EPIDEMIOLOGY OF UPPER GASTROINTESTINAL BLEEDING

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Abstract

Background There have been many conflicting changes in the prevalence of the risk factors for upper gastrointestinal bleeding and therefore it is not clear what the current trends in mortality or incidence are, nor which factors are important in driving these trends. As populations in many countries are ageing with an increasing burden of co-morbidity, this thesis investigates whether the relationship between non gastrointestinal co-morbidity and upper gastrointestinal bleeding might be an explanation for current trends. I hypothesised that non gastrointestinal co-morbidity was responsible for a large proportion of bleeds in the population and the deaths that occur following a bleed.

Methodology Large scale routine population based data records were used to assess the current incidence and mortality trends of upper gastrointestinal bleeding in England, as well as more in depth studies of predictors of its occurrence and subsequent mortality. The databases were examined and compared to external sources to assess their representativeness, and methods for defining cases in linked primary and secondary care were developed. The specific questions addressed in the studies were:

1. **What are the current trends and variations in occurrence of upper gastrointestinal bleeding?** Incidence rates and adjusted incidence rate ratios were calculated by quintiles of socioeconomic status, age group, sex, re-

gion, and calendar year.

2. **Has there been an improvement in 30 day mortality following upper gastrointestinal bleeding?** A nested case control study using Hospital Episodes Statistics from England 1999-2007 examined mortality trends by age, sex, co-morbidity and type of bleed.

3. **Does non gastrointestinal co-morbidity predict upper gastrointestinal bleeding?** A matched nested case control study used the linked Hospital Episodes Statistics and General Practice Research Database to examine non gastrointestinal co-morbidity as a risk factor adjusted for other known risk factors for bleeding. Sequential population attributable fractions were calculated to estimate what each risk factor contributed to the disease burden.

4. **What are the excess causes of death following upper gastrointestinal bleeding?** Causes of death by ICD 10 category were extracted following a bleed from the linked Office for National Statistics death register. Crude mortality rates and excess cumulative incidence functions were calculated; the latter adjusted for the competing risks between different causes of death.

Results

1. A higher incidence of upper gastrointestinal bleeding was observed in the north of England, but this variation was dwarfed by the variation associated with deprivation. Areas of greater deprivation had 2-3 fold higher rates of hospitalisation for upper gastrointestinal bleeding than areas of less deprivation suggesting that strong modifiable risk factors exist.

2. Over the last decade there was a 20% improvement in 28 day mortality fol-

lowing upper gastrointestinal bleeding, and those admitted with bleeding were increasingly older and had more co-morbidity.

3. A combined measure of non gastrointestinal co-morbidity was a significant independent predictor of upper gastrointestinal bleeding and explained a greater proportion of the burden of bleeding (19%) than any other risk factor in the population, including medications such as aspirin and NSAIDs.

4. More than half the absolute excess risk of death was due to co-morbidity not related to the upper gastrointestinal tract.

Conclusions Non gastrointestinal co-morbidity both strongly predicts an event of upper gastrointestinal bleeding, and is responsible for a large proportion of the subsequent long term mortality. The magnitude of the association in the population explains both why its incidence had not decreased, and why the improvements in mortality were observed irrespective of endoscopic management or bleed type. Furthermore a bleed can be an indicator for a re-assessment of the severity of co-existing non gastrointestinal morbidity.

Published papers from this thesis

1. Crooks, CJ, Card, TR, & West, J. (2011). Reductions in 28-day mortality following hospital admission for upper gastrointestinal hemorrhage. Gastroenterology, 141(1)62-70. doi: 10.1053/j.gastro.2011.03.048

2. Crooks CJ, West J, Card TR. (2012). Upper gastrointestinal haemorrhage and deprivation: a nationwide cohort study of health inequality in hospital admissions. Gut. 61(4)514-20. doi: 10.1136/gutjnl-2011-300186

3. Crooks CJ, Card TR, West J. (2012) Defining upper gastrointestinal bleeding from linked primary and secondary care data and the effect on occurrence and 28 day mortality. BMC health services research. 12(392). doi: 10.1186/1472-6963-12-392

4. Crooks, C. J., West, J., Card, T. R. (2013). Co-Morbidities Affect Risk of Non-Variceal Upper Gastrointestinal Bleeding. Gastroenterology. Published online ahead of print: doi: 10.1053/j.gastro.2013.02.040

5. Crooks, C. J., Card, T. R., West, J. (2013). Excess Long-Term Mortality following Non-Variceal Upper Gastrointestinal Bleeding: A Population-Based Cohort Study. PLoS medicine, 10(4), e1001437. doi: 10.1371/journal.pmed.1001437

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CHAPTER 1

Introduction

CHAPTER 1: INTRODUCTION:

Upper gastrointestinal haemorrhage is the commonest emergency medical admission for gastroenterology in the UK and has a significant inpatient mortality of 10%[1,2] that has not improved over the last two decades.[3–5] Although the overall incidence of gastro-duodenal ulcer bleeding has remained stable during the 1990s, in the elderly it increased by over 30%.[6,7] It is likely that this increase is related to higher rates of co-morbidities, increased prescriptions for these co-morbidities and interactions between the two. However outside of critical care, where primary prevention for stress ulceration is routinely prescribed, peptic ulceration is not thought to be related to co-morbidities.[8] Previous studies modelling the predictors of upper gastrointestinal haemorrhage have instead focused on medications, and have been limited by selected populations, small numbers, limited ascertainment of co-morbidities or failure to adjust for geographical variations.

As well as this increasing incidence, the elderly have a two fold higher long-term mortality following an episode of upper gastrointestinal haemorrhage compared to their controls.[9,10] However it is not known if this is caused by co-morbidity or whether the upper gastrointestinal haemorrhage itself increases the mortality. If such bleeding is a marker of coexisting morbidity and an associated decline in health, then focusing resources on improving acute treatment may not improve mortality. Instead a comprehensive approach to care focused on optimising the treatment of co-morbidities would be more effective, similar to that currently provided for elderly patients following hip fractures.[11]

It is vital to understand the current occurrence, outcomes and causes of upper gastrointestinal haemorrhage to inform and improve effective future management and service provision for patients. Therefore, after summarising the literature on the epidemiology of upper gastrointestinal bleeding I will address the following questions:

CHAPTER 1: INTRODUCTION:

1. What is the occurrence of upper gastrointestinal haemorrhage within England by region, year and deprivation?

2. Has there been a change in upper gastrointestinal mortality over the last decade?

3. Do co-morbidities predict the occurrence of upper gastrointestinal haemorrhage independently of known risk factors?

4. What are the causes of excess death following an upper gastrointestinal bleed?

CHAPTER 2

Background

This chapter will examine the previously published literature on the occurrence, causes and outcomes of upper gastrointestinal haemorrhage for both variceal and non variceal bleeding.

2.1 Clinical summary

Upper gastrointestinal haemorrhage is defined as acute bleeding into the lumen of the gastrointestinal tract above the ligament of Trietz, typically presenting with haematemesis or melaena. It is the commonest emergency medical admission for gastroenterology,[2] has an overall 28 day case fatality in the range 2-14%[3,12] and is associated with a significant burden on health care resources. Upper gastrointestinal bleeding is commonly categorised as variceal (from oesophageal or gastric varices) or non variceal bleeding. Non variceal bleeding is more common and can be further subdivided by its causes. The proportions of upper gastrointestinal bleeding admissions in each category are shown in table 2.1. Variceal bleeding is reported as a lower proportion of overall bleeds in larger population based studies than in hospital derived case series. However comparisons between studies are difficult as many hospital studies only report cases that had an endoscopy performed, therefore excluding a large proportion of patients who, without an endoscopy, do not have a specific category of bleed identified.

2.2 Occurrence and trends

2.2.1 Non variceal bleeding

The reported incidence of upper gastrointestinal bleeding varies widely as can be seen from table 2.2.

Table 2.1: Diagnoses of patients presenting with upper gastrointestinal haemorrhage

Country	Year	Restricted to endoscoped cases?	Mallory-Weiss syndrome	Erosive inflammation	Varices	Ulceration	Malignancy	Other	Unspecified diagnosis	Number
Hospital based studies										
Cameroon[13]	1990	Yes		22%	14%	47%				172
Israel[14]	1994	Yes		20%	13%	46%		21%		321
Kenya[15]	1994	Yes			35%	36%			7%	97
Canada[16]	2004	Yes		25%	***	50%			5%	2,484
Zambia[17]	2008	Yes	1%	18%	26%	29%	8%	3%	15%	179
Italy[18]	2008	Yes	5%	13%	***	66%	6%	2%	7%	1,844
Togo[19]	2010	Yes	11%	16%	18%	41%				44
Europe[20]	2011	Yes		33%	***	35%				2,655
England*[1]	2011	Yes	5%	59%	11%	36%	4%	3%	17%	5,004
Egypt[21]	2011	Yes	2%	12%	31%	31%	2%	8%	16%	724
Population based studies										
Scotland*[22]	1993		7%	47%	6%	28%	2%	7%	29%	1,882
England[23]	1993	No	5%	24%	4%	31%	4%	6%	25%	4,137
Crete[24]	1999	No		34%	4%	48%	3%	3%	7%	353
Netherlands[3]	2000	No		20%	7%	46%	5%	8%	14%	769
USA[12]	2006	No		12%	9%	34%		4%	41%	**
Wales[25]	2007	No	6%	24%	3%	22%	1%		44%	22,299
Italy[26]	2009	No	3%	14%	12%	50%	5%	9%	5%	539
USA[27]	2009	No		17%	2%	53%		15%		30,500****

*Multiple diagnoses allowed
**Percentages from the population extrapolated from the 20% national inpatient sample of admissions.
Blank cells = Information not available in paper
***These studies excluded variceal bleeds
****Percentages extrapolated from Premier Perspective hospital discharge database, a non random database representing 1 in 6 USA admissions.

Table 2.2: Variations in incidence of acute admissions for upper gastrointestinal bleeding

Year of estimate	Country	Number of bleeds for estimate	Crude Incidence per 100,000 person years	Indirect Age Standardised Incidence	95% Confidence Interval	Study type
1991[28]	USA	3,294	36*	71	(68 - 73)	139 Military facilities
1993[23]	England	3,508	89	77	(74 - 79)	74 hospitals in 4 regions
1993[22]	Scotland	1,720	157	135	(129 - 142)	19 hospitals in one region
1996[29]	France	2,133	84	73	(70 - 76)	29 hospitals in one region
1999[24]	Crete	21	149	137	(84 - 209)	All hospitals in one region
1999-2007[25]	Wales	22,299	119^{+}	99	(98 - 101)	National admissions database
2000[3]	Netherlands	769	48	45	(43 - 47)	10 hospitals in Amsterdam region
2002[30]	Scotland	211	99	83	(72 - 95)	Single Hospital
2003[4]	Canada	13,017	53**	50	(49 - 51)	National admissions database
2004[26]	Italy	21	74	59	(36 - 90)	Single Hospital
2005[31]	Greece	353	98	85	(76 - 94)	3 hospitals in one region
2006[32]	Spain	291	66	55	(49 - 62)	Single Hospital
2006[12]	USA	N/A	82***	89	(88 - 90)	National Inpatient Sample
2007[33]	Israel	864	17****	17	(16 - 18)	National admissions database
2009[27]	USA	30,500	61***	65	(64 - 66)	Premier Perspective database

Where the paper reports incidence trends over time the most recent incidence estimate is shown ($^{+}$apart from Button *et al* who report an average)
Blank cells = Information not available in paper
*Military population - standardised using 2010 military population estimates from the DoD, Population Representation of the Military Services, FY2010: table B-15
**More restrictive definition requiring combinations of codes for non ulcer codes
***Estimates from the population extrapolated from the 20% national inpatient sample without including or Primier Perspective database. Both estimates did not include unspecified bleeding which had an estimated admission rate of 56/100,000 and 53/100,000 population respectively in 2009.
****Only specific upper gastrointestinal bleed codes with a diagnosed underlying cause (e.g. no haematemesis, melaena or unspecified codes were included)

Recent large European and North American studies suggest figures for the incidence of upper gastrointestinal bleeding in the region of 50-100/100,000 person years. Though some of the geographical differences in incidence around the world are doubtless genuine, some of the variation in the figures may be a consequence of different case definitions, management systems, timing of studies and study methodology. For example a low incidence has been reported from a military population.[28] However the highest incidence estimates were reduced when indirectly standardised for age (table 2.2), and two of the lower incidence figures came from studies which used restrictive definitions of upper gastrointestinal bleeds.[33,34] Differences in clinical management may also account for some of the geographical variation when the case definition depends on hospitalisation; for example within the USA the proportion of patients managed without a hospital admission varied by more than two fold between states (19-45%).[35]

Regional incidence within one country can also vary widely. The incidence in north west Scotland has been estimated to be 172/100,000,[22] the incidence in Wales has been estimated to be 134/100,000,[25] and the incidence in middle England has been estimated to be between 43/100,000 around Oxford[36] to 103/100,000 around the Thames and the Midlands.[23]

The reason for these large regional differences within the UK is often thought to be deprivation. There is some prior, albeit limited, evidence of a socioeconomic gradient in this disease from two UK base studies. A small study of less than 2000 patients from the north west of Scotland demonstrated a 2 fold difference in the occurrence of upper gastrointestinal haemorrhage between the least and most deprived, while a recent report from Wales also indicated that those from most deprived areas have the highest rate of hospitalization for upper gastrointestinal haemorrhage.[22,25] However both these studies found higher hospitalisation rates than previous studies and this raises questions of how their popu-

lations and cases were defined. Furthermore both studies only reported crude combined variceal and non variceal haemorrhage estimates and their methodology and limited size mean they did not investigate whether differences in age, gender, year or region might be responsible for the socioeconomic gradient.

It is unclear to what extent changes in incidence over time are similarly explained, and to what extent they reflect changes in underlying risk factors. Over the last two decades many countries including the USA, Canada, Israel, Netherlands, Greece and Italy have reported reductions in overall upper gastrointestinal bleeding admissions of between 10 and 40%.[3,4,12,26,27,31,33] However, there are also some conflicting studies, particularly from peptic ulcers in older age groups.[6,7,25,37]

2.2.2 Variceal bleeding

In contrast to non variceal bleeding there is little literature on the occurrence of variceal bleeding separately from non variceal bleeding, but the proportions of variceal bleeding reported in the larger population based studies was between 3 and 9% (table 2.1) suggesting an incidence of between 2.1 and 8.1 per 100,000 person years. Reports from the USA National Inpatient Sample reported an 11% increase in variceal admission rates comparing 1998 to 2006,[12] but in another study in similar data comparing 2001 to 2009 there was a 9% decrease.[27] The studies did however use different code lists, hospitals contributing to the Premier perspective database might not be representative of the USA hospital population, and the sampling frame used for the USA National Inpatient Sample more than doubled in size over the study periods. A Swedish study found around 400 variceal bleed admissions a year, with a stable incidence between 4-6/100,000 since 1987.[38] In the UK the prevalence and incidence of cirrhosis is increasing,[39,40] but the effect on the occurrence of variceal bleeding is not

known.

2.2.3 Healthcare costs

Healthcare costs vary between countries, but the expense related to upper gastrointestinal bleeding is a consistently large proportion of these costs. Non variceal haemorrhage is associated with a median length of hospital stay of 4-5 days[1,35] and variceal haemorrhage 7-9 days.[41] Using the National Inpatient Sample from USA (restricted to patients who survived to discharge) the costs for an uncomplicated non variceal bleed were $3402 and when associated with complications $5632.[42] For variceal haemorrhage the costs were $6612 and $23,207 respectively. However within the USA a higher proportion of upper gastrointestinal haemorrhage admissions are managed in an ITU setting.[43] In contrast, lower estimates were derived from Canada for non variceal haemorrhage at $1883, and these costs increased with age and decreased with previous history of peptic ulcer disease. In Ireland the average cost for a non variceal haemorrhage admission is €2,537, however interestingly 75% of the expenditure is on patients with a Rockall score ≤ 3.[44] In England the National Health Service tariff pays £2,462 for an emergency admission for upper gastrointestinal bleed with complications, £1,268 without complications and £416 when patients are discharged the same day.[45] In the recent National Upper Gastrointestinal Bleed Audit 6% of patients were discharged the same day, and 26% had ongoing bleeding requiring further intervention or causing death.[46] This suggests a cost for the NHS in the region of £150,000,000 per 100,000 patients admitted with bleeding.

2.3 Mortality trends

2.3.1 Natural history

The natural history of a condition is the course it would take without an intervention and, for a frequently mortal condition such as upper gastrointestinal bleeding with established interventions we cannot simply observe this. What we can do is to look at the outcome of the condition with treatment, and how changes in therapy have altered mortality.

At the beginning of the 20th century hospital mortality from haematemesis and melaena due to peptic ulcers was reported to be over 20% for patients over 40 years old.[47] Mortality was higher in older patients and in those in whom bleeding recurred. The first advance in bleeding management was the use of generous blood transfusions guided by measured haemoglobin concentration given in a controlled intravenous drip.[48] Surgery was advocated following resuscitation when bleeding continued or reoccurred for those who were diagnosed with peptic ulceration, though the selection of patients and reported mortality varied widely and was controversial.[47,49] Indeed generous early eating regimes apparently demonstrated a strikingly low hospital mortality.[50]

However comparisons of the mortality from these early case series are difficult, as cases and deaths not thought to be due to be directly from bleeding, such as malignancy or cirrhosis, were often excluded.[47] Concerning this Lewin and Truelove commented "...it is noteworthy that the literature shows that most series with a low fatality rate have come from interested single physicians presenting their own cases, whereas studies of gross hospital figures commonly indicate a much less favourable prognosis....We believe that mass hospital figures are more truly representative of the dangers of haematemesis than are the results obtained by a few specialists, provided that the data are handled

with an appreciation of possible fallacies".[51] Lewin and Truelove's case series in 1949 (median age about 50 years) of all presentations with haematemesis and melaena in Oxford estimated a high mortality of 19% following chronic ulcers, 7% following acute ulcers, 24% following other diagnoses, and 33% where no diagnosis was made.

By the 1960-70s medical management was similar to that developed during the 1930s with early feeding and generous blood transfusions guided by haemoglobin measurement. Following medical management over 70% of peptic ulcer bleeds and 44% of variceal bleeds resolved with no further bleeding.[52,53] Surgery was mostly reserved for those with unstable ulcer bleeding, whereas other causes such as varices and gastric cancer where not amenable to emergency treatment. Gastroscopy was recommended acutely for early diagnosis where a barium meal was inconclusive.[54] In 1967-8 the overall mortality in Aberdeen was reported to be 14% for all admissions over 12 years old with haematemesis and melaena (median age about 60 years), but this increased to 29% if further bleeding occurred.[53] Age and co-morbidity were consistently predictors of further bleeding, and for specific diagnoses mortality for peptic ulcer bleeding was 5%, for variceal bleeding was 24%, for other causes was 47%, and for undiagnosed bleeding was 12%.

Over the last few decades improvements in endoscopic therapy have been shown to reduce risks of rebleeding, for example by the increased use of combination therapies[55] and variceal banding.[56] The use of proton pump inhibitors has been demonstrated to reduce stomach pH and promote clot stability,[57] a similar approach to that originally intended by early feeding. For variceal haemorrhage the use of antibiotics and glypression at the time of variceal bleeding has also been shown to reduce mortality.[58,59] At the same time that these improvements have been developed, the age of those admitted has risen. The median age of patients being admitted with bleeding from non variceal causes during the last

two decades is around 70 years old.[1,23]

2.3.2 Recent trends in short term case fatality for non variceal bleeding

There has been a wide variation of overall short term mortality from non variceal haemorrhage with low estimates from the USA and some of Europe, and higher estimates from elsewhere in Europe (see table 2.3). However mortality in longitudinal population cohorts of upper gastrointestinal bleeds remains unchanged at about 10-14%.[3,25] Increasing age and co-morbidity confounding the effects of therapy improvements have been proposed as the likely explanation.[60]

The consistent tendency noted at the start of the last century for co-morbidity and advanced age to predict worse short term outcomes has been extended by a number of authors to develop risk stratification strategies to aid in selecting the appropriate level of care. Well validated scores include the Rockall and Blatchford scores[63,64] which allow selection of the lowest risk patients for early discharge.[65–67] Major risk factors predicting death included old age, co-morbidities, shock at presentation, continued or recurrent bleeding, and onset of bleeding while hospitalized for other causes. Ulcers with active bleeding or stigmata of recent bleeding, such as a visible vessel or an adherent clot, also predict re bleeding and mortality risk.

2.3.3 Recent trends in short term case fatality for variceal haemorrhage

The inpatient mortality of variceal haemorrhage remains on average higher than that of non-variceal bleeding with large studies suggesting a mortality of 11-40%.[68,69] Estimates of short term mortality are generally limited by small

Table 2.3: 30 day or in hospital mortality for non variceal upper gastrointestinal haemorrhage reported from population based studies with n>1000.

Year of study	Country	Size	Inpatient or 28 day mortality[+]
1983-2004[26]	Italy	1126	16-9%
1993[23]	England	4486	14%
1993-2000[3]	Netherlands	1582	14-13%
1993-2003[4]	Canada	95,905	4%*
1996-2000[61]	France	1165	12 - 7%
1996-2007[33]	Israel	12,074	8-7%**
1997[22]	Scotland	1882	7%
1998-2006[12]	USA(NIS)	(20% stratified sample)	4-3%
1999-2007[25]	Wales	24,421	10%
2001-2009[27]	USA(Premier Perspective)	30,500	3 -2%
2004[35]	USA (Medicare)	5617 (5% stratified sample)	8%***
2005[62]	France	1665	11%

[+]A range indicates the change in mortality over the course of the study
*Excluded melaena; gastrointestinal bleeding, unspecified; haemorrhage of oesophagus
**Excluded haematemesis; melaena; non specific GI bleeding
***Excluded melaena; non specific GI bleeding
Blank cells = Information not available in paper

sample sizes, however studies with more than 1000 patients show a persistently higher mortality than for non variceal haemorrhage that is reducing over time (table 2.4). Most deaths occur within the first 2 weeks.[70] Variceal bleeding is itself recognised as a prognostic indicator of the progression of cirrhosis.[71] The outcomes following variceal bleeding are generally related to the underlying severity of cirrhosis as demonstrated by the fact that general prognostic scores for cirrhosis, such as MELD or Child-Pugh, are useful predictors of mortality and rebleeding following variceal haemorrhage.[72–74]

Table 2.4: Mortality from variceal haemorrhage from studies n>1000

Year	Country	Size	Mortality +	Follow up time
1970-2000[69]	Many*	1475	55-40%	Various follow up times
1981-1991[75]	USA (Veteran Affairs)	4975	30 - 21%	30 days
1988-2004[76]	USA (NIS)		18-12%	In patient
1996-2000[61]	France	5980	20% - 11%	In patient
1998-2005[68]	USA (NIS)	36,734	11%	In patient
2004[77]	USA (NIS)	6000	11%	In patient

Blank cells = Information not available in paper
+A range indicates the change in mortality over the course of the study
*Control groups in randomised controlled trials

2.4 Risk factors for bleeding

2.4.1 Risk factors for non variceal upper gastrointestinal haemorrhage

Risk factors for the population burden of peptic ulcers Peptic ulceration and erosion is the most frequently identified cause of upper gastrointestinal haemorrhage. Its incidence has been variously described as declining over the last two decades (For example; Sweden 1987 - 2005 (64-35/100,000),[78] Spain 1996 - 2005 (55-26/100,000),[79] USA 2001-2009 (49-32/100,000)[27]) or as decreasing

among young people but increasing in the elderly.[3,6,7,26,37] Changes in the occurrence of peptic ulcer bleeding should reflect trends in underlying risk factors if the diagnostic pathways remain consistent. For peptic ulceration a study by Weil *et al.* identified that NSAIDs and anti platelet medication were associated with the highest reported attributable fractions.[80] However Weil *et al.* used only self reported illness, an unmatched analysis for matched data, and incorrectly interpreted the adjusted fractions as being exclusive of each other and therefore summing them to 100%. In another hospital based study comparing cases with peptic ulcer bleeds to controls attending cardiology and neurology clinics, Helicobacter pylori was associated with a 5 fold increase in bleeding episodes independently of aspirin and proton pump inhibitor use.[81]

Table 2.5: Estimated adjusted attributable fractions for peptic ulcer bleeding (derived from Weil *et al.*)[80]

	Attributable Fraction
Previous Peptic Ulcer	19%
Smoking	2%
Heart failure	5%
Diabetes	4%
Steroids	3%
Anticoagulants	3%
NSAIDs	22%
Aspirin	11%

Helicobacter pylori Helicobacter pylori was historically the most important cause of peptic ulceration. It is generally acquired during childhood, and prevalence is reducing with generations[82] and among peptic ulcer bleeding admissions.[83,84] However a recent systematic review suggested that Helicobacter pylori prevalence in peptic ulcer bleeding is under estimated and that the mean prevalence remains high at 72% in some study populations.[85] The lowest prevalence estimates among peptic ulcer bleeds were reported from UK, Italy, Netherlands and Denmark ($< 50\%$), though country was not found to be a significant predictor of Helicobacter pylori prevalence in multivariate analysis. Helicobac-

ter pylori does not appear to further potentiate the individual risks of medications such as NSAIDS, rather the increased risk from Helicobacter pylori is merely additive with that from medications.[86]

Medications *NSAIDs:* As stated above NSAIDs and anti platelet agents are important risk factors for upper gastrointestinal bleeding. NSAID use carries a relative risk of gastrointestinal bleeding events of 3.8 (3.6 - 4.1)[87] which is removed by cessation, and this translates for non selective NSAIDS users in clinical trials into an incidence of upper gastrointestinal bleeding of up to 560 per 100,000 person years.[88] Selective cyclo-oxygenase-2 inhibitors are associated with lower risks than non selective NSAIDs[89] but although there has been an increase in their prescription over the last decade, there has been minimal change in the overall prescription of NSAIDS and it is unlikely the changes account for any overall trends in bleeding incidence.[30,31,90]

Aspirin: 1% of patients on low dose aspirin (the most commonly used antiplatelet agent) have a gastrointestinal bleed within 28 months (number needed to harm per year = 248).[91] With increasing use of these drugs the contribution of aspirin to bleeding is probably increasing as suggested by the near doubling of the rate of bleeding admissions over 6 years that were prescribed aspirin or anticoagulants in the north east of Scotland.[30] Prescribing decisions are therefore a balance between the risks and benefits of these drugs. For example low dose aspirin given for low risk primary prevention (1% cardiovascular risk over 5 years) prevents 1-4 myocardial infarctions a year and causes 2-4 gastrointestinal bleeding events with no improvement in mortality.[92] For patients with high cardiovascular risk or for secondary prevention anti platelet and anti coagulants are increasingly given in combinations and this can further increase risk of a bleed. A recent meta analysis shows low dose aspirin increases the risk of bleeding from the gastrointestinal tract by 31%, a further 81% when combined

with clopidogrel, and a further 91% when combined with warfarin.[93]

PPIs: Proton pump inhibitors consistently reduce the risk of bleeding associated with NSAIDS by 67%[94] and their use has a demonstratable cost benefit.[95] In patients on low dose aspirin the risk of bleeding is similarly reduced,[93] however there has been some concern about proton pump inhibitors reducing the efficacy of clopidogrel when co prescribed. A large cohort study reassuringly did not find an increased cardiovascular risk and estimated that only if the cardiovascular risk was increased by more than 19% would the risks of proton pump inhibitors outweigh their benefits.[96] A randomised controlled trial of proton pump inhibitors for patients on dual anti platelet therapy found a reduction in upper gastrointestinal bleeding (HR 0.13 (0.03-0.56)) with no difference in cardiovascular outcomes (HR 0.99 (0.68-1.44)).[97]

Other medications: Other drug associations with bleeding which have been reported include an up to 3 fold increased risk from SSRIs,[98–100] 2 fold increased risk from spironolactone[101,102], 2.5 fold increased risk from iron supplementation[103], 2-4 fold increased risk from corticosteriods,[104] and 3 fold increased risk from bisphosphonates.[105,106]

Co-morbidities It is difficult to ascertain with certainty from current literature the role of co-morbidities in causing gastrointestinal bleeding independent of their therapies. It is widely assumed that the high 1-3% incidence of gastrointestinal bleeding during the month following an acute coronary syndrome (ACS)[97,107,108] is largely related to therapies. However this is not necessarily the case and cannot be assessed without an appropriate comparison group. Acute renal failure also has a high incidence of upper gastrointestinal bleeding 13%[109] with a subsequent increase in mortality (adjusted OR 2.6(1.3-5.1)), and following surgical procedures at two university hospitals (n=25,845), a high gastrointestinal bleeding incidence was reported at 0.39% of patients, with an associated

mortality of 31%.[110] Most of this bleeding was due to erosive gastritis (70%) or ulceration (18%) and occurred in the sicker patients with sepsis and or multi organ dysfunction, as well as in those who were prescribed NSAIDS during the admission.

Other There are a number of other risk factors for gastrointestinal haemorrhage. Higher alcohol intake for example is associated with a higher risk.[111] Ex drinkers however remain at a slightly lower yet still elevated risk (after adjusting for smoking, previous ulcers, aspirin and NSAIDS) suggesting that there is an underlying confounder associated with alcohol excess.[112] Smoking is also a risk factor,[80,113] and its effect may be mediated through altering the ulcerative effects of Helicobacter pylori.[114] It is possible likewise that smoking to some extent mediates a steep socio-economic gradient long shown to exist for peptic ulcer disease[115] and more recently for upper gastrointestinal haemorrhage also.[22,25] Differences in prescribing practices, alcohol consumption or Helicobacter pylori prevalence may also contribute to this gradient. Finally high altitudes are associated with an increased incidence of gastrointestinal haemorrhage among migrant workers,[116] as well as among acclimatised people.[117] This is possibly as part of the syndrome of both acute and chronic altitude sickness,[118] though interestingly in the latter bleeding can actually be therapeutic in avoiding complications of high blood cell counts.

2.4.2 Risk factors for variceal haemorrhage

Oesophageal and gastric varices are a complication of portal hypertension usually due to cirrhosis. Among cirrhotic patients admitted with upper gastrointestinal haemorrhage, 78-87% are due to bleeding varices.[70,119] The predictors of variceal haemorrhage therefore are the causes of cirrhosis and its progres-

sion, and the subsequent development of portal hypertension. That the incidence of variceal haemorrhage is not increasing despite the increase in cirrhosis could therefore be because of improved primary prevention with increased use of banding and beta blockers, or because cirrhosis is being diagnosed earlier.[12,38] Acute precipitants of variceal haemorrhage in patients with known varices include excess alcohol consumption the week before admission, constipation and vomiting.[120]

2.5 Causes of excess death

Causes of death following upper gastrointestinal haemorrhage have changed. Papers published in the 1930s-1960s suggested that about 50% of patients who died were dying from exsanguination before treatment or from re-bleeding. In contrast more recent studies following endoscopic therapy have found only 18 - 30% of deaths were bleeding related.[121–124] However these uncontrolled studies focused on small cohorts of patients who underwent endoscopy to diagnose peptic ulcers and therefore might not be representative of all those presenting with upper gastrointestinal haemorrhage. Furthermore comparisons with matched controls would be necessary to assess whether mortality from co-morbidities is in excess of that expected in a similar population who have not experienced bleeding. A recent trial has demonstrated that in the short term patients with known cardiovascular risk factors benefit from an early reintroduction of aspirin to reduce their cardiovascular death, and this supports the hypothesis that treating co-morbidity and accepting some rebleeding risk reduces excess death following a bleed, albeit in a restricted subgroup of patients.[125]

The only controlled studies of causes of death that have been done were in small bleeding peptic ulcer cohorts in the early 1990s, and these found mortality was

elevated 2 fold for up to 5 years following a bleed, compared to the general population.[9,10,126] Much of this long term increase in mortality appeared related to co-morbidity, particularly cancer and cardiovascular disease[10] and up to 50% was associated with smoking related diseases.[9] However both these studies were small, and the study by Ruigomez *et al.*[10] did not have cause of death information but imputed the information from co-morbidity recorded prior to the bleed, and the study by Hudson *et al.*[9] found an expected survival greater than 100% in controls and therefore used comparisons with national statistics in their analysis.

CHAPTER 3

Outline and aims of thesis

3.1 Outline of thesis

This thesis investigates the contemporary trends in the occurrence and mortality of upper gastrointestinal bleeding (Chapter 5 - 6) and the underlying causes and consequences that are driving these trends (Chapter 8 - 9). An unselected study population was necessary to accurately ascertain occurrence and mortality estimates that are representative of the general population. Therefore the English Hospital Episodes Statistics dataset was selected as it records all admissions to English NHS hospitals. Its validity for this purpose is assessed and discussed in chapter 4. For the more detailed studies on the causes of both upper gastrointestinal bleeding and its subsequent mortality it was necessary to have longitudinal data with prospective recording of potential risk factors and confounders. Therefore routine primary care data linked with both secondary care and death certificate data were used. The validity of this linked data and a new method for defining a cohort within it are discussed in chapter 7.

3.2 Aims of thesis

1. What is the occurrence of upper gastrointestinal haemorrhage within England by region, year and deprivation?

   Chapter 5: Upper gastrointestinal haemorrhage occurrence and deprivation: a nationwide cohort study of health inequality in hospital admissions

2. Has there been a change in upper gastrointestinal mortality over the last decade?

   Chapter 6: Reductions in 28-Day Mortality Following Hospital Admission for Upper Gastrointestinal Hemorrhage

3. Do co-morbidities predict the occurrence of upper gastrointestinal haemorrhage independently of known risk factors?

   Chapter 8: Co-morbidity is an important risk factor for the population burden of non variceal upper gastrointestinal bleeding: A population based case control study

4. What are the causes of excess death following an upper gastrointestinal bleed?

   Chapter 9: Excess long term mortality and its causes following non variceal haemorrhage: A population based cohort study

CHAPTER 4

Validity of using HES to measure upper gastrointestinal bleeding

4.1 Introduction

The Hospital Episodes Statistics database (HES) contains information on all admissions to an NHS hospital in England, with over 12 million new records added each year and is the largest national admissions database in the world. It therefore provides an ideal population based dataset to assess occurrence and outcomes of hospitalised conditions such as acute upper gastrointestinal haemorrhage. However the dataset is fully anonymised and it is not possible to work backwards to identify upper gastrointestinal bleed patients from the HES records for validation against hospital notes. There have been concerns about the accuracy of routine hospital admissions coding, in particular the coding of specific operations and the ascertainment of death for generating mortality rates for specific hospitals. However, a systematic review found a 91% median accuracy in diagnostic coding prior to my study period, and the most recent audit of selected samples of UK hospital data confirmed accuracy approaching 90%.[127] Other comparisons of procedure coding have reported similar or higher rates of coding in the HES database compared to specialist clinical databases[128,129] and with specific regard to upper gastrointestinal haemorrhage the incidence of peptic ulcer haemorrhage in the HES data from 1992-1995 has been shown to be comparable to the 1993 regional BSG audit (32 v 29 per 100,000 per year respectively).[6] Furthermore within the study period of this thesis there have been no systematic changes in coding as the ICD-10 coding system has been in continuous use in HES from 1995 to present. However a more recent audit of upper gastrointestinal bleeding within England has been carried out by the NHS Blood and Transplant and British Society of Gastroenterology in 2007. This has provided an opportunity for a more contemporary and more comprehensive external validation of the coding of upper gastrointestinal bleeding in HES.

4.2 Methods

The NHS Blood & Transplant and British Society of Gastroenterology's 2007 audit of upper gastrointestinal bleeding management was a prospective national web based audit that occurred between 1st May and 31st June 2007.[1] 257 participating hospitals were requested to identify all inpatient and acute bleeds admitted to hospital in those 16 years and over during the 2 month period, and 217 hospitals participated. Bleeds were defined in the audit by haematemesis, melaena or laboratory evidence for acute blood loss from the upper gastrointestinal tract. Patients with iron deficiency anaemia were not included unless there was other evidence for an upper gastrointestinal haemorrhage.

Hospital Episodes Statistics (HES) is managed by the NHS information centre and is available for research with ethical approval. All NHS hospitals within England are required to contribute to the database. There are currently 168 acute trusts in England; however each of these trusts can manage more than one hospital and over time trusts can merge and split. Over the 2 months of the national audit approximately 150 - 200 providers were contributing to the database.

The available data consists of a number of records for each admission, which are called episodes. Each episode represents the time period of the admission that a patient was under the clinical care of a particular consultant team during their inpatient stay. A unique patient identifier allows all records for each patient to be identified and linked together. Each episode's time span is defined with a start and finish date as well as being assigned an admission and discharge date for the whole period of the inpatient stay. Each episode will have up to 14 diagnoses coded using ICD 10 (international classification of diseases, 10th revision); and up to 12 procedures coded using the United Kingdom Tabular List of the Classification of Surgical Operations and Procedures (version OPCS4).

This database has been linked to the Office for National Statistics (ONS) death register since 1998.

Table 4.1: ICD 10 codes used to define upper gastrointestinal bleeding

Variceal bleeding	**ICD 10 codes**
Oesophageal varices with haemorrhage	I85.0
Non variceal bleeding	**ICD 10 codes**
Mallory Weiss syndrome	K22.6
Oesophageal haemorrhage	K22.8
Acute or chronic gastric ulcer with haemorrhage including perforation with haemorrhage	K25.0, K25.2, K25.4, K25.6
Acute or chronic duodenal ulcer with haemorrhage including perforation with haemorrhage	K26.0, K26.2, K26.4, K26.6
Acute or chronic peptic ulcer with haemorrhage including perforation with haemorrhage	K27.0, K27.2, K27.4, K27.6
Acute or chronic gastro-jejunal ulcer with haemorrhage including perforation with haemorrhage	K28.0, K28.2, K28.4, K28.6
Haematemesis	K92.0
Melaena	K92.1
Unspecified gastrointestinal haemorrhage*	K92.2

*Admissions were excluded if they were coded with unspecified gastrointestinal haemorrhage (K92.2) and had a lower gastrointestinal endoscopy/diagnosis code but no upper gastrointestinal endoscopy code.

Initially all valid hospital admissions that were coded for an upper gastrointestinal haemorrhage during the audit time period were extracted from HES along with the linked details of death from the Office for National Statistics (ONS) national death register. All admissions were selected where the patient was 15 years or older (chosen to allow the more detailed ONS 5 year age band denominators to be used whilst being similar to the lower age limit of previous British Society of Gastroenterology audits of mortality in gastrointestinal haemorrhage,[1,23]) and had an ICD 10 code that specifically implied either variceal gastrointestinal haemorrhage or non-variceal haemorrhage (table 4.1). This ICD 10 code list has previously been used in hospital data.[4,25] Episodes were excluded with: Day case admission codes with no overnight stay (the

majority of these admissions were for an outpatient endoscopy and would not have represented an acute presentation of haemorrhage but either a complication of endoscopy or a follow up endoscopy to a previous bleed), invalid date codes as flagged by HES, date codes that were out of chronological order, invalid date of birth codes, invalid gender codes, or duplicate records for one episode.

Subsequently, to allow comparisons with the audit, only those admissions in the time period of the audit that occurred in hospitals contributing to the audit were selected. The hospitals in which these admissions occurred were selected initially based on the provider code within HES. Remaining admissions were assigned to a hospital based on the closest hospital with a gastrointestinal department to the lower super output area of residence. Geographical details and provider codes were obtained from NHS connecting for health. Records within the national audit were also restricted to those that occurred within England and would therefore be expected to be recorded within HES. Recorded numbers of admissions, deaths, and endoscopies were then compared across both data sources. Short term mortality was defined as a date of death within 28 days of the start of the recorded episode of upper gastrointestinal haemorrhage. This included deaths that occurred after discharge from hospital but within the 28 days. The date and fact of death was obtained from the ONS death register using a deterministic matching algorithm based on NHS number, date of birth, postcode and sex.[130]

4.3 Results

Figure 4.1 shows the initial selection of all valid bleed cases from HES. We selected from these cases all that were in the time period of the audit and from

hospitals contributing to the national audit (figure 4.2). Figure 4.3 shows the selection of English cases made within the national audit. The national audit identified 77% of the number of upper gastrointestinal bleeds recorded in England. Endoscopy was recorded in 55.6% of all records in the BSG audit compared to 46.3% of matched HES data.

Figure 4.1: Flowchart of exclusions from study population

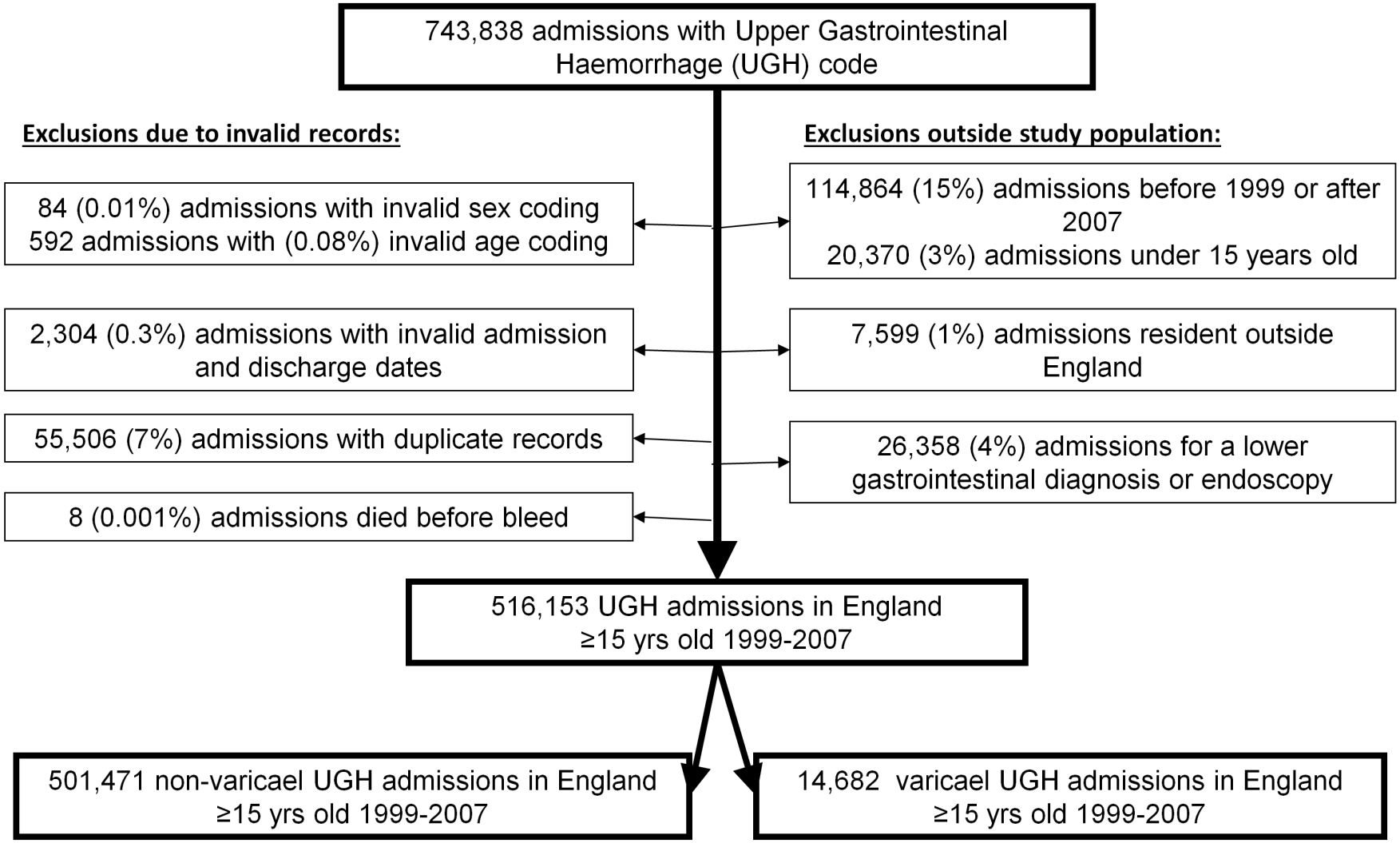
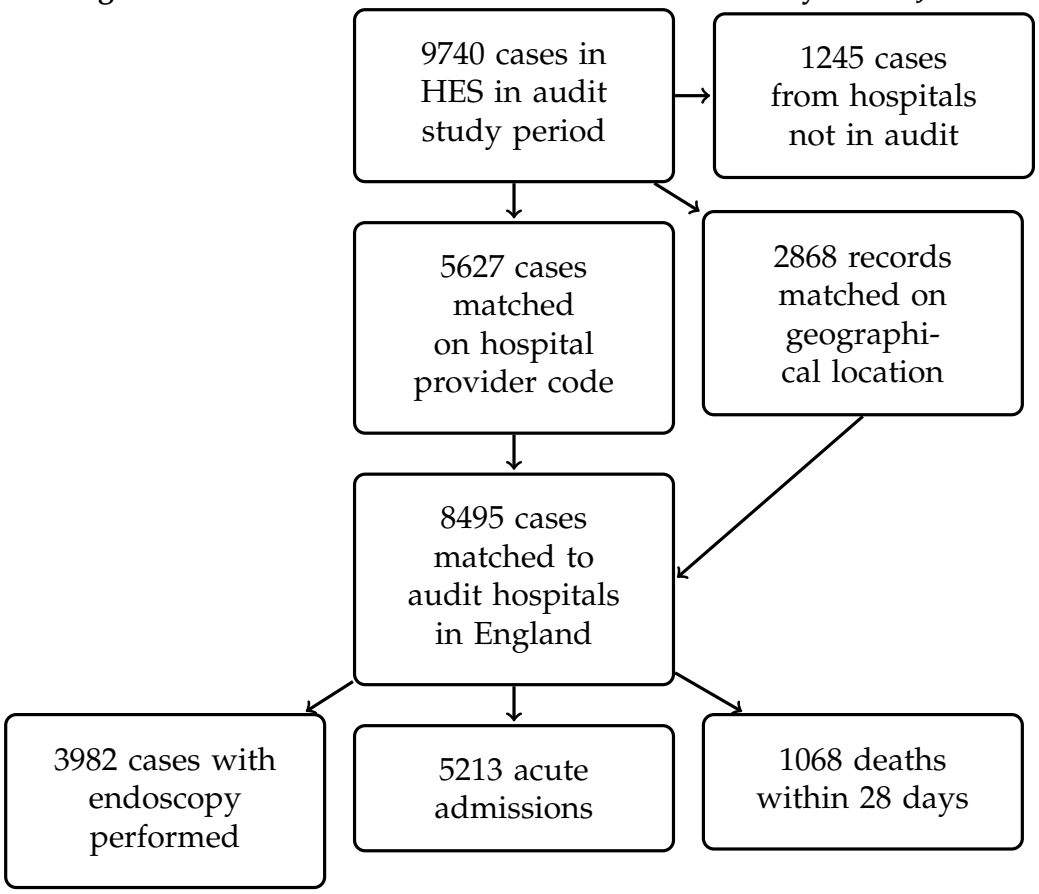
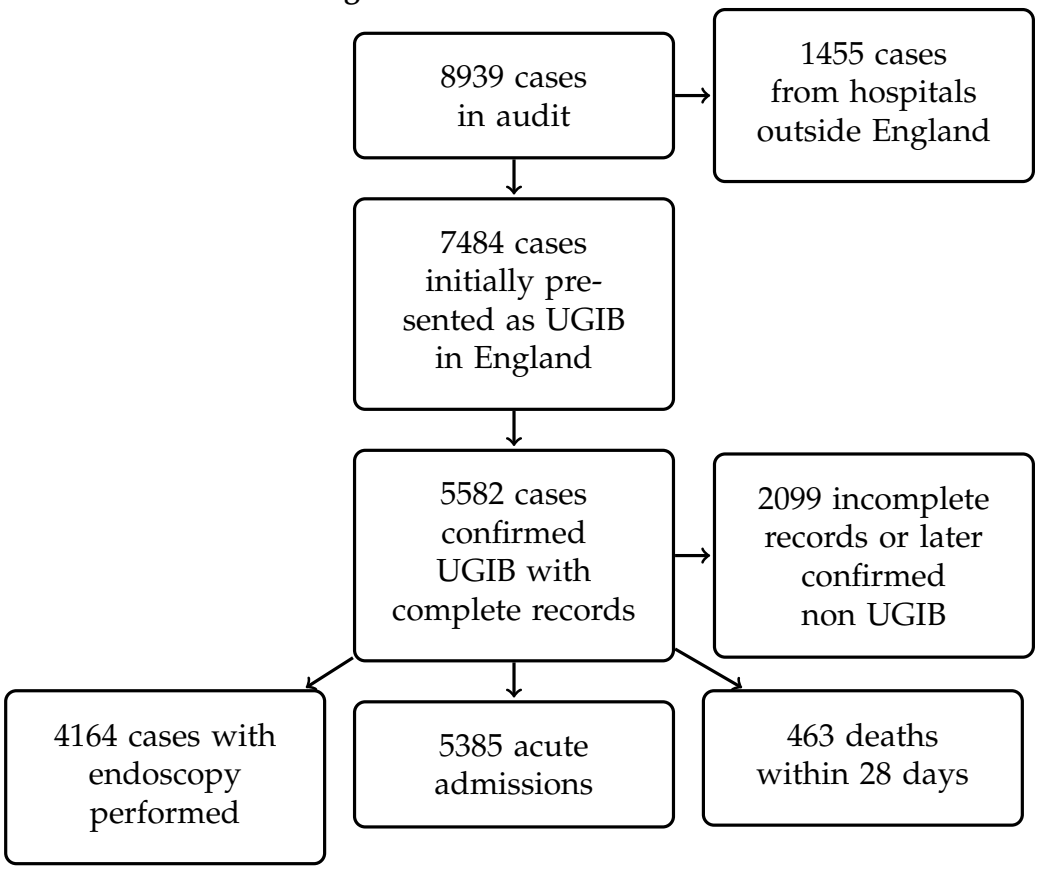


Figure 4.2: Flow chart of cases identified in HES 1st May to 31st June 2007



(UGIB - upper gastrointestinal bleed)

Figure 4.3: Flow chart of audit cases.



(UGIB - upper gastrointestinal bleed)

More deaths within 28 days and prior to discharge were identified using the ONS linked HES dataset than in the national audit (p=0.007, chi^2=7.2, d.f.=1) (see table 4.2).

Similar numbers of procedures where recorded in the two datasets over the audit period, however interventions such as blood transfusions were poorly recorded in HES compared to the national audit (see table 4.3).

Table 4.2: Number of deaths recorded prior to discharge following upper gastrointestinal bleed admissions

Dataset	Number of deaths from participating hospitals	Case fatality%	(95% confidence intervals)
BSG (complete records only)	463	8.3	(7.6 - 9.0)
HES (prior to discharge)	911	10.6	(10.0 - 11.4)

Table 4.3: Interventions recorded with upper gastrointestinal bleed admissions

	Number in national audit	Percentage of all audit records	Percentage in complete records only	Number in HES dataset	Percentage of HES dataset
Upper GI Endoscopy	4164	55.64	74.60	3982	46.33
Therapeutic upper GI Endoscopy	979	13.08	17.54	828	9.63
Upper GI operations	108	1.44	1.93	199	2.32
Blood transfusions	2367	31.63	42.40	351	4.08

4.4 Conclusions

During the recent national audit of upper gastrointestinal bleeding, HES recorded reassuringly similar numbers for upper gastrointestinal bleed hospital admissions and procedures. It was not possible to measure sensitivity and specificity as individual records can not be compared across the datasets due to the anonymisation, however the similar numbers of bleeds in HES and audit indicate that coding in HES had a reasonable sensitivity in recording the incidence of upper gastrointestinal haemorrhage. Furthermore the similar proportions of endoscopy performed in each dataset suggest that HES had not incor-

rectly coded large numbers of admissions as upper gastrointestinal bleeding, and therefore that HES has a reasonable specificity and accuracy in its coding of bleed admissions. The value of HES data is its complete national coverage, linkage to small area statistics, lack of selection bias, and accurate recording of hospitalisation rates. It is therefore a suitable comprehensive data source for measuring the incidence of upper gastrointestinal bleeding within England and its variation therein. With its linkage to the Office for National Statistics death register it is also able to capture all deaths within this population, and is therefore a suitable data source for an unbiased measurement of mortality following a bleed.

However the strength of the audit in providing data to permit detailed analysis of the predictors of bleeding and mortality, procedures, medications, blood transfusions, and the calculation of risk scores cannot be reproduced in the HES data. On its own HES can not therefore be used to answer all the questions in this PhD that require details of risk factors for death and bleeding such as medications and co-morbidities. The comprehensive nature of the UK primary care service does provide this information at a population level, and within a smaller sample of the English population routine electronic primary care data has been linked to secondary care data. Chapter 7 examines the suitability of this smaller dataset for the later more detailed studies in this PhD on upper gastrointestinal bleeding. First, however, the following two chapters use the HES data validated in this chapter to detail the current incidence and mortality trends of upper gastrointestinal bleeding.

CHAPTER 5

Upper gastrointestinal bleeding occurrence and deprivation: a nationwide cohort study of health inequality in hospital admissions

5.1 Introduction

The current patterns of occurrence of upper gastrointestinal bleeding over time and across different geographical regions are important in understanding its burden and to suggest potential modifiable risk factors. One study from Wales reported that there had been no change in incidence between 1999 and 2007, however it only assessed the combined variceal and non variceal incidence and compared only two time points without assessing the data inbetween.[25] Other national studies in the UK have only reported on gastro-duodenal ulcers from England, Wales and Scotland.[6,7] These demonstrated stable hospitalisation rates through the 1990s in England and Wales, but found an increase in the elderly of over 30%. This is contrary to global reports of peptic ulceration declining as a result of falling Helicobacter pylori and peptic ulcer prevalence.[5,12,90]

Large differences in incidence also exist between regional studies within the UK, as discussed in section 2.2.1, and these are often thought to be due to deprivation. Identifying whether such a strong socioeconomic gradient exists is important as it points towards identifiable and modifiable risk factors; for example Helicobacter pylori can be eradicated, the consumption of alcohol reduced, and the prescribing of NSAIDs curtailed.

It would be expected that within England variceal bleeding might be increasing as a consequence of the rise in the prevalence of cirrhosis,[39] but whether this has occurred is not known. Reports from the USA National Inpatient Sample show an 11% increase in variceal admission rates comparing 1998 to 2006, but a conflicting 9% decrease comparing 2001 to 2009.[12,27] The studies did however use different code lists, and the sampling frame used more than doubled in size over the study periods. Other trend studies of upper gastrointestinal bleeding admissions only reported proportions of variceal bleeding and were small

(n<200 for each year).[3,61]

I therefore aimed to accurately estimate the hospitalisation rates for upper gastrointestinal haemorrhage and its relation to time, region and socioeconomic status, whilst adjusting for differences in age and sex. To achieve this I used 7 years of all hospital admissions from the whole population of England.

5.2 Methods

5.2.1 Study population

A retrospective cohort study was designed for the whole English population using the Hospitals Episodes Statistics database (HES) to identify upper gastrointestinal bleeds between 1st January 1999 and 31st December 2007. Mid-year estimates of the English population 15 years and older were available between 1999 and 2007 by region, 5 year age band, and sex, from the Office for National Statistics (ONS) website under crown copyright. However mid year estimates by small area statistics for socioeconomic status were only available between 2001 and 2007 and for broader age bands from 16 years. Small areas are defined by lower super output areas and include around 400 homes. These are defined to cover a consistent geographical area over the time of this study.

5.2.2 Admissions for gastrointestinal haemorrhage

Inclusion criteria

All admissions in patients 16 years or older, with a primary diagnosis of upper gastrointestinal haemorrhage in the admission episode between 1st January 1999 (2001 for the analysis by socioeconomic status) and 31st December 2007,

were selected. Upper gastrointestinal haemorrhage was defined as an ICD 10 code using the same code list as table 4.1.

Exclusion criteria

Admissions were excluded for the same reasons as in chapter 4: Day case admission codes with no overnight stay (the majority of these admissions were for an outpatient endoscopy and would not have represented an acute presentation of haemorrhage but either a complication of endoscopy or a follow up endoscopy to a previous bleed), invalid date codes as flagged by HES, date codes that were out of chronological order, invalid date of birth codes, invalid gender codes, or duplicate records for one episode. Additionally inpatient bleeds with a bleeding code later than the initial admission date were also excluded to select admissions with a higher probability of being an acute bleed on admission.

5.2.3 Exposures

The main exposures of interest were year of bleed and the socioeconomic status of the lower super output area of the residence of the patient. Lower super output areas are small geographical areas defined by the Office for National Statistics to include about 400 houses with consistent boundaries over time. Lower super output areas from the whole country were grouped into quintiles, from the least deprived to the most deprived, by their ranking in the Indices of Multiple Deprivation for England (2007).[131] The English indices of multiple deprivation are derived from 38 indicators grouped into 7 empirically weighted domains that are used to rank lower super output areas from the least to most deprived. The 7 domains, their weights, and some of their indicators are listed and discussed in detail in "The English Indices of Deprivation 2007".[131] Analysis by deprivation was limited to the years 2001-2007 as population data by

lower super output area was only available for this time period.

Other exposures of age, sex, and region were extracted as potential confounders. Region was defined by the regional government office of the home residence at time of admission. The recorded age was grouped into age bands of 15-29 years, 30-59 years, 60-79 years, and older than 80 years. For analyses including deprivation, the age bands chosen for men were 16-29, 30-44, 45-64, and >65, and for women were 16-29, 30-44, 45-59, and >60. These age bands were chosen as those available in the respective ONS denominator data and reflected UK retirement ages at the time.

Associated diagnoses coded during an upper gastrointestinal bleeding admission were also extracted based on ICD 10 codes for Mallory Weiss tear (K22.6), gastritis or duodenitis (K29._), oesophagitis (K20._), peptic ulcer (K25._, K26._, K27._, K28._), or malignancy (C15-7._). Mortality was defined as in the previous study.

5.2.4 Statistical analysis

I analysed variceal and non-variceal haemorrhage admissions separately. After the exclusions described above, hospitalisation rates were calculated by quintiles of socioeconomic status, age group, sex, region, and year. Poisson regression was used to adjust the hospitalisation rates by year or by socioeconomic status for each of these potential confounders. Variables that changed the incidence rate ratios were judged to be confounders and remained in the model. I examined whether the effect of socioeconomic status changed by year by including interaction terms between socioeconomic status and year. Logistic regression was used to adjust odds ratios for 28 day mortality in each deprivation quintile for age, sex and year of admission. All analyses were performed using Stata version 11 (Stata Corp).

5.2.5 Subgroup and Sensitivity Analyses

I repeated analyses of the socioeconomic gradient by aetiological subgroups of non variceal upper gastrointestinal haemorrhage (gastritis/duodenitis, Mallory Weiss syndrome, oesophagitis, gastric ulcer, duodenal ulcer and malignancy) to determine whether relationships seen were specific to one or more of them. I then performed four more sensitivity analyses. Firstly to assess the possibility of under reporting I expanded the definition for variceal haemorrhage to include all admissions coded for oesophageal haemorrhage (K22.8). Secondly to assess the effect of possible over reporting I restricted the definition of non variceal haemorrhage to admissions with either an associated coded intervention or outcome which I defined as an endoscopy, blood transfusion or death within 14 days of the recorded bleed date. I then re-assessed whether any gradients differed when the analysis was restricted to either the first admission or a subsequent readmission for each patient. Finally I examined whether restricting the analysis to patients with no previous recording of alcohol related diseases altered any gradients I found.

5.3 Results

5.3.1 Study population

516,153 upper gastrointestinal bleed admissions were identified between 1999 & 2007 (see figure 4.1), of which 313,111 were coded as the primary diagnosis in the first episode of an admission and were therefore used for the analysis of incidence over time. Restricting to 2001-2007 and to people 16 years and older for the analysis by deprivation (when linked socioeconomic data was available for the denominator) reduced the number of bleeds to 245,438 (see figure 5.1).

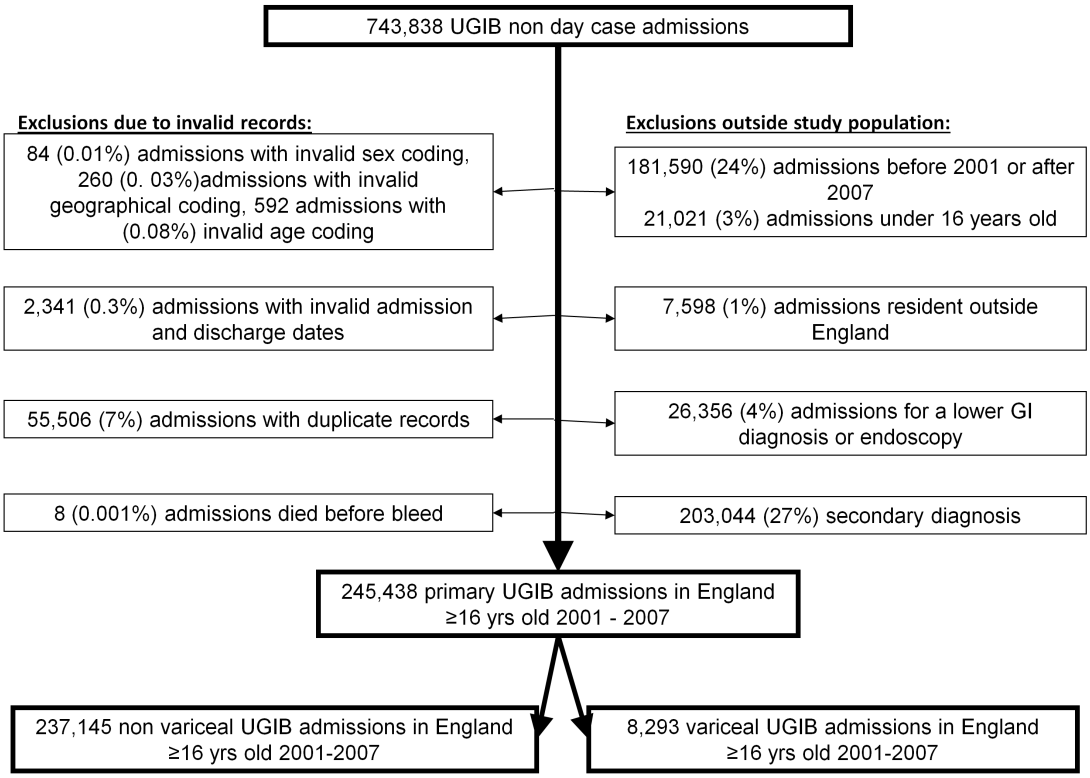


Figure 5.1: Flowchart of exclusions from study population for study of associations with deprivation

237,145 (97%) bleed admissions were coded as non variceal haemorrhage and 8,293 (3%) as variceal haemorrhage.

5.3.2 Crude incidence rates

Incidence by year

The average annual hospitalisation rate from 1999 to 2007 for non-variceal haemorrhage was 85.3/100,000 (95% confidence interval 85.0 - 85.6/100,000). The hospitalisation rate for non variceal bleeding was 82.4/100,000 (95% confidence interval 82.1 - 82.7/ 100,000) and for variceal bleeding was 2.94/100,000 (95% confidence interval 2.89 - 3.00). The crude hospitalisation rate of non variceal bleeding was higher with older age, in the north and in males, but it varied only slightly by year, peaking in 2005 (table 5.1). Although the hospitalisation rates

for variceal bleeding had greater uncertainty due to smaller numbers, there was a similar lack of a trend by year (table 5.2). For variceal bleeding the relative hospitalisation rates peaked between 60 and 79 years old and then decreased in the older age group.

Incidence by deprivation

Between 2001 and 2007 the crude socioeconomic gradient between the most and least deprived quintiles was greater for variceal haemorrhage than non variceal haemorrhage (Rate Ratio (RR) for non variceal haemorrhage 2.00, 95% confidence interval 1.98 - 2.03; RR for variceal haemorrhage 2.49, 95% confidence interval 2.32 - 2.67). The regional hospitalisation rates for variceal and non variceal haemorrhage are shown in figure 5.2, with higher rates of hospitalisation in the north of the country. The increase in hospitalisation with deprivation was observed in all regions, and was of far greater magnitude than any regional differences for both variceal and non variceal bleeds (see figure 5.3, only non variceal bleeds shown). The gradient was also present in all age strata (figure 5.4, only non variceal bleeds shown). During the study period there was only a slight year on year change in hospitalisation rates. Cross tabulations of crude rates for each IMD quintile by age group, gender, procedures, and associated diagnoses are shown in table 5.3.

5.3.3 Multivariate analysis

Incidence by year

After adjusting for changes in age and sex there was no evidence for an association between variceal bleeding and year (test for association p=0.09, test for trend p=0.11). Region did not alter the interpretation of a trend over time for

Table 5.1: Hospitalisations and number of non variceal bleed admissions by year, gender and age

Variable	Number of upper non variceal gastrointestinal haemorrhage admissions	Hospitalisations per 100,000 per year	IRR	Adjusted IRR*	95% confidence interval	
Year						
1999	32025	80.83	1.00	1.00		
2000	32561	81.65	1.01	1.00	(0.99	1.02)
2001	32165	80.08	0.99	0.98	(0.96	0.99)
2002	32348	80.01	0.99	0.97	(0.96	0.99)
2003	33712	82.81	1.02	1.00	(0.99	1.02)
2004	34548	84.25	1.04	1.02	(1.00	1.03)
2005	35422	85.53	1.06	1.03	(1.01	1.05)
2006	35076	83.99	1.04	1.01	(0.99	1.02)
2007	34635	82.25	1.02	0.98	(0.97	1.00)
Gender						
Male	169504	95.29	1.00	1.00		
Female	132988	70.28	0.74	0.62	(0.62	0.63)
Age						
<30	29202	33.79	1.00	1.00		
30 to 59	90785	48.69	1.44	1.45	(1.43	1.47)
60 to 79	99405	132.72	3.93	4.00	(3.95	4.05)
≥80	83100	429.71	12.72	13.80	(13.61	13.98)
Region						
London	34511	63.74	1.00			
North East	21385	113.54	1.78		(1.75	1.81)
North West	48528	97.40	1.53		(1.51	1.55)
Yorkshire and Humber	32427	87.61	1.37		(1.35	1.40)
East Midlands	27264	86.87	1.36		(1.34	1.38)
West Midlands	33292	85.86	1.35		(1.33	1.37)
East of England	27290	67.84	1.06		(1.05	1.08)
South East	44454	74.64	1.17		(1.15	1.19)
South West	33341	89.32	1.40		(1.38	1.42)

IRR = Incidence Rate Ratio
*Poisson model with age, sex and year

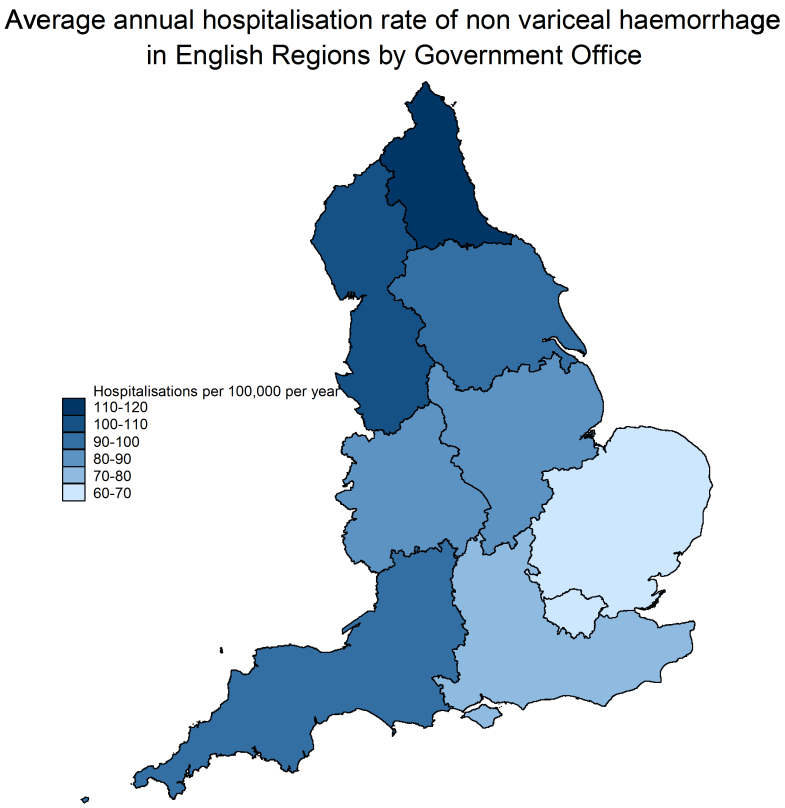
Table 5.2: Hospitalisations and number of variceal bleed admissions by year, gender and age

Variable	Number of upper variceal gastrointestinal haemorrhage admissions	Hospitalisations per 100,000 per year	IRR	Adjusted IRR*	95% confidence interval	
Year						
1999	1131	2.85	1.00	1.00		
2000	1163	2.92	1.02	1.02	(0.94	1.11)
2001	1099	2.74	0.92	0.95	(0.88	1.03)
2002	1139	2.82	0.95	0.98	(0.90	1.06)
2003	1177	2.89	0.98	1.00	(0.93	1.09)
2004	1274	3.11	1.05	1.08	(1.00	1.17)
2005	1160	2.80	1.03	0.98	(0.91	1.07)
2006	1254	3.00	1.01	1.05	(0.97	1.14)
2007	1222	2.90	0.98	1.02	(0.94	1.10)
Gender						
Male	6991	3.93	1.00	1.00		
Female	3628	1.92	0.50	0.48	(0.46	0.50)
Age						
<30	269	0.31	1.00	1.00		
30 to 59	6418	3.44	10.27	10.64	(9.42	12.02)
60 to 79	3328	4.44	13.26	14.02	(12.38	15.87)
≥80	604	3.12	9.32	10.88	(9.42	12.56)
Region						
London	1703	3.15	1.00			
North East	657	3.49	1.11		(1.01	1.21)
North West	1773	3.56	1.13		(1.06	1.21)
Yorkshire and Humber	963	2.60	0.83		(0.76	0.90)
East Midlands	856	2.73	0.87		(0.80	0.94)
West Midlands	1328	3.42	1.09		(1.01	1.17)
East of England	787	1.96	0.62		(0.57	0.68)
South East	1639	2.75	0.87		(0.82	0.94)
South West	913	2.45	0.78		(0.72	0.84)

IRR = Incidence Rate Ratio
*Poisson model with age, sex and year

Table 5.3: Crude Hospitalisation Rates per 100,000 population (95% confidence intervals)

Quintiles of Deprivation (IMD 2007)	1 = Least deprived	2	3	4	5 = Most deprived	Total (million person years)
Age (years)						
<30	5.13 *(4.94,5.32)*	6.48 *(6.27,6.69)*	8.64 *(8.41,8.89)*	13.16 *(12.86,13.46)*	22.99 *(22.59,23.40)*	63
30 to 44	8.13 *(7.90,8.37)*	10.33 *(10.07,10.60)*	14.29 *(13.98,14.60)*	21.64 *(21.25,22.02)*	38.56 *(38.04,39.09)*	79
45-64*	17.59 *(17.25,17.94)*	20.93 *(20.55,21.30)*	24.15 *(23.75,24.55)*	31.65 *(31.19,32.12)*	45.82 *(45.25,46.39)*	76
>=65*	73.50 *(72.80,74.21)*	86.01 *(85.26,86.77)*	88.91 *(88.14,89.68)*	90.72 *(89.93,91.51)*	93.16 *(92.35,93.98)*	65
Gender						
Male	55.55 *(54.94,56.16)*	66.05 *(65.38,66.71)*	73.55 *(72.85,74.25)*	87.27 *(86.50,88.04)*	117.72 *(116.81,118.64)*	140
Female	48.81 *(48.24,49.38)*	57.70 *(57.09,58.33)*	62.44 *(61.80,63.09)*	69.90 *(69.21,70.59)*	82.82 *(82.05,83.59)*	150
Procedures						
Upper GI endoscopy	51.15 *(50.57,51.74)*	60.42 *(59.78,61.05)*	65.86 *(65.20,66.53)*	74.67 *(73.96,75.39)*	91.45 *(90.65,92.26)*	
Therapeutic endoscopy	8.35 *(8.12,8.59)*	9.76 *(9.51,10.02)*	10.48 *(10.22,10.75)*	11.57 *(11.29,11.85)*	13.79 *(13.48,14.11)*	
Upper GI surgery	2.90 *(2.76,3.04)*	3.32 *(3.18,3.48)*	3.56 *(3.41,3.72)*	4.14 *(3.97,4.31)*	4.78 *(4.60,4.97)*	
Diagnoses						
Gastric Ulcer	10.07 *(9.81,10.33)*	11.95 *(11.67,12.24)*	12.52 *(12.23,12.81)*	14.17 *(13.86,14.48)*	16.82 *(16.48,17.17)*	
Duodenal Ulcer	13.16 *(12.86,13.46)*	15.38 *(15.06,15.71)*	16.57 *(16.24,16.90)*	17.85 *(17.50,18.20)*	20.90 *(20.52,21.29)*	
Mallory Weiss	5.29 *(5.10,5.48)*	6.44 *(6.24,6.65)*	7.32 *(7.10,7.54)*	9.45 *(9.20,9.71)*	13.47 *(13.16,13.78)*	
Gastritis/ Duodenititis	12.50 *(12.21,12.79)*	15.20 *(14.89,15.53)*	16.82 *(16.48,17.16)*	19.58 *(19.22,19.95)*	24.56 *(24.15,24.98)*	
Oesophagitis	13.63 *(13.33,13.93)*	15.84 *(15.52,16.17)*	17.41 *(17.07,17.76)*	19.53 *(19.17,19.90)*	23.06 *(22.66,23.47)*	
Varices	2.87 *(2.74,3.02)*	3.48 *(3.33,3.64)*	3.99 *(3.83,4.16)*	4.92 *(4.74,5.11)*	7.28 *(7.05,7.51)*	
Malignancy	3.00 *(2.86,3.15)*	3.45 *(3.30,3.61)*	3.60 *(3.45,3.76)*	3.54 *(3.39,3.70)*	3.71 *(3.55,3.88)*	
Population at risk over whole study period (millions)	57	58	58	56	54	



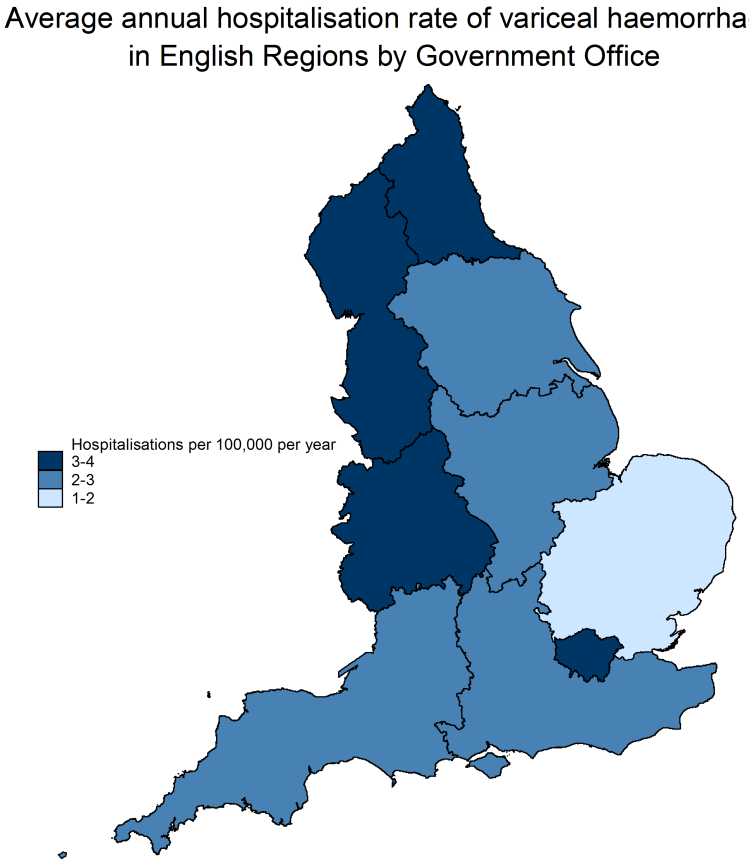


Figure 5.2: Hospitalisation rates of upper gastrointestinal haemorrhage by Regional Government Office

(a) Non variceal haemorrhage (b) Variceal haemorrhage.

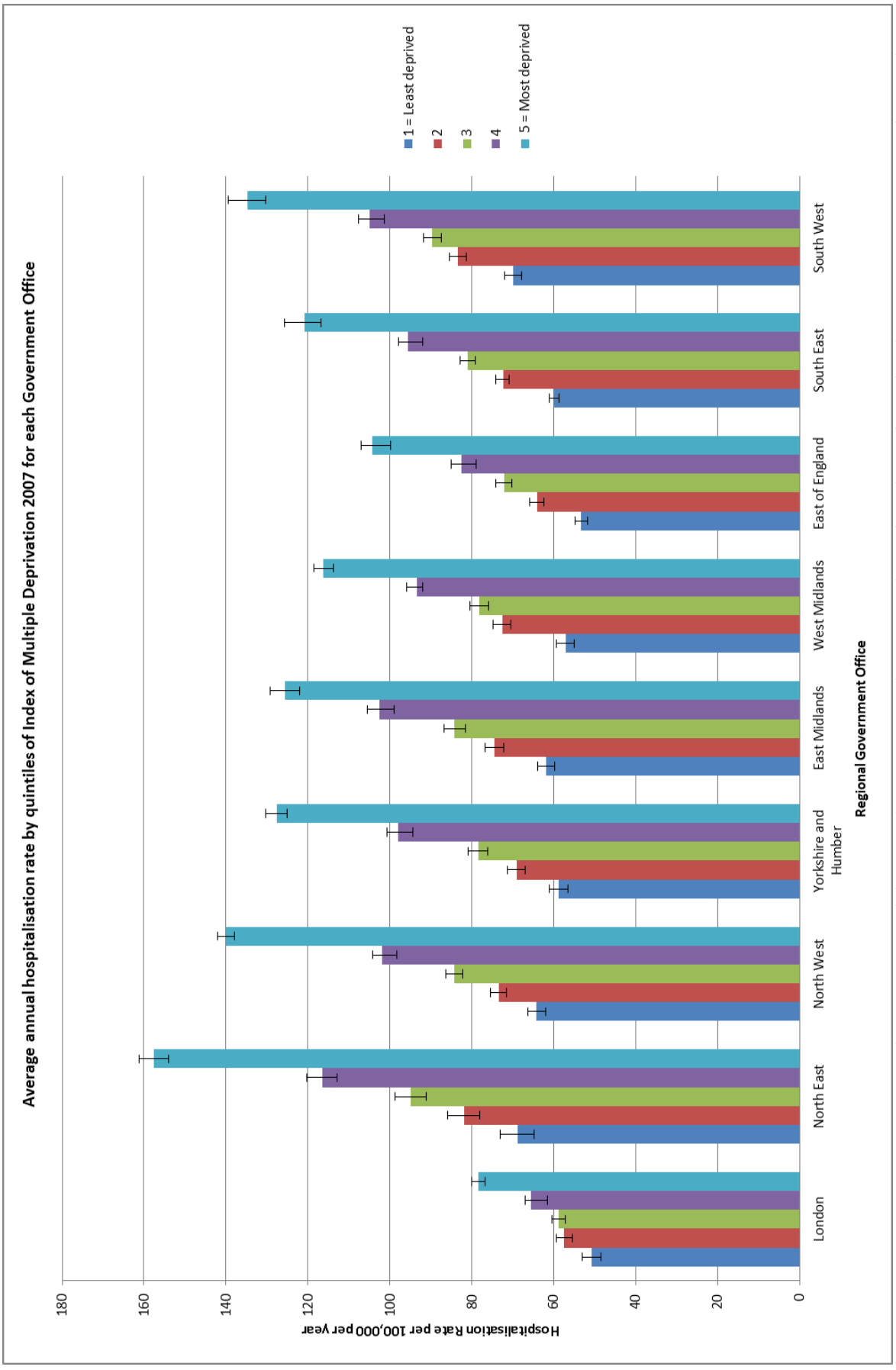


Figure 5.3: Average annual non variceal hospitalisation rate by quintiles of Index of Multiple Deprivation 2007 for each Government Office

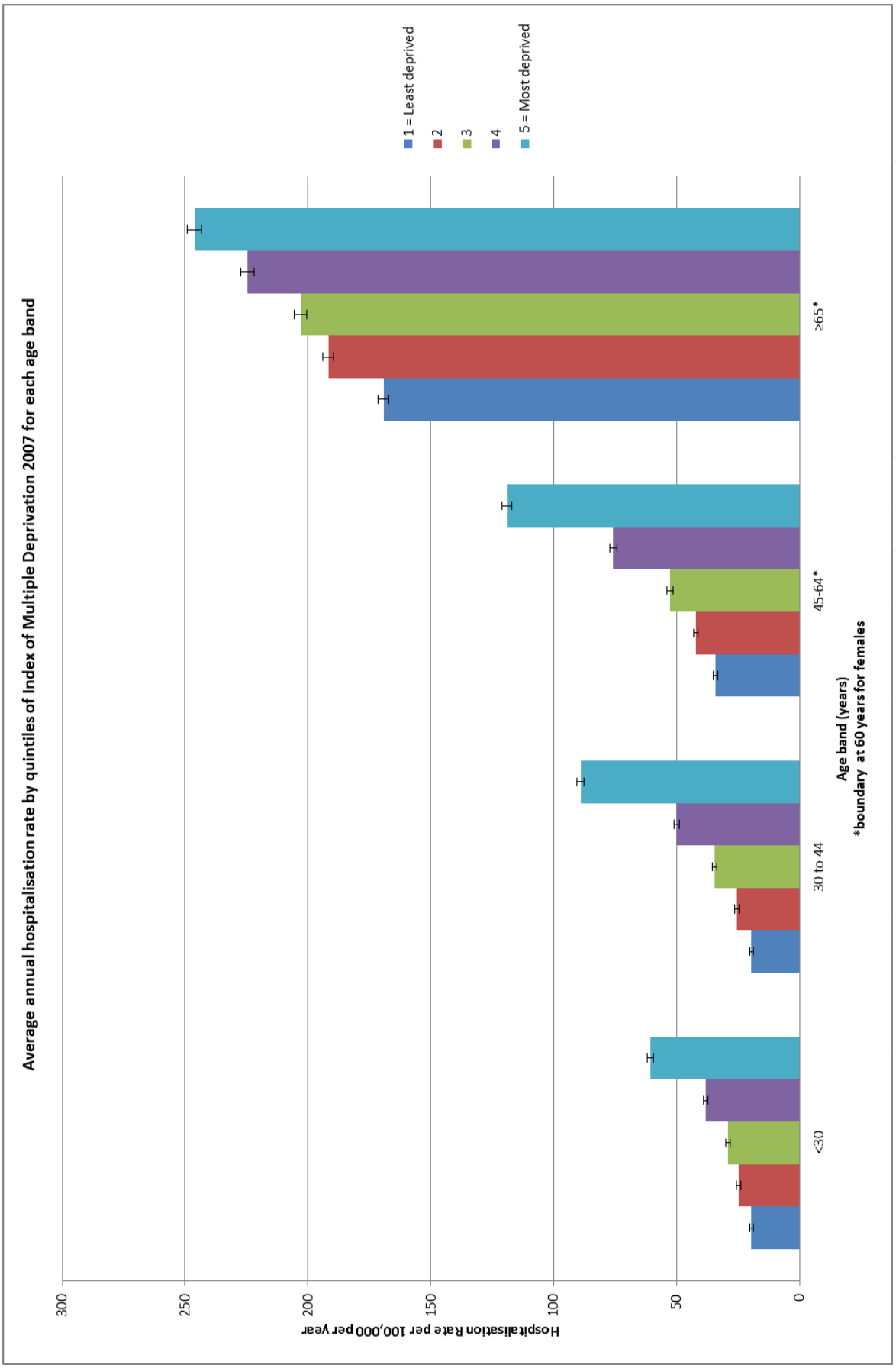


Figure 5.4: Average annual non variceal hospitalisation rate by quintiles of Index of Multiple Deprivation 2007 for each age band

either variceal or non variceal bleeding so it was not included as a confounder in the regression models. A sensitivity analysis for variceal bleeding using a broader definition that included the code for oesophageal bleeding did not alter the finding of no trend in hospitalisation by year (age and sex adjusted test for trend p=0.507). A second sensitivity analysis restricting the definition of variceal bleeding to admissions with an intervention (such as endoscopy) or outcome (such as death) also did not demonstrate an association (p=0.225). In contrast for non variceal bleeding although there was weak evidence for a minimal year on year increase in hospitalisation (IRR 1.001, 95% confidence interval 1.000 - 1.003, test for trend p=0.0463) a sensitivity analysis restricted to admissions with intervention or death actually demonstrated a fall in hospitalisation (IRR 0.969, 95% confidence interval 0.967 - 0.971, test for trend p<0.0001).

Incidence by deprivation

Incidence rate ratios of hospitalisation by socioeconomic status were adjusted for age and sex using Poisson regression, and this further increased the difference between the least and most deprived quintiles for non variceal (RR 2.22, 95% confidence interval 2.20-2.25) and variceal haemorrhage RR 2.93, 95% confidence interval 2.73-3.14). The inclusion of region or year in the model did not alter the estimates. However, a likelihood ratio test for an interaction between year and socioeconomic status demonstrated that there was strong evidence for an increase in inequality over the study period (non variceal p<0.0001, variceal p=0.0068. See figure 5.5, only non variceal haemorrhage shown).

There was no significant association between socioeconomic status and adjusted 28 day mortality for non variceal haemorrhage (p=0.07, likelihood ratio test for association), and although for variceal haemorrhage 28 day mortality increased for some quintiles (p=0.004, likelihood ratio test for association), there

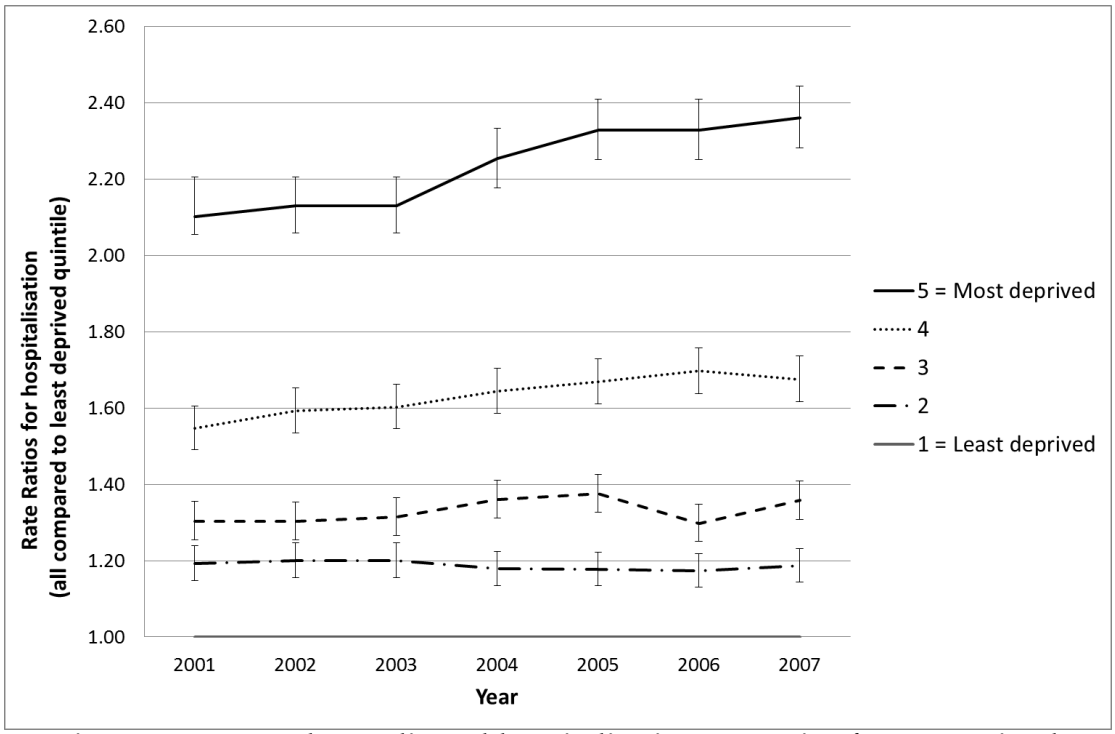


Figure 5.5: Age and sex adjusted hospitalisation rate ratios for non variceal haemorrhage by year for each quintile of deprivation compared to the least deprived quintile.

was no clear pattern or trend observed with increasing deprivation (table 5.4).

Sub group analysis

The hospitalisation gradient by deprivation was found in all sub groups of diagnoses associated with non variceal haemorrhage admissions (table 5.5), and consistent with the main analysis the 28 day case fatality was not significantly associated with deprivation in any sub group (table 5.6).

Sensitivity analysis

The first sensitivity analysis for the socioeconomic gradient expanded the definition of variceal haemorrhage and this reduced the magnitude of the association slightly, but the comparison of most to least deprived quintiles still showed a significant difference RR 2.60, 95% confidence interval 2.44 - 2.76). The sec-

Table 5.4: Crude and adjusted odds ratios for 28 day mortality in each deprivation quintile.

IMD 2007 Quintile	Number of 28 day deaths	Crude OR	Adjusted OR*	95% Confidence Interval
Non variceal haemorrhage				
1=Least Deprived	3947	1	1	
2	4819	1.02	1.04	(0.99 1.08)
3	5083	0.97	1.06	(1.01 1.11)
4	5209	0.86	1.06	(1.02 1.11)
5=Most Deprived	5348	0.69	1.04	(0.99 1.08)
Variceal haemorrhage				
1=Least Deprived	195	1	1	
2	255	1.13	1.14	(0.92 1.40)
3	268	0.96	1	(0.81 1.22)
4	396	1.26	1.33	(1.10 1.61)
5=Most Deprived	503	1.12	1.23	(1.03 1.49)
*Adjusted by logistic regression for age and sex				

Table 5.5: Age and gender adjusted rate ratios for upper gastrointestinal haemorrhage admission by associated diagnoses.

Age and gender adjusted IRR (95% confidence intervals)					
IMD 2007 Quintiles	1 = Least deprived	2	3	4	5 = Most deprived
Gastritis/Duodenitis	1	1.21 (1.16,1.26)	1.39 (1.33,1.44)	1.71 (1.64,1.78)	2.22 (2.14,2.31)
Mallory Weiss Syndrome	1	1.22 (1.15,1.29)	1.39 (1.31,1.46)	1.79 (1.70,1.89)	2.61 (2.48,2.74)
Oesophagitis	1	1.16 (1.11,1.21)	1.33 (1.28,1.39)	1.57 (1.51,1.63)	2 (1.92,2.08)
Gastric Ulcer	1	1.16 (1.11,1.21)	1.26 (1.20,1.31)	1.54 (1.48,1.61)	1.9 (1.83,1.98)
Duodenal Ulcer	1	1.16 (1.12,1.21)	1.3 (1.25,1.35)	1.52 (1.46,1.57)	1.89 (1.82,1.96)
Malignancy	1	1.16 (1.04,1.29)	1.22 (1.09,1.35)	1.31 (1.17,1.46)	1.49 (1.34,1.66)

Table 5.6: Age and gender adjusted odds ratios for 28 day mortality in each deprivation quintile by associated diagnoses.

Age and gender adjusted OR for case fatality (95% confidence intervals)					
IMD 2007 Quintiles	1 = Least deprived	2	3	4	5 = Most deprived
Gastritis/Duodenitis	1	1.09 (0.90,1.31)	1.09 (0.90,1.32)	1.14 (0.94,1.37)	1.07 (0.88,1.29)
Mallory Weiss Syndrome	1	0.87 (0.58,1.31)	1.18 (0.81,1.73)	1.10 (0.75,1.61)	1.15 (0.79,1.68)
Oesophagitis	1	0.88 (0.74,1.04)	1.01 (0.86,1.19)	1.09 (0.93,1.28)	1.08 (0.92,1.27)
Gastric Ulcer	1	1.01 (0.87,1.17)	1.04 (0.90,1.20)	1.05 (0.91,1.21)	1.22 (1.06,1.40)
Duodenal Ulcer	1	1.11 (1.00,1.25)	1.10 (0.99,1.23)	1.17 (1.04,1.30)	1.19 (1.06,1.33)
Malignancy	1	1.13 (0.90,1.41)	0.98 (0.78,1.23)	1.06 (0.84,1.33)	1.21 (0.96,1.52)

ond sensitivity analysis restricted the definition of non variceal haemorrhage to admissions coded with an intervention or death, and following this the socioeconomic gradient was still apparent RR 1.92 (95% confidence interval 1.89-1.95, adjusted for age and sex).

The third sensitivity analysis was stratified by initial admission and subsequent readmission. Restricting to the first admission for each patient did not substantially alter the gradients by deprivation (tables 5.7 & 5.8). However there was a steeper gradient by deprivation for readmissions for both non variceal haemorrhage (adjusted rate ratio comparing most to least deprived 3.25 (3.15-3.36)) and variceal haemorrhage (adjusted rate ratio comparing most to least deprived 2.69 (2.45-2.94)). Finally, excluding patients with a previous admission related to alcohol did not alter any of the overall deprivation gradients.

Regression diagnostics

The deviance statistic and Pearson statistic were calculated for the Poisson models and neither were significant (p=1.0 for both deprivation and time trend models) consequently there was no evidence to reject the use of the Poisson

Table 5.7: Hospitalisation by deprivation quintile for first and subsequent non variceal upper gastrointestinal haemorrhage admission

IMD 2007 Quintiles	Crude hospitalisation rates *	Adjusted rate ratios**	95% confidence intervals
First Admission			
1 = Least Deprived	50.96	1	
2	60.18	1.17	(1.15,1.18)
3	65.18	1.29	(1.27,1.31)
4	74.64	1.56	(1.54,1.59)
5 = Most Deprived	93.99	2.05	(2.02,2.08)
Readmission			
1 = Least Deprived	8.89	1	
2	11.25	1.26	(1.22,1.31)
3	13.35	1.54	(1.48,1.59)
4	16.83	2.04	(1.97,2.11)
5 = Most Deprived	25.90	3.25	(3.15,3.36)

*per 100,000 population
**adjusted for age and gender

model for this data.

5.4 Discussion

There was no strong evidence for large changes in the occurrence of variceal or non variceal bleeding over the time period of the study. There was strong evidence for large regional variations in the occurrence of bleeding, but these were dwarfed by the variation in occurrence by socioeconomic status. Those who live in the most disadvantaged areas of England have a 2 to 3 times higher rate of hospitalisation for upper gastrointestinal haemorrhage compared to people living in the most affluent areas. It is improbable that living in a particular residential area itself causes upper gastrointestinal haemorrhage, but rather that more deprived people have risk factors that more affluent people have been able to avoid. According to my findings if the whole population experienced the same levels of risk as the most affluent, up to 10,000 admissions costing a total of at least £20 million ($34 million),[42] and over 1000 deaths could be prevented each year in England. As the causes of many upper gastrointestinal

Table 5.8: Hospitalisation by deprivation quintile for first and subsequent variceal upper gastrointestinal haemorrhage admission

IMD 2007 Quintiles	Crude hospitalisation rates *	Adjusted rate ratios**	95% confidence intervals
First Admission			
1 = Least Deprived	1.21	1	
2	1.45	1.21	(1.10,1.34)
3	1.68	1.47	(1.33,1.62)
4	1.98	1.85	(1.68,2.03)
5 = Most Deprived	2.74	2.69	(2.45,2.94)
Readmission			
1 = Least Deprived	0.68	1	
2	0.78	1.16	(1.01,1.33)
3	0.98	1.52	(1.34,1.73)
4	1.28	2.09	(1.85,2.36)
5 = Most Deprived	1.98	3.35	(2.98,3.76)

*per 100,000 population
**adjusted for age and gender

haemorrhages are known and are modifiable, the prevention of these admissions and deaths is potentially achievable.

My study provides a complete national picture for England of the increased risk of upper gastrointestinal haemorrhage hospitalisation associated with areas of higher deprivation. It therefore provides the first demonstration that this steep gradient is present in all regions of the country and is independent of age and sex. My large study population allows us for the first time to demonstrate socioeconomic associations with both variceal and non variceal haemorrhage, and by including all hospital admissions for upper gastrointestinal bleeding in England I have minimised the effect of selection bias and have adequately adjusted for the effects of demographic differences across England. There are of course weaknesses in the methodology of using small area statistics. Firstly by assessing deprivation at lower super output area level I may incorrectly assign an area's average risk of deprivation to individuals with very different personal economic circumstances. This may explain the lesser association with deprivation observed in London, where the close proximity of rich and poor households might have increased the possibility of this type of misclassifica-

tion. However, although the effects of this ecological bias could have been in either direction and were unknown, I believe that the misclassification was most likely to be non-differential and the effect would therefore be to reduce observed associations. The other possible error from using small area statistics was some residual confounding by age due to the use of broad age categories chosen to match those in ONS denominator data. However this residual confounding is unlikely to explain the association I observed, since the age adjustment that was possible increased the strength of the association rather than reduced it. Apart from small area statistics the other potential weakness in my study is the accuracy of routine hospital admissions coding. However it seems unlikely that coding inaccuracies would have been associated with the socioeconomic status of a patient, so any coding errors would have reduced rather than caused the magnitude of the association I observed. Furthermore this error is likely to be small as the most recent audit of UK hospital data shows accuracy approaching 90%,[127] and the incidence of peptic ulcer haemorrhage in HES data from 1992-1995 has been shown to be comparable to the 1993 regional BSG audit (32 v 29 per 100,000 per year respectively).[6]

One specific concern about the coding in my study is the possibility of underreporting of variceal haemorrhage which I found to be less frequently reported than in the recent BSG audit.[1] However my finding was similar to that of the 1993 BSG audit (4%) and other studies,[3,23] and the socioeconomic gradient was robust against a sensitivity analysis that broadened the definition of variceal bleeding. Another concern about coding is that over reporting of cases that were not real bleeds may have occurred. However restricting cases to only those with a recorded intervention (such as endoscopy) or outcome (such as death) did not substantially alter the association with socioeconomic status.

Previous studies support the validity of my findings; Button et al. in a recent study from Wales used routine data to demonstrate a crude two fold difference

in upper gastrointestinal bleed hospitalisation between the least and most deprived.[25] However their study was ten times smaller than ours and did not investigate if this inequality was confounded by type of bleed, region, age, gender or year. Blatchford et al, in a regional study of 1,882 patients in the north west of Scotland 15 years ago, found no association of case fatality with socioeconomic status measured by Carstairs score, but observed a two fold increase in the unadjusted incidence of upper gastrointestinal haemorrhage between the least and most affluent quartiles.[22] I have expanded on these studies and used a more comprehensive measure of deprivation than the latter to demonstrate that this gradient is present in all regions of the country, for all ages, both men and women, and is steeper for variceal than non variceal haemorrhage. My study also found a North to South gradient in crude hospitalisation that was mostly explained by deprivation, and this is similar to the report of Woods et al. who identified a North to South gradient in all cause mortality that was also mostly attributable to deprivation.[132]

Deprivation influenced mortality in my study far less than it influenced hospitalisations. This reassuringly suggests that admissions from deprived areas are receiving comparable hospital care to those from less deprived areas, however it also implies that the focus for reducing inequality in upper gastrointestinal bleeding should be to prevent and treat its causes rather than further modify acute services. This is potentially achievable as many risk factors are already known and modifiable. For example Helicobacter pylori, which is simple to eradicate, is known to have a higher prevalence in deprived areas from crowded childhood living conditions.[133] Other lifestyle risk factors for causes of bleeding such as smoking, larger waist circumferences, and alcohol related diseases, are also more common in populations with higher levels of deprivation and could be modifiable through effective public health interventions.[134–136] However, the sub group analysis excluded previous alcohol related admissions

and this did not reduce any of the inequality in bleeding occurrence. Another potential cause of the inequality observed is that harmful prescribing practices have been shown to be increased for people with lower socioeconomic status;[137] lower skilled occupations had a higher chronic NSAID use (OR 1.4) than skilled workers despite a higher prevalence of dyspepsia.[138] This latter study included NSAIDs purchased without a prescription (i.e 'over the counter'), so as omeprazole is also obtainable in the UK without prescription, proton pump inhibitor use could be encouraged with NSAIDS in deprived areas.

In conclusion, I have demonstrated that people from areas of greater deprivation have higher rates of hospitalisation for upper gastrointestinal haemorrhage than are explained by random error or measured confounding. There are therefore opportunities to identify modifiable risk factors, and therefore interventions, to prevent disease in more deprived areas and to reduce the 10,000 excess admissions and 1000 excess deaths associated with deprivation, and thus make the most of currently scarce economic resources.

Additionally I have not demonstrated the decrease in the occurrence of non variceal haemorrhage that might have been expected following reported decreases in peptic ulcers world wide.[139] My findings show that the persisting incidence observed by Higham *et al* of peptic ulcer admissions in the 1990s has continued for upper gastrointestinal haemorrhage admissions in the 2000s.[6]

Both findings in this study raise questions about which risk factors are responsible for the burden of upper gastrointestinal bleeding in the general population, and therefore are responsible for its persisting incidence over time and the higher incidence observed with deprivation. One potential explanation is that age and co-morbidity are increasing over time, and I examine this in chapter 6 along with the trends in upper gastrointestinal bleed mortality.

CHAPTER 6

Reductions in 28-Day Mortality Following Hospital Admission for Upper Gastrointestinal Bleeding

6.1 Introduction

Changes in management have been shown in randomised controlled trials to improve outcome from gastrointestinal haemorrhage, but the largest observational studies of mortality trends following upper gastrointestinal haemorrhage report no improvement in overall mortality over the last two decades.[3–5] This failure to demonstrate an improvement suggests either, that clinical guidelines[140,141] derived from the results of randomised controlled trials are not generalisable to the clinical population, that they are not being implemented appropriately, or that the patients have changed at the same time as the treatments. This latter explanation, with increasing age and co-morbidity confounding the effects of therapy, has been proposed as the likely explanation.[60,121] However this has not been proven because to reliably measure the effect of changes in age and co-morbidity on mortality necessitates larger studies than have been published. Therefore, I aimed to investigate current trends in mortality following admission from upper gastrointestinal haemorrhage in England and investigate whether these can be explained by population changes in age and co-morbidity.

6.2 Methods

6.2.1 Study population

Inclusion criteria

All admissions 15 years or older which had an ICD 10 code for upper gastrointestinal haemorrhage (as described in table 4.1), with a date of haemorrhage between January 1st 1999 and December 31st 2007 were extracted. Data was available for 2008 to allow complete follow up of mortality for admissions occurring in December 2007. Subsequent re-admissions with upper gastrointesti-

nal haemorrhage were included in the study and recorded as a re-admission.

Exclusion criteria

The study population was geographically limited to patients who were resident within England at the time of hospital admission and exclusions made as described in chapter 4.1.

6.2.2 Outcome

Short term mortality was defined as in previous chapters as a date of death within 28 days of the start of the recorded episode of upper gastrointestinal haemorrhage. This included deaths that occurred after discharge from hospital but within the 28 days. The date and fact of death was obtained from the ONS death register using a deterministic matching algorithm based on NHS number, date of birth, postcode and sex.[130]

6.2.3 Exposures

The main exposure of interest was defined as the year of upper gastrointestinal haemorrhage. Charlson index,[142] sex, and age were assessed as potential confounders. The Charlson index was calculated for each upper gastrointestinal haemorrhage admission based on the diagnoses coded for all admissions up to and including the first upper gastrointestinal haemorrhage admission for each patient. This is a well validated weighted co-morbidity score derived from unselected hospital admissions that predicts 1 year mortality following hospital discharge. It has since been used in many contexts and has repeatedly measured the burden of co-morbidity reliably. The original paper demonstrated a graded increase in the risk in mortality associated with a cumulative score. The

different co-morbidities were assigned weights of 1, 2, 3 and 6 depending on their association with mortality. Where a graded effect was observed within a disease, for example in diabetes or malignancy, these diseases were further stratified according to their severity. The conditions included in the original score (in order of weighting) were myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, and acquired immunodeficiency syndrome. For analysis and reporting the score was combined into 3 groups; no co-morbidity(0), a single co-morbidity(1) and multiple or serious co-morbidity(2). For analysis of variceal haemorrhage the co-morbidity of liver disease was excluded from the calculation of Charlson index, as most variceal patients will have liver disease. The Charlson index has been adapted and validated for ICD 10 coding in administrative data[143,144] and has previously been used in HES.[145]

The recorded age was grouped into age bands of 15-29 years, 30-59 years, 60-79 years, and older than 80 years. I calculated the length of inpatient stay as the number of days between admission and discharge dates. I categorised admissions as either having a higher probability of being an acute bleed on admission (if an upper gastrointestinal haemorrhage was coded on the first episode in a non-elective admission) or as lower probability of being an acute bleed on admission with a higher probability of being an inpatient bleed (if the coding occurred after the first episode within a non-elective admission, or during an elective (non-emergency) admission). Hereafter these are referred to respectively as acute admissions and inpatient bleeds.

6.2.4 Statistical analysis

I analysed variceal and non variceal haemorrhage admissions separately. After the exclusions described above, 28 day case fatalities were calculated by age group, sex, year, grouped Charlson index, and acute or inpatient haemorrhage. A case control study analysis was carried out with cases defined as patients who had died by 28 days and controls as patients who were alive at 28 days. The primary exposure of interest was defined as year of upper gastrointestinal haemorrhage. A logistic regression model was constructed to adjust for the change in mortality over the study period by sex, age group and Charlson index. Variables that changed the odds of mortality were judged to be confounders. I assessed whether there was a trend in mortality over time, and whether this could be modelled as a linear trend using likelihood ratio tests. In addition, to determine if the changes in mortality varied for different ages, gender and co-morbidities, the model was also tested for interactions between each of the variables and year of bleed with likelihood ratio testing. If there was evidence against the null hypothesis of no interaction, stratified results were presented. The use of the a priori age groups was assessed against alternative groupings of 5 year age bands or age as a linear variable. All analysis was performed using Stata version 10 (StataCorp LP, Texas).

6.2.5 Sensitivity analyses

First I assessed the use of an alternative measure of co-morbidity called the Elixhauser index[146] that was derived to predict mortality during the inpatient stay. However it combined the outcome of mortality with financial costs and has not been previously validated within HES, so it was not used for my primary analysis.

Secondly, I performed two sensitivity analyses to assess the effect of inaccuracies in coding. To assess the effect of under reporting I expanded the definition for variceal haemorrhage to include all admissions coded for oesophageal haemorrhage (K22.8) and then re-assessed the trends in mortality. Then to assess whether there was over reporting of cases that might not be a genuine upper gastrointestinal haemorrhage, I analysed separately those who had and those who did not have an intervention of upper gastrointestinal endoscopy recorded (as defined by an OPCS4 code for an endoscopic procedure of the upper gastrointestinal tract).

Further sensitivity analyses were performed stratifying mortality trends by additional diagnoses for gastritis/duodenitis, Mallory Weiss syndrome, any peptic ulcer, gastric ulcer, duodenal ulcer and malignancy. I also performed a sensitivity analysis comparing trends in mortality that occurred before discharge and trends in mortality that occurred after discharge. The calculation of post discharge mortality excluded patients who had died as inpatients. Finally I assessed whether using a higher minimum age limit of 18 years altered the results.

6.3 Results

6.3.1 Study Population and exclusions

There were 516,153 upper gastrointestinal haemorrhage admissions identified after exclusions (shown in figure 4.1 in chapter 4) of which 501,471 (97%) were non variceal bleeds, and 14,682 (3%) were variceal bleeds.

6.3.2 Mortality ascertainment

74,992 deaths occurred within 28 days of the date of upper gastrointestinal haemorrhage giving an overall case fatality rate of 14.5% (95% confidence interval 14.4-14.6%). Of these 10,977 deaths (15%) occurred after discharge from hospital but within 28 days of haemorrhage. Only 312 (3%) of post discharge deaths were coded as a subsequent hospital admission within the HES dataset.

The population characteristics for non variceal and variceal haemorrhage are shown in table 6.1. The median age for non variceal bleeds was 71 years (inter quartile range 50-81 years) and for variceal bleeds was 55 years (inter quartile range 45-66 years). 46% of those presenting with non variceal haemorrhage had no co-morbidity recorded, compared to 67% of those presenting with variceal haemorrhage after the exclusion of liver disease from the calculation of co-morbidity. The population age structure and co-morbidity varied over the study period (figure 6.1) with a peak in the proportion of non variceal admissions over 80 years old in 2002. This matched the peak in case fatality in the same year (table 6.1). There was a reduction over time in the proportion of those presenting with variceal haemorrhage who were over 60 years old (figure 6.1). The co-morbidity for both groups increased over the study period. Median length of stay for non variceal haemorrhage was 4 days (inter quartile range 1-8 days) and for variceal haemorrhage was 7 days (inter quartile range 4-12 days). The length of stay reduced over the study period for non variceal haemorrhage from 4 (2-8 days) to 3 (1-6 days) ($p<0.001$ non parametric test for trend) but there was no reduction for variceal haemorrhage.

Non variceal and variceal haemorrhage

The overall 28 day case fatality following a non variceal haemorrhage admission was 14%, and following a variceal haemorrhage admission was 23% (table

Table 6.1: Population Characteristics for mortality study

	Non-variceal bleed admissions				Variceal bleed admissions			
	Number of Admissions (n)	Percentage of all Admissions	28 Day Deaths (n)	28 Day Case Fatality (%)	Number of Admissions (n)	Percentage of all Admissions	28 Day Deaths (n)	28 Day Case Fatality (%)
Year								
1999	51843	10.3	7644	14.7	1559	10.6	384	24.6
2000	53206	10.6	7865	14.8	1592	10.8	399	25.1
2001	53268	10.6	7952	14.9	1496	10.2	374	25.0
2002	53735	10.7	7990	14.9	1581	10.8	383	24.2
2003	55656	11.1	8155	14.7	1619	11.0	382	23.6
2004	57450	11.5	8075	14.1	1768	12.0	395	22.3
2005	59362	11.8	8251	13.9	1612	11.0	349	21.7
2006	58737	11.7	8042	13.7	1736	11.8	360	20.7
2007	58214	11.6	7632	13.1	1719	11.7	360	20.9
Total	501471	100.0	71606	14.3	14682	100.0	3386	23.1
Gender								
Male	276304	55.1	36681	13.3	9565	65.1	2201	23.0
Female	225167	44.9	34925	15.5	5117	34.9	1185	23.2
Age								
<30	39973	8.0	213	0.5	375	2.6	40	10.7
30 to 59	135507	27.0	7488	5.5	8749	59.6	1858	21.2
60 to 79	174181	34.7	26300	15.1	4688	31.9	1216	25.9
$\geq$80	151810	30.3	37605	24.8	870	5.9	272	31.3
Charlson index								
0	229941	45.9	15657	6.8	9825	66.9	2120	21.6
1	150004	29.9	20462	13.6	3832	26.1	964	25.2
2	121526	24.2	35487	29.2	1025	7.0	302	29.5
Bleed as acute admission or as inpatient								
Acute	295887	59.0	31199	10.5	10176	69.3	2041	20.1
Inpatient	205584	41.0	40407	19.7	4506	30.7	1345	29.8
Number of admissions								
Single	373132	74.4	61564	16.5	6802	46.3	2269	33.4
Multiple	128339	25.6	10042	7.8	7880	53.7	1117	14.2

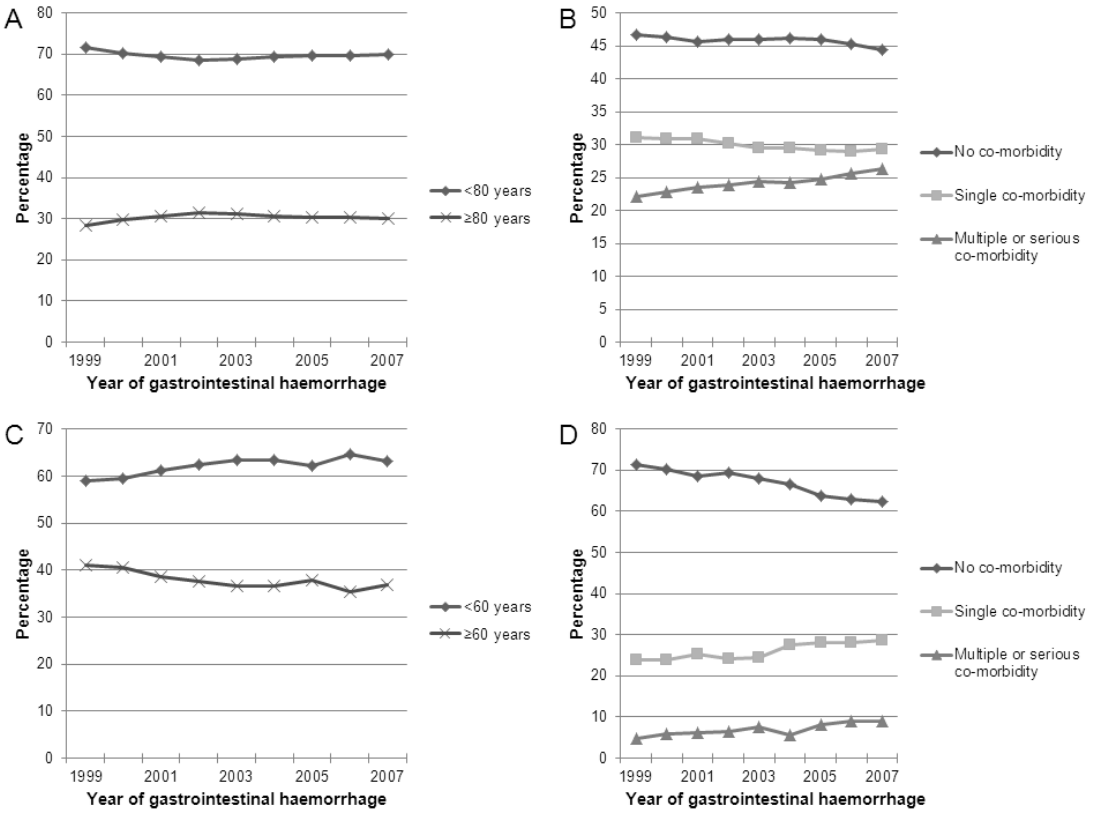


Figure 6.1: Trends in age and co-morbidity measured by grouped Charlson Index .

(Percentage of population shown) A Percentage of non variceal haemorrhage patients in each age band. B Percentage of non variceal haemorrhage patients in each co-morbidity group. C Percentage of variceal haemorrhage patients in each age band. D Percentage of variceal haemorrhage patients in each co-morbidity group.

6.1). From 1999 - 2007 the unadjusted 28 day mortality following non variceal haemorrhage reduced from 14.7% to 13.1% (unadjusted odds ratio 0.87 (0.84-0.90, 95% confidence interval). The unadjusted mortality following variceal haemorrhage reduced from 24.6% to 20.9% (unadjusted odds ratio 0.81 (0.69-0.95, 95% confidence interval).

Acute haemorrhage on admission compared with inpatient haemorrhage

28 day mortality for an acute admission with haemorrhage reduced over the study period for non variceal haemorrhage from 11.3% to 9.3% (unadjusted odds ratio 0.81, 95% confidence interval 0.77-0.85), and for variceal haemorrhage from 21.3 to 17.3% (unadjusted odds ratio 0.77, 95% confidence interval 0.62-0.95). 28 day mortality for cases with an inpatient haemorrhage also reduced over the study period, for non variceal haemorrhage from 20.0% to 18.4% (unadjusted odds ratio 0.91, 95% confidence interval 0.86-0.95), and for variceal haemorrhage from 32% to 29% (unadjusted odds ratio 0.88, 95% confidence interval 0.67-1.14).

6.3.3 Multivariate analysis

The odds of mortality for each year were altered when adjusted separately for each of the potential confounders of age, sex and Charlson Index. The slight peak in mortality in 2002 was removed when adjusting for the increase in age in 2002. Adjusting for increases in co-morbidity had the largest effect on the reduction in mortality. The multivariate model adjusting for all these variables is shown in table 6.2. Age and co-morbidity were stronger confounders for non variceal than variceal haemorrhage.

There was evidence of a linear trend in mortality over time, for both non variceal

Table 6.2: Logistic regression model predicting 28 day mortality

	Non-Variceal bleeding			Variceal bleeding		
Year of Presentation	**Unadjusted odds ratio**	**Adjusted odds ratio***	**95% CI**	**Unadjusted odds ratio**	**Adjusted odds ratio***	**95% CI**
1999	1.00	1.00		1.00	1.00	
2000	1.00	0.98	(0.94 - 1.01)	1.02	1.02	(0.87 - 1.20)
2001	1.01	0.97	(0.93 - 1.00)	1.02	1.02	(0.86 - 1.20)
2002	1.01	0.95	(0.92 - 0.99)	0.98	0.98	(0.83 - 1.15)
2003	0.99	0.94	(0.90 - 0.97)	0.94	0.95	(0.80 - 1.11)
2004	0.95	0.90	(0.86 - 0.93)	0.88	0.88	(0.75 - 1.03)
2005	0.93	0.89	(0.86 - 0.92)	0.85	0.83	(0.70 - 0.98)
2006	0.92	0.85	(0.82 - 0.88)	0.80	0.79	(0.67 - 0.94)
2007	0.87	0.80	(0.77 - 0.83)	0.81	0.80	(0.67 - 0.94)
Age						
<30 years	1.00	1.00		1.00	1.00	
30-59 years	10.09	7.22	(6.37 - 8.19)	1.93	1.92	(1.44 - 2.55)
60-79 years	30.04	16.80	(14.84 - 19.02)	2.51	2.37	(1.77 - 3.17)
>=80 years	55.62	34.14	(30.15 - 38.65)	3.26	3.05	(2.22 - 4.20)
Sex						
Male	1.00	1.00		1.00	1.00	
Female	1.20	1.01	(0.99 - 1.03)	1.01	0.96	(0.88 - 1.04)
Charlson Index						
0	1.00	1.00		1.00	1.00	
1	2.16	1.70	(1.66 - 1.74)	0.99	1.17	(1.07 - 1.27)
2	5.64	4.37	(4.28 - 4.47)	1.31	1.37	(1.18 - 1.58)

haemorrhage and variceal haemorrhage (p<0.001), and there was minimal evidence to suggest that a linear model was inappropriate for the data (test for departure from a linear trend; non variceal haemorrhage p=0.061, variceal haemorrhage p=0.94). The adjusted average annual reduction in odds of mortality for non variceal haemorrhage was 2.5% (average annual OR 0.97, 95% confidence interval 0.97-0.98) and for variceal haemorrhage was 3.5% (average annual OR 0.96, 95% confidence interval 0.95-0.98).

Further analyses for interactions demonstrated different time trends for different ages and different levels of co-morbidity for non variceal haemorrhage (likelihood ratio tests for interactions of both age and co-morbidity with year p<0.001), but not for variceal haemorrhage (year and age p=0.29, year and co-morbidity p=0.67). Consequently the age stratum specific average annual changes in odds of mortality for non-variceal haemorrhage were presented in table 6.3. The annual improvement in odds of mortality was minimal for those presenting 80 years and older compared to all the other age groups. Further stratifying the model by age and co-morbidity (table 6.4) demonstrated that within each age specific stratum the improvement in mortality did not differ by the level of co-morbidity. Therefore the final model of a linear trend in 28 day mortality for non variceal haemorrhage is the model shown in table 6.3, with confounding by co-morbidity adjusted for by logistic regression, and effect modification demonstrated by stratifying the results by age. The final model of a linear trend in 28 day mortality for variceal haemorrhage demonstrated only confounding by both co-morbidity and age with no effect modification.

6.3.4 Sensitivity analyses

The first sensitivity analysis used the Elixhauser index to adjust for co-morbidity and this showed a slightly increased average annual reduction compared to us-

Table 6.3: Age stratified logistic regression model predicting 28 day mortality for non variceal haemorrhage

	Adjusted Odds ratio*	95 % confidence interval
Change in mortality for an increment of one year**		
< 30 years	0.92	(0.88 - 0.97)
30-59 years	0.97	(0.96 - 0.97)
60-79 years	0.97	(0.96 - 0.97)
>= 80years	0.99	(0.98 - 0.99)

*Adjusted for co-morbidity by Charlson index and sex
**Year as a continuous variable

Table 6.4: Age and co-morbidity stratified logistic regression model predicting 28 day mortality

Age	Charlson Index	Adjusted Odds ratio*	95 % confidence interval
Change in mortality for an increment of one year**			
<80 years			
	0	0.96	(0.95 - 0.97)
	1	0.96	(0.95 - 0.97)
	2	0.95	(0.95 - 0.96)
>=80 years			
	0	1.00	(0.99 - 1.01)
	1	0.99	(0.98 - 0.99)
	2	0.98	(0.97 - 0.99)

* Adjusted for sex
**Odds ratio for year as a continuous variable

ing the Charlson index to adjust for co-morbidity (non variceal haemorrhage OR 0.96, 95% confidence interval 0.96-0.97). However the overall model with the Elixhauser index did not have as good a fit to the data as when the Charlson index was used to adjust for co-morbidity.

Secondly, I performed two sensitivity analyses to assess the effect of inaccuracies in coding. A repeat analysis was conducted including oesophageal haemorrhage codes (K22.8) as a variceal haemorrhage admission, and this estimated an annual reduction in odds of mortality of 3.6% (average annual OR 0.96, 95% confidence interval 0.95-0.98). I then found a similar reduction in non variceal haemorrhage admissions that had an endoscopy recorded (average annual OR 0.97, 95% confidence interval 0.96-0.97), to those that did not have an endoscopy recorded (average annual OR 0.96, 95% confidence interval 0.96-0.97). This was also the case for variceal haemorrhage, though as only a few cases did not have an endoscopy there was greater uncertainty (with endoscopy: average annual OR 0.98, 95% confidence interval 0.96-0.99; without endoscopy: average annual OR 0.95, 95% confidence interval 0.92-0.98).

Stratifying the results by associated diagnoses of gastritis/duodenitis, Mallory Weiss syndrome, any peptic ulcer, gastric ulcer, duodenal ulcer or malignancy, associated with non variceal haemorrhage found similar reductions in mortality following all these diagnoses (see table 6.5). Re-analysing the trends only for mortality prior to discharge demonstrated the same reduction in inpatient mortality as in the main analysis (non variceal average annual adjusted mortality OR=0.97, 95% confidence interval 0.97- 0.98). In contrast the mortality after discharge increased slightly, (non variceal average annual adjusted mortality OR=1.02, 95% confidence interval 1.02-1.03). Finally the use of alternative 5 year groupings for age did not alter the analysis neither did an alternative minimum age limit of 18 years.

Table 6.5: Trends in 28 day mortality for diagnoses associated with an upper gastrointestinal haemorrhage

Diagnosis associated with upper gastrointestinal haemorrhage	Adjusted odds ratio*	95% confidence intervals
	Change in mortality for an increment of one year**	
No specific diagnosis	0.97	(0.97– 0.98)
Gastritis/Duodenitis	0.96	(0.94– 0.98)
Mallory Weiss Syndrome	0.96	(0.95– 0.97)
Any Peptic Ulcer	0.96	(0.93— 0.99)
Gastric Ulcer	0.94	(0.93–0.95)
Duodenal Ulcer	0.96	(0.95– 0.97)
Malignancy	0.95	(0.95–0.96)

*Adjusted for age, sex and co-morbidity by Charlson index
**Year as a continuous variable

6.3.5 Regression diagnostics

Delta beta statistics were calculated for the final model and these were all less than one. These measured the standardised change in the coefficients when observations with each covariate pattern were deleted. This indicated that no individual covariate pattern was particularly influential on the estimated coefficients. Outliers with influence on the overall model fit were estimated by delta Chi-squared statistics values over 3. This measured the change in Chi-squared value for the model with the deletion of each observation. These outliers were generally patients with a lower predicted mortality who nevertheless died. These accounted for 1% of the study population and if excluded the overall reduction in mortality over the study remained at 20%.

6.4 Discussion

The failure of previous studies to demonstrate improvements in mortality after upper gastrointestinal haemorrhage at the population level calls into question the value of therapeutic changes which are of proven benefit to individuals. In an increasingly challenging economic environment clinicians will need to be

able to demonstrate that increased therapeutic expenditure really does bring benefits. That 28 day mortality for equivalent patients, following hospital admission for both non variceal and variceal upper gastrointestinal haemorrhage, has reduced by 2 and 3% respectively year on year in England over the period 1999 to 2007 is therefore of great importance.

6.4.1 Strengths and limitations

When, as in this case, a study's findings differ from the previous literature, we must ask whether this is because the current or previous studies were in error, or whether they are in reality observing different things. The data source chosen for my study provides key advantages. The study is the largest to date of mortality after hospital admission for gastrointestinal haemorrhage and therefore has power to demonstrate trends that would be missed in smaller studies. It also has power to demonstrate variations in trends between subgroups of the population such as the smaller reduction in mortality in those over 80 years old with non variceal haemorrhage. The provision within the dataset of information on the previously suggested confounders of age and co-morbidity is also of great benefit, and has allowed us to clearly show and correct for this confounding.

Another key advantage of the current study is the linkage of clinical data with the ONS death register, ensuring that almost all deaths are captured in the study population. Hospital admission data only captures deaths occurring before discharge, which I found to be 86% of the deaths occurring within 28 days. Studies without such linkage will have missed a proportion of these deaths, since post discharge deaths will have been difficult to capture. Furthermore any change in this capture over time may have biased results. The linkage used in the current study, depending as it does on deterministic matching, still leaves potential for

some underestimation of mortality but the robustness of the linkage coupled with its uniform methodology throughout the study period mean that bias due to this is unlikely to have occurred. The reduction in length of stay over the course of the study further emphasises the importance of identifying deaths following discharge to accurately calculate trends in mortality. The slight increase in post discharge mortality might imply that the observed earlier discharge of patients was inappropriate, however if management in hospital was no longer of benefit to a patient who is dying, then discharge might well be the most appropriate decision. The observed trends might therefore indicate a shift of previously unavoidable inpatient mortality into the post discharge period.

Patients who died in the emergency department before admission for endoscopy were not included in my study, as hospital admissions data contains information only on admitted patients. However, as acute admission to hospital for all upper gastrointestinal haemorrhage was standard practice within England, the admissions data will have captured almost all other relevant bleed presentations. Patients who had a non specific code for gastrointestinal haemorrhage with a colonoscopy but no gastroscopy were excluded, but it is possible that these could have had an upper gastrointestinal bleed if they had died before a planned gastroscopy. However this would be unlikely as usual practice would be to perform a gastroscopy before colonoscopy due to the easier access and greater therapeutic potential of gastroscopy.

The coding of upper gastrointestinal haemorrhage has been discussed in chapter 4. This of course does not exclude variation in rates of coding over the study period affecting my estimates. For example if the potential error in coding was systematically changing over time with increased coding of patients' co-morbidity rather than patients having more co-morbidity, then clearly that could bias my results. However the different trends in co-morbidity for variceal and non variceal bleed admissions, and different trends in mortality in differ-

ent age and co-morbidity strata, suggests that there was no systematic change in co-morbidity coding over the time period of my study. Under-reporting of the co-morbidities in the Charlson index may have resulted in incomplete adjustment for co-morbidity. However, although the alternative Elixhauser index assessed almost twice the number of co-morbidities, it did not alter the adjustment of co-morbidity in the model. Co-morbidity adjustment by either index increased the magnitude of the mortality reduction, and therefore any residual confounding in this regard would only, I believe, cause an underestimate of the real mortality trend in my study.

6.4.2 Other studies

A PubMed search, to December 2012, found the largest comparable population based study for non variceal haemorrhage mortality trends used a Canadian hospital discharge database with ICD 10 and ICD 9 codes. However it identified less than a third of the number of bleeds used for this study (n=142,363) and was not able to identify a reduction in case fatality for non variceal haemorrhage between 1993 and 2003.[4] The researchers adjusted for changes in age, but not for changes in co-morbidity. They also only identified deaths that occurred before discharge. The low mortality identified in this study (3.5%) is similar to other North American,[12] and Mediterranean studies,[5,147] but is much lower than other European studies.[3,26,61] However, a study of Medicare patients in the US found that the proportion being managed as outpatients varied between states from 18.6%-45.3%.[35] These differences in practice would lead to differences in inpatient study populations and confound comparisons with countries such as England where outpatient management is not routine.

Although reports from US National Inpatient Sample showed a 23% reduction in upper gastrointestinal haemorrhage mortality from 96/100,000 in 1998

to 82/100,000 in 2006,[12] and a similar 23% reduction from 78/100,000 in 2001 to 61/100,000 in 2009,[27] these incidence estimates are inconsistent with each other despite being from the same data source with the same case definitions. Another report from the US National Inpatient Sample noted an adjusted reduction in variceal haemorrhage from 18% to 12%.[76] However, the number of cases in these studies is extrapolated from a 20% sample and although a number of weighting procedures are used, the estimates remain susceptible to selection bias. Furthermore in the study period of these reports, the number of states in the sampling frame almost doubled from 22 to 40. The reports therefore compare different populations from each time period.

One smaller study from Wales (n=24,421) used the same ICD 10 definitions as my study and also found an overall reduction in case fatality, but did not report variceal and non variceal haemorrhage mortality trends separately or trends in different age and co-morbidity strata.[25] Other non variceal haemorrhage studies from Spain(n=17,663),[5] the Netherlands (n=1,720),[3] Greece (n=1,304)[147], France (n=1,165)[61] and Italy (n=1,126),[26] did not identify reductions in non variceal inpatient mortality. Although these were large studies they may have been underpowered to detect a change, and none of them adjusted the trends in case fatality for changes in co-morbidity. Furthermore, none of these studies identified deaths that occurred after discharge. The remainder of studies contained less than 1000 patients and therefore could not provide accurate estimates of mortality trends.

For variceal haemorrhage the largest study on mortality after hospitalisation due to varices (n=12,281; compared to 14,682 for this study) did not differentiate between haemorrhage and non-haemorrhage admissions.[38] The next largest study (n=1475) compared variceal haemorrhage mortality between control groups in randomised trials 1960-2000 and showed a similar reduction in mortality.[69] However these control groups were from different geographical

populations with different study exclusion criteria. Comparisons were therefore susceptible to selection bias. Other studies of trends in variceal haemorrhage mortality contained less than 1000 patients.

The other finding of note in my study, in relation to variceal haemorrhage, was the small proportion of overall haemorrhages which they represent. In the context of the increasing burden of liver disease[39] and an apparent increase in variceal haemorrhage in the recent BSG audit,[1] a higher proportion might have been expected. My finding however was similar to that from the 1993 BSG audit (4%) and to other studies.[23] It is possible that some of the variceal haemorrhage in my study may have been incorrectly coded to oesophageal haemorrhage, but a sensitivity analysis, assuming the most likely misclassification of all oesophageal haemorrhage codes being miscoded variceal bleeds, did not alter the adjusted reduction in mortality.

The previous difficulties in detecting a reduction in mortality might imply that we are reaching the point where mortality becomes unavoidable due to age and co-morbidity. However as the mortality in my study continued to improve right up to the end of the study period, improvements in management would appear to be continuing to have an impact on mortality following gastrointestinal haemorrhage. The reasons for the reduction in mortality I have observed are likely to be complex. There were similar reductions in mortality whether or not an endoscopy was recorded and for all associated diagnoses, implying that endoscopic therapy was not a major contributor to the reduction in mortality. Instead my data perhaps suggests that improvement in standard non endoscopic care has led to improved survival; such as the routine administration of intravenous proton pump inhibitor infusions, the routine use of risk scoring, the implementation of standardised clinical guidelines, and subsequent local auditing of practice.[140,141,148]

In conclusion, contrary to previous smaller studies, I have found an encouraging substantial improvement in mortality following hospital admission for upper gastrointestinal haemorrhage. My study shows that this is partially obscured by increases in age and co-morbidity. This improvement is likely the result of changes in the care of gastrointestinal haemorrhage over the last decade, but it also suggests the need to focus our ongoing attention on the elderly who may not yet have benefited to the maximum possible extent from these changes. The recent demonstration of underutilisation of endoscopic techniques in the UK, coupled with the fact that other interventions such as use of proton pump inhibitors are more readily available to the admitting physician worldwide, may suggest areas which could be further improved.[57,140,141,149,150]

CHAPTER 7

Defining cases in linked HES and GPRD data

7.1 The Linked Dataset as a Sample of the GPRD

Electronic health records are cheap, convenient, and provide power for studies that would be unfeasible in bespoke patient cohorts. Previously in this PhD (chapter 4) I have used secondary care data (Hospital Episodes Statistics - HES) to measure upper gastrointestinal haemorrhage and found the numbers of cases and procedures identified were comparable to a national hospital audit.[151] However for the remaining studies in this PhD, more comprehensive prescription and co-morbidity data were required for each patient prior to their hospital admission. As this was either unavailable or incomplete in secondary care data, I used primary care data (General Practice Research Database - GPRD) in which the coding for upper gastrointestinal bleeding has been shown to be valid in 99% of cases by chart review (95 cases confirmed out of 96 cases assessed).[100] To retain the advantages of hospital data procedural coding, multiple hospital diagnoses, and accurate admission dates, I took the opportunity to use linked GPRD, HES and ONS (Office for National Statistics) data. The linkage did not cover the entire GPRD at the time of the PhD, but had only been performed for consenting practices. This might have selected an unrepresentative sample of the underlying database. Therefore comparisons between the linked dataset, the whole GPRD, and the UK population are assessed in this chapter in section 7.2.2. Individuals have been mapped between the databases by anonymised patient identifiers as part of the linking process for the GPRD by a trusted third party. However the clinical events and coding within these linked individuals have not been defined. Therefore in section 7.3 different methods of identifying the codes that correspond to the same event within the linked dataset are assessed by comparing the effect of different case definitions on mortality and occurrence.

7.2 Comparison of linked dataset to GPRD and ONS populations

7.2.1 Description of linked dataset

Hospital Episodes Statistics.

The HES database has been described in chapter 4.

General Practice Research Database.

The GPRD contains longitudinal primary care data that are validated and individualised for over 46 million person years since 1987, and reflect the observations, diagnoses made, and therapies prescribed by general practitioners in addition to any information communicated from secondary care.[152] The comprehensive English primary care system means that the population registered to the GPRD is representative of the general English population.[153] The data are subject to regular checks to ensure data is being recorded reliably and consistently, and a practice's data is only used when it is of high enough quality to be used in research, referred to as "up to standard."[154] The GPRD has been extensively validated for a wide range of diagnoses with a mean positive predictive value of 89%.[155] The data are coded using the Read code system (in use in the NHS since 1985 and managed by the UK Terminology Centre)

Linkage.

The anonymised patient identifiers from GPRD, HES, and ONS death register have been linked with deterministic matching using the NHS number, date of birth, postcode and sex[156] (as was previously done to link ONS data to HES[130]).

As HES only covers English hospitals, practices in Northern Island, Wales and Scotland were excluded. For this study I used the January 2011 download of GPRD GOLD data, in which 51.3% of GPRD primary care practices within England consented for their data to be linked.

7.2.2 Comparison of linked dataset with estimates of the UK population

The representativeness of the population in the linked dataset was assessed by comparisons with the whole GPRD and estimates of the general UK population available from the ONS. The comparisons were made on June 30th 1999 and June 30th 2009.

Age and sex

Figures 7.1 and 7.2 show the population pyramids in 1999 and 2009.

The population pyramid in the linked dataset had a similar age and sex structure to that in the whole GPRD in both 1999 and 2009. However infants and young adults were under-represented when compared to the ONS data. The GPRD database and the linked dataset included a lower proportion of 12-28 years old in 1999 and 18-28 years old in 2009 when compared to the ONS estimates. Older ages were conversely slightly over-represented.

Region

Figures 7.3 and 7.4 show the proportion of the population from each region in the GPRD database, linked dataset and ONS estimates. As the linkage was only available for English primary care practices only English regions were included.

Yorkshire, East Midlands and the North East were under represented in the

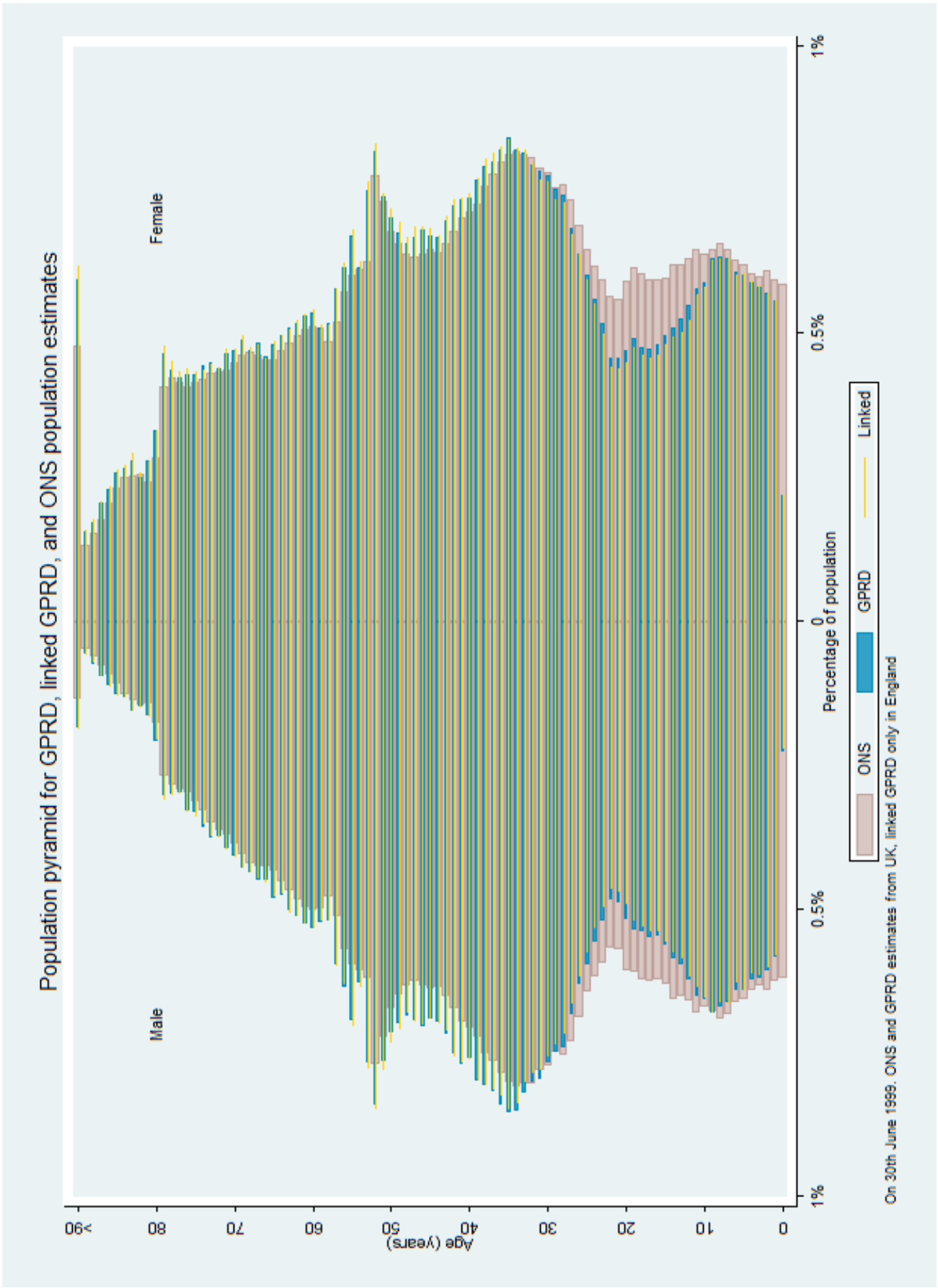


Figure 7.1: Proportion of GPRD, linked dataset and ONS UK population estimates by age and sex in 1999

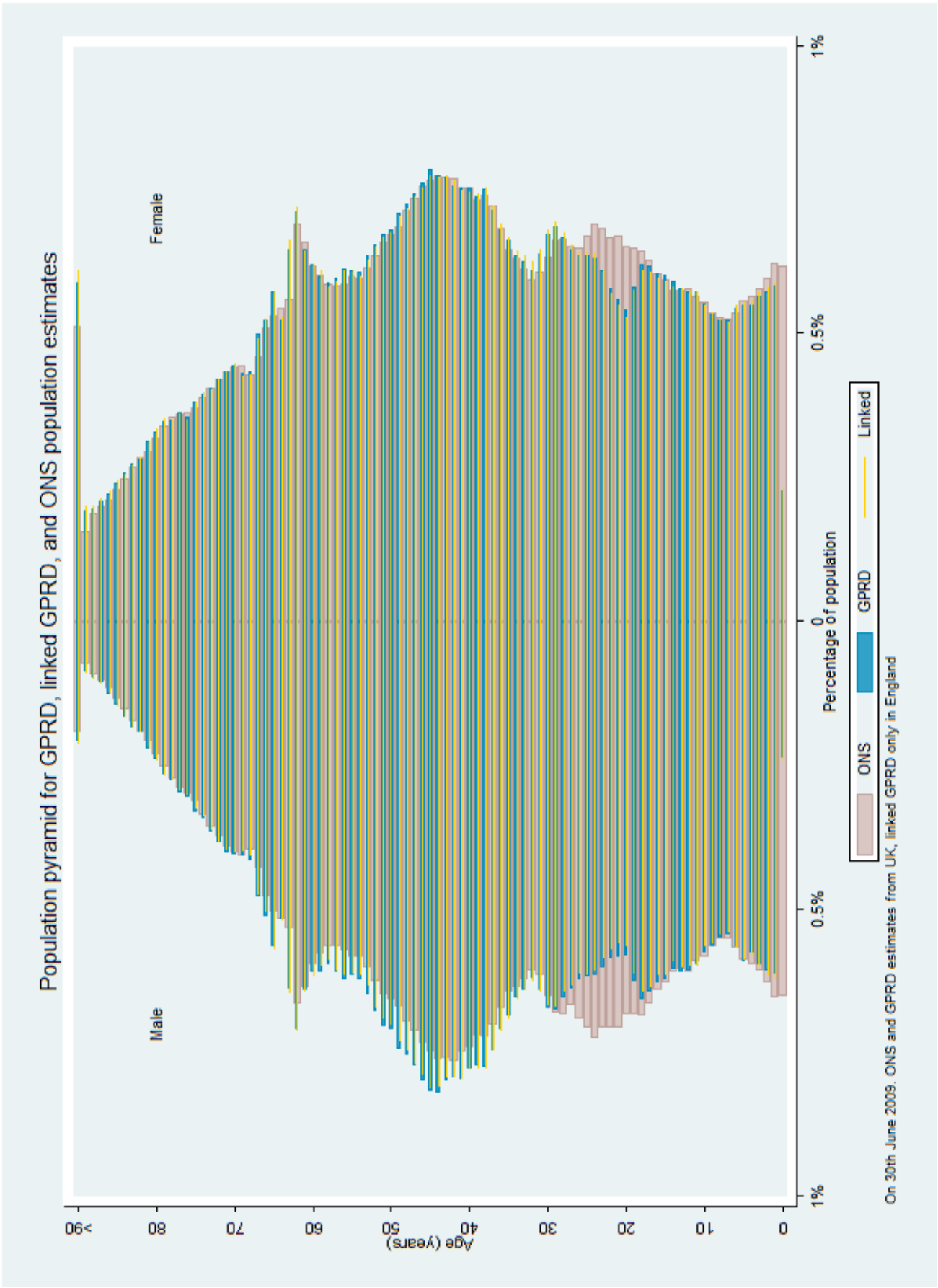


Figure 7.2: Proportion of GPRD, linked dataset and ONS UK population estimates by age and sex in 2009

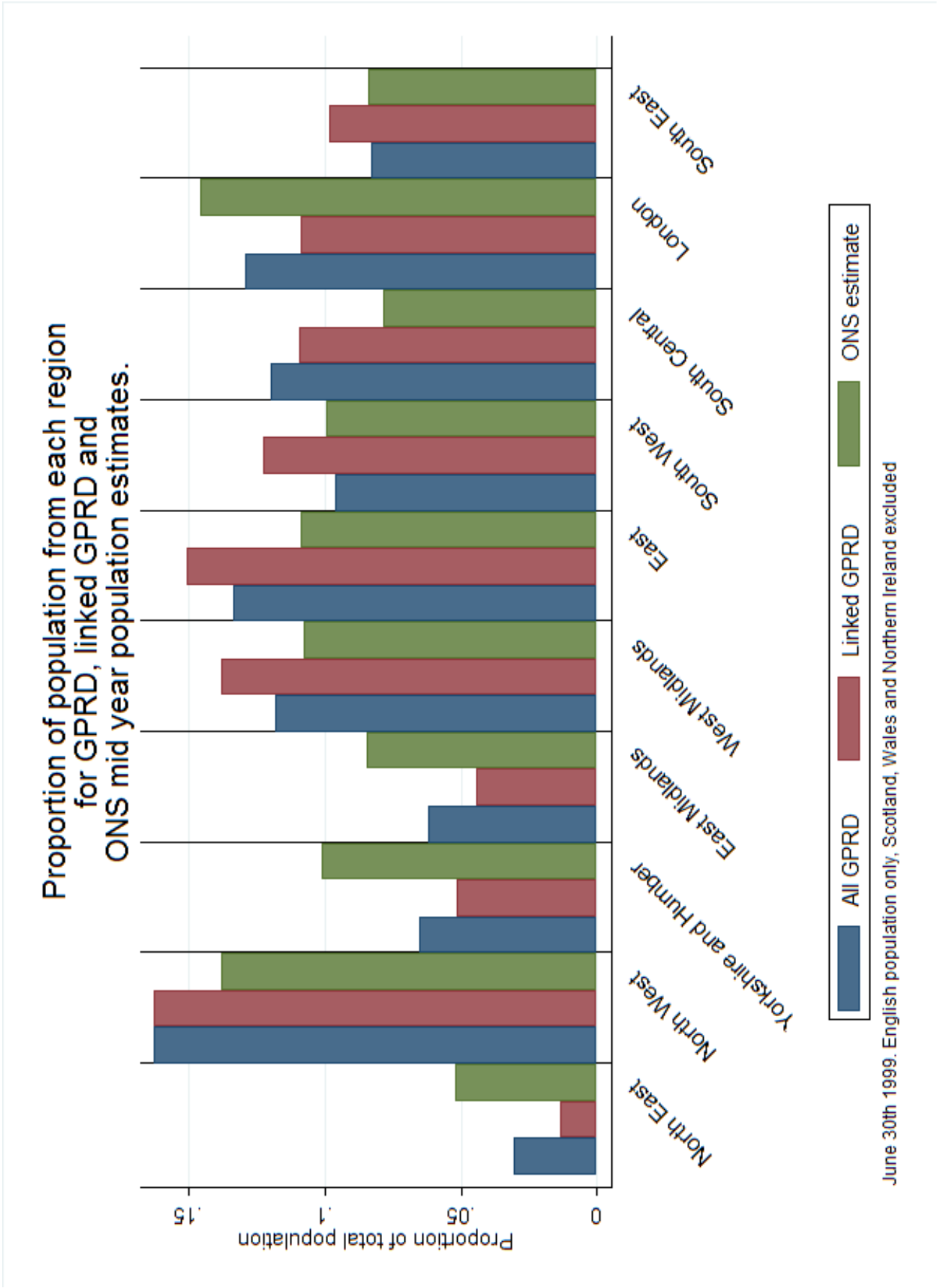


Figure 7.3: Proportion of GPRD, linked dataset and ONS UK population estimates by region in 1999

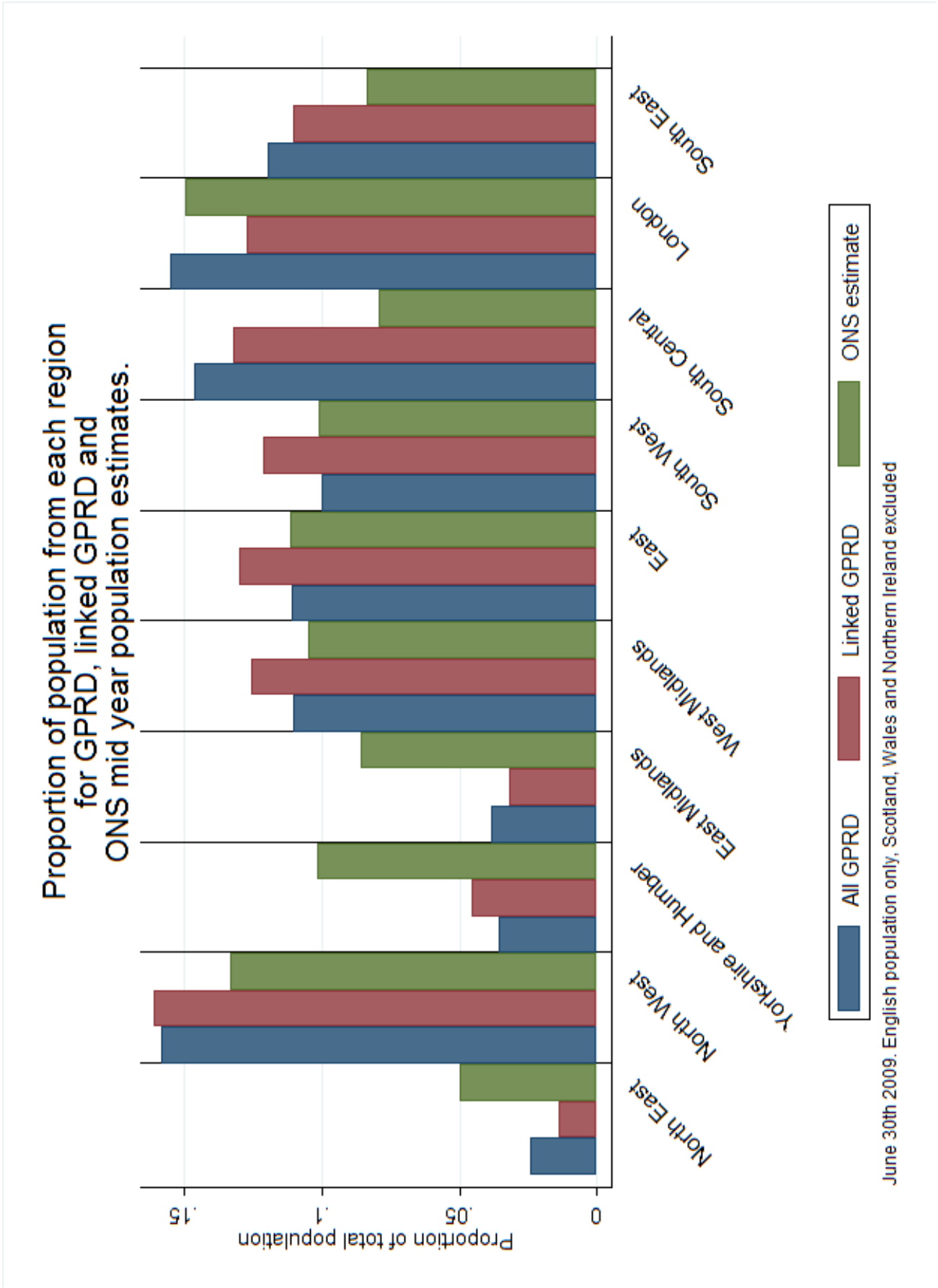


Figure 7.4: Proportion of GPRD, linked dataset and ONS UK population estimates by region in 2009

GPRD database and linked dataset compared to the ONS data in both 1999 and 2009. Other regions were correspondingly over represented.

7.2.3 Interpretation

The North East, East Midlands and Yorkshire were under represented by an absolute proportion of 5% of the GPRD. This is likely to be a consequence of the lower uptake in these regions of first the DOS based VAMP ('Value Added Medical Products') and then the Microsoft-Windows based Vision software systems by primary care.[157] This software was the basis for the GPRD data collection. Interestingly these regions that were under-represented in the GPRD were the same regions that have been over-represented in the QRESEARCH database that utilises the competing EMIS software system ('Egton Medical Information Systems').[158]

As the regional differences were associated with deprivation and upper gastrointestinal haemorrhage, potential selection bias might be introduced into my studies. However I have already identified that the variation by region was mostly explained by the socioeconomic status within that with region, therefore the GPRD linkage to the ONS Index of Multiple Deprivation quintiles permits the assessment of any potential confounding by deprivation and therefore by region. Furthermore as the planned studies involve comparisons with controls matched from the patients' primary care practice, controls will be exactly matched by region, and so internal comparisons will be less susceptible to bias. With regard to generalisability to the English population, there will still be considerable numbers of participants from the under-represented regions contributing to the study and its results.

There was a low proportion of the population in the GPRD compared to the population in the ONS who were younger than one year. This potentially re-

flects a delay in parents registering infants with a general practitioner. Teenagers and young adults were also under represented in the GPRD database and linked dataset, and this probably reflects the transitory nature of this life stage. Young adults are theoretically more mobile after leaving home whilst they develop new careers and training (for example by attending university) and this might delay registering with a general practitioner until they become more established or have ill health. With respect to this PhD however, upper gastrointestinal bleeds were relatively infrequent in this age group (8% of non variceal bleeds in my earlier studies in HES with a 30 day mortality of 0.5%), so this is unlikely to have an important effect on my results. Furthermore comparisons are to be made with age matched controls, and there are considerable numbers from these age groups still contributing to the study population allowing valid internal comparisons to be made.

7.2.4 Conclusion

The linked dataset is likely to provide a representative sample of the UK population with regard to those who experience upper gastrointestinal bleeding. Infants and young adults are under represented, but these are not groups that contribute to the majority of bleeding episodes according to the secondary care data already examined in chapter 5, and therefore the linkage is unlikely to introduce any significant bias or confounding to the studies in this PhD. However any observations that are made in those under 30 years old will need to be interpreted with caution.

For the same reasons any investigation of variations in incidence of bleeding by region within the GPRD or linked dataset might also be effected by selection bias and need to be treated cautiously. However for the planned studies on aetiology and outcomes of upper gastrointestinal bleeding only internal com-

parisons were made and the effect of region cannot assessed as controls were matched exactly on the primary care practice of the cases.

7.3 Defining upper gastrointestinal bleeding from linked primary and secondary care data and the effect on occurrence and 28 day mortality

7.3.1 Introduction

The initial attempts to define a cohort of upper gastrointestinal bleeding from the linked HES and GPRD demonstrated discrepancies in the cases detected. I have therefore investigated the reasons for this by studying alternative methods of defining cases (separately in each dataset or various combinations from both datasets) and to what extent the choice between these methods effects my results.

7.3.2 Aim and Objectives

To investigate in a defined population with primary and secondary care data how case definition sensitivity and specificity is associated with 28 day mortality.

To achieve this I will:

1. Define upper gastrointestinal haemorrhage separately within primary care and secondary care data.

2. Define time windows and acceptable codes for concurrent coding of bleed events in the linked datasets.

3. Assess the effect of different case definitions made in linked primary and secondary care data on 28 day mortality.

7.3.3 Methods

Defining upper gastrointestinal haemorrhage separately within primary care and secondary care data.

Defining cases in the General Practice Research Database Primary care bleed events were defined in GPRD using Read codes that indicated a definite diagnosis or symptom of upper gastrointestinal bleed. Codes for unspecified gastrointestinal bleeding were also included to be consistent with previously published ICD 10 code lists in chapter 4.1,[25,159,160] and were similarly excluded if they had a code for a lower gastrointestinal diagnosis or procedure.

Primary care bleed events were excluded if the patient was 15 years old or younger, had temporary registration, had invalid date codes, was coded as elective or daycase, or occurred outside the observed and up to standard time period. The start of the observed and up to standard time period was defined as the latest of; the up to standard data collection date, 1st April 1997 (start of matching of GPRD and HES), or 3 months post current primary care registration. The purpose of the latter exclusion was to avoid matching of prevalent events recorded during a new patient registration. Previously Lewis *et al* reported that 3 months was an appropriate time window to exclude for acute events,[161] and I have confirmed this by assessing the incidence of specific upper gastrointestinal bleed codes in the GPRD by month over the first year (figure 7.5). This demonstrated that the incidence of new bleed codes fell close to the baseline level by 3 months. The end of the observed time period was defined by the earliest of; date of death, date of transfer out of practice, 31st August 2010

(end of matched HES data in current linkage) or the last collection date for the practice.

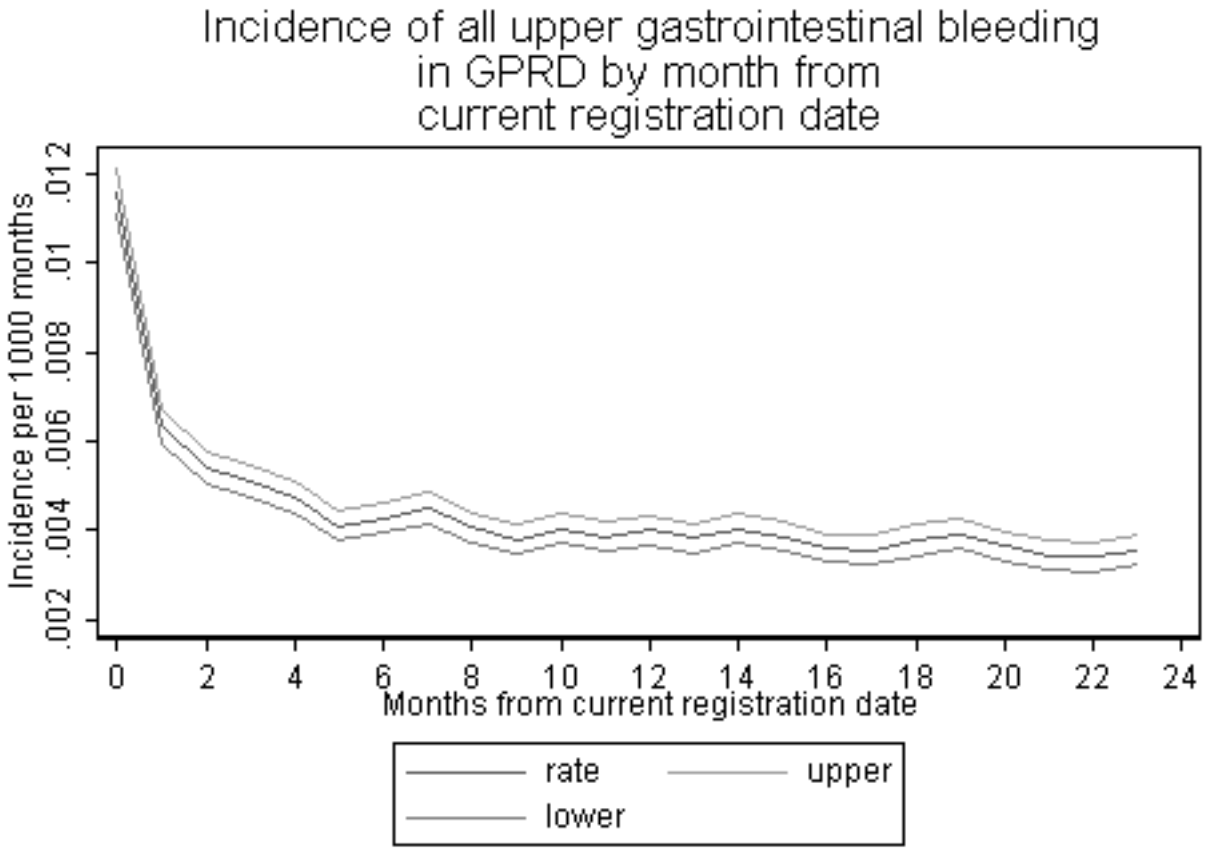


Figure 7.5: Incidence of upper gastrointestinal bleeding in GPRD by month from current registration date

Defining cases in the Hospital Episodes Statistics database Secondary care bleed admissions were defined in HES using the ICD 10 code list used in chapter 4.1.[159,160] Multiple admissions were included for each patient.

Secondary care events were excluded if the patient was 15 years old or younger, had temporary registration in primary care, had invalid date codes, was coded as elective or daycase, or occurred outside the observed and up to standard time period as defined in the previous section for GPRD.

Defining concurrent events in the linked datasets

Defining time windows for concurrent codes in primary and secondary care The standard within the NHS for hospital communications is that a discharge letter, with a minimum of the main discharge diagnosis and prescriptions, should be sent to the primary care doctor within 24 hours of discharge.[162] A time difference greater than 2 months was judged too long for delivery of discharge letters and its subsequent coding, and I therefore used 2 months as the cut off for associating separate events from the linked datasets. Time periods allowing for intermediate delays in primary care coding were defined for less than 2 months, 1 month, 2 weeks, or 1 week pre or post the event defined in either primary or secondary care. An event of upper gastrointestinal bleeding might have been coded first in either primary care prior to referral or in secondary care on the admission date. I therefore selected the earlier of the two dates as the index date for the 28 day case fatality analysis.

Defining acceptable concurrent codes in primary and secondary care An upper gastrointestinal bleed code in one database could have a number of legitimate corresponding codes in the linked datasets instead of a specific code for upper gastrointestinal bleeding - for example outcomes such as death or collapse, underlying diagnoses such as cancer, or procedures such as oesophagogastroduodenoscopy. To allow for this heterogeneity in coding, 'probable' and 'possible' groups of ICD 10 and Read codes were selected that could plausibly be coded following an upper gastrointestinal bleed. 'Probable' codes were defined as those specifying a likely symptom, cause, therapy, investigation or outcome of upper gastrointestinal haemorrhage. 'Possible' codes were defined as those that non specifically indicated a change in health state without indicating an alternative diagnosis to a gastrointestinal bleed (see table 7.1, 1=Most

probable, 16=Less probable, full code lists are in appendix A.1 and A.2). This was based on the clinical judgement of the authors (2 consultant gastroenterologists and 1 trainee gastroenterologist).

Category Order	Group name	Group definition	Probable or possible codes
1	Upper GI bleed cause	Code for known upper GI bleed diagnosis or cause. e.g. ulcer, oesophagitis, NSAID or Aspirin use, cirrhosis, upper GI malignancy etc.	Probable
2	Upper GI bleed symptom	Symptoms indicating upper GI bleed e.g. melaena, haematemesis etc.	Probable
3	Upper GI endoscopy	Any upper GI endoscopy code (Not ERCP/EUS).	Probable
4	Death (any cause)	Any code associated with death.	Probable
5	Blood transfusion	Any code for blood transfusion or cross matching.	Probable
6	Upper GI procedure	Any code for an upper GI procedure plausible for managing a bleeding episode.	Probable
7	GI bleed symptom	Any general code for GI bleed (not specifically upper or lower).	Probable
8	Upper GI diagnosis	Any other code for an upper GI pathology that might be associated with an upper GI bleed.	Possible
9	Hospital	Any code for referral, admission or discharge to hospital in a general or related specialty.	Possible
10	Upper GI symptom	Any other code for symptoms of upper GI pathology e.g. vomiting.	Possible
11	GI symptom or diagnosis	Other GI diagnoses or non specific GI symptoms(e.g. pain) excluding lower GI symptoms.	Possible
12	Alcohol	Any code indicating alcohol consumption or complications.	Possible
13	Anaemia	Any code for anaemia excluding chronic deficiency anaemias and fatigue.	Possible
14	Coagulation	Any code indicating primary or secondary clotting abnormality, or use of anti coagulation therapy.	Possible
15	Collapse	Any code indicating collapse, fall or loss of consciousness.	Possible
16	Other codes	Other codes specifying a change in health state with no specific diagnosis	Possible

Table 7.1: Categories of Read or ICD 10 Codes that Might be Associated with a Hospital Admission for Upper Gastrointestinal Haemorrhage.

Listed in Order of how Probable a Code Category Would be Associated with an Upper Gastrointestinal Haemorrhage Admission (1=Most Probable)

Classification of case definitions of upper gastrointestinal bleeding in linked primary and secondary care data.

I defined four case definitions of differing specificity and assessed how this altered my study population with regard to occurrence and case fatality. All four case definitions required at least a specific upper gastrointestinal bleeding code from one database with or without a code from the linked dataset that was of differing specificity; from the broad and sensitive case definition 1 that requires no linked code, to the restrictive and specific case definition 4 requiring a specific bleeding code. For each case definition the cases that were initially defined from the individual datasets (identified as (a) for HES and (b) for GPRD) were pooled and duplicates excluded. Duplicate events were identified as those that occurred within the 2 month time window I used for defining corresponding codes.

Definition 1 - All secondary and primary care defined events This broad and sensitive definition selected all possible cases of upper gastrointestinal bleeding from the linked data. All cases defined by a specific Read or ICD 10 bleed code in either database were combined and duplicate events were excluded.

Definition 2a & 2b- Primary and secondary care events that had a concurrent 'Probable' or 'Possible' code in the linked dataset This definition selected all cases of upper gastrointestinal bleeding that had either a supporting code (probable code) in the linked data or a less specific code (possible code) that did not contradict the bleeding diagnosis. Therefore for each upper gastrointestinal bleed defined in either dataset from definition 1, a specific bleed code, probable code or possible code was searched for in the linked dataset within the 2 month time window and selected in the hierarchical order of the categories listed in table 7.1 . Each primary care event was matched to only one hospital

admission that was closest in time and vice versa.

Definition 3a & 3b) - Primary and Secondary care events that had a concurrent 'Probable' code in the linked dataset This definition selected all cases of upper gastrointestinal bleeding that had a code in the linked data that supported the diagnosis of bleeding. This required restricting the cases defined in 2a & 2b to only those with a more specific probable code in the linked dataset.

Definition 4 - Primary and secondary care events with specific bleed codes in both GPRD and HES To provide a very specific case definition only those with a specific upper gastrointestinal bleed code in both primary and secondary care datasets were selected.

Analysis: Incidence and 28 day all cause case fatality by case definition

The incidence was calculated per 100,000 person years using the underlying number of people registered in the GPRD as the denominator. Incidence was calculated by pooling each of the case definitions from the GPRD and HES by combining cases from both (a) and (b) for each of the definitions above and removing duplicates.

Finally I assessed the effect of each of these case definitions on the results of my intended studies in linked primary and secondary care data. Within the general population registered to a linked GPRD primary care practice, I calculated the numbers of cases identified by each case definition and the subsequent all cause 28 day case fatality. Dates of all deaths within 28 days following an upper gastrointestinal bleed admission date or primary care event date were ascertained using the linkage between the GPRD primary care practices and the UK ONS death register.

7.3.4 Results

Defining upper gastrointestinal bleeding separately within primary care and secondary care data.

Between 1st April 1997 and 30th August 2010 26,957 acute upper gastrointestinal bleed admissions were defined in HES by specific ICD 10 bleed codes and 30,223 acute upper gastrointestinal bleed events were defined in GPRD by the specific Read bleed codes. Combining these events defined 45,510 unique upper gastrointestinal bleed events, 26% with a specific code in both datasets, 34% with a code only in HES and 41% with a code only in GPRD. The proportion of all events defined by specific bleed codes from both databases varied by year between 22%-27% but there was no clear trend over time.

Classification of case definitions of upper gastrointestinal bleeding in primary and secondary care

The flow chart in figure 7.6 shows the selection of adult upper gastrointestinal bleeding events for each of my four case definitions. The percentages given in the flow chart are of the 45,472 pooled unique events in box 1. Of the 26,964 secondary care defined bleeds in box 1a, 81% had a 'Probable' or 'Possible' code in primary care within 2 months (box 2a, figure 7.6). By comparison 62% of the 30,176 primary care defined bleeds in box 1b had a 'Probable' or 'Possible' secondary care code within 2 months (box 2b, figure 7.6). Further details of the timings of the closest 'Possible' or 'Probable' codes to the defining upper gastrointestinal bleed code date are shown in tables 7.2 & 7.3.

Figure 7.6: Flowchart of Selection of GPRD Events Closest in Time to an Upper Gastrointestinal Bleed Admission Defined in HES

Percentages shown are percentage of pool of combined unique events in box 1.
GPRD- General Practice Research Database; HES - Hospital Episodes Statistics; ICD 10 - International Classification of Diseases 10th Edition; GI - Gastrointestinal; READ- Read code

Table 7.2: Timing of probable or possible primary care events to secondary care defined upper gastrointestinal bleed admissions

	Time difference between hospital and primary care event:		
	Frequency	Percentage	Cumulative percentage
Exact match	17020	63.12	63.12
1 day prior or 1 week post	2004	7.43	70.55
2 weeks pre or post event	710	2.63	73.19
1 month pre or post event	1005	3.73	76.91
2 months pre or post event	1099	4.08	80.99
$>$ 2 months or no associated code	5126	19.01	100.00
Total	26964	100.00	

Table 7.3: Timing of probable or possible secondary care events to primary care defined upper gastrointestinal bleed events

	Time difference between hospital and primary care event:		
	Frequency	Percentage	Cumulative percentage
Exact match	15672	51.93	51.93
1 day prior or 1 week post	1352	4.48	56.41
2 weeks pre or post event	470	1.56	57.97
1 month pre or post event	615	2.04	60.01
2 months pre or post event	578	1.92	61.92
$>$ 2 months or no associated code	11490	38.08	100.00
Total	30177	100.00	

Incidence and 28 day all case fatality by case definition

Incidence was calculated for each of the pooled case definitions and these are shown in table 7.4. Incidence followed a similar pattern by case definition to the crude numbers in figure 7.6.

Pooled case definitions	Incidence per 100,000	95% confidence interval
1a & 1b	224	(222-226)
2a & 2b	136	(134-138)
3a & 3b	114	(112-115)
4a & 4b	58	(57-59)

Table 7.4: Pooled incidence for each case definition per 100,000 person years.

(Pooled between GPRD defined cases and HES defined cases)

4,916 deaths were identified within 28 days of a bleed event using the linked ONS death register. 28 day mortality was calculated for each of the different case selections (figure 7.7). Secondary care defined events had almost twice

Figure 7.7: 28 Day Case Fatality of Different Definitions of Upper Gastrointestinal Bleed Events From HES and GPRD Linked Data

Percentages shown with 95% Confidence Intervals
GPRD- General Practice Research Database; HES - Hospital Episodes Statistics; ICD 10 - International Classification of Diseases 10th Edition; GI - Gastrointestinal; READ- Read code; PATID - Patient Identifier in GPRD

the case fatality of primary care defined events; 13.1% compared to 7.7% (box (1a) versus box (1b) in figure 7.7). Overall 28 day case fatality for all events defined in either GPRD or HES was 10.8% (box (1)). Selecting events from the combined datasets with an associated 'Probable' or 'Possible' code reduced the 28 day case fatality slightly (10.3%, box (2)) in figure 7.7). Restricting the events to only those with a 'Probable' code had minimal effect on case fatality (10.5%, box (3)) in figure 7.7). However further restricting events to those that were defined by specific upper gastrointestinal haemorrhage codes in both primary and secondary care was associated with a much lower case fatality (8.1%, box (4) compared to 10.5%, box (3)) in figure 7.7).

7.3.5 Discussion

This study assessed the effect of different case definitions of upper gastrointestinal bleeding on its measured incidence and mortality in linked primary and secondary care data. I used the record linkage between the world's largest hospital admissions database and one of the most commonly used primary care databases from the UK. Cases defined only in hospital data were at twice the risk of dying compared to those defined only in primary care data. Furthermore I found that the most specific case definition, which was restricted to specific bleed codes from both datasets, excluded severe cases and resulted in a lower 28 day case fatality. In contrast the more sensitive case definitions, using the broader possible or probable code lists, retained the more severe cases and did not reduce the overall case fatality. Therefore studies that are too restrictive in their case definitions will fail to capture the full heterogeneity of coding that follows complex or severe clinical events, and potentially introduce selection bias.

Reassuringly I found that 81% of upper gastrointestinal bleed events coded in

secondary care had a probable or possible record in primary care within two months. However less than two thirds of upper gastrointestinal bleed events coded in primary care were associated with a hospital admission within the same time window. This seems to conflict with previous validation of the GPRD using anonymised chart review in which upper gastrointestinal bleed coding was found to have a positive predictive value of 99% (95 cases confirmed out of 96 cases assessed)[100]. This could represent the bias in assessing a small sample of records from self selecting GP practices. Alternatively primary care could potentially be recording sub acute bleeding episodes or symptoms that were historical at the time of the consultation, and therefore these patients did not require acute hospital admission. This is supported by the lower 28 day case fatality in events defined in GPRD alone compared to those also defined in HES. Coded bleeding events with no hospital admission were potentially interesting to investigate but were not representative of the acute bleeds described in studies of upper gastrointestinal bleeding management.[141,163]

One of the limitations of this study is that it is not permissible to validate individual records from the national HES database against the original clinical chart records. However HES has been comparable with national gastrointestinal bleed audits (chapter 4) and I believe that the linkage of GPRD and HES, and the comparison presented in this chapter, provides a more comprehensive and less biased assessment of the validity of the coding from both datasets than from small sample validation, as all potential cases were assessed and compared. Furthermore this linkage allows the comparison of coding by primary care doctors against the coding by trained hospital personnel using secondary care doctors' notes, thereby supporting any resulting case definitions from two separate and independent data sources.

There have been other databases linked for a range of purposes. However many, like those based on Health Maintenance Organisations, are limited by in-

complete or selected population coverage because they are not based on a comprehensive population based primary health care system.[164,165] Scandinavian linked databases are the most established,[166,167] but they do not have the richness of the data collection in primary care that the GPRD offers, such as lifestyle factors, practice and individual socioeconomic status, occupation status, diagnoses, procedures, health promotion, referrals, and now the linkages with the respective hospital admission data, national death register and specialist clinical databases. Prior to the linkage of HES and GPRD it has only been possible to compare these databases using aggregated measures,[168] such as in chapter 4, however the record level linkage in this study avoids the ecological bias to which aggregated comparisons are susceptible. The use of both primary and secondary care has previously been shown to be beneficial in defining chronic diseases such as diabetes,[169,170] but primary care data had been found to have a lower positive predictive value for acute events.[171] My study supports this finding for the acute event of upper gastrointestinal haemorrhage, and I propose that this issue can be addressed and improved upon by the use of linked hospital data.

I initially began this investigation to develop specific case definitions that minimise misclassification bias on effect estimates when testing aetiological hypotheses.[172] To achieve this I now intend to use a specific upper gastrointestinal bleed code in one dataset with a probable or specific code in the linked dataset (box 3a & 3b, figure 7.6). This will select the most plausible cases of acute upper gastrointestinal haemorrhage without excluding severe cases (box 3, figure 7.7). This definition will therefore be used to derive a cohort of upper gastrointestinal bleed patients for the studies in the remainder of this PhD.

In contrast to an aetiological study, studies that estimate incidence require a broader and more sensitive case definition to be sure of capturing all cases of the disease in question.[172] For incidence studies I therefore propose using all

hospital defined cases with the addition of primary care defined cases that have a plausibly coded hospital admission (figure 7.6, box (1a) and box (2b)). A sensitivity analysis that also included the events defined only in primary care (box 1b) would then provide an upper estimate of bleed events in the population. The previous studies in this PhD on trends in mortality and incidence in chapters 5 & 6 were performed before this linked data was available. However based on the study in this current chapter over 80% of cases identified in HES would be expected to have a plausible code in primary care. The inclusion of primary care defined cases that had a plausibly coded hospital admission would have been expected to then identify an additional 12% of cases. The benefits in using this smaller linked dataset for investigating incidence and mortality trends would have therefore been far outweighed by the larger size, information on areas of residence, and the comprehensive national coverage of HES.

In this study I have been able to establish case definitions for upper gastrointestinal bleeding based on linked primary and secondary care data, and shown that linked data can be used to avoid excluding severe events. I have shown that hospital data was invaluable in accurately identifying acute bleeding events in primary care data that were severe enough to require hospital admission, and the primary care introduced a wealth of long term diagnosis data and prescription data to the secondary care data. In addition there was a close match in timing in primary and secondary care between relevant codes for upper gastrointestinal haemorrhage. Finally I have shown that the choice of definition in linked data has a clear effect on the mortality of the chosen population. My methods may not be generalisable to the definition of chronic diseases in linked databases, as chronic disease diagnoses are usually made in outpatient clinics and primary care. However I believe my findings are likely to be generalisable and relevant to other acute severe events, such as myocardial infarction or venous thromboembolism that are investigated, diagnosed, and managed during

an acute hospital admission.

CHAPTER 8

Co-morbidity is an important risk factor for the population burden of non variceal upper gastrointestinal bleeding: A population based case control study

8.1 Introduction

Helicobacter pylori infection, non steroidal anti inflammatory medications (NSAIDs) and aspirin are believed to be the main causes of non variceal upper gastrointestinal bleeding,[173] and with the discovery of proton pump inhibitors (PPIs) and Helicobacter pylori eradication therapy the burden of peptic ulcer disease has been decreasing.[139] Despite this upper gastrointestinal haemorrhage remains the commonest acute medical admission for gastroenterology,[2] and its incidence in population based studies remains almost unchanged.[160,174] This suggests that other (previously unidentified) risk factors are contributing to its population burden.

Although historically non gastrointestinal co-morbidity was believed to be associated with stress ulceration,[175] this role of co-morbidity in the aetiology of gastrointestinal bleeding is not now recognised apart from in extreme illness: Sicker cirrhotic patients have an increased risk of variceal bleeding,[176] and sicker patients in intensive therapy units (ITU) have an increased risk of non variceal bleeding.[177] However outside of ITU, the effect of co-morbidity has only been assessed indirectly as a confounder in studies that focussed on the effect of medications on gastrointestinal bleeds.[103] Though these studies do support a role for co-morbidity they do not allow us to understand whether it is an important contributor to the persisting burden of upper gastrointestinal bleeding. However over the last decade, as the proportion of bleed patients with co-morbidity has increased,[160] it is plausible that this exposure to co-morbidity could itself be responsible for the persisting incidence of bleeding.

I have therefore conducted a study aimed primarily at assessing whether co-morbidity may have an important role in the aetiology of upper gastrointestinal bleeding. To do this I have conducted a case control study and formed a model fully corrected for known measured risk factors of upper gastrointesti-

nal bleeding. I have then calculated the additional explanatory effect of adding co-morbidity to my model.

8.2 Methods

8.2.1 Study design

A matched case control study.

8.2.2 Data

To provide the detailed longitudinal data and necessary power for this study I have used the recently linked English Hospital Episodes Statistics (HES) data and General Practice Research Database (GPRD). Ethical approval for this study was obtained from the Independent Scientific Advisory Committee for MHRA database research. 51% of English practices in GPRD have consented to record level linkage of their population to HES. This records all hospital admissions from the defined primary care population between 1st April 1997 to 31st August 2010.

8.2.3 Cases definition

All subjects with a specific code for non variceal upper gastrointestinal bleed in either primary or secondary care were selected who also had a corresponding code for a likely symptom, cause, therapy, investigation or outcome of upper gastrointestinal haemorrhage in the linked dataset (chapter 7). Variceal bleeds or non specific gastrointestinal bleed codes with either a lower gastrointestinal diagnosis or procedure were excluded. Further exclusions were temporary pa-

tients, children 15 years old and younger, cases with invalid date codes or cases outside the 'up to research standard' observed time periods. Patients were required to be registered with the primary care practice for at least 3 months prior to an upper gastrointestinal bleed event to avoid including prevalent cases that might have been coded at the initial registration consultation. Only the first event for each patient was included. I have previously demonstrated that this selection strategy minimises selection bias in studies of upper gastrointestinal bleeding in these data.[178] A secondary analysis was then stratified by whether the specific bleed code or supporting code referred to a peptic ulcer (Read codes J11.... to J14.... or ICD 10 codes K25.. to K28..). These codes had the highest positive predictive values (>95%) for peptic ulcers and upper gastrointestinal complications when validated in English primary care routine records.[179]

8.2.4 Matched Controls

Each case was age (+/- 5 years) and sex matched, without replacement, to 5 controls who were alive at the time of the gastrointestinal bleed and registered to the same primary care practice. Controls were required to have been registered with the primary care practice for at least 3 months prior to the match date to be consistent with the definition for cases.

8.2.5 Exposures

Potential final common causal pathways were defined *a priori* for; erosions & ulceration, varices, angiodysplasia, fistula & trauma, and coagulopathy; and code lists were derived for diagnoses and medications that might be associated with each pathway based on published literature (figure 8.1, unlinked boxes represent potential confounders).

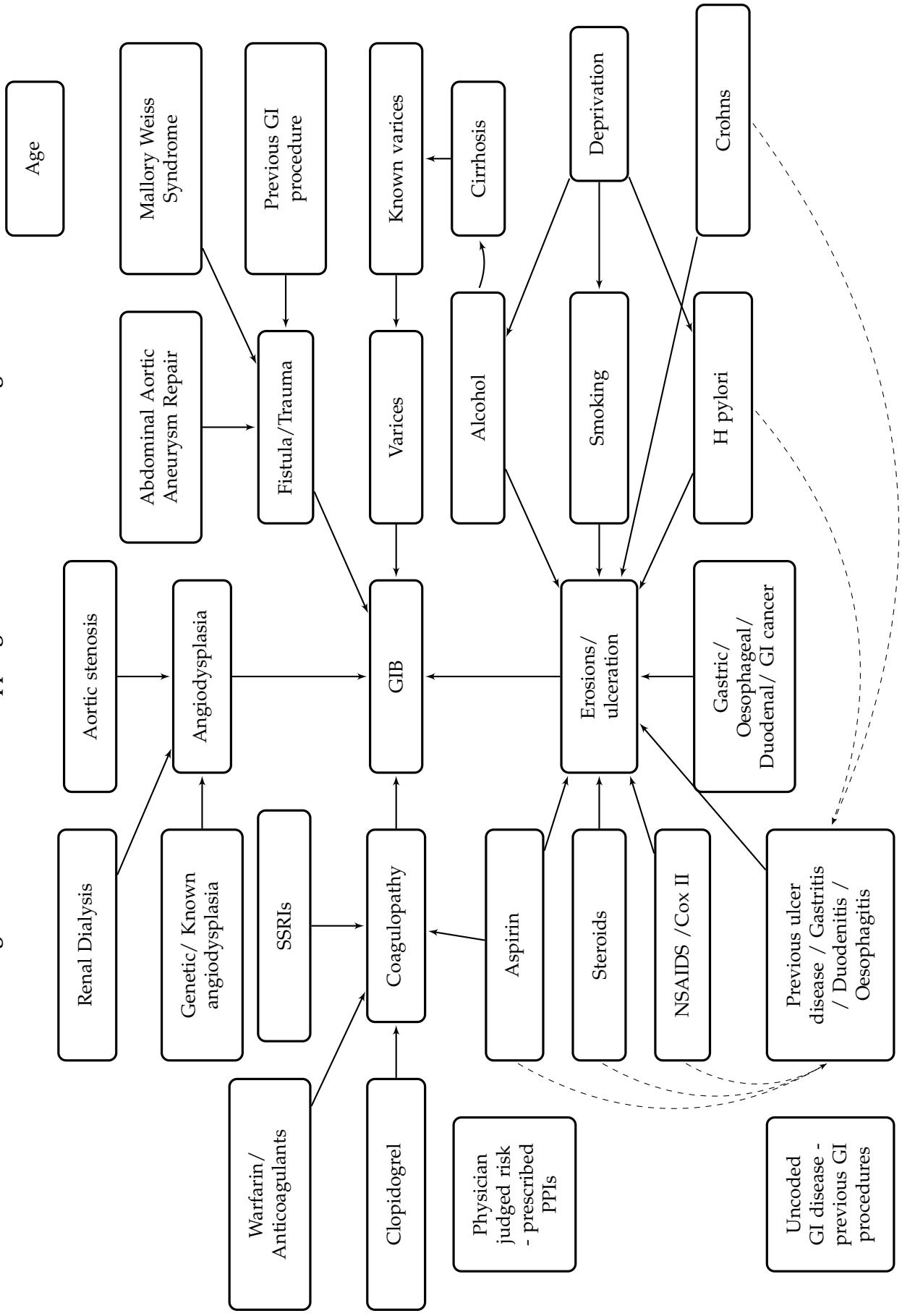


Figure 8.1: Risk factors for upper gastrointestinal haemorrhage

Medication risk factors were included if there was a coded prescription within the year prior to the admission. Exposures coded within 2 months of the admission date were excluded to avoid identifying events and prescriptions related to the actual bleed event. Proton pump inhibitors (PPIs) were included as an indicator of physicians' judgement of the risk of upper gastrointestinal haemorrhage that was not captured by other measured risk factors. Alcohol consumption was classified as either non drinker, alcohol mentioned, ex alcohol dependency, alcohol excess, alcohol complications and missing. Smoking was classified as never smoked, current smoker, ex smoker and missing. Although patients with coded variceal bleeds were excluded, cirrhosis was included as a risk factor as cirrhotic patients can have non variceal bleeds. Cirrhosis was classified as uncomplicated, with varices, with ascites, or with encephalopathy or liver failure coded. All other exposures were binary variables.

8.2.6 Co-morbidity

Co-morbidity was defined using the Charlson index.[142] This is a well validated weighted co-morbidity score that predicts 1 year mortality following hospital discharge. Any codes used to define risk factors of upper gastrointestinal bleeding in figure 8.1 were excluded when calculating the index, i.e. peptic ulcer and cirrhosis codes. For clarity in reporting the index was summarised as no co-morbidity, single co-morbidity, and multiple or severe co-morbidity.

8.2.7 Analysis

Unadjusted analysis

Unadjusted odds ratios were calculated for each exposure using conditional logistic regression to allow for the matched study design.

Multivariate analysis

Adjusted odds ratios for each exposure of interest were calculated with conditional logistic regression adjusting for all exposures in addition to age, proton pump inhibitor use and previous gastrointestinal procedures. As calendar year, gender and primary care practice were precisely matched on, it was not necessary to include them in the model. Co-morbidity was added last, and its association with bleeding tested using a likelihood ratio test. The variance inflation factor (a measure of the increase in model variance due to correlation between variables) was calculated for each exposure of interest to assess the effect of correlation between variables. All exposures with a variance inflation factor over 5 were excluded from the final conditional logistic regression model.[180] The final model was then stratified into cases with a recording of peptic ulcer and those without. All analysis was performed using Stata version 12 (StataCorp LP, Texas).

Sequential (or 'extra') population attributable fractions

Sequential (or 'extra') population attributable fractions (PAF) were calculated for each exposure, using the prevalence among the cases and the respective coefficients from the conditional logistic regression model.[181] Sequential population attributable fractions differ from the standard adjusted population attributable fractions that are usually presented in papers. Sequential population attributable fractions are calculated by estimating the additional proportion of cases attributable to each exposure, after removing the proportion of cases already attributed to the combined effect of all remaining exposures in the model (see algorithm 1). 95% confidence intervals for these estimates were obtained by bootstrapping with 500 repetitions for each exposure.[182] The final model was then stratified into cases with a recording of peptic ulcer and those without.

Algorithm 1 Adjusted sequential population attributable fractions

Exposure sets stratified by:
$_i$ $=_{1....I}$ Risk factors
$_j$ $=_{1....J}$ Levels of confounders

For each strata $RR_{i|j}$ & $\rho_{i,j}$ are estimated:

$RR_{i|j}$= stratum odds ratio for the effect of $X_{i|j}$ compared to $X_{0|j}$
$\rho_{i,j}$ = Proportion of cases in each stratum exposed to X_i and level of confounders $_j$

Then the total PAF predicted for the model can be estimated:

$$PAF_{i|j} = 1 - \sum_{i=1}^{I} \sum_{j=1}^{J} \rho_{ij} RR_{i|j}^{-1}$$

Each risk factor $_{i=I}$ is alternately assigned as another level of the confounding $_{j,i=I}$.
The odds ratios for the remaining set of risk factors $_m$ $=_{1...M}$ are then re-estimated:

$$\left(X_{I|j} \in X_{i|j}\right) \bigcap \left(X_{I|j} \notin X_{m|j}\right)$$

$RR_{m|j,i=I}$ = stratum odds ratio for the effect of $X_{m|j,i=I}$ compared to $X_{0|j,i=I}$

The extra or sequential PAF for each risk factor i is then calculated:

$$extraPAF_{1|j} = PAF_{i|j} - PAF_{m|j}$$

The risk ratio is estimated by the odds ratio from the case control study

Sensitivity analyses

Previous studies of risk factor medications such as NSAIDs[87] have been conducted in study populations that excluded patients with known risk factors for gastrointestinal bleeding. To allow comparisons with these, I therefore re-estimated the crude odds ratios for each of the risk factor medications after excluding any cases and their controls with non medication bleed risk factors. To assess the effect the choice of the exposure time window around the bleed event on the effect of NSAIDs we also re-estimated a model that included NSAID use up to 30 days before the index date.

Two further sensitivity analyses were performed to assess the effect of potential under reporting. First the analysis was restricted to those over 65 years old, who were eligible for free prescriptions, to assess the effect of potential under reporting of non prescribed NSAID use. With regard to this 'over the counter use', non differential under reporting has been shown to reduce the measured effect of prescribed medications.[183] This in our study would cause an underestimate of the effect of NSAIDs. However in England certain groups receive free prescriptions, such as patients over 65 years old or those with certain chronic disease, and these groups have been shown to purchase far fewer medications over the counter than those who have to pay for prescriptions.[184,185] Therefore restricting the analysis to patients over the age of 65 should reduce any confounding by 'over the counter use'.

Secondly, multiple imputation was used to re-estimate the association with co-morbidity by imputing missing values for alcohol and smoking status. Alcohol and smoking were categorised as binary exposures of excess alcohol or current smoking to fit the logistic regression imputation model. All previously extracted exposures were used in the imputation model with addition of the socio-economic status, and 20 sets of imputations were calculated. Socio-

economic status was measured by the Index of Multiple Deprivation quintiles obtained from linked Office for National Statistics data.

Finally, to assess the effect of using the aggregated and weighted Charlson index, the model was re-estimated to assess the effect of the individual component co-morbidities from the Charlson index.

8.3 Results

8.3.1 Cases and matching

16,355 unique cases were identified with a first non variceal bleed; 13,372 with specific code in HES, 10,938 with a specific code in GPRD, and 7,955 with a specific code in both datasets. 99.7% (16,304) of the cases were matched to 5 controls each and only 8 cases (0.05%) were not matched to any controls. The median observed time prior to admission for cases was 7.4 years (inter quartile range 3.4-11.5) compared to 7.5 years (inter quartile range 3.5 - 11.5) for controls.

8.3.2 Unadjusted analysis

Table 8.1 shows the proportion of cases and controls with each exposure. The proportion of cases with no co-morbidity recorded was lower than previously found in HES cases (21% versus 46%, chapter 6), and this demonstrates the benefit of the linked primary care data in providing a more detailed longitudinal medical record than hospital admissions alone. As expected aspirin and NSAIDs were the most frequently prescribed risk factor medications, and peptic ulcer and gastritis/duodenitis/oesophagitis were the most frequent risk factor diagnoses. All *a priori* risk factors were associated with upper gastrointestinal bleeding. Peptic ulcers were coded in 4,823 patients, 29% of cases, and the exposures stratified by coding of peptic ulcer are shown in table 8.2.

8.3.3 Multivariate analysis and population attributable fractions

There was strong evidence for an association between the non gastrointestinal Charlson index and upper gastrointestinal bleeding after adjusting for all measured risk factors (single co-morbidity adjusted OR 1.43 (1.35-1.52), multiple

Table 8.1: Proportion of cases and controls exposed 2 months prior to bleed date or match date

	Controls (n)	Percentage exposed	Cases (n)	Percentage exposed
CHARLSON INDEX	.	.	.	.
No Co-morbidity	30194	37.0	3440	21.0
Single Co-morbidity	18714	22.9	3222	19.7
Multiple or Severe	32728	40.1	9693	59.3
GASTROINTESTINAL	.	.	.	.
Cirrhosis-none coded	81385	99.7	16004	97.9
Cirrhosis-only	65	0.1	63	0.4
Cirrhosis-Varices	62	0.1	65	0.4
Cirrhosis-Ascites	86	0.1	172	1.1
Cirrhosis-Encephalopathy	38	0.0	51	0.3
Gastritis, duodenitis or oesophagitis	7904	9.7	3051	18.7
Peptic Ulcer	3830	4.7	1852	11.3
H pylori	1964	2.4	609	3.7
Angiodysplasia	14	0.0	6	0.0
Mallory Weiss syndrome	34	0.0	96	0.6
Crohns disease	222	0.3	114	0.7
GI cancer	2494	3.1	1174	7.2
LIFESTYLE				
Alcohol-Not coded	61536	75.4	11026	67.4
Alcohol-Non Drinker	1485	1.8	375	2.3
Alcohol-Ex Drinker	176	0.2	64	0.4
Alcohol-Mentioned	4317	5.3	977	6.0
Alcohol-Over limits	14073	17.2	3763	23.0
Alcohol-Complications	49	0.1	150	0.9
Smoking-Not coded	51751	63.4	9187	56.2
Smoking-Non Smoker	11666	14.3	2332	14.3
Smoking-Ex Smoker	4075	5.0	888	5.4
Smoking-Passive	5574	6.8	1455	8.9
Smoking-Current	8570	10.5	2493	15.2
MEDICATIONS				
Aspirin	18079	22.1	5392	33.0
NSAIDs	12722	15.6	3820	23.4
COX II inhibitors	168.7	2.1	605	3.7
Clopidogrel	1297	1.6	668	4.1
Oral steroids	4135	5.1	1578	9.6
Anticoagulants	3799	4.7	1617	9.9
SSRIs	4813	5.9	2025	12.4
OTHER DIAGNOSES				
Aortic stenosis	782	1.0	350	2.1
Repair of AAA	307	0.4	115	0.7
Dialysis	70	0.1	88	0.5
CONFOUNDERS				
Upper GI procedure	10471	12.8	3438	21.0
PPI	10909	13.4	4585	28.0
Age (median and interquartile range)	72	57-81	73	57-82

Table 8.2: Proportion of cases exposed 2 months prior to bleed date stratified by coding of peptic ulcer

	Peptic ulcer coded (frequency)	Percentage exposed	No peptic ulcer coded (frequency)	Percentage exposed
CHARLSON INDEX	.	.	.	.
No Co-morbidity	883	18.3	2557	22.2
Single Co-morbidity	916	19.0	2306	20.0
Multiple or Severe	3024	62.7	6669	57.8
GASTROINTESTINAL	.	.	.	.
Cirrhosis-none coded	4753	98.5	11251	97.6
Cirrhosis-only	17	0.4	46	0.4
Cirrhosis-Varices	8	0.2	57	0.5
Cirrhosis-Ascites	32	0.7	140	1.2
Cirrhosis-Encephalopathy	13	0.3	38	0.3
Gastritis, duodenitis or oesophagitis	710	14.7	2341	20.3
Peptic Ulcer	864	17.9	988	8.6
H pylori	162	3.4	447	3.9
Angiodysplasia	1	0.0	5	0.0
Mallory Weiss syndrome	11	0.2	85	0.7
Crohns disease	19	0.4	95	0.8
GI cancer	254	5.3	920	8.0
LIFESTYLE	.	.	.	.
Alcohol-Not coded	3299	68.4	7727	67.0
Alcohol-Non Drinker	97	2.0	278	2.4
Alcohol-Ex Drinker	20	0.4	44	0.4
Alcohol-Mentioned	284	5.9	693	6.0
Alcohol-Over limits	1105	22.9	2658	23.0
Alcohol-Complications	18	0.4	132	1.1
Smoking-Not coded	2753	57.1	6434	55.8
Smoking-Non Smoker	646	13.4	1686	14.6
Smoking-Ex Smoker	288	6.0	600	5.2
Smoking-Passive	405	8.4	1050	9.1
Smoking-Current	731	15.2	1762	15.3
MEDICATIONS	.	.	.	.
Aspirin	1831	38.0	3561	30.9
NSAIDs	1431	29.7	2467	21.4
COX II inhibitors	222	4.6	383	3.3
Clopidogrel	198	4.1	470	4.1
Oral steroids	428	8.9	1150	10.0
Anticoagulants	427	8.9	1190	10.3
SSRIs	460	9.5	1565	13.6
OTHER DIAGNOSES	.	.	.	.
Aortic stenosis	125	2.6	225	2.0
Repair of AAA	36	0.7	79	0.7
Dialysis	30	0.6	58	0.5
CONFOUNDERS	.	.	.	.
Previous upper GI procedure	817	16.9	2621	22.7
Previous PPI use	906	18.8	3679	31.9
Age (median and interquartile range)	75	64-83	72	54-82

or severe co-morbidity adjusted OR 2.26 (2.14-2.38), p<0.0001 likelihood ratio test). Table 8.3 shows the adjusted odds ratios and PAFs from the final model for each exposure. The variables for angiodysplasia and dialysis had the highest variance inflation factors, 1.48 & 2.35 respectively. As both of these were less than the *a priori* threshold of 5, all exposures were included in the final conditional logistic regression model. Stratifying this model demonstrated similar associations with co-morbidity whether or not peptic ulcer coding was present, and slightly higher associations for a peptic ulcer with exposure previous peptic ulcers, NSAID or aspirin use (table 8.4). Associations with other risk factors were higher in the non peptic ulcer cohort.

The proportion of cases attributable in the population to the combined effect of all available measured exposures was 48%, not including the effect of non gastrointestinal co-morbidity. The additional proportion of cases attributable to non gastrointestinal co-morbidity (or the sequential population attributable fraction (PAF)) was 20%, and this was higher in magnitude than for any other measured exposure (Table 8.5). The next largest PAFs were 3%, for aspirin and NSAID use. The PAF for co-morbidity associated with peptic ulcer bleeds was slightly lower than that for non ulcer bleeds (18 vrs 21%) with a higher contribution from previous peptic ulcer bleeds and aspirin and NSAIDs (table 8.6). In contrast, for non ulcer bleeds the SAF was slightly increased for gastrointestinal cancer, alcohol, anticoagulants and SSRIs.

8.3.4 Sensitivity analyses

The crude odds ratios were re-estimated for medications after excluding cases with non medication risk factors and these are shown in table 8.7. NSAID use in the main analysis was strongly associated with bleeding with an OR 1.67, and this increased to 2.80 with the exclusion of non medication risk factors. The cor-

Table 8.3: Final adjusted model with Charlson Index measuring co-morbidity for non variceal upper gastrointestinal bleeding .

	Adjusted OR	Lower 95% CI	Upper 95% CI
CHARLSON INDEX	.	.	.
No Co-morbidity	1.00	1.00	1.00
Single Co-morbidity	1.43	1.35	1.52
Multiple or Severe	2.26	2.14	2.38
GASTROINTESTINAL			
Cirrhosis-none	1.00	1.00	1.00
Cirrhosis-only	3.89	2.61	5.77
Cirrhosis-Varices	3.75	2.51	5.61
Cirrhosis-Ascites	5.96	4.46	7.96
Cirrhosis-Encephalopathy	5.05	3.14	8.10
Gastritis, duodenitis or oesophagitis	1.46	1.39	1.55
Peptic Ulcer	2.11	1.98	2.26
H pylori	0.96	0.86	1.07
Angiodysplasia	1.67	0.58	4.80
Mallory Weiss syndrome	12.39	8.16	18.82
Crohns disease	2.19	1.71	2.81
GI cancer	2.13	1.97	2.31
LIFESTYLE			
Alcohol-Not	1.00	1.00	1.00
Alcohol-Non Drinker	1.25	1.10	1.42
Alcohol-Ex Drinker	1.39	1.01	1.92
Alcohol-Mentioned	1.05	0.96	1.14
Alcohol-Over limits	1.42	1.35	1.49
Alcohol-Complications	9.33	6.48	13.44
Smoking-Not	1.00	1.00	1.00
Smoking-Non Smoker	0.97	0.92	1.04
Smoking-Ex Smoker	0.94	0.86	1.02
Smoking-Passive	1.03	0.95	1.11
Smoking-Current	1.29	1.22	1.37
MEDICATIONS			
Aspirin	1.50	1.43	1.57
NSAIDs	1.59	1.52	1.66
COX II inhibitors	1.52	1.37	1.69
Clopidogrel	1.74	1.57	1.94
Oral steroids	1.38	1.29	1.48
Anticoagulants	1.94	1.81	2.08
SSRIs	1.72	1.62	1.83
OTHER DIAGNOSES			
Aortic stenosis	1.58	1.38	1.82
Repair of AAA	1.29	1.02	1.64
Dialysis	3.59	2.55	5.05
CONFOUNDERS			
Upper GI procedure	1.10	1.04	1.15
PPI	1.59	1.52	1.67
age	1.09	1.08	1.10

(age, year, practice and gender matched)

Table 8.4: Final adjusted model with Charlson Index measuring co-morbidity for non variceal upper gastrointestinal bleeding stratified by coding of peptic ulcer.

	Peptic ulcer			Non peptic ulcer		
	Adjusted OR	Lower 95% CI	Upper 95% CI	Adjusted OR	Lower 95% CI	Upper 95% CI
CHARLSON INDEX	.	.	.	.	.	.
No Co-morbidity	1.00	1.00	1.00	1.00	1.00	1.00
Single Co-morbidity	1.45	1.30	1.62	1.42	1.33	1.52
Multiple or Severe	2.28	2.06	2.52	2.27	2.13	2.42
GASTROINTESTINAL	.	.	.	.	.	.
Cirrhosis-none	1.00	1.00	1.00	1.00	1.00	1.00
Cirrhosis-only	3.98	2.03	7.80	3.80	2.30	6.27
Cirrhosis-Varices	2.33	0.92	5.94	4.15	2.63	6.54
Cirrhosis-Ascites	4.67	2.63	8.29	6.85	4.85	9.65
Cirrhosis-Encephalopathy	3.16	1.39	7.20	6.66	3.70	12.01
Gastritis, duodenitis or oesophagitis	1.22	1.10	1.36	1.58	1.48	1.68
Peptic Ulcer	4.36	3.92	4.85	1.37	1.25	1.49
H pylori	1.04	0.85	1.27	0.94	0.83	1.06
Angiodysplasia	1.71	0.16	18.64	1.49	0.44	5.00
Mallory Weiss syndrome	3.75	1.43	9.84	16.54	10.23	26.77
Crohns disease	1.18	0.68	2.05	2.65	1.99	3.54
GI cancer	1.45	1.23	1.69	2.45	2.23	2.70
LIFESTYLE	.	.	.	.	.	.
Alcohol-Not	1.00	1.00	1.00	1.00	1.00	1.00
Alcohol-Non Drinker	1.14	0.89	1.47	1.30	1.11	1.51
Alcohol-Ex Drinker	1.58	0.89	2.81	1.30	0.88	1.93
Alcohol-Mentioned	1.02	0.87	1.20	1.04	0.94	1.16
Alcohol-Over limits	1.34	1.22	1.47	1.45	1.36	1.54
Alcohol-Complications	3.88	1.70	8.87	11.85	7.76	18.10
Smoking-Not	1.00	1.00	1.00	1.00	1.00	1.00
Smoking-Non Smoker	0.99	0.88	1.11	0.96	0.90	1.04
Smoking-Ex Smoker	0.96	0.82	1.13	0.92	0.83	1.03
Smoking-Passive	0.95	0.82	1.09	1.06	0.97	1.16
Smoking-Current	1.35	1.21	1.51	1.28	1.19	1.37
MEDICATIONS	.	.	.	.	.	.
Aspirin	1.69	1.56	1.82	1.42	1.34	1.50
NSAIDs	2.21	2.04	2.39	1.37	1.29	1.45
COX II inhibitors	1.81	1.51	2.17	1.42	1.24	1.62
Clopidogrel	2.04	1.68	2.48	1.70	1.49	1.93
Oral steroids	1.31	1.16	1.49	1.40	1.29	1.51
Anticoagulants	1.67	1.47	1.90	2.10	1.94	2.28
SSRIs	1.47	1.30	1.66	1.84	1.71	1.97
OTHER DIAGNOSES	.	.	.	.	.	.
Aortic stenosis	1.79	1.41	2.26	1.46	1.23	1.75
Repair of AAA	1.33	0.87	2.04	1.27	0.95	1.68
Dialysis	5.56	2.95	10.48	2.92	1.94	4.41
CONFOUNDERS	.	.	.	.	.	.
Previous upper GI procedure	0.88	0.80	0.98	1.20	1.13	1.28
PPI	0.82	0.74	0.91	2.01	1.90	2.13
Age	1.10	1.08	1.11	1.09	1.08	1.10

(age, year, practice and gender matched)

Table 8.5: Sequential Population Attributable Fractions (PAF) for each risk factor for non variceal upper gastrointestinal haemorrhage.

Sequential Population Attributable Fractions[a,b]	(Percentages)	95% confidence intervals	
NON GASTROINTESTINAL CO-MORBIDITY	19.80	18.43	21.18
GASTROINTESTINAL	.	.	.
Cirrhosis	0.49	0.41	0.57
Gastritis, duodenitis or oesophagitis	1.98	1.66	2.30
Peptic Ulcer	2.05	1.81	2.28
Helicobacter pylori	-0.04	-0.15	0.08
Angiodysplasia	0.01	-0.01	0.02
Mallory Weiss syndrome	0.29	0.22	0.37
Crohns disease	0.14	0.08	0.19
GI cancer	1.11	0.96	1.27
LIFESTYLE	.	.	.
Alcohol use	2.89	2.39	3.39
Smoking	0.83	0.27	3.42
MEDICATIONS	.	.	.
Aspirin	2.95	2.54	3.36
NSAIDs	3.07	2.72	3.42
COX II inhibitors	0.33	0.23	0.44
Clopidogrel	0.34	0.26	0.43
Oral steroids	0.59	0.44	0.74
Anticoagulants	1.19	1.04	1.35
SSRIs	1.58	1.36	1.80
OTHER DIAGNOSES	.	.	.
Aortic stenosis	0.16	0.10	0.22
Repair of aorta	0.03	0.00	0.06
Dialysis	0.07	0.04	0.09

[a] Age, year, practice and gender matched and adjusted for PPI use, previous upper gastrointestinal procedures and age. [b] The estimate in each row are calculated separately conditional on all the other variables in the model. They should therefore not be interpreted as summing over the column to 100%. Sequential PAF estimates the additional proportion of non variceal bleeding cases attributable to each risk factor after cases attributable to all the other risk factors in the model have been removed.

Table 8.6: Sequential Population Attributable Fractions (PAF) for each risk factor for non variceal upper gastrointestinal haemorrhage stratified by peptic ulcer coding.

Sequential Population Attributable Fractions[a,b] (percentage)	Peptic ulcer	Non peptic ulcer
NON GASTROINTESTINAL CO-MORBIDITY	18.44	20.50
GASTROINTESTINAL	.	.
Cirrhosis	0.32	0.57
Gastritis, duodenitis or oesophagitis	0.69	2.74
Peptic Ulcer	5.31	0.69
Helicobacter pylori	0.05	-0.07
Angiodysplasia	0.01	0.00
Mallory Weiss syndrome	0.06	0.39
Crohns disease	0.02	0.19
GI cancer	0.35	1.48
LIFESTYLE	.	.
Alcohol use	1.93	3.30
Smoking	0.80	0.81
MEDICATIONS	.	.
Aspirin	3.99	2.42
NSAIDs	5.40	2.00
COX II inhibitors	0.47	0.28
Clopidogrel	0.38	0.35
Oral steroids	0.36	0.66
Anticoagulants	0.78	1.41
SSRIs	0.74	2.02
OTHER DIAGNOSES	.	.
Aortic stenosis	0.22	0.12
Repair of aorta	0.02	0.03
Dialysis	0.09	0.05

[a] Age, year, practice and gender matched and adjusted for PPI use, previous upper gastrointestinal procedures and age. [b] The estimate in each row are calculated separately conditional on all the other variables in the model. They should therefore not be interpreted as summing over the column to 100%. Sequential PAF estimates the additional proportion of non variceal bleeding cases attributable to each risk factor after cases attributable to all the other risk factors in the model have been removed.

responding adjusted odds ratios associated with NSAIDs were 1.59 with non medication risk factors included and 1.78 without. Altering the exposure window for NSAIDs to 30 days rather than 60 days prior before the bleed slightly increased the effect of NSAIDS, but did not alter effect on the other results including co-morbidity

Table 8.7: The association of medications with upper gastrointestinal bleeding after excluding patients with non medication risk factors .

	Crude OR	Adjusted* OR	Lower 95% CI	Upper 95% CI
Aspirin	2.39	1.73	1.60	1.87
NSAIDs	2.80	1.78	1.64	1.93
COX II inhibitors	2.59	1.50	1.23	1.83
Clopidogrel	7.30	2.15	1.70	2.73
Oral steroids	1.23	1.23	1.08	1.41
Anticoagulants	4.83	2.26	1.99	2.57
SSRIs	2.78	1.52	1.34	1.71

(age, year, practice and gender matched)
*Adjusted for all other variables in table and in figure 8.1

Restricting the analysis to those over 65 years old increased the proportion of cases attributable to the combined effect of all exposures from 48% to 63%, and reduced the additional proportion of cases attributable to non gastrointestinal co-morbidity from 19.8% to 16.1%. Re-estimating the model using multiple imputation for missing alcohol and smoking status (modelled as binary exposures), slightly reduced the PAF associated with co-morbidity from 22.9% to 22.4%. Restricting this multiple imputation sensitivity analysis to those older than 65 years reduced the PAF associated with co-morbidity further to 18.7%.

Finally the full model was re-estimated for each component of the Charlson index (table 8.8). The contribution of these individual co-morbidities was minimal in comparison to their combined weighted effect in the Charlson index in the main analysis.

Table 8.8: The adjusted association of the component co-morbidities of Charlson index with non variceal bleeding

	Cases exposed(%)	OR*	Lower 95% CI	Upper 95% CI	PAF*(%)
Myocardial Infarction	13.98	1.04	0.97	1.10	0.12
Congestive Cardiac Disease	19.90	1.49	1.41	1.58	1.95
Peripheral Vascular Disease	11.17	1.31	1.23	1.41	0.70
Cerebrovascular Disease	23.13	1.13	1.08	1.19	0.79
Dementia	8.98	1.40	1.30	1.50	1.00
Chronic Pulmonary Disease	31.80	1.11	1.06	1.16	1.10
Rheumatological Disease	10.13	1.06	0.99	1.13	0.17
Uncomplicated Diabetes	17.88	1.01	0.96	1.06	0.04
Hemiplegia	4.73	1.79	1.62	1.97	0.67
Renal Disease	14.42	1.71	1.61	1.82	1.74
Diabetes with Complications	12.30	1.00	0.94	1.06	-0.01
Any Malignancy	13.11	1.21	1.14	1.28	0.78
Lymphoproliferative disorders	2.21	1.95	1.70	2.24	0.43
Metastatic Solid Tumour	5.89	2.35	2.14	2.57	1.29
HIV / AIDS	0.06	0.69	0.31	1.55	-0.00

(year, practice and gender matched)
*Adjusted for all other variables in table and in figure 8.1

8.3.5 Regression diagnostics

Delta beta statistics were calculated and were all less than one. These measure the standardised change in the coefficients when that matched group was deleted. This indicated that no individual matched group's covariate pattern was particularly influential on the estimated co-efficients. Outliers with influence on the overall model fit were estimated by delta chi-squared statistics values over 3. These measured the change in the overall chi-squared value for the model with the deletion of each matched group. These outliers were found to be patients with no recorded risk factors who nevertheless had a bleed event. Excluding these patients (about 10%) from the model obviously improved its predictive ability and increased the association of serious or multiple co-morbidity with bleeding to an odds ratio of 3. However these exclusions were judged as inappropriate as the resulting estimates would no longer represent the study population. This was a useful reminder that there remain further unmeasured

risk factors in the population not included in this study.

8.4 Discussion

This study has demonstrated that a combined measure of non gastrointestinal co-morbidity is a significant independent predictor of upper gastrointestinal bleeding, even after accounting for all other recognised and measured risk factors. Furthermore it explained a greater proportion of the burden of bleeding than any other risk factor in the population. The effect of this combined measure of non gastrointestinal co-morbidity was far in excess of that which would be expected from its constituent diseases.

The association of co-morbidities with upper gastrointestinal bleeding has been studied previously, but only in smaller secondary care surveys with co-morbidity as a confounder and not as the primary exposure. I searched PubMed using variants of co-morbidity, aetiology, causality, risk factors and gastrointestinal haemorrhage, however no studies were identified that set out to address the question of this chapter. Studies were most frequently designed to measure the association of a single medication whilst adjusting for any confounding by co-morbidity.[98,99] Two assessed a larger range of medications in cross sectional hospital based surveys.[80,103] However peptic ulcer disease was included in the measure of overall co-morbidity in the latter study and in the former study the authors used an unmatched analysis on matched data, incorrectly summed the adjusted population attributable fractions and assumed the remaining proportion were due to 'unmeasured factors'. Other studies assessed higher alcohol intake,[111] Helicobacter pylori,[81] smoking,[114] acute renal failure,[109] and acute myocardial infarction[107] and found associations with upper gastrointestinal bleeding. However these studies were in small selected hospitalised cohorts

(n<1000 bleeds) with limited assessments of individual co-morbidity and no measure of their population attributable fractions.

My study has a number of important strengths when compared to these previous works because I set out specifically to assess the degree to which non gastrointestinal co-morbidity predicts non variceal upper gastrointestinal bleeding after removing the effects of all the available known risk factors in a much larger general population. My method of defining cases and exposures utilised information from both primary and secondary care, maximising the evidence supporting each case whilst not excluding severe events.[178] Furthermore due to the comprehensive coverage of the English primary care system my study's results are likely to be generalisable to the whole English population and further afield. Consequently I was able to estimate the additional attributable fraction for co-morbidity in the English population that was not already attributable to other risk factors.[181]

However I need to consider other explanations for my observed association of co-morbidity with upper gastrointestinal bleeding. A potential weakness of my study is the inevitable imperfect data on some recognised risk factors which may have caused us to underestimate their importance. The GPRD contains comprehensive recording of all available diagnoses and prescriptions. However underreporting is likely to have occurred for Helicobacter pylori infection, NSAID use, alcohol and smoking. In the case of Helicobacter pylori there was inevitably under-reporting since there was no population screening. However if the underreporting of Helicobacter pylori infection were to explain my study's findings it would have to be strongly associated with co-morbidity and the evidence for this is conflicting and underpowered.[186,187] Furthermore in studies of ischaemic heart disease, for which there is the largest body of evidence, any significant association with Helicobacter pylori was minimal after adjustments for confounding.[188] In my study the apparent protective effect of

recognised Helicobacter pylori after adjustments for confounding was not surprising, since Helicobacter pylori will have been eradicated when found.

NSAID use might also have been underreported as NSAIDs can be bought from a pharmacy without a prescription, potentially explaining the low association between NSAIDs and bleeding in my study compared to a previous meta analysis.[87] However the studies used in this particular meta analysis excluded patients with other known gastrointestinal bleeding risk factors, and when I made the same exclusions in my study the association of bleeding with NSAIDs increased and became comparable to the figures in the literature. Furthermore although the association with co-morbidity reduced when I restricted my analysis to those over 65 (who were less likely to buy their own medications due to free prescriptions), it was not to the extent needed to explain my findings. Indeed part of this reduction was merely due to the increase in other risk factors seen with age. Finally alcohol and smoking status had missing data, but there was only a minimal effect on the PAF of co-morbidity when missing data was imputed conditional on all available data and socioeconomic status. The assumption in the sensitivity analysis that the data was 'missing at random', conditional on the available information, might have been incorrect. However as the addition of alcohol and smoking did not alter the association with co-morbidity after adjusting for the other risk factors, the effect of this data being 'missing not at random' will have been minimal.

I believe potential under reporting of exposures therefore does not explain the association that I have found between upper gastrointestinal bleeding and a general measure of co-morbidity. This suggests that co-morbidity itself or other factors not included in my study that are associated with co-morbidity might be causing the association. It is possible that other medications not included in the study were responsible for some of this association, however we are not aware of any additional prescribed or non prescribed medication that would

fulfil the requirements of common usage and a strong association with bleeding. Historically non gastrointestinal co-morbidity itself was commonly recognised as a risk factor for upper gastrointestinal bleeding.[175] However this concept of stress ulceration is no longer accepted and is only recognised in patients on ITU exposed to severe acute physiological stresses from ventilation, coagulopathy, liver failure, renal failure, septic shock or nutritional support.[177] The stresses from chronic co-morbidities in our study are unlikely to be as severe as on ITU, and therefore what we are describing is likely to have a different mechanism to that seen in stress ulceration as it is currently recognised. Many potential mechanisms can be hypothesised; for example reduced epithelial microperfusion in cardiac failure,[189] decreased oxygen levels in chronic obstructive pulmonary disease,[190,191] the poor nutritional status in many diseases, or the platelet and clotting dysfunction in end stage renal failure.[109,192] However it is unlikely that there is a single mechanism that accounts for the association we found but rather that multiple illnesses and mechanisms have a cumulative effect, as shown by the graded effect of the Charlson index and by table 6 where no individual disease accounted for the magnitude of the overall association with co-morbidity.

My findings contrast with current beliefs that the main burden of bleeding in the general population comes from known iatrogenic causes, such as NSAIDs prescribed for analgesia or anti-platelet agents prescribed for cardiac and cerebrovascular disease,[193] and that this burden would be reduced by increasing PPI use.[194] I have demonstrated that the extra contribution of these medications to bleeding cases was not large after considering the contributions of other risk factors present in the population. Therefore simply increasing PPI prescriptions in patients on high risk medications may not have as large an impact as previously thought. In contrast, the largest measurable burden of upper gastrointestinal haemorrhage in this study was clearly attributable to co-morbidity.

Although this might be interpreted as a reason for the incidence of bleeding to remain stubbornly high in an ageing population necessitating increased gastroenterology services, it alternatively suggests that focusing preventative efforts on those with co-morbid disease might provide greater gains.

CHAPTER 9

Excess long term mortality and its causes following non variceal haemorrhage: A population based cohort study

9.1 Introduction

The causes of excess deaths following an acute medical event can demonstrate areas where mortality can be improved. For example three quarters of deaths following a myocardial infarction were due to the cardiovascular disease itself, but after a stroke, two fifths of deaths were due to related respiratory infections and cardiovascular disease.[195,196] In contrast, the long term outcomes of upper gastrointestinal haemorrhage are poorly understood, despite it being the most frequent gastroenterology admission to acute medicine. There has rightly been a focus on the high mortality in the first 30 days of which 60-80% was attributed to co-morbidity.[121,122] However these were uncontrolled studies of hospital derived peptic ulcer bleed cohorts and they did not assess whether the deaths were in excess of those expected from a comparable group without bleeding.

Controlled studies have been limited to 2 peptic ulcer cohorts from the early 1990s with fewer than 150 deaths.[9,10] These showed an excess mortality unrelated to the bleeding event itself but the studies disagreed on which causes of death were increased. Other studies were not population based,[126] or were so long ago as to be mostly irrelevant with respect to current management of bleeding.[197] On this point an increasing proportion of non variceal bleeds over the last 2 decades do not have underlying peptic ulcers, thereby reducing the relevance of these previous cause of death studies to current clinical practice.[198]

Therefore to identify where interventions might reduce mortality following an upper gastrointestinal non variceal bleed I have investigated the causes of death by age and time in the 5 years following a non variceal bleed, and compared them with deaths in a matched sample of the general population.

9.2 Methods

9.2.1 Data

To provide the detailed longitudinal data and necessary power for this study I have used the recently linked English Hospital Episodes Statistics (HES) data, General Practice Research Database (GPRD) and Office for National Statistics death register described in chapter 7. Ethical approval for this study was obtained from the Independent Scientific Advisory Committee for MHRA database research.

9.2.2 Cohort

Population

I selected as exposed all patients with a first non variceal upper gastrointestinal bleed. A bleed was defined by a specific code for an upper gastrointestinal non variceal bleed in either primary or secondary care who had a supporting code in the linked dataset (see chapter 7).[178] All patients in the study therefore had a hospital admission at the time of their bleed, reflecting national guidelines at the time of the study.[148] Variceal bleeds or non specific gastrointestinal bleed codes with either a lower gastrointestinal diagnosis or procedure were excluded. Further exclusions were temporary patients, children under 16 years old, cases with invalid date codes or cases outside the up to research standard observed time periods. Patients were required to be registered with the primary care practice for at least 3 months prior to an upper gastrointestinal bleed event to avoid including prevalent cases that might have been coded at the initial registration consultation. Follow up started on the day of the first bleed.

Comparison group

For each case five age ($+/-5$ years) and sex matched controls were selected who were alive at the time of the bleed and registered to the same general practice. Controls were required to have been registered with the primary care practice for at least 3 months prior to the match date to be consistent with the definition for cases. These were the same controls used in chapter 8.

Causes of death

Dates of death for the whole cohort were extracted from the linked data using the Office of National Statistics death register. All deaths in England are coded and recorded in the Office of National Statistics Death register from death certificates using the WHO guidelines.[199] These define causes of death by ICD 10 codes with the main underlying cause established for each death using standardised rules. For this study I analysed the underlying cause of death by the 4 most frequent ICD 10 chapter headings of Neoplasms (ICD chapters C & D), Circulatory (ICD chapter I : including cerebrovascular and ischaemic heart disease), Respiratory (ICD chapter J), Digestive disease (ICD chapter K) and the remaining less frequent chapter headings grouped together in an "Other causes" category. Neoplasms were further subdivided between upper gastrointestinal malignancies and other neoplasms. Causes of death prior to 2001 were coded under the ICD 9 classification in the Office of National Statistics death register and were therefore assigned to the relevant ICD 10 chapter headings.

Follow up

Patients were followed up from the date of gastrointestinal bleed or matching until either death or censoring of the patient record (defined as the earliest of the

end of registration with GPRD practice, end of practice data, or the end of the linked Office of National Statistics data linkage (31st December 2010)). Follow up did not stop if a subsequent bleed occurred, but continued until death or censoring of the patient record.

9.2.3 Analysis

Crude mortality rates

Crude numbers of deaths and rates per 1000 person years following upper gastrointestinal bleed were calculated overall and by the most frequent ICD 10 chapter headings. These rates were then stratified by age group and year post bleed. Age was grouped into $<$50, 50-59, 60-69, 70-79, and $\geq$80 years old. The time post bleed was stratified into the first 30 days, 1 month to 1 year, and 1 year to 5 years.

Adjusted analysis

Crude mortality rates are calculated for those still alive and at risk at each time point. However, when studying specific causes of death, this group of survivors might not be representative of the initial cohort, since deaths from other causes can select out those with relevant risk factors. One method to adjust for this bias uses cumulative incidence functions (CIF) that calculate the probability of overall survival from all causes, combined with the instantaneous hazard of death for each specific cause (see algorithm 2).[200] CIF were therefore calculated for each cause of death using baseline survival functions and hazard ratios from Cox proportional hazards modelling. The models were stratified by age group, adjusted for gender, and split at 1 month, 1 year, 3 years and 5 years. The excess risk was calculated as the difference between the CIF for cases exposed

to a bleed and the CIF for unexposed controls. 95% confidence intervals were derived by bootstrapping (500 iterations). All analysis was performed using Stata version 12 (StataCorp LP, Texas).

Algorithm 2 Cumulative incidence function (CIF) adjusting for competing risks

$$\text{CIF at time}_{i=I} \text{ for cause of death}_{j=J} = \text{survival from all causes to time}_{i=I-1} * \text{hazard of death from cause}_{j=J} \text{ at time}_{i=I}$$

$$= \sum_{0}^{i} \left\{ \prod_{0}^{i=I-1} \left(1 - \sum_{1}^{j} (baseline\ hazard_{(i,j)}.HR_{(i,j)}) \right) .(baseline\ hazard_{(i=I,j=J)}.HR_{(i=I,j=J)}) \right\}$$

HR= Hazard Ratio

Sensitivity analyses

I assessed whether the excess mortality associated with a bleed for each cause of death was confounded by pre-existing co-morbidity, excess alcohol, or smoking status, and whether it varied by the site of bleed. Pre-existing co-morbidity was measured by the Charlson index (a weighted co-morbidity score predicting one year mortality[142]) using both hospital and primary care records prior to 2 months before the bleeding episode. Smoking status was defined as a current smoker, and excess alcohol status as excess alcohol use or alcohol related complications. Site of bleed was categorised as oesophageal, gastric, duodenal or unspecified.

9.3 Results

16,355 unique people who had a non variceal upper gastrointestinal bleed were identified in the linked primary and secondary care dataset with 6242 subsequent deaths. 8 cases (0.05%) could not be matched to controls and were therefore excluded from the study. Baseline demographics are shown for the bleed

cases and the matched controls in table 9.1 along with the numbers of deaths for each of the ICD 10 chapter headings. For clarity of presentation in the remainder of the results, deaths not attributed to one of the most frequent ICD 10 chapter headings were grouped together as "Other causes". The overall median follow up time from index date was 3.2 years (interquartile range 0.4 - 5.2), and for those who were censored without death was 4.8 years .

Table 9.1: Numbers, deaths and follow up time by exposure to upper gastrointestinal bleeding within 5 years of bleeding

	Exposed	%	Unexposed	%
COHORT (N)	16355	.	81523	.
Deaths	6424	.	11643	.
Personyears	40137	.	274043	.
GENDER (N = PATIENTS)	.	.	.	.
Male	8800	53.8	43836	53.8
Female	7555	46.2	37687	46.2
AGE (N = PATIENTS)	.	.	.	.
<60 years	4698	28.7	24009	29.5
60-69 years	2512	15.4	13223	16.2
70-79 years	4178	25.5	22110	27.1
≥80 years	4967	30.4	22181	27.2
NUMBER (& %) OF DEATHS	.	.	.	.
Neoplasms	1948	30.3	2615	22.5
Circulatory	1704	26.5	4443	38.2
Digestive	1042	16.2	390	3.3
Respiratory	787	12.3	1724	14.8
Genitourinary	138	2.1	265	2.3
Psychiatric	119	1.9	398	3.4
Neurological	110	1.7	321	2.8
Infections	99	1.5	122	1.0
External	88	1.4	228	2.0
Symptoms	80	1.2	346	3.0
Endocrine	77	1.2	158	1.4
Musculoskeletal	49	0.8	95	0.8
Dermatological	27	0.4	35	0.3
Haematological	26	0.4	19	0.2
Poisoning	13	0.2	9	0.1
Congenital	6	0.1	6	0.1
Unassigned code	7	0.1	7	0.1
Uncoded	104	1.6	462	4.0

9.3.1 Crude mortality rates

The crude mortality rate in the first 5 years following an upper gastrointestinal bleed was 16.0 per 100 person years, 95% confidence interval 15.6 - 16.4. This changed over time from 35.7 deaths per 100 person years (95% confidence interval 34.7- 36.8) in the first year to 7.3 deaths per 100 person years (95% confidence interval 7.0- 7.7) over the subsequent 4 years. The rates and risk of death were 10-15% lower for women than men, but the relative differences between causes of death were similar. Therefore table 9.2 shows the numbers of deaths and crude rates by ICD 10 category stratified by time post bleed. In the first month after a bleed the mortality rate was increased for all causes of death, but the highest mortality rate was from non malignant digestive disease (48 per 100 person years), and this was mostly due to causes related to the upper gastrointestinal tract (35 per 100 person years). For the remainder of the first year the highest mortality rates were from neoplasms (8.4 per 100 person years), half of which were from sites outside the gastrointestinal tract. Circulatory and respiratory mortality rates were also increased over the first year, but to a lesser extent than for digestive disease and neoplasms. However by 5 years the category with the highest mortality rate was circulatory disease (2.5 per 100 person years).

Table 9.3 shows the crude rates by cause of death by different age groups. The mortality rates for each of the causes of death increased with age except for the mortality rate from liver disease, which decreased with age. The highest mortality rate in the younger age groups was from neoplasms and digestive disease, whereas in older age groups the highest mortality rates were from circulatory disease, comprising mainly of ischaemic heart disease (3.2 per 100 person years) and cerebrovascular disease (3.3 per 100 person years).

Table 9.2: Mortality rate per 100 person years, stratified by cause of death by ICD 10 headings in the 5 years post bleed.

	1st month deaths (n)	Rate	95% CI	1 month to 1 year deaths (n)	Rate	95% CI	1 year to 5 years deaths (n)	Rate	95% CI
Neoplasms	**521**	**41.3**	(37.9-45.0)	**920**	**8.4**	(7.8-8.9)	**507**	**1.8**	(1.7-2.0)
Oesophagus	85	6.7	(5.5-8.3)	151	1.4	(1.2-1.6)	53	0.2	(0.1-0.2)
Stomach	61	4.8	(3.8-6.2)	152	1.4	(1.2-1.6)	52	0.2	(0.1-0.2)
Colon	21	1.7	(1.1-2.6)	37	0.3	(0.2-0.5)	35	0.1	(0.1-0.2)
Pancreas	37	2.9	(2.1-4.1)	66	0.6	(0.5-0.8)	19	0.1	(0.0-0.1)
Digestive(other)	39	3.1	(2.3-4.2)	58	0.5	(0.4-0.7)	46	0.2	(0.1-0.2)
Respiratory	50	4.0	(3.0-5.2)	88	0.8	(0.6-1.0)	75	0.3	(0.2-0.3)
Skin or Bone	12	1.0	(0.5-1.7)	18	0.2	(0.1-0.3)	9	0.0	(0.0-0.1)
Breast	28	2.2	(1.5-3.2)	27	0.2	(0.2-0.4)	21	0.1	(0.0-0.1)
Prostate	34	2.7	(1.9-3.8)	55	0.5	(0.4-0.7)	43	0.2	(0.1-0.2)
Circulatory	**378**	**30.0**	(27.1-33.2)	**621**	**5.6**	(5.2-6.1)	**705**	**2.5**	(2.3-2.7)
IHD	134	10.6	(9.0-12.6)	209	1.9	(1.7-2.2)	292	1.0	(0.9-1.2)
Pulmonary circulatory disease	20	1.6	(1.0-2.5)	12	0.1	(0.1-0.2)	16	0.1	(0.0-0.1)
Heart - other	50	4.0	(3.0-5.2)	104	0.9	(0.8-1.1)	113	0.4	(0.3-0.5)
CVA	83	6.6	(5.3-8.2)	197	1.8	(1.6-2.1)	197	0.7	(0.6-0.8)
Respiratory	**189**	**15.0**	(13.0-17.3)	**302**	**2.7**	(2.5-3.1)	**296**	**1.1**	(0.9-1.2)
Respiratory infections	86	6.8	(5.5-8.4)	130	1.2	(1.0-1.4)	119	0.4	(0.4-0.5)
Chronic Airway disease	48	3.8	(2.9-5.1)	71	0.6	(0.5-0.8)	108	0.4	(0.3-0.5)
ILD	16	1.3	(0.8-2.1)	23	0.2	(0.1-0.3)	22	0.1	(0.1-0.1)
Digestive	**608**	**48.2**	(44.6-52.2)	**258**	**2.3**	(2.1-2.7)	**176**	**0.6**	(0.5-0.7)
Upper GI	436	34.6	(31.5-38.0)	96	0.9	(0.7-1.1)	43	0.2	(0.1-0.2)
Lower GI	80	6.3	(5.1-7.9)	52	0.5	(0.4-0.6)	51	0.2	(0.1-0.2)
Liver or gallbladder	82	6.5	(5.2-8.1)	100	0.9	(0.7-1.1)	74	0.3	(0.2-0.3)
Pancreas	6	0.5	(0.2-1.1)	8	0.1	(0.0-0.1)	8	0.0	(0.0-0.1)
Other	**171**	**13.6**	(11.7-15.8)	**329**	**3.0**	(2.7-3.3)	**339**	**1.2**	(1.1-1.4)
Uncoded	**45**	**3.6**	(2.7-4.8)	**38**	**0.3**	(0.3-0.5)	**21**	**0.1**	(0.0-0.1)
Total	**1912**	**151.7**	(145.1-158.7)	**2468**	**22.4**	(21.6-23.4)	**2044**	**7.3**	(7.0-7.7)

Rows containing cells with 5 or less events are not shown.

Table 9.3: Mortality rate per 100 person years, stratified by cause of death by ICD 10 headings and age group in the 5 years post bleed.

	≤60 yrs deaths (n)	Rate	95% CI	60-69 yrs deaths (n)	Rate	95% CI	70-79 yrs deaths (n)	Rate	95% CI	≥80 yrs deaths (n)	Rate	95% CI
Neoplasms	**158**	**1.1**	(0.9-1.3)	**296**	**4.5**	(4.0-5.0)	**487**	**4.8**	(4.4-5.2)	**486**	**6.4**	(5.9-7.0)
Oesophagus	21	0.1	(0.1-0.2)	55	0.8	(0.6-1.1)	73	0.7	(0.6-0.9)	55	0.7	(0.6-0.9)
Stomach	20	0.1	(0.1-0.2)	37	0.6	(0.4-0.8)	74	0.7	(0.6-0.9)	73	1.0	(0.8-1.2)
Colon	7	0.0	(0.0-0.1)	9	0.1	(0.1-0.3)	23	0.2	(0.1-0.3)	33	0.4	(0.3-0.6)
Pancreas	9	0.1	(0.0-0.1)	27	0.4	(0.3-0.6)	26	0.3	(0.2-0.4)	23	0.3	(0.2-0.5)
Digestive(other)	17	0.1	(0.1-0.2)	21	0.3	(0.2-0.5)	32	0.3	(0.2-0.4)	34	0.4	(0.3-0.6)
Respiratory	16	0.1	(0.1-0.2)	37	0.6	(0.4-0.8)	65	0.6	(0.5-0.8)	45	0.6	(0.4-0.8)
Breast	8	0.1	(0.0-0.1)	13	0.2	(0.1-0.3)	14	0.1	(0.1-0.2)	13	0.2	(0.1-0.3)
Circulatory	**68**	**0.5**	(0.4-0.6)	**135**	**2.0**	(1.7-2.4)	**388**	**3.8**	(3.4-4.2)	**735**	**9.7**	(9.0-10.4)
IHD	33	0.2	(0.2-0.3)	58	0.9	(0.7-1.1)	165	1.6	(1.4-1.9)	245	3.2	(2.9-3.7)
Heart - other	13	0.1	(0.1-0.2)	21	0.3	(0.2-0.5)	46	0.4	(0.3-0.6)	137	1.8	(1.5-2.1)
CVA	12	0.1	(0.0-0.1)	30	0.5	(0.3-0.6)	99	1.0	(0.8-1.2)	253	3.3	(3.0-3.8)
Respiratory	**28**	**0.2**	(0.1-0.3)	**54**	**0.8**	(0.6-1.1)	**176**	**1.7**	(1.5-2.0)	**340**	**4.5**	(4.0-5.0)
Respiratory infections	11	0.1	(0.0-0.1)	10	0.2	(0.1-0.3)	57	0.6	(0.4-0.7)	171	2.3	(1.9-2.6)
Chronic Airway disease	10	0.1	(0.0-0.1)	31	0.5	(0.3-0.7)	76	0.7	(0.6-0.9)	62	0.8	(0.6-1.0)
Digestive	**120**	**0.8**	(0.7-1.0)	**59**	**0.9**	(0.7-1.1)	**106**	**1.0**	(0.9-1.3)	**149**	**2.0**	(1.7-2.3)
Upper GI	11	0.1	(0.0-0.1)	8	0.1	(0.1-0.2)	43	0.4	(0.3-0.6)	77	1.0	(0.8-1.3)
Lower GI	11	0.1	(0.0-0.1)	9	0.1	(0.1-0.3)	34	0.3	(0.2-0.5)	49	0.6	(0.5-0.9)
Liver or gallbladder	95	0.7	(0.5-0.8)	36	0.5	(0.4-0.8)	24	0.2	(0.2-0.3)	19	0.3	(0.2-0.4)
Other	**91**	**0.6**	(0.5-0.8)	**53**	**0.8**	(0.6-1.0)	**181**	**1.8**	(1.5-2.0)	**343**	**4.5**	(4.1-5.0)
Uncoded	**7**	**0.0**	(0.0-0.1)	**13**	**0.2**	(0.1-0.3)	**9**	**0.1**	(0.0-0.2)	**30**	**0.4**	(0.3-0.6)
Total	**472**	**3.3**	(3.0-3.6)	**610**	**9.2**	(8.5-9.9)	**1347**	**13.2**	(12.5-13.9)	**2083**	**27.5**	(26.3-28.7)

1st year excluded. Rows containing cells with 5 or less events are not shown.

9.3.2 Adjusted analysis

The graphs in the lefthand columns of figures 9.1- 9.5 show the cumulative incidence functions unadjusted for competing risks for the most frequent causes of death by ICD 10 chapter headings stratified by age group. These can be seen to be increasingly overestimating the risks of death with increasing age, and therefore mortality, when compared with the graphs in panels (a). The graphs in panels (a) show the absolute cumulative risk (CIF) now appropriately adjusted for competing risks. By 5 years after an upper gastrointestinal bleed the cumulative risk of death due to malignant or non malignant gastrointestinal causes ranged from 3.7% ($\leq$50 years) to 14.8% ($\geq$80 years). In contrast the cumulative risk of death due to non gastrointestinal causes ranged from 4.2% ($\leq$50 years) to 46.7% ($\geq$80 years) by 5 years following an upper gastrointestinal bleed.

The graphs in panels (b) of figures 9.1 - 9.5 show the excess risk of death (or excess CIF) associated with a bleed adjusted for competing risks. Overall there was an absolute excess risk of death of 26% compared to matched controls and this peaked in the 70 to 79 year old age group. The excess cumulative risk of death due to malignant or non malignant gastrointestinal causes ranged from 3.7% ($\leq$50 years) to 13.0% ($\geq$80 years). In contrast the excess cumulative risk of death due to non gastrointestinal causes ranged from 3.9% ($\leq$50 years) to 19.1% ($\geq$80 years). Therefore over half the excess cumulative risk of death was due to non gastrointestinal causes of death. Table 9.4 shows that the 95% confidence intervals for the excess CIF values exclude the null for all causes of death apart from respiratory disease (which was limited by small numbers).

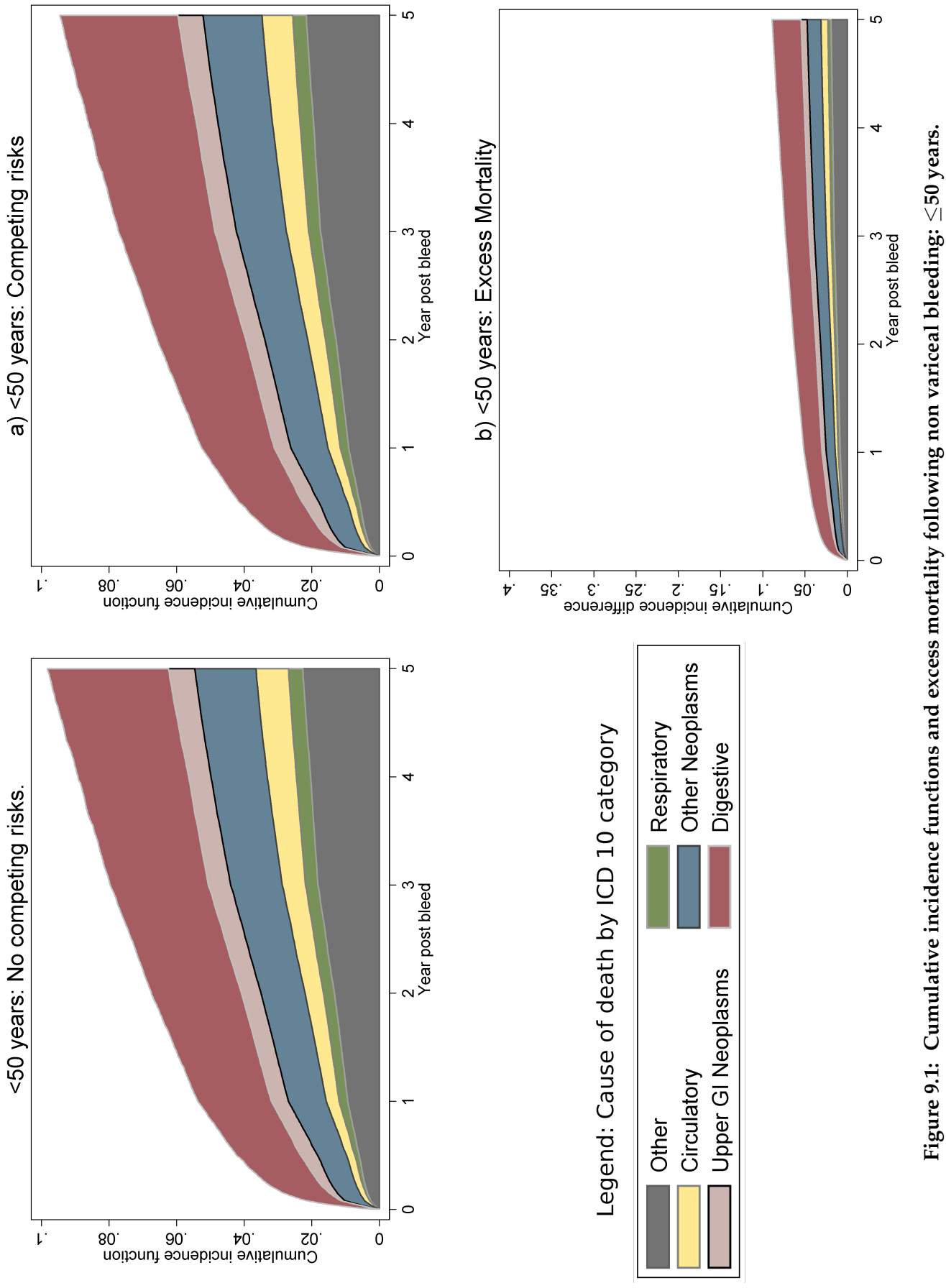


Figure 9.1: Cumulative incidence functions and excess mortality following non variceal bleeding: ≤50 years.

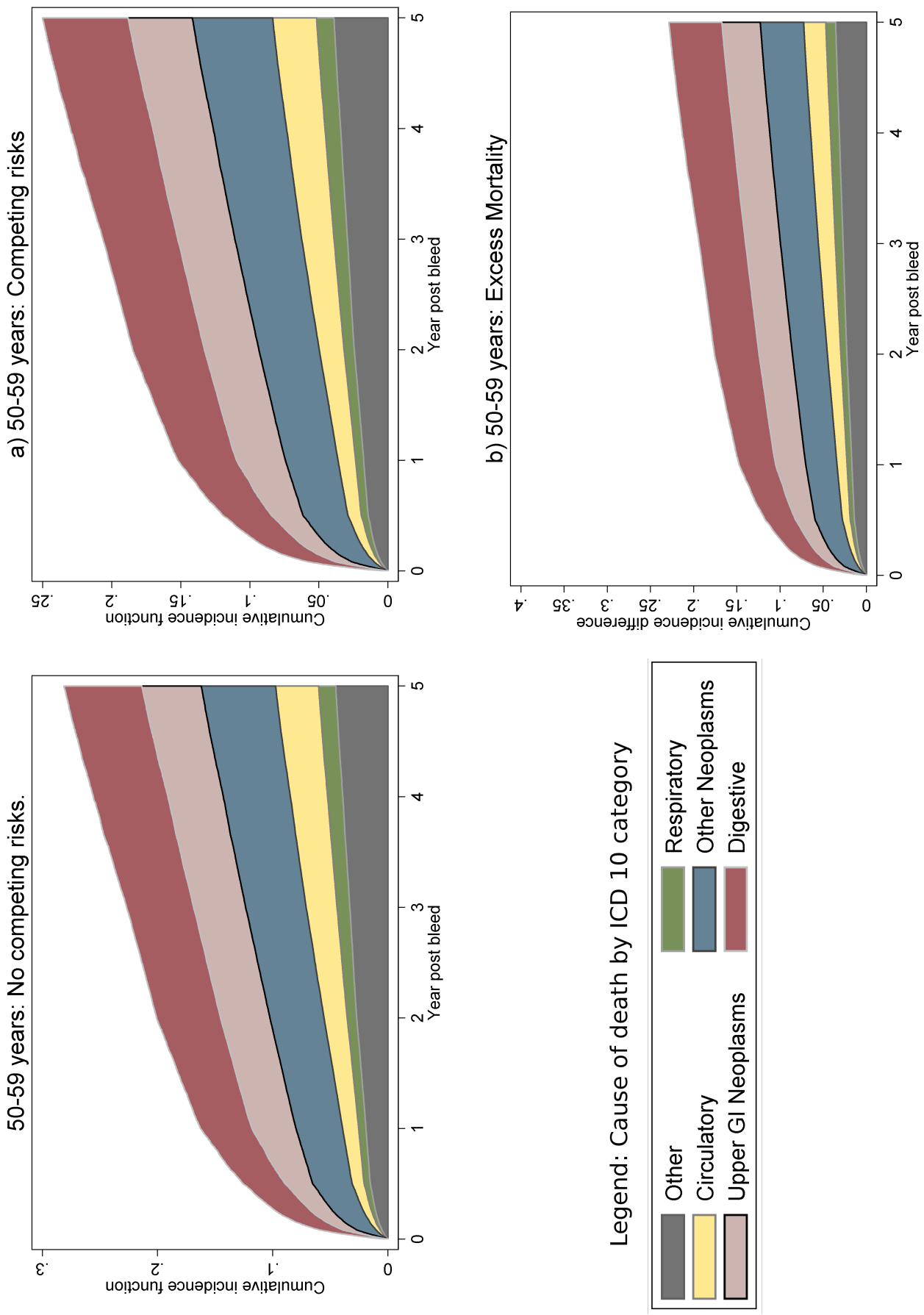


Figure 9.2: Cumulative incidence functions and excess mortality following non variceal bleeding: 50-59 years.

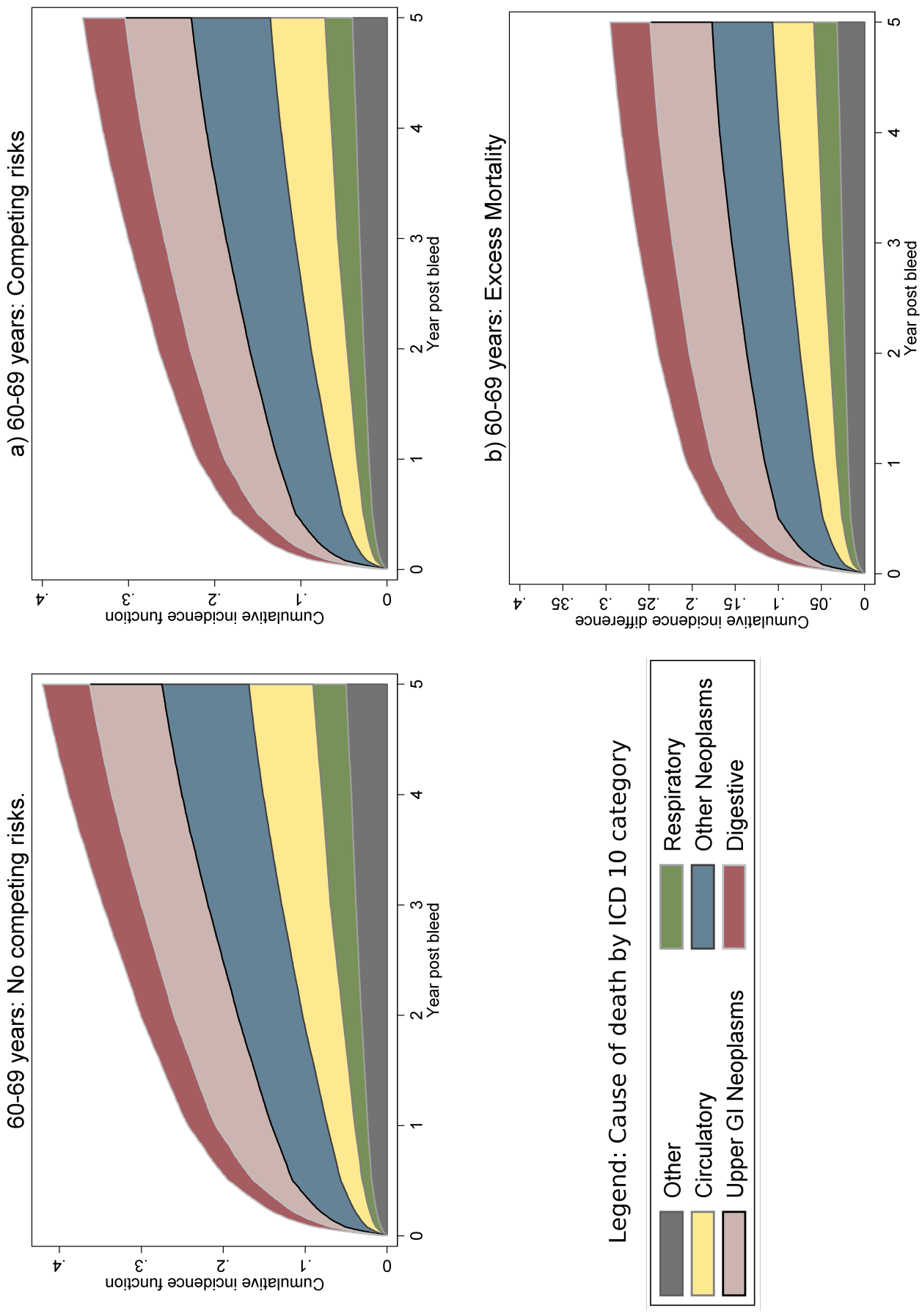


Figure 9.3: Cumulative incidence functions and excess mortality following non variceal bleeding: 60-69 years.

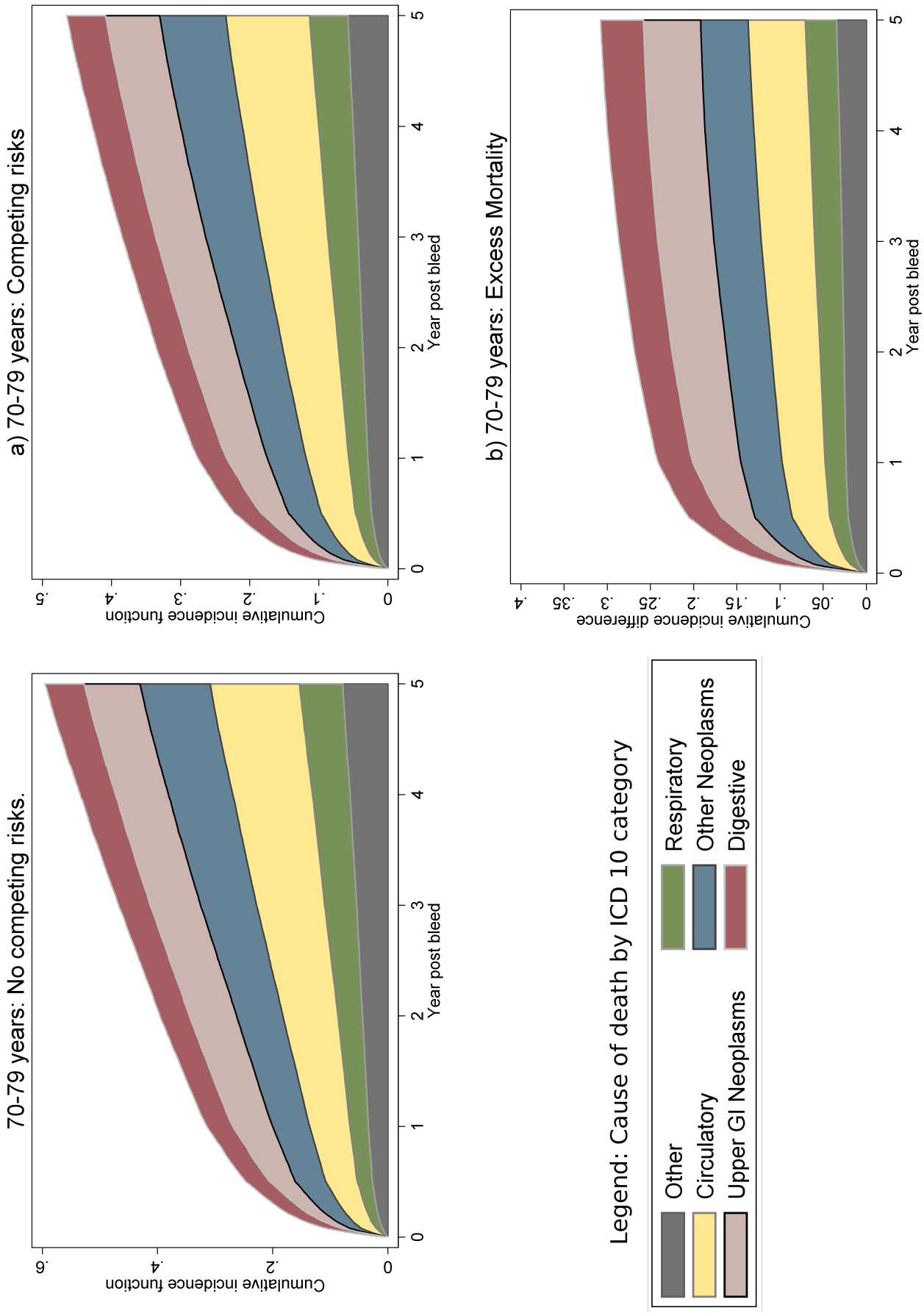


Figure 9.4: Cumulative incidence functions and excess mortality following non variceal bleeding: 70-79 years.

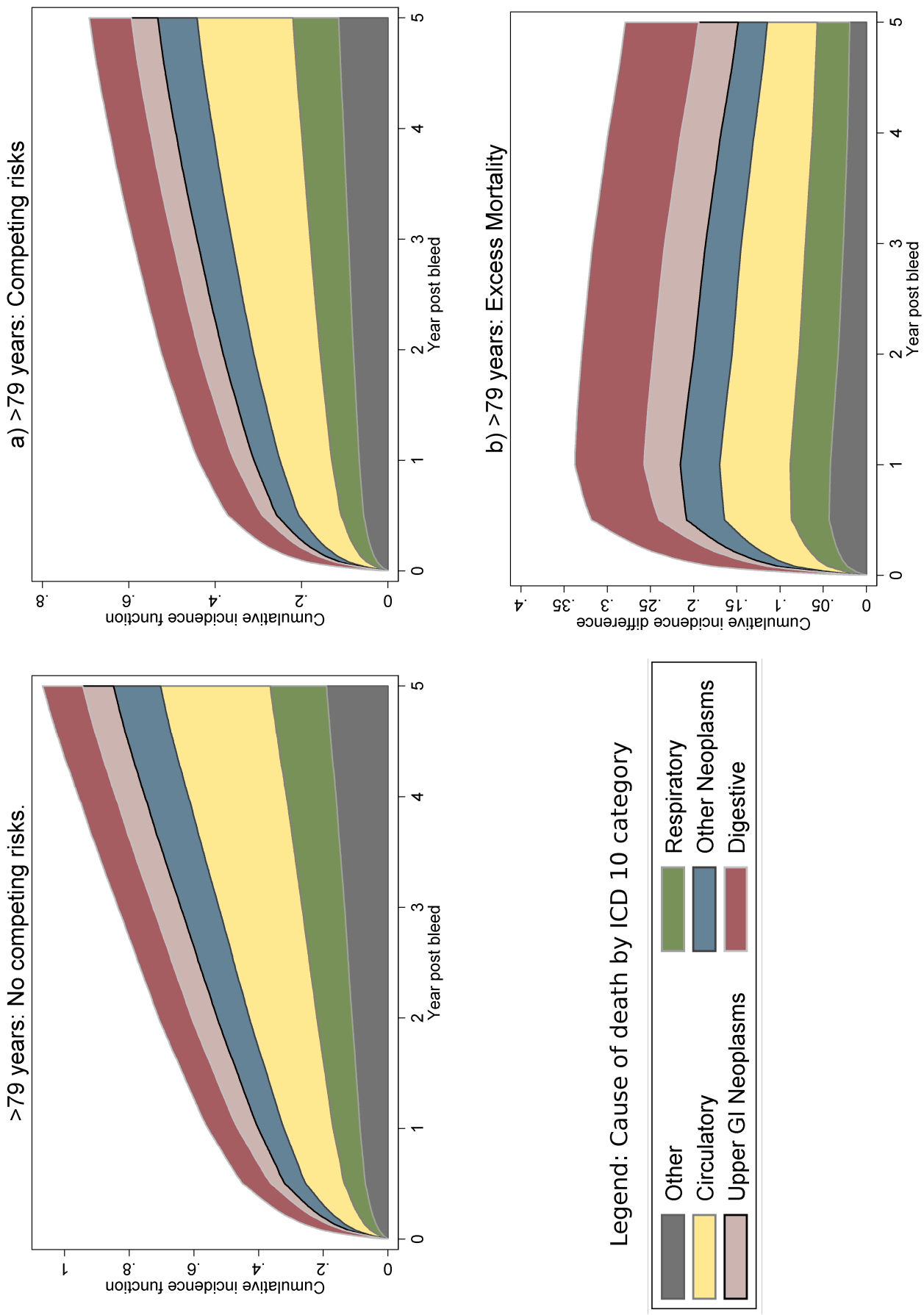


Figure 9.5: Cumulative incidence functions and excess mortality following non variceal bleeding: $\geq$ 80 years.

Table 9.4: Excess cumulative incidence function post bleed by time post bleed.

95% confidence intervals obtained by bootstrapping (500 iterations).

		1 month		1 year		5 years	
		eCIF	(95% CI)	**eCIF**	**(95% CI)**	**eCIF**	**(95% CI)**
Upper GI Neoplasms	$\leq$ 50 years	0.11	(-0.00-0.22)	0.43	(0.22-0.64)	0.61	(0.33-0.89)
	50-59 years	1.15	(-0.30-2.59)	3.11	(1.53-4.68)	3.62	(2.02-5.22)
	60-69 years	1.76	(-0.35-3.87)	5.58	(3.33-7.82)	6.58	(4.28-8.89)
	70-79 years	1.47	(-0.28-3.21)	4.76	(2.91-6.61)	5.65	(3.70-7.59)
	$\geq$ 80 years	1.20	(-0.12-2.52)	3.83	(2.35-5.31)	4.41	(2.79-6.03)
Other Neoplasms (Not Upper GI)	$\leq$ 50 years	0.51	(0.27-0.75)	1.00	(0.64-1.36)	1.29	(0.86-1.72)
	50-59 years	1.45	(0.93-1.96)	3.45	(2.63-4.27)	4.17	(3.17-5.18)
	60-69 years	2.39	(1.83-2.96)	5.65	(4.54-6.75)	6.64	(5.22-8.06)
	70-79 years	1.82	(1.39-2.25)	4.68	(3.70-5.65)	5.23	(3.87-6.59)
	$\geq$ 80 years	1.95	(1.50-2.40)	4.82	(3.52-6.11)	4.38	(2.65-6.12)
Cardiovascular	$\leq$ 50 years	0.14	(0.02-0.26)	0.38	(0.17-0.60)	0.62	(0.32-0.92)
	50-59 years	0.37	(0.11-0.64)	1.44	(0.92-1.96)	2.36	(1.53-3.19)
	60-69 years	1.12	(0.74-1.49)	3.04	(2.31-3.78)	4.66	(3.52-5.80)
	70-79 years	2.40	(1.89-2.91)	5.25	(4.19-6.32)	6.44	(4.76-8.12)
	$\geq$ 80 years	3.92	(3.21-4.63)	8.66	(6.30-11.03)	7.64	(3.97-11.30)
Respiratory*	$\leq$ 50 years	0.03	(.)	0.24	(.)	0.31	(.)
	50-59 years	0.16	(.)	0.58	(.)	1.04	(.)
	60-69 years	0.56	(.)	1.28	(.)	2.08	(.)
	70-79 years	0.97	(.)	2.46	(.)	3.24	(.)
	$\geq$ 80 years	2.28	(.)	4.95	(.)	4.56	(.)
Digestive	$\leq$ 50 years	1.01	(0.28-1.75)	2.28	(1.43-3.14)	3.04	(2.06-4.02)
	50-59 years	1.96	(0.25-3.67)	4.04	(2.23-5.84)	5.33	(3.45-7.22)
	60-69 years	1.93	(0.27-3.59)	3.15	(1.47-4.83)	3.90	(2.17-5.63)
	70-79 years	2.60	(0.67-4.53)	4.01	(2.05-5.98)	4.45	(2.46-6.43)
	$\geq$ 80 years	6.43	(2.43-10.42)	8.19	(4.20-12.17)	8.56	(4.58-12.54)
Other	$\leq$ 50 years	0.26	(0.09-0.44)	0.95	(0.61-1.29)	1.65	(1.10-2.19)
	50-59 years	0.53	(0.21-0.85)	1.90	(1.26-2.53)	3.09	(2.17-4.02)
	60-69 years	0.70	(0.42-0.98)	1.85	(1.31-2.38)	2.37	(1.63-3.11)
	70-79 years	0.92	(0.65-1.19)	2.58	(1.99-3.17)	3.06	(2.15-3.97)
	$\geq$ 80 years	2.29	(1.78-2.80)	4.37	(2.96-5.78)	2.54	(0.58-4.50)

eCIF - The absolute difference in the cumulative incidence function between patients with non variceal bleeding and age, sex, year, and general practice matched controls without non variceal bleeding. * Unable to calculate confidence intervals for respiratory causes of death due to small numbers.

9.3.3 Sensitivity analyses

Table 9.5 shows the excess mortality at 5 years associated with a bleed when adjusted for prior co-morbidity, alcohol or smoking. Adjusting for smoking and alcohol had no effect on the excess mortality, whilst adjusting for prior co-morbidity slightly reduced the point estimates for non gastrointestinal co-morbidity. However the significant excess risk of death for all causes persisted with confidence intervals overlapping with those from the main analysis. When I examined in more detail the prior medical history of patients exposed to a bleed, 54% of those who subsequently died from a neoplasm did not have a neoplasm coded before the bleed, and 41% of those who died from a cardiovascular death did not have cardiovascular disease coded before the bleed. Finally when examined by bleed site the excess risks were unchanged from the main analysis.

9.4 Discussion

I have determined the cumulative excess risk of death in the 5 years following a non variceal upper gastrointestinal bleed. I have done this in a large unselected population cohort by underlying cause whilst adjusting for competing risks. This showed that although there was an excess risk of death from gastrointestinal causes, over half the total excess risk of death was from unrelated non gastrointestinal causes. The largest absolute increases were from neoplastic and cardiovascular disease, but half of those who died from these two causes were not diagnosed prior to the upper gastrointestinal bleed. This suggests that in addition to indicating upper gastrointestinal pathology an upper gastrointestinal bleed is either a cause of non gastrointestinal co-morbidity, a flag for undiagnosed co-morbidity, or an indicator of a decline in health from ex-

Table 9.5: Excess cumulative incidence function at 5 years post bleed by age group adjusted for lifestyle factors and co-morbidity

95% confidence intervals obtained by bootstrapping (500 iterations).

Adjusted for:		Gender only^{+}		Alcohol and smoking		Co-morbidity	
		eCIF	(95% CI)	**eCIF**	**(95% CI)**	**eCIF**	**(95% CI)**
Upper GI Neoplasms	$\leq$ 50 years	0.61	(0.33-0.89)	0.63	(0.33-0.92)	0.60	(0.32-0.87)
	50-59 years	3.62	(2.02-5.22)	3.79	(2.55-5.03)	3.44	(2.3-4.59)
	60-69 years	6.58	(4.28-8.89)	6.67	(4.88-8.46)	5.97	(4.18-7.76)
	70-79 years	5.65	(3.70-7.59)	5.63	(4.21-7.05)	5.03	(3.31-6.74)
	$\geq$ 80 years	4.41	(2.79-6.03)	4.39	(3.07-5.71)	4.07	(2.57-5.56)
Other Neoplasms (Not Upper GI)	$\leq$ 50 years	1.29	(0.86-1.72)	1.26	(0.78-1.75)	1.18	(0.73-1.63)
	50-59 years	4.17	(3.17-5.18)	4.05	(2.67-5.42)	3.23	(2.11-4.34)
	60-69 years	6.64	(5.22-8.06)	6.39	(4.38-8.39)	4.75	(3.1-6.4)
	70-79 years	5.23	(3.87-6.59)	5.11	(3.39-6.82)	3.66	(2.04-5.28)
	$\geq$ 80 years	4.38	(2.65-6.12)	4.34	(2.4-6.28)	3.19	(1.53-4.84)
Cardiovascular	$\leq$ 50 years	0.62	(0.32-0.92)	0.65	(0.32-0.97)	0.50	(0.25-0.76)
	50-59 years	2.36	(1.53-3.19)	2.21	(1.29-3.14)	1.50	(0.85-2.16)
	60-69 years	4.66	(3.52-5.80)	4.50	(2.95-6.04)	2.93	(1.83-4.02)
	70-79 years	6.44	(4.76-8.12)	6.32	(4.05-8.59)	4.05	(2.14-5.96)
	$\geq$ 80 years	7.64	(3.97-11.30)	7.66	(3.41-11.91)	5.31	(1.97-8.65)
Respiratory*	$\leq$ 50 years	0.31	(.)	0.26	(.)	0.21	(.)
	50-59 years	1.04	(.)	0.99	(.)	0.72	(.)
	60-69 years	2.08	(.)	1.92	(.)	1.33	(.)
	70-79 years	3.24	(.)	3.15	(.)	2.14	(.)
	$\geq$ 80 years	4.56	(.)	4.51	(.)	3.22	(.)
Digestive	$\leq$ 50 years	3.04	(2.06-4.02)	2.38	(1.7-3.05)	2.86	(2.05-3.68)
	50-59 years	5.33	(3.45-7.22)	4.20	(2.98-5.42)	4.70	(3.34-6.06)
	60-69 years	3.90	(2.17-5.63)	3.53	(2.51-4.55)	3.66	(2.55-4.77)
	70-79 years	4.45	(2.46-6.43)	4.09	(3.13-5.06)	4.12	(2.8-5.44)
	$\geq$ 80 years	8.56	(4.58-12.54)	8.23	(6.33-10.13)	8.18	(5.78-10.57)
Other	$\leq$ 50 years	1.65	(1.10-2.19)	1.55	(0.95-2.14)	1.33	(0.83-1.83)
	50-59 years	3.09	(2.17-4.02)	3.11	(2.01-4.21)	2.53	(1.63-3.44)
	60-69 years	2.37	(1.63-3.11)	2.46	(1.51-3.41)	1.97	(1.15-2.79)
	70-79 years	3.06	(2.15-3.97)	3.29	(2.09-4.48)	2.70	(1.45-3.95)
	$\geq$ 80 years	2.54	(0.58-4.50)	2.73	(0.45-5.01)	2.68	(0.28-5.07)

eCIF - The absolute difference in the cumulative incidence function between patients with non variceal bleeding and age, sex, year, and general practice matched controls without non variceal bleeding. Co-morbidity was measured by the Charlson Index, alcohol defined as excess alcohol or alcohol complications, and smoking status as current smoker.
$^{+}$As in table 9.4.
* Unable to calculate confidence intervals for respiratory causes of death due to small numbers.

isting co-morbidity. My findings contrast with that for other acute life limiting medical events where three quarters of the excess death following a myocardial infarction were shown to be due to the cardiovascular disease, and two thirds of the excess death following a stroke were shown to be due to related respiratory infections, cardiovascular or the cereberovascular disease itself.[195,196]

The main strengths of this study compared to previous studies are its larger size, follow up, competing risk adjustment, and general population setting. This allowed us to calculate more accurate, unbiased and detailed mortality rates for different causes of death than has previously been done. To achieve this I have used linked electronic primary and secondary health care records in which the definition of bleeding has previously been found to be accurate. In HES the incidence of peptic ulcer haemorrhage (1992-1995) was comparable to the 1993 regional BSG audit (32 v 29 per 100,000 per year respectively).[6] More recently similar numbers of all upper gastrointestinal bleed hospital admissions and related procedures were recorded in HES compared with those recorded in the 2007 prospective national UK audit.[151] In the GPRD the positive predictive value of an upper gastrointestinal bleed code was 99% using anonymised chart review.[100,201] I have further strengthened the case definition for my study by requiring evidence from both databases to be present to define a bleed.[178]

The information on the fact and cause of death in my study was likely to be accurate, as this was extracted from the Office of National Statistics death registry that uses standardised WHO guidelines. This was the only feasible method to to ascertain cause of death in a standardised way for my large study population. Underlying cause of death information was used to avoid the effect of changes in coding requirements over time.[202]

There have been a number of studies of cause of death during the first 30 days following an upper gastrointestinal bleed.[121,122,125,203,204] The largest was from

Hong Kong. However it assessed only peptic ulcer bleeds from one hospital and only reported the proportion of deaths from each cause with no comparison group.[121]

In contrast, there have been only a few studies examining causes of death in the long term following a bleed. Studies in the 1980s and 1990s followed up peptic ulcer cohorts post surgical treatment rather than upper gastrointestinal bleeds (shown in table 9.6). These studies were susceptible to the selection bias inherent in surgical cohorts[205] and furthermore they are now dated as the cohorts were completed in the 1980s before ulcer treatment was radically changed by the introduction of Helicobacter pylori eradication[206] and proton pump inhibitors.[207,208] The studies that did follow up upper gastrointestinal bleeding included only patients with proven peptic ulcers who had survived the first 30 days.(table 9.6)

Table 9.6: Previous literature on long term outcome following peptic ulcer cohorts > 30 days

	Operated peptic ulcer						
First Author	**Caygill**	**McIntosh**	**Macintyre**	**Lindell**	**Staël von Holstein**	**Svanes**	**Duggan**
Operation	Vagotomy	Gastric ulcer cohort	Duodenal ulcer operation	Unoperated peptic ulcer	Partial gastrectomy	Perforated peptic ulcer	Peptic ulcer operation
Year published	1991[209]	1991[210]	1994[211]	1994[212]	1995[205]	1999[213]	1999[214]
Follow up (years)	?	10	<20	12	<20	18.8	<20
Total deaths	577	305	791	121	399	817	224
Neoplasms	32.8	17.4	31.7	26.4	22.3	10.8	10.7
Upper GI	2.6	1.6	0.02	5.0	1.8	1.2	
Respiratory	12.3	4.6	0.03		7.5	3.8	
Cardiovascular*		51.5	35.5	47.1	49.9	13.8	42.9
Respiratory		10.8	8.0		9.5	4.0	13.8
Digestive**		7.2	2.8	9.9	5.3	8.8	10.3
	Bleeding peptic ulcer						
First Author	**Smart**	**Rorbaek-Madsen**	**Kubba**	**Hudson**	**Ruigomez**		
Year published	1986[197]	1994[215]	1997[126]	1995[9]	2000[10]		
Follow up (years)	<8	<8	<6.5	2.8 (mean)	2.8 (mean)		
Total deaths	77	45	30	142	155		
Neoplasms	16.9		10.0	23.9	12.9		
Upper GI	1.3		0.0	3.5			
Respiratory	1.3		0.0	7.0			
Cardiovascular*	24.7		66.7	34.5	36.8		
Respiratory	5.2		16.7	19.7	17.4		
Digestive**	6.5	6.7	6.7	5.6	9.0		

*Cardiovascular definitions varied from ischaemic heart disease only to including cereberovascular disease. **Digestive disease definitions varied from peptic ulcer related to non malignant GI disease

The largest study by Ruigomez *et al* consisted of 978 patients with 155 deaths.[10] However cause of death information was not available, and cause of death was imputed by the most recently recorded co-morbidity, increasing the risk of missclassification. An upper age limit also meant that the study's age distribution differed considerably from my unselected cohort, so it was no longer representative of those currently presenting with bleeds. The next largest and arguably better study was able to obtain death certificate data from the national death register, and was therefore similar to my study in being able to ascertain the causes of death in a standardised manner.[9] However the study was restricted to one city and to patients over 60 years old who were hospitalised with endoscopically proven peptic ulcers (n=487, deaths=142). This limits its generalisability to a contemporary population and introduces a selection bias towards those deemed suitable for an endoscopy. In both studies, mortality rates were not calculated, no adjustment for competing risks was made, and neither study had the power to assess causes of death by age or time post bleed. In contrast, I have been able to calculate stratified excess risks for different causes of death adjusted for competing risks within a large population based cohort.

I have shown that following an upper gastrointestinal bleed there was a considerable excess of all causes of death, and over half of this was due to non gastrointestinal co-morbidity, particularly neoplastic and cardiovascular disease. This excess in death was not explained by co-morbidity such as cancer or cardiovascular disease diagnosed prior to the admission. An upper gastrointestinal bleed is therefore either a cause or an indicator of a deterioration in non gastrointestinal co-morbidity. This means a patient who has an upper gastrointestinal bleed warrants a re-assessment of their co-morbidity in the follow up period to their bleeding episode.

CHAPTER 10

Overall discussion

10.1 Summary of findings in this thesis

- **Chapter 4:** Hospital Episodes Statistics data recorded reassuringly similar numbers for upper gastrointestinal bleed hospital admissions and procedures to those in a national audit.

- **Chapter 5:** The occurrence of upper gastrointestinal haemorrhage was unchanged over the last decade. This was contrary to what was expected given the trends in known risk factors, for example increased PPI use and Helicobacter pylori eradication.

- **Chapter 5:** A higher incidence of upper gastrointestinal haemorrhage was observed in the north of England, but this was dwarfed by the variation in occurrence associated with deprivation. Areas of greater deprivation had 2-3 fold higher rates of hospitalisation for upper gastrointestinal haemorrhage than areas of less deprivation suggesting strong modifiable risk factors.

- **Chapter 6:** There has been an improvement in 28 day mortality following upper gastrointestinal haemorrhage over the last decade.

- **Chapter 6:** Those admitted with bleeding were increasingly older and had more co-morbidity, and these confounders partially obscured the changes in mortality.

- **Chapter 7:** Linked primary and secondary cared data can provide detailed longitudinal data and allows assessment of potential selection biases in the individual datasets.

- **Chapter 8:** A combined measure of non gastrointestinal co-morbidity was a significant independent predictor of upper gastrointestinal bleeding and explained a greater proportion of the burden of bleeding than any other

risk factor in the population, including common medications such as aspirin and NSAIDs.

- **Chapter 8:** The effect of a combined measure of non gastrointestinal co-morbidity was far in excess of that expected from the effect of its constituent diseases.

- **Chapter 9:** Non gastrointestinal co-morbidity contributed to the majority of the excess risk of death following upper gastrointestinal bleeding, even after adjusting for pre-existing co-morbidity.

10.2 Interpretation and clinical consequences

This thesis has shown in a series of studies that, on a population level, non variceal upper gastrointestinal bleeding occurrence and its mortality was a consequence of the burden of co-morbidity in that population. This association was less marked in younger patients, however both bleeds and co-morbidity were less prevalent in younger age groups. Therefore the association with co-morbidity explained some of the trends in mortality and occurrence, and given the large population attributable fraction of bleeding associated with co-morbidity was likely to account for at least some of the steep socioeconomic gradient I identified.

One possible explanation for the contribution of co-morbidity to upper gastrointestinal bleeding would be the under reporting of Helicobacter pylori infection if the infection was strongly associated with co-morbidity. However the evidence for this is currently conflicting and underpowered.[186,188] Alternatively the association of co-morbidity and upper gastrointestinal bleeding might be due to a form of stress ulceration occurring similar to that observed on ITU.[177] Although this has been disregarded as unimportant,[8] on a popu-

lation level the effect might become measurable and important and therefore produce the results observed in this thesis.

Caution is always needed when attempts are made to derive clinical messages for use at an individual level from associations averaged across a whole population. However my studies provide a useful balance to the messages from previous research (many linked to pharmaceutical funding) that often implied that NSAID misuse and the underutilisation of PPIs or selective NSAIDs were the main contribution to the burden of bleeds in the population.[193,194,216–219]

The studies in this thesis also suggest that bleeding should not be treated in isolation by gastroenterologists, and that gastroenterologists need to retain a wider medical perspective. In the short term there was the expected excess mortality from upper gastrointestinal pathology that gastroenterologists appropriately focus on managing. However the strong association with non gastrointestinal co-morbidity and death mean that the status and management of co-existing illness needs to be re-assessed at the time of the bleed, particularly in the elderly.

10.3 Future work

I have identified and planned three initial avenues of investigation following this thesis.

The results in this thesis have relied on the Charlson index as a measure of co-morbidity. This was chosen as it has been used in a wide range of settings and consistently been shown to predict mortality. However it was derived in 1987 in a hospitalised cohort and validated in breast cancer patients. Contemporary scores for use in linked primary and secondary care data such as in this thesis are therefore lacking. I have obtained funding to derive a score in the linked data which will initially involve Bayesian data mining to ensure that diagnoses

are not being missed, as well as bootstrapping the model building, and performing extensive validation and calibration.

Cardiovascular disease consistently is associated with gastrointestinal bleeding, and gastrointestinal bleeding following a myocardial infarction is associated with worse outcomes. Furthermore cardiovascular disease remained an important cause of excess death in my study following a bleed. However there is ongoing debate as to the risk of bleeding after myocardial infarction, particularly because of the risk of the combinations of medications used in its treatment. I therefore intend to explore in detail the specific risks associated with the combinations of medications following a myocardial infarction and the time periods of highest risk.

The socioeconomic gradient I identified in this thesis deserves further detailed investigation into the underlying causes. To do this I require detailed lifestyle, prescribing and co-morbidity information in the underlying population. This is now available in the linked data I used in this PhD. However I was not able to examine this within this thesis due to the matching performed. A future unmatched study will therefore be able to identify what the aetiological factors are that contribute to this inequality.

10.4 Conclusion

This thesis has used newly available linked population data that provides a complete longitudinal record of a patients' diagnoses, admissions, demographics and prescriptions within the general population. Therefore, in addition to describing trends in mortality and occurrence in the largest population based studies to date, I have also been able to show for the first time the population attributable fractions of the risk factors for bleeding and the predictors and causes

of its excess death properly adjusted for competing risks. All these studies have clearly shown the importance of co-morbidity in the occurrence and outcome of upper gastrointestinal bleeding and provided a comprehensive description of its contemporary epidemiology.

Bibliography

[1] Hearnshaw SA, Logan RFA, Lowe D, et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut; 2011;60(10):1327–35.

[2] Williams JG, Roberts SE, Ali MF, et al. Gastroenterology services in the UK. The burden of disease, and the organisation and delivery of services for gastrointestinal and liver disorders: a review of the evidence. Gut; 2007;56 Suppl 1:1–113.

[3] van Leerdam ME, Vreeburg EM, Rauws EAJ, et al. Acute upper GI bleeding: did anything change?: Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. The American Journal of Gastroenterology; 2003;98(7):1494–1499.

[4] Targownik LE, Nabalamba A. Trends in management and outcomes of acute nonvariceal upper gastrointestinal bleeding: 1993-2003. Clin Gastroenterol Hepatol; 2006;4(12):1459–1466.

[5] Lanas A, García-Rodríguez LA, Polo-Tomás M, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. The American journal of gastroenterology; 2009;104(7):1633–41.

[6] Higham J, Kang JY, Majeed A. Recent trends in admissions and mortal-

ity due to peptic ulcer in England: increasing frequency of haemorrhage among older subjects. Gut; 2002;50(4):460–464.

[7] Kang JY, Elders A, Majeed A, et al. Recent trends in hospital admissions and mortality rates for peptic ulcer in Scotland 1982-2002. Aliment Pharmacol Ther; 2006;24(1):65–79.

[8] Herzig SJ, Vaughn BP, Howell MD, et al. Acid-suppressive medication use and the risk for nosocomial gastrointestinal tract bleeding. Archives of internal medicine; 2011;171(11):991–7.

[9] Hudson N, Faulkner G, Smith SJ, et al. Late mortality in elderly patients surviving acute peptic ulcer bleeding. Gut; 1995;37(2):177–181.

[10] Ruigomez A, Rodriguez LAG, Hasselgren G, et al. Overall mortality among patients surviving an episode of peptic ulcer bleeding. J Epidemiol Community Health; 2000;54(2):130–133.

[11] Vidan M, Serra JA, Moreno C, et al. Efficacy of a Comprehensive Geriatric Intervention in Older Patients Hospitalized for Hip Fracture: A Randomized, Controlled Trial. Journal of the American Geriatrics Society; 2005;53(9):1476–1482.

[12] Zhao Y, Encinosa W. Hospitalizations for Gastrointestinal Bleeding in 1998 and 2006. HCUP Statistical Brief; 2008;65(December):1–12.

[13] Ndjitoyap Ndam EC, Koki Ndombo PO, Fouda OA, et al. [Upper digestive system hemorrhages in Cameroon (apropos of 172 cases examined via endoscopy)]. Médecine tropicale : revue du Corps de santé colonial; 1990;50(2):181–4.

[14] Zimmerman J, Meroz Y, Siguencia J, et al. Upper gastrointestinal hemor-

rhage. Comparison of the causes and prognosis in primary and secondary bleeders. Scand J Gastroenterol; 1994;29(9):795–798.

[15] Lule GN, Obiero ET, Ogutu EO. Factors that influence the short term outcome of upper gastrointestinal bleeding at Kenyatta National Hospital. East Afr Med J; 1994;71(4):240–245.

[16] Barkun A, Sabbah S, Enns R, et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic Hemostasis and Proton Pump Inhibition are Associated with Improved Outcomes in a Real-Life Setting. The American Journal of Gastroenterology; 2004;99(7):1238–1246.

[17] Kelly P, Katema M, Amadi B, et al. Gastrointestinal pathology in the University Teaching Hospital, Lusaka, Zambia: review of endoscopic and pathology records. Trans R Soc Trop Med Hyg; 2008;102(2):194–199.

[18] Marmo R, Koch M, Cipolletta L, et al. Predictive factors of mortality from nonvariceal upper gastrointestinal hemorrhage: a multicenter study. Am J Gastroenterol; 2008;103(7):1639–47; quiz 1648.

[19] Djibril AM, Tomta K, Balaka K, et al. [Hematemesis in Togo: findings of a 12-month study in an intensive care unit]. Médecine tropicale : revue du Corps de santé colonial; 2010;70(3):311–2.

[20] Lanas A, Aabakken L, Fonseca J, et al. Clinical predictors of poor outcomes among patients with nonvariceal upper gastrointestinal bleeding in Europe. Alimentary pharmacology & therapeutics; 2011;33(11):1225–33.

[21] Gado AS, Ebeid BA, Abdelmohsen AM, et al. Clinical outcome of acute upper gastrointestinal hemorrhage among patients admitted to a govern-

ment hospital in Egypt. Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association;;18(1):34–9.

[22] Blatchford O, Davidson LA, Murray WR, et al. Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. BMJ; 1997;315(7107):510–514.

[23] Rockall TA, Logan RF, Devlin HB, et al. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. BMJ; 1995;311(6999):222 – 6.

[24] Paspatis GA, Matrella E, Kapsoritakis A, et al. An epidemiological study of acute upper gastrointestinal bleeding in Crete, Greece. Eur J Gastroenterol Hepatol; 2000;12(11):1215–1220.

[25] Button LA, Roberts SE, Evans PA, et al. Hospitalized incidence and case fatality for upper gastrointestinal bleeding from 1999 to 2007: a record linkage study. Alimentary Pharmacology & Therapeutics; 2011;33(1):64–76.

[26] Loperfido S, Baldo V, Piovesana E, et al. Changing trends in acute upper-GI bleeding: a population-based study. Gastrointest Endosc; 2009;70(2):212–224.

[27] Laine L, Yang H, Chang SC, et al. Trends for Incidence of Hospitalization and Death Due to GI Complications in the United States From 2001 to 2009. The American Journal of Gastroenterology; 2012;.

[28] Yavorski RT, Wong RK, Maydonovitch C, et al. Analysis of 3,294 cases of upper gastrointestinal bleeding in military medical facilities. Am J Gastroenterol; 1995;90(4):568–573.

[29] Czernichow P, Hochain P, Nousbaum JB, et al. Epidemiology and course of acute upper gastro-intestinal haemorrhage in four French geographical areas. Eur J Gastroenterol Hepatol; 2000;12(2):175–181.

[30] Taha AS, Angerson WJ, Knill-Jones RP, et al. Upper gastrointestinal haemorrhage associated with low-dose aspirin and anti-thrombotic drugs - a 6-year analysis and comparison with non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther; 2005;22(4):285–289.

[31] Theocharis GJMD, Thomopoulos KCMD, Sakellaropoulos GMD, et al. Changing Trends in the Epidemiology and Clinical Outcome of Acute Upper Gastrointestinal Bleeding in a Defined Geographical Area in Greece. Journal of Clinical Gastroenterology; 2008;42(2):128–133.

[32] Jurado Hernandez AM, de Teresa Galvan J, Ruiz-Cabello Jimenez M, et al. [Evolution in the epidemiology of non-variceal upper digestive hemorrhage from 1985 to 2006]. Rev Esp Enferm Dig; 2008;100(5):273–277.

[33] Hershcovici T, Haklai Z, Gordon ES, et al. Trends in acute non-variceal bleeding in Israel in 1996-2007: A significant decrease in the rates of bleeding peptic ulcers. Digestive and Liver Disease; 2010;42(7):477–481.

[34] Targownik LE, Al-Mamfud A. The prevalence of risk factors for gastrointestinal complications and use of gastroprotection among persons hospitalized for cardiovascular disease. Alimentary pharmacology & therapeutics; 2006;23(6):743–9.

[35] Cooper GS, Kou TD, Wong RC. Outpatient management of nonvariceal upper gastrointestinal hemorrhage: unexpected mortality in Medicare beneficiaries. Gastroenterology; 2009;136(1):108–114.

[36] Berry AR, Collin J, Frostick SP, et al. Upper gastrointestinal haemorrhage in Oxford. A prospective study. J R Coll Surg Edinb; 1984;29(3):134–138.

[37] Ohmann C, Imhof M, Ruppert C, et al. Time-trends in the epidemiology of peptic ulcer bleeding. Scandinavian Journal of Gastroenterology; 2005;40(8):914–920.

[38] Stokkeland K, Brandt L, Ekbom A, et al. Improved prognosis for patients hospitalized with esophageal varices in Sweden 1969-2002. Hepatology; 2006;43(3):500–505.

[39] Fleming KM, Aithal GP, Solaymani-Dodaran M, et al. Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: a general population-based study. J Hepatol; 2008;49(5):732–738.

[40] Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. Lancet; 2006;367(9504):52–6.

[41] Hobolth L, Krag A, Bendtsen F. The recent reduction in mortality from bleeding oesophageal varices is primarily observed from Days 1 to 5. Liver international : official journal of the International Association for the Study of the Liver; 2010;30(3):455–62.

[42] Viviane A, Alan BN. Estimates of costs of hospital stay for variceal and nonvariceal upper gastrointestinal bleeding in the United States. Value Health; 2008;11(1):1–3.

[43] Targownik LE, Gralnek IM, Dulai GS, et al. Management of acute nonvariceal upper gastrointestinal hemorrhage: comparison of an American and a Canadian medical centre. Can J Gastroenterol; 2003;17(8):489–495.

[44] Gleeson F, Clarke E, Lennon J, et al. Outcome of accident and emergency room triaged patients with low risk non-variceal upper gastrointestinal haemorrhage. Irish medical journal; 2006;99(4):114–7.

[45] "Department of Health". Tariff for Admitted Patient Care & Outpatient Procedures; 2011.

[46] Hearnshaw S, Logan R, M M, et al.. Results of the UK Audit of 6500 Patients with Acute Upper Gastrointestinal Bleeding; 2008.

[47] Jones FA. Haematomesis and melaena with special reference to bleeding peptic ulcer. British medical journal; 1947;2(4525):477–82.

[48] Marriott HL, Kekwick A. Continuous Drip Blood Transfusion: (Section of Surgery). Proceedings of the Royal Society of Medicine; 1936;29(4):337–8.

[49] Bohn G. Haematemesis as a Surgical Problem. BMJ; 1949;2(4628):630–633.

[50] Meulengracht E. Medical Treatment of Peptic Ulcer. British Medical Journal; 1939;2(4101):321–4.

[51] Lewin DC, Truelove S. Haematemesis. BMJ; 1949;1(4600):383–386.

[52] Ward-McQuaid JN, Pease JC, Smith AM, et al. Surgery in Bleeding Peptic Ulcers. Gut; 1960;1(3):258–265.

[53] Jones PF, Johnston SJ, McEwan AB, et al. Further haemorrhage after admission to hospital for gastrointestinal haemorrhage. British Medical Journal; 1973;3(5882):660–4.

[54] Chandler GN, Cameron AD, Nunn AH, et al. Early Investigations of Haematemesis. Gut; 1960;1(1):6–13.

[55] Calvet X, Vergara M, Brullet E, et al. Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. Gastroenterology; 2004;126(2):441–450.

[56] Gonzalez R, Zamora J, Gomez-Camarero J, et al. Meta-analysis: Combination Endoscopic and Drug Therapy to Prevent Variceal Rebleeding in Cirrhosis. Annals of Internal Medicine; 2008;149(2):109–122.

[57] Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane database of systematic reviews (Online); 2006;Jan 25(1):CD002094.

[58] Tellez-avila F, Gluud C, Chavez-Tapia NC, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. Alimentary pharmacology & therapeutics; 2011;34(5):509–18.

[59] Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. Cochrane database of systematic reviews (Online); 2003;29 Oct(1):CD002147.

[60] Lanas A. Editorial: Upper GI Bleeding-Associated Mortality: Challenges To Improving A Resistant Outcome. Am J Gastroenterol; 2010;105(1):90–92.

[61] Di Fiore F, Lecleire S, Merle V, et al. Changes in characteristics and outcome of acute upper gastrointestinal haemorrhage: a comparison of epidemiology and practices between 1996 and 2000 in a multicentre French study. Eur J Gastroenterol Hepatol; 2005;17(6):641–647.

[62] Lecleire S, Di Fiore F, Merle V, et al. Acute upper gastrointestinal bleeding in patients with liver cirrhosis and in noncirrhotic patients: epidemiology and predictive factors of mortality in a prospective multicenter population-based study. J Clin Gastroenterol; 2005;39(4):321–327.

[63] Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. Gut; 1996;38(3):316–321.

[64] Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet; 2000;356(9238):1318–21.

[65] Longstreth GF, Feitelberg SP. Outpatient care of selected patients with acute non-variceal upper gastrointestinal haemorrhage. Lancet; 1995;345(8942):108–111.

[66] Packham CJ, Rockall TA, Logan RFA. Outpatient care for selected patients with acute upper gastrointestinal bleeding. The Lancet; 1995;345(8950):659–660.

[67] Stanley AJ, Ashley D, Dalton HR, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. Lancet; 2009;373(9657):42–47.

[68] Myers RP, Kaplan GG, Shaheen AM. The effect of weekend versus weekday admission on outcomes of esophageal variceal hemorrhage. Can J Gastroenterol; 2009;23(7):495–501.

[69] McCormick PA, O'Keefe C. Improving prognosis following a first variceal haemorrhage over four decades. Gut; 2001;49(5):682–685.

[70] Pinto HC, Abrantes A, Esteves AV, et al. Long-term prognosis of patients with cirrhosis of the liver and upper gastrointestinal bleeding. Am J Gastroenterol; 1989;84(10):1239–1243.

[71] de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. Journal of Hepatology; 2005;43(1):167–76.

[72] del Olmo JA, Pena A, Serra MA, et al. Predictors of morbidity and mor-

tality after the first episode of upper gastrointestinal bleeding in liver cirrhosis. J Hepatol; 2000;32(1):19–24.

[73] Chen WT, Lin CY, Sheen IS, et al. MELD score can predict early mortality in patients with rebleeding after band ligation for variceal bleeding. World Journal of Gastroenterology; 2011;17(16):2120–5.

[74] Bambha K, Kim WR, Pedersen R, et al. Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut; 2008;57(6):814–820.

[75] El-Serag HB, Everhart JE. Improved survival after variceal hemorrhage over an 11-year period in the Department of Veterans Affairs. Am J Gastroenterol; 2000;95(12):3566–3573.

[76] Jamal MM, Samarasena JB, Hashemzadeh M. Decreasing in-hospital mortality for oesophageal variceal hemorrhage in the USA. Eur J Gastroenterol Hepatol; 2008;20(10):947–955 10.1097/MEG.0b013e32830280c7.

[77] Ananthakrishnan AN, McGinley EL, Saeian K. Outcomes of Weekend Admissions for Upper Gastrointestinal Hemorrhage: A Nationwide Analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association; 2009;7(3):296–302.e1.

[78] Ahsberg K, Ye W, Lu Y, et al. Hospitalisation of and mortality from bleeding peptic ulcer in Sweden: a nationwide time-trend analysis. Alimentary Pharmacology & Therapeutics; 2011;33(5):578–84.

[79] Lanas a, García-Rodríguez LA, Polo-Tomás M, et al. The changing face of hospitalisation due to gastrointestinal bleeding and perforation. Alimentary Pharmacology & Therapeutics; 2011;33(5):no–no.

[80] Weil J, Langman MJS, Wainwright P, et al. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. Gut; 2000;46(1):27–31.

[81] Lanas A, Fuentes J, Benito R, et al. Helicobacter pylori increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. Alimentary Pharmacology and Therapeutics; 2002;16(4):779–786.

[82] Brown LM. Helicobacter Pylori: Epidemiology and Routes of Transmission. Epidemiologic Reviews; 2000;22(2):283–297.

[83] Feinstein LB, Holman RC, Yorita Christensen KL, et al. Trends in hospitalizations for peptic ulcer disease, United States, 1998-2005. Emerg Infect Dis; 2010;16(9):1410–1418.

[84] Bakkevold KE. Time trends in incidence of peptic ulcer bleeding and associated risk factors in Norway 1985-2008. Clinical and Experimental Gastroenterology; 2010;3(3):71–77.

[85] Sánchez-Delgado J, Gené E, Suárez D, et al. Has H. pylori prevalence in bleeding peptic ulcer been underestimated? A meta-regression. The American Journal of Gastroenterology; 2011;106(3):398–405.

[86] Cullen DJE, Hawkey GM, Greenwood DC, et al. Peptic ulcer bleeding in the elderly: relative roles of Helicobacter pylori and non-steroidal anti-inflammatory drugs. Gut; 1997;41(4):459–462.

[87] Hernandez-Diaz S, Rodriguez LAG. Association Between Nonsteroidal Anti-inflammatory Drugs and Upper Gastrointestinal Tract Bleeding/Perforation: An Overview of Epidemiologic Studies Published in the 1990s. Arch Intern Med; 2000;160(14):2093–2099.

[88] Salvo F, Fourrier-Réglat A, Bazin F, et al. Cardiovascular and gastrointestinal safety of NSAIDs: a systematic review of meta-analyses of randomized clinical trials. Clinical pharmacology and therapeutics; 2011;89(6):855–66.

[89] Chang CH, Chen HC, Lin JW, et al. Risk of hospitalization for upper gastrointestinal adverse events associated with nonsteroidal anti-inflammatory drugs: a nationwide case-crossover study in Taiwan. Pharmacoepidemiology and Drug Safety; 2011;20(7):763–71.

[90] Cai S, GarciaRodriguez LA, Massa-Gonzalez EL, et al. Uncomplicated peptic ulcer in the UK: trends from 1997 to 2005. Aliment Pharmacol Ther; 2009;30(10):1039–1048.

[91] Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. British Medical Journal; 2000;321(7270):1183.

[92] Hayden M, Pignone M, Phillips C, et al. Aspirin for the Primary Prevention of Cardiovascular Events: A Summary of the Evidence for the U.S. Preventive Services Task Force. Ann Intern Med; 2002;136(2):161–172.

[93] Lanas A, Wu P, Medin J, et al. Low doses of acetylsalicylic Acid increase risk of gastrointestinal bleeding in a meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association; 2011;9(9):762–768.e6.

[94] Vonkeman HE, Fernandes RW, van der Palen J, et al. Proton-pump inhibitors are associated with a reduced risk for bleeding and perforated gastroduodenal ulcers attributable to non-steroidal anti-inflammatory drugs: a nested case-control study. Arthritis Research & Therapy; 2007;9(3):R52.

[95] Abraham NS, Hartman C, Hasche J. Reduced hospitalization cost for upper gastrointestinal events that occur among elderly veterans who are gastroprotected. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association; 2010;8(4):350–6; quiz e45.

[96] Ray WA, Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. Ann Intern Med; 2010;152(6):337–345.

[97] Bhatt DLDL, Cryer BLBL, Contant CFCF, et al. Clopidogrel with or without Omeprazole in Coronary Artery Disease. New England Journal of Medicine; 2010;363(20):1909–1917.

[98] Dalton SOS, Johansen C, Mellemkjaer L, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Archives of Internal Medicine; 2003;163(1):59–64.

[99] van Walraven C, Mamdani MM, Wells PS, et al. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ (Clinical research ed); 2001;323(7314):655–8.

[100] Abajo FJ, Garcia Rodriquez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. British Medical Journal-International Edition; 1999;319(7217):1106–1109.

[101] Gulmez SE, Lassen AT, Aalykke C, et al. Spironolactone use and the risk of upper gastrointestinal bleeding: a population-based case-control study. Br J Clin Pharmacol; 2008;66(2):294–299.

[102] Russo A, Autelitano M, Bisanti L. Spironolactone and gastrointestinal bleeding: a population based study. Pharmacoepidemiol Drug Saf; 2008;17(5):495–500.

[103] Gallerani M, Simonato M, Manfredini R, et al. Risk of hospitalization for upper gastrointestinal tract bleeding. J Clin Epidemiol; 2004;57(1):103–110.

[104] Nielsen G. Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. The American Journal of Medicine; 2001;111(7):541–545.

[105] Donahue JGJG, Chan KAA, Andrade SESE, et al. Gastric and duodenal safety of daily alendronate. Archives of Internal Medicine; 2002;162(8):936–42.

[106] Marshall JK, Rainsford KD, James C, et al. A randomized controlled trial to assess alendronate-associated injury of the upper gastrointestinal tract. Alimentary Pharmacology and Therapeutics; 2000;14(11):1451–1457.

[107] Al-Mallah M, Bazari R, Jankowski M, et al. Predictors and outcomes associated with gastrointestinal bleeding in patients with acute coronary syndromes. Journal of Thrombosis and Thrombolysis; 2007;23(1):51–55.

[108] Ng FH, Wong SY, Lam KF, et al. Gastrointestinal Bleeding in Patients Receiving a Combination of Aspirin, Clopidogrel, and Enoxaparin in Acute Coronary Syndrome. The American Journal of Gastroenterology; 2008;103(4):865–871.

[109] Fiaccadori E, Maggiore U, Clima B, et al. Incidence, risk factors, and prognosis of gastrointestinal hemorrhage complicating acute renal failure. Kidney Int; 2001;59(4):1510–1519.

[110] Pollard TR, Schwesinger WH, Page CP, et al. Upper Gastrointestinal Bleeding Following Major Surgical Procedures: Prevalence, Etiology, and Outcome. Journal of Surgical Research; 1996;64(1):75–78.

[111] Kelly JP, Kaufman DW, Koff RS, et al. Alcohol consumption and the risk of major upper gastrointestinal bleeding. The American Journal of Gastroenterology; 1995;90(7):1058–64.

[112] Watanabe H, Kamijima Y, Sato T, et al. Ex-drinking may be a surrogate for unmeasured risk factors for upper gastrointestinal bleeding: reappraisal and an additional survey of subjects from a case-control study in Japan. European Journal of Epidemiology; 2009;24(3):143–7.

[113] Kaplan RC, Heckbert SR, Koepsell TD, et al. Risk Factors for Hospitalized Gastrointestinal Bleeding Among Older Persons. Journal of the American Geriatrics Society; 2001;49(2):126–133.

[114] Stack WA, Atherton JC, Hawkey GM, et al. Interactions between Helicobacter pylori and other risk factors for peptic ulcer bleeding. Alimentary Pharmacology & Therapeutics; 2002;16(3):497–506.

[115] Pulvertaft CN. Comments on the incidence and natural history of gastric and duodenal ulcer. Postgraduate Medical Journal; 1968;44(514):597–602.

[116] Wu TY, Ding SQ, Liu JL, et al. High-altitude gastrointestinal bleeding: an observation in Qinghai-Tibetan railroad construction workers on Mountain Tanggula. World Journal of Gastroenterology; 2007;13(5):774.

[117] Villanueva Palacios J, López de Guimaraes D, Avila Polo F. [Upper digestive tract hemorrhage in the Peruvian Andes: report of 115 cases observed in Huaraz]. Revista de gastroenterología del Perú : órgano oficial de la Sociedad de Gastroenterología del Perú; 1996;16(2):99–104.

[118] Berríos J, Sedano O, Calle E, et al. [Upper digestive hemorrhage in the inhabitants of high altitudes in Peru]. Revista de gastroenterología del Perú : órgano oficial de la Sociedad de Gastroenterología del Perú; 1996;16(1):13–8.

[119] D'Amico G, De Franchis R, Gennaro D'Amico RDF. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology; 2003;38(3):599–612.

[120] Liao WC, Hou MC, Chang CJ, et al. Potential Precipitating Factors of Esophageal Variceal Bleeding: A Case-Control Study. The American Journal of Gastroenterology; 2010;106(1):96–103.

[121] Sung JJY, Tsoi KKF, Ma TKW, et al. Causes of Mortality in Patients With Peptic Ulcer Bleeding: A Prospective Cohort Study of 10,428 Cases. Am J Gastroenterol; 2009;105(1):84–89.

[122] Nahon S, Pariente A, Nalet B, et al. Causes of mortality related to peptic ulcer bleeding in a prospective cohort of 965 French patients: a plea for primary prevention. Am J Gastroenterol; 2010;105(8):1902–1903.

[123] Vreeburg EM, Snel P, de Bruijne JW, et al. Acute upper gastrointestinal bleeding in the Amsterdam area: incidence, diagnosis, and clinical outcome. Am J Gastroenterol; 1997;92(2):236–243.

[124] Hasselgren G, Blomqvist A, Eriksson S, et al. Short and long term course of elderly patients with peptic ulcer bleeding–analysis of factors influencing fatal outcome. Eur J Surg; 1998;164(9):685–691.

[125] Sung JJY, Lau JYW, Ching JYL, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding. Annals of Internal Medicine; 2010;152(1):1.

[126] Kubba AK, Choudari C, Rajgopal C, et al. Reduced long-term survival following major peptic ulcer haemorrhage. British Journal of Surgery; 1997;84(2):265–268.

[127] Commission A. Improving data quality in the NHS Annual report on the PbR assurance programme. London; 2010.

[128] Aylin P, Bottle A, Majeed A. Use of administrative data or clinical databases as predictors of risk of death in hospital: comparison of models. BMJ; 2007;334(7602):1044–1047.

[129] Aylin P, Lees T, Baker S, et al. Descriptive Study Comparing Routine Hospital Administrative Data with the Vascular Society of Great Britain and Ireland's National Vascular Database. European Journal of Vascular and Endovascular Surgery; 2007;33(4):461–465.

[130] HES. A guide to linked HES-ONS mortality data. The Health and Social Care Information Centre; 2011;2.1(August):1–18.

[131] Communities, Government L, Noble M, et al. The English Indices of Deprivation 2007. Communities; 2007;.

[132] Woods LM, Rachet B, Riga M, et al. Geographical variation in life expectancy at birth in England and Wales is largely explained by deprivation. Journal of Epidemiology and Community Health; 2005;59(2):115–120.

[133] Sitas F, Forman D, Yarnell JW, et al. Helicobacter pylori infection rates in relation to age and social class in a population of Welsh men. GUT; 1991;32(1):25–28.

[134] Hemmingsson T, Lundberg I, Romelsjo A, et al. Alcoholism in social classes and occupations in Sweden. Int J Epidemiol; 1997;26(3):584–591.

[135] Goddard E. General household survey 2006: Smoking and drinking among adults 2006. Newport: Office for National Statistics; 2008.

[136] Huerta MC, Borgonovi F. Education, alcohol use and abuse among young adults in Britain. Social Science & Medicine; 2010;71(1):143–151.

[137] Odubanjo E, Bennett K, Feely J. Influence of socioeconomic status on the quality of prescribing in the elderly - a population based study. Br J Clin Pharmacol; 2004;58(5):496–502.

[138] Rossignol M, Abouelfath A, Lassalle R, et al. The CADEUS study: burden of nonsteroidal anti-inflammatory drug (NSAID) utilization for musculoskeletal disorders in blue collar workers. Br J Clin Pharmacol; 2009;67(1):118–124.

[139] Sung JJY, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Alimentary Pharmacology & Therapeutics; 2009;29(9):938–46.

[140] Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. N Engl J Med; 2008;359(9):928–937.

[141] Barkun ANN, Bardou M, Kuipers EJJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med; 2010;152(2):101–113.

[142] Charlson MEE, Pompei P, Ales KLL, et al. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. Journal of Chronic Diseases; 1987;40(5):373–383.

[143] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care; 2005;43(11):1130–1139.

[144] Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. American Journal of Epidemiology; 2011;173(6):676–82.

[145] Nuttall M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. Journal of Clinical Epidemiology; 2006;59(3):265–273.

[146] Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care; 1998;36(1):8–27.

[147] Thomopoulos KC, Vagenas KA, Vagianos CE, et al. Changes in aetiology and clinical outcome of acute upper gastrointestinal bleeding during the last 15 years. Eur J Gastroenterol Hepatol; 2004;16(2):177–182.

[148] Palmer KR. Non-variceal upper gastrointestinal haemorrhage: guidelines. Gut; 2002;51 Suppl 4(suppl 4):iv1–iv6.

[149] Bernard B, Grange JD, Khac ENN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology; 1999;29(6):1655–1661.

[150] Hearnshaw SA, Logan RFa, Lowe D, et al. Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: results of a nationwide audit. Gut; 2010;59(8):1022–1029.

[151] Crooks CJ, West J, Hearnshaw SA, et al. Hospital admission database or specialist national audits for monitoring gastrointestinal bleeding? both are vital to monitoring our clinical practice. Gut; 2011;60(Suppl 1):A187.

[152] Walley T, Mantgani A. The UK General Practice Research Database. Lancet; 1997;350(9084):1097–9.

[153] Hollowell J. The General Practice Research Database: quality of morbidity data. Popul Trends; 1997;87:36–40.

[154] Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ; 1991;302(6779):766–768.

[155] Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. British Journal of Clinical Pharmacology; 2010;69(1):4–14.

[156] Eaton, SC and Williams, T J and Puri, S and vanStaa T. The feasibility of linking the English Hospital Episode Statistics to the GPRD. Pharmacoepidemiology & Drug Safety; 2008;17(S1):S214.

[157] Wood L, Coulson R. Revitalizing the General Practice Research Database: plans, challenges, and opportunities. Pharmacoepidemiology and Drug Safety; 2001;10(5):379–83.

[158] Hippisley-Cox J, Vingradova Y, Coupland C, et al. Comparison of key practice characteristics between general practices in England and Wales and general practices in the QRESEARCH database. NHS Information Centre; 2005;20th Novem(1.0):8–9.

[159] Crooks C, Card T, West J. Reductions in 28-day mortality following hospital admission for upper gastrointestinal hemorrhage. Gastroenterology; 2011;141(1):62–70.

[160] Crooks CJ, West J, Card TR. Upper gastrointestinal haemorrhage and

deprivation: a nationwide cohort study of health inequality in hospital admissions. Gut; 2012;61(4):514–20.

[161] Lewis JD, Bilker WB, Weinstein RB, et al. The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiology and Drug Safety; 2005;14(7):443–51.

[162] Mudge J. Discharge from hospital: pathway, process and practice. Health and Social Care Joint Unit and Change Agents Team; 2003.

[163] Sung JJY, Chan FKL, Chen M, et al. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. Gut; 2011;60(9):1170–7.

[164] Selby JV. Linking automated databases for research in managed care settings. Annals of internal medicine; 1997;127(8 Part 2):719.

[165] Weissman JS, Hasnain-Wynia R. Advancing Health Care Equity through Improved Data Collection. New England Journal of Medicine; 2011;364(24):2276–2277.

[166] N F Olivarius and H Hollnagel and A Krasnik and P A Pedersen and H Thorsen. The Danish National Health Service Register. A tool for primary health care research. Danish Medical Bulletin; 1997;44:449–453.

[167] Furu K, Wettermark B, Andersen M, et al. The Nordic countries as a cohort for pharmacoepidemiological research. Basic & clinical pharmacology & toxicology; 2010;106(2):86–94.

[168] Gupta D. Epidemiology of pneumothorax in England. Thorax; 2000;55(8):666–671.

[169] Morgan CL, Currie CJ, Stott NCH, et al. Estimating the prevalence of diagnosed diabetes in a health district of Wales: the importance of using primary and secondary care sources of ascertainment with adjustment for death and migration. Diabetic Medicine; 2000;17(2):141–145.

[170] Harvey JN. Estimation of the prevalence of diagnosed diabetes from primary care and secondary care source data: comparison of record linkage with capture-recapture analysis. Journal of Epidemiology & Community Health; 2002;56(1):18–23.

[171] Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. The British Journal of General Practice; 2010;60(572):e128–36.

[172] Dicker RC. Designing Studies in the Field. In: Gregg MB, editor. Field Epidemiology. 3rd ed. 198 Madison Avenue, New York, New York 10016: Oxford University Press; 2008. p. 141–142.

[173] Yeomans ND. The ulcer sleuths: The search for the cause of peptic ulcers. Journal of Gastroenterology and Hepatology; 2011;26 Suppl 1:35–41.

[174] Lewis JD, Bilker WB, Brensinger C, et al. Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s: relationship to sales of nonsteroidal anti-inflammatory drugs and acid suppression medications. The American Journal of Gastroenterology; 2002;97(10):2540–9.

[175] Breckenridge IM, Walton EW, Walker WF. Stress ulcers in the stomach. British Medical Journal; 1959;2(5163):1362–4.

[176] Fleming KM, Aithal GP, Card TR, et al. The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study. Alimentary Pharmacology & Therapeutics; 2010;32(11-12):1343–50.

[177] Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. N Engl J Med; 1994;330(6):377–381.

[178] Crooks CJ, Card TR, West J. Defining upper gastrointestinal bleeding from linked primary and secondary care data and the effect on occurrence and 28 day mortality. BMC health services research; 2012;12(1):392.

[179] Margulis AV, García Rodríguez LA, Hernández-Díaz S. Positive predictive value of computerized medical records for uncomplicated and complicated upper gastrointestinal ulcer. Pharmacoepidemiology and drug safety; 2009;18(10):900–9.

[180] Stine R. Graphical Interpretation of Variance Inflation Factors. The American Statistician; 1995;49(1):53–56.

[181] Eide G. Sequential and average attributable fractions as aids in the selection of preventive strategies. Journal of Clinical Epidemiology; 1995;48(5):645–655.

[182] Llorca J, Delgado-Rodríguez M. A comparison of several procedures to estimate the confidence interval for attributable risk in case-control studies. Statistics in medicine; 2000;19(8):1089–99.

[183] Yood MU, Campbell UB, Rothman KJ, et al. Using prescription claims data for drugs available over-the-counter (OTC). Pharmacoepidemiology and drug safety; 2007;16(9):961–8.

[184] Hopper S, Pierce M. Aspirin after myocardial infarction: the importance of over-the-counter use. Fam Pract; 1998;15 Suppl 1:S10–3.

[185] Bedson J, Whitehurst T, Lewis M, et al. Factors affecting over-the-counter

use of aspirin in the secondary prophylaxis of cardiovascular disease. Br J Gen Pract; 2001;51(473):1001–1003.

[186] Franceschi F, Gasbarrini A. Helicobacter pylori and extragastric diseases. Best practice & research Clinical gastroenterology; 2007;21(2):325–34.

[187] Chen Y, Segers S, Blaser MJ. Association between Helicobacter pylori and mortality in the NHANES III study. Gut; 2013;p. 1–8.

[188] Wald NJ, Law MR, Morris JK, et al. Helicobacter pylori infection and mortality from ischaemic heart disease: negative result from a large, prospective study. BMJ (Clinical research ed); 1997;315(7117):1199–201.

[189] De Backer D, Creteur J, Dubois MJ, et al. Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. American Heart Journal; 2004;147(1):91–99.

[190] Christensen S, Thomsen RW, Torring ML, et al. Impact of COPD on Outcome Among Patients With Complicated Peptic Ulcer. Chest; 2008;133(6):1360–1366.

[191] Huang KW, Luo JC, Leu HB, et al. Chronic obstructive pulmonary disease: an independent risk factor for peptic ulcer bleeding: a nationwide population-based study. Alimentary pharmacology & therapeutics; 2012;.

[192] Luo JC, Leu HB, Huang KW, et al. Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne; 2011;183(18):E1345–51.

[193] Lin KJ, Hernández-Díaz S, García Rodríguez LA. Acid suppressants re-

duce risk of gastrointestinal bleeding in patients on antithrombotic or anti-inflammatory therapy. Gastroenterology; 2011;141(1):71–9.

[194] van Soest EM, Valkhoff VE, Mazzaglia G, et al. Suboptimal gastroprotective coverage of NSAID use and the risk of upper gastrointestinal bleeding and ulcers: an observational study using three European databases. Gut; 2011;60(12):1650–9.

[195] Brø nnum Hansen H, Jø rgensen T, Davidsen M, et al. Survival and cause of death after myocardial infarction: the Danish MONICA study. Journal of Clinical Epidemiologypidemiology; 2001;54(12):1244–50.

[196] Vernino S, Brown RD, Sejvar JJ, et al. Cause-specific mortality after first cerebral infarction: a population-based study. Stroke; 2003;34(8):1828–32.

[197] Smart HL, Langman MJ. Late outcome of bleeding gastric ulcers. Gut; 1986;27(8):926–928.

[198] Jairath V, Barkun AN. Nonvariceal upper GI bleeding: it's not just about peptic ulcers. Gastrointestinal Endoscopy; 2012;75(2):273–5.

[199] World Health Organisation. Rules and guidelines for mortality and morbidity coding. In: DIMDI, editor. International Classification of Diseases and Related Health Problems. Tenth Revision. Volume 2. 2nd ed. Geneva: WHO; 2004. p. 31–92.

[200] Andersen PK, Geskus RB, de Witte T, et al. Competing risks in epidemiology: possibilities and pitfalls. International Journal of Epidemiology; 2012;p. 1–10.

[201] Abajo FD. Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations. BMC Clinical Pharmacology; 2001;.

[202] Goldacre MJ, Duncan ME, Cook-Mozaffari P, et al. Trends in mortality rates comparing underlying-cause and multiple-cause coding in an English population 1979-1998. Journal of Public Health Medicine; 2003;25(3):249–53.

[203] RAMSOEKH D, VANLEERDAM M, RAUWS E, et al. Outcome of Peptic Ulcer Bleeding, Nonsteroidal Anti-inflammatory Drug Use, and Infection. Clinical Gastroenterology and Hepatology; 2005;3(9):859–864.

[204] Katschinski BD, Logan RF, Davies J, et al. Audit of mortality in upper gastrointestinal bleeding. Postgraduate medical journal; 1989;65(770):913–7.

[205] Stael von Holstein CC, Anderson H, Eriksson SB, et al. Mortality after remote surgery for benign gastroduodenal disease. Gut; 1995;37(5):617–22.

[206] Marshall B, Warren JR, Blincow E, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of campylobacter pylori. The Lancet; 1988;332(8626-8627):1437–1442.

[207] Archambault AP, Pare P, Bailey RJ, et al. Omeprazole (20 mg daily) versus cimetidine (1200 mg daily) in duodenal ulcer healing and pain relief. Gastroenterology; 1988;94(5 Pt 1):1130–4.

[208] Bate CM, Wilkinson SP, Bradby GV, et al. Randomised, double blind comparison of omeprazole and cimetidine in the treatment of symptomatic gastric ulcer. Gut; 1989;30(10):1323–1328.

[209] Caygill CP, Knowles RL, Hall R. Increased risk of cancer mortality after vagotomy for peptic ulcer: a preliminary analysis. European Journal of Cancer Prevention; 1991;1(1):35–7.

[210] McIntosh JH, Byth K, Piper DW. Causes of death amongst a population of gastric ulcer patients in New South Wales, Australia. Scandinavian Journal of Gastroenterology; 1991;26(8):806–11.

[211] Macintyre I, F O'Brien F. Death from malignant disease after surgery for duodenal ulcer. GUT; 1994;35(4):451–454.

[212] Lindell G, Celebioglu F, Stael von Holstein C, et al. On the natural history of peptic ulcer. Scandinavian Journal of Gastroenterology; 1994;29:979–982.

[213] Svanes C, Lie Sa, Lie RT, et al. Causes of death in patients with peptic ulcer perforation: a long-term follow-up study. Scandinavian Journal of Gastroenterology; 1999;34(1):18–24.

[214] Duggan JM, Zinsmeister AR, Kelly KA, et al. Long-term survival among patients operated upon for peptic ulcer disease. Journal of Gastroenterology and Hepatology; 1999;14(11):1074–1082.

[215] Rorbaek-Madsen M, Fischer L, Thomsen H, et al. Late Outcome of Bleeding Gastric Ulcer: Five to Eight Years' Follow-up. Scandinavian Journal of Gastroenterology; 1994;29(11):983–987.

[216] Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut; 2006;55(12):1731–1738.

[217] Targownik LE, Metge CJ, Leung S. Underutilization of gastroprotective strategies in aspirin users at increased risk of upper gastrointestinal complications. Alimentary Pharmacology and Therapeutics; 2008;28(1):88–96.

[218] Massó González EL, García Rodríguez LA. Proton pump inhibitors reduce the long-term risk of recurrent upper gastrointestinal bleeding: an observational study. Alimentary Pharmacology & Therapeutics; 2008;28(5):629–37.

[219] Targownik LE, Metge CJ, Leung S, et al. The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs. Gastroenterology; 2008;134(4):937–944.

Appendices

APPENDIX A

Supporting ICD 10 and Read codes

Table A.1: Category of supporting ICD 10 codes in Hospital Episodes Statistics for cases defined by a specific Read code in the General Practice Research Database

Category	ICD 10 codes	Frequency
GI bleed symptom	D62 , K922 , K9229	5595
Upper GI bleed cause	C150 , C152 , C153 , C154 , C155 , C158 , C159 , C160 , C161 , C162 , C163, C164 , C165 , C166 , C168 , C169 , C170 , D001 , D130 , D131 , D132 , D139, D371 , D379 , I81 , I850 , I864 , I982 , K20 , K210 , K221 , K223 , K226 K250 , K252 , K254 , K255 , K256 , K260 , K261 , K262 , K264 , K265 , K266, K270 , K274 , K275 , K280 , K284 , K285 , K290 , K291 , K292 , K293 , K294 K295 , K296 , K297 , K298 , K299 , K317 , K500 , K508 , K509 , K766 , K767, S363 , T390 , T393 , Y451 , Y453 , Z850	5521
Upper GI endoscopy	Y604 , Y614	3923
Upper GI bleed symptom	K920 , K921	884

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Table A.1 –ICD 10 codes continued from previous page

Category	ICD 10 codes	Frequency
GI symptom or diagnosis	B161 , B169 , B171 , B178 , B180 , B181 , B182 , B188 , B189 , C171 , C178, C220 , C229 , C250 , C258 , C259 , C269 , C482 , C762 , C787 , C788 , C798, C80 , C97 , D099 , D133 , D134 , D367 , D369 , D372 , D377 , E164 , I780, I820 , K550 , K551 , K558 , K559 , K561 , K562 , K563 , K564 , K565 , K566, K630 , K631 , K632 , K633 , K638 , K639 , K710 , K711 , K713 , K716 , K718 K719 , K720 , K721 , K729 , K730 , K732 , K738 , K739 , K740 , K741 , K743 K744 , K745 , K746 , K750 , K751 , K753 , K754 , K758 , K759 , K760 , K761 K762 , K763 , K765 , K768 , K769 , K770 , K860 , K910 , K911 , K912 , K913 K918 , K928 , K929 , K938 , M352 , O266 , Q433 , Q438 , Q439 , Q446 , Q447 Q458 , R100 , R101 , R102 , R103 , R104 , R160 , R162 , R17 , R18 , R190, R193 , R198 , R850 , R855 , R857 , R859 , R890 , R895 , R897 , R899 , R933, R945 , R948 , T478 , T479 , Y538 , Y539 , Z221 , Z225 , Z400 , Z434 , Z871, Z8713 , Z904	535
Upper GI diagnosis	K219 , K220 , K222 , K224 , K225 , K228 , K229 , K230 , K231 , K238 , K30 K310 , K311 , K312 , K313 , K314 , K315 , K316 , K318 , K319 , K440 , K441, K449 , K450 , K451 , K458 , K460 , K469 , Q391 , Q393 , Q394 , Q396 , Q401,Q402 , Q403 , S368 , T181 , T182 , T183 , T189 , Z903	453
Upper GI symptom	O210 , O211 , O218 , O219 , R11 , R12 , R13	347

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Table A.1 –ICD 10 codes continued from previous page

Category	ICD 10 codes	Frequency
General care	W000 , W002 , W004 , W008 , W009 , W010 , W0109 , W011 , W0114 , W0119 , W012, W0129 , W013 , W014 , W0149 , W015 , W016 , W018 , W0188 , W019 , W0199 , W021, W023 , W024 , W029 , W030 , W031 , W033 , W034 , W035 , W038 , W039 , W040, W042 , W044 , W049 , W050 , W051 , W052 , W054 , W058 , W059 , W060 , W0609, W061 , W0619 , W062 , W0629 , W068 , W069 , W070 , W0709 , W071 , W072 , W0729, W074 , W075 , W079 , W080 , W081 , W082 , W088 , W089 , W090 , W091 , W098, W099 , W100 , W1009 , W101 , W102 , W103 , W104 , W105 , W108 , W109 , W110, W115 , W116 , W118 , W119 , W125 , W129 , W130 , W131 , W132 , W134 , W138, W139 , W140 , W148 , W149 , W160 , W170, W171 , W172 , W174 , W175 , W177, W178 , W179 , W1799 , W180 , W1809 , W181 , W1819 , W182 , W1829 , W183 , W184, W185 , W186 , W188 , W189 , W190 , W1909 , W191 , W1919 , W192 , W1923 , W1929, W193 , W194 , W1949 , W195 , W198 , W199 , W1999 , W200 , W205 , W206 , W209 W213 , W220 , W221 , W222 , W223 , W224 , W225 , W226 , W227 , W228 , W229, W230 , W231 , W232 , W234 , W236 , W238 , W239 , W241 , W250 , W2508 , W252, W254 , W255 , W256 , W258 , W259 , W260 , W268 , W269 , W270 , W272 , W274, W276 , W279 , W280 , W289 , W290 , W298 , W299 , W310 , W312 , W315 , W316, W3162 , W318 , W319 , W344 , W349 , W4059 , W406 , W440 , W441 , W442 , W449, W4499 , W450 , W451 , W455 , W458 , W459 , W490 , W492 , W496 , W499 , W500, W503 , W508 ,	

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Table A.1 –ICD 10 codes continued from previous page

Category	ICD 10 codes	Frequency
	W509 , W5098 , W510 , W511 , W513 , W514 , W518 , W519 , W540, W544 , W548 , W549 , W550 , W558 , W559 , W570 , W573 , W579 , W5799 , W599, W600 , W609 , W6099 , W640 , W642 , W649 , W699 , W740 , W748 , W780 , W781, W782 , W789 , W790 , W791 , W792 , W799 , W7999 , W800 , W802 , W809 , W839, W840 , W842 , W849 , W850 , W877 , W882 , W909 , W948 , X000 , X011 , X020, X039 , X049 , X060 , X069 , X080 , X089 , X090 , X099 , X100 , X102 , X109, X110 , X120 , X121 , X129 , X149 , X150 , X159 , X160 , X162 , X169 , X175, X186 , X190 , X195 , X199 , X209 , X219 , X239 , X258 , X292 , X310 , X314, X318 , X319 , X329 , X332 , X360 , X391 , X394 , X398 , X399 , X400 , X401, X402 , X408 , X409 , X4099 , X410 , X411 , X412 , X418 , X419 , X420 , X421, X422, X424 , X428 , X429 , X430 , X439 , X440 , X441 , X442 , X448 , X449, X450 , X458 , X459 , X469 , X470 , X476 , X478 , X479 , X490 , X491 , X498, X499 , X4999 , X500 , X5008 , X5009 , X501 , X502 , X503 , X504 , X505 , X506, X508 , X5089 , X509 , X5099 , X519 , X530 , X539 , X580 , X581 , X582 , X588, X589 , X5899 , X590 , X5909 , X591 , X592 , X593 , X594 , X595 , X596 , X598, X5989 , X599 , X5999 , X600 , X6009 , X601 , X602 , X604 , X608 , X609 , X6099, X610, X6109 , X611 , X612 , X614 , X615 , X618 , X619 , X6199 , X620 , X622, X624 , X628 , X629 , X6299 , X630 , X638 , X639 , X640 , X642 , X648 , X649, X6499 , X650 , X651 , X652 , X654 , X658 , X659 , X6599 , X660 , X669 , X670, X678 , X680 , X689 , X690 , X691 , X698 , X699 , X700 , X701 , X702 , X709, X718 , X749 , X760 , X770 , X771 , X780 , X781 , X782 , X788 , X789 , X790, X791 , X792 , X795 , X799 , X800 , X804 , X808 , X818 , X824 , X830 , X831, X832 , X834 ,	

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Table A.1 –ICD 10 codes continued from previous page

Category	ICD 10 codes	Frequency
	X838 , X839 , X840 , X841 , X842 , X849 , X853 , X866 , X870, X900 , X932 , X950 , X979 , X990 , X992 , X994 , X999 , Y000 , Y001 , Y004, Y008 , Y009 , Y010 , Y040 , Y041 , Y042 , Y044 , Y045 , Y048 , Y049 , Y0499, Y053 , Y070 , Y079 , Y080 , Y084 , Y088 , Y089 , Y090 , Y094 , Y095 , Y098, Y099 , Y100 , Y109 , Y110 , Y112 , Y119 , Y120 , Y129 , Y139 , Y140 , Y149, Y150 , Y159 , Y179 , Y190 , Y199 , Y218 , Y219 , Y249 , Y280 , Y281 , Y289, Y292 , Y294 , Y300 , Y304 , Y309 , Y331 , Y332 , Y340 , Y341 , Y342 , Y349, Y3499 , Y95 , Z000 , Z005 , Z006 , Z008 , Z013 , Z018 , Z0180 , Z019 , Z031, Z036 , Z038 , Z039 , Z040 , Z043 , Z048 , Z049 , Z080 , Z081 , Z082 , Z087, Z088 , Z089 , Z090 , Z092 , Z097 , Z098 , Z099 , Z120 , Z121 , Z128 , Z129 Z132 , Z138 , Z1380 , Z480 , Z488 , Z489 , Z508 , Z515 , Z518 , Z519 , Z530, Z531 , Z532 , Z538 , Z539 , Z547 , Z548 , Z549 , Z593 Z728 , Z729 , Z750, Z751 , Z752 , Z753 , Z758 , Z759 , Z764 , Z858, Z878 , Z910 , Z911 , Z922, Z924 , Z929	329
Alcohol	E244 , F100 , F101 , F102 , F103 , F104 , F105 , F108 , F109 , G312 , G621, G721 , I426 , K700 , K701 , K702 , K703 , K704 , K709 , R780 , T510 , T511 T519 , Y905 , Y906 , Y908 , Y910 , Y911, Y912 , Y913 , Y919 , Z502 , Z714, Z721	268
Anaemia	D649	176
Upper GI procedure	Z431 , Z931	140

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APPENDIX A: SUPPORTING ICD 10 AND READ CODES:

Table A.1 –ICD 10 codes continued from previous page

Category	ICD 10 codes	Frequency
General symptom or diagnosis	B378 , B379 , B948 , C768 , C772 , C778 , C779 , C786 , D479 , D484 , D487 D489 , D630 , E519 , G92 , G934 , R231 , R402 , R520 , R529 , R53 , R54, R58 , R688 , R69 , T394 , T398 , T399 , T475 , T485 , T490 , T509 , T658, T659 , T788 , T789 , Y430 , Y431 , Y433 , Y454 , Y458 , Y459 , Y560 , Y578 Y579 , Z511 , Z514 , Z859 , Z860	137
Collapse	E86 , I950 , I951 , I952 , I958 , I959 , R031 , R42 , R55 , R570 , R571, R578 , T794 , T795 , Z990 , Z991 , Z998 , Z999	105
General procedure	T412 , T801 , T802 , T808 , T809 , T810 , T811 , T812 , T813 , T814 , T815, T816 , T817 , T818 , T819 , T855 , T864 , T868 , T869 , T884 , T885 , T886, T887 , T888 , T889 , T915 , T96 , T981 , T983 , Y482 , Y484 , Y600 , Y606, Y610 , Y618 , Y638 , Y649 , Y652 , Y654 , Y658 , Y66 , Y701 , Y703 , Y710, Y711 , Y712 , Y730 , Y732 , Y733 , Y738 , Y741 , Y772 , Y773 , Y778 , Y780 Y792 , Y793 , Y801 , Y808 , Y812 , Y822 , Y828 , Y830 , Y831 , Y832 , Y833, Y834 , Y836 , Y838 , Y839 , Y842 , Y845 , Y847 , Y848 , Y849 , Y880 , Y881, Y882 , Y883 , Y899 , Z540 , Z948 , Z988	67
Coagulation	D65 , D683 , D684 , D688 , D689 , D698 , D699 , E561 , O723 , T455 , T456, Y442 , Y443 , Y444 , Y445 , Z921	63
Nutrition	R630 , R634 , R638 , R64 , Z594	26
Confusion	R401 , R410	17
Death	I460 , I469 , R092 , R960 , R99	16
Blood transfusion	Y446 , Y449 , Z513	3
GI procedure	Z934 , Z944 , Z980	2

APPENDIX A: SUPPORTING ICD 10 AND READ CODES:

Table A.2: Category of supporting Read code in the General Practice Research Database for cases defined in Hospital Episodes Statistics

Category	Read codes	Frequency
Upper GI bleed symptom	14C8.00, 14C9.00, 14CD.00, 14CD.11, 1994 1994.11, 1995, 19E4.00, 19E4.11, 19E4.12, 4736 4737, 4737.11, 4A23.00, 4A23.11, 4A24.00 4A24.11, J680.00, J680.11, J681.00, J681.12 J681.13, J68z000 J68z200	7527
Upper GI bleed cause	14C1.00, 14C1.11, 14C1.12, 14C5.00, 14C6.00, 14CB.00, 1675, 1675.11, 1675.12, 1956, 1J0D.00 2274, 2274.11, 67I8.00, 7609300 , 760C.00 760C000, 760C100, 760C300, 760C400, 760C500, 760C600, 760C700, 760Cy00, 760Cz00, 760F.00, 760F100, 760F400, 760H000, 761D.00, 761D.11, 761D000, 761D100, 761D200, 761D300, 761D400, 761D500 , 761D600, 761D700, 761D800, 761Dy00, 761Dz00 ,761J.00, 761J.11, 761J000, 761J100, 761J111, 761Jy00 761Jz00, 761K.00, 761K000, 761M.00, 761M000 ,7624000, 7624011, 7625000, 7627, 7627000 7627100, 7627200, 8Hn9.00, A074313 B1...11, B10..00, B10z.00, B10z.11, B11..00, B11..11, B110.00, B110000, B110100, B110111, B110z00, B111.00, B111000, B111100, B111z00, B112.00, B113.00, B114.00, B115.00, B116.00, B117.00, B118.00, B119.00, B11y.00, B11y000, B11y100, B11yz00, B11z.00, B12..00, B120.00, B121.00, B574.00, B574000, B574z00, B70X.00, B71..00, B710.00, B710.11, B710100, B710300, B710z00, B711.00, B711.11, B711000, B711100, B711200, B711300, B711400, B711z00, B712.00, B712000, B712011, B712z00, C310400, G762000, G81..00, G85..11, G85..12, G850.00, G851.00, G852.00, G852000, G852100, G852200, G852300, G852z00,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	G857.00, G858.00, J101.00, J101100, J101112, J101113, J101114, J101115, J101200, J101300, J101400, J101500, J101600, J101611, J101y00, J101z00, J102.00, J102000, J102100, J102200, J102300, J102400, J102500, J102z00, J103.00, J103.11, J103.12, J103400, J103z00, J104.00, J107.00, J108.00, J10y000, J10y300, J10y400, J10y411, J10y412, J11..00, J11..11, J11..12, J110.00, J110000, J110100, J110111, J110200, J110300, J110y00, J110z00, J111.00, J111000, J111100, J111111, J111200, J111211, J111300, J111400, J111y00, J111z00, J112.00, J112z00, J113.00, J113z00, J11y.00, J11y000, J11y100, J11y200, J11y400, J11yy00, J11yz00, J11z.00, J11z.11, J11z.12, J12..00, J120.00, J120000, J120100, J120200, J120300, J120400, J120y00, J120z00, J121.00, J121000, J121100, J121111, J121200, J121211, J121300, J121400, J121y00, J121z00, J122.00, J123.00, J124.00, J125.00, J126.00, J12y.00, J12y000, J12y100, J12y200, J12y300, J12y400, J12yy00, J12yz00, J12z.00, J13..00, J13..11, J130.00, J130000, J130100, J130200, J130300, J130y00, J130z00, J131.00, J131000, J131100, J131200, J131400, J131y00, J131z00, J13y.00, J13y000, J13y100, J13y200, J13y300, J13y400, J13yz00, J13z.00, J14..00, J14..11, J14..12, J14..13, J14..14, J14..15, J140.00, J140100, J140z00, J141.00, J14y.00, J14y100, J14y200, J14yz00, J14z.00, J15..00, J150.00, J150000, J151.00, J151000, J151100, J151200, J151z00, J152.00, J153.00, J154.00, J154000, J154100, J154200, J154300, J154400, J154z00, J155.00, J156.00, J157.00, J15z.00, J17y800, J17y900, J40..11, J400000, J431000, J4z0.00, J502000, J612.00, J612.11, J612.12, J612000, J615.11, J615100, J615300, J615400, J615500, J615600, J615700, J615800, J615812, J615C00, J615D00, J615H00, J615y00, J615z00, J615z11, J615z12,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	J615z13, J61y300, J622.00, J622.11, J623.00, J624.00, Jyu1200, Jyu1300, Jyu4000, R024.00, R024111, R095.00, TJ53.00, TJ53.11, TJ56.11, U605100, U605111, U605112, U605200, U605211, U605212, U605213, U605214, U605215, U605216, U605300, U605311, U605312, U605313, U605314, & U605315	3722
GI bleed symptom	14CA.00, 14CA.11, 25T0.00, J68..00, J68z.00, J68z.11, J68z100, J68zz00	2335
Upper GI endoscopy	316C.00, 36...00, 361..00, 3611, 3612, 3613, 3614, 3614000, 3615, 3615000, 361Z.00, 36Z..00, 4, JO..00, 4, JO0.00, 760D.00, 760D000, 760D100, 760D200, 760D300, 760D311, 760D313, 760D400, 760D500, 760D600, 760D700, 760Dy00, 760Dz00, 760E.00, 760E.11, 760E000, 760E100, 760E200, 760E300, 760Ey00, 760Ez00, 760Ez11, 760F300, 760G.00, 760G.11, 760G000, 760G100, 760G200, 760G300, 760G311, 760G400, 760Gy00, 760H.00, 760H100, 760Hy00, 761E.00, 761E.11, 761E000, 761E100, 761E200, 761E211, 761E300, 761E500, 761E600, 761E700, 761E800, 761Ey00, 761Ez00, 761F.00, 761F.11, 761F000, 761F100, 761F200, 761F300, 761F400, 761F500, 761F700, 761Fy00, 761Fz00, 761Fz11, 761Fz12, 761G200, 761G211, 761G400, 761L.00, 761L000, 761Ly00, 761Lz00, 761y.00, 761z.00, 7624100, 7624200, 7624y00, 7624z00, 7625, 7625.11, 7625y00, 7625z00, 7625z11	2240

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
Death	22J..00, 22J..11, 22J..12, 22J..13, 22J..14, 22J1.00, 22J2.00, 22J3.00, 22J4.00, 22J5.00, 22J6.00, 22J7.00, 22JZ.00, 4K9..00, 4K91.00, 4K92.00, 4K94.00, 4K95.00, 4K96.00, 4K9Z.00, 8HG..00, 8HG..11, 94...00, 94...11, 941..00, 9411, 9412, 9413, 9414, 941Z.00, 942..00, 943..00, 9431, 9432, 9433, 943Z.00, 944..00, 9441, 9442, 9443, 944Z.00, 945..00, 9451, 9452, 9453, 9454, 945Z.00, 946..00, 947..00, 947..11, 9471, 9472, 9473, 947Z.00, 948..00, 948..11, 9481, 9482, 9483, 9484, 948Z.00, 949..00, 949..11, 949..12, 949..13, 949..14, 9491, 9492, 9493, 9494, 9495, 9496, 9497, 9498, 9499, 949A.00, 949B.00, 949C.00, 949Z.00, 94A..00, 94A..11, 94B..00, 94B..11, 94C..00, 94C0.00, 94D..00, 94E..00, 94F..00, 94Z..00, 94Z0.00, 94Z1.00, 94Z2.00, 94Z3.00, 94Z4.00, 94Z5.00, R2...12, R21..00, R210.00, R210000, R210100, R210200, R210z00, R211.00, R212.00, R212000, R212100, R212z00, R213.00, R213000, R213100, R213z00, R21z.00, R2y..00, R2yz.00, R2z..00	1305
Upper GI symptom	194..00, 194..11, 1942, 1943, 1944, 1944.11, 194Z.00, 1952, 1952.11, 1954, 1955, 1955.11, 1957, 1958, 1972, 198..00, 198..11, 198..12, 1982, 1983, 1984, 198Z.00, 199..00, 199..11, 199..12, 199..14, 1992, 1992.11, 1992.12, 1993, 1996, 1997, 1998, 199Z.00, 19FZ.11, 4A25.11, 4A26.11, 4A27.00, 4A2A.11, 4A2Z.00, 4A3..00, 4A4..00, 4, A4..11, 4, A42.00, 4, A4Z.00, 4, A5..00, 4, A5..11, 4, A51.00, 4, A5Z.00, 4, A6..00, 4, AZ..00, 4, JD7.00, 4JN1.00, 4JS4.00, 7N3..00, 7N30.00,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	7N30000, 7N30100, 7N30200, 7N30300, 7N30700, 7N30z00, 7N35000, J101111, J10y500, J10yz00, J10z.00, J162.00, J162.11, J162000, J162100, J162z00, J16y.00, J16y000, J16y100, J16y200, J16y211, J16y300, J16y400, J16y411, J16y500, J16y700, J16y800, J16y900, J16yz00, J16z.00, J16z100, J17..00, R070.00, R070000, R070100, R070200, R070300, R070400, R070z00, R070z11, R070z12, R071.00, R071000, R071z00, R072.00, R072000, R072z00, R07A.00	835
Anaemia	145..11, 1674, 1674.11, 2272, 2272.11, 2272.12, 2C2..11, 421B.00, 4222, 423..00, 423..11, 4234, 4235, 4243, 4254, 4255, 4256, 426..00, 4262, 4263, 4266, 4267, 426Z.00, 42E8.00, 42R4200, 42X..00, 42X0.00, 42X2.00, 42bC.00, D211.00, D211.11, D21y.00, D21yy00, D21yz00, D21z.00, D2y..00, D2z..00, R026000, R026011	722
General symptom or diagnosis	1....00, 13C6.00, 13C6.11, 13CA.00, 13CC.00, 142..12, 142..13, 14O..00, 14Z..00, 16...00, 16...11, 16...12, 16...13, 16E..00, 16E..11, 16E..12, 16E0.00, 16G..00, 16Z..00, 16Z3.00, 16Z7.00, 16Z8.00, 16Z9.00, 16ZZ.00, 1828, 1829, 182Z.00, 1D...00, 1, D1..00, 1, D13.00, 1D13.11, 1D13.12, 1D18.00, 1D1Z.00, 1J...00, 1M...00, 1O0..00, 1W...00, 1Y...00, 1Z...00, 1Z0..00, 1Z00.00, 1Z01.00, 2....00, 2....11, 2....12, 21...00, 211..00, 212..00, 2121, 2122, 2123, 2124, 2125, 2125.11, 2126, 2126.11, 2126.12, 2126.13, 2126.14, 2127,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	2127.11, 2128, 2128.11, 2129, 212A.00, 212A.11, 212B.00, 212C.00, 212D.00, 212E.00, 212F.00, 212Z.00, 21Z..00, 22...00, 221..00, 2211, 2212, 2213, 2214, 2215, 221Z.00, 222..00, 2221, 2222, 2224, 2229, 2229.11, 2229.12, 2229.13, 222F.00, 222G.00, 222M.00, 223..00, 2231, 2252, 2253, 2271, 66W..00, 7N22000, 87...00, 87...11, 871..00, 8711, 8712, 8713, 8713.11, 871Z.00, 872..00, 872..11, 872..12, 8721, 8722, 8723, 8724, 872Z.00, 873..00, 8731, 8732, 8733, 8733000, 8733100, 8734, 8735, 873Z.00, C19..00, G8y0.00, R....00, R....11, R....12, R0...00, R00..00, R00z200, R00z211, R00zB00, R07..00, R070111, R073300, R073400, R2...00, R2...11, R2...13, R2...14, R200.00, R200.11, R201.00, R2y4.00, R2y4000, R2y4z00, R2yy.00, ZQ1..00, ZQ32.00	494
Coagulation	1455.11, 1456, 14P1.00, 16B..00, 16B2.00, 16B3.00, 1928, 4130, 4224, 42Q..12, 42Q..13, 42Q2.00, 42Q3.00, 42Q4.00, 42Q5.00, 42Q5000, 42Q6.00, 42Q7.00, 42Q8.00, 42Q8100, 42QE.00, 42QE100, 42QV.00, 42QW.00, 42QX.00, 42QZ.00, 42Qn.00, 42Qt.00, 42Qu.00, 42Qv.00, 42h0.00, 66Q..00, 66Q..11, 66Q1.00, 66Q2.00, 66Q3.00, 66Q4.00, 66Q5.00, 66Q6.00, 66Q7.00, 66Q8.00, 66Q9.00, 66QA.00, 66QB.00, 66QC.00, 66QD.00, 66QE.00, 66QF.00, 66QG.00, 88A5.00, B937.14, B937W00, B937W11, D1...00, D10y.00,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	D10z.00, D11..00, D110.00, D110.11, D110000, D110100, D110200, D110400, D110z00, D111.00, D111000, D111100, D111300, D111400, D111500, D111y00, D111z00, D3...00, D30..00, D30..11, D300.00, D300.11, D300.12, D301.00, D301.11, D301.12, D302.00, D302.11, D302.12, D303.00, D303000, D303100, D303111, D303200, D303300, D303400, D303500, D303600, D303611, D303700, D303800, D303900, D303y00, D303z00, D304.00, D305.00, D305000, D305100, D306.00, D306.11, D306.12, D307.00, D307000, D307100, D307200, D307211, D307y00, D307z00, D308.00, D309.00, D30A.00, D30B.00, D30z.00, D31..00, D310.00, D310000, D310011, D310012, D310100, D310z00, D311.00, D311.11, D311000, D311011, D311z00, D312.00, D312.11, D312.12, D312000, D312100, D312z00, D313.00, D313.11, D313.12, D313.13, D313.14, D313.15, D313000, D313011, D313012, D313100, D313111, D313200, D313211, D313300, D313y00, D313z00, D313z11, D314.00, D314100, D314y00, D314z00, D315.00, D31X.00, D31y.00, D31y000, D31y011, D31yz00, D31z.00, D3y..00, D3y0.00, D3z..00, R027.00, R027.11, R027000, R027z00, TJ42.00, TJ42000, TJ42100, TJ42z00, TJ43.00	329

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
GI symptom or diagnosis	1612.12, 19...00, 19...11, 19...12, 195..00, 195Z.00, 196..00, 196..11, 196..12, 1962, 1963, 1964, 1965, 1965.11, 1968, 1969, 196Z.00, 197..00, 197..11, 197..12, 197..13, 197..14, 1971, 1973, 1974, 1975, 1976, 1977, 1978, 197A.00, 197A.11, 197B.00, 197C.00, 197D.00, 197Z.00, 19A..00, 19A1.00, 19A2.00, 19A3.00, 19A4.00, 19AZ.00, 19Z..00, 19ZZ.00, 25...00, 25...11, 25...12, 251..00, 2511, 2512, 2513, 2514, 2515, 2516, 2516.11, 251Z.00, 258..00, 258..11, 2581, 2582, 2583, 2584, 2584.11, 2585, 2586, 2587, 2587.11, 2587.12, 258Z.00, 259..00, 2591, 2592, 2593, 259Z.00, 25A..00, 25A1.00, 25A2.00, 25A3.00, 25AZ.00, 25B..00, 25B1.00, 25B2.00, 25B3.00, 25B4.00, 25C..00, 25C..11, 25C..12, 25C..14, 25C..15, 25C1.00, 25C2.00, 25C3.00, 25C4.00, 25C5.00, 25C6.00, 25C7.00, 25C8.00, 25C9.00, 25CA.00, 25CZ.00, 25D..00, 25D..11, 25D1.00, 25D2.00, 25D3.00, 25D4.00, 25D6.00, 25D8.00, 25D9.00, 25DA.00, 25DZ.00, 25E..00, 25E1.00, 25E2.00, 25E3.00, 25E5.00, 25E6.00, 25E8.00, 25EA.00, 25EZ.00, 25F..00, 25F1.00, 25F2.00, 25F2.11, 25FZ.00, 25G..00, 25G..11, 25G1.00, 25G2.00, 25G3.00, 25G4.00, 25GZ.00, 25H..00, 25H1.00, 25H2.00, 25H3.00, 25H9.00, 25HA.00, 25HZ.00, 25I..00, 25I1.00, 25I2.00, 25I3.00, 25I5.00, 25I6.00, 25J..00, 25J1.00, 25J2.00, 25J3.00, 25J4.00, 25J5.00, 25J6.00, 25J7.00, 25J8.00, 25J9.00, 25JA.00, 25JZ.00, 25K..00, 25K1.00, 25K2.00, 25K3.00, 25K4.00, 25KZ.00, 25L..00, 25L1.00, 25L2.00, 25LZ.00, 25M..00, 25M1.00, 25M2.00, 25MZ.00, 25N..00, 25N1.00, 25N2.00, 25NZ.00, 25O..00, 25O1.00, 25O2.00, 25O3.00, 25O4.00, 25OZ.00, 25P..00, 25P..11, 25P..12, 25P1.00, 25P2.00, 25P3.00, 25P4.00, 25P5.00, 25P6.00, 25PZ.00,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	25Q..00, 25Q..11, 25Q1.00, 25Q5.00, 25Q6.00, 25QZ.00, 25R..00, 25R1.00, 25R2.00, 25R3.00, 25RZ.00, 25S..00, 25S1.00, 25S2.00, 25S3.00, 25S3.11, 25S4.00, 25S5.00, 25SZ.00, 25V..00, 25V0.00, 25Z..00, 3167, 43W9.00, 43WA.00, 4A25.00, 4A26.00, 4JD6.00, 4JM..00, 4JM0.00, 4JM2.00, 4JM3.00, 4JN0.00, 4JO1.00, 68W3.00, 68W4.00, 761H300, 7N30400, 7N30500, 7N30600, 7N33.00, 7N33000, 7N33100, 7N33200, 7N33300, 7N33311, 7N33400, 7N33500, 7N33600, 7N33z00, 7N34.00, 7N34000, 7N34100, 7N34y00, 7N3z.00, J....00, J1...00, J1...11, J1...12, J10y200, J154111, J16y412, J16y600, J344.00, J502100, J521.00, J521.11, J57z.00, J6y..00, J6z..00, Jy...00, R07z.00, R07z.11, R07zz00, R09..00, R090.00, R090000, R090100, R090200, R090300, R090311, R090312, R090400, R090500, R090600, R090700, R090800, R090900, R090A00, R090B00, R090C00, R090D00, R090E00, R090F00, R090H00, R090J00, R090K00, R090N00, R090y00, R090z00, R091.00, R091000, R091z00, R093.00, R093000, R093100, R093111, R093200, R094.00, R095000, R095z00, R096.00, Ryu1.00, Ryu1100, Ryu1200, Ryu1300	328
Hospital	13F8.00, 13F8.11, 13F8100, 13F8200, 67IL.00, 67IM.00, 6A1..00, 6A1..11, 8B1..00, 8H...00, 8H1..00, 8H1..11, 8H11.00, 8H12.00, 8H13.00, 8H14.00, 8H2..00, 8H21.00, 8H22.00, 8H24.00, 8H2Z.00, 8H36.00, 8H37.00, 8H39.00, 8H3Z.00, 8H4..00, 8H4..11, 8H4..12, 8H41.00, 8H42.00, 8H47.00, 8H48.00, 8H4D.00, 8H4J.00, 8H4Z.00, 8H4b.00, 8H4l.00, 8H5..00, 8H5..11, 8H51.00, 8H5J.00, 8H5K.00, 8H5Z.00, 8H6..00, 8H61.00, 8H61.11, 8H63.00, 8H64.00, 8H65.00, 8H66.00, 8H68.00, 8H6D.00, 8H6Z.00, 8H7..00,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	8H7a.00, 8H7h.00, 8H7o.00, 8HC1.00, 8HE..00, 8HE2.00, 8HEZ.00, 8HF..00, 8HF..11, 8HF..12, 8HM..00, 8HM1.00, 8HM8.00, 8HMG.00, 8HMS.00, 8HMZ.00, 8HN..00, 8HN0.00, 8HN1.00, 8HN2.00, 8HN3.00, 8HN4.00, 8HN5.00, 8HN6.00, 8HN7.00, 8HN8.00, 8HN9.00, 8HNA.00, 8HNB.00, 8HNC.00, 8HND.00, 8HNE.00, 8HNZ.00, 8HO..00, 8HO1.00, 8HO2.00, 8HOZ.00, 8HV0.00, 8HVF.00, 8HVG.00, 8HVM.00, 8HVN.00, 8HVY.00, 8HX..00, 8HX0.00, 8HX1.00, 8HX2.00, 8HY..00, 8HZ..00, 8HZ0.00, 8Ha..00, 8Hb..00, 8Hd..00, 8, Hd0.00, 8Hg5.00, 8Hi..00, 8Hk5.00, 8Hl..00, 8Hl0.00, 8Hm..00, 8Hm1.00, 9N19.00, 9N19.11, 9N1B.00, 9N36.00, 9N36.11, 9N3L.00, 9NC..00, 9NC1.00, 9NC8.11, 9Y...00, 9Y0..00, 9Y1..00, 9Y2..00, ZL16.00, ZL16.11, ZL16100, ZL16111, ZL16200, ZL16211, ZL17.00, ZL18.00, ZL18C00, ZL18D00, ZL18L00, ZL18L11, ZL18R00, ZL18S00, ZL19.00, ZL19100, ZL1A100, ZL1G.00, ZL1GD00, ZL1GD11, ZL1GE00, ZL1GE11, ZL1GF00, ZL1GF11, ZL1GH00, ZL1GJ00, ZL5..00, ZL51.00, ZL51.11, ZL51.12, ZL51.13, ZL52.00, ZL56.00, ZL56.11, ZL56100, ZL56200, ZL56211, ZL57.00, ZL57100, ZL5A.00, ZL5A200, ZL5A211, ZL5AD00, ZL5AE00, ZL5G500, ZL5GA00, ZL5GA11, ZL5GB00, ZL5GB11, ZL5GC00, ZL5GC11, ZL5GE00, ZL9..00, ZL91.00, ZL91.11, ZL91.12, ZL92.00, ZL96.00, ZL96.11, ZL96100, ZL96111, ZL96200, ZL96211, ZL97.00, ZL97100, ZL9A.00, ZL9AE00, ZL9AF00, ZL9AL00, ZL9AL11, ZL9AL12, ZL9G.00, ZL9GC00, ZL9GC11, ZL9GD00, ZL9GD11, ZL9GE00, ZL9GE11, ZL9GG00, ZL9GM00, ZL9GN00, ZL9GP00, ZLD2G00, ZLD2G11, ZLD2H00,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	ZLD2H11, ZLD2I00, ZLD2I11, ZLD2L00, ZLD2R00, ZLD3.00, ZLD3E00, ZLD3F00, ZLD3L00, ZLD3L11, ZLD4.00, ZLD4700, ZLD4711, ZLD4800, ZLD4811, ZLD4900, ZLD4911, ZLD4A00, ZLD4B00, ZLD4D00, ZLEQ700, ZLEQ711, ZLEQ800, ZLEQ811, ZLEQ900, ZLEQ911, ZLF3.00, ZLG..00, ZLG1.00, ZLG2.00, ZLG3.00, ZLG3100, ZLG3200, ZLG4.00, ZLG4100, ZLG5.00, ZLG5100, ZLG5200, ZLG6.00, ZLG6100, ZLG6300, ZLG6400, ZLG6411, ZLG6500, ZLG6511, ZLG8.00	294
Collapse	1479, 147A.00, 147B.00, 147C.00, 147D.00, 16D..00, 16D1.00, 16D5.00, 1B6..00, 1B6..11, 1B6..12, 1B6..13, 1B62.00, 1B65.00, 1B65.11, 1B66.00, 1B66.11, 1B68.00, 2225, 2235, 2236, 2236.11, 2236.12, 2236.13, 2236.14, 2237, 2238, 2239, 223Z.00, 224..00, 2241, 2242, 2243, 2244, 224Z.00, C365.00, C365000, C365100, C365200, C365z00, G575.00, G575.11, G575.12, G575000, G575100, G575200, G575300, G575z00, G87..00, G870.11, R000.00, R000.11, R000.12, R000000, R000200, R000300, R000311, R000400, R000500, R000z00, R002.00, R002.11, R002000, R002100, R002200, R002300, R002400, R002500, R002600, R002700, R002z00, R003.00, R003000, R004000, R004100, R004200, R055.00, R055000, R055011, R055100, R055111, R200.12, R2y0.00, R2y0100, R2y1.00, R2y1000, R2y1100, R2y1z00, SP20.11, U10..00, U100.00, U100000, U100200, U100300, U100400, U100500, U100z00, U101.00, U101000, U101100, U101200, U101300, U101400, U101500, U101600, U101700, U101y00, U101z00,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	U102.00, U102000, U102300, U102400, U102700, U102y00, U102z00, U103.00, U103000, U103300, U103y00, U103z00, U104.00, U104000, U104100, U104600, U105.00, U105000, U105100, U105500, U105700, U106.00, U106000, U106100, U106200, U107.00, U107000, U107200, U107600, U107y00, U107z00, U108.00, U108000, U108100, U108600, U108z00, U109.00, U109000, U109200, U109z00, U10A.00, U10A000, U10A100, U10A400, U10A500, U10A511, U10Ay00, U10Az00, U10B.00, U10B000, U10B600, U10By00, U10Bz00, U10C.00, U10C600, U10Cz00, U10D.00, U10D000, U10D100, U10D300, U10D600, U10Dz00, U10E.00, U10E000, U10Ez00, U10F000, U10F100, U10F300, U10G.00, U10G300, U10G600, U10H.00, U10H000, U10H200, U10H300, U10H400, U10H500, U10H600, U10Hy00, U10Hz00, U10J.00, U10J000, U10J100, U10J200, U10J300, U10J400, U10J600, U10Jy00, U10Jz00, U10z.00, U10z000, U10z100, U10z300, U10z400, U10z600, U10zy00, U10zz00	280
Alcohol	136..00, 1361.11, 1363, 1364, 1365, 1366, 1368, 1369, 136C.00, 136D.00, 136E.00, 136F.00, 136G.00, 136H.00, 136I.00, 136J.00, 136K.00, 136L.00, 136O.00, 136P.00, 136Q.00, 136R.00, 136S.00, 136T.00, 136V.00, 136W.00, 136X.00, 136Z.00, 13Y8.00, 1462, 1B1c.00, 2577, 2577.11, 66e..00, 66e0.00, 6792, 67H0.00, 8H35.00, 8H7p.00, 8HkG.00, E01..00, E010.00, E010.11, E010.12, E011.00, E011000, E011100, E011200, E011z00, E012.00, E012.11, E012000, E013.00, E014.00, E014.11, E015.00, E01y.00, E01y000,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	E01yz00, E01z.00, E23..00, E23..11, E23..12, E230.00, E230.11, E230000, E230100, E230200, E230300, E230z00, E231.00, E231.11, E231000, E231100, E231200, E231300, E231z00, E23z.00, E250.00, E250.11, E250.12, E250.13, E250.14, E250000, E250100, E250200, E250300, E250z00, Eu10.00, Eu10000, Eu10011, Eu10100, Eu10200, Eu10211, Eu10212, Eu10213, Eu10300, Eu10400, Eu10411, Eu10500, Eu10511, Eu10512, Eu10513, Eu10514, Eu10600, Eu10611, Eu10700, Eu10711, Eu10712, Eu10800, Eu10y00, Eu10z00, F375.00, J610.00, J611.00, J613.00, J613000, J617.00, J617000, J671000, R103.00, U80..00, U800.00, U801.00, U802.00, U803.00, U804.00, U805.00, U806.00, U807.00, U808.00, U81..00, U811.00, U812.00, U813.00, U814.00	251
Upper GI diagnosis	43k7.00, 4JM1.00, 4JN..00, A074500, AB20100, AB20z00, J10..00, J100.00, J100.11, J100.12, J100000, J101000, J103000, J103100, J103200, J103211, J103300, J103311, J105.00, J105.11, J105.13, J105.14, J105.15, J105000, J106.00, J106000, J106100, J106200, J106300, J106400, J106500, J106z00, J10y.00, J10y100, J10y413, J160.00, J161.00, J170.00, J170.11, J170000, J170100, J170200, J170z00, J171.00, J172.00, J174000, J175.00, J176.00, J17y.00, J17y000, J17y100, J17y300, J17y500, J17y600,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	J17yz00, J17z.00, J1y..00, J1z..00, J34..00, J34..11, J34..12, J340.00, J341.00, J342.00, J343.00, J347.00, J348.00, J34y.00, J34y.11, J34z.00, J34z000, Jyu1000, Jyu1400, PA30.00, PA31.00, PA31.11, PA32.00, PA32000, PA32100, PA32111, PA32z00, PA33.00, PA34.00, PA35.00, PA36.00, PA37.00, PA3y.00, PA3z.00, PA4..00, PA40.00, PA42.00, PA43.00, PA44.00, PA45.00, PA4z.00, PA5..00, PA50.00, PA51.00, PA51.11, PA52.00, PA52.11, PA5y.00, PA5z.00, PA6..00, PA7..00, PA70.00, PA70.11, PA71.00, PA73.00, PA74.00, PA75.00, PA76.00, PA77.00, PA78.00, PA7z.00, PAy..00, PAz..00, PAz0.00, PAz1.00, PAz2.00, PAzz.00, PAzz.11, PB13000	152
Confusion	1B67.00, 1B67.11, 1B69.00, 1B6A.00, 2232, 2232.11, 2233, 2234, 225..00, 225..11, 2251, 2841, 2841.11, E030.00, E030.11, E030.12, E030000, E030100, E030200, E030300, E030400, E030z00, E031.00, E031.11, E031000, E031z00, Eu04.12, R009.00, R009.11, R009000	92
Upper GI procedure	7022000, 7022012, 7022100, 7022111, 7022112, 7022200, 7022300, 7022400, 7022y00, 7022z00, 7022z11, 76...00, 76...11, 760..00, 760..11, 7600, 7600.11, 7600000, 7600011, 7600012, 7600013, 7600100, 7600111, 7600300, 7600y00, 7600z00, 7601, 7601.11, 7601000, 7601111, 7601200, 7601213, 7601400, 7601y00, 7601z00, 7602, 7602.11, 7602000, 7602300, 7602y00, 7602z00, 7602z11, 7603, 7603000, 7603100, 7604, 7604000, 7604100, 7604300, 7604500, 7604z00, 7605, 7605000, 7605100, 7605200, 7605y00, 7606, 7606200,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	7606300, 7606y00, 7606z00, 7607, 7607.11, 7607000, 7607200, 7607211, 7607300, 7607y00, 7607z00, 7607z11, 7608, 7608000, 7608011, 7608100, 7608200, 7608300, 7608311, 7608y00, 7608z00, 7609, 7609000, 7609100, 7609200, 7609400, 7609y11, 7609z00, 760A.00, 760A.11, 760A000, 760A011, 760A100, 760A200, 760B.00, 760B000, 760B100, 760By00, 760Bz00, 760Hz00, 760J.00, 760J300, 760J312, 760J500, 760Jy00, 760Jz00, 760K.00, 760y.00, 760z.00, 761..00, 761..11, 7610, 7610.11, 7610.12, 7610000, 7610100, 7610300, 7610400, 7610y00, 7610z00, 7611, 7611.11, 7611000, 7611011, 7611012, 7611100, 7611200, 7611211, 7611212, 7611213, 7611214, 7611215, 7611216, 7611300, 7611400, 7611500, 7611600, 7611700, 7611800, 7611900, 7611A00, 7611y00, 7611z00, 7612, 7612000, 7612100, 7612111, 7612200, 7612300, 7612400, 7612500, 7612y00, 7614, 7614000, 7614100, 7614111, 7614200, 7614y00, 7614z00, 7615, 7615.11, 7615000, 7615100, 7615200, 7615y00, 7615z00, 7616, 7616000, 7616011, 7616012, 7616013, 7616014, 7616015, 7616100, 7616200, 7616300, 7616600, 7616y00, 7616z00, 7617, 7617.11, 7617.12, 7617000, 7617111, 7617112, 7617200, 7617300, 7617500, 7617y00, 7617z00, 7618, 7618000, 7618100, 7618200, 7618y00, 7618z00, 7619, 7619.11, 7619000, 7619100, 7619y00, 7619z00, 761A.00, 761A000, 761A100, 761A200, 761A300, 761A400, 761Ay00, 761Az00, 761B.00, 761B.11, 761B000, 761B011, 761B100, 761B200, 761B211, 761B212, 761B213, 761B300,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	761B500, 761B600, 761By00, 761Bz00, 761C.00, 761C000, 761C100, 761Cy00, 761Cz00, 761Gy00, 761Gz00, 761Hy00, 761Hz00, 762..00, 7620, 7620.11, 7620000, 7620100, 7620200, 7620y00, 7620z00, 7620z11, 7621000, 7621100, 7621z00, 7622, 7622100, 7622200, 7622y00, 7622z00, 7623, 7623000, 7623100, 7623200, 7623300, 7623400, 7623411, 7623500, 7623700, 7623y00, 7623z00, 7624, 7626, 7626100, 7626y00, 7626z00, 7627y00, 7627z00, 762y.00, 762z.00, 8HS..00, 8HS..11, J522.00, J522000, J522100, J522200, J522211, J522212, J522z00, J523.00, J524100	39
Blood transfusion	14S1.00, 4311, 434..00, 4341, 4342, 4343, 434Z.00, 435..00, 435..11, 7L13.00, 7L13000, 7L13100, 7L13200, 7L13300, 7L13500, 7L13y00, 7L13z00, 7L14.00, 7L14000, 7L14100, 7L14200, 7L14300, 7L14311, 7L14y00, 7L14z00, 7L15.00, 7L15000, 7L15100, 7L15200, 7L15300, 7L15400, 7L15800, 7L15y00, 7L15z00, 7L16.00, 88...11	36
GI procedure	14U2.00, 14U5.00, 1984.11, 585F.00, 7603300, 7603311, 7606000, 7606011, 7606100, 760D312, 760J000, 760J100, 760J200, 760K.11, 760K.12, 760K000, 760K011, 760K012, 760K100, 760K200, 760K300, 760K400, 760K500, 760Ky00, 760Kz00, 760L.00, 760L.11, 760L000, 760L011, 760L012, 760L100, 760L111, 760L200, 760L211, 760L300, 760L311, 760L312, 760L500, 760L600, 760L611, 760L700, 760L800, 760Ly00, 760Lz00, 760M.00,	

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
	760M000, 760M200, 760Mz00, 7613, 7613000, 7613100, 7613111, 7613200, 7613300, 7613400, 7613500, 7613600, 7613y00, 7613z00, 7617100, 7617400, 7617600, 761A500, 761E400, 761E900, 761EA00, 761G000, 761G100, 761G212, 761G300, 761H.00, 761H000, 761H100, 761H200, 7623711, 7626000, 782B.00, 782B.11, 782B000, 782B011, 782B100, 782B111, 782By00, 782Bz00, 782C.00, 782C000, 782Cy00, 782Cz00, 782D.00, 782D000, 782D100, 782D200, 782D300, 782D400, 782D500, 782D600, 782Dy00, 782Dz00, 782E.00, 782E000, 782E100, 782E200, 782Ey00, 782Ez00, 782F.00, 782F000, 782F100, 782F200, 782F300, 782F400, 782Fy00, 782Fz00, 782G.00, 782G000, 782G100, 782G200, 782Gy00, 782Gz00, 782Gz11, 782Gz12, 782H.00, 782H000, 782Hy00, 782Hz00, 782J.00, 782J000, 782J100, 782Jy00, 782Jz00, 782K.11, 782Kz00, 782L.00, 782L300, 782L400, 782Ly00, 782Lz00, 782M.12, 782M000, 782M100, 782M200, 782M400, 782M500, 782Mz00, 782N.00, 782N000, 782Nz00, J16..00, J173.00, J173100, J173200, J173300, J173z00, J174.00, J174100, J174200, J174300, J174400, J174z00, J177.00, J177.11, J178.00, J178.11, J17y200, J17y400, J17y700, J345.00, J346.00, J500000, J500100	34
Nutrition	161..00, 1612, 1612.11, 1623, 1625, 1625.11, C2...00, C20..00, C201.00, C20z.00, C20zX00, C21..00, C22..00, C23..00, C230.00, C231.00, C232.00, C233.00, C234.00, C23y.00, C23z.00, C23z.11, C23z.12	25

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Table A.2 –Read codes continued from previous page

Category	Read codes	Frequency
General care	1GZ..00, 1H...00, 1H0..00, 1H0..11, 1H1..00, 1H2..00, 1H3..00, 1I...00, 1J0..00, 1R...00, 1R0..00, 1R1..00, 431..00, 431..11, 4312, 4313, 4314, 4315, 431Z.00, 432..00, 4321, 4322, 4323, 4324, 4325, 432Z.00, 433..00, 4331, 4332, 4333, 4334, 4334000, 4335, 4336, 4337, 4338, 433Z.00, 4344, 436..00, 4361, 4362, 436Z.00, 437..00, 437..11, 4371, 4372, 4373, 4374, 4375, 4376, 437Z.00, 43S..00, 43S0.00, 43c0.00, 43x0.00, 43x1.00, 43x2.00, 43x3.00, 43x4.00, 43x5.00, 43x6.00, 62L..00, 62L2.00, 62LZ.00, 6A...00, 8CB..00, 8H3U.00, ZLG6200	15
General procedure	89...00, 89...11, 89...12, 89...13, 89...14, 891..00, 892..00, 8920, 8921, 8922, 8923, 893..00, 8934, 8935, 89Z..00, 8A...00, 8A1..00	15