the Cox regression models (see Table 4.15 *vs* Table 4.18 and Table 4.16 *vs* Table 4.19). There was generally a clear socioeconomic gradient with higher hazards in the deprived groups for both cancers, for both overall and net survival (Table 4.18 and Table 4.19). As observed in the previous analyses, chronic comorbidities were consistently associated with increased mortality rates also for net survival (Table 4.18 and Table 4.19).

For the TVCs, HRs and EHRs change over time. Table 4.20 and Table 4.21 illustrate the point estimates of the HRs and EHRs for the TVCs at 90 days, six months and one year since diagnosis. For both cancers, the effect of age on hazard decreased over time. Emergency presentation had a waxing effect on hazard for both cancers under the overall and net survival settings. Regarding the site of cancer, HR and EHR of sigmoid colon cancer were lower than right-sided colon cancer at 90 days from diagnosis; however, HR and EHR of descending colon cancer also decreased to that of sigmoid colon cancer over the time. Rectal cancer continuously had lower mortality rates than rectosigmoid cancer. However, the hazard of rectal cancer increased over time, suggesting that the increased mortality rates after six months could be due to the local recurrence, which often occurs in rectal cancer. When comparing the HRs and EHRs of the stages, EHRs expanded substantially in stage IV. The inflations imply that the reference group of patients with stage I rarely died from cancer. The effect of tumour grade on HRs/EHRs changed over time, but the worse grades (poorly differentiated or undifferentiated tumours) persistently had double the rate of that in the better grades (well or moderately differentiated tumours) after adjusting for other factors. The effects of major surgery and acute comorbidities on HRs/EHRs changed over time only among colon cancer patients but were both highest in the first period (90 days since diagnosis).

Table 4.18 Hazard ratios (overall survival) and excess hazard ratios (net survival) of death using multivariable FPM with TVCs for colon cancer, England

Variable	Overall survival		Net survival	
	HR*	95% CI	EHR*	95% CI
SES				
1 (least deprived)	1.00		1.00	
2	1.03	(0.97, 1.09)	1.01	(0.95, 1.08)
3	1.05	(0.99, 1.11)	1.01	(0.94, 1.07)
4	1.13	(1.07, 1.19)	1.09	(1.02, 1.16)
5 (most deprived)	1.16	(1.09, 1.23)	1.09	(1.01, 1.16)
Sex	**TVC**		**TVC**	
Age	**TVC**		**TVC**	
Year of diagnosis				
2010	1.00		1.00	
2011	0.97	(0.92, 1.01)	0.95	(0.90, 1.00)
2012	0.95	(0.90, 0.99)	0.95	(0.90, 1.00)
2013	0.94	(0.87, 1.01)	0.93	(0.85, 1.02)
Cancer site	**TVC**		**TVC**	
Stage	**TVC**		**TVC**	
Histology				
Adenocarcinoma	**TVC**		1.00	
asc/scc			0.78	(0.56, 1.10)
Non-epithelial tumours			0.73	(0.60, 0.89)
Tumour grade	**TVC**		**TVC**	
Emergency presentation	**TVC**		**TVC**	
Major surgery for primary lesion	**TVC**		**TVC**	
Number of chronic comorbidities				
0	1.00		1.00	
1	1.22	(1.15, 1.28)	1.22	(1.14, 1.30)
2	1.69	(1.51, 1.89)	1.78	(1.55, 2.04)
3+	1.48	(1.17, 1.88)	1.40	(1.04, 1.89)
Number of acute comorbidities	**TVC**		**TVC**	

Abbreviations: 95% CI, 95% confidence interval; asc, adenosquamous cell carcinoma; EHR, excess hazard ratio; HR, hazard ratio; scc, squamous cell carcinoma; SES, socioeconomic status; TVC, time-varying covariate. * All variables are mutually adjusted. For SES only, adjusted HRs/EHRs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted.

Table 4.19 Hazard ratios (overall survival) and excess hazard ratios (net survival) of death using multivariable FPM with TVCs for rectal cancer, England

Variable	Overall survival		Net survival	
	HR*	**95% CI**	**EHR***	**95% CI**
SES				
1 (least deprived)	1.00		1.00	
2	0.97	(0.90, 1.04)	0.95	(0.87, 1.04)
3	1.05	(0.97, 1.13)	1.02	(0.93, 1.12)
4	1.04	(0.96, 1.12)	0.99	(0.90, 1.09)
5 (most deprived)	1.16	(1.08, 1.26)	1.10	(1.00, 1.21)
Sex				
Male	1.00		1.00	
Female	0.92	(0.87, 0.96)	0.97	(0.91, 1.03)
Age	**TVC**		**TVC**	
Year of diagnosis				
2010	1.00		1.00	
2011	0.96	(0.91, 1.02)	0.99	(0.92, 1.07)
2012	0.89	(0.84, 0.95)	0.91	(0.85, 0.98)
2013	0.94	(0.84, 1.04)	1.01	(0.89, 1.15)
Cancer site	**TVC**		**TVC**	
Stage				
I	1.00		1.00	
II	2.21	(1.74, 2.82)	6.17	(3.01, 12.64)
III	2.45	(1.96, 3.06)	10.04	(5.02, 20.10)
IV	7.93	(6.43, 9.79)	35.63	(17.95, 70.73)
Histology	**TVC**		**TVC**	
Tumour grade	**TVC**		**TVC**	
Emergency presentation	**TVC**		**TVC**	
Major surgery for primary lesion				
Received	1.00		1.00	
Not received	2.89	(2.74, 3.05)	3.65	(3.39, 3.92)
Number of chronic comorbidities				
0	1.00		1.00	
1	1.37	(1.27, 1.48)	1.38	(1.26, 1.52)
2	1.86	(1.58, 2.18)	2.00	(1.64, 2.43)
3+	2.70	(1.94, 3.76)	3.21	(2.16, 4.76)
Number of acute comorbidities				
0	1.00		1.00	
1	1.31	(1.21, 1.41)	1.35	(1.23, 1.49)
2	1.69	(1.43, 2.01)	1.79	(1.46, 2.20)
3+	2.12	(1.46, 3.08)	2.41	(1.57, 3.72)

Abbreviations: 95% CI, 95% confidence interval; EHR, excess hazard ratio; HR, hazard ratio; SES, socioeconomic status; TVC, time-varying covariate. * All variables are mutually adjusted. For SES only, adjusted HRs/EHRs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted.

Table 4.20 Point estimates of hazard ratios (overall survival) and excess hazard ratios (net survival) of death for time-varying covariates at 90 days, 6 months and 1 year since diagnosis using multivariable FPM with TVCs and interaction between SES and stage for colon cancer, England

Variable	**Overall survival**						**Net survival**					
	90 days		**6 months**		**1 year**		**90 days**		**6 months**		**1 year**	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**EHR**	**95% CI**	**EHR**	**95% CI**	**EHR**	**95% CI**
SES	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Sex												
Male	1.00		1.00		1.00		1.00		1.00		1.00	
Female	0.96	(0.91, 1.02)	0.94	(0.88, 1.00)	0.93	(0.88, 0.98)	1.00	(0.93, 1.07)	0.98	(0.90, 1.06)	0.97	(0.91, 1.04)
Age												
<65	1.00		1.00		1.00		1.00		1.00		1.00	
65–79	1.67	(1.54, 1.82)	1.50	(1.38, 1.64)	1.41	(1.31, 1.52)	1.57	(1.44, 1.72)	1.36	(1.20, 1.54)	1.19	(1.07, 1.33)
80–99	2.65	(2.42, 2.89)	2.42	(2.20, 2.66)	2.31	(2.14, 2.50)	2.15	(1.94, 2.39)	1.76	(1.49, 2.09)	1.40	(1.19, 1.66)
Year of diagnosis	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Cancer site												
Right-sided colon[#]	1.00		1.00		1.00		1.00		1.00		1.00	
Transverse colon[#]	1.15	(1.06, 1.25)	1.09	(1.00, 1.20)	1.02	(0.94, 1.11)	1.13	(1.03, 1.25)	1.10	(0.97, 1.24)	1.01	(0.90, 1.13)
Left-sided colon[#]	0.77	(0.72, 0.82)	0.73	(0.68, 0.79)	0.78	(0.73, 0.82)	0.73	(0.67, 0.79)	0.67	(0.59, 0.75)	0.72	(0.66, 0.78)
Descending colon	0.93	(0.81, 1.08)	0.72	(0.59, 0.88)	0.74	(0.64, 0.84)	0.90	(0.76, 1.07)	0.65	(0.48, 0.89)	0.67	(0.55, 0.82)
Sigmoid colon	0.74	(0.69, 0.80)	0.73	(0.68, 0.79)	0.78	(0.73, 0.83)	0.71	(0.65, 0.77)	0.67	(0.59, 0.75)	0.72	(0.67, 0.79)
Overlapping site or unspecified	1.23	(1.09, 1.39)	1.05	(0.90, 1.23)	1.01	(0.89, 1.14)	1.21	(1.05, 1.39)	1.02	(0.82, 1.26)	0.95	(0.80, 1.13)
Stage												
I	1.00		1.00		1.00		1.00		1.00		1.00	
II	1.78	(1.34, 2.36)	1.79	(1.37, 2.35)	1.78	(1.39, 2.28)	2.79	(1.44, 5.40)	2.74	(1.38, 5.42)	3.21	(1.63, 6.32)
III	2.53	(1.92, 3.33)	3.53	(2.72, 4.58)	3.95	(3.12, 5.02)	5.13	(2.70, 9.73)	7.86	(4.05, 15.23)	11.10	(5.74, 21.45)
IV	8.45	(6.49, 11.01)	12.63	(9.81, 16.26)	14.02	(11.14, 17.64)	19.20	(10.19, 36.18)	32.33	(16.77, 62.34)	45.81	(23.84, 88.05)

Table 4.20 continued

Variable	Overall survival						Net survival					
	90 days		6 months		1 year		90 days		6 months		1 year	
	HR	95% CI	HR	95% CI	HR	95% CI	EHR	95% CI	EHR	95% CI	EHR	95% CI
Histology							**Changed to proportional hazard**					
Adenocarcinoma	1.00		1.00		1.00							
asc/scc	1.14	(0.71, 1.84)	0.95	(0.55, 1.62)	0.80	(0.49, 1.30)						
Non-epithelial tumours	0.98	(0.74, 1.29)	0.74	(0.54, 1.03)	0.61	(0.46, 0.80)						
Tumour grade												
Well/moderately differentiated	1.00		1.00		1.00		1.00		1.00		1.00	
Poorly/undifferentiated	2.02	(1.89, 2.15)	2.31	(2.16, 2.48)	2.01	(1.90, 2.13)	2.21	(2.05, 2.38)	2.63	(2.36, 2.94)	2.23	(2.07, 2.41)
Emergency presentation												
No	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.73	(1.59, 1.89)	1.81	(1.68, 1.95)	1.86	(1.76, 1.97)	1.72	(1.50, 1.97)	1.87	(1.69, 2.08)	1.97	(1.82, 2.13)
Major surgery for primary lesion												
Received	1.00		1.00		1.00		1.00		1.00		1.00	
Not received	3.83	(3.55, 4.13)	3.58	(3.33, 3.84)	2.91	(2.72, 3.11)	4.20	(3.81, 4.63)	3.88	(3.53, 4.25)	3.02	(2.75, 3.32)
Number of chronic comorbidities	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Number of acute comorbidities												
0	1.00		1.00		1.00		1.00		1.00		1.00	
1	1.26	(1.16, 1.36)	1.14	(1.03, 1.25)	1.16	(1.08, 1.24)	1.24	(1.12, 1.36)	1.11	(0.96, 1.28)	1.14	(1.03, 1.26)
2	1.61	(1.40, 1.86)	1.44	(1.20, 1.74)	1.42	(1.23, 1.64)	1.57	(1.33, 1.85)	1.44	(1.12, 1.84)	1.39	(1.14, 1.70)
3+	2.35	(1.81, 3.05)	1.73	(1.19, 2.52)	1.88	(1.46, 2.42)	2.41	(1.75, 3.30)	1.70	(0.99, 2.94)	2.04	(1.46, 2.86)

Abbreviations: 95% CI, 95% confidence interval; asc, adenosquamous carcinoma; EHR, excess hazard ratio; HR, hazard ratio; SES, socioeconomic status; scc, squamous cell carcinoma. # Right-sided colon includes ascending colon, hepatic flexure, caecum and appendix. Transverse colon includes transverse colon and splenic flexure. Left-sided colon includes descending colon and sigmoid colon.

Table 4.21 Point estimates of hazard ratios (overall survival) and excess hazard ratios (net survival) of death for time-varying covariates at 90 days, 6 months and 1 year since diagnosis using FPM with TVCs and interaction between SES and stage for rectal cancer, England

Variable	Overall survival						Net survival					
	90 days		6 months		1 year		90 days		6 months		1 year	
	HR	95% CI	HR	95% CI	HR	95% CI	EHR	95% CI	EHR	95% CI	EHR	95% CI
SES	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Sex	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Age												
<65	1.00		1.00		1.00		1.00		1.00		1.00	
65–79	1.86	(1.63, 2.13)	1.74	(1.56, 1.93)	1.59	(1.44, 1.76)	1.75	(1.51, 2.02)	1.59	(1.42, 1.79)	1.41	(1.27, 1.57)
80–99	3.09	(2.69, 3.55)	3.07	(2.74, 3.44)	3.01	(2.71, 3.34)	2.43	(2.07, 2.85)	2.39	(2.09, 2.73)	2.21	(1.95, 2.51)
Year of diagnosis	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Cancer site												
Rectosigmoid junction	1.00		1.00		1.00		1.00		1.00		1.00	
Rectum	0.82	(0.73, 0.93)	0.88	(0.80, 0.98)	0.91	(0.83, 1.00)	0.80	(0.70, 0.92)	0.85	(0.75, 0.95)	0.86	(0.77, 0.96)
Overlapping site or unspecified	0.51	(0.12, 2.08)	0.81	(0.31, 2.11)	0.67	(0.29, 1.54)	0.42	(0.07, 2.40)	0.75	(0.25, 2.27)	0.70	(0.28, 1.75)
Stage	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Histology												
Adenocarcinoma	1.00		1.00		1.00		1.00		1.00		1.00	
asc/scc	0.96	(0.62, 1.48)	1.09	(0.78, 1.53)	0.93	(0.64, 1.37)	0.99	(0.62, 1.56)	1.10	(0.76, 1.58)	0.91	(0.60, 1.37)
Non-epithelial tumours	1.72	(1.22, 2.42)	1.40	(0.92, 2.13)	1.25	(0.86, 1.81)	1.71	(1.20, 2.44)	1.47	(0.95, 2.26)	1.36	(0.93, 2.00)
Tumour grade												
Well/moderately differentiated	1.00		1.00		1.00		1.00		1.00		1.00	
Poorly/undifferentiated	1.96	(1.74, 2.20)	2.17	(1.98, 2.39)	2.00	(1.82, 2.19)	2.10	(1.84, 2.38)	2.34	(2.10, 2.60)	2.16	(1.95, 2.40)
Emergency presentation												
No	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.63	(1.39, 1.92)	1.57	(1.38, 1.79)	1.63	(1.47, 1.81)	1.57	(1.27, 1.95)	1.64	(1.41, 1.91)	1.78	(1.58, 2.00)
Major surgery for primary lesion	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Number of chronic comorbidities	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					
Number of acute comorbidities	**Proportional hazard assumption holds**						**Proportional hazard assumption holds**					

Abbreviations: 95% CI, 95% confidence interval; asc, adenosquamous carcinoma; EHR, excess hazard ratio; HR, hazard ratio; SES, socioeconomic status; scc, squamous cell carcinoma

Hazard ratios and excess hazard ratios of death by SES

The adjusted HRs estimated by the multivariable FPMs with TVCs and interaction between SES and stage agreed with the figures estimated by the multivariable Cox regression models (see Table 4.17 and Table 4.22). As seen in the Cox regression models using completed data, there was a gradient towards higher HRs among deprived groups for colon cancer patients with stage I, II and III, and rectal cancer patients with stage I, II, III and IV. A similar trend was also confirmed for EHRs in net survival.

Table 4.22 Stage-specific hazard ratios (overall survival) and excess hazard ratios (net survival) of death using multivariable FPM with TVCs and interaction between SES and stage for colon and rectal cancer, England

	Colon				Rectum			
	Overall survival[a]		Net survival[b]		Overall survival[c]		Net survival[d]	
	HR	**95% CI**	**EHR**	**95% CI**	**HR**	**95% CI**	**EHR**	**95% CI**
Stage I								
SES								
1 (least deprived)	1.00		1.00		1.00		1.00	
2	1.03	(0.78, 1.36)	1.11	(0.49, 2.51)	1.01	(0.77, 1.33)	1.33	(0.57, 3.11)
3	1.00	(0.75, 1.32)	0.65	(0.23, 1.85)	1.11	(0.85, 1.45)	1.36	(0.58, 3.20)
4	1.03	(0.77, 1.38)	1.04	(0.44, 2.47)	1.14	(0.87, 1.50)	1.31	(0.54, 3.14)
5 (most deprived)	1.17	(0.87, 1.57)	1.46	(0.64, 3.31)	1.44	(1.10, 1.90)	1.96	(0.84, 4.54)
Stage II								
1 (least deprived)	1.00		1.00		1.00		1.00	
2	1.01	(0.88, 1.16)	0.95	(0.74, 1.22)	0.98	(0.80, 1.20)	0.89	(0.64, 1.23)
3	1.11	(0.97, 1.28)	1.01	(0.78, 1.31)	1.15	(0.95, 1.40)	1.14	(0.85, 1.54)
4	1.37	(1.20, 1.57)	1.53	(1.21, 1.94)	1.14	(0.93, 1.39)	1.15	(0.85, 1.56)
5 (most deprived)	1.44	(1.25, 1.66)	1.57	(1.23, 2.00)	1.33	(1.08, 1.63)	1.40	(1.03, 1.90)
Stage III								
1 (least deprived)	1.00		1.00		1.00		1.00	
2	1.17	(1.05, 1.30)	1.16	(1.02, 1.33)	0.98	(0.85, 1.13)	0.97	(0.80, 1.16)
3	1.11	(1.00, 1.23)	1.06	(0.93, 1.22)	1.07	(0.93, 1.24)	1.04	(0.86, 1.25)
4	1.19	(1.07, 1.33)	1.12	(0.98, 1.29)	1.12	(0.97, 1.30)	1.12	(0.93, 1.34)
5 (most deprived)	1.33	(1.19, 1.48)	1.28	(1.11, 1.47)	1.07	(0.92, 1.25)	1.03	(0.85, 1.25)
Stage IV								
1 (least deprived)	1.00		1.00		1.00		1.00	
2	0.97	(0.90, 1.04)	0.97	(0.90, 1.04)	0.95	(0.86, 1.06)	0.95	(0.85, 1.06)
3	1.01	(0.93, 1.08)	0.99	(0.92, 1.07)	1.00	(0.90, 1.11)	0.99	(0.89, 1.11)
4	1.05	(0.97, 1.13)	1.04	(0.96, 1.12)	0.96	(0.86, 1.07)	0.93	(0.83, 1.04)
5 (most deprived)	1.01	(0.93, 1.09)	0.98	(0.90, 1.07)	1.13	(1.01, 1.26)	1.08	(0.96, 1.21)

Abbreviations: 95% CI, 95% confidence interval; EHR, excess hazard ratio; HR, hazard ratio; SES, socioeconomic status. Model a, b: adjusted for sex^T, age^T, year of diagnosis, site^T, stage^T, histology^{T*}, tumour grade^T, emergency presentation^T, major surgery^T, chronic and acute^T comorbidities (T: time-varying covariate. * Histology is time-varying covariate only in Model a). Model c, d: adjusted for sex, age^T, year of diagnosis, site^T, stage, histology^T, tumour grade^T, emergency presentation^T, major surgery, chronic and acute comorbidities.

Third analysis (Graphical figures of measures of difference by SES)

From the FPMs fitted in the second analysis, I estimated three measures of difference in graphs: hazard/excess hazard difference between the least and the most deprived groups, survival curves of the two groups and survival difference between the two groups (Figure 4.11 to Figure 4.22). For all figures, results were shown by each sex and stage. Year of diagnosis was set at 2010, age group at under 65 years old, cancer site at right-sided colon in colon cancer and rectosigmoid junction in rectal cancer, histology of adenocarcinoma, tumour grade of well/moderately differentiated tumours, no emergency presentation, received major surgery and having no chronic or acute comorbidities.

For colon cancer, the hazard difference marked positive values in all stages; the most deprived group had a larger mortality rate than the least deprived group. In stages II and III, the difference hit a sharp peak around 20 per 1,000 PYs at the very beginning, but in stage III, the figure again demonstrated a gradual increase over time (Figure 4.11). As expected from the hazard difference, the least deprived group had higher overall survival than the most deprived group in all stages (Figure 4.12). The gap in overall survival was largest in stage III, reaching approximately 5% at the 3-year point (Figure 4.13). The excess hazard difference showed similar patterns to the hazard difference but marked below 0 in stage IV (Figure 4.14). As the excess mortality rate of the most deprived was lower than that of the least deprived group in stage IV, the net survival of the most deprived group was slightly better than the least deprived group in this stage (Figure 4.15). The difference in net survival was largest in stage III, reaching around 4% at the 3-year point (Figure 4.16).

For rectal cancer, the hazard difference marked positive values in all stages as for colon cancer but was largest in stage IV (Figure 4.17). The difference in overall survival in stage IV extended to 4% at the 3-year point, followed by 3% in stage II (Figure 4.18 and Figure 4.19). The patterns of the excess hazard difference were comparable to that of the hazard difference. In stages I and III, the gap was almost null, whereas more than 5/1,000 PYs of the difference was observed in stages II and IV (Figure 4.20). The most deprived group had worse net survival than the least deprived group in all stages (Figure 4.21); however, the gap expanded no more than 3% for all stages. Only in stage II, the 95% CI of the gap remained below 0 throughout (Figure 4.22).

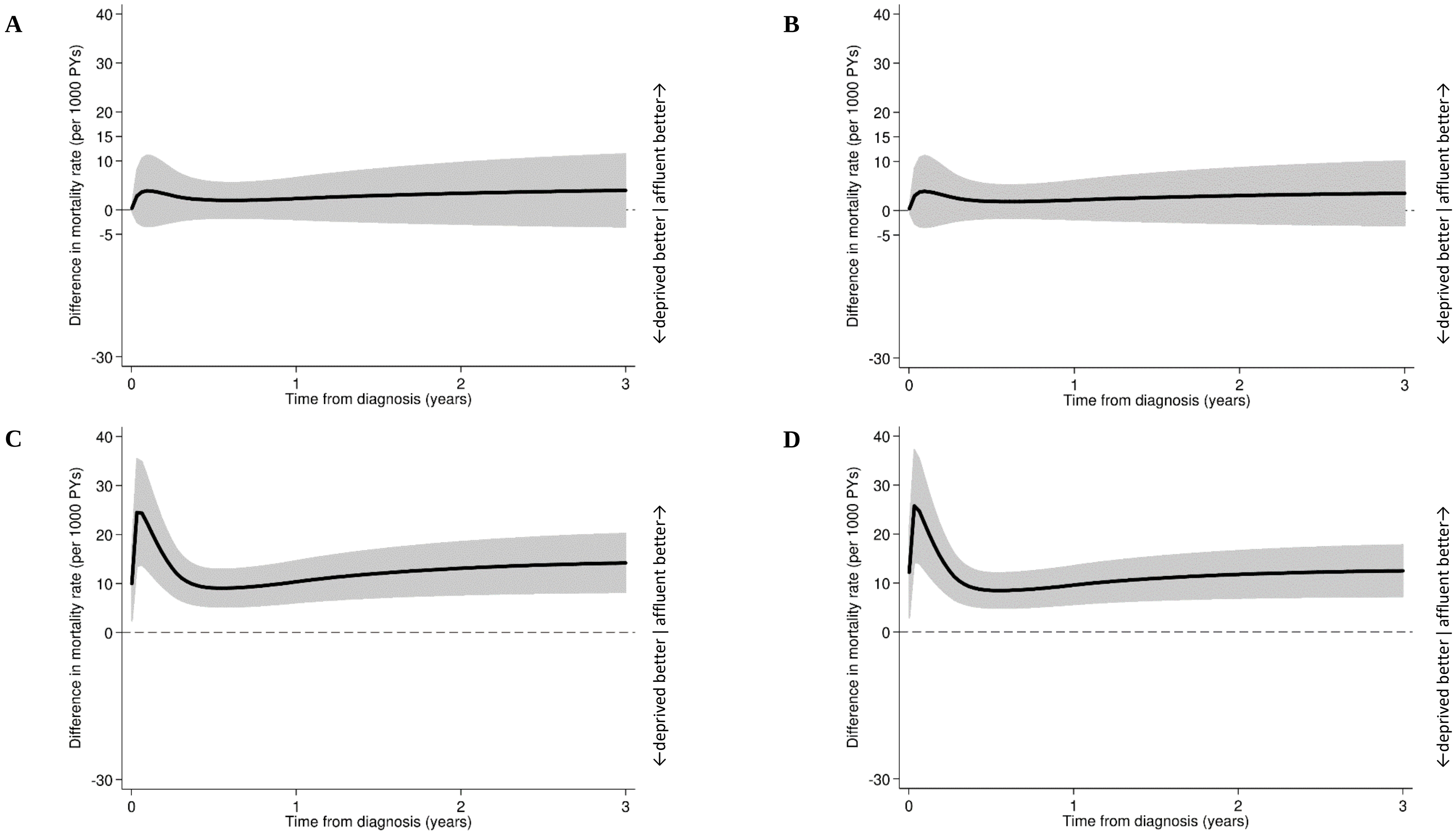

Figure 4.11 Hazard difference between the least and the most deprived groups for colon cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

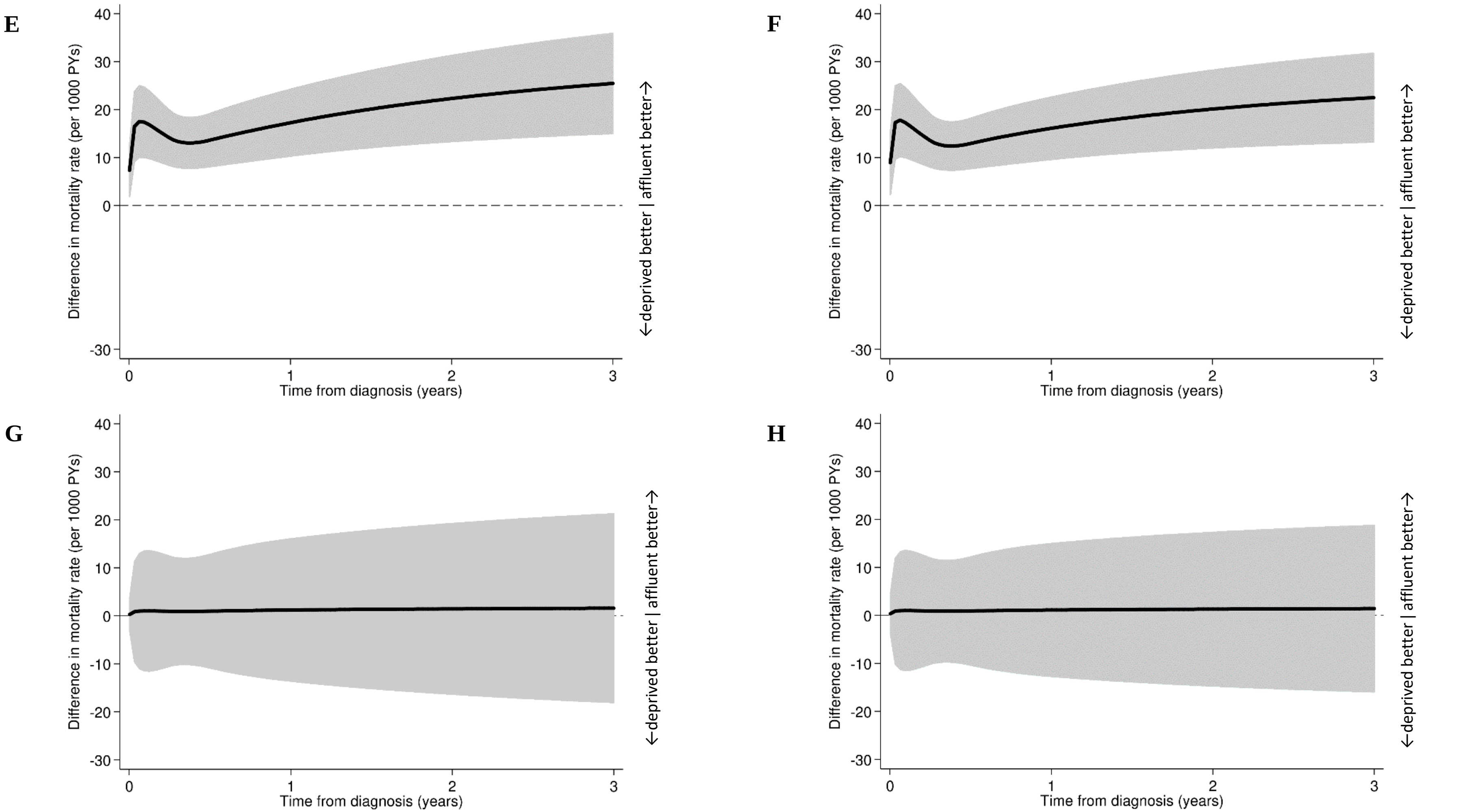

Figure 4.11 continued (hazard difference between the least and the most deprived groups for colon cancer, England)
(E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

Abbreviations: 1000 PYs, 1000 person-years.

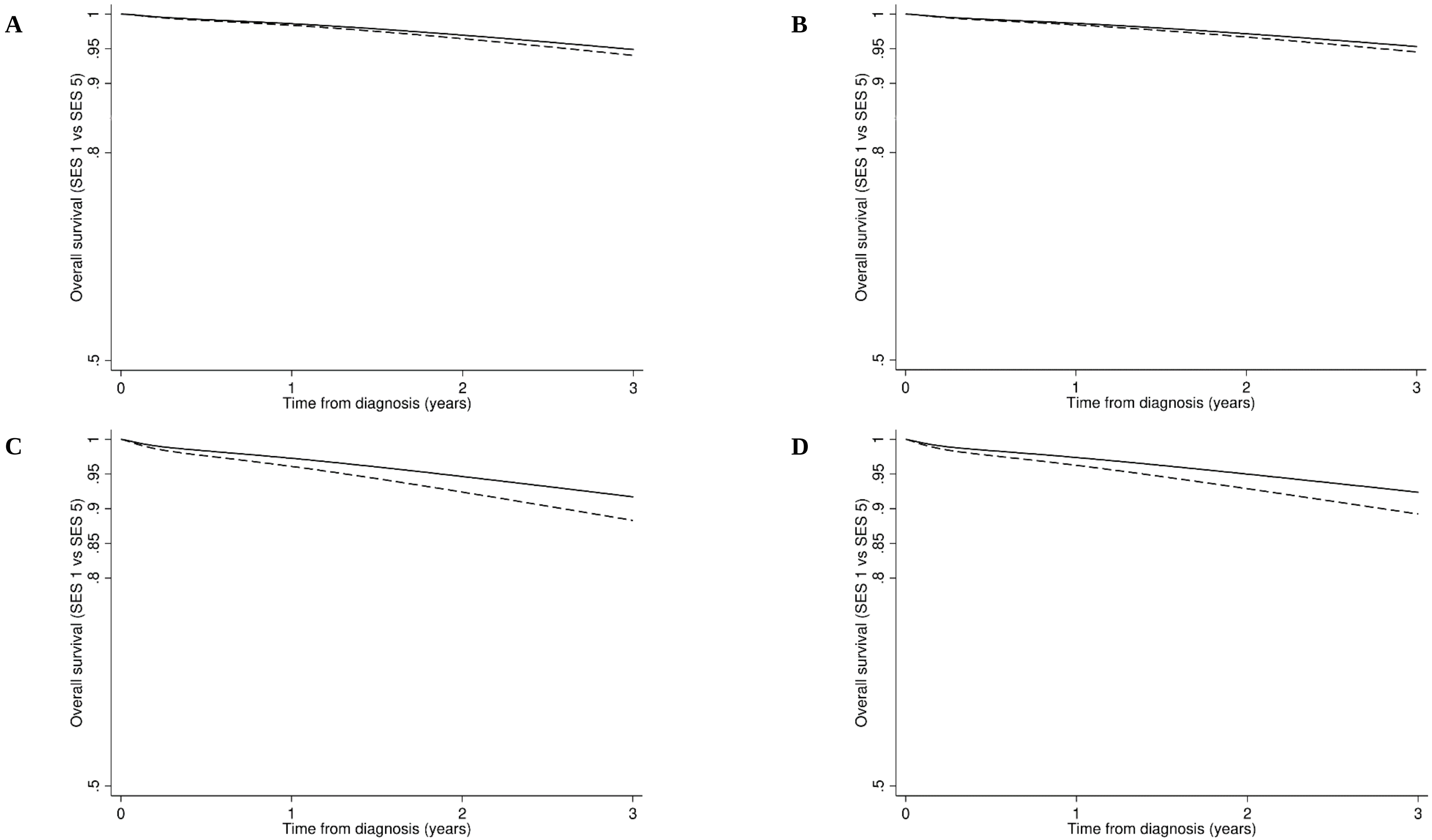

Figure 4.12 Overall survival of the least deprived group (SES 1, solid line) and the most deprived group (SES 5, dotted line) for colon cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

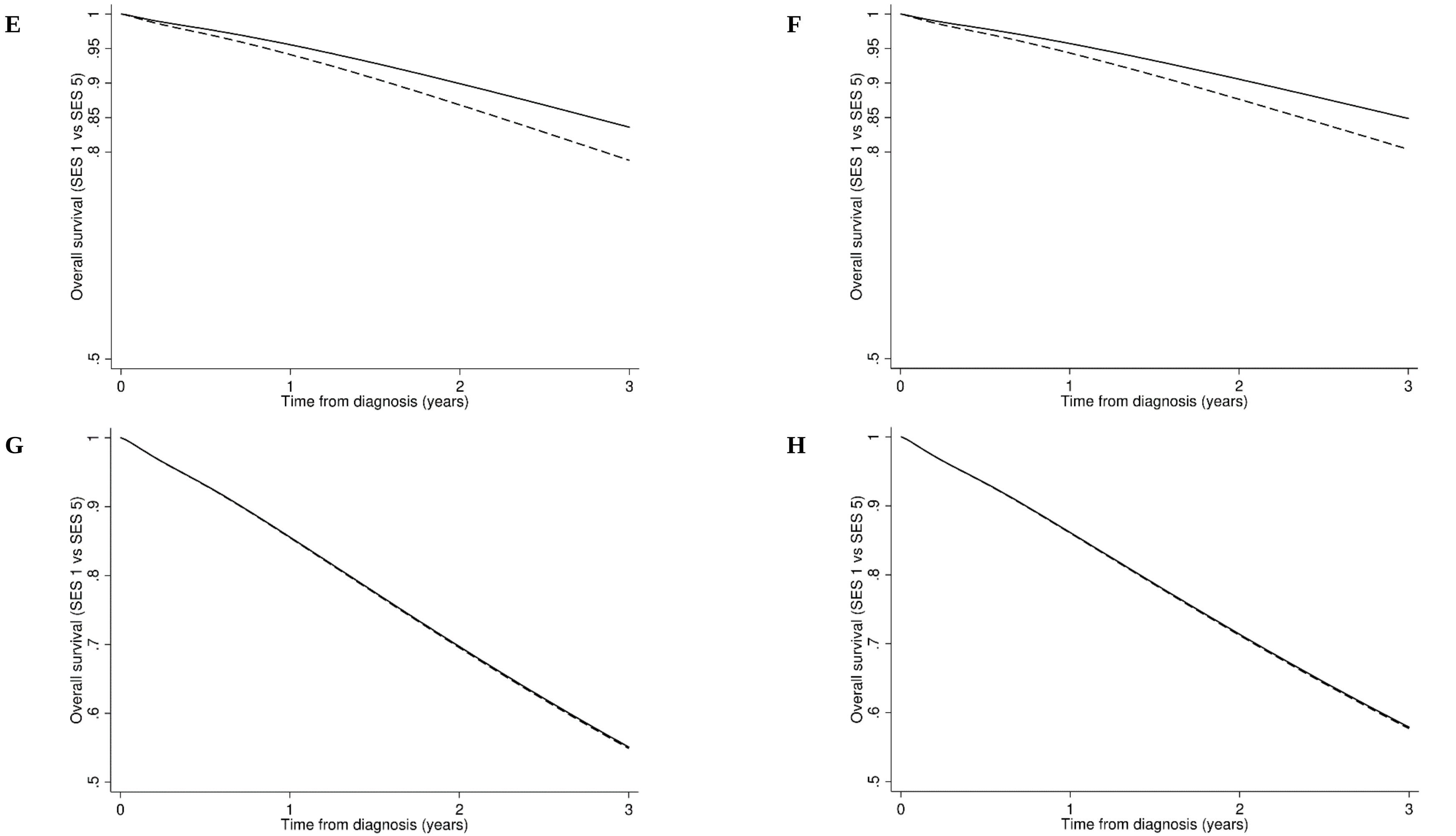

Figure 4.12 continued (overall survival of the least deprived (SES 1, solid line) and the most deprived (SES 5, dotted line) for colon cancer, England) (E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

Abbreviations: SES, socioeconomic status.

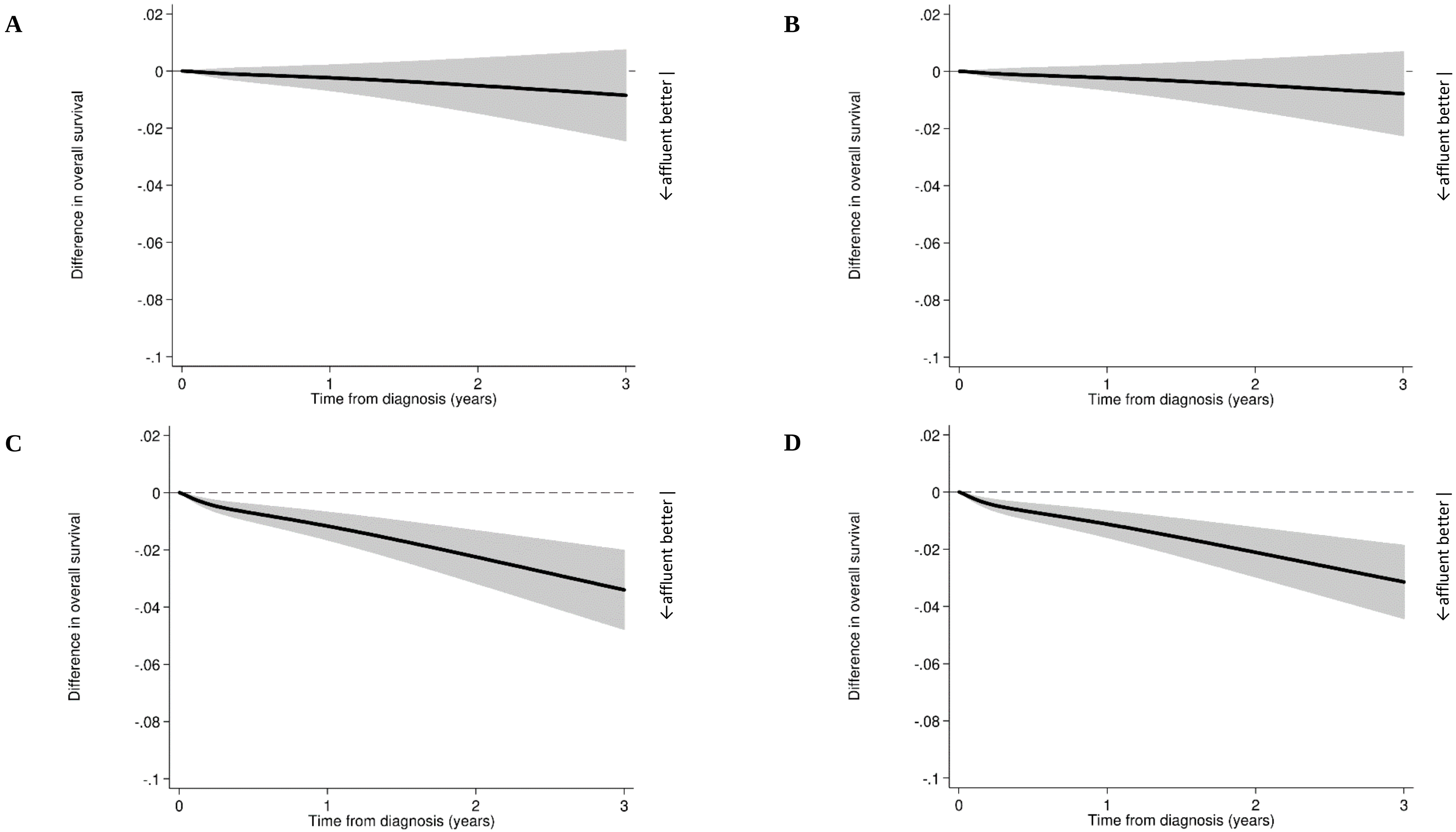

Figure 4.13 Difference in overall survival between the least and the most deprived groups for colon cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

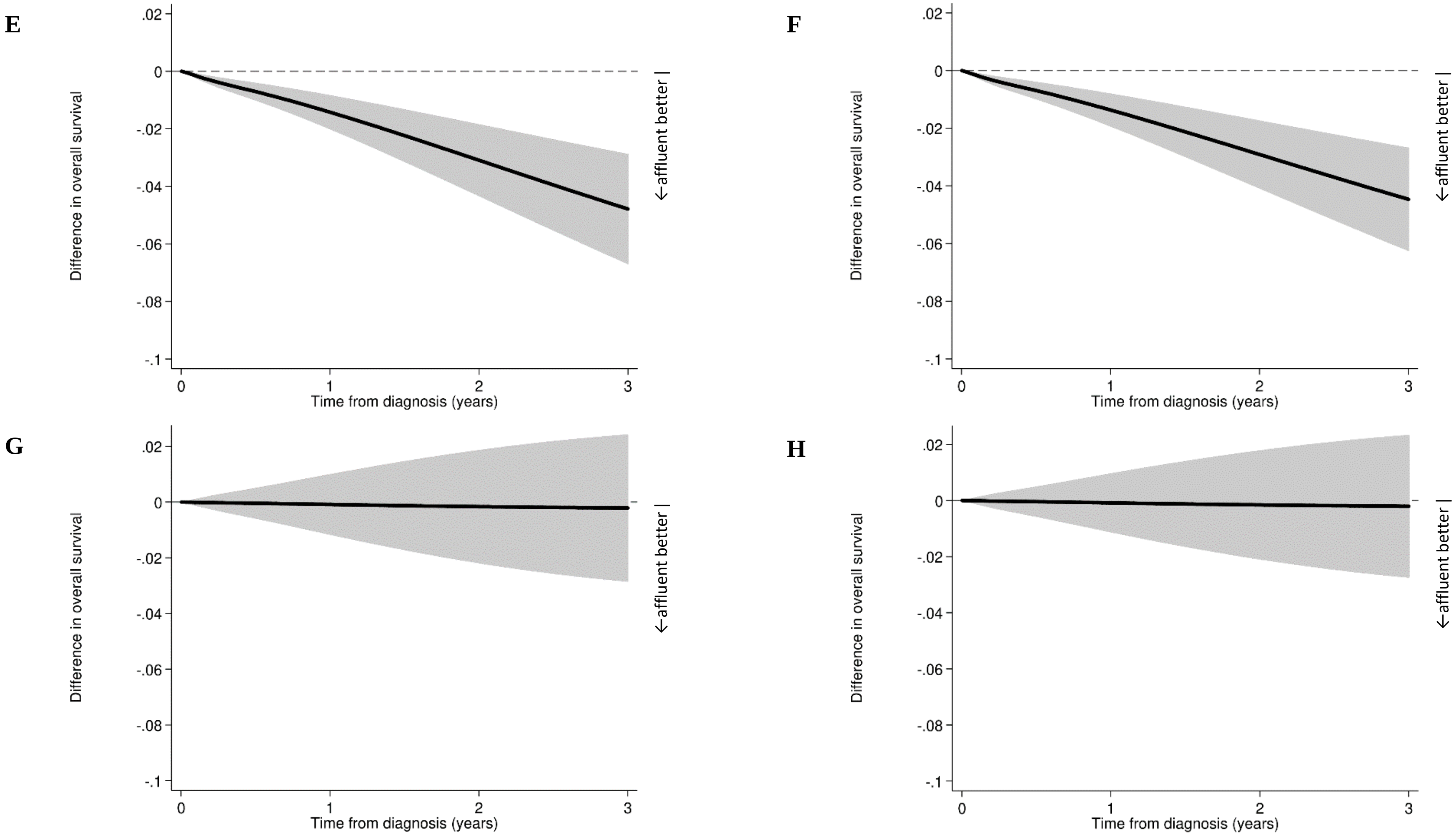

Figure 4.13 continued (difference in overall survival between the least and the most deprived groups for colon cancer, England)
(E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

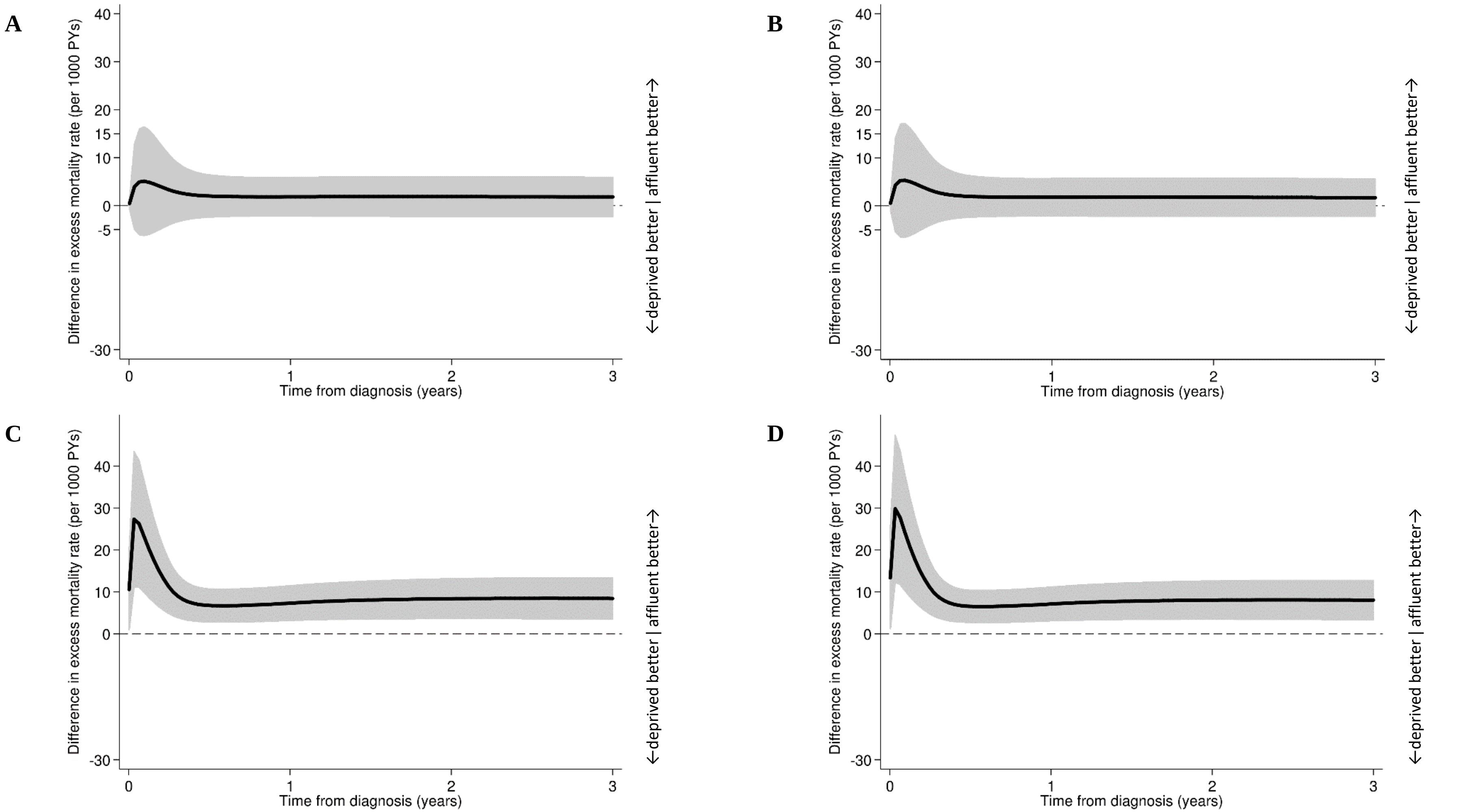

Figure 4.14 Excess hazard difference between the least and the most deprived groups for colon cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

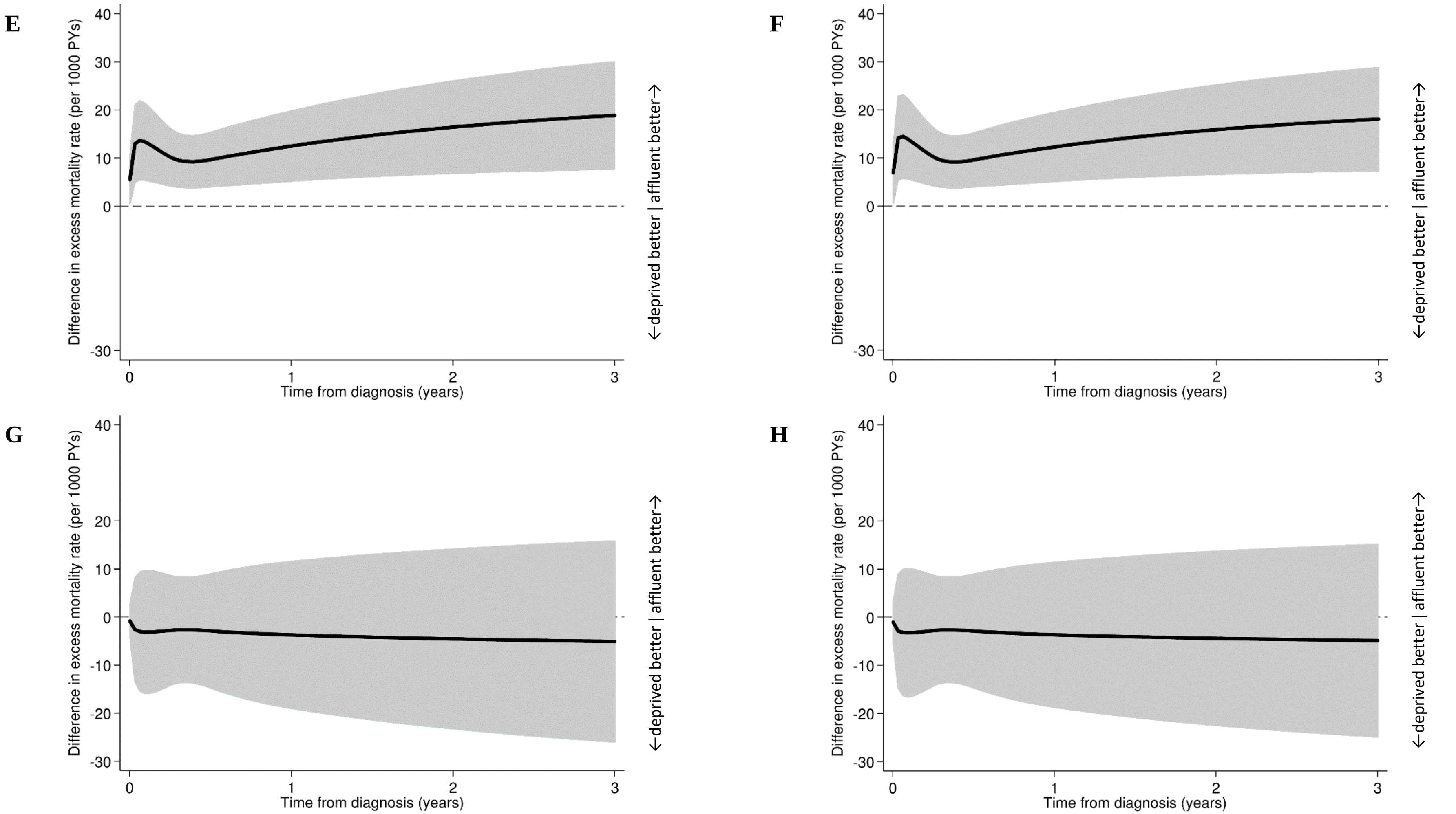

Figure 4.14 continued (excess hazard difference between the least and the most deprived groups for colon cancer, England)
(E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

Abbreviations: 1000 PYs, 1000 person-years.

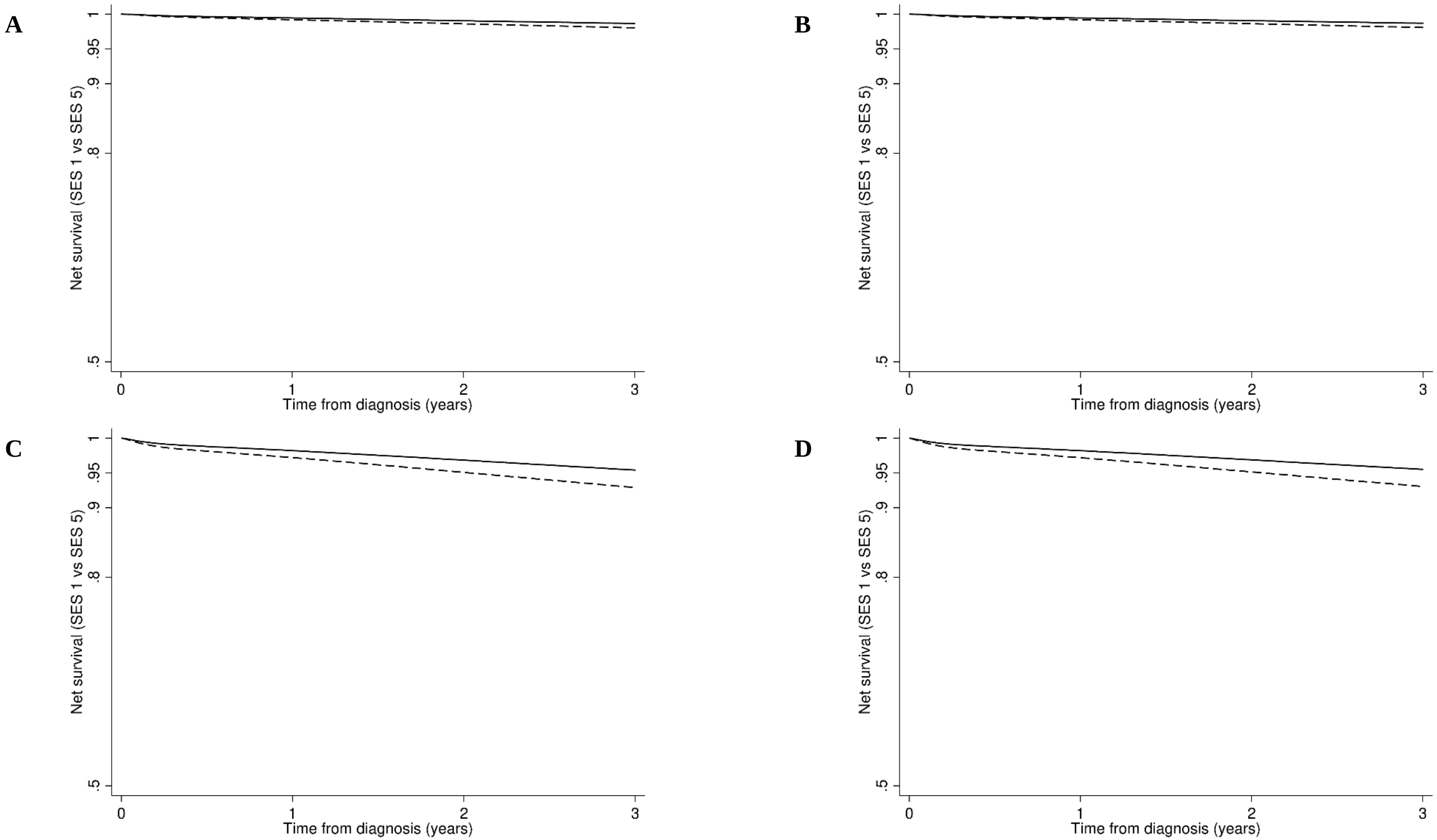

Figure 4.15 Net survival of the least deprived group (SES 1, solid line) and the most deprived group (SES 5, dotted line) for colon cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

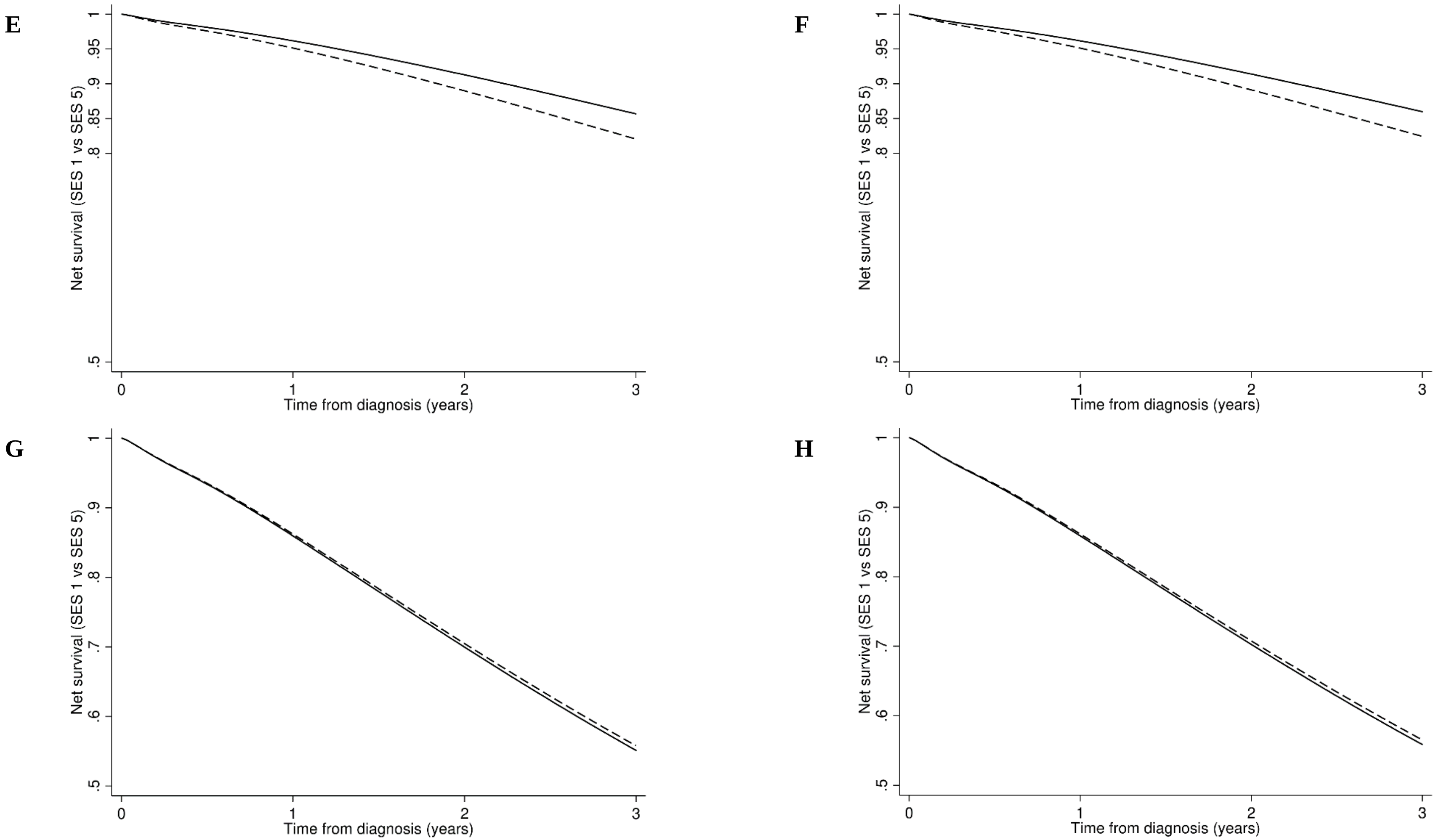

Figure 4.15 continued (net survival of the least deprived group [SES 1, solid line] and the most deprived group [SES 5, dotted line] for colon cancer, England) (E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

Abbreviations: SES, socioeconomic status.

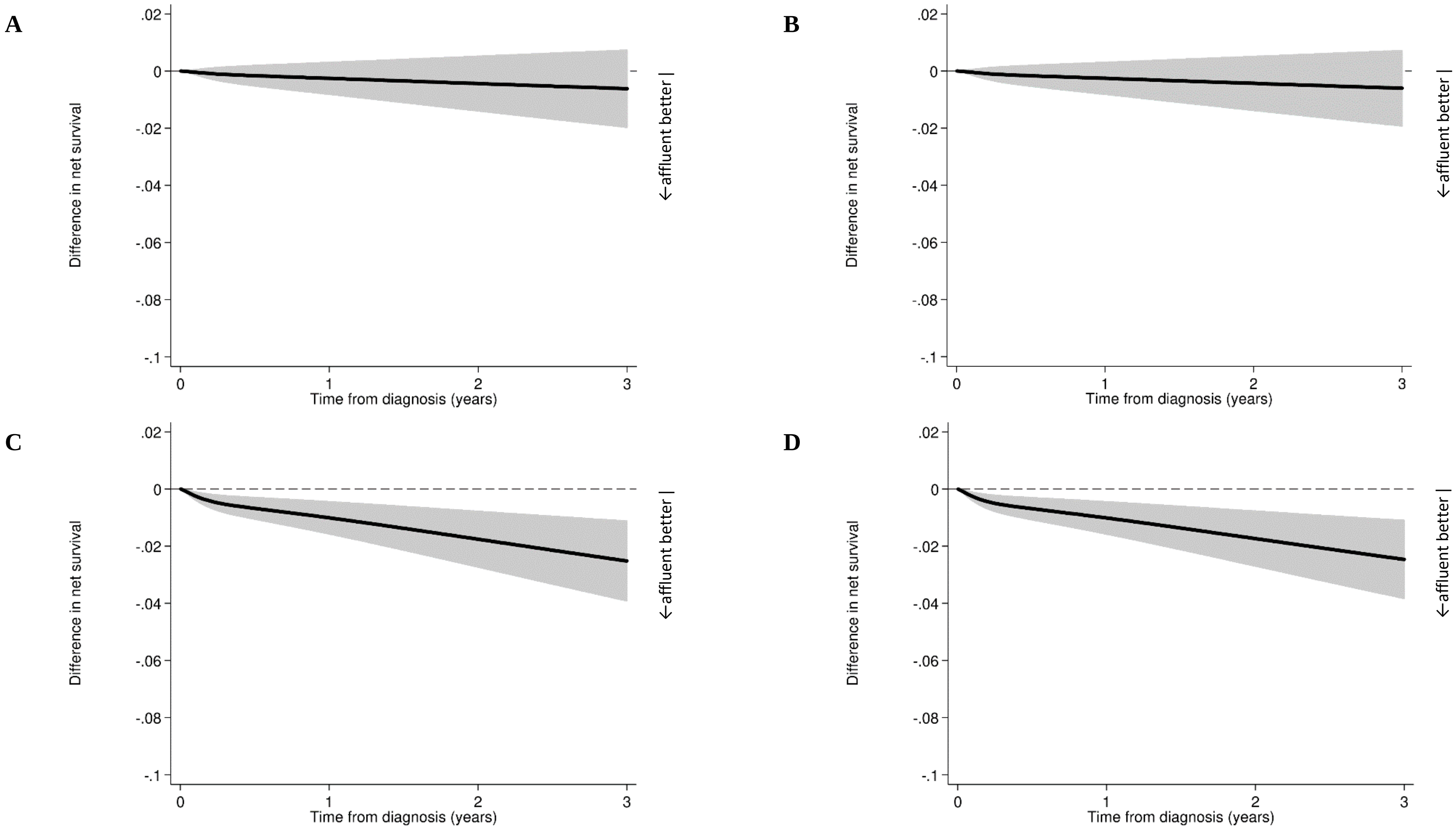

Figure 4.16 Difference in net survival between the least and the most deprived groups for colon cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

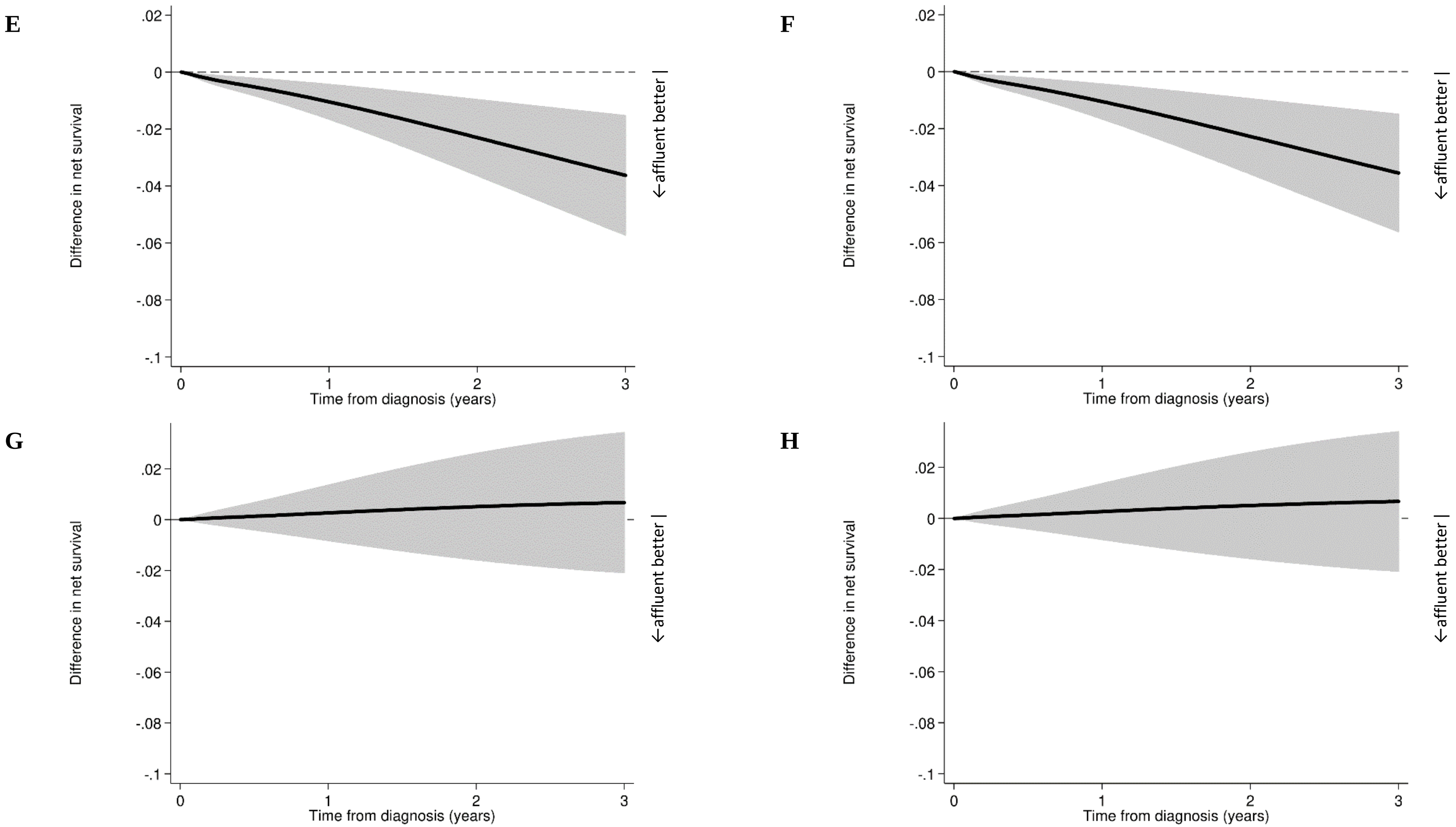

Figure 4.16 continued (difference in net survival between the least and the most deprived groups for colon cancer, England)
(E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

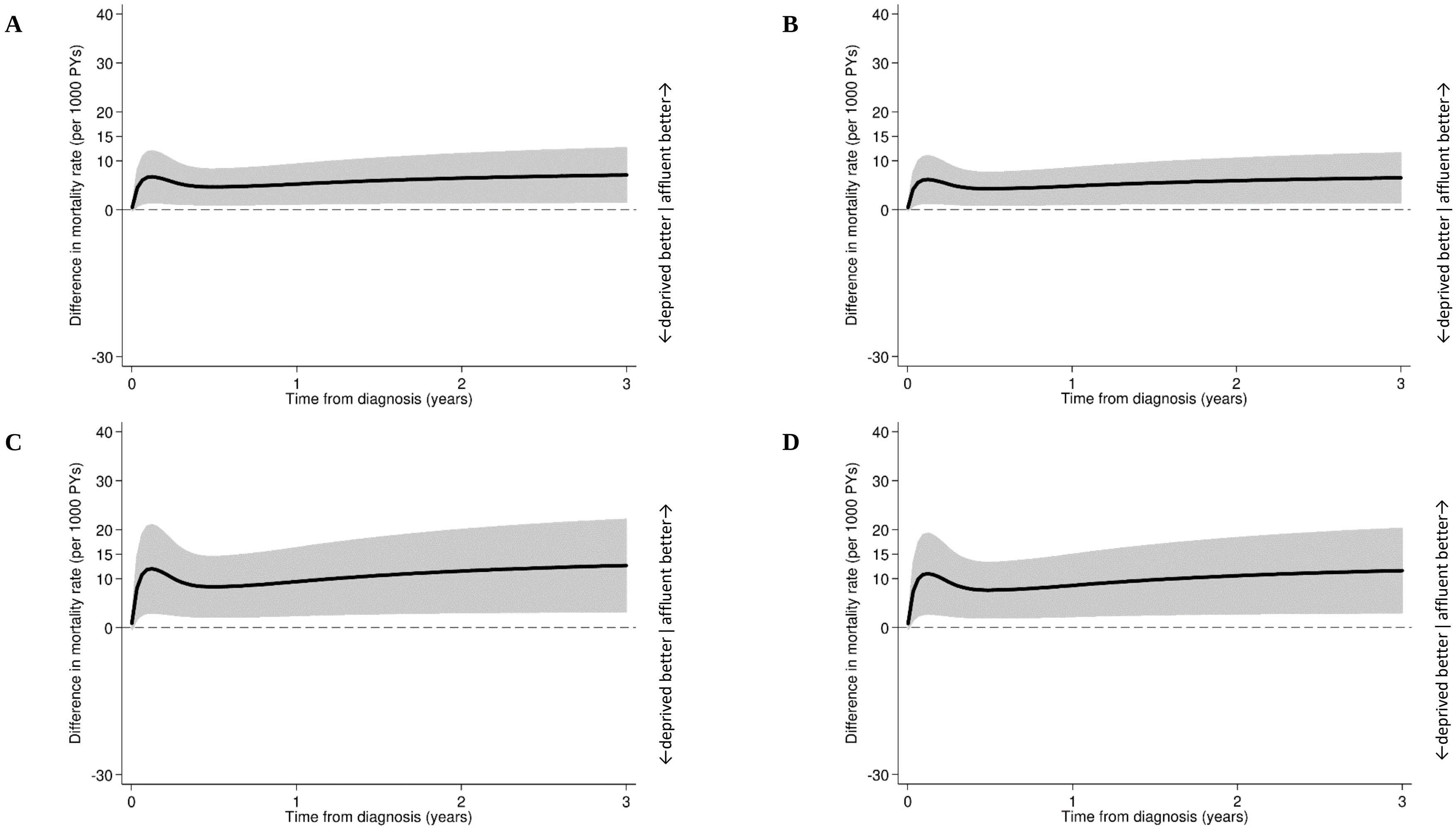

Figure 4.17 Hazard difference between the least and the most deprived groups for rectal cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

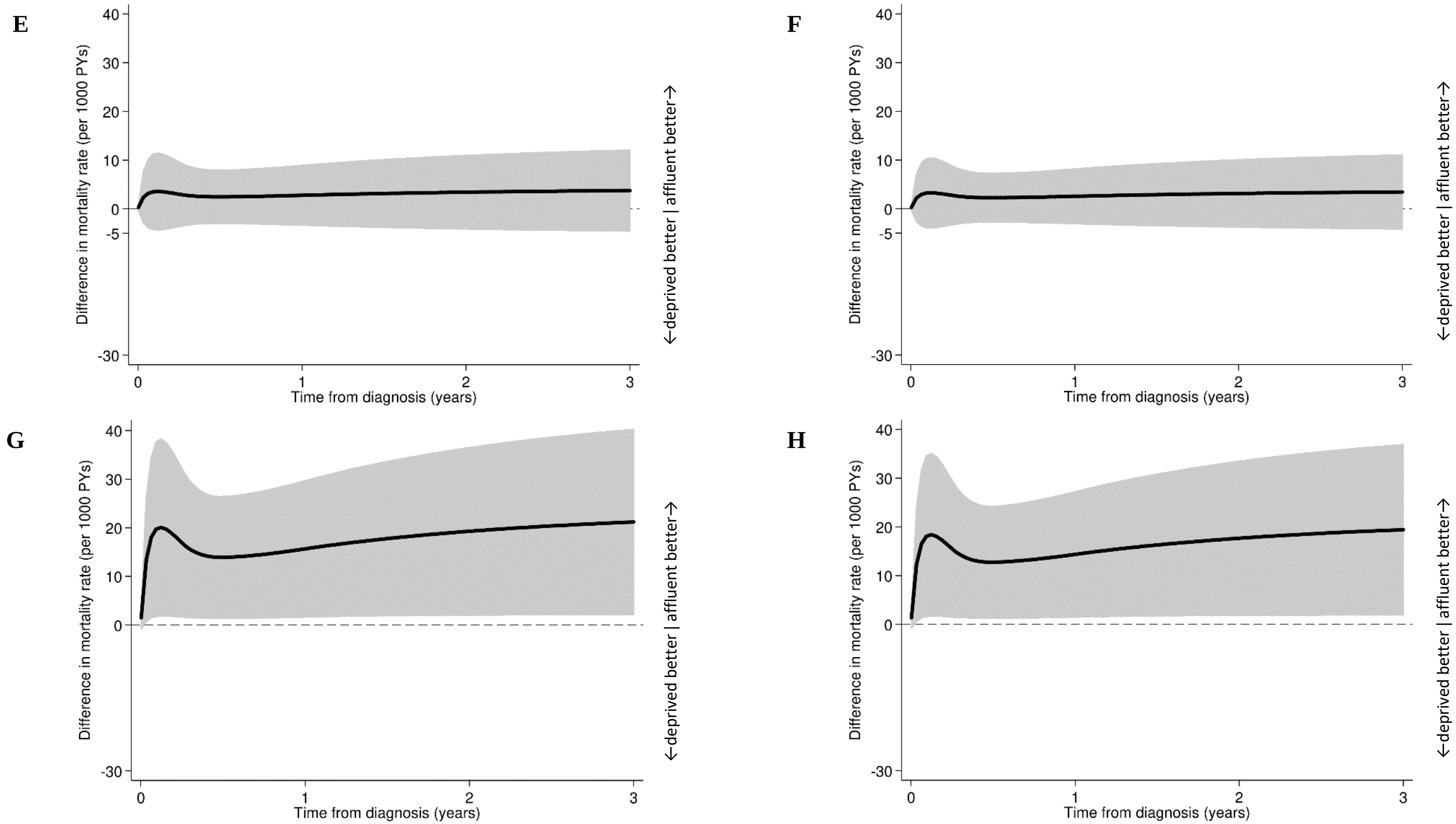

Figure 4.17 continued (hazard difference between the least and the most deprived groups) for rectal cancer, England (E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

Abbreviations: 1000 PYs, 1000 person-years.

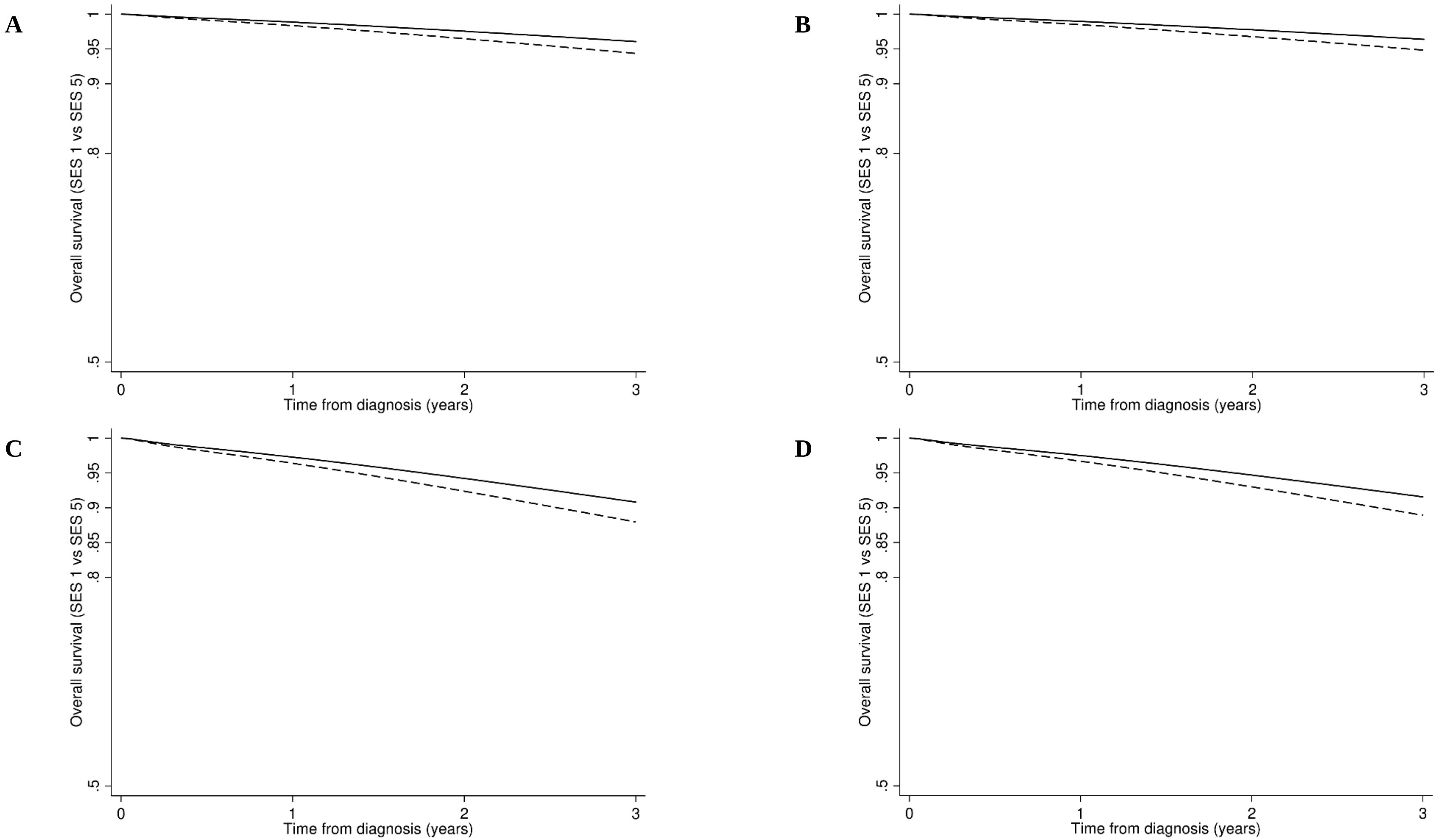

Figure 4.18 Overall survival of the least deprived group (SES 1, solid line) and the most deprived group (SES 5, dotted line) for rectal cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

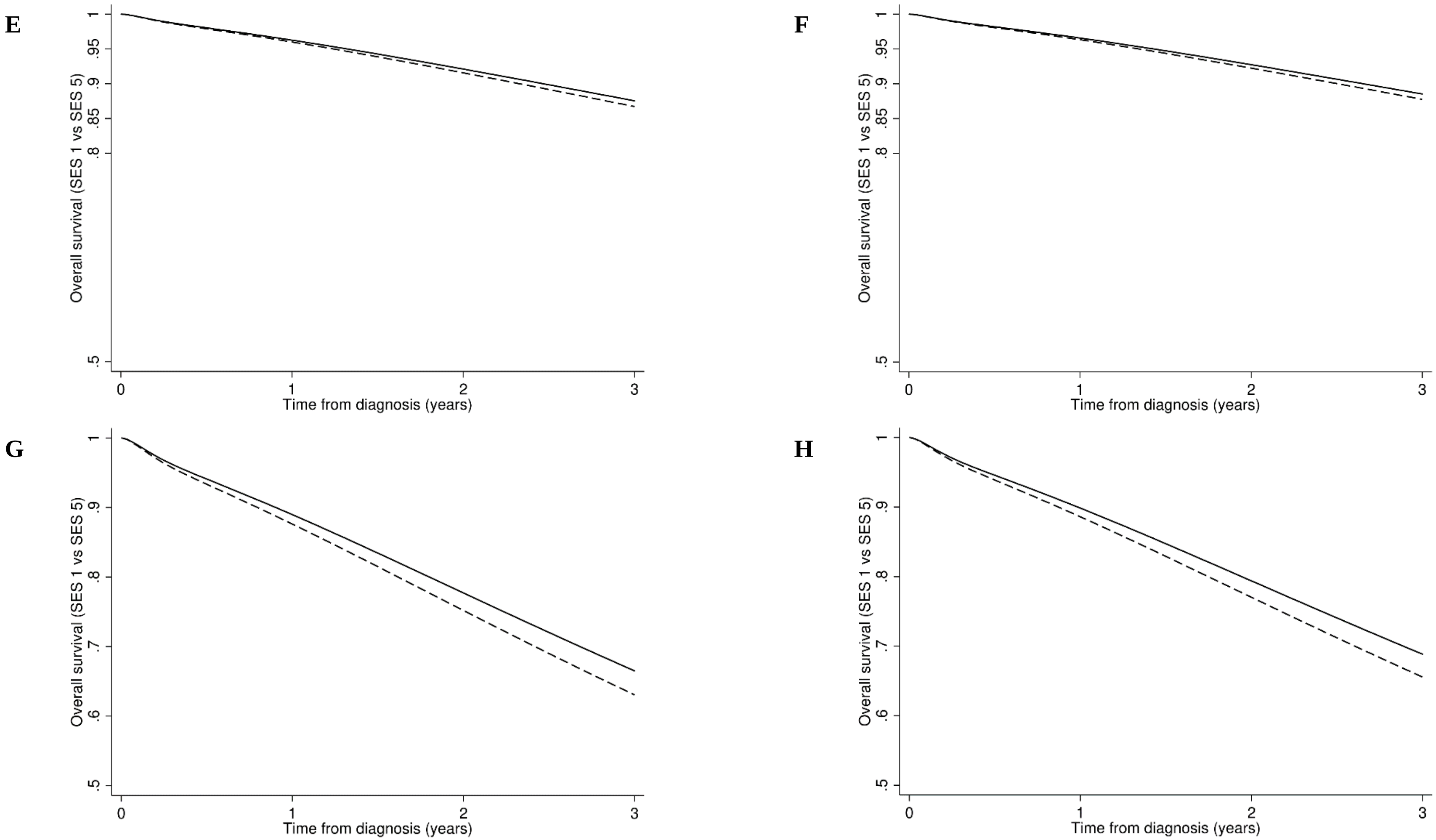

Figure 4.18 continued (overall survival of the least deprived group [SES 1, solid line] and the most deprived group [SES 5, dotted line] for rectal cancer, England) (E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

Abbreviations: SES, socioeconomic status.

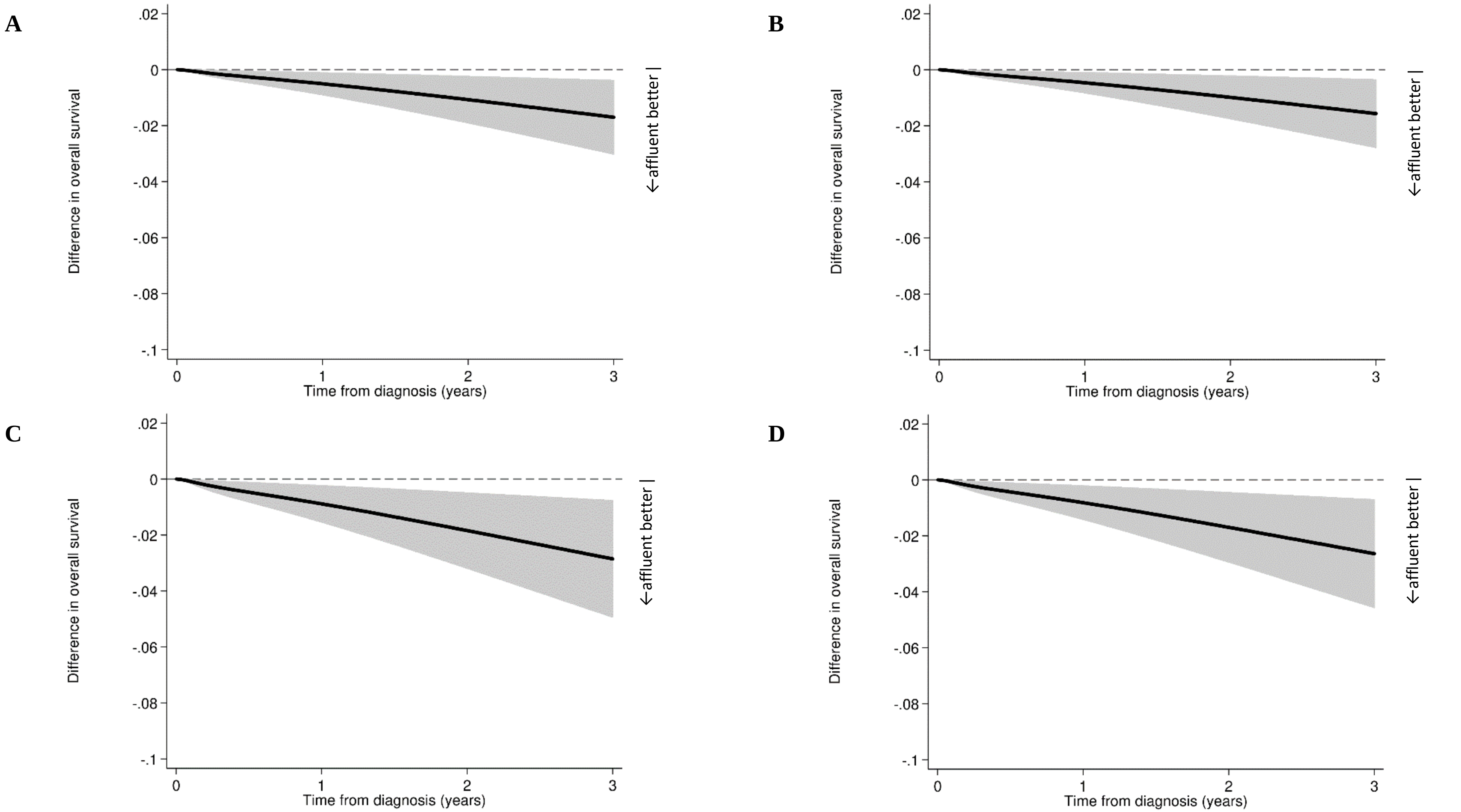

Figure 4.19 Difference in overall survival between the least and the most deprived groups for rectal cancer, England
(A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

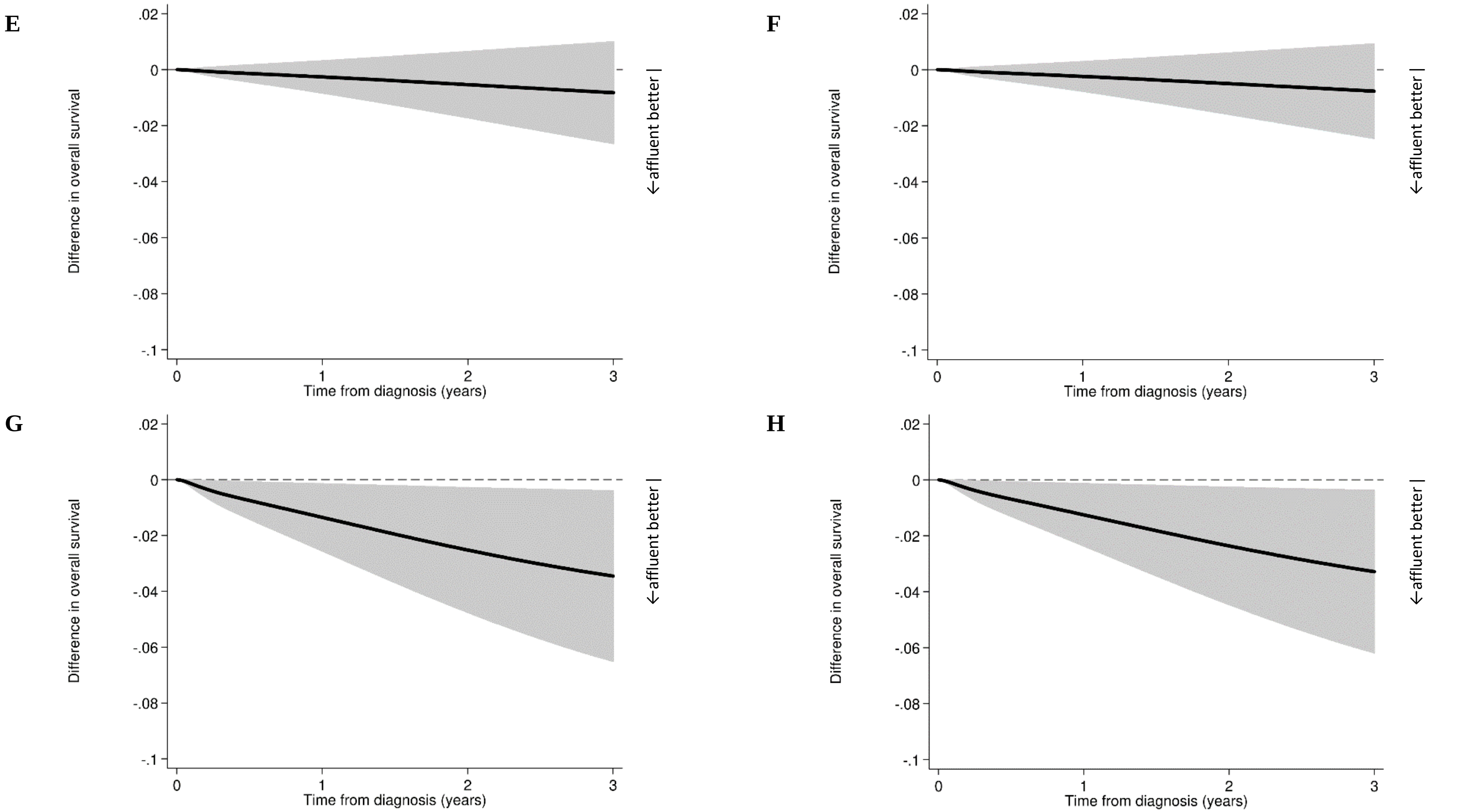

Figure 4.19 continued (difference in overall survival between the least and the most deprived groups for rectal cancer, England)
(E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

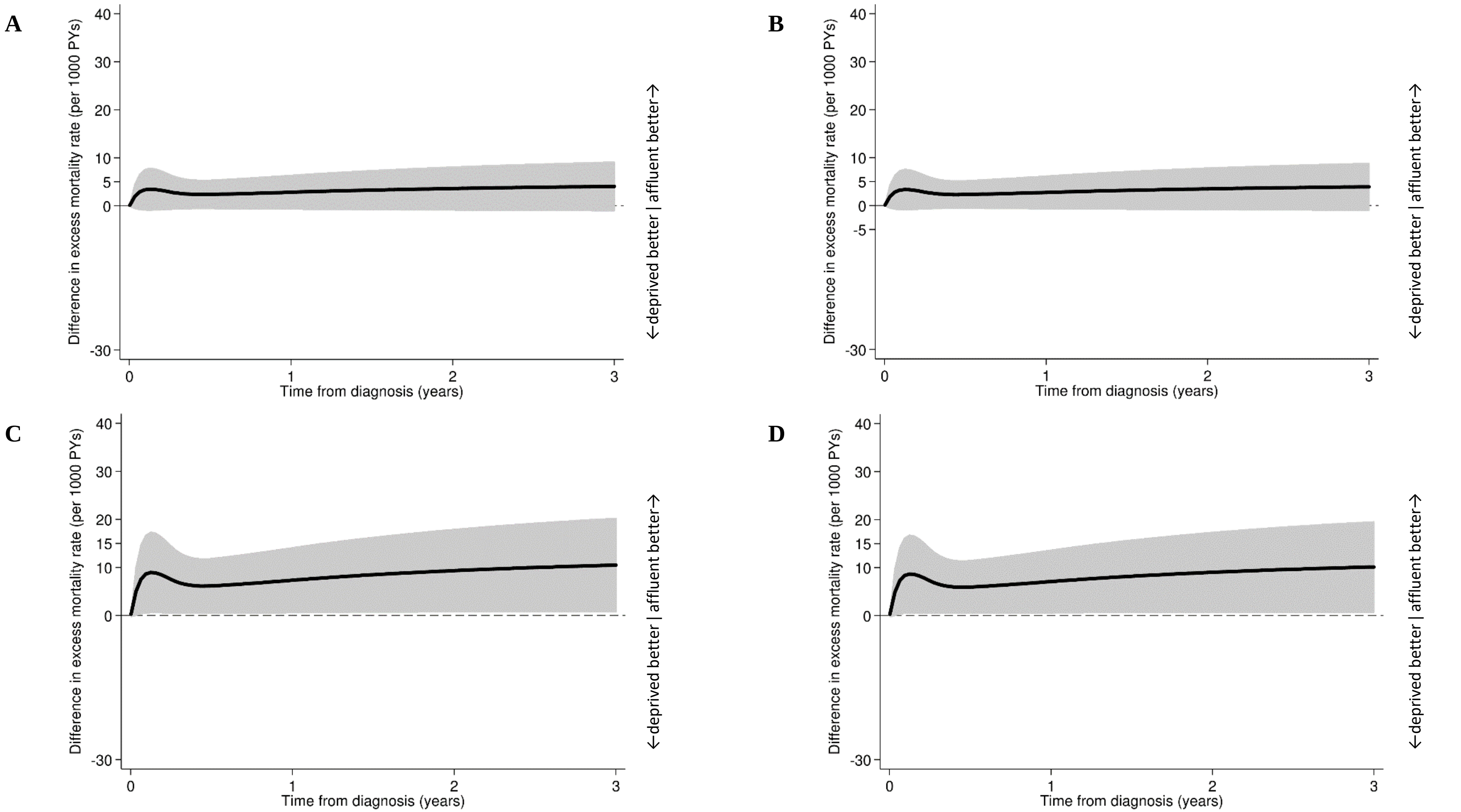

Figure 4.20 Excess hazard difference between the least and the most deprived groups for rectal cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

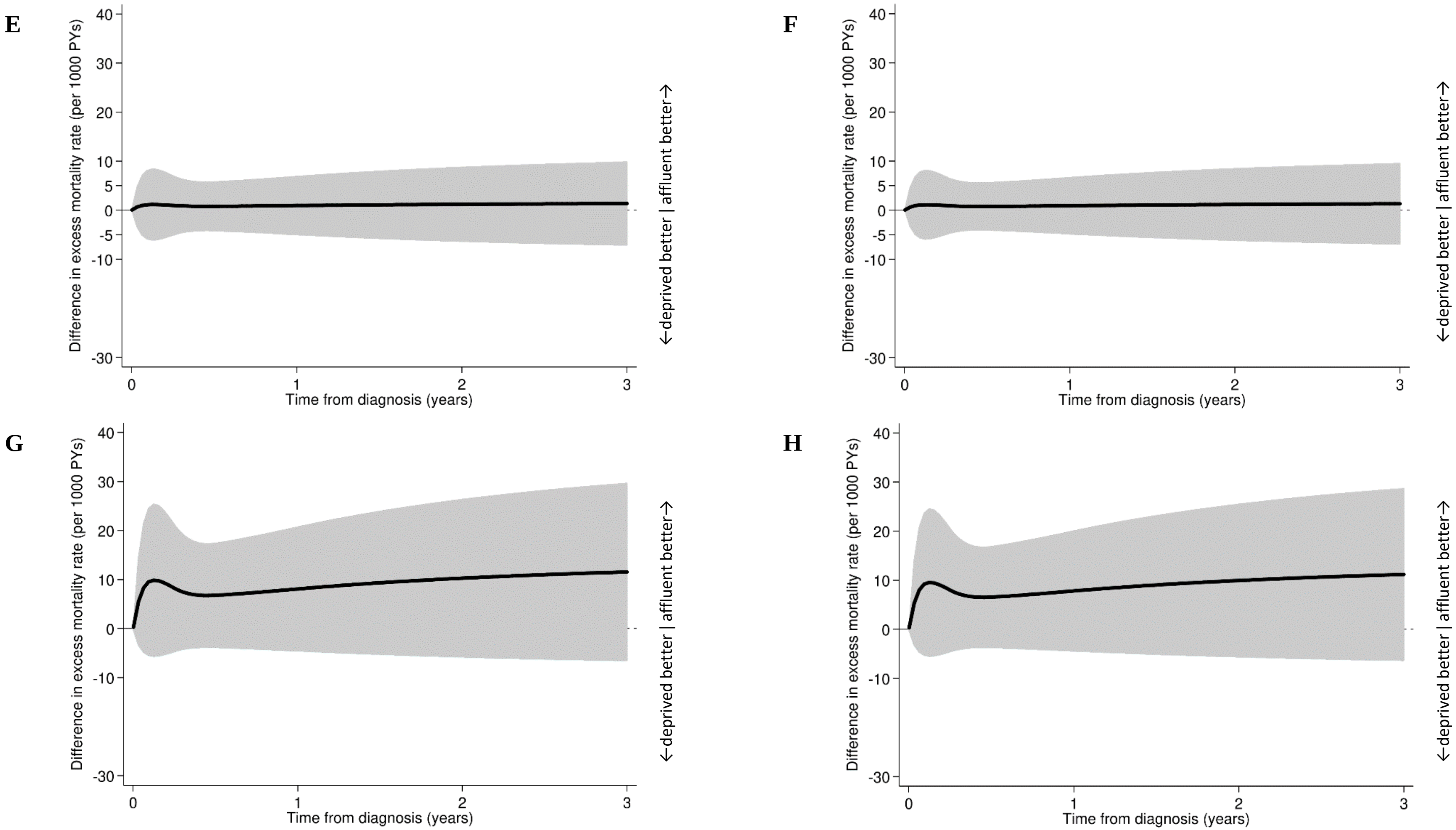

Figure 4.20 continued (excess hazard difference between the least and the most deprived groups) for rectal cancer, England
(E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

Abbreviations: 1000 PYs, 1000 person-years.

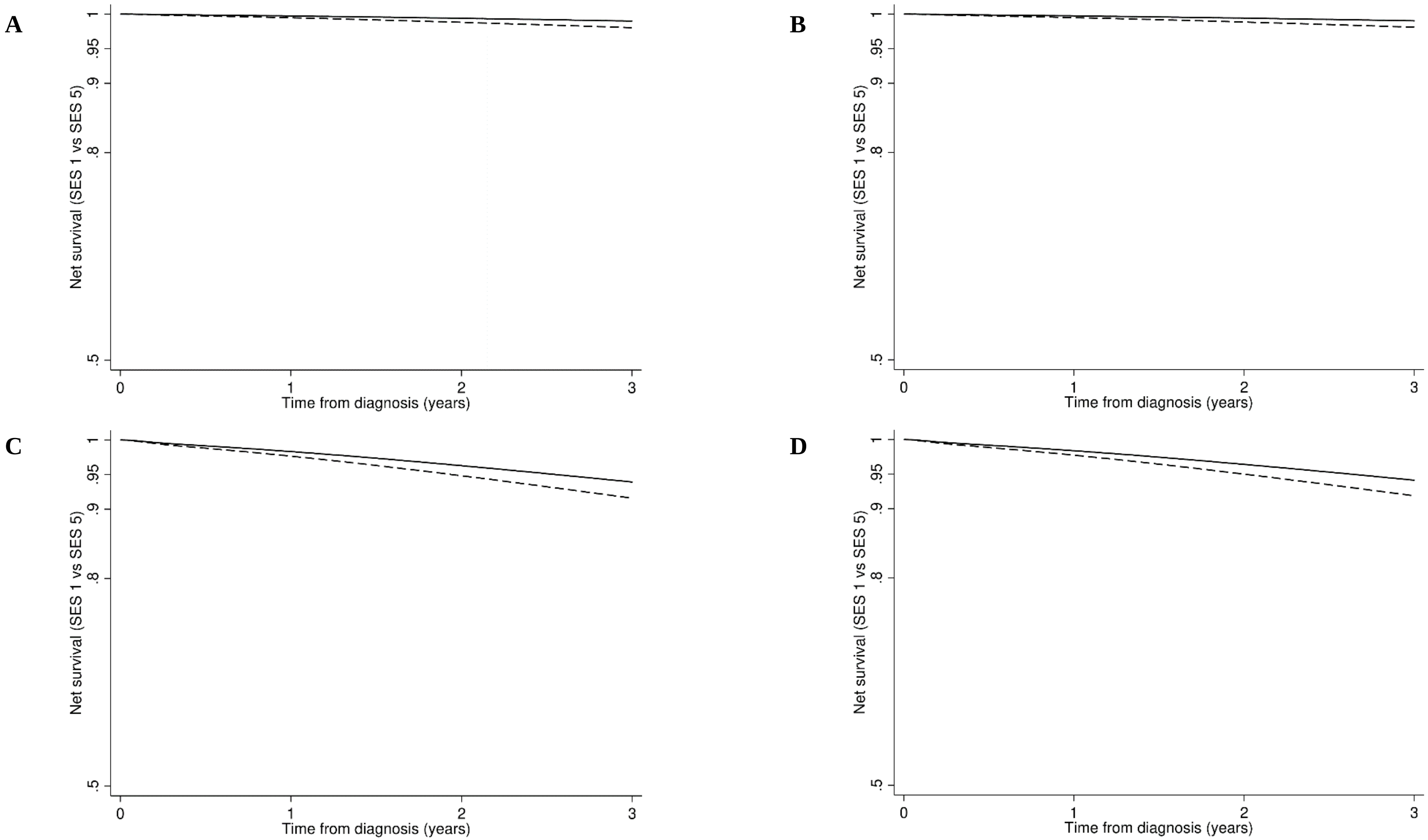

Figure 4.21 Net survival of the least deprived group (SES 1, solid line) and the most deprived group (SES 5, dotted line) for rectal cancer, England (A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

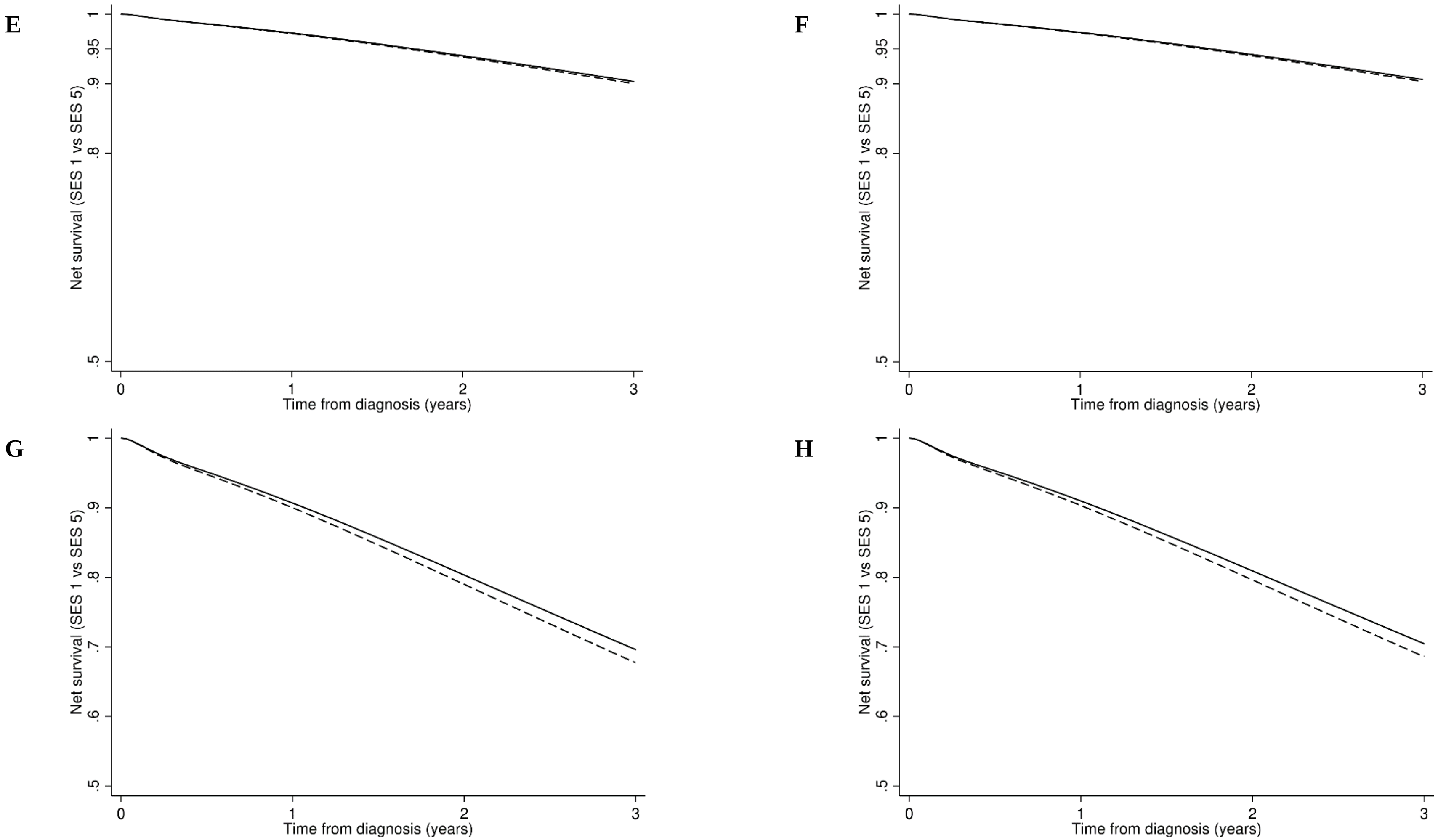

Figure 4.21 continued (net survival of the least deprived group [SES 1, solid line] and the most deprived group [SES 5, dotted line] for rectal cancer, England) (E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

Abbreviations: SES, socioeconomic status.

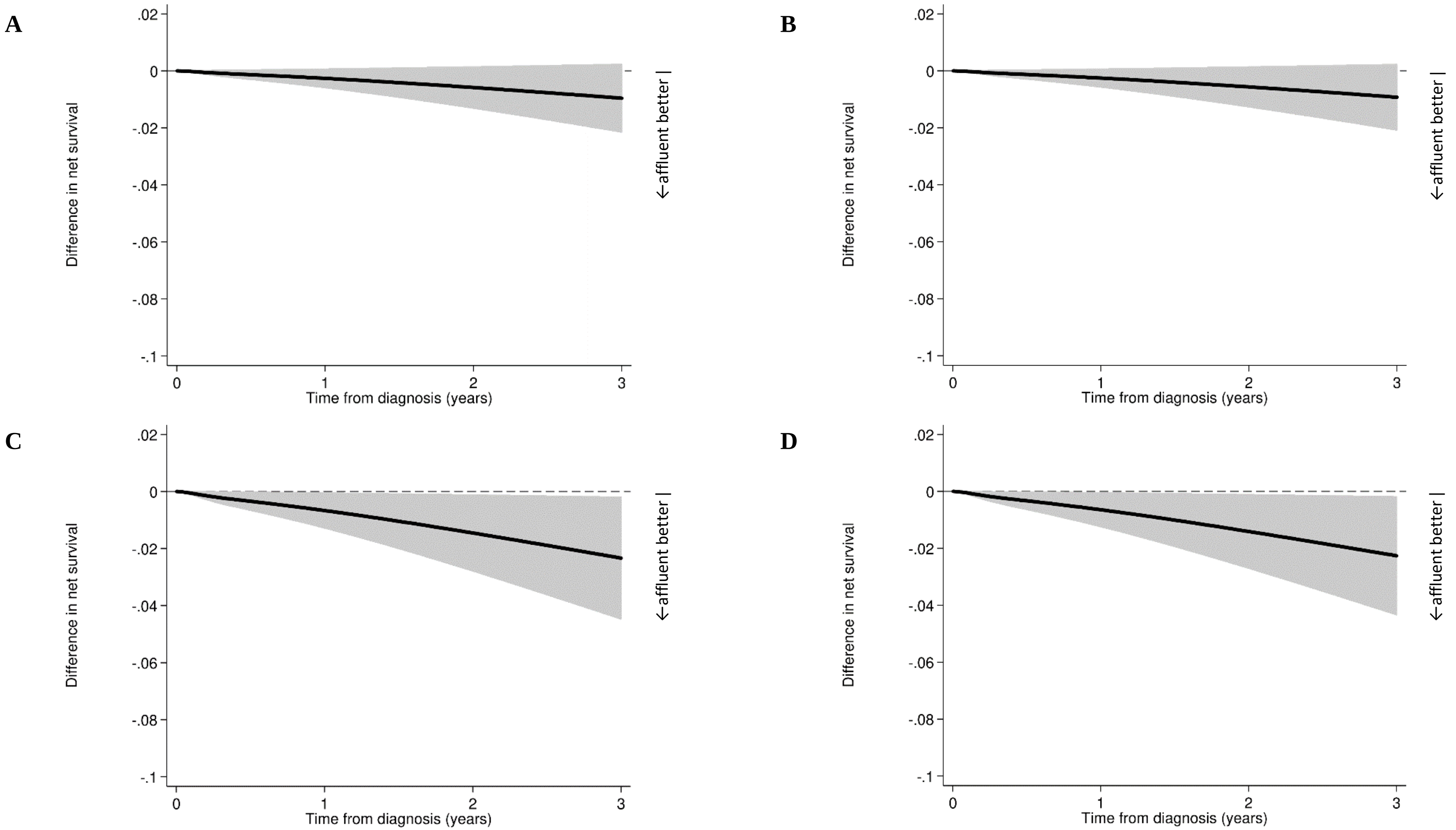

Figure 4.22 Difference in net survival between the least and the most deprived groups for rectal cancer, England
(A) Stage I, male (B) stage I, female (C) stage II, male (D) stage II, female

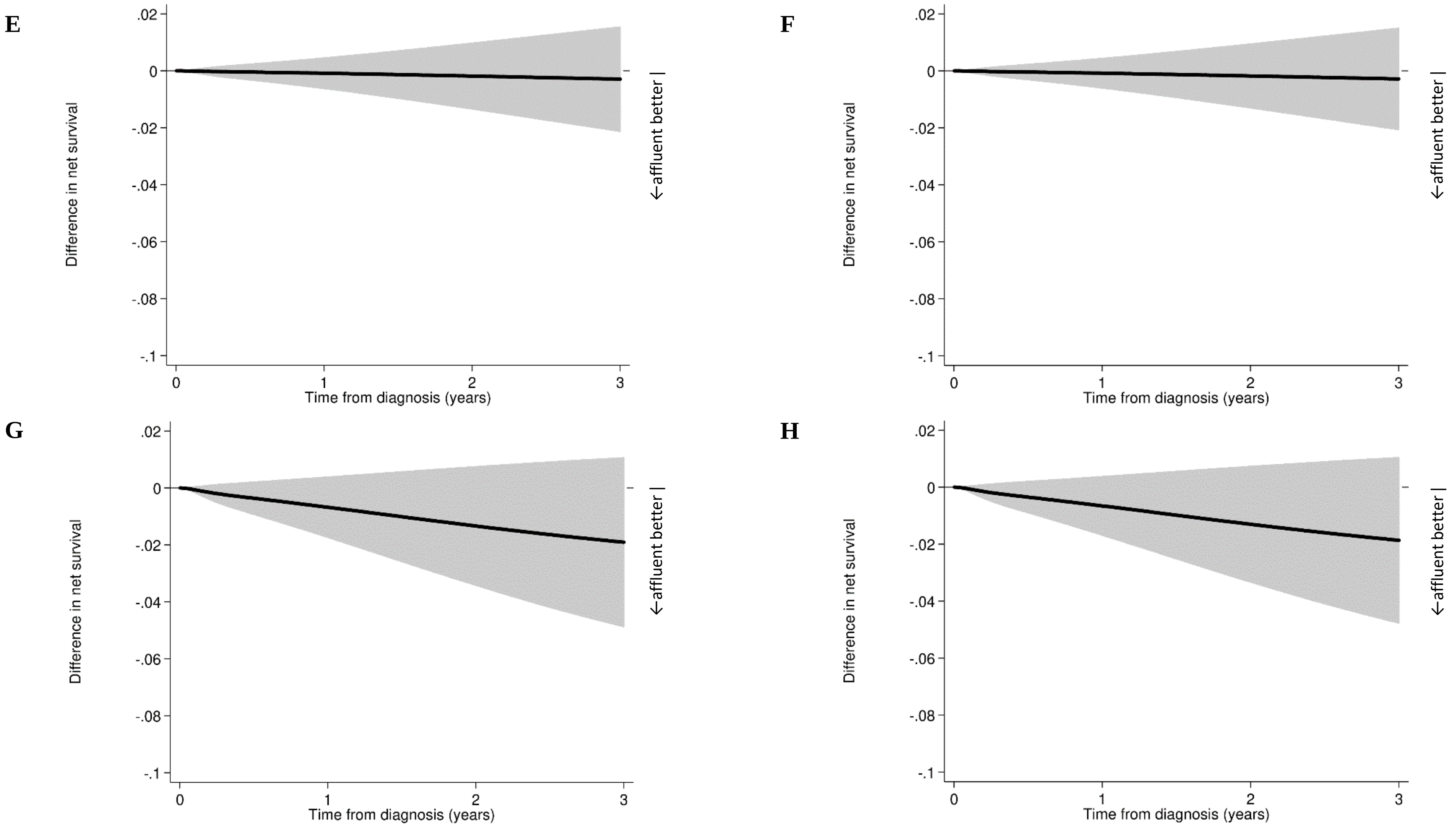

Figure 4.22 continued (difference in net survival between the least and the most deprived groups for rectal cancer, England)
(E) Stage III, male (F) stage III, female (G) stage IV, male (H) stage IV, female

4.4.3 Summary of findings

Increased age, worse tumour grade, emergency presentation, increased number of acute/chronic comorbidities and non-receipt of major surgery were associated with worse survival. Socioeconomic inequalities in survival were observed, but stage and emergency presentation decreased the gap to some extent. Non-receipt of surgery and increased number of acute comorbidities affected survival especially shortly after diagnosis for colon cancer. Emergency presentation had a waxing effect on survival. In Cox regression analyses, the socioeconomic trend towards higher HRs in the deprived groups was clear among colon cancer patients with stages II and III, and rectal cancer patients with stages I and II. There was also a weak trend for colon cancer with stage I and rectal cancer with stages III and IV.

In addition to the relative measures (HRs), I provided absolute measures (differences) in mortality rate and survival. The hazard difference and survival difference between the least and the most deprived groups were estimated using the FPM incorporating TVCs for overall and net survival. The survival difference between the least and the most deprived groups was noticeable among colon cancer patients with stages II and III, and rectal cancer patients with stages I, II and IV.

4.5 Mediation analysis

Chapter 4.1 demonstrated that there was a socioeconomic gradient favouring the affluent in receipt of major surgery, particularly for rectal cancer with stage II to IV, when potential confounders were adjusted. **Chapter 4.4** illustrated a survival gap between the least and the most deprived groups, particularly for colon cancer with stage II and III and rectal cancer with stage I, II and IV, under the overall survival setting.

In this sub-chapter, I combined these two analyses and proceeded with a mediation analysis to understand the potential magnitude of the effect of inequalities in cancer care on socioeconomic inequalities in survival at several time points.

4.5.1 Methods

Outcome measure

The outcome measure was conditional mortalities set at three time points: 90 days, six months and one year since diagnosis. The main interest was to see the magnitude of the effect of socioeconomic inequalities in stage distribution, emergency presentation and surgical treatment on the conditional mortalities. Those three variables were treated as mediators having NIE, and the magnitude of the effects of the mediators was derived as 'proportion mediated' (NIE out of TCE) in mediation analysis. Details of the definitions are described in **Chapter 3**.

Analysis strategy

All results were derived in ratios in log-odds of death by five SES groups using g-computation, which employs Monte Carlo simulations. The TCE is the sum of effects that SES has on the log-odds of death after all variables are fitted in the designed model. The NIE of SES is the effect of SES on the log-odds of death, mediated by stage plus chronic and acute comorbidities in Figure 4.23 for example. 'Proportion mediated' measures how much effect of the TCE is mediated through the effect of NIEs.

Figure 4.23, Figure 4.24 and Figure 4.25 are the DAGs of the three conducted analyses. The first mediation analysis focuses on the effect of the socioeconomic inequalities in stage distribution on the inequalities in conditional mortality at 90 days, six months and one year. The second mediation analysis focuses on the effect of the socioeconomic inequalities in emergency presentation on the inequalities in conditional mortalities at the three time points. The third mediation analysis focuses on the effect of socioeconomic inequalities in treatment (binary outcome yes/no of the receipt of major surgery for the primary lesion) on the inequalities in conditional mortalities at the three time points.

In the first analysis, stage was defined as a mediator, affecting socioeconomic inequalities in conditional mortalities at several time points. In addition, chronic and acute comorbidities were defined as mediators affected by SES and affecting conditional mortalities but were not directly associated with the stage (Figure 4.23). The NIE in this DAG is the effect of the three mediators measured *en bloc*. In the second analysis, a variable of the main interest, emergency presentation, was added to the first mediation model (Figure 4.24). The NIE in this DAG is the effect of the four mediators measured *en bloc*. Then, in the third analysis, a variable of the main interest, receipt of major surgery, was added to the second model (Figure 4.25). Emergency presentation, stage and comorbidities were treated as post-exposure confounders; they were affected by SES and affected both the variable 'treatment' and the outcome of conditional mortalities.

The difference in PM, between the first and second mediation models, indicates the magnitude of the effect of emergency presentation on the inequalities in survival status. The difference in PM, between the second and third mediation models, indicates the magnitude of the effect of receipt of major surgery on the inequalities in survival status.

In all analyses, sex, age and year of diagnosis were defined as baseline confounders. Age was treated as a continuous variable having a spline function after centred around the mean. As in the previous analyses, SES was categorised into five groups, stage into four, and comorbidities into four groups, with 0 indicating no comorbidities and +3 indicating three or more comorbidities.

To separate the effect of the main interest on the outcome at several duration of time, conditional mortalities were coded binary (0 alive, 1 dead) at three time points at 90 days, six months and one year. Patients who died before 90 days from diagnosis were coded 1 at 90 days mortality and were not included in the conditional mortality at the next time period (i.e. six months). Patients who survived more than 90 days were coded 0 or 1 in the conditional mortality at six months, depending on their vital status at six months from diagnosis. Similarly, patients who survived more than six months were included in the conditional mortality at one year.

Bootstrap was conducted 1,000 times using Monte Carlo simulation in each analysis with the outcome of conditional mortality at 90 days, six months and one year. Stage information was missing at approximately 30% for both colon and rectal cancer. Emergency presentation was missing at 9.8% for colon, and 6.7% for rectal cancer. Stage and emergency presentation were therefore imputed 30 times by single stochastic imputation using chained equations within the g-computation.

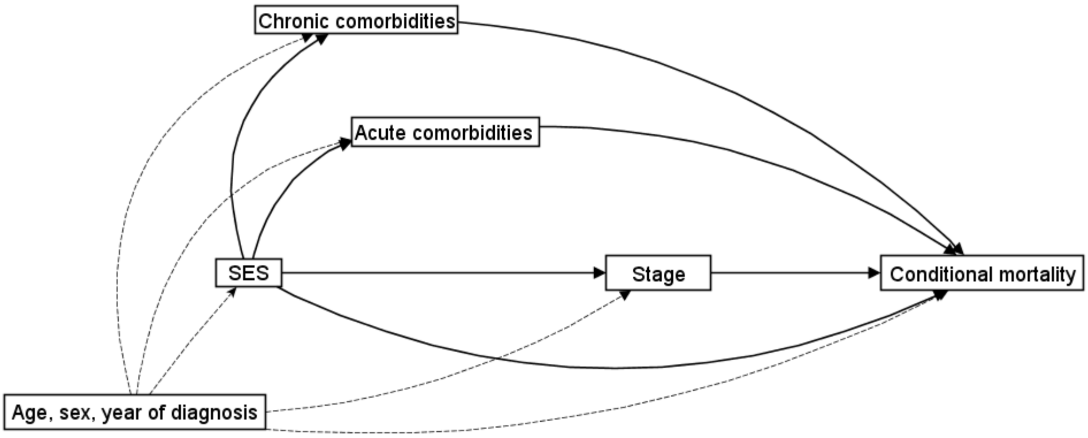

Figure 4.23 DAG of the first mediation analysis

Chronic/acute comorbidities and stage were the mediators. Age, sex and year of diagnosis were the baseline confounders.

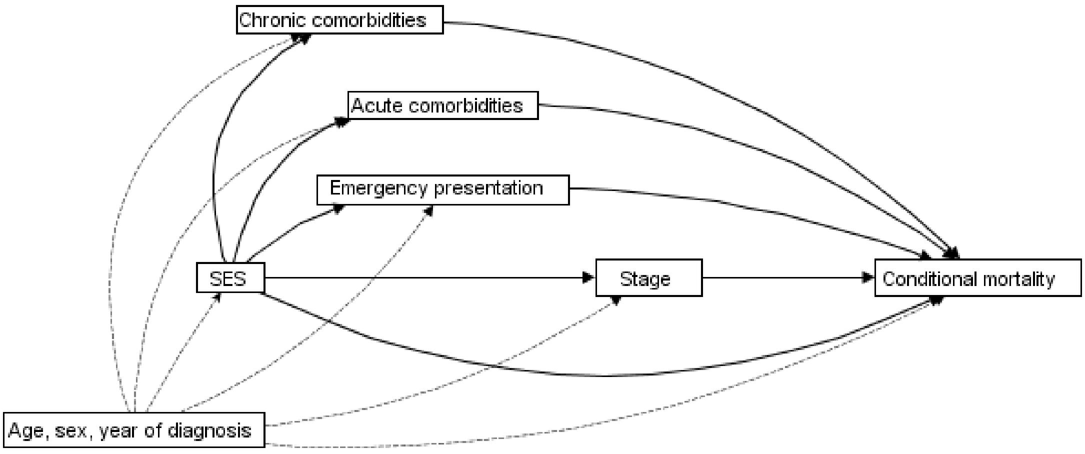

Figure 4.24 DAG of the second mediation analysis

Chronic/acute comorbidities, emergency presentation and stage were the mediators. Age, sex and year of diagnosis were the baseline confounders.

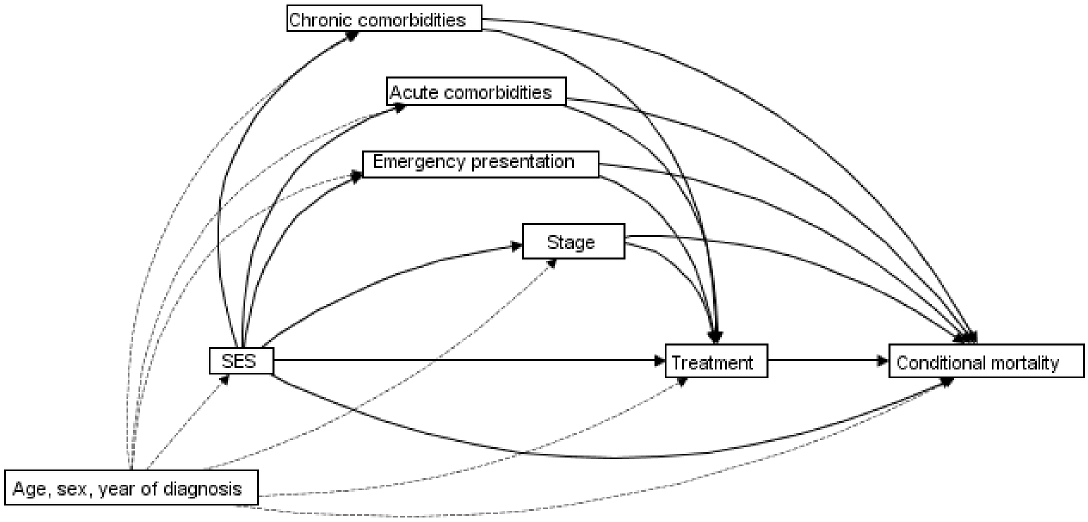

Figure 4.25 DAG of the third mediation analysis

Treatment (binary outcome: received major surgery for the primary lesion yes/no) was the mediator. Chronic/acute comorbidities, emergency presentation and stage worked as post-exposure confounders, which were affected by SES and affected treatment and conditional mortality. Age, sex and year of diagnosis were the baseline confounders.

4.5.2 Results

The ORs of death among SES groups at three time points are displayed in Figure 4.26 and Figure 4.27. The TCE and NIE with stage (denoted as St) show the results of the first analysis, stage and emergency presentation (denoted as St & EmPr) the second analysis, and stage, emergency presentation and treatment (denoted as St & EmPr & Tx) the third analysis.

The three mediation analyses modelled clear slopes by SES in ORs of the TCEs. For colon cancer, the slopes of the TCE slightly flattened over time, while for rectal cancer, the slopes did not level out throughout. For both cancers, NIEs in all time points showed no clear socioeconomic trends for the first and second analyses; however, the NIEs in ORs of all SES groups marked over 1 in the third analysis.

The PMs by the mediators (NIE divided by TCE in the log-odds scale of SES 5 when odds of SES 1 were set at the reference of 1) are illustrated in Figure 4.28. In the first mediation analysis, stage (and comorbidities) mediated the effect of SES on survival status over 20% at all three time points for both cancers. For rectal cancer, stage and comorbidities explained the increased odds of death in the most deprived group by more than 30%.

When emergency presentation was modelled as an additional mediator in the second analysis, the proportion, which the model explains the effect of SES on the survival status, improved at all time points for both cancers. The largest improvement in PM was observed at six months since diagnosis of rectal cancer with +20%, followed by the same time point with +17% for colon cancer. However, surgical treatment less contributed to the inequalities in survival status. When treatment was modelled as an additional mediator in the third mediation analysis, the proportion, which the model explains the effect of SES on the survival status, showed little improvement or rather reduction, especially in rectal cancer. For rectal cancer, the third analysis with treatment explained approximately 30% of the inequalities in survival status at all time points. For colon cancer, the third analysis with treatment explained over 50% of the inequalities in survival status at six months and one year but remained below 30% at 90 days since diagnosis.

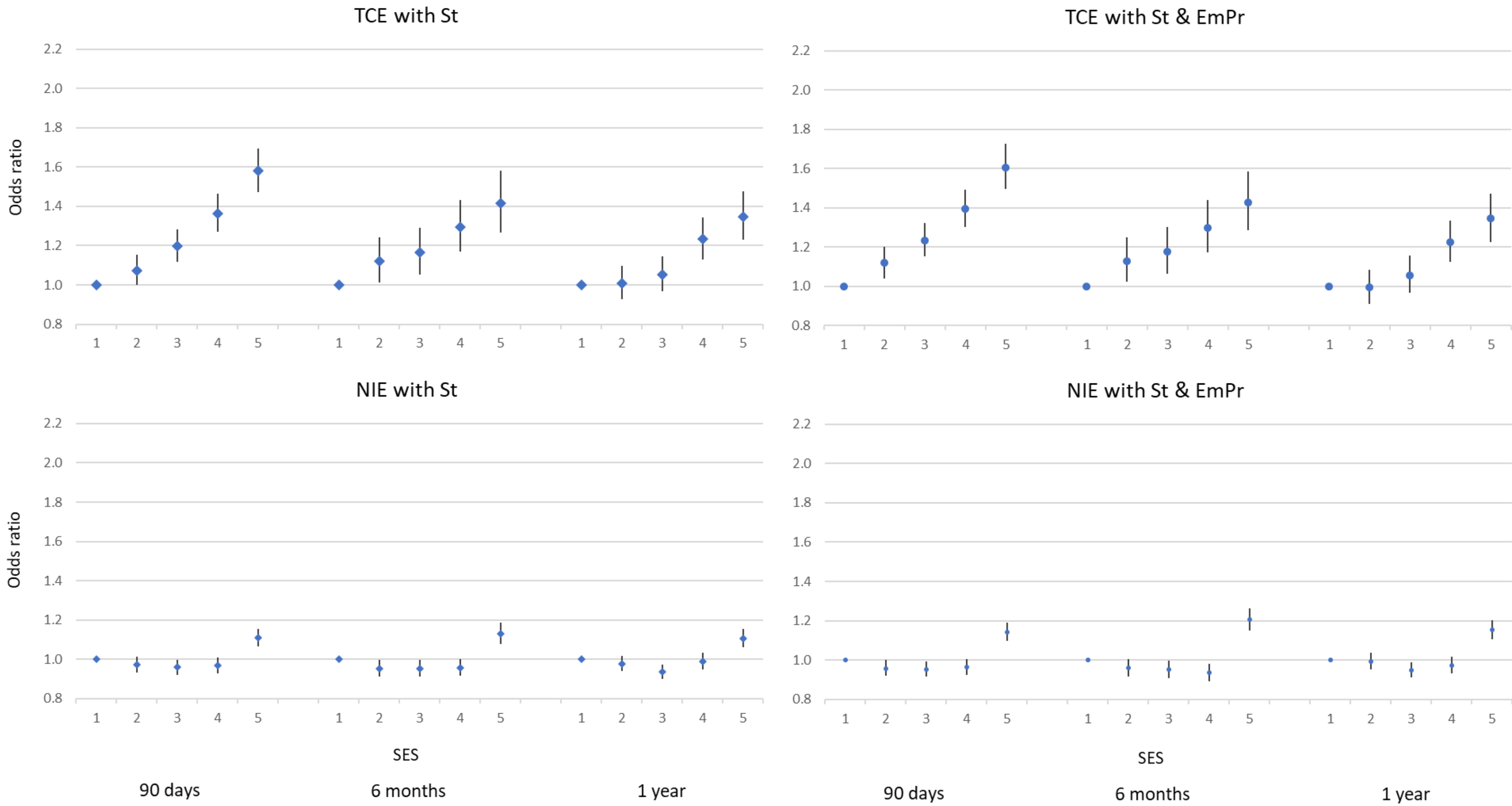

Figure 4.26 Total causal effect and natural indirect effect in odds ratios of death at 90 days, 6 months, 1 year since diagnosis for colon cancer, England

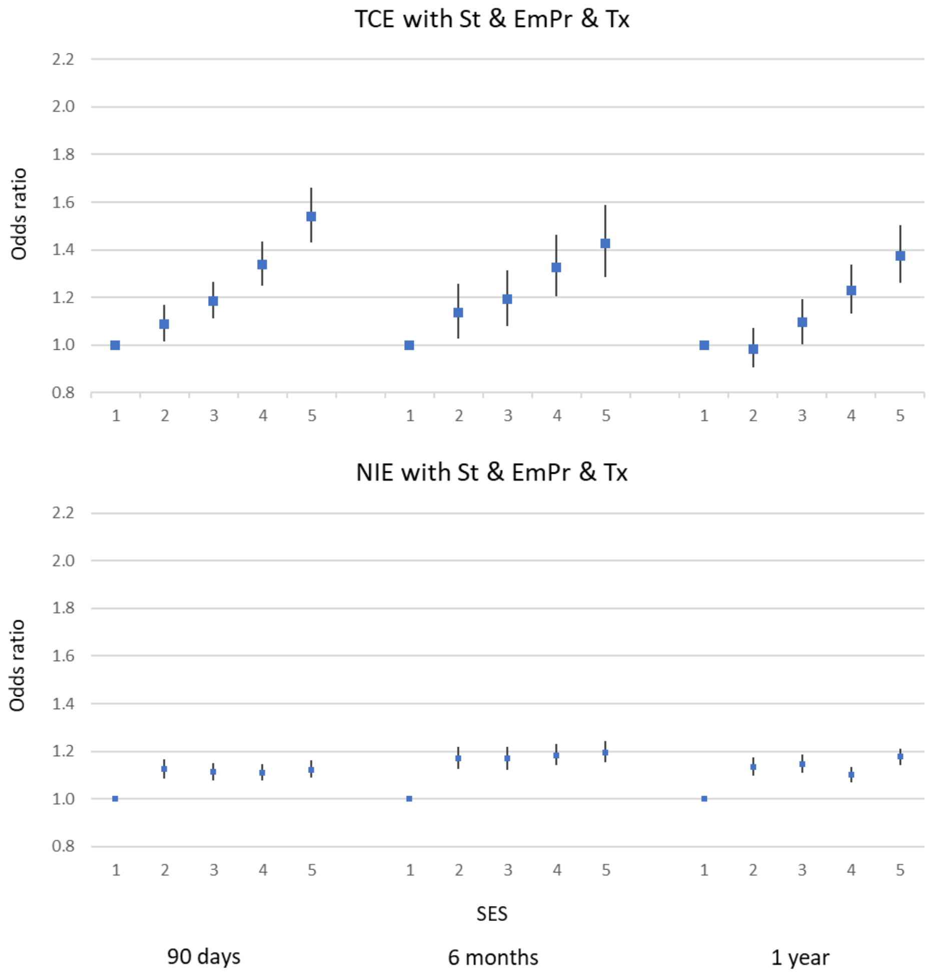

Figure 4.26 continued

Abbreviations: EmPr, emergency presentation; NIE, natural indirect effect; SES, socioeconomic status; St, stage; TCE, total causal effect; Tx, treatment.

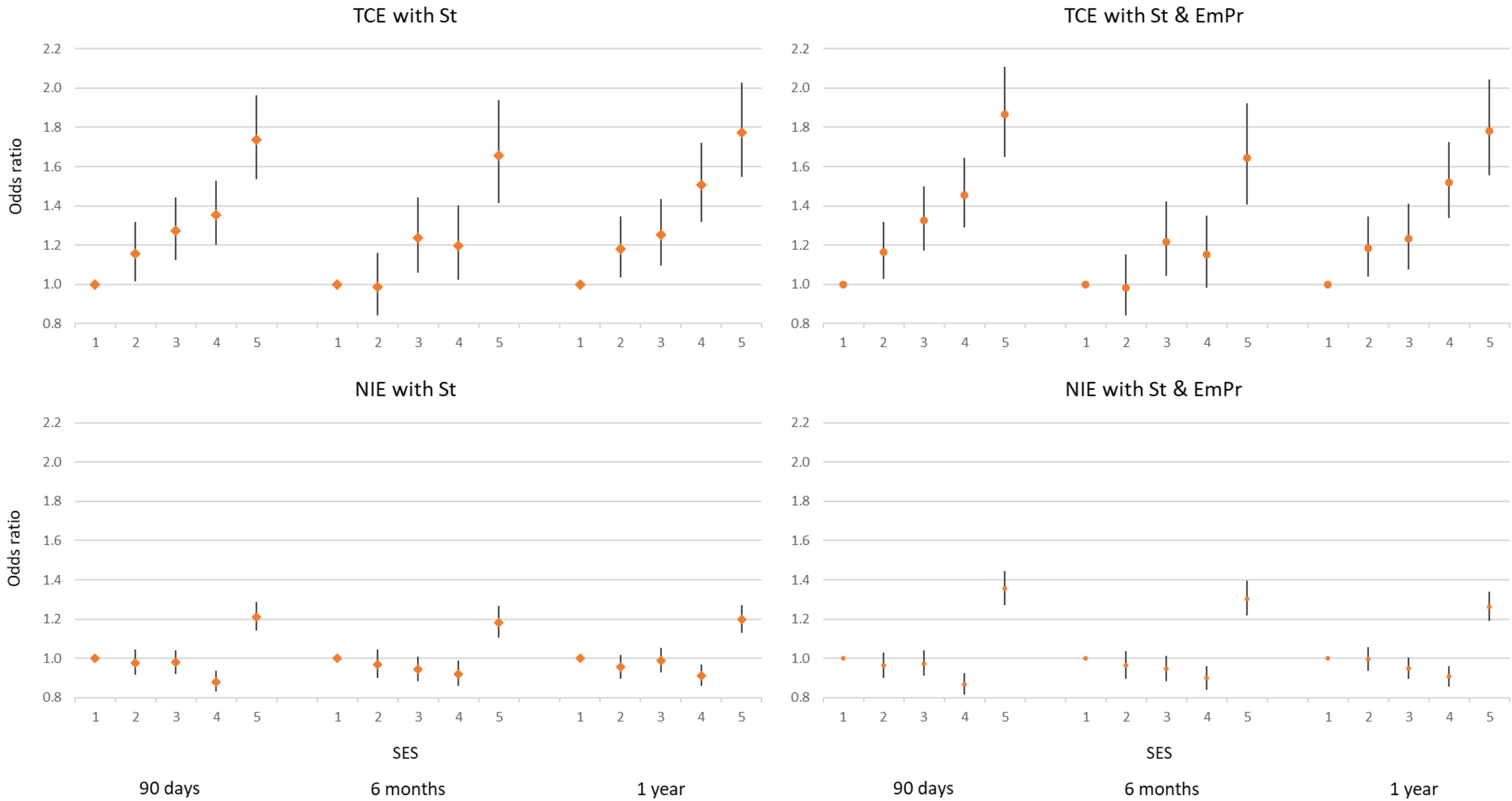

Figure 4.27 Total causal effect and natural indirect effect in odds ratios of death at 90 days, 6 months, 1 year since diagnosis for rectal cancer, England

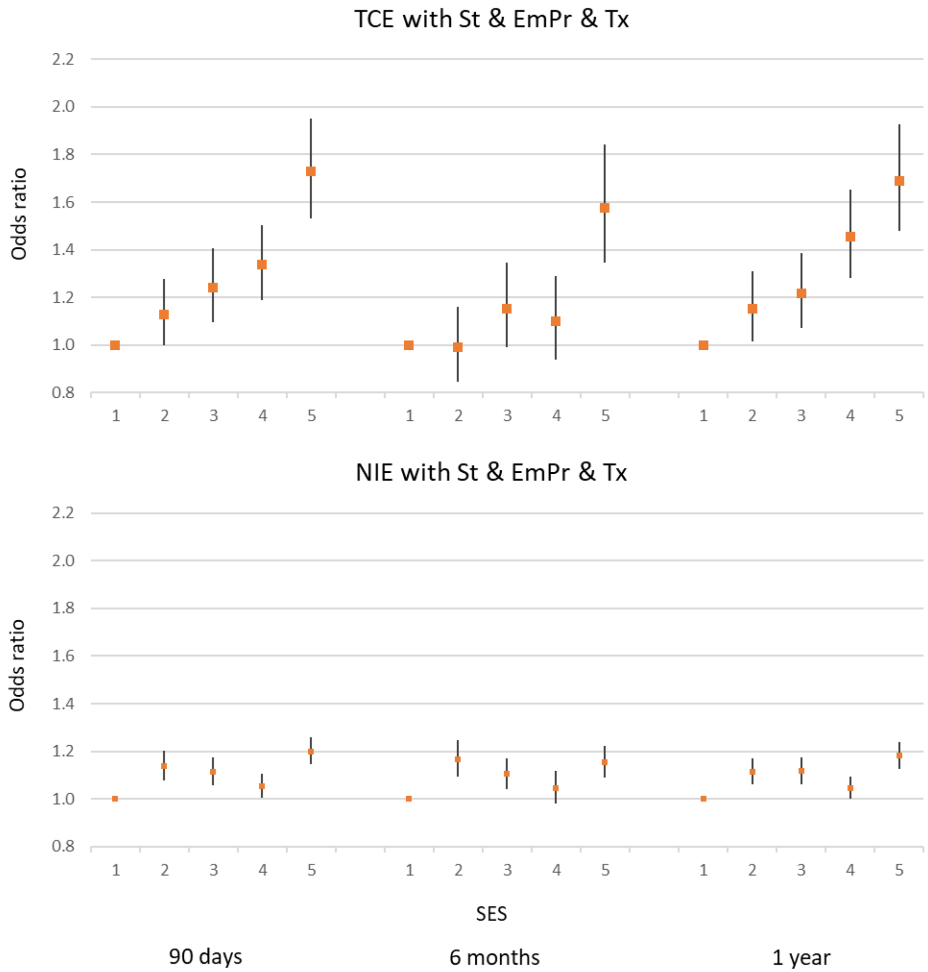

Figure 4.27 continued

Abbreviations: EmPr, emergency presentation; NIE, natural indirect effect; SES, socioeconomic status; St, stage; TCE, total causal effect; Tx, treatment.

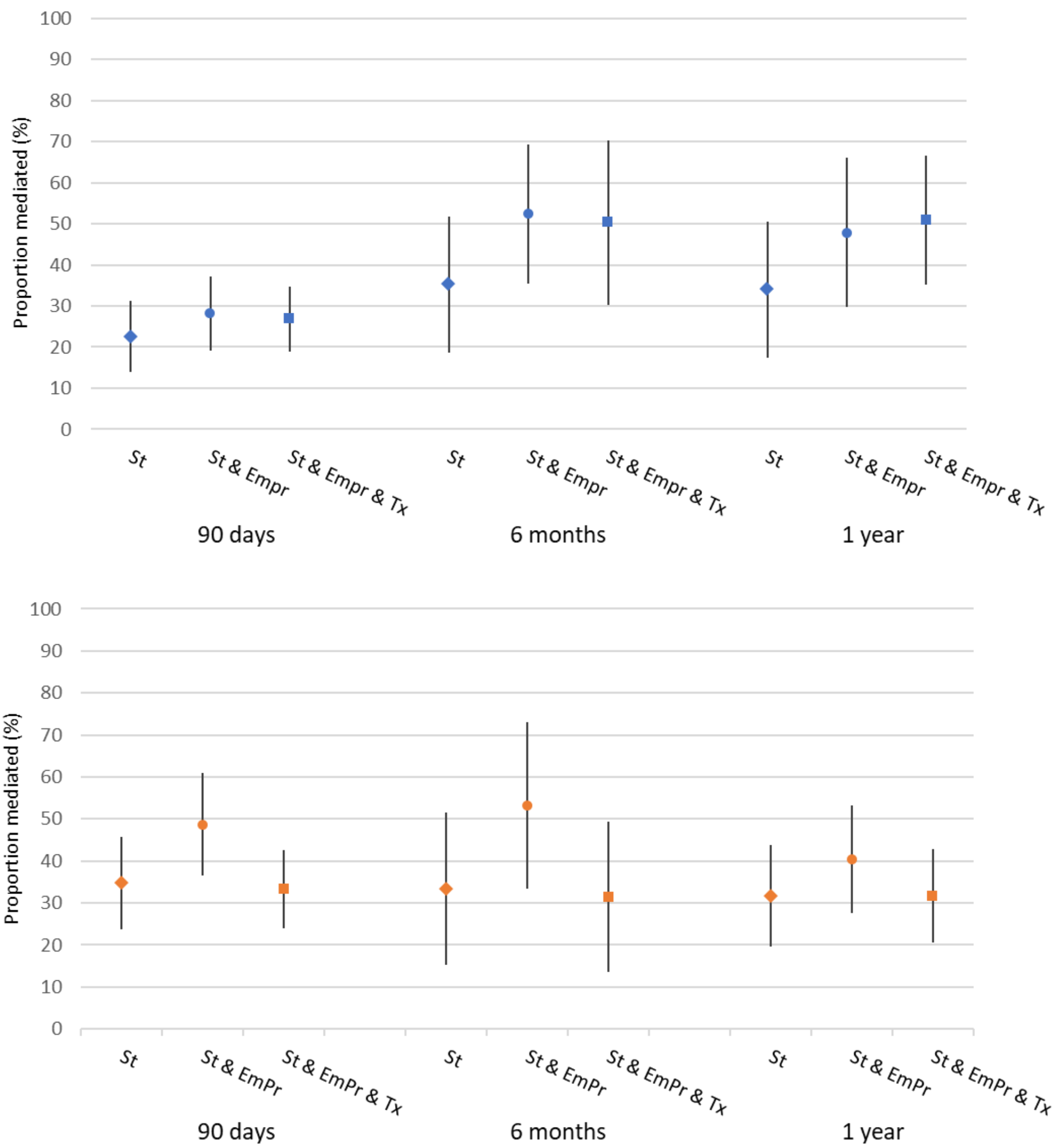

Figure 4.28 Proportion mediated in three mediation analyses with mediators of stage, stage and emergency presentation, and stage, emergency presentation and surgical treatment for colon (upper graph) and rectal cancer (lower graph), England

Abbreviations: EmPr, emergency presentation; St, stage; Tx, treatment.

4.5.3 Summary of findings

Socioeconomic inequalities in stage distribution, comorbidities and emergency presentation explained the socioeconomic inequalities in survival status by at least 20% in both colon and rectal cancer. Stage, comorbidities, emergency presentation and treatment inequalities greatly contributed to the socioeconomic inequalities in survival status by more than 50% for colon cancer after six months since diagnosis, but these factors explained the inequalities in survival status by only 30% in the early timeline for both cancers.

Results of the 90-day conditional mortality revealed that the known factors (stage, comorbidities, emergency presentation and receipt of surgical treatment) played a relatively minor role in socioeconomic inequalities in survival status for both cancers in the early timeline. Regarding conditional mortality at six months, the effect of emergency presentation increased PM by 20% compared to a model with stage and comorbidities as mediators. The results mean that the survival gap could further be reduced by 20%, if emergency presentation were equalised between the most and the least deprived groups, in addition to 30% of the gap being cancelled by equalising the distribution of stage and comorbidities between the two groups. No further improvement in PM in the third analysis means that the additional effect of equalising the percentage in receipt of surgery on reducing the gap in survival status deemed to be small, especially for rectal cancer patients. For colon cancer patients, as demonstrated in **Chapter 4.1**, the percentage in receipt of surgery was relatively equalised among SES groups; this is considered to be the reason the PM in the third model did not improve from the second mediation model.

4.6 Discussion

4.6.1 Socioeconomic inequalities in receipt of surgery and postoperative mortality

For colon cancer, receipt of major surgery and time to treatment did not differ among SES groups, but postoperative mortality was worse among the deprived groups in stages II to IV. The differences in postoperative mortality among SES groups have three potential reasons. Firstly, quality of care might be different (i.e. different types of hospital or difference in the characteristics of hospitals) among SES groups. For instance, lower SES groups may be treated in hospitals that have a smaller number of ICU beds, a smaller number of medical staff or unspecialised doctors. Secondly, some biological factors (e.g. factors at the molecular level) may exist, which could also be associated with SES but were not measured. However, it is unlikely that biological factors would affect such short-term postoperative mortality. Thirdly, some behavioural factors, which are closely related to both SES and mortality, may exist [213]. Potential examples include smoking status, nutrition status, progression of the CRC stage after diagnosis and existence of family or social care. If a patient smokes or in low nutrition status, the patient is likely to have major postoperative complications such as respiratory complications or leakage [213-215]. Stage of CRC could have progressed more among lower SES groups compared with the least deprived group while awaiting treatment. Although there was no difference in time from diagnosis to treatment for colon cancer, the time from recognition of symptoms to diagnosis could be longer in the deprived groups because of differences in health-seeking behaviour; time to diagnosis, otherwise called the ‘appraisal interval’ and ‘help-seeking interval’ [177], was not incorporated in this analysis. If a patient has no family members or carers after discharge and experiences complications, late readmission or aggravated complications can be expected.

For rectal cancer with stages II to IV, the deprived groups were less likely to receive major surgery. Although there was a socioeconomic trend towards worse postoperative mortality among the deprived groups, evidence was relatively weak compared with that of colon cancer. These facts suggest that once patients receive surgery, the quality of care provided seems to be uniform (i.e. the quality of hospitals may not vary) regardless of SES group. Some rectal cancer patients may require neoadjuvant therapy, such as CRT or SCPRT. Through the therapy courses, patients might have been selected before undergoing surgery for a few potential reasons. If a patient could not attend the neoadjuvant therapy because of low access to facilities, this could also affect the further treatment choices. This accessibility might be related to SES due to geographical distance or job inflexibility [92, 148, 216]. Alternatively, adherence to treatment may be low in deprived groups [213, 217]. Another reason for the selection of surgical treatment could be related to performance status. Lastly, patients who were able to care for a stoma by themselves or family members might be more likely to be selected for surgery.

To conclude, the results presented in **Chapter 4.1** and **Chapter 4.2** indicate that colon cancer patients receive surgery equally, but the quality of care (surgical and postoperative care) may vary among SES groups, possibly across the hospitals. Rectal cancer patients might be selected for surgery based on unmeasured factors, but patients from different SES groups seem to receive a standardised quality of care. The unmeasured factors could be related to receipt of neoadjuvant therapy, access issues or behavioural factors, which may also vary among SES groups.

Careful interpretation is needed for the analyses in **Chapter 4.1**. The outcome in **Chapter 4.1** is a binary variable of whether receiving major surgery for the primary lesion. Among patients with either colon or rectal cancer with stage I or IV, not receiving major surgery does not necessarily mean inappropriate care. For some patients with stage I, having only an endoscopic resection (e.g. EMR or ESD) can be a sufficient treatment option intending cure. However, there was no information on whether the stage I patients had unfavourable histological findings, and data regarding why major surgery for the primary lesion was not performed were mostly missing.

Similarly, for patients with stage IV, there was little information on why the major surgery was not performed. In stage IV, indication for major surgery for the primary lesion largely depends on clinical factors (performance status, the severity of obstruction or bleeding symptoms, whether the patient reacted to chemotherapy aiming conversion therapy and extent of metastasis to other organs), which are not fully captured in the population data. Neither palliative intent nor curative intent was clear among stage IV patients.

Misclassification of the outcome could occur because of the aforementioned reasons; thus, at this point, the results of **Chapter 4.1** and **Chapter 4.2** may only be interpretable with certainty for CRC patients with stage II or III, who have a potential for cure if treated appropriately.

4.6.2 Socioeconomic inequalities in survival and their mediators

In **Chapter 4.2**, higher prevalence of emergency presentation and urgent operation (surgery within seven days of diagnosis) in the deprived groups was observed among colon cancer patients. The fact suggests that, in addition to improving the quality of postoperative care, reducing emergency presentation may also reduce the survival gap among SES groups. In fact, since 2012, significant efforts have been made to standardise and improve the quality of care for those undergoing emergency laparotomy [218, 219].

In **Chapter 4.4**, the FPM estimated that the HRs of emergency presentation increased over time in both cancers. Mediation analyses also suggested that the survival gap, especially after six months of diagnosis, was mediated at around 20% by the inequalities in emergency presentation. Over 27% of the emergency presenters were in stage IV (**Chapter 4.1.2**). Some emergency presentations may be inevitable [220]. Although factors associated with emergency presentation are known to include a higher stage [220], the fact that emergency presentation affected survival after six months, independent of stage, suggests that emergency presentation may also be associated with other biological factors, behavioural factors or access issues. Potential biological factors include tumour grade, site or symptoms. Emergency presenters had fewer recorded ‘red flag symptoms’ than non-emergency presenters [220, 221]. However, no studies have explored the association between those factors and SES. In this thesis, no association was found between tumour grade and SES. Although the GP consultation pattern was shown to be the same among emergency presenters and non-emergency presenters [221], behavioural factors and healthcare access may not only affect the mode of presentation and receipt of surgery, but overall interactions between the patient and the healthcare system: receipt of neoadjuvant therapy, adjuvant therapy or attendance at follow-up. For colon cancer, the hazard difference between SES 1 and SES 5 marked the first peak shortly after diagnosis but continued widening in stage III after six months from diagnosis. The figures in **Chapter 4.4** refer to the patients who did not have emergency presentation, but those figures also support the existence of unmeasured factors related to survival (e.g. receipt of adjuvant therapy or attendance at follow-up after surgery).

For rectal cancer patients, despite the gap in receipt of surgery, mediation analyses confirmed that the survival gap, particularly observed in stage II, was mediated by inequalities in emergency presentation but less so through inequalities in receipt of surgical treatment. The combined results imply that even if surgical treatment is provided with an equal percentage to all SES groups, the survival gap may not be reduced. The aforementioned potential unmeasured factors may partly mediate the remaining pathway in socioeconomic inequalities in survival, but not through the differences in emergency presentation, comorbidities, stage and receipt of surgical treatment.

4.6.3 Insights into factors associated with receipt of surgery, postoperative mortality and survival

As illustrated in Table 4.1 and Table 4.2, a socioeconomic gradient towards a worse stage among lower SES groups was observed only for rectal cancer. These findings are in line with a previous study in Denmark [222] and may be symptom-related. Colon cancer patients may have vague symptoms that are confused with other benign conditions equally for all SES groups. On the other hand, rectal cancer patients may have rectal bleeding, which is more obvious and easier to be aware of; however, diagnosis can be delayed in the lower SES groups because of their health-seeking behaviour or poor communication with GPs. As Sinding *et al.* (2014) noted [11], patients with a louder voice (i.e. more affluent patients) may attract the attention of GPs more easily than less privileged patients.

Chapter 4.2 and **Chapter 4.4** revealed that the different effects of colon cancer site on postoperative mortality and survival. Transverse colon cancer had higher odds of postoperative death than cancer of the right-sided colon, while long-term survival was similar between the two sites. One potential reason for the higher postoperative mortality in transverse colon cancer may be a higher probability of leakage in the transverse colon than in the right-sided colon due to anatomical structure related to the blood supply.

In colon cancer, as cancer locates more distal, odds of not receiving surgery increased; right-sided colon cancers were more selected to surgery for some reasons. Stage advantaged sigmoid colon cancer for the postoperative 30-day mortality. Sigmoid colon cancer had lower hazard of death systemically than right-sided colon cancer. Descending colon cancer had the same hazard of death as the right-sided colon cancer at 90 days from diagnosis. For longer-term survival beyond 90 days, the hazard of death for both descending and sigmoid colon cancer was systemically lower than right-sided colon cancer. The difference between the descending and sigmoid colon, in terms of 90-day survival, may be influenced by uncontrolled confounding.

Rectal cancer had more than twice the odds of not receiving surgery when compared with rectosigmoid cancer, but survival was 10–20% better in rectal cancer than rectosigmoid cancer, both at 90 days and 6 months from diagnosis. One potential reason for observing the difference in survival between the two sites is covering stoma; for a patient without a defunctioning stoma, leakage may become fatal. In contrast, the postoperative 30-day mortality was not different between the two sites (in **Chapter 4.2**); site was not associated with the short-term mortality in rectal cancer. This disagreement of the results in short-term postoperative mortality (30 days) and survival in the longer term (90 days from diagnosis and more) is unclear. As described as one of the potential problems in data acquisition in **Chapter 1.3.9**, data regarding complication rates and stoma rates were missing in approximately 40%. Thus, failure-to-rescue rates were not able to be analysed. More detailed clinical information may be needed to investigate further for the explanations.

When the results of colon and rectal cancer were compared, colon cancer had higher emergency presentations, but patients received surgery equally by SES. Colon cancer patients had a clearer socioeconomic gradient in postoperative mortality. To combine all these results, whether or not specialists managed a patient may be a possible explanation for the inequalities in postoperative mortality in colon cancer. Treatment by non-specialists may reduce disparities in receipt of surgery, but especially for emergency cases, postoperative mortality may be worse than the specialists' management.

Regarding long-term survival, left-sided colon cancer had a lower mortality rate than cancers of the right-sided colon. The results agree with other studies [223, 224], and this difference could be associated with biological factors. Cancer with *BRAF* mutations, which are often associated with right-sided colon cancer, may have resulted in lower survival than cancer with *KRAS* mutations, which is often seen in left-sided colon cancer.

This is the first study that differentiates comorbidities in chronic and acute phases. Analyses on receipt of surgery and postoperative morality revealed that chronic and acute comorbidities influence those outcomes to different degrees. The presence of chronic comorbidities was associated with over 4.5 times higher odds of not receiving surgery compared with having no chronic comorbidities, whereas the presence of acute comorbidities was associated with less than 2.5 times higher odds of not receiving surgery compared with having no acute comorbidities. In contrast, up to a sevenfold increase in odds of postoperative death was observed in patients with acute comorbidities compared with patients without acute comorbidities. Up to a fourfold increase in odds of postoperative death was observed in patients with chronic comorbidities compared with the patients without chronic comorbidities. These results indicate that chronic comorbidities have a more significant influence on receipt of surgery, but acute comorbidities have a more significant influence on postoperative 30-day mortality.

In the analyses described in **Chapter 4.2** and **Chapter 4.4**, postoperative mortality was higher in obese patients than patients with BMI<30 among colon cancer patients, but obesity was not associated with survival. Previous studies have suggested that obesity is associated with postoperative complications such as leakage, which could lead to higher mortality rates [225-227]. However, hypoalbuminemia, which suggests long-term malnutrition, is also associated with leakage, and body weight loss of more than 10% is associated with both leakage and higher postoperative mortality [215, 225, 228]; the effect of those factors may outweigh the effect of obesity on survival. When measuring surgical outcomes, postoperative complications and quality of treatment (30-day mortality in this thesis, others include recurrence) should be addressed separately.

Chapter 5: Colorectal cancer in Osaka, Japan

In **Chapter 5**, I explored factors associated with receipt of major surgery and survival and investigated whether socioeconomic inequalities in care and survival existed among patients registered at OUH, Japan.

5.1. Factors associated with receipt of major surgery and socioeconomic inequalities in receipt of surgery

The first analysis examined factors associated with not receiving major surgery for the primary lesion as the first definitive treatment. The second analysis explored whether there was any time difference in receiving major surgery among SES groups.

5.1.1 Methods

Study population

Of the patients with CRC registered with hospital-based cancer registry data at OUH, the residents of Osaka Prefecture were included in the analysis. Patients were diagnosed with colon or rectal cancer between 2012 and 2015 and followed up until the end of July 2018. The inclusion criteria were primary CRC of any histological type and age at diagnosis younger than 100 years old. Tis (carcinoma *in situ*) was excluded from the analysis.

Outcome measure

The outcome in the first analysis was set as a binary measure (0 yes, 1 no) of whether a patient received major surgery for the primary lesion. I explored factors associated with receipt of surgery and investigated whether it differed by SES group.

I extracted the date and type of operation procedure of the first major surgery from the DPC data and supplemented the hospital-based cancer registry data. In the analysis of the patients in England, extraction of the date of major surgery for the primary lesion was restricted from 30 days before diagnosis to 180 days after diagnosis. To capture all treatment information, especially for patients with rectal cancer, no such time restriction was set for the analysis in OUH.

As in the England context, the first analysis was extended to the second analysis to examine factors associated with time to treatment and whether it varied by SES group. The outcome for the second analysis was the number of days from diagnosis to the first definitive surgery among patients who have received major surgery for the primary lesion.

Analysis strategy

In the first analysis, I fitted logistic regression with *a priori* exposure of SES. To derive days from diagnosis to treatment in the second analysis, I applied linear regression as in **Chapter 4.1**. As the number of days from diagnosis to treatment was right-skewed, the outcome was log-transformed. After the log-transformation, the outcome became normally distributed.

Because of sparse data, stage was categorised into two groups: non-metastatic stages (localised, positive regional lymph nodes and invasion to adjacent organs) and with distant metastases. Site was categorised into colon and rectum. The number of comorbidities was also categorised into two groups (0 and ≥1). In Japan, as seen in Table 5.1, most patients who come to university hospitals are referred from clinics at the primary care level. Therefore, referral routes were categorised into two groups, i.e. referral from other clinics/hospitals and others. Obesity at diagnosis was not included in this analysis, as there were only eleven overweight patients with BMI ≥30 in total. Histology, tumour grade and emergency presentation were excluded from this analysis for the same reason.

Clinical information such as emergency presentations, comorbidities, use of ICU and ADL was extracted from the episodes of the first definitive treatment recorded in the DPC data and linked to the hospital-based cancer registry data. Of all patients registered with the hospital-based cancer registry, 25% was missing DPC information.

Stage and clinical information of interest (comorbidities, ADL and Brinkman index) were missing: in 16.5% of patients for stage, and 24.1% for clinical information. These variables were imputed 25 times with chained equations. Distributions of the imputed stage (non-metastasis or metastasis), comorbidities (0 or 1 and more), ADL and Brinkman index (binary: 0 or more than 0) are shown in Appendix 10. The covariates used for the imputation included sex, age group, SES group, cancer site, receipt of major surgery for the primary lesion (binary: 0 yes, 1 no), vital status (dead or alive) at the end of follow-up and Nelson-Aalen estimator.

To explore whether the models and results were robust, I conducted sensitivity analyses for both the first and second analyses, using data with complete cases only.

For all analyses, I started from bivariable analyses with *a priori* interest variable, SES, to assess the changes in the association between SES and the outcome, i.e. the confounding effect of each variable. Each variable was also retained in the multivariable analysis based on the Wald test (p-value< 0.05) of the bivariable analysis, since the likelihood ratio test in each of the imputed dataset does not incorporate uncertainty [208]. Variables were finally selected by backward elimination. A removed variable was added to the multivariable model again as a confounder if a model with the variable changed the effect of SES (e.g. OR of the most deprived group in the first analysis) by more than 10%. Age group and sex were added as *a priori* confounders. An interaction term between SES and stage was added as the main interest.

5.1.2 Results

There were 710 patients with colon or rectal cancer in total. The baseline characteristics of the patients with colon or rectal cancer are shown in Table 5.1. Nearly 40% had cancer in the rectosigmoid junction or rectum. Over 50% of patients were males, and the median age of the patients at OUH (66.8 years) was lower than that of the patients in England (median age of patients in England: 73.9 for colon, 70.8 for rectal cancer).

There were much fewer patients from the most deprived group (11.3% of total) than from the least deprived group (38.7%). There was no clear trend by SES for most characteristics except the median age at diagnosis; the most deprived group was approximately four years younger than the least deprived group. Stage information was missing for 16.5% of patients, without a socioeconomic trend in the missingness. Stage distribution neither had a clear trend among SES groups. Overall, 70% were diagnosed at other clinics or hospitals before the consultation at OUH. In total, 443 patients (62.4%) received major surgery for the primary lesion without differences by SES groups. Only one patient in the second SES group died within 30 days of the major surgery; thus, the postoperative 30-day mortality at OUH was 0.23%. Of the total number of patients, 4.1% received neoadjuvant therapy. After a consultation at OUH, around 20% were referred to other hospitals for treatment.

Regarding information from DPC data, emergency presentation (unplanned or emergency hospitalisation) at the first definitive treatment was seen in less than 4% of patients, with no gradient among SES groups. There was no socioeconomic gradient in the number of comorbidities, ADL, Brinkman index or obesity. Around 40% of the total patients had comorbidities. The overall mean BMI was 21.6. Use of ICU was 4.5% of the total patients who received major surgery for the primary lesion; the ICU use was mostly confined to the patients who underwent other major surgeries for the comorbidities during the same hospitalisation episode. Of the 20 patients who were admitted to the ICU, two patients with oesophageal cancer, one with pancreatic cancer and one with gastric cancer received major surgery for the simultaneous cancer and underwent surgery for CRC in the same episode.

Table 5.1 Baseline characteristics of patients with colon or rectal cancer at Osaka University Hospital, Japan

	Total number	SES				
		1st (least deprived)	2nd	3rd	4th	5th (most deprived)
Total number	710	275	135	121	99	80
(%)	100	38.7	19.0	17.0	13.9	11.3
Median age at diagnosis	66.8	65.7	65.8	66.0	68.6	70.0
IQR	58.8–74.1	58.2–73.7	57.7–73.1	54.9–72.8	63.3–73.2	61.9–75.8
Female (%)	303 (42.7)	106 (38.6)	65 (48.2)	49 (40.5)	47 (47.5)	36 (45.0)
Death at the end of follow-up (%)	188 (26.5)	70 (25.5)	30 (22.2)	40 (33.1)	29 (29.3)	19 (23.8)
Year of diagnosis (%)						
2012	161 (22.7)	64 (23.3)	35 (25.9)	28 (23.1)	18 (18.2)	16 (20.0)
2013	176 (24.8)	71 (25.8)	29 (21.5)	28 (23.1)	24 (24.2)	24 (30.0)
2014	173 (24.4)	66 (24.0)	41 (30.4)	28 (23.1)	22 (22.2)	16 (20.0)
2015	200 (28.2)	74 (26.9)	30 (22.2)	37 (30.6)	35 (35.4)	24 (30.0)
Cancer site (%)						
Right-sided colon	151 (21.3)	61 (22.2)	31 (23.0)	18 (14.9)	20 (20.2)	21 (26.3)
Transverse colon	48 (6.8)	18 (6.6)	6 (4.4)	12 (9.9)	3 (3.0)	9 (11.3)
Left-sided colon	218 (31.0)	85 (30.9)	32 (23.7)	42 (34.7)	37 (37.4)	22 (27.5)
Rectosigmoid junction or rectum	268 (37.8)	103 (37.5)	59 (43.7)	45 (37.2)	35 (35.4)	26 (32.5)
Overlapping site	25 (3.5)	8 (2.9)	7 (5.2)	4 (3.3)	4 (4.0)	2 (2.5)
Stage at diagnosis (%)						
Localised	364 (51.3)	141 (51.3)	82 (60.7)	48 (39.7)	51 (51.5)	42 (52.5)
Positive regional lymph nodes	67 (9.4)	28 (10.2)	10 (7.4)	14 (11.6)	5 (5.1)	10 (12.5)
Invasion to adjacent organs	41 (5.8)	18 (6.6)	2 (1.5)	9 (7.4)	9 (9.1)	3 (3.8)
Distant metastasis	121 (17.0)	49 (17.8)	19 (14.1)	26 (21.5)	15 (15.2)	12 (15.0)
Missing	117 (16.5)	39 (14.2)	22 (16.3)	24 (19.8)	19 (19.2)	13 (16.3)

Table 5.1 continued

	Total number	SES				
		1st (least deprived)	2nd	3rd	4th	5th (most deprived)
Histology (%)						
Adenocarcinoma	648 (91.3)	247 (89.8)	122 (90.4)	113 (93.4)	90 (90.9)	76 (95.0)
Adenosquamous cell, squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-epithelial tumours	27 (3.8)	14 (5.1)	7 (5.2)	0 (0.0)	4 (4.0)	2 (2.5)
Missing	35 (4.9)	14 (5.1)	6 (4.4)	8 (6.6)	5 (5.1)	2 (2.5)
Tumour grade (%)						
Well/moderately differentiated	595 (84.5)	227 (82.6)	111 (82.2)	99 (81.8)	86 (86.9)	72 (90.0)
Poorly differentiated/undifferentiated	12 (1.7)	6 (2.2)	3 (2.2)	2 (1.7)	0 (0.0)	1 (1.3)
Missing	97 (13.8)	42 (15.3)	21 (15.6)	20 (16.5)	13 (13.1)	7 (8.8)
Route to OUH (%)						
Referral from other clinics/hospitals	578 (81.4)	228 (82.9)	112 (83.0)	95 (78.5)	76 (76.8)	67 (83.8)
Self-referral	38 (5.4)	16 (5.8)	8 (5.9)	7 (5.8)	6 (6.1)	1 (1.3)
Followed up for other diseases in OUH	80 (11.3)	27 (9.8)	12 (8.9)	14 (11.6)	15 (15.2)	12 (15.0)
Screening	8 (1.1)	2 (0.7)	3 (2.2)	3 (2.5)	0 (0.0)	0 (0.0)
Health check-up	3 (0.4)	1 (0.4)	0 (0.0)	1 (0.8)	1 (1.0)	0 (0.0)
Others	3 (0.4)	1 (0.4)	0 (0.0)	1 (0.8)	1 (1.0)	0 (0.0)
Place of diagnosis (%)						
OUH	210 (29.6)	77 (28.0)	41 (30.4)	39 (32.2)	33 (33.3)	20 (25.0)
Other clinics or hospitals	500 (70.4)	198 (72.0)	94 (69.6)	82 (67.8)	66 (66.7)	60 (75.0)
Treatment (%)						
Received open major surgery for primary lesion at OUH	42 (5.9)	13 (4.7)	5 (3.7)	11 (9.1)	8 (8.1)	5 (6.3)
Received laparoscopic major surgery for primary lesion at OUH	401 (56.5)	150 (54.6)	83 (61.5)	62 (51.2)	56 (56.6)	50 (62.5)
Treatment/follow-up at OUH (no record of major surgery)	123 (17.3)	54 (19.6)	26 (19.3)	19 (15.7)	16 (16.2)	8 (10.0)
Referral to other hospitals for treatment	137 (19.3)	56 (20.4)	18 (13.3)	28 (23.1)	19 (19.2)	16 (20.0)
No visit to OUH after diagnosis	7 (1.0)	2 (0.7)	3 (2.2)	1 (0.8)	0 (0.0)	1 (1.3)
Postoperative 30-day mortality (%)*	1 (0.2)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Received neoadjuvant therapy (%)	29 (4.1)	12 (4.4)	6 (4.4)	6 (5.0)	1 (1.0)	4 (5.0)

Table 5.1 continued

	Total number	SES				
		1st (least deprived)	2nd	3rd	4th	5th (most deprived)
From linked DPC data						
Linked to hospital-based cancer registry data	539 (75.9)	204 (74.2)	105 (77.8)	90 (74.4)	76 (76.8)	64 (80.0)
No hospital episodes linked**	171 (24.1)	71 (25.8)	30 (22.2)	31 (25.6)	23 (23.2)	16 (20.0)
Emergency presentation (%)						
Planned hospitalisation	514 (72.4)	194 (70.6)	104 (77.0)	83 (68.6)	70 (70.7)	63 (78.8)
Unplanned or emergency hospitalisation	25 (3.6)	10 (3.6)	1 (0.7)	7 (5.8)	6 (6.1)	1 (1.3)
Use of ICU (%)*						
No	407 (91.9)	150 (92.0)	80 (90.9)	71 (97.2)	59 (92.2)	47 (85.5)
Yes	20 (4.5)	7 (4.3)	3 (3.4)	1 (1.4)	2 (3.1)	7 (12.7)
Number of acute comorbidities (%)						
0	406 (57.2)	163 (59.3)	80 (59.3)	64 (52.9)	55 (55.6)	44 (55.0)
1	97 (13.7)	30 (10.9)	24 (17.8)	17 (14.1)	13 (13.1)	13 (16.3)
2	30 (4.2)	9 (3.3)	1 (0.7)	7 (5.8)	7 (7.1)	6 (7.5)
3+	6 (0.9)	2 (0.7)	0 (0.0)	2 (1.7)	1 (1.0)	1 (1.3)
Obesity at diagnosis (BMI>30) (%)	11 (1.6)	2 (0.7)	2 (1.5)	2 (1.7)	3 (3.0)	2 (2.5)
Brinkman index>0 (%)	210 (29.6)	76 (27.6)	44 (32.6)	39 (32.2)	27 (27.3)	24 (30.0)
Modified ADL (%)						
Completely independent	268 (37.8)	107 (38.9)	60 (44.4)	36 (29.8)	33 (33.3)	32 (40.0)
Need support	271 (50.3)	97 (35.3)	45 (33.3)	54 (44.6)	43 (43.4)	32 (40.0)

Abbreviations: ADL, activities of daily living; BMI, body mass index; DPC, diagnostic procedure combinations; ICU, intensive care unit; IQR, interquartile range; OUH, Osaka University Hospital; SES, socioeconomic status. * Denominator is the number of patients who received major surgery for the primary lesion (n=443). ** The same percentage is missing for all variables below, except the use of ICU.

First analysis (logistic regression for receipt of major surgery and odds ratios by SES)

In total, 442 patients (62.4%) received major surgery for the primary lesion (Table 5.1). The first analysis using logistic regression included all 710 patients with imputed data. In sensitivity analysis using completed data, 480 patients (67.6% of total) were included.

Table 5.2 demonstrates the results of bivariable and multivariable analyses of logistic regression for receipt of surgery. To show the overall change in the effect of SES, the adjusted ORs of SES in those tables were based on a model without interaction between SES and stage. For the rest, adjusted ORs were based on the multivariable model with interaction between SES and stage (final model).

Factors associated with receipt of major surgery

The adjusted ORs among the SES groups in Table 5.2 show that there is no evidence that the deprived groups are failing to receive major surgery. Rather, there was a socioeconomic gradient favouring deprived groups in receipt of surgery. Sensitivity analysis using completed data also showed the same results but with a bias towards even better receipt of surgery for the deprived groups.

Older patients had the same odds of receiving surgery as young patients. Female patients were more likely to receive surgery than male patients, but this was not statistically significant. Presence of comorbidities was not associated with receipt of surgery, but patients with comorbidities tended to have lower odds of not receiving surgery. Neither year of diagnosis nor cancer site (colon or rectum) was related to receipt of surgery. Patients with history of smoking were more likely to receive surgery than patients without a smoking history, but the variable was finally not included in the multivariable model. Patients not referred from clinics were 50% more likely to receive major surgery at OUH than patients referred from clinics. The majority were followed up at OUH for other diseases, followed by self-referral. Sensitivity analysis showed that the referral route was not associated with receipt of surgery. Instead, patients with lower ADL (i.e. needing support in ADL) were more likely to receive major surgery at OUH than patients with fit for ADL.

Table 5.2 Odds ratios of not receiving major surgery for primary lesion using logistic regression for colorectal cancer, Osaka University Hospital, Japan

Variable	**Bivariable analysis**			**Multivariable analysis Multiple imputation (n=710)**			**Multivariable sensitivity analysis Complete cases (n=480)**		
	OR*	**95% CI**	**p-value[†]**	**OR****	**95% CI**	**p-value[†]**	**OR****	**95% CI**	**p-value[†]**
SES									
1 (least deprived)	1.00			1.00			1.00		
2	0.78	(0.51, 1.19)		0.79	(0.49, 1.27)		0.57	(0.26, 1.23)	
3	0.96	(0.62, 1.48)	0.16[‡]	0.80	(0.49, 1.32)	0.19[‡]	0.58	(0.25, 1.31)	0.08[‡]
4	0.80	(0.49, 1.28)		0.87	(0.51, 1.49)		0.51	(0.20, 1.34)	
5 (most deprived)	0.66	(0.39, 1.12)		0.66	(0.36, 1.18)		0.53	(0.20, 1.33)	
Sex									
Male	1.00			1.00		0.10	1.00		0.16
Female	0.95	(0.70, 1.29)	0.74	0.74	(0.52, 1.06)		0.66	(0.36, 1.19)	
Age									
<60	1.00			1.00			1.00		
60–69	0.82	(0.55, 1.22)	0.54[‡]	0.89	(0.57, 1.39)	0.96[‡]	0.93	(0.44, 1.90)	0.38[‡]
70–99	0.87	(0.60, 1.28)		1.00	(0.65, 1.53)		1.34	(0.65, 2.77)	
Year of diagnosis									
2012	1.00								
2013	0.73	(0.47, 1.14)	0.17						
2014	1.04	(0.67, 1.61)	0.88						
2015	0.93	(0.61, 1.43)	0.75						
Cancer site									
Colon	1.00								
Rectum	1.05	(0.77, 1.44)	0.75						
Stage									
No metastasis	1.00						1.00		
Metastasis	6.81	(4.40, 10.55)	<0.001				5.13	(2.12, 12.41)	<0.001
Stage[§]									
No metastasis	1.00			1.00					
Metastasis	6.58	(4.22, 10.27)	<0.001	6.07	(3.10, 11.91)	<0.001			

Table 5.2 continued

Variable	Bivariable analysis*			Multivariable analysis Multiple imputation (n=710)			Multivariable sensitivity analysis Complete cases (n=480)		
	OR	95% CI	p-value†	OR**	95% CI	p-value†	OR**	95% CI	p-value†
Route									
Referral from clinics/hospitals	1.00			1.00					
Others	0.51	(0.33, 0.78)	0.002	0.47	(0.29, 0.75)	0.002			
Comorbidities									
0	1.00								
1+	0.68	(0.40, 1.15)	0.15						
Comorbidities§									
0	1.00								
1+	0.77	(0.46, 1.28)	0.31						
Modified ADL									
Completely independent	1.00						1.00		
Need support	0.50	(0.32, 0.80)	0.004				0.44	(0.24, 0.81)	0.008
Modified ADL§									
Completely independent	1.00								
Need support	0.65	(0.35, 1.20)	0.16						
Brinkman index									
0	1.00								
>0	0.65	(0.41, 1.03)	0.066						
Brinkman index§									
0	1.00								
>0	0.63	(0.39, 1.01)	0.055						

Abbreviations: 95% CI, 95% confidence interval; ADL, activities of daily living; OR, odds ratio; SES, socioeconomic status. * Adjusted for SES in all variables. **All variables are mutually adjusted. For SES only, adjusted ORs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. † P-value of Wald test. ‡ P-value of Wald test for trend. § Multiply imputed.

Receipt of major surgery by SES

The stage-specific ORs, when interaction between SES and stage was added, are shown in Table 5.3. Although evidence is weak (p=0.09), there was a socioeconomic gradient in receipt of surgery in the non-metastatic stages favouring the deprived groups. The adjusted OR of the most deprived group on non-receipt of surgery was 0.47 (95% CI 0.22, 1.00) with imputed data. No clear trend was seen in the metastatic stage. Similar socioeconomic trends were seen in sensitivity analyses using completed data.

In the bivariable analysis, stage enhanced the effect of SES on the odds of non-receipt of surgery by more than 10%.

Table 5.3 Stage-specific oddds ratios of not receiving major surgery for primary lesion using multivariable logistic regression with interaction between SES and stage for colorectal cancer, Osaka University Hospital, Japan

	Multiple imputation[a]			Complete cases[b]		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
No metastasis						
SES						
1 (least deprived)	1.00		0.09	1.00		0.08
2	0.80	(0.46, 1.40)		0.55	(0.22, 1.36)	
3	0.80	(0.43, 1.48)		0.45	(0.15, 1.37)	
4	0.86	(0.45, 1.62)		0.45	(0.15, 1.39)	
5 (most deprived)	0.47	(0.22, 1.00)		0.12	(0.02, 0.90)	
Metastasis						
1 (least deprived)	1.00		0.60	1.00		0.28
2	0.74	(0.28, 1.99)		0.67	(0.17, 2.60)	
3	0.85	(0.34, 2.12)		0.93	(0.27, 3.23)	
4	0.90	(0.28, 2.87)		0.75	(0.12, 4.68)	
5 (most deprived)	2.17	(0.45, 10.39)		7.06	(0.68, 73.05)	

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SES, socioeconomic status. All p-values are of Wald test for trend. Model a: adjusted for sex, age, stage (imputed), route. Model b: adjusted for sex, age, stage, modified ADL (activities of daily living).

Further analysis of the 267 patients who did not receive major surgery showed that 72 patients (27.0%) had localised stage, 76 (28.5%) had distant metastasis and 96 (36.0%) had missing stage information. Among them, the least deprived group was more likely to have a localised stage (p=0.008, Wald test for trend), which may not require major surgical treatment. Moreover, 137 patients (51.3%) of the total cases who did not receive surgery at OUH were referred to other hospitals for treatment: twenty-nine cases (40.0%) of the patients with localised, 36 cases (47.4%) of the patients with a metastatic stage. The records showed no socioeconomic trend for referral or other treatment plans (treatment at OUH, follow-up at OUH or no visit). Of the 23 patients who had stages with the potential for cure (positive regional lymph nodes or invasion to adjacent organs) but did not receive surgery at OUH, 16 patients were referred to other hospitals for treatment. Another six patients were recorded as treated or followed up at OUH. Those developed metastatic disease (e.g. obstructive jaundice due to metastasis from CRC) or had severe comorbidities (e.g. acute subdural haemorrhage, primary malignancy in other organs). One patient in SES 2 did not appear to OUH visit after diagnosis. Patients with colon cancer were more likely to be referred to other hospitals compared with patients with rectal cancer ($p<0.001$, chi square test). The presence of comorbidities or ADL were not associated with referral.

An additional analysis, in which not only major surgery but also minor surgery (endoscopic resection for the localised stage) was defined as a success in receiving treatment, showed a similar socioeconomic gradient towards higher treatment receipt in the more deprived groups for the non-metastatic stage.

Second analysis (linear regression for days from diagnosis to treatment and its difference by SES)

The study population in the second analysis was firstly restricted to 443 patients who received major surgery for the primary lesion. A total of 102 patients died without receiving major surgery. Half of the 102 patients had a metastatic stage, and stage was missing for the remaining 30%, but there was no socioeconomic trend for stage distribution and stage missingness. Of the 443 patients who received major surgery, seven patients who underwent surgery within seven days of the date of diagnosis (four patients from SES 1, one each from SES 3, 4 and 5) were excluded from the analysis. An eventual total of 394 patients were included in the linear regression analysis for time to treatment.

Eleven patients received major surgery after more than 180 days from diagnosis. Of the eleven patients, nine had neoadjuvant chemotherapy. No patients were diagnosed, underwent surgery and died on the same day.

The results of mean days to treatment and the ratios using linear regression are shown in Table 5.4. When not adjusting for other conditions but SES, the mean days from diagnosis to treatment was 41.8 (95% CI 37.7, 46.4) for the least deprived group (reference days for the reference group in bivariable analysis, Table 5.4). When potential associated factors with the time length were adjusted in multivariable analysis, the mean days to treatment were 41.5 (95% CI 36.6, 47.2) for the reference group (least deprived group, male, mean age 65.7 years, colon cancer). There was no evidence that the more deprived groups experienced delays compared with the least deprived group.

When the association of age and the number of days was analysed in bivariable analysis, age was better associated in quadratic term than the linear term or categorised groups (likelihood ratio test $p<0.05$). However, in a multivariable regression model, age was associated with the number of days linearly. No patients were missing comorbidities or Brinkman index and days from diagnosis to treatment (outcome) at the same time; therefore, the results were identical in the analyses using imputed and completed data.

In a multivariable regression model, other than SES and *a priori* confounders (age and sex), the site of cancer showed evidence of an association with time to treatment. When other covariates were set as reference (SES 1, male, mean 65.7 years), patients with rectal cancer experienced 36% longer (95% CI 19%, 54%) time to treatment than patients with colon cancer. There was no evidence that the delay was associated with other potential factors, such as stage, referral route, number of comorbidities, ADL or Brinkman index.

Table 5.4 Reference number of days from diagnosis to major surgery for primary lesion and ratios using linear regression for colorectal cancer, Osaka University Hospital, Japan

	Bivariable analysis			Multiple regression		
				Complete cases (n=394)		
	Days	**95% CI**		**Days**	**95% CI**	
Reference (geometric mean) days in SES 1	41.8	(37.7, 46.4)		41.5	(36.6, 47.2)	
	e^{β}*	**95% CI**	**p-value†**	**e^{β}**	**95% CI**	**p-value†**
SES						
1 (least deprived)	1.00			1.00		
2	1.08	(0.91, 1.29)		1.06	(0.90, 1.26)	
3	1.02	(0.84, 1.23)	0.97‡	1.01	(0.84, 1.21)	0.92‡
4	0.89	(0.73, 1.08)		0.90	(0.75, 1.09)	
5 (most deprived)	1.10	(0.89, 1.35)		1.10	(0.90, 1.35)	
Sex						
Male	1.00			1.00		
Female	0.89	(0.79, 1.02)	0.09	0.91	(0.81, 1.03)	0.51
Age						
Mean age at diagnosis	65.7	SD 11.9				
Age as linear term (10-year increase)	0.97	(0.91, 1.03)	0.29	0.98	(0.92, 1.03)	0.38
Age as quadratic term	††		0.02††	††		0.01††
Year of diagnosis						
2012	1.00					
2013	1.08	(0.91, 1.29)	0.39			
2014	1.03	(0.85, 1.24)	0.76			
2015	1.03	(0.86, 1.24)	0.75			
Cancer site						
Colon	1.00			1.00		
Rectum	1.35	(1.19, 1.54)	<0.001	1.36	(1.19, 1.54)	<0.001
Stage						
No metastasis	1.00					
Metastasis	1.11	(0.89, 1.39)	0.36			
Stage§						
No metastasis	1.00					
Metastasis	1.11	(0.89, 1.38)	0.36			
Route						
Referral from clinics/hospitals	1.00					
Others	1.02	(0.88, 1.19)	0.77			
Number of acute comorbidities§§						
0	1.00					
1+	1.12	(0.98, 1.30)	0.11			
Modified ADL						
Completely independent	1.00					
Need support	0.92	(0.81, 1.05)	0.21			
Modified ADL§						
Completely independent	1.00					
Need support	0.92	(0.81, 1.04)	0.20			
Brinkman index§§						
0	1.00					
>0	1.11	(0.98, 1.27)	0.10			

Abbreviations: 95% CI, 95% confidence interval; ADL, activities of daily living; SD, standard deviation; SES, socioeconomic status. * Adjusted for SES in all variables. † P-value of the null hypothesis that the coefficient (β) is 0 ($e^{\beta}=1$) when all other variables were set as the reference group. ‡ P-value for linear trend. †† When age is put as a quadratic term, in bivariable analysis, log(days) is derived from α(constant) + β_1(0 in SES=1) + β_2(age−mean age) + β_3(age−mean age)^2. P-value of likelihood ratio test comparing linear and quadratic models. § Multiply imputed. §§ No patients were missing comorbidities or Brinkman index and days from diagnosis to treatment (outcome) at the same time, therefore the results of the analysis using multiply imputed data were identical to the results of the analysis using complete cases.

5.1.3 Summary of findings

Among the patients with non-metastatic stages, there was weak evidence that the more deprived groups had lower odds of not receiving major surgery; however, the majority of the non-recipients had localised or metastatic stage. The more affluent non-recipients were likely to have a localised stage. Of the non-recipients, 51% were referred to other hospitals for treatment, and patients with colon cancer were more likely to be referred compared with patients with rectal cancer. No socioeconomic gradient in receipt of surgery was observed for patients with the metastatic stage. The multivariable logistic regression model with imputed data and the model with completed data varied, meaning that the models may not be robust. At OUH, patients not referred from other clinics or hospitals (the majority were followed up at OUH for other diseases) or with lower ADL were more likely to receive surgery than the patients referred through clinics or with fit ADL.

The mean time to treatment at OUH was approximately 40 days and was consistent through the different SES groups. Patients with rectal cancer experienced a longer time from diagnosis to treatment than patients with colon cancer.

5.2 Survival by socioeconomic status

This analysis investigated general patterns of survival and mortality rates by SES without controlling for any other factors.

5.2.1 Methods

Outcome measure

Mortality rates and the difference in survival among SES groups were set as the outcomes. Firstly, to estimate mortality rates, the number and positions of the knots in a model of the baseline hazard were explored.

Analysis strategy

Since there is no lifetable for deriving net survival for the patient population in this analysis, I analysed overall survival only. I fitted the Royston-Parmar FPM, which models basic cumulative hazard by restricted cubic spline functions. I modelled the number and positions of the internal knots for the baseline hazard without any covariates. The number and positions of the internal knots were set in the same ways as in **Chapter 4.3** and were compared with the default knots, which varied from 2 to 5 df. A model with the smallest AIC was selected.

After selecting a model with a plausible number and positions of the knots, I estimated the survival curves for each SES group not adjusting for other covariates. I compared the curves derived by the FPM and the survival curves derived by the Kaplan-Meier method but used the AIC to determine how SES acts (proportional or time-varying). The difference in mortality rate per 1,000 PYs and the difference in survival between SES 1 and SES 5 were estimated by the FPM.

5.2.2 Results

Number and positions of knots in null FPM

Figure 5.1 shows the mortality rate per 1,000 PYs modelled by the FPM changing the number and position of the knots. Table 5.5 shows the AIC by the number and position of the knots. From the wavy figures in the models with three internal knots, df 4 and df 5 (Figure 5.1) and the AIC in Table 5.5, models with three or more internal knots were likely to be overfitted. The smallest AIC suggests that the model with one internal knot at 1.5 years from the time of diagnosis is the best model.

Not only the number of the knots in the model but also the shapes of the mortality rates in Japan differed considerably from that in England; the figure of the mortality rate in England showed a concave shape, whereas that in Japan showed a convex shape, peaking around six months from diagnosis.

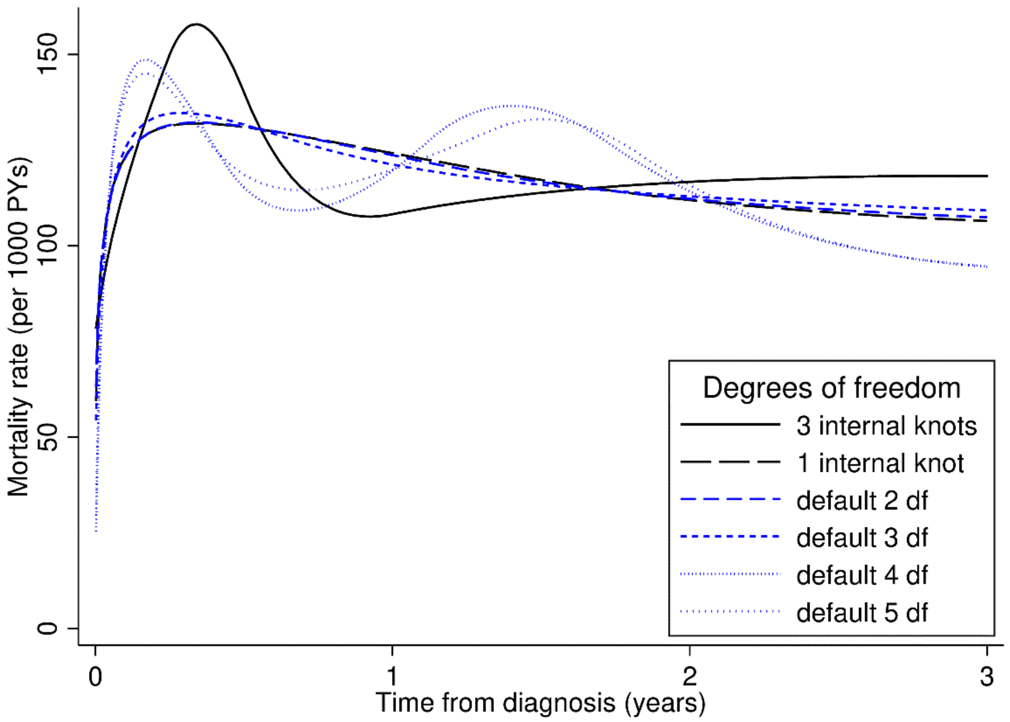

Figure 5.1 Mortality rate for colorectal cancer, Osaka University Hospital, Japan

Abbreviations: 1000 PYs, 1000 person-years; df, degrees of freedom.

Table 5.5 AIC by number and position of knots for colorectal cancer, Osaka University Hospital, Japan

Number and position of knots	AIC
3 internal knots (at 90 days, 6 months, 1 year)	1080.6
1 internal knot (at 1.5 years)	1078.1
Default 2df (1 internal knot: 50 centiles)	1078.1
Default 3df (2 internal knots: 33, 67 centiles)	1080.0
Default 4df (3 internal knots: 25, 50, 75 centiles)	1080.1
Default 5df (4 internal knots: 20, 40, 60, 80 centiles)	1082.7

Abbreviations: AIC, Akaike information criterion; df, degrees of freedom. The positions of the knots sit on the noted centiles of the distribution of uncensored log event-times.

Survival curves and difference in mortality rate, survival by SES

Figure 5.2 shows survival curves derived by (a) FPM with SES treated as proportional, and (b) the Kaplan-Meier method. It is apparent that the graph (a) disagrees with the graph (b), meaning that the assumption of the proportional hazard among SES groups in the FPM may not be suitable. The survival curves of the most and the least deprived groups cross each other in the Kaplan-Meier graph. The crossed curves indicate that the effect of SES interacts with time. Therefore, SES was treated as a TVE having an internal knot at 1.5 years from diagnosis using FPM in the graph (c). Graph (c) agrees with the curves derived by the Kaplan-Meier method in the graph (b). However, as shown in Table 5.6, the AIC of the FPM with SES treated as proportional was smaller than that of the FPM with TVE. The log- cumulative hazards and mortality rates by five SES groups, when SES is treated as proportional, are shown in Figure 5.2 (d) and (e). The curves of the mortality rate for the least and the most deprived groups run closely together, and there is no ordered gradient by SES group.

Table 5.6 AIC of FPMs with SES (proportional or TVE), Osaka University Hospital, Japan

Model	AIC
SES (proportional)	1078.0
SES (TVE)	1084.7

Abbreviations: AIC, Akaike information criterion; SES, socioeconomic status; TVE, time-varying effect.

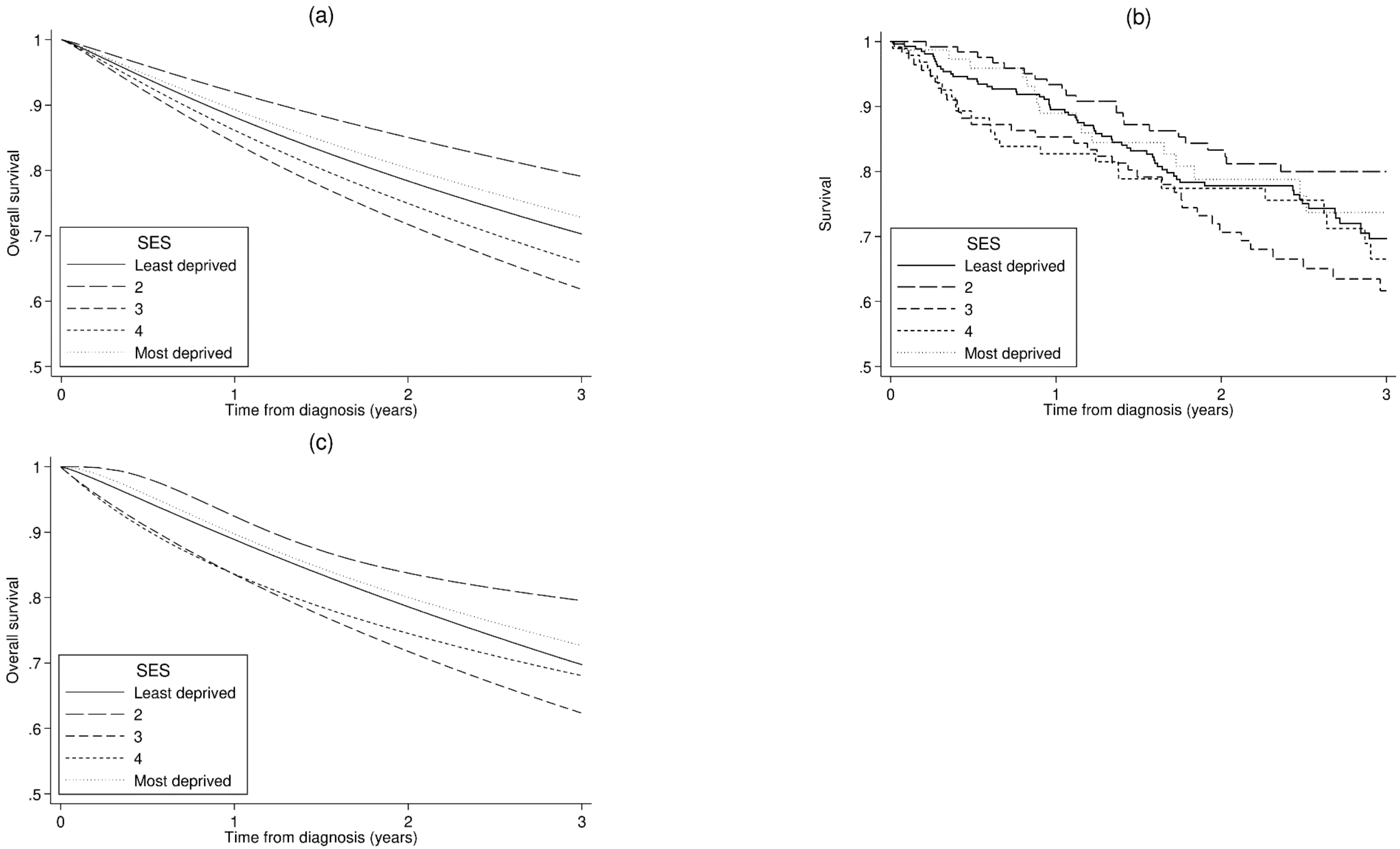

Figure 5.2 (a) Overall survival curves by FPM (SES as proportional) (b) survival curves by Kaplan-Meier method (c) survival curves by FPM (SES treated as time-varying effect) for colorectal cancer, Osaka University Hospital, Japan

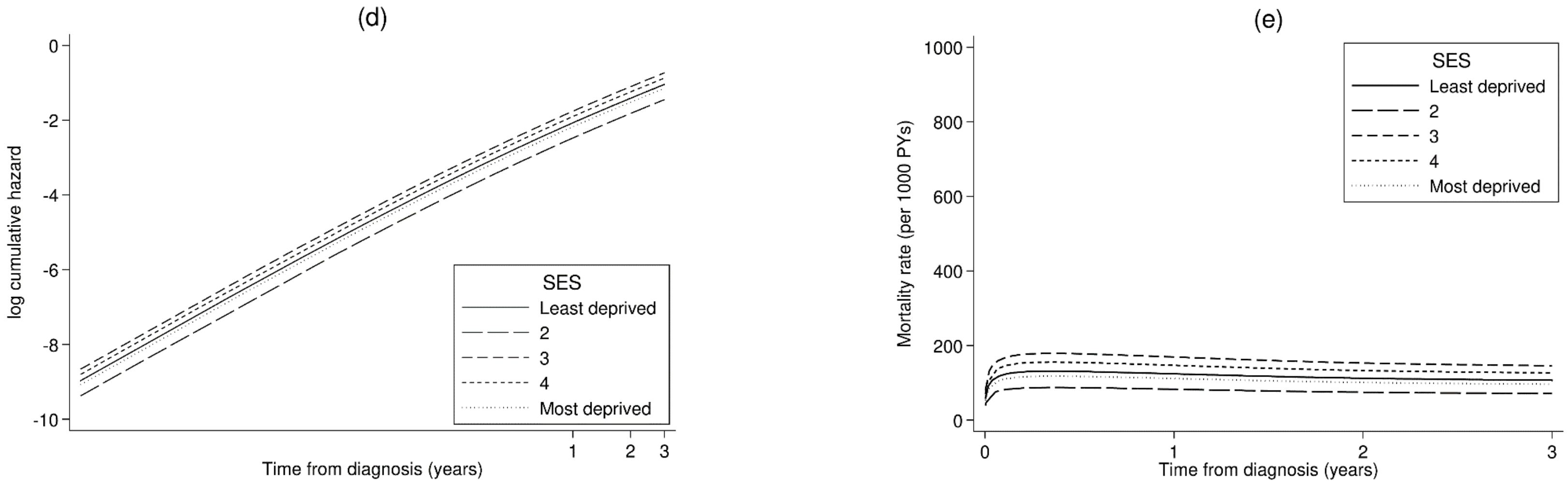

Figure 5.2 continued. (d) Log-cumulative hazards (e) mortality rates by SES group for colorectal cancer, Osaka University Hospital, Japan (SES treated as proportional)

Abbreviations: 1000 PYs, 1000 person-years; SES, socioeconomic status.

Figure 5.3 visualises the differences in mortality rate and survival. All graphs show that there is no strong evidence of a difference in survival between the least and the most deprived groups throughout time until the 3-year point from diagnosis.

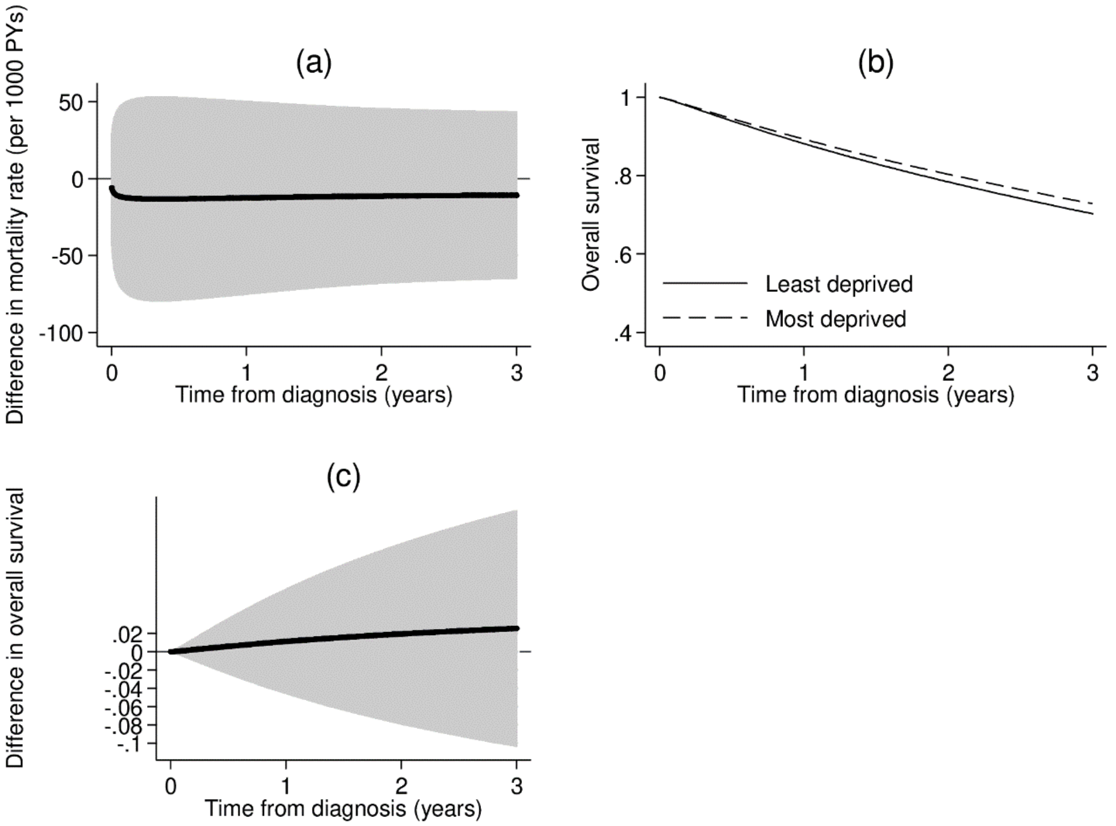

Figure 5.3 (a) Difference in mortality rate per 1000 PYs (b) overall survival (%) in the most and least deprived groups (c) difference in overall survival (%) between the most and the least deprived groups for colorectal cancer, Osaka University Hospital, Japan

Abbreviations: 1000 PYs, 1000 person-years. (a) Difference between the least and the most deprived groups. (c) A positive value means that the most deprived group has better survival than the least deprived group.

5.2.3 Summary of findings

When no potential related factors were adjusted, there was no clear socioeconomic trend in overall survival. The hazard of death appeared proportional by SES; however, the graphs show that the difference between the most and the least deprived groups, in terms of mortality rate and survival, is close to zero.

5.3 Factors associated with survival and socioeconomic inequalities in survival

In **Chapter 5.2**, general patterns of survival by SES group was demonstrated, without adjusting for any other factors. In this sub-chapter, I explored factors associated with survival and examined whether survival varied by SES after adjusted for the associated factors.

5.3.1 Methods

Outcome measure

As with the analyses of the England data (**Chapter 4.4**), I conducted three analyses in this sub-chapter. In the first and second analysis, I explored mortality rate ratios (i.e. HR of death) by SES and potential factors associated with survival. In the third analysis, measures of difference by SES group were presented graphically. The entry for all the survival analyses was the date of diagnosis. Three graphical measures were presented by each stage for overall survival: difference in mortality rates between the least deprived group (SES 1) and the most deprived group (SES 5), survival curves of the SES 1 and the SES 5 and survival difference of the two SES groups. Since there is no lifetable by SES for deriving net survival for Osaka Prefecture, I analysed overall survival only.

Analysis strategy

Firstly, I fitted Cox regression to explore associated factors for survival. Both imputed and completed data were used for the Cox regression analysis. I started with bivariable analysis for all potential factors one at a time with the main effect (SES) included. The variables which had strong evidence for association (at $p<0.05$ significance level at the Wald test) with the outcome were retained to a multivariable model. Variables were further removed by backward elimination. An interaction term between SES and stage was added as the main interest.

Secondly, for each variable in the final multivariable Cox regression model with completed data, I tested the proportional hazard assumption based on Schoenfeld residuals. If a variable did not hold the proportional hazard assumption, I next fitted an FPM with the same variables selected in the final Cox regression model and treated the variable as a TVC. As in **Chapter**

4.4, Cox regression analysis using imputed data was considered as a sensitivity analysis. Histology, tumour grade, emergency presentation and obesity were excluded from this analysis because of insufficient observations in each group. Age at diagnosis and sex were included as *a priori* confounders. In the FPM, the positions of the knots for both SES and non-TVCs were set at a time point of 1.5 years since diagnosis only. If there were any TVCs in the multivariable FPM, the knot was also set at 1.5 years since diagnosis.

Lastly, in the third analysis, differences in mortality rate and overall survival were shown with figures using the multivariable FPM fitted in the second analysis.

5.3.2 Results

First analysis (Cox regression for overall survival and hazard ratios by SES)

The first analysis using Cox regression included 480 patients in completed data and 710 patients in imputed data. Table 5.7 presents the HRs in bivariable and multivariable analyses. To show the overall change in the effect of SES, the adjusted HRs of SES in those tables were based on a model without interaction between SES and stage. For the rest, adjusted HRs were based on the multivariable model with interaction between SES and stage (final model).

Factors associated with survival

Table 5.7 demonstrated no clear trend in the adjusted HRs of SES. Male, older age, metastatic stage, presence of comorbidities and low ADL were associated with worse survival in completed data. The adjusted mortality rate for female patients was half that of male patients. Stage and ADL confounded the effect of sex on survival. Patients aged 70+ had more than double the adjusted mortality rate compared with patients under 60 years old. Patients with comorbidities had double the adjusted mortality rate that of patients with no comorbidities. Patients with low ADL had more than 2.5 times higher adjusted mortality rate compared with the patients with fit ADL. The route was not associated with survival. Receipt of surgery was not associated with survival in completed data, but sensitivity analysis showed that patients who did not receive surgery had more than a twofold increase in the hazard of death compared with patients who received surgery.

Table 5.7 Hazard ratios of death using Cox regression for colorectal cancer, Osaka University Hospital, Japan

Variable	Bivariable analysis			Multivariable sensitivity analysis Multiple imputation (n=710)			Multivariable analysis Complete cases (n=480)		
	HR*	95% CI	p-value	HR**	95% CI	p-value	HR**	95% CI	p-value
SES									
1 (least deprived)	1.00		0.53	1.00		0.62	1.00		0.54
2	0.66	(0.41, 1.08)		0.77	(0.46, 1.27)		0.83	(0.42, 1.63)	
3	1.36	(0.90, 2.05)		1.29	(0.83, 2.02)		1.19	(0.65, 2.19)	
4	1.18	(0.74, 1.87)		1.25	(0.75, 2.07)		1.09	(0.54, 2.17)	
5 (most deprived)	0.89	(0.52, 1.55)		0.88	(0.50, 1.56)		0.56	(0.23, 1.36)	
Sex									
Male	1.00			1.00			1.00		
Female	0.90	(0.65, 1.23)	0.51	0.68	(0.48, 0.96)	0.03	0.56	(0.34, 0.93)	0.02
Age									
<60	1.00		<0.001	1.00		0.003	1.00		0.005
60–69	1.38	(0.88, 2.17)		1.27	(0.78, 2.09)		1.44	(0.70, 2.98)	
70–99	2.10	(1.38, 3.18)		1.93	(1.21, 3.07)		2.46	(1.22, 4.96)	
Year of diagnosis									
2012	1.00								
2013	0.72	(0.46, 1.12)	0.15						
2014	1.13	(0.74, 1.74)	0.57						
2015	1.40	(0.89, 2.19)	0.14						
Cancer site									
Colon	1.00		0.85						
Rectum	1.03	(0.75, 1.41)							
Stage									
No metastasis	1.00						1.00		
Metastasis	6.37	(4.49, 9.05)	<0.001				6.81	(3.36, 13.79)	<0.001
Stage§									
No metastasis	1.00			1.00					
Metastasis	6.70	(4.81, 9.33)	<0.001	5.91	(3.42, 10.21)	<0.001			

Table 5.7 continued

Variable	Bivariable analysis			Multivariable sensitivity analysis Multiple imputation (n=710)			Multivariable analysis Complete cases (n=480)		
	HR*	95% CI	p-value	HR**	95% CI	p-value	HR**	95% CI	p-value
Route									
Referral from clinics/hospitals	1.00								
Others	1.10	(0.76, 1.59)	0.62						
Major surgery for primary lesion									
Received	1.00			1.00					
Not received	3.63	(2.65, 4.97)	<0.001	2.45	(1.69, 3.57)	<0.001			
Number of acute comorbidities									
0	1.00						1.00		
1+	1.59	(1.04, 2.42)	0.03				1.99	(1.24, 3.19)	0.004
Number of acute comorbidities§									
0	1.00								
1+	1.34	(0.89, 2.01)	0.16						
Modified ADL									
Completely independent	1.00						1.00		
Need support	2.77	(1.75, 4.36)	<0.001				2.59	(1.54, 4.33)	<0.001
Modified ADL§									
Completely independent	1.00			1.00					
Need support	2.28	(1.36, 3.80)	0.002	2.47	(1.51, 4.02)	<0.001			
Brinkman index									
0	1.00								
>0	1.07	(0.72, 1.61)	0.73						
Brinkman index§									
0	1.00								
>0	0.98	(0.67, 1.44)	0.94						

Abbreviations: 95% CI, 95% confidence interval; ADL, activities of daily living; HR, hazard ratio; SES, socioeconomic status. * Adjusted for SES in all variables. **All variables are mutually adjusted. For SES only, adjusted HRs are shown without interaction between SES and stage. For other variables, interaction between SES and stage is adjusted. † P-value of Wald test. ‡ P-value of Wald test for trend. § Multiply imputed.

Hazard ratios of death by SES

Analyses of completed data demonstrated no clear socioeconomic gradient in the adjusted HRs (Table 5.8). A gradient towards increased HRs in the deprived groups was found only for non-metastatic stages with imputed data but with a high p-value for trend.

Bivariable analyses implied that ADL confounded the effect of SES on survival. The HR of the most deprived group was reduced by 15% when ADL was adjusted. Other factors influenced the socioeconomic inequalities in survival in a negligible magnitude in bivariable analyses.

Table 5.8 Stage-specific hazard ratios using multivariable Cox regression with interaction between SES and stage for colorectal cancer, Osaka University Hospital, Japan

	Multiple imputation[a]			Complete cases[b]		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
No metastasis						
SES						
1 (least deprived)	1.00		0.24	1.00		0.77
2	0.85	(0.40, 1.84)		0.78	(0.32, 1.88)	
3	1.14	(0.53, 2.45)		0.72	(0.29, 1.83)	
4	1.35	(0.65, 2.83)		1.03	(0.43, 2.49)	
5 (most deprived)	1.47	(0.67, 3.23)		0.82	(0.30, 2.24)	
Metastasis						
1 (least deprived)	1.00		0.72	1.00		0.55
2	0.72	(0.36, 1.43)		0.92	(0.32, 2.61)	
3	1.38	(0.77, 2.47)		1.87	(0.82, 4.26)	
4	1.18	(0.58, 2.37)		1.11	(0.35, 3.51)	
5 (most deprived)	0.54	(0.21, 1.36)		0.21	(0.03, 1.65)	

Abbreviations: HR, hazard ratio; SES, socioeconomic status. All p-values are of Wald test for trend. Model a: adjusted for sex, age, stage (imputed), major surgery, modified ADL (activities of daily living). Model b: adjusted for sex, age, stage, comorbidities, modified ADL.

Second analysis (Flexible parametric model for overall survival and hazard ratios by SES)

The first analysis using multivariable Cox regression with completed data was next applied to an FPM in the second analysis to address variables violating the proportional hazard assumption.

To identify TVCs, I checked the proportional hazard assumption in each variable of the multivariable Cox regression model derived in the first analysis. The proportional hazard assumption was violated only for SES. SES was treated as a TVE (time-varying 'effect' but not time-varying 'covariate' as SES is the main interest) in the FPM. Other variables, namely sex, age group, stage, comorbidities and ADL did not interact with time.

Factors associated with survival

As seen in the left column of Table 5.9, adjusted HRs of the non-TVCs in the FPM showed close agreement with the adjusted HRs in the Cox regression models (see also Table 5.7). There was no clear socioeconomic gradient, but patients who were male, in the older age groups, with metastatic stage, with comorbidities or with low ADL had a higher adjusted hazard of death compared with patients with the reference characteristics.

Hazard ratios of death by SES

The right columns of Table 5.9 show the point estimates of the adjusted HRs for SES at one year and 1.5 years since diagnosis when SES was treated as a TVE. In non-metastatic stages, when compared with the least deprived group, the hazard of death was smaller in the most deprived group at the 1-year point, but it increased at 1.5 years since diagnosis. In the metastatic stage, the most deprived group consistently had a lower hazard of death than the least deprived group.

Table 5.9 Hazard ratios of death and point estimates of stage-specific hazard ratios (overall survival) for time-varying effect at 1 year and 1.5 years since diagnosis using multivariable FPM with TVE and interaction between SES and stage for colorectal cancer, Osaka University Hospital, Japan

Variable			**Point estimate of time-varying effect**							
			No metastasis				**Metastasis**			
			1 year		**1.5 years**		**1 year**		**1.5 years**	
	HR*	**95% CI**	**HR****	**95% CI**	**HR****	**95% CI**	**HR****	**95% CI**	**HR****	**95% CI**
SES										
1 (least deprived)	1.00		1.00		1.00		1.00		1.00	
2	0.83	(0.43, 1.64)	1.18	(0.41, 3.41)	0.64	(0.24, 1.71)	1.21	(0.37, 3.91)	0.66	(0.20, 2.11)
3	1.21	(0.66, 2.21)	0.56	(0.20, 1.59)	0.66	(0.26, 1.69)	1.59	(0.65, 3.87)	1.87	(0.79, 4.43)
4	1.10	(0.55, 2.19)	1.16	(0.42, 3.22)	0.65	(0.23, 1.83)	1.04	(0.29, 3.73)	0.58	(0.15, 2.21)
5 (most deprived)	0.57	(0.24, 1.38)	0.90	(0.18, 4.63)	1.76	(0.55, 5.64)	0.22	(0.02, 2.33)	0.43	(0.05, 3.61)
Sex			**Proportional hazard assumption holds**				**Proportional hazard assumption holds**			
Male	1.00									
Female	0.54	(0.33, 0.89)								
Age			**Proportional hazard assumption holds**				**Proportional hazard assumption holds**			
<60	1.00									
60–69	1.41	(0.69, 2.89)								
70–99	2.31	(1.16, 4.63)								
Stage			**Proportional hazard assumption holds**				**Proportional hazard assumption holds**			
No metastasis	1.00									
Metastasis	7.01	(3.46, 14.23)								
Comorbidities			**Proportional hazard assumption holds**				**Proportional hazard assumption holds**			
0	1.00									
1+	1.92	(1.19, 3.07)								
Modified ADL			**Proportional hazard assumption holds**				**Proportional hazard assumption holds**			
Completely independent	1.00									
Need support	2.66	(1.59, 4.47)								

Abbreviations: 95% CI, 95% confidence interval; ADL, activities of daily living; HR, hazard ratio; SES, socioeconomic status. * All variables are mutually adjusted. For SES only, adjusted HRs are shown without interactions between SES and time, SES and stage. For other variables, interactions between SES and time, SES and stage are adjusted. ** All variables are mutually adjusted with interactions between SES and time, SES and stage. HRs of SES are stage-specific.

Third analysis (Graphical figures of measures of difference by SES)

From the FPM fitted in the second analysis, I estimated three measures of difference in graphs: difference in mortality rate between the least and the most deprived groups, survival curves of the two groups and survival difference between the two groups (Figure 5.4 to Figure 5.6). For all figures, results were shown by each sex and stage. Age group was set at under 60 years old, with no acute comorbidities and with fit ADL.

The hazard difference fluctuated around zero with wide 95% CIs in non-metastatic stages, whereas in metastatic stage, the difference was generally below zero throughout; the most deprived group had a lower mortality rate than the least deprived group for the metastatic stage only (Figure 5.4). As expected from the hazard difference, the survival curves of the least and the most deprived groups crossed at around the 1.5-year point, showing little difference between the two (Figure 5.5). The gap in overall survival between the two groups was estimated to be less than 1% for non-metastatic stages throughout. Overall survival was better in the most deprived group in the metastatic stage, with the difference reaching over 10% at the 3-year point since diagnosis; however, its lower 95% CI was on the boundary of 0% most of the time (Figure 5.6).

5.3.3 Summary of findings

Male, older age, presence of comorbidities and low ADL were associated with worse survival. The socioeconomic gradient in the HRs of death was not clear; however, the FPM, which treated SES as a TVE, estimated a favourable survival in the most deprived group for the metastatic stage.

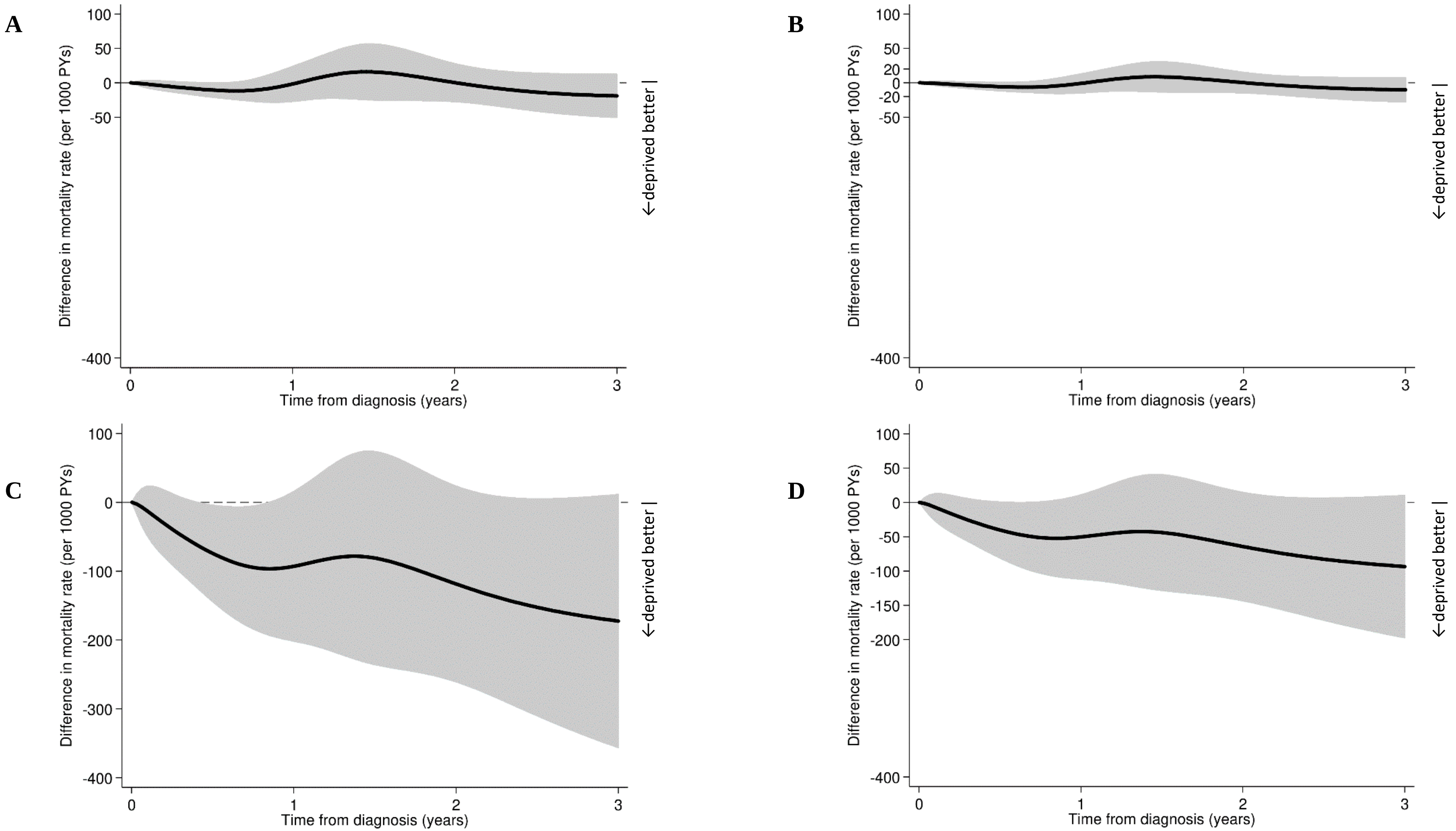

Figure 5.4 Hazard difference between the least and most deprived groups for colorectal cancer, Osaka University Hospital, Japan (A) Non-metastatic stages, male (B) non-metastatic stages, female (C) metastatic stage, male (D) metastatic stage, female

Abbreviations: 1000 PYs, 1000 person-years.

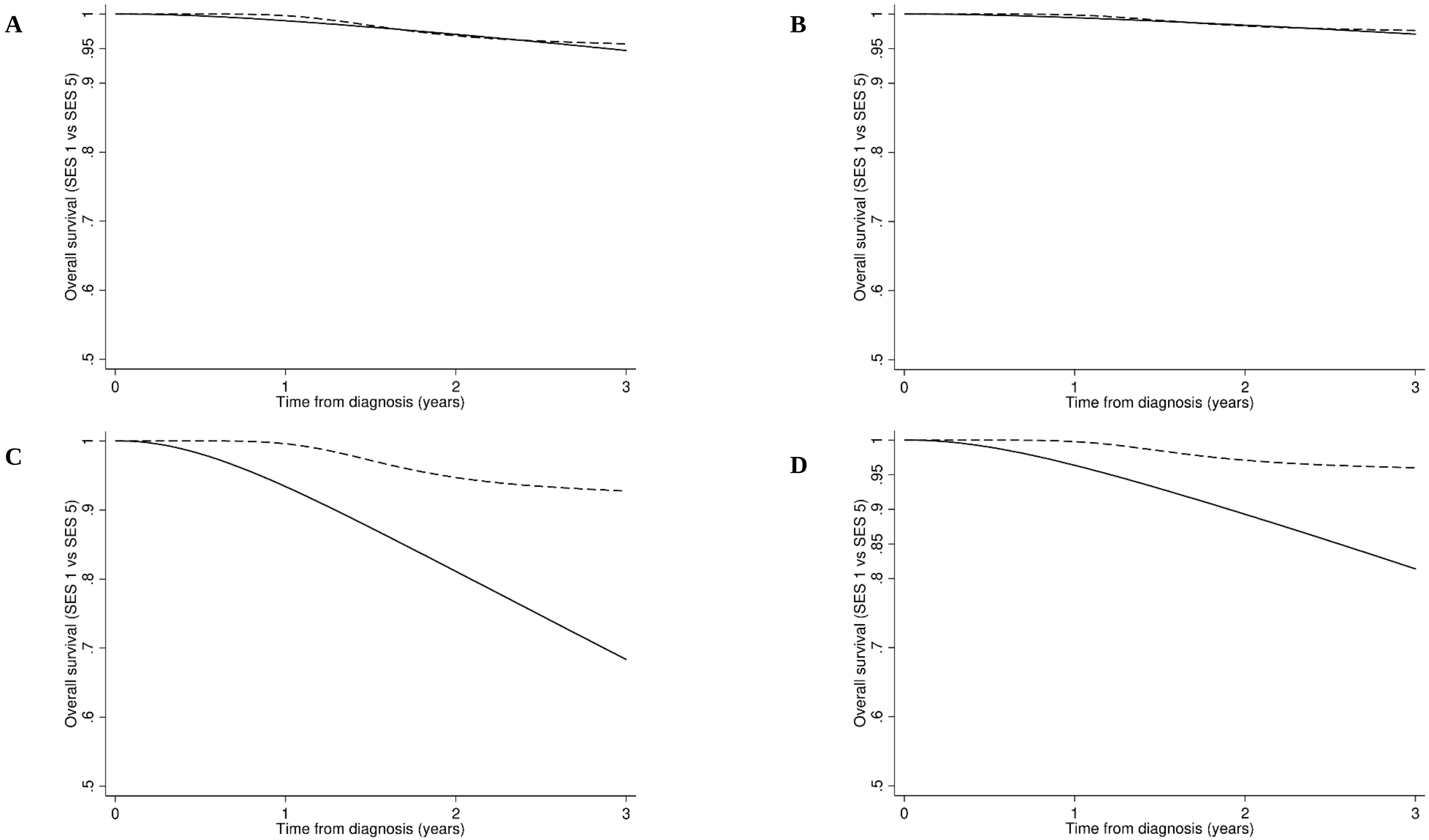

Figure 5.5 Overall survival of the least deprived group (SES 1, solid line) and the most deprived group (SES 5, dotted line) for colorectal cancer, Osaka, Japan (A) Non-metastatic stages, male (B) non-metastatic stages, female (C) metastatic stage, male (D) metastatic stage, female

Abbreviations: SES, socioeconomic status.

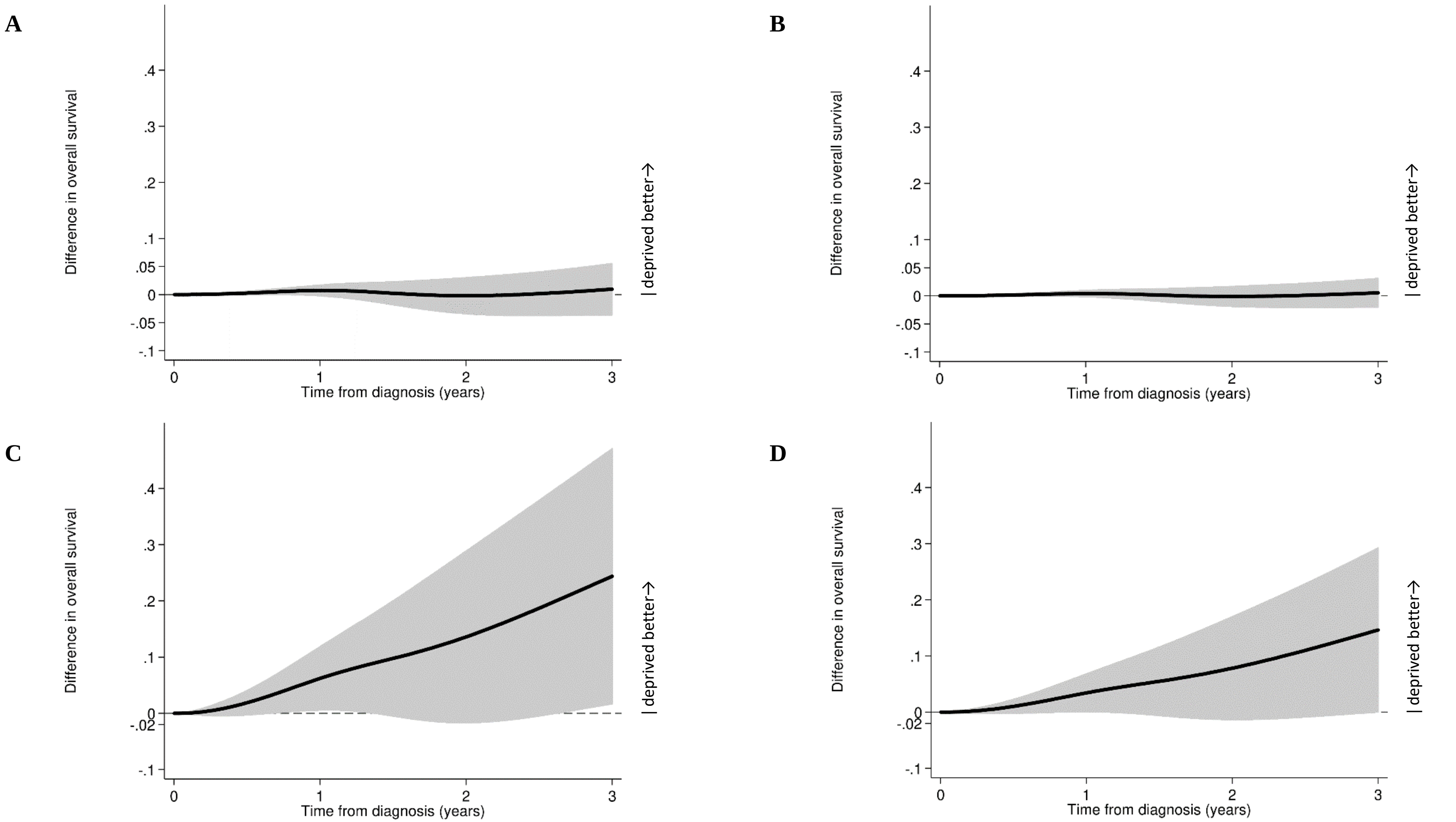

Figure 5.6 Difference in overall survival between the least and the most deprived groups for colorectal cancer, Osaka, Japan
(A) Non-metastatic stages, male (B) non-metastatic stages, female (C) metastatic stage, male (D) metastatic stage, female

5.4 Discussion

5.4.1 Socioeconomic inequalities in receipt of surgery

Patients with CRC at OUH were generally less deprived and the characteristics of the patients, including stage, did not vary among SES groups. There was weak evidence that the deprived groups were more likely to receive major surgery in non-metastatic stages; however, an additional analysis confirmed that patients who did not receive surgery at OUH mostly had localised or metastatic stage. Among the patients who did not receive surgery at OUH, the affluent groups were more likely to have a localised stage. Records on treatment plan reinforced the evidence that patients, who did not receive surgery at OUH, were referred to other hospitals or received some treatment/follow-up at OUH. Patients with a potential for cure, who did not receive major surgery and were followed up at OUH, developed metastasis to other organs after diagnosis or had severe comorbidities. To conclude, it is likely that, except the patients who failed to attend, all patients with CRC at OUH, irrespective of their SES, received stage-appropriate care.

As seen in England, time to treatment did not vary by SES. In a particular setting like a teaching hospital in the present analysis, patients who were already followed up for other diseases before diagnosis of CRC, may be prioritised to continue CRC treatment at the same hospital. Further analysis showed that patients who were not referred from clinics had lower ADL ($p<0.001$, chi square test).

The mean time from diagnosis to treatment at OUH was slightly longer than that observed in England. The finding is in line with a previous study, which showed a longer time to treatment in teaching hospital settings [153]. Patients with rectal cancer may have a longer time to treatment since the assessment of stage and resectability in rectal cancer requires additional diagnostic tests (e.g. MRI, ERUS). The present analysis also showed that some patients who received surgery more than 180 days after diagnosis mostly had neoadjuvant therapy. In England, the distribution of days in time to treatment for rectal cancer showed a truncated figure when surgery information was restricted to 180 days since diagnosis. When analysing time to surgical treatment, especially for rectal cancer, information on surgical treatment may need to be captured for a longer period.

In **Chapter 2**, I described the characteristics of the healthcare system in Japan is that specialists exist in the primary care level. As we can see, 70% of the patients were diagnosed as CRC in other clinics or hospitals before consultation at OUH. The fact reflects that diagnosis is mainly made in the primary care level. Referral to other hospitals also reflects the healthcare system in Japan, which offers free movement among institutions. To avoid possibly longer waiting times in teaching hospitals, patients that do not require complex treatment strategies or highly advanced surgical techniques, such as colon cancer cases, may be likely to be referred to non-teaching hospitals.

However, considering that large proportion of CRC patients in Osaka Prefecture are treated in non-teaching hospitals, patients coming to OUH (both referrals from other clinics/hospitals and self-referral) are likely to have caused selection bias in the study population. There are no referral criteria for PCPs of which patients to refer to OUH; thus, referral to OUH largely depends on a patient's preference. In addition to the unique settings of teaching hospitals, when investigating socioeconomic inequalities in survival, data from a single hospital may not be suitable, as a selection bias occurs in that situation.

5.4.2 Socioeconomic inequalities in survival

The difference in overall survival for non-metastatic stages was almost null. Overall survival was estimated to be better in the most deprived group for the metastatic stage only but with very wide 95% CIs.

The two findings for non-metastatic stages: no socioeconomic difference in receipt of care, and no difference in survival, suggest that no conclusion can be drawn from this analysis. Using the situation of a randomised controlled trial for example; in the OUH setting, the baseline characteristics being similar among SES groups means that the characteristics are matched among SES groups, but intervention has only one arm (i.e. equal treatment for all SES groups). If there is no other arm for comparison (e.g. unequal treatment for different SES groups), we cannot conclude that the outcome, equal survival among SES groups, is due to the intervention (equal treatment).

The potential reasons for not observing inequalities can be related to statistical problems. The number of patients was small, and the patients were heavily skewed to a higher SES in a single institution. The wide CIs in all analyses also imply that the statistical power for detecting the difference in important characteristics may be weak. The data in the present study were from a single institution, but a previous study that reported socioeconomic inequalities in survival used population-based data from multiple institutions [2].

Although patients at OUH might have selection bias, within the selected population, both care and survival were equally achieved by SES. Within-hospital variation of care is unlikely; however, inter-hospital variation may exist. Indubitably, stage may also be one of the potential contributors for observing the inequalities.

5.4.3 Strengths and limitations

The strength of the analysis at OUH is that important clinical information, such as stage, comorbidities, BMI, Brinkman index and ADL was available for more than 70% of the total cases. Information on surgery was recorded not only for CRC but also for other diseases. ADL and detailed information on surgery and comorbidities enabled identification of the clinical characteristics of the patients.

This analysis, which includes the most recent years, also presented that most of the surgery was laparoscopic rather than open, and that ICU use was mostly limited to the patients with severe comorbidities, which required major surgeries. Neoadjuvant therapy use at OUH was low, being approximately 10% of all rectal cancer cases.

One limitation is the size and specific characteristics of the study population. The data were from one university hospital in an affluent area. The results of the analysis on receipt of surgery showed the specific features of teaching hospitals, where patients with low ADL or who are being followed up for other diseases were more likely to receive surgery at the same hospital.

Since the population is not representative of the whole population in Osaka Prefecture, the patterns of receipt of cancer care and survival may be not applicable to the general population. Another limitation may be the use of DPC data. Unlike HES data in England, DPC is a costing data similar to diagnosis-related groups. Comorbidities might not be recorded in DPC if no costs for the comorbidities were incurred in the hospital episode. Thus, misclassification of the comorbidities may occur.

Lastly, I could not analyse net survival because there are no lifetables based on SES. Future studies should include more patients from multiple institutions and investigate net survival.

Chapter 6: Discussion

6.1 Main findings

This study demonstrated socioeconomic gaps in survival graphically, over time by each stage, using multivariable FPM incorporating comorbidities. The results in **Chapter 4** revealed that, among patients with stage II and III, who have a potential for cure, a survival gap existed for both cancers in England.

Surgical treatment was relatively equally received in patients with colon cancer. However, higher postoperative mortality in the deprived groups suggests that the quality of care received may have varied by SES.

To the best of our knowledge, this study employed mediation analysis for the first time to examine the magnitude of the effect of patient, tumour and treatment factors on survival inequalities in CRC. Although treatment was not received equally among different SES groups in rectal cancer, results of the mediation analyses imply that intervening on the inequalities in receipt of surgical treatment may not reduce the survival inequalities. Disparities in the distribution of stage, comorbidities and emergency presentation played an essential role in the survival inequalities. However, for both cancers, around 50% of the survival inequalities remain unexplained.

For Japan, this study assessed the socioeconomic differences in receipt of care and survival at one of DCHs. Disease stage, comorbidities, surgical treatment and survival were equally distributed among SES groups within a single hospital, which provides an inconclusive answer for the inequalities in survival observed previously.

6.2 Strengths and limitations

All analyses were based on routinely collected data, such as cancer registry data, HES or DPC. The use of national cancer registry data linked with clinical information from HES provided an overall picture of how patient factors (age, sex and comorbidities), tumour factors (site, stage, histology and tumour grade) and healthcare system factors interact and affect survival at the national level. For Japan, this study investigated the mechanism of socioeconomic inequalities in survival incorporating detailed clinical factors using DPC data.

The analyses in England included important tumour factors, i.e. not only stage but also tumour grade and histology. One limitation is that the difference by SES, in terms of some histological types (mucinous, signet-cell carcinoma *vs* other adenocarcinomas), was not explored. This was because some CRC were recorded without detailed histological information (e.g. neoplasm, carcinoma) in both countries. These histological types (around 10% of total colon cancer and 5% of total rectal cancer cases in England, and 5% of total cases in Japan) were grouped into adenocarcinoma; thus, misclassification may exist.

The time to treatment did not vary among different SES groups for colon cancer in England. The truncated distribution in time to treatment for rectal cancer suggests that some patients may have received surgery after 180 days. The data in Japan supported the prolonged time to treatment in patients with rectal cancer who received neoadjuvant therapy. Because of the high use in neoadjuvant therapy, treatment options and timeline for rectal cancer may be complex and challenging to capture, particularly in the European countries. There is evidence that the delay in adjuvant therapy is related to poorer survival [229, 230]. However, there is mixed evidence on whether other delays affect survival [176]. As Walter *et al.* (2012) suggested, the definition of ‘delay’ is not clearly defined, and time to treatment should be measured in time intervals (e.g. days) to make studies comparable [177]. Further research is needed to explore which kind of intervals, and to what extent it matters to survival.

Regarding the time from diagnosis to treatment, the advantage of using linear regression is that the actual figures of the days can be derived. Some studies obtained HRs using Cox regression for examining socioeconomic difference in time to treatment [133, 156, 157, 159]; however, the assumption in such a regression is that all patients will have the outcome (in time to treatment analysis, the outcome is receipt of surgery) if followed up long enough after the right-truncation in time. The assumption is, in reality, not correct; some patients will receive treatment, but some will not, or will die before receiving treatment. Cure models can be used [231], or death can be treated as a competing risk for treatment [232]; however, for the patients who died before receiving treatment, it will never be known whether they had or had not been planning to receive treatment before their death. Therefore, I derived the outcome in days by linear regression rather than HRs by Cox regression. Hazard ratios are not easily clinically interpretable, and the results in the present study provide the average day to treatment, which is meaningful clinically and for public health.

When analysing time to treatment, patients who received urgent operation were removed. I defined ‘urgent operation’ as the surgery performed within seven days of diagnosis. The cut-off days defined may be arbitrary; however, while the patients who received surgery within three days of diagnosis exceeded 25% of all patients who received surgery, the patients who received surgery four to seven days from the date of diagnosis included 2.1% for colon cancer patients in England. Therefore, the cut-off days for the definition of urgent operation are considered to make little change in the results.

I extracted data on comorbidities based on Charlson comorbidity index but separated acute and chronic comorbidities. I assumed that the two variables (acute/chronic) on comorbidity reflect correctly the health status of the patients. Information on some key comorbidities may be missing differentially by deprivation because the index does not capture severity for some comorbidities. However, it would then reinforce the hypothesis of inequalities in care by SES in the healthcare system. One can notice that, after adjusting for individual factors, difference in probability of receiving surgery by SES weakened (but there is a strong gradient by comorbidity); these results by SES would be difficult to explain if the information on comorbidity was biased. The disadvantage of lack of information on severity of comorbidities might have been affected the results of analysis in this thesis though it is assumed that distinguishing acute and chronic comorbidities improved collection of information on performance status. How chronicity and severity of the comorbidities affect socioeconomic inequalities in cancer care and survival would be important to investigate in further studies.

Comorbidities were categorised in four groups with counted numbers, and only the trend among the groups was explored with the Wald test. Th categorisation may lose power regarding dose-response effect [233]; thus, splines or fractional polynomials could be further sought. The benefit of fractional polynomials is that estimation of the dose-response effect, confounding the effect of SES on an outcome, can be estimated in a smoothed line. However, the number of comorbidities would never take a non-discrete number, and less than 1% of patients had three or more comorbidities. The present analyses aimed to identify the association between comorbidities and outcomes but not the prediction of the outcomes. For those reasons, there will be no benefit seeking splines or fractional polynomials in the dose-response effect of the comorbidities. For predicting outcomes, assessment of individual comorbidity and clinical data with more detailed information would be appropriate [234-237].

The difference in HRs and survivals between the least and the most deprived groups was estimated using FPM. Previous studies used Cox regressions to explore associated factors and derive HRs by SES. For clinical and public health perspective, measures of difference may be more useful to describe socioeconomic inequalities. The estimations derived by FPM may be biased since the estimations can be used only for completed data but not for imputed data (i.e. FPM currently does not support multiply imputed data). Regarding the data from England, 55.4% of total patients with colon cancer and 59.1% of patients with rectal cancer were analysed using FPM. For data in Japan, 67.6% of total patients were analysed. However, sensitivity analysis enabled the estimation of bias; considering the results of sensitivity analyses using imputed data in Cox regression, particularly for England, the socioeconomic differences in mortality rate and survival may be underestimated.

Lastly, ecological measures, i.e. IMD for England and ADI for Japan, were used to define SES. We are aware that the ecological measures may differ from the individual level of deprivation, and misclassification may exist. The misclassification may lead to either of underestimation (e.g. dilution effect [238]) or overestimation of the observed inequalities in treatment and survival, as seen in a previous study in Japan [239]. ADI was built using an approach similar to EDI (European Deprivation Index). ADI and IMD are not comparable. However, when measuring inequalities in cancer survival at the population level, it was demonstrated that the most important element was the size of the area how the indices are defined, rather than the type of measure [238].

6.3 Future studies

Multilevel analysis was not used for the data from England, which is one of the limitations of this study. Data of hospitals were not available at around 10%. Multilevel imputation could not be conducted since the hospital information is likely to be missing systematically. Considering both surgeons and hospital facilities may influence the postoperative outcomes, using hospital rather than Trust as the cluster level is likely to be more appropriate, particularly for surgical treatment; however, the multilevel imputation model may contain interactions and become complex, which leads to convergence problems [240]. The lack of considering the random effect is also problematic in mediation analysis. For instance, the effect of a mediator on an outcome (e.g. surgical treatment as a mediator and 90-day mortality as an outcome) is likely to differ by hospital. However, the consistency assumption underlying the mediation analysis does not allow such difference (random effect) among hospitals [241]. In that case, categorising hospitals by volume or specialisation [141, 242-244], and including the variable as a mediator-outcome confounder affected by exposure may be applied in future research (Figure 6.1).

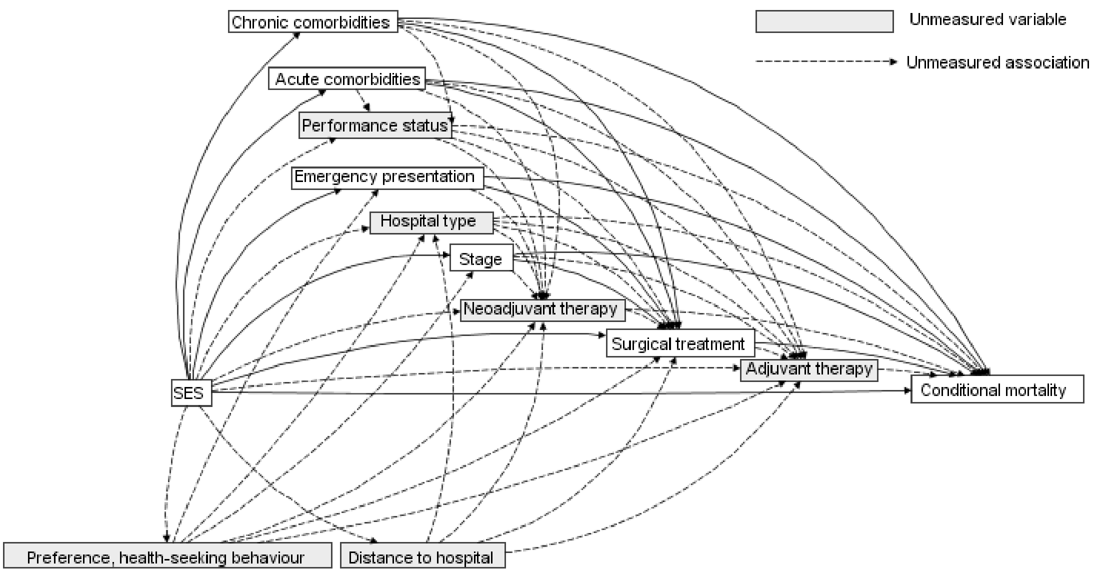

Figure 6.1 DAG including important unmeasured factors

Hospital type can be categorised by hospital volume or specialist type.

As discussed in **Chapter 4.6**, the results for England implied several unmeasured confounders. Important factors related to both SES and receipt of treatment could be a patient's preference or health-seeking behaviour. If preference is the reason for a patient not choosing care, no judgement can be made to deem it unfair. However, the clear socioeconomic gradient in emergency presentation and survival suggests that the situation is caused systematically. Persistent inequalities are seen in those figures in England [245, 246], also suggesting that the situation may have some room for improvement. Health-seeking behaviour may influence time to diagnosis or mode of presentation [111, 220]. Some previous studies suggest that the distance or time to hospital, rather than SES, is associated with inequalities in receipt of cancer care [118, 149, 154]. In Japan, patients in the low SES group cited distance as one reason for the delay in seeking healthcare [92]. When it comes to the inequalities in receipt of cancer care, it is essential to distinguish between disparities in geographical access to treatment and disparities in quality of treatment [111]. Information on performance status or ASA grade was also missing in the data from England. As seen in the analyses in Japan, performance status (measured as ADL) may influence survival independently from comorbidities. Although ADL and comorbidities apparently represent similar meanings of the general condition of a patient, the collinearity of the two variables was only 13.8%.

Other important unmeasured treatment factors are the use of neoadjuvant and adjuvant therapy. The patient pathway map and literature review in **Chapter 2** demonstrated growing evidence of inequalities in every step of cancer care in CRC. In addition to the receipt of surgical treatment, investigating socioeconomic variations in the use of chemotherapy or radiotherapy, in relation to survival, would be of interest for CRC. For colon cancer in England, the survival gap was most significant in stage III (**Chapter 4.4.2**). On the contrary, for rectal cancer, the survival gap was smallest in stage III. These results indicate that the use of chemotherapy, for colon cancer, may also have influenced the survival inequalities, and the rectal cancer patients who underwent surgery might be the selected groups of patients, who have received neoadjuvant therapy.

Lastly, in relation to the 30-day postoperative mortality, further details for the quality of postoperative care were not explored in this thesis because of large proportion of missingness in postoperative complications and stoma procedure.

6.4 Recommendations for England and Japan

Findings of this thesis and supplemental information are summarised in Table 6.1.

Table 6.1 Summary of findings and general statistics in England and Japan

	England	Japan
Localised (stage I)	Colon 8.6% Rectum 16.6%	51.3% (OUH, colon and rectum) 25.7% (DCHs, colon and rectum, UICC stage, 2008)*
Distance metastasis (stage IV)	Colon 22.5% Rectum 19.0%	17.0% (OUH) 20.1% (DCHs, colon and rectum, UICC stage, 2008)*
Emergency presentation	Colon 24.5% Rectum 11.1%	3.6% (OUH) No data nationwide

England: all figures are from analyses in this thesis. Japan: figures in upper lines are from analyses in this thesis. Figures in lower lines are from national statistics. * Source: Cancer Statistics in Japan ’16 [247]. Data provided from 296 DCHs.

In England, when compared with Japan, Table 6.1 demonstrates that, the percentage of the patients diagnosed with a localised stage is much smaller than in Japan, and a substantial percentage of the patients present emergently. The fact may suggest barriers in access to both diagnosis and treatment.

For the patients with emergency presentations, firstly, triaging the vital emergency (e.g. obstruction and perforation) cases is necessary. Patients without vital emergency should then return to the normal patient pathway. In both vital and non-vital emergency cases, patients should have safe operations and managed by specialist surgeons. To improve the quality of care, two ways may be selected: centralisation of specialised-team hospitals: or to keep the distribution of hospitals and aim to improve the quality of care as a whole. The first choice may be easier and less costly. However, geographical access may be hampered; thus, socioeconomic inequalities may become worse. Considering that colon cancer is common and large number is expected nationwide, the latter choice may reduce socioeconomic inequalities in cancer care access, and then survival. Also, screening uptake may have effect on reducing emergency presentation [248]. In future studies, relationship among SES, screening uptake, emergency presentation and survival should be investigated.

For Japan, information at the prefecture or national level was not able to obtain in this study. Therefore, existence of socioeconomic inequalities in both cancer care and survival was unclear and yet to be studied. Not only from DCHs but also non-DCHs, data are needed to be examined for inequalities. Linkage of other databases, such as national clinical database, may be effective to capture the disparities in clinical management. National clinical database includes detailed information on comorbidities, surgery (procedure, operation time and amount of blood loss) and complications of each case. Further studies and recommendations may include topics as follows.

- **Future studies and recommendations for England**
  - *Future studies*
    - Triage of emergency presentations: identification of vital emergency cases and non-vital emergency cases.
    - Identification of reason for socioeconomic inequalities in postoperative mortality especially for colon cancer cases (e.g. operation by specialists or non-specialists).
    - Assessment of quality of postoperative care by SES: exploration of stoma rates, complication rates, failure to rescue rates by SES.
    - Further assessment of receipt of treatment: exploration of receipt of chemotherapy, radiotherapy by SES.
    - Collection of individual data on screening uptake and emergency presentation to examine the relationship between screening uptake and accessibility to diagnosis in different SES.
  - *Recommendations*
    - Reduction of emergency presentation
    - Promote safer surgery operated by specialist surgeons to reduce the survival gap between the least and the most deprived patients.
- **Future studies and recommendations for Japan**
  - *Future studies*
    - Assessment of quality of postoperative care by SES: linkage of national cancer registry data, DPC data and nationwide clinical database.
  - *Recommendations*
    - Collection of data at the prefectural or national level not only from DCHs but also from non-DCHs to capture differential access to cancer care.

An important point in the healthcare system is that the funding and resources in healthcare are not public good (public good: a service or a good, which is non-excludable and non-rival in consumption). If we pursue the goal of ‘equity in a health outcome’, it may mean that someone improves but some others decrease their health. We are also aware that socioeconomic inequalities in a health outcome are often seen, but not all of them are ‘inequity’, which is considered unfair [249]. Priority should be set for solving the inequalities [249]. Needless to say, the mechanism of how the socioeconomic inequalities in health (in this thesis, cancer survival) occur, may involve multifactorial pathways, with complex interactions between the healthcare system and biological, behaviour, lifestyle and environmental factors of a patient, but not a single dominant pathway [250, 251]. Although the proportion of the patients diagnosed without symptoms is small, reports suggest that socioeconomic inequalities in screening participation exist in both countries [252-254]. The difference in up-stream factors (e.g. lifestyle and behavioural/environmental factors) is not easily modifiable. However, understanding the potential mechanisms and magnitude of the healthcare effect on survival inequalities would provide insight into which level of change can be made in the healthcare systems and into what aspects efforts should be expended.

The WHO guideline on referral policy recommends that the potential for curative therapy should be assessed at the primary care level [255]. It also mentions the pointlessness of referring advanced-stage patients to major hospitals, since these patients may only be offered palliative care. Colorectal cancer has a good chance for cure if diagnosed, treated and followed up appropriately and in a timely manner; therefore, there is a good reason for prioritising reduction of the socioeconomic gap in CRC survival. This thesis aims to understand the role of the healthcare system and the potential for improving equity further by amending healthcare access. The access has already been greatly ensured by the UHC, and it is expected to be modifiable by minor changes in the present system.

6.5 Conclusion

In England, socioeconomic inequalities in survival existed for CRC patients with the stages of potential for cure. Reducing emergency presentation for both colon and rectal cancer and improving postoperative care for colon cancer may reduce the survival inequalities. For rectal cancer, further study is needed to understand the mechanism of the survival inequalities.

In Japan, further investigation with a larger population is needed to capture the survival inequalities and understand its mechanism.

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Appendix 1 Ethics approvals

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LONDON SCHOOL *of* HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Prof Michel Coleman
Professor of Epidemiology and Vital Statistics
Department of Non-communicable Disease Epidemiology (NCDE)
Epidemiology and Population Health (EPH)
LSHTM

6 April 2018

Dear Michel

Study Title: Cancer Survival Programme

LSHTM Ethics Ref: 11984

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	Michel Coleman CV 6 Sep 2016	01/09/2016	1
Investigator CV	Bernard Rachet CV October 2016	03/10/2016	1
Protocol / Proposal	Cancer Survival Programme protocol for Leo	08/11/2016	1
Local Approval	17CAG0012 approval letter 13 Mar 2017	13/03/2017	1
Local Approval	13-LO-0610 111683 Ack of APR 06.04.2017	06/04/2017	1
Local Approval	PIAG 3-06(f) 2008 annual review outcome letter 2017	08/05/2017	1
Local Approval	16.LO.0450_Acknowledgment_of_progress_report_21.07.17	21/07/2017	1
Local Approval	PIAG 1-05(c) 2007 annual review outcome 31-08-2017	31/08/2017	1
Local Approval	REC Reference 07_MRE01_52 _ Acknowledgement of progress report 04 01 18	04/01/2018	1
Covering Letter	Response to LSHTM ethics questions_11984	08/03/2018	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

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Mari Kajiwara
RD Student
LSHTM

13 August 2018

Dear Mari,

Re: Research Degree Project

Thank you for submitting further information following the audit initiated by Professor Della Freeth, former Pro-Director (Learning & Teaching) in 2017. The aim of the audit was to assure the School that all Research Degree (RD) candidates had obtained the appropriate approvals before they start their projects.

The Research Governance Committee considered the initial results of this audit and recommended further action. As a result, a sub-group of the Research Governance Committee reviewed RD projects without valid LSHTM ethics approval in their name, as this has been a requirement since 2014.

As members of this sub-group of the Research Governance Committee, we have reviewed your project and supporting documents. We are satisfied that the aims and analyses are sufficiently detailed in your supervisor(s)' project, LSHTM ref 11984 as well as local approvals.

Should other data collection or analytical methods not detailed in the existing ethics approval be required for your project, please submit an application to the LSHTM ethics committee prior to any further data collection or analysis of the data/tissue.

Should you have any queries, please contact Patricia Henley in the first instance.

Yours sincerely,

[redacted]	[redacted]	[redacted]
Prof Sasha Shepperd	**Prof Audrey Prost**	**Ms Patricia Henley**
Pro-Director Learning	Head of the Doctoral College	Head of Research Governance & Integrity

Cc Bernard Rachet, EPH

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LONDON SCHOOL *of* HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Mrs Mari Saito
LSHTM

28 January 2019

Dear Mari,

Study Title: Cancer survival under causal inference framework using linked dataset (in-hospital cancer registry data and Diagnosis Procedure Combination data) (Japan)

LSHTM Ethics Ref: 16219

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Mari Kajiwara Research Plan OsakaUni 2018 JAPAN	19/07/2018	1
Local Approval	Mari Kajiwara Ethical Approval OsakaUni 2018 JAPAN	30/08/2018	1
Investigator CV	2018_CV_Mari_Kajiwara_Saito	14/11/2018	1
Protocol / Proposal	2018 Mari Kajiwara Saito English Translated Japan Research Plan OsakaUni JAPAN	15/11/2018	1
Investigator CV	CV SSR_Rachet_July 2018	15/11/2018	1
Covering Letter	Cover Letter Mari Kajiwara Saito 16219	17/01/2019	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

[redacted]
Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

様式 3

承認番号	18127

Approval number: 18127

西暦 2018 年 08 月 30 日

審査結果通知書

Notification of Ethical Review

国立大学法人　大阪大学医学部附属病院長　殿

Dear Director of the Osaka University

国立大学法人　大阪大学医学部附属病院
観察研究倫理審査委員会委員長
祖父江　友孝　公印省略

Chair
Observational Research Ethics Committee
Osaka University
Tomotaka SOBUE

審査依頼のあった件について審査結果を下記のとおり通知します。

The further information has been considered.

記

課　題　名 Study title	院内がん登録情報と電子カルテ（診療録）のリンケージによるがん生存率の因果推論的研究 Cancer survival using linked dataset (hospital-based cancer registry data and Diagnosis Procedure Combination data)
審　査　事　項	■研究の実施の可否 □研究の継続の可否 □重篤な有害事象　□安全性情報等　□研究に関する変更 □研究計画書からの逸脱　□継続審査 □その他 ()
審　査　区　分	□委員会審査 ■迅速審査 □審査対象外
審　査　結　果 Results	■承認　□条件付き承認 □修正の上承認　□却下 □既に承認した事項を取り消す [□中断　□中止　□その他：　] □保留する Approved
「承認」以外の場合の理由	
研　究　期　間 Duration of the study	2018 年 08 月 30 日　～　2019 年 03 月 31 日　30 Aug 2018 to 31 March 2019
備　考	

西暦 2018 年 08 月 30 日
30 Aug 2018

研究責任者

診療科（部）名：環境医学

職　名：准教授

氏　名：喜多村祐里　殿

Chief Investigator
Enviromental Medicine and Population Sciences,
Department of Social Medicine
Associate Professor
Dr Yuri Kitamura

依頼のあった研究に関する審査事項について上記のとおり決定しましたので通知致します。

国立大学法人　大阪大学医学部附属病院長
木村　正　公印省略

Appendix 2 Histology grouping

Histological group	
Adenocarcinoma	papillary adenocarcinoma (pap)
	tubular adenocarcinoma (tub)
	medullary carcinoma (med)
	poorly differentiated adenocarcinoma (por)
	mucinous adenocarcinoma (muc)
	signet-ring cell carcinoma (sig)
	undifferentiated carcinoma
	villous adenocarcinoma
	tubulovillous adenocarcinoma
	neoplasm
	carcinoma
Adenosquamous and squamous cell carcinoma	adenosquamous carcinoma (asc)
	squamous cell carcinoma (scc)
	mixed types of epithelial tumours
	goblet cell carcinoid of appendix*
Non-epithelial tumour and others	adenocarcinoid tumour
	carcinoid tumour**
	endocrine cell carcinoma**
	neuroendocrine tumour (NET: WHO)
	carcinoid tumour of appendix
	non-epithelial tumour (mesenchymal tumour)
	lymphoma
	malignant melanoma
	others

Modification from sources: WHO Classification of Tumours Pathology and Genetics of Tumours of the Digestive System 4th edition (2010) and Japanese Classification of Colorectal Carcinoma 8th edition (2013).

* Goblet cell carcinoid of appendix was categorised as a sub-type of adenocarcinoma (epithelial tumour) in Japanese Classification of Colorectal Carcinoma 8th edition.

** Endocrine cell tumours (carcinoid tumour and endocrine cell carcinoma) in Japanese Classification of Colorectal Carcinoma 8th edition were classified as one of the NET in WHO Classification of tumours of the colon and rectum 4th edition.

Appendix 3 Operation code and name for colon cancer, England

OPCS code	
H04.1	Proctocolectomy NEC, Panproctocolectomy and Ileostomy
H04.2	Panproctocolectomy and anastomosis of ileum to anus and creation of pouch HFQ
H04.3	Panproctocolectomy and anastomosis of ileum to anus NEC
H04.8	Other specified total excision of colon and rectum
H04.9	Panproctocolectomy NEC, Total excision of colon and rectum, unspecified-
H05.1	Total colectomy and anastomosis of ileum to rectum
H05.2	Total colectomy and ileostomy and creation of rectal fistula HFQ
H05.3	Total colectomy and ileostomy NEC
H05.8	Total excision of colon, other specified
H05.9	Total excision of colon, Unspecified
H06.1	Extended right hemicolectomy and end to end anastomosis
H06.2	Extended right hemicolectomy and anastomosis of ileum to colon
H06.3	Extended right hemicolectomy and anastomosis NEC
H06.4	Extended right hemicolectomy and ileostomy HFQ
H06.8	Other specified extended excision of right hemicolon
H06.9	Extended excision of Right hemicolon, unspecified, excision of Right colon and surrounding tissue
H07.1	Right hemicolectomy and end to end anastomosis of ileum to colon, Ileocaecal resection
H07.2	Right hemicolectomy and side to side anastomosis of ileum to transverse colon,
H07.3	Right hemicolectomy and anastomosis NEC
H07.4	Right hemicolectomy and ileostomy HFQ
H07.8	Other specified other excision of right hemicolon
H07.9	Other excision of right hemicolon, unspecified; Right hemicolectomy NEC
H08.1	Transverse colectomy and end to end anastomosis
H08.2	Transverse colectomy and anastomosis of ileum to colon
H08.3	Transverse colectomy and anastomosis NEC
H08.4	Transverse colectomy and ileostomy HFQ
H08.5	Transverse colectomy and exteriorisation of bowel NEC (CODE COLOSTOMY SPERATELY)
H08.8	Other specified excision of transverse colon
H08.9	Excision of transverse colon, unspecified
H09.1	Left hemicolectomy and end to end anastomosis of colon to rectum
H09.2	Left hemicolectomy and end to end anastomosis of colon to colon
H09.3	Left hemicolectomy and anastomosis NEC
H09.4	Left hemicolectomy and ileostomy HFQ
H09.5	Left hemicolectomy and exteriorisation of bowel NEC (CODE COLOSTOMY SEPERATELY)
H09.8	Excision of left hemicolon, Other specified
H09.9	Left hemicolectomy NEC, Excision of left hemicolon, Unspecified
H10.1	Sigmoid colectomy and end to end anastomosis of ileum to rectum
H10.2	Sigmoid colectomy and anastomosis of colon to rectum
H10.3	Sigmoid colectomy and anastomosis NEC

Appendix 3 continued (Operation code and name for colon cancer, England)

H10.4	Sigmoid colectomy and ileostomy HFQ
H10.5	Sigmoid colectomy and exteriorisation of bowel NEC
H10.8	Other specified excision of sigmoid colon
H10.9	Unspecified excision of sigmoid colon
H11.1	Colectomy and end to end anastomosis of colon to colon NEC
H11.2	Colectomy and side to side anastomosis of ileum to colon NEC
H11.3	Colectomy and anastomosis NEC
H11.4	Colectomy and ileostomy NEC
H11.5	Colectomy and exteriorisation of bowel (CODE COLOSTOMY SEPERATELY)
H11.8	Other excision of colon, other specified
H11.9	Hemicolectomy NEC; Colectomy NEC, Other excision of colon, unspecified;
H29.1	Subtotal excision of colon and rectum and creation of colonic pouch and anastomosis of colon to anus
H29.2	Subtotal excision of colon and rectum and creation of colonic pouch NEC
H29.3	Subtotal excision of colon and creation of colonic pouch and anastomosis of colon to rectum
H29.4	Subtotal excision of colon and creation of colonic pouch NEC
H29.8	Subtotal excision of colon, Other specified
H29.9	Subtotal excision of colon, Unspecified
H33.1	Abdominoperineal excision of rectum and end colostomy; APR; SCAPER
H33.2	Proctectomy and anastomosis of colon to anus
H33.3	Anterior resection of rectum and anastomosis of colon to rectum using staples
H33.4	Anterior resection of rectum and anastomosis NEC
H33.5	Hartmann procedure, Rectosigmoidectomy and closure of rectal stump and exteriorisation of bowel (CODE COLOSTOMY SEPERATELY)
H33.6	Anterior resection of rectum and exteriorisation, (CODE COLOSTOMY SEPARATELY)
H33.7	Perineal resection of rectum HFQ
H33.8	Anterior Resection of Rectum NEC, Rectosigmoidectomy and anastomosis of colon to rectum Excision of rectum, other specified
H33.9	Rectosigmoidectomy NEC, Excision of rectum, unspecified;
H34.1	Open excision of lesion of rectum: Open removal of polyp; Yorke Mason
H40.1	Trans-sphincteric excision of mucosa of rectum
H40.2	Trans-sphincteric excision of lesion of rectum
H40.8	Other specified operations on rectum through anal sphincter
H40.9	Unspecified operations on rectum through anal sphincter
X14.1	Total exenteration of pelvis
X14.3	Posterior exenteration of pelvis
X14.8	Other specified clearance of pelvis

Appendix 4 Operation code and name for rectal cancer, England

OPCS code	
H04.1	Proctocolectomy NEC, Panproctocolectomy and Ileostomy
H04.2	Panproctocolectomy and anastomosis of ileum to anus and creation of pouch HFQ
H04.3	Panproctocolectomy and anastomosis of ileum to anus NEC
H04.8	Other specified total excision of colon and rectum
H04.9	Panproctocolectomy NEC, Total excision of colon and rectum, unspecified-
H05.1	Total colectomy and anastomosis of ileum to rectum
H05.2	Total colectomy and ileostomy and creation of rectal fistula HFQ
H05.3	Total colectomy and ileostomy NEC
H05.8	Total excision of colon, other specified
H05.9	Total excision of colon, Unspecified
H06.1	Extended right hemicolectomy and end to end anastomosis
H06.2	Extended right hemicolectomy and anastomosis of ileum to colon
H06.3	Extended right hemicolectomy and anastomosis NEC
H06.4	Extended right hemicolectomy and ileostomy HFQ
H06.9	Extended excision of Right hemicolon, unspecified, excision of Right colon and surrounding tissue
H07.1	Right hemicolectomy and end to end anastomosis of ileum to colon, Ileocaecal resection
H07.2	Right hemicolectomy and side to side anastomosis of ileum to transverse colon,
H07.3	Right hemicolectomy and anastomosis NEC
H07.4	Right hemicolectomy and ileostomy HFQ
H07.8	Other specified other excision of right hemicolon
H07.9	Other excision of right hemicolon, unspecified; Right hemicolectomy NEC
H08.1	Transverse colectomy and end to end anastomosis
H08.3	Transverse colectomy and anastomosis NEC
H08.4	Transverse colectomy and ileostomy HFQ
H08.5	Transverse colectomy and exteriorisation of bowel NEC (CODE COLOSTOMY SPERATELY)
H08.8	Other specified excision of transverse colon
H09.1	Left hemicolectomy and end to end anastomosis of colon to rectum
H09.2	Left hemicolectomy and end to end anastomosis of colon to colon
H09.3	Left hemicolectomy and anastomosis NEC
H09.4	Left hemicolectomy and ileostomy HFQ
H09.5	Left hemicolectomy and exteriorisation of bowel NEC (CODE COLOSTOMY SEPERATELY)
H09.8	Excision of left hemicolon, Other specified
H09.9	Left hemicolectomy NEC, Excision of left hemicolon, Unspecified
H10.1	Sigmoid colectomy and end to end anastomosis of ileum to rectum
H10.2	Sigmoid colectomy and anastomosis of colon to rectum
H10.3	Sigmoid colectomy and anastomosis NEC
H10.4	Sigmoid colectomy and ileostomy HFQ
H10.5	Sigmoid colectomy and exteriorisation of bowel NEC
H10.8	Other specified excision of sigmoid colon

Appendix 4 continued (Operation code and name for rectal cancer, England)

H10.9	Unspecified excision of sigmoid colon
H11.1	Colectomy and end to end anastomosis of colon to colon NEC
H11.2	Colectomy and side to side anastomosis of ileum to colon NEC
H11.3	Colectomy and anastomosis NEC
H11.4	Colectomy and ileostomy NEC
H11.5	Colectomy and exteriorisation of bowel (CODE COLOSTOMY SEPERATELY)
H11.8	Other excision of colon, other specified
H11.9	Hemicolectomy NEC; Colectomy NEC, Other excision of colon, unspecified;
H29.1	Subtotal excision of colon and rectum and creation of colonic pouch and anastomosis of colon to anus
H29.2	Subtotal excision of colon and rectum and creation of colonic pouch NEC
H29.3	Subtotal excision of colon and creation of colonic pouch and anastomosis of colon to rectum
H29.4	Subtotal excision of colon and creation of colonic pouch NEC
H29.8	Subtotal excision of colon, Other specified
H29.9	Subtotal excision of colon, Unspecified
H33.1	Abdominoperineal excision of rectum and end colostomy; APR; SCAPER
H33.2	Proctectomy and anastomosis of colon to anus
H33.3	Anterior resection of rectum and anastomosis of colon to rectum using staples
H33.4	Anterior resection of rectum and anastomosis NEC
H33.5	Hartmann procedure, Rectosigmoidectomy and closure of rectal stump and exteriorisation of bowel (CODE COLOSTOMY SEPERATELY)
H33.6	Anterior resection of rectum and exteriorisation, (CODE COLOSTOMY SEPARATELY)
H33.7	Perineal resection of rectum HFQ
H33.8	Anterior Resection of Rectum NEC, Rectosigmoidectomy and anastomosis of colon to rectum Excision of rectum, other specified
H33.9	Rectosigmoidectomy NEC, Excision of rectum, unspecified;
H34.1	Open excision of lesion of rectum: Open removal of polyp; Yorke Mason
H34.2	Open cauterisation of lesion of rectum, Diathermy
H34.5	Open destruction of lesion of rectum NEC
H34.8	Open removal of lesion of rectum, other specified
H40.1	Trans-sphincteric excision of mucosa of rectum
H40.2	Trans-sphincteric excision of lesion of rectum
H40.3	Trans-sphincteric destruction of lesion of rectum
H40.8	Other specified operations on rectum through anal sphincter
H40.9	Unspecified operations on rectum through anal sphincter
X14.1	Total exenteration of pelvis
X14.2	Anterior exenteration of pelvis
X14.3	Posterior exenteration of pelvis
X14.8	Other specified clearance of pelvis
X14.9	Clearance of pelvis, unspecified

Appendix 5 List of chronic and acute comorbidities

Chronic comorbidities	Count	Acute comorbidities	Count
Chronic heart failure	1	Chronic heart failure	1
Dementia	1	Dementia	1
Chronic pulmonary disease	1	Chronic pulmonary disease	1
Connective tissue disease	1	Connective tissue disease	1
Diabetes mellitus with end organ complication	1	Diabetes mellitus with end organ complication	1
Hemiplegia	1	Hemiplegia	1
Chronic renal disease, moderate to severe	1	Chronic renal disease, moderate to severe	1
Liver disease, moderate to severe	1	Liver disease, moderate to severe	1
HIV (Human Immunodeficiency Virus) infection	1	HIV (Human Immunodeficiency Virus) infection	1
Malignancy (not colorectal cancer)	1	Myocardial infarction	1
		Peripheral vascular disease	1
		Cerebrovascular disease	1
		Peptic ulcer disease	1
		Malignancy (not colorectal cancer)	1

Chronic comorbidities were defined as the medical conditions that were recorded 0.5–5 years before diagnosis of colorectal cancer.

Acute comorbidities were defined as the medical conditions that were recorded for the first time 0–0.5 years before diagnosis of colorectal cancer.

In England, both chronic and acute comorbidities were used. In Japan, only acute comorbidities were used.

Appendix 6 Operation code and name for colorectal cancer, Japan

K7191	Colectomy (partial)
K7192	Colectomy (hemicolectomy)
K719-21	Laparoscopic colectomy (partial or hemicolectomy)
K719-22	Laparoscopic colectomy (total or subtotal)
K7193	Colectomy (total, subtotal resection or operation for malignancy)
K719-3	Laparoscopic colectomy for malignancy
K719-5	Total colectomy and proctectomy with anastomosis of pouch and anal canal
K720	Resection of colon tumour by laparotomy (including cecum tumour resection)
K7391	Transanal resection of rectal tumour (including polyp resection)
K7393	Resection of rectal tumour (laparotomy or transanal)
K7401	Proctectomy
K7402	Low anterior resection
K7403	Proctectomy, resection of rectum (super low anterior resection) (transanal anastomosis of colonic pouch and anal canal)
K7404	Proctectomy, resection of rectum
K740-21	Laparoscopic proctectomy
K740-22	Laparoscopic low anterior resection
K740-23	Laparoscopic resection of rectum
K645	Total exenteration of pelvis

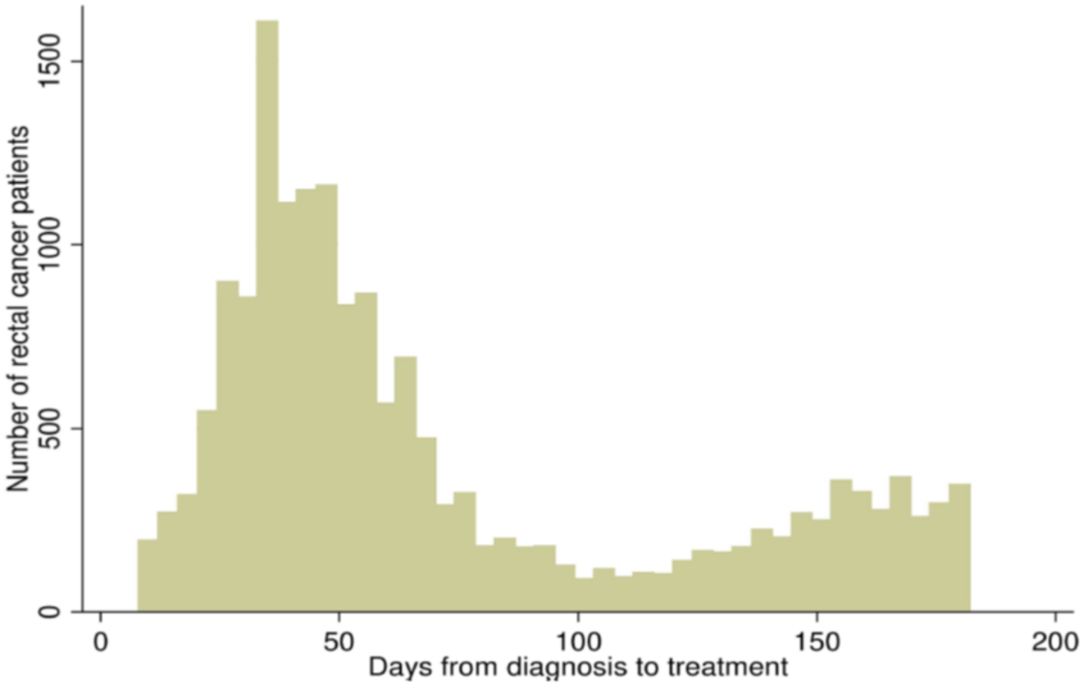
Appendix 7 Distribution of imputed variables, England

Colon cancer	**SES**				
	1 (affluent)	**2**	**3**	**4**	**5 (deprived)**
Stage (%)					
I	13.7	12.7	13.0	12.2	12.2
II	27.1	27.6	26.6	25.9	26.4
III	25.4	25.5	24.8	24.8	25.0
IV	33.8	34.2	35.6	37.0	36.4
Histology (%)					
Adenocarcinoma	97.9	97.9	97.9	97.8	97.5
asc, scc	0.3	0.4	0.4	0.4	0.4
Non-epithelial tumours	1.7	1.7	1.7	1.8	2.1
Tumour grade (%)					
Well/moderately differentiated	79.4	79.6	78.9	79.8	79.7
Poorly/undifferentiated	20.6	20.4	21.1	20.2	20.3
Emergency presentation (%)					
No	75.3	73.5	72.6	70.2	66.6
Yes	24.7	26.5	27.4	29.8	33.4

Rectal cancer	**SES**				
	1 (affluent)	**2**	**3**	**4**	**5 (deprived)**
Stage (%)					
I	23.9	22.3	22.7	21.0	20.1
II	20.7	20.6	20.3	21.1	19.8
III	29.4	29.9	29.7	29.1	29.6
IV	26.0	27.1	27.3	28.8	30.5
Histology (%)					
Adenocarcinoma	97.5	97.8	97.2	97.1	96.4
asc, scc	1.1	1.2	1.4	1.5	1.5
Non-epithelial tumours	1.4	1.1	1.3	1.5	2.1
Tumour grade (%)					
Well/moderately differentiated	86.6	87.0	85.7	85.9	86.1
Poorly/undifferentiated	13.4	13.0	14.3	14.1	13.9
Emergency presentation (%)					
No	90.1	89.0	87.8	86.3	82.9
Yes	9.9	11.0	12.2	13.7	17.1

Abbreviations: asc, adenosquamous cell carcinoma; scc, squamous cell carcinoma; SES, socioeconomic status.

Appendix 8 Distribution of time to treatment (days from diagnosis to major surgery) in rectal cancer patients, England



Appendix 9 Distribution of imputed variables, Japan

	SES				
	1 (affluent)	**2**	**3**	**4**	**5 (deprived)**
Stage (%)					
No metastasis	76.9	77.7	68.6	79.4	79.1
Metastasis	23.1	22.3	31.4	20.6	21.0
Number of comorbidities (%)					
0	80.7	77.0	69.5	73.7	69.1
1+	19.3	23.0	30.5	26.3	30.9
Brinkman index (%)					
0	64.6	61.5	58.6	67.9	64.8
>0	35.4	38.5	41.4	32.1	35.3
Modified ADL (%)					
Completely independent	54.3	59.6	40.8	46.5	51.7
Need support	45.7	40.4	59.2	53.5	48.3

Abbreviations: ADL, activities of daily living; SES, socioeconomic status.