

Weight loss as a feature of cancer in primary care

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Abstract

Background

Unexpected weight loss (UWL) is a non-specific symptom posing a diagnostic challenge to general practitioners (GPs). It can be associated with several conditions including cancer. There are no international or national clinical guidelines to support GPs to select patients with UWL for cancer investigation.

Aim

The overall aim is to provide the evidence necessary to allow GPs to identify which patients with UWL should undergo testing for cancer.

Methods

Six studies are included in this thesis. Firstly, an evidence synthesis of studies investigating the diagnostic accuracy of UWL as a diagnostic feature of cancer in primary care patients. Following this, a series of five linked studies using electronic health records data from the UK: i) a cohort study about weight recording in NHS primary care from 2000 to 2017 to establish whether weight records could be used to define weight loss; ii) an internal validation study of weight related coding to determine which codes can be used most reliably to define UWL; iii) a time-to-event matched cohort analysis of the association between UWL and cancer to ascertain the time period of increased risk for a cancer diagnosis following a presentation with UWL, for cancer overall and by cancer site and stage; iv) a cross-sectional diagnostic accuracy study investigating the predictive value of risk factors, symptoms, signs and blood test results in patients with UWL; v) the derivation and validation of prediction models to estimate cancer risk in

patients with UWL, leading to the creation of simple clinical risk scores to stratify cancer risk using gender, age, risk factors, symptoms and blood tests.

Results

Weight recording is not a routine activity in UK primary care. It occurs too infrequently to define UWL in epidemiological studies. Validated UWL codes represent $\geq 5\%$ weight loss over six months. Coded UWL is a strong predictor of cancer diagnosis within three months of presentation to primary care. The commonest cancers in people with UWL were pancreas, cancer of unknown primary, gastro-oesophageal, lymphoma, hepatobiliary, lung, bowel and renal tract. Men aged 50 years and older who have smoked and people with co-occurring clinical features or blood test abnormalities were at greatest risk. Clinical features typically associated with specific cancer sites are markers of several cancer types when they occur with UWL. The simple clinical risk scores showed excellent discrimination, calibration and clinical utility. A risk score that prioritised ruling-out cancer investigation (sensitivity 97.5%) corresponded to 35 people with UWL being referred for investigation for each person with cancer referred and 1,730 people spared referral for each person with cancer not referred.

Conclusion

A GP's decision to code UWL is predictive of several but not all cancers. Risk factors, co-occurring clinical features, and blood test results can be used to select patients with UWL for urgent investigation. These findings will inform future clinical guidelines.

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1. My motivation to study this topic

When I was training to become a general practitioner (GP), three patients consulted me during a short space of time with unexpected weight loss (UWL).

For each patient I asked myself the same question, *“does this patient have cancer?”*

My clinical training had reinforced there is a strong link between UWL and the diagnosis of cancer. Like most doctors, my training had mainly taken place in the hospital (secondary care). I had been taught mainly by hospital specialists who used hospital patients as teaching cases. These patients had been referred by their GPs because they were assessed to be the most unwell out of all the patients attending primary care.

Working in this setting, I was starting to realise that, compared with hospital patients, considerably fewer patients consulting their GP had a serious diagnosis to explain their symptoms. In fact, I was beginning to understand that it was much more common for no cause to be found for symptoms we had been taught were “red-flags” for serious diseases such as cancer.

I still asked: *“does this patient have cancer?”*

Each of my patients with weight loss were quite different. The first was a slim man in his forties who weighed himself each morning and had noticed losing ten kilograms over a couple of months. He had lost his appetite and had some pain just under his ribs. He exercised regularly, something that had not changed, and had not been dieting, but had been finding his work increasingly stressful. The second patient was a woman in her late fifties who was obese and had previously smoked. She had recently noticed that her clothes were loose but had no idea over what time period she had lost weight or what her weight was beforehand. She felt bloated but no abnormalities were found on examination. She had not been exercising differently from usual, her diet remained

unchanged, and her family and work life had been uneventful. The third patient was a sixty-five year old man who had been getting up at night to urinate more frequently. I had referred him to a specialist and started him on a new medication. He had always been slim and had actively dieted for years to stay healthy. He noticed his weight was less than usual after buying a new set of bathroom scales with his friends and family agreeing that he looked slimmer.

In each of these cases I decided that the question was not, *“does this patient have cancer?”* but rather, *“how much should I investigate this patient for cancer?”* None of them had recent weight measurements in their electronic health records (EHRs). We agreed to check some blood tests and to review the situation again in two weeks when the results had been reported. Whilst waiting, I read the limited guidance available to me about UWL as a symptom of cancer in primary care.

These clinical scenarios are replicated across the UK and internationally. GPs, such as myself, are faced with daily dilemmas about how best to investigate patients attending primary care with UWL. Providing evidence to support the decision making of my frontline colleagues and to optimise outcomes for these patients provides the motivation for my research and this thesis.

2. Background

This chapter outlines the causes of UWL, existing guidelines for its investigation in primary care, and the UK context of symptomatic cancer diagnosis. By describing the background to the thesis I identify the current evidence gaps. The chapter concludes by summarising these evidence gaps and the research questions that my thesis seeks to answer.

2.1. Why do people lose weight?

UWL is a symptom of a wide range of benign and serious conditions related to almost any bodily system and clinical domain with multiple diagnoses possible in each domain (Table 2.1-1). UWL might be caused by organic disease, such as an overactive thyroid gland or chronic obstructive pulmonary disease (COPD). When it occurs it often signifies severe or uncontrolled disease, such as end-stage heart failure. UWL can also be the consequence of mental illness, social deprivation, addiction, frailty, and the medications we prescribe or patients buy. In addition, many patients intentionally lose weight through diet, exercise and medical interventions such as medication or bariatric surgery. With so many possible causes of UWL, it can be challenging for clinicians to identify the culprit. This is especially true in primary care, where GPs have limited time and resources.

Table 2.1-1. Possible causes of unexpected weight loss

Clinical domain	Differential diagnosis
Cardiovascular	End-stage heart failure (cardiac cachexia).
Endocrine	Adrenal insufficiency, diabetes, hyperthyroidism.
Gastrointestinal	Diarrhoea, colitis, malabsorption, mesenteric ischaemia.
Infection	Chronic infection (e.g. HIV, tuberculosis).
Malignancy	Solid tumours more commonly than haematological malignancy.
Medication	Antidepressants, antiepileptics, anxiolytics, diuretics, laxatives, stimulants.
Neurological	Dementia, multiple sclerosis, neuromuscular disease, Parkinson's disease, stroke.
Psychiatric	Anorexia nervosa, anxiety, bulimia, depression.
Renal	End-stage renal failure (uremic cachexia).
Respiratory	Chronic obstructive pulmonary disease (COPD), interstitial lung disease, vasculitis.
Rheumatologic	Rheumatoid arthritis.
Social	Excess alcohol, neglect, opiates, poor oral health, poverty, smoking.

2.2. Weight loss as a cancer symptom

In patients with cancer, UWL can be precipitated by related biochemical, behavioural, functional and metabolic factors depending on the type of cancer and its location (Table 2.2-1) (1). For example, a tumour growing in the oesophagus might lead to difficulty swallowing, pain, reflux or regurgitation that in turn triggers a change in diet or reduction in food intake. If located lower in the gastrointestinal (GI) tract, for example in the pancreas or bowel, the cancer may cause malabsorption or diarrhoea resulting poor nutritional uptake and weight loss. Alternatively, a cancer might not disrupt the GI tract but may produce chemicals, such as cytokines or hormones that disrupt the bodily mechanisms used to maintain and control weight (weight homeostasis). A growing tumour may also lead to low-grade inflammation causing fatigue, low mood and poor appetite. Given that there are many possible mechanisms that may lead to weight loss in patients with many types of cancer, weight loss is considered a non-specific cancer symptom. In comparison, symptoms such as coughing up blood or a breast lump are considered specific symptoms (sometimes referred to as “red-flag” or “alarm” symptoms) as they are strongly linked to an individual cancer site (2).

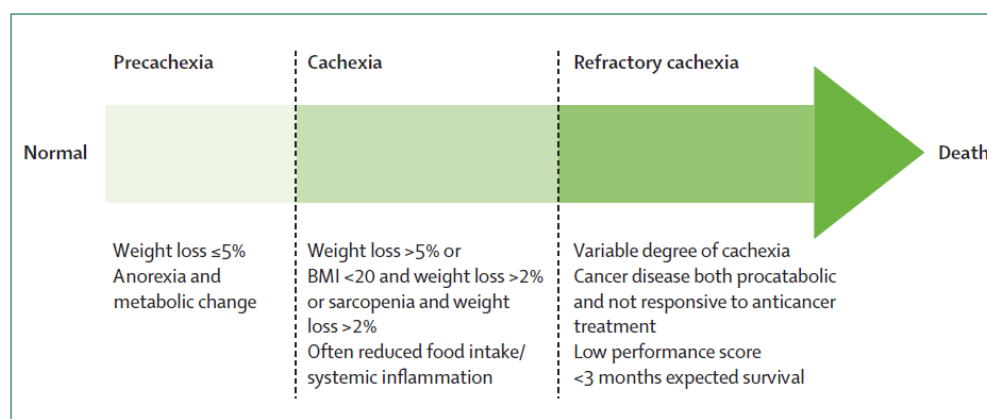
Table 2.2-1. Pre-diagnosis causes of weight loss in cancer

Cytokine-, peptide- and hormone- induced anorexia and metabolic changes.
Symptom distress – depression, pain, nausea, diarrhoea, constipation, fatigue.
Gastrointestinal (GI) dysfunction – altered taste, obstruction, dysmotility, fistula, malabsorption.
Cancer cachexia (pre-cachexia, cachexia, refractory cachexia).

2.3. Cancer cachexia as a cause of weight loss

As described in Table 2, cachexia can be a cause of pre-diagnosis weight loss in cancer. The term comes from the Greek words *kakos* (bad) and *hexis* (condition) (3). In cancer, cachexia is a multifactorial syndrome that most commonly presents with weight loss due to progressive skeletal muscle loss (sarcopenia) with or without fat loss (4). It combines negative protein and energy balance driven by combinations of reduced food intake, systemic inflammation and abnormal metabolism that cannot be fully reversed by conventional nutritional support (4). In addition to weight loss, the clinical features of cancer cachexia syndrome (CCS) include anorexia, fatigue, anaemia and hypoalbuminemia. Prior clinically apparent weight loss, early (or pre-) cachexia is characterized by subtle clinical and metabolic changes that precede low-grade weight loss, such as inflammation and impaired glucose tolerance, (3, 4) (Figure 2.3-1). Despite there being a rapidly growing evidence base regarding the assessment of cachexia in patients with known cancer using imaging and blood tests, almost no research has been conducted into using cachexia as a diagnostic feature in patients without a known cancer diagnosis, and no research has been conducted on cachexia detection in primary care (5).

Figure 2.3-1. The stages of cachexia (4)



2.4. Weight loss and cancer stage

Cancers are staged based on the size or extent of the primary cancer (T), the number and location of lymph nodes that the cancer has spread to (N), and the presence of evidence that the cancer has spread past the lymph nodes (metastasis - M) (6). Based on the combination of T N and M scores, a Stage is assigned from 0-IV. The higher the Stage the more advanced the cancer and the poorer the prognosis. Staging varies by cancer site. Box 2.4-1 gives an example of pancreatic cancer staging (6).

Box 2.4-1: Pancreatic cancer staging.

Tx	Primary tumour could not be assessed		
T0	No evidence of primary tumour		
Tis	Carcinoma in situ		
T1	Tumour invades lamina propria or muscular layer		
T1a	Tumour invades lamina propria		
T1b	Tumour invades muscular layer		
T2	Tumour invades perimuscular connective tissue; no extension beyond serosa or in to liver		
T3	Tumour perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one another organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extra hepatic bile ducts		
T4	Tumour invades main portal vein or hepatic artery or invades two or more extra hepatic organs or structures		
Regional Lymph Nodes (N):			
Nx	Regional Lymph Nodes cannot be assessed		
N0	No Regional Lymph Node metastasis		
N1	Metastases to nodes along the cystic duct, common bile duct, common hepatic artery, and portal vein		
Distant Metastasis (M):			
M0	No Distant Metastasis		
M1	Distant Metastasis		
Staging Groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

UWL is most often thought to be a symptom of more advanced cancer, with weight loss and cachexia often conflated, however hospital and lab-based studies have revealed that weight loss may occur at any stage and grade of cancer (7). However, only a few studies have examined weight loss detected in primary care in relation to the stage of cancer: an American case-control study found that there was no association between weight loss and stage of pancreatic cancer (8), whilst an English case-control study found no association between weight loss and stage IV (metastasized) prostate, colorectal, lung and breast cancer (9). Meanwhile, an equivalent positive predictive value (PPV) for weight loss and colorectal cancer was reported by Swedish and English case-control studies despite the former including stages I-III (PPV 1.0%, 95% confidence interval (CI) 0.3 to 3.0) and the latter including more advanced cancers, stages I-IV (1.2%, 95% CI 0.91 to 1.6) (10, 11). It remains to be established whether UWL detected in primary care represents a less advanced stage of cancer compared to cases picked up in patients under hospital care. This is important because patients who are diagnosed earlier, when their cancer is less advanced, are more likely to receive curative treatment and live longer (3)

2.5. Identifying weight loss in primary care

Weight loss can be difficult to detect. It may be missed or misattributed due to a number of physiological and measurement factors: i) being overweight increases the risk of cancer and the challenge of detecting weight loss (12); ii) a gradual decline in muscle mass is expected from the sixth decade of life (13); and iii) day-to-day fluctuations of +/- 2kg can occur because of changes in fluid balance and gut contents (14). Furthermore, weight measurement is not routine practice in many health systems unless patients have particular clinical problems. Clinicians record weight status in kilograms, pounds or

as body mass index (BMI) hampering longitudinal comparisons (15) the interpretation of which is further complicated by intentional weight loss and exercise. It is unclear from the literature if patients attending UK primary care have their weight measured and recorded sufficiently often to detect weight loss associated with a new cancer diagnosis.

2.6. How much weight loss over how long?

The magnitude of weight loss that best indicates underlying cancer in primary care also remains poorly defined. To date, only one primary care study directly used weight measurements to identify weight loss in relation to cancer diagnosis. This UK case-control study investigated the risk of colorectal cancer and found an odds ratio of 1.2 (95% CI 0.99 to 1.5) for 5-9.9% weight loss increasing to 2.5 (95% CI 2.1 to 3.0) for $\geq 10\%$ loss (6). The percentage loss of weight is likely to be the most clinically relevant measure as change relative to baseline weight is more meaningful than absolute change (14). However, this study defined weight loss using the highest recorded weight in the preceding two years, possibly leading to under- or over-estimations as more recent weight changes may have been missed.

Furthermore, almost all studies in this area are retrospective observational studies that define weight loss using a code entered into the primary care EHR. These codes appear to be based on a GP's decision that the degree of weight loss is sufficiently concerning to justify recording it. No studies were found that reported weight measurement data associated with each weight loss code, that have quantified how much weight loss has occurred, or established whether patient reported weight loss is more accurate at identifying disease than weight loss measured in clinic.

It is unclear how recently weight loss must have occurred to indicate the presence of cancer. Studies have investigated the diagnostic utility of weight loss occurring in the past two years often reporting it in combination with other symptoms (16, 17). However they give no indication of the relative timing of these symptoms compared to each other or to the cancer diagnosis. Although it seems more plausible that only weight loss in the recent past signifies the presence of cancer, at present there is no direct evidence of this from patients attending primary care.

2.7. Clinical guidelines on the investigation of UWL

There are no national or international guidelines on the investigation of weight loss in primary care. Several clinical reviews suggest plausible approaches to the investigation of the wide differential diagnosis in patients with UWL (1, 14, 18-20). Cancer is included as one possible outcome in these reviews. However, as was true in my training, the data underpinning these clinical reviews comes from a different spectrum of patients to those seen in primary care, typically older people hospitalised for investigation (1, 14, 18-20).

Box 2.7-1. Spectrum bias

Spectrum bias (or the spectrum effect) describes the variation between settings in the performance of tests (in this case symptoms) used to predict, screen for, and diagnose disease. In particular, the predictive use of a test (in this case weight loss to predict cancer) may be different when it is applied in a general population (primary care) rather than in the study sample in which it was first developed (such as elderly hospitalised patients) .

The effect of using data from a different patient population to answer questions about another population is called spectrum bias or the spectrum effect (Box 2.7-1) (21).

There is no consensus between these clinical reviews about the amount of weight loss that should prompt further investigation. In general, they recommend a thorough clinical history covering a wide range of body systems and differential diagnoses. This should be supplemented by questions focussed on diet and nutritional status, a full systems physical examination, a broad panel of laboratory tests and a chest x-ray (Table 2.7-1).

The next step is even less clearly defined, with some authors recommending that further investigation should be, *“indicated by clues obtained by the aforementioned tests”* (14). Some specify ultrasound (USS) (1, 14, 19) or computer tomography (CT) (1) imaging whilst others recommend a watch-and-wait strategy if all tests are clear – either for three months (18) or six months (19). From reading these reviews, it is difficult for a clinician to identify which lines of enquiry are most suited to ruling-in or ruling-out individual cancers in amongst broad investigative strategies designed to catch all possible causes of weight loss.

Table 2.7-1. Summary of approaches to investigating weight loss from clinical reviews

(1, 14, 18-20)

Vanderschueren 2005	Rolland 2006	McMinn 2011	Gaddey 2014	Wong 2014
Population – adults.	Population – outpatient older adults.	Population – older adults.	Population – older adults.	Population – adults.
Losses of >5% in 6-12 should prompt clinical evaluation. Seek numerical verification of weight loss and confirm involuntary. Past and present medical history and associated complaints including: Tobacco/alcohol use Medications (e.g., diuretics, digoxin, biguanides, leflunomide, SSRI's) Psychosocial factors (e.g., bereaved, institutionalized, mental health) Dietary history Travel history Sexual risk behaviour Thorough physical examination Baseline tests: CBC with differential, Renal function, LFTs, Albumin, TFTs, blood sugar, markers of inflammation, iron studies, urinalysis, faecal occult blood tests. CXR, USS abdo and pelvis Additional investigations as indicated by clues obtained by the aforementioned tests	Weight Loss >5% in 6 months. Assess for biochemical dehydration and complete: Is SNAQ questionnaire positive (<14 points) 1. My appetite is: A. V. poor, B. Poor, C. Average, D. Good, E. V. good. 2. I feel full after eating: A. a few mouthfuls, B. 1/3 of a meal, C. >1/2 a meal, D. most of the meal, E. hardly ever. 3. Food tastes: A. V. bad, B. Bad, C. Average, D. Good, E. V. good. 4. Meals I normally eat each day: A. <1, B. 1, C. 2, D. 3, E. > 3. Score: A=1, B=2, C=3, D=4, E=5. SNAQ negative: Suspected sarcopenia trial of resistance exercise training. Suspected malabsorption: test A or beta-carotene SNAQ positive: Suspected cachexia: test CRP and Albumin. Suspected anorexia: use MEALS ON WHEELS mnemonic. M: Medication effects E: Emotional problems (esp. depression) A: Anorexia nervosa, alcoholism L: Late life paranoia S: Swallowing disorders O: Oral factors (poorly fitting dentures, caries) N: No money W: Wandering and other dementia related behaviours H: Hyper/hypothyroidism, hyperparathyroidism, hypoadrenalism E: Enteric problems E: Eating problems (e.g. inability to feed self) L: Low salt, low cholesterol diet S: Stones, social problems (e.g. isolation, poverty, mobility).	5% of body weight is lost over 6-12 months, although smaller losses may be important in frail elderly people. Comprehensive history and physical exam using meals on wheels mnemonic and the 9Ds of weight loss in elderly: Dementia Depression Disease (acute and chronic) Dysphagia Dysgeusia Diarrhoea Drugs Dentition Dysfunction (functional disability) Don't know Baseline tests: FBC, Renal function, LFTs incl GGT, Albumin, TFTs, CRP, ESR, glucose, LDH, CXR, Urinalysis, FOBT. If initial history, examination, and investigations are normal, three months of "watchful waiting" is preferable to further blind investigations.	Unintentional weight loss ≥ 5% within six to 12 months. If no baseline weight is available, evidence of change in clothing size, confirmation of weight loss by a relative or friend, and a numerical estimate of weight loss can be used. History and physical examination, in particular asking about fever, fatigue, dysphagia, oral/gum problems, dyspnoea, exertional fatigue, indigestion, abdominal pain, change in stool pattern, early satiety. Medications, social and psychological history. Assess nutritional status e.g. using the Nutritional Health Checklist. Baseline tests: CBC, basic metabolic panel, LFTs, TFTs, CRP, ESR, glucose, LDH, CXR, FOBT, and possibly abdo USS If baseline test results are negative, close observation for three to six months is justified.	Unintentional weight loss ≥ 5% within six to 12 months. Use clinical judgement to guide investigation in patients with weight loss <5% or longer duration. History and physical exam covering differential diagnoses (table 1). Baseline tests: CBC, LFTs, Albumin, Renal function, Glucose, Calcium, TSH, HIV, ESR, CRP, LDH, PSA, CXR. Consider Abdominal USS or CT and age-appropriate screening for breast, colorectal and cervical cancer.

2.8. UK NICE guidelines for the investigation of suspected cancer

In the UK, the 2015 National Institute of Health and Care Excellence (NICE) guidelines for suspected cancer (NG12) reported UWL to be a feature of seven cancers in primary care: colorectal, gastric, lung, lymphoma, oesophageal, ovarian and pancreatic cancer (22). NICE cited PPVs ranging from 0.4-3% across these cancer sites, and a cumulative PPV of 7.1% across all cancer sites. In this context the PPV can be thought of as the risk of cancer in patients with UWL. 7.1% is greater than the 3% threshold used by NICE to signify a clinical situation that warrants urgent investigation for cancer (22). The NICE guidelines made specific recommendations about which patients should undergo further investigation for cancer (Table 2.9-1).

2.9. Limitations of the NICE guidelines.

There are important limitations of the NICE guidance to highlight. Firstly, the methods used to estimate the PPVs of weight loss are inaccurate, partly due to the limitations of the available data. No study was identified that reported the PPV for weight loss across all cancer sites and, for several cancer sites no studies had been conducted to estimate PPVs of weight loss. Therefore, the estimated cumulative PPV included in the guidance – which is produced by adding the PPVs of each cancer site together - necessarily omits some sites and their contribution to the total. In addition, some studies may not have used a population representative of patients presenting with UWL in primary care. For example, one included study reported a PPV of 35.7%, far exceeding that expected for a cancer symptom in primary care (23, 24). Furthermore, most studies examined the

association between UWL and a diagnosis of cancer within the next two years but it is plausible that this association will vary over time.

Table 2.9-1. NICE recommendations for the investigation of unexplained weight loss (22)

Age	Unexplained weight loss AND:	Action	Cancer
N/A	Lymphadenopathy or Splenomegaly	Urgent specialist referral*	Lymphoma
N/A	Female	CA125 test in primary care	Ovarian
≥40y	Abdominal pain	Urgent specialist referral*	Colorectal
	Ever-smoked or Asbestos exposure	Urgent chest X-ray	Lung
	Never-smoker AND cough or Fatigue or Shortness of breath or Chest pain or Appetite loss		
<50y	Rectal bleeding	Consider urgent specialist referral	Colorectal
≥50y		Faecal Occult Blood Test	
≥55y	Upper abdominal pain or Reflux or Dyspepsia	Urgent gastroscopy	Gastro-oesophageal
	Thrombocytosis or Nausea and vomiting	Non-urgent gastroscopy	
≥60y	Diarrhoea or Back pain or Abdominal pain or/ Nausea or Vomiting or Constipation or New onset diabetes	Consider urgent abdominal CT scan	Pancreas

**to be assessed within 2 weeks*

N/A: not applicable; y: years; CT: computed tomography;

Secondly, a major clinical limitation of the NICE guidance is how GPs should interpret and implement the guidance based on studies that characterised weight loss by doctors' use of the term weight loss given the weaknesses of the evidence base as described previously. Most studies cited in the NICE guidelines define weight loss on the basis of a coded entry in the primary care EHR. This entry is often based on a report of weight loss (volunteered by, or elicited from, the patient) rather than measured weight change. Consequently, the NICE guidance could not define the degree of weight loss or the time period of loss that should prompt referral.

Finally, although weight loss was recognised as a symptom of a number of cancers, NICE largely recommends the investigation of single cancer sites based on clinical features co-occurring with weight loss (Table 2.9-1). In some cases this is for site specific imaging, such as a chest x-ray for shortness of breath and weight loss in a patient aged 40 years or older. In other cases a referral to a specialist is recommended, for example to rule out bowel cancer in a patient younger than 50 years with rectal bleeding and weight loss. There are only three scenarios included in the guidance where NICE recommending investigating weight loss occurring without other symptoms. They advise: a chest x-ray for smokers, a blood test for ovarian cancer in women, and a faecal occult blood test for colorectal cancer in patients aged ≥ 50 years old. If these tests are negative, the GP is left uncertain whether their patient requires further investigation.

2.10. Diagnostic pathways for investigating cancer symptoms

Based on the NICE guideline recommendations, Clinical Commissioning Groups (CCGs) and hospital trusts in the NHS developed a system of fast-track referral routes, known as the two-week-wait (2WW) pathways, for combinations of symptoms and signs that result in a PPV of $\geq 3\%$ for cancer. These pathways investigated patients with “red-flag” symptoms of single cancer sites. Within this context, cancers with non-specific symptom signatures, such as myeloma and pancreatic cancer, have been shown to be associated with longer intervals between presentation and diagnosis, a lower likelihood of being diagnosed via urgent GP referral and a higher likelihood of being diagnosed as an emergency (25, 26). Longer intervals, often called diagnostic delays, are linked to poorer cancer outcomes (27, 28). Research from primary care has since shown that approximately half of patients who will ultimately be shown to have cancer present with non-specific symptoms (29, 30).

The evidence gaps highlighted throughout this chapter must be addressed to help GPs select patients with UWL for referral and if non-specific symptom care pathways are to be implemented in the NHS.

3. Aims, objectives and thesis outline.

The overall aim and objectives of this thesis are outlined below.

3.1. Aim

The overall aim of this thesis is to provide the evidence necessary to allow GPs to identify which patients with unexplained weight loss should undergo testing for cancer.

3.2. Objectives

The main objectives of this thesis are to:

1. Summarise the evidence for a link between UWL and cancer in primary care?
2. Establish whether weight is recorded often enough in UK primary electronic health care records to define UWL.
3. Investigate which codes entered in the UK primary health care electronic records most reliably define UWL.
4. Ascertain when cancer is diagnosed in patients who present to primary care with UWL.
5. Determine which cancer types and cancer stages are associated with primary care patients with UWL.
6. Understand which risk factors, clinical features and blood test results can be used to select patients with UWL for referral for cancer investigation.

3.3. Thesis outline

The remainder of this thesis details six studies designed to meet the six objectives and a final discussion chapter. The six analysis chapters are outlined as follows:

Chapter Four: Weight loss as a predictor of cancer in primary care: a systematic review and meta-analysis

This chapter reports a diagnostic test accuracy review of the available literature about weight loss as a symptom of cancer in primary care. It allows a detailed description of current research in this field, including research published since the NICE guidelines were collated and an assessment of the methodological biases associated with the study designs and populations included. From this thorough understanding of the literature base, I was able to further refine the research questions covered in the subsequent chapters.

Chapter Five: Determinants and extent of weight recording in UK primary care: an analysis of 5 million adults' electronic health records from 2000 to 2017

This chapter details a large cohort study examining who has their weight measured in primary care. I was motivated to understand why weight measurements had not been used to define weight loss in all but one study included in the systematic review reported in Chapter Four. In particular, I sought to identify whether there were subgroups of patients for which weight measurements could be used to define weight loss and whether these subgroups were representative of the wider primary care population. I therefore describe patterns of weight recording and repeat weight recording over seventeen years with reference to patient characteristics, clinical events, symptoms and diagnoses.

Chapter Six: The internal validation of weight change coding using weight measurement data within the UK primary care electronic health record

Chapter Six details a study of weight related coding in UK primary care electronic health records using the available weight records to determine which weight related codes

most reliably define patients with unexpected weight loss. This study was necessary as Chapter Five highlighted that weight measurement data is frequently incomplete or insufficient to define weight loss alone. Furthermore, this validation study is good practice when selecting the codes used to define exposure variables in electronic health records research (31).

Chapter Seven: The association between unexpected weight loss and cancer diagnosis in patients attending primary care: a matched cohort analysis of 65,000 presentations over 14 years using routinely collected electronic health record data.

This chapter uses the codes found in Chapter Six to most reliably define unexpected weight loss to identify weight loss in a matched cohort study. This study investigates what type of cancer is diagnosed in patients attending primary care with UWL compared to those attending without UWL. This analysis uses a range of time-to-event methods to establish the period of greatest likelihood of a cancer diagnosis following a GP attendance with UWL and to further explore the important biases identified in Chapter Four.

Chapter Eight: Prioritising patients with unexpected weight loss for cancer investigation in primary care: a diagnostic accuracy study using routinely collected electronic health records data from 65,000 presentations

In Chapter Eight, I investigate which risk factors, clinical features and test results are predictive of cancer in primary care when they co-occur with weight loss, within the period of greatest cancer risk as defined in Chapter Seven. The aim of this study was to identify whether combinations could be used in clinical guidance to rule-in patients for cancer investigation given that the predictive value of weight loss alone is not high

enough to warrant cancer investigation in the majority of patients in primary care. A limitation of this chapter was the poor rule-out ability of co-occurring clinical features.

Chapter Nine: Derivation, internal cross-validation, and net-benefit analysis of risk scores to rule-in and rule-out cancer investigation in patients with unexpected weight loss.

This final analysis chapter builds on Chapter Eight by using multiple imputation techniques to replace missing risk factor and blood test data, and then deriving and validating prediction models for cancer diagnosis. As Chapter Eight showed that the absence of additional symptoms and signs provides false reassurance in patients with weight loss, this chapter focusses on the additional benefit of being able to use combinations of normal and abnormal blood tests within a prediction model to rule-in and rule-out the need for additional cancer investigation. Following cross-validation, I present two simple-to-use risk scores that GPs could utilise in clinical practice to select patients for further cancer investigation, for further monitoring in primary care or for no further testing.

3.4. Dissemination of results

Content from Chapter Two (Background), Chapter Four (systematic review), Chapter Six (validation study), and the protocol underpinning Chapters Five to Nine have been published, and as such, sections of the methods, results and discussions are reproduced (32-36). The remaining analytical chapters have been submitted to journals or prepared for submission. This work has not been submitted for any other course or qualification at the University of Oxford or elsewhere.

4. Weight loss as a predictor of cancer in primary care: a systematic review and meta-analysis.

4.1. Background to this chapter.

No systematic review and meta-analysis examines the association between unexpected weight loss (UWL) and cancer in primary care populations. Existing clinical guidelines provide an incomplete estimate of the risk of cancer in patients with UWL as they have combined risk estimates from heterogeneous studies and, for some cancer sites, no studies providing estimates were found.

4.2. Objectives

The objectives of Chapter Four are to review the existing literature to examine:

- the diagnostic value of UWL, alone and in combination with other clinical features for cancer in primary care patients;
- how the predictive value of UWL varies by cancer type, cancer stage, gender and age.

4.3. Method

I had previously conducted a review of the diagnostic test accuracy of a blood test (carcino-embryonic antigen, CEA) for detecting recurrent colorectal cancer (37). I was interested to see how these methods could be applied when a symptom (UWL) was used as the diagnostic test, the setting was primary rather than specialist care, and the diagnosis was primary rather than recurrent cancer. I followed standard Cochrane diagnostic test accuracy review methodology (38) and adhered to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) reporting guidelines,

adapted to suit a review of diagnostic studies (39). I registered the review with the online international prospective register of systematic reviews (PROSPERO) (38).

4.3.1. Types of studies

All study types were included without restriction, including cross-sectional diagnostic test accuracy studies, retrospective and prospective cohort studies, and randomised controlled trials (RCTs) that directly compared UWL in primary care to a reference standard for cancer diagnosis. Case-control studies were included in the knowledge that their resulting estimates of test accuracy can be influenced by the ratio of cases to controls and exaggerated by the omission of patients with a suspected diagnosis. This broad inclusion criteria enabled the investigation and critique of the methods used. Studies were only included if they presented data in a way that would allow the extraction of a 2 x 2 table for weight loss and cancer or reported the diagnostic accuracy of UWL combined with additional symptoms.

4.3.2. Participants

Adult participants (18 years or over) presenting to primary care were included whilst studies of adolescents and children were excluded. Participants from the “community” or the “general population” were also included as proxies for primary care. Patients presenting to the emergency department were excluded as they may have more acute or advanced disease. Studies of patients referred from primary care to a secondary care clinic were also excluded because, in these cases, GPs have already identified patients they perceive to be at higher risk of cancer and this could distort the apparent predictive value of UWL (21). Patients from hospital populations were excluded for the same reason.

4.3.3. Index test – unexpected weight loss

The index test was UWL or UWL combined with other symptoms. No restrictions were placed on the method for defining weight loss *a priori* to allow comparison of the different techniques. The most common definition of weight loss was anticipated to be a coded entry in the GP's EHR with alternatives including objective weight measurements and patient interview or questionnaire responses. UWL was distinct from expected (or planned) weight loss achieved through diet and exercise, as planned weight loss is not regarded as a symptom of (or risk factor for) cancer. If the authors were not explicit about whether weight loss was unexpected or expected, the default position was to classify weight loss as unexpected.

4.3.4. Reference standard – cancer diagnosis

The reference standard was a record of confirmed diagnosis of cancer. The method of confirmation was not specified *a priori* but it could include cancer registry entry, histology, code or free text entry in the GP EHR or by another source judged to be reliable.

Studies that ascertained a cancer diagnosis within five years of the index date were included to explore the lead time distribution of weight loss. Symptom incidence has been shown to be higher in lung cancer cases compared to controls two years before diagnosis, accelerating markedly in the last six months (40). Mean symptom lead times of 5.5 months for lung cancer and 4.9 months for colorectal cancer have been reported (40, 41). No studies were found that had presented the incidence of weight loss in this way.

4.3.5. Literature searches

The electronic databases Embase (OvidSP) [1974-23/10/2015], Medline (OvidSP) [1946-25/10/2015], and the Science Citation Index & Conference Proceedings Citation Index (Web of Science Core Collection) [1946-25/10/2015] were searched. The search terms used for each database are reported in Table 4.3.5-1, Table 4.3.5-2, and Table 4.3.5-3. No language limits were applied to the searches however no non-English results were identified Duplicates, animal related studies, case reports, letters, comment articles and editorials were excluded at this stage.

Table 4.3.5-1. Web of Science search strategy

Set	Results	Search
1	1,195	TITLE: (((cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?) and (weight* or bmi or body mass index) and (loss or lose or chang* or reduc* or low*)))
2	335,903	TITLE: (weight or bmi or "body mass index") OR TOPIC: ((weight NEAR/3 (loss or lose or lost or losing or chang* or reduc*))) OR TOPIC: (((bmi or "body mass index") NEAR/3 (chang* or reduc* or low)))
3	2,064,990	TOPIC: (cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?)
4	1,291,015	TITLE: (diagnos*) OR TOPIC: (((cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?) NEAR/5 (diagnos* or detect*))) OR TITLE: (presentation or presenting or feature? or manifest* or symptom*) OR TOPIC: (((clinical or diagnos*) NEAR/2 (feature? or manifest* or symptom* or present*)))
5	669,170	TOPIC: (referral? or referred or refer) OR TOPIC: (((general or family) NEAR/2 (practi* or physidian? or doctor?))) OR TOPIC: (office? or visit* or clinic or clinics)
6	1,908,049	#5 OR #4
7	4,037	#6 AND #3 AND #2
8	5,050	#7 OR #1
9	709	#7 OR #1 DOCUMENT TYPES: (PROCEEDINGS PAPER OR MEETING ABSTRACT)
10	4,360	#7 OR #1 DOCUMENT TYPES: (ARTICLE OR REVIEW)
11	5,069	#9 or #10

Table 4.3.5-2. Embase search strategy

# ▲	Searches	Results
1	exp *neoplasm/ and exp *weight reduction/	681
2	((cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?) and (weight* or bmi or body mass index) and (loss or lose or lost or losing or chang* or reduc* or low*)).ti.	1,660
3	exp *neoplasm/	2,800,602
4	(cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?).ti,ab.	3,404,462
5	3 or 4	3,974,065
6	weight reduction/	117,588
7	*bodymass/	18,082
8	*bodyweight/	31,186
9	(weight or bmi or body mass index).ti.	114,266
10	(weight adj3 (loss or lose or lost or losing or chang* or reduc*)).ti,ab.	144,285
11	((bmi or body mass index) adj3 (chang* or reduc* or low)).ti,ab.	14,076
12	6 or 7 or 8 or 9 or 10 or 11	296,698
13	*Diagnosis/	60,341
14	*early diagnosis/ or cancer diagnosis/	101,793
15	exp *Neoplasm/di	554,914
16	diagnos*.ti.	592,865
17	((cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?) adj5 (diagnos* or detect*)).ti,ab.	383,096
18	(presentation or presenting or feature? or manifest* or symptom*).ti.	398,593
19	((clinical or diagnos*) adj2 (feature? or manifest* or symptom* or present*)).ti,ab.	377,827
20	patient referral/	71,422
21	(referral? or referred or refer).ti,ab.	319,972
22	general practitioner/	70,697
23	general practice/	73,600
24	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.	123,004
25	(office? or visit* or clinic or clinics).ti,ab.	585,155
26	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	2,858,068
27	5 and 12 and 26	16,205
28	(exp animals/ or nonhuman/) not human/	5,853,330
29	(rat or rats or rodent? or mice or mouse or cow or cows or cattle or calf or calves or ewe? or sheep or goat or ruminant? or pig or pigs or minipig? or chicken? or horse or horses or murine or bovine or ovine or porcine or animal?).ti.	1,933,509
30	exp juvenile/ not exp adult/	1,905,694
31	(child* or infan* or baby or babies or p?ediatric* or preschool* or pre-school* or toddler?).ti.	1,083,787
32	28 or 29 or 30 or 31	8,168,299
33	27 not 32	14,556
34	(comment or editorial or letter).pt.	1,408,055
35	33 not 34	14,101
36	case report.ti.	222,443
37	35 not 36	12,842

Table 4.3.5-3. Medline search strategy

# ▲	Searches	Results
1	exp *neoplasms/ and *weight loss/	599
2	((cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?) and (weight* or bmi or body mass index) and (loss or lose or lost or losing or chang* or reduc* or low*)).ti.	1,224
3	exp neoplasms/	2,787,539
4	(cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?).ti,ab.	2,682,980
5	3 or 4	3,448,016
6	weight loss/	27,457
7	body mass index/	92,073
8	Body Weight/	169,174
9	(weight or bmi or body mass index).ti.	92,205
10	(weight adj3 (loss or lose or lost or losing or chang* or reduc*)).ti,ab.	102,586
11	((bmi or body mass index) adj3 (chang* or reduc* or low)).ti,ab.	9,321
12	6 or 7 or 8 or 9 or 10 or 11	377,478
13	*Diagnosis/	13,360
14	*early diagnosis/ or "early detection of cancer"/	12,811
15	exp *Neoplasms/di [Diagnosis]	246,407
16	diagnos*.ti.	486,363
17	((cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?) adj5 (diagnos* or detect*)).ti,ab.	282,475
18	(presentation or presenting or feature? or manifest* or symptom*).ti.	321,570
19	((clinical or diagnos*) adj2 (feature? or manifest* or symptom* or present*)).ti,ab.	273,510
20	"Referral and Consultation"/	54,597
21	(referral? or referred or refer).ti,ab.	223,637
22	general practitioners/ or physicians, family/ or physicians, primary care/	19,302
23	general practice/ or family practice/	66,562
24	Office Visits/	5,857
25	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.	97,966
26	(office? or visit* or clinic or clinics).ti,ab.	407,258
27	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	2027,740
28	5 and 12 and 27	7,991
29	exp animals/ not humans.sh.	4,132,479
30	(rat or rats or rodent? or mice or mouse or cow or cows or cattle or calf or calves or ewe? or sheep or goat or ruminant? or pig or pigs or minipig? or chicken? or horse or horses or murine or bovine or ovine or porcine or animal?).ti.	1,712,966
31	(exp infant/ or exp child/ or a adolescent/) not exp adult/	1,606,289
32	(child* or infan* or baby or babies or p?ediatric* or preschool* or pre-school* or toddler?).ti.	900,861
33	29 or 30 or 31 or 32	6,263,526
34	28 not 33	6,963
35	(case reports or comment or editorial or letter).pt.	3,104,438
36	34 not 35	5,049

4.3.6. Searching other resources

The reference lists of retrieved reviews were checked and a PubMed “related articles” search performed for all included studies. The principal investigator of each included study was emailed to ask if they were aware of any further relevant literature, to clarify methodological queries and to ask for any unpublished data relevant to this review. No authors offered additional data.

4.3.7. Study selection and data extraction

Two reviewers independently screened all titles and abstracts identified by the searches. They assessed full-text articles for those (1) deemed relevant based on title and abstract and (2) where a decision could not be made at the screening stage. Data were extracted from eligible studies using an extraction guide that was refined after piloting. A third review author resolved any discrepancies.

4.3.8. Quality assessment

To assess the methodological quality of the included studies, the QUADAS-2 tool was used (42), a set of criteria for assessing the quality of diagnostic accuracy studies. Two reviewers assessed the quality of all articles independently and then discussed any disagreements. When consensus could not be reached, a third reviewer moderated. The quality assessment results were used to provide a descriptive evaluation of the overall quality of the included studies and to investigate potential sources of heterogeneity in the sensitivity analyses.

4.3.9. QUADAS-2 domains

QUADAS-2 consists of four domains: patient selection, index test, reference standard, and the flow of patients through the study and timing of the index test in relation to the reference standard (42). Signalling questions are provided to guide the judgement of the risk of bias across these four domains (42). Within each domain, I attached a greater importance to signalling questions that would have a greater likelihood of biasing the results. Blinding was heavily weighted in the index test domain as recall bias could arise if the symptom of UWL was elicited after the cancer diagnosis. Highest weighting was given to correct classification of cancer in the reference standard domain, as blinding was unnecessary for studies using an objective method. The inclusion of all patients in the final analysis was weighted most in the flow and timing domain to address selection bias, followed by use of an appropriate interval between UWL and cancer to address ascertainment bias, and then reference standard consistency, as the same method was used within each study.

4.3.10. Statistical analyses

Cancer type, population, study design, data source, recruitment period, follow-up period, definition of weight loss (index test), definition of cancer (reference standard), and the inclusion and exclusion criteria of each study was tabulated.

Basic demographic data were presented for each study alongside binary diagnostic accuracy data (2 x 2 tables) grouped by cancer site. A 2 x 2 table was extracted for individual subgroups, where available, and subgroups combined if appropriate.

Subgroups included the method used to define UWL, data source, follow-up period, age-group, and gender.

Accuracy (43) and The Evidence Base of Clinical Diagnosis (44) informed my choice of inferential statistics. I will define them here as I use them throughout this thesis.

4.3.10.1. Sensitivity and specificity

Sensitivity is the proportion of people with cancer who have UWL calculated using the formula $TP/TP+FN$ (Box 4.3.10-1). Specificity is the proportion of people without cancer who do not have UWL calculated using the formula $TN/TN+FP$. A test with 100% sensitivity will correctly identify all patients with disease with no FN results. A test with 100% specificity will correctly identify the all patients without disease with no FP results. For any given test there is typically a trade-off between sensitivity and specificity, meaning as one parameter increases the other decreases.

Box 4.3.10-1. Diagnostic definitions

This box describes the four possible outcomes of applying a diagnostic test. In this case, the test is positive when UWL is present and negative when UWL is absent.

	People with cancer	People without cancer
People with UWL	True Positives (TP) are people who have UWL and have cancer.	False Positives (FP) are people who have UWL but do not have cancer.
People without UWL	False Negatives (FN) are people who do not have UWL but do have cancer.	True Negatives (TN) are people who do not have UWL and do not have cancer.

4.3.10.2. Likelihood ratios

In this thesis, the positive likelihood ratio (PLR) is the ratio between the proportion of people with cancer who have UWL and the proportion of people without cancer who have UWL and is calculated using sensitivity/one-specificity. The negative likelihood ratio (NLR) is the ratio between the proportion of people with cancer who do not have UWL and the proportion of people without cancer who do not have UWL and is calculated using one- sensitivity/specificity.

The discriminatory value of a test (or symptom) is its ability to distinguish the presence of disease from its absence, in this case the ability of UWL to identify underlying cancer. A test has no discriminative value if the PLR or NLR is equal to one. The higher a PLR, and the lower a NLR, the greater the discriminatory value of the test. A rule of thumb is that a test with a $PLR \geq 5$ is good for ruling in disease and a test with a $NLR \leq 0.2$ is good for ruling out disease (45, 46).

4.3.10.3. Positive predictive values

The positive predictive value (PPV) is the proportion of patients with a positive test who have the disease of interest, in this case the proportion of patients with UWL who have cancer. The PPV can also be described as the risk of disease in a patient with a positive test. The UK's National Institute for Health and Care Excellence (NICE) suspected cancer guidance based its recommendations for cancer investigation on clinical situations for which the PPV was $\geq 3\%$ (45, 46).

The PPV (or the posterior odds) is calculated as the prior odds x PLR. Therefore, as the prior odds of disease (or the prevalence) increases so does the PPV. Not all studies report the prevalence of cancer in the included population. This is unproblematic for

large database cohort studies with comprehensive sampling as the cancer prevalence can be derived from the 2 x 2 table. Ascertaining prevalence is more troublesome in smaller cohort studies, due to the questionable representativeness of their sample, and in case-control studies, the participants of which represent a subset of the background population.

Some authors adjust PPVs from case control studies to account for the potentially higher risk of cancer in the consulting population than the background population (47).

Adjustment involves dividing the PPV by the proportion of control patients who consulted during the study period (all cases consulted). Such studies appear to be in the minority and these adjustments are difficult to include in meta-analysis.

Given the importance of calculating accurate PPVs in this context, I explored three methods of estimation (44, 48):

- i. Bayes theorem using the pooled sensitivity, specificity and prevalence derived from meta-analysis of the studies included in this review. I was unable to rely on this option as few studies reported the background prevalence.
- ii. Bayes theorem using the pooled sensitivity and pooled specificity derived from studies included in this review and the incidence of disease using UK data for the corresponding age-groups as reported by Cancer Research UK (CRUK) (49). The limitation with this method is that the national incidence may not represent the incidence in the consulting primary care population who are symptomatic and therefore anticipated to have higher cancer incidence.

- iii. Bivariate meta-analysis of PPVs reported in this review with prevalence included as a co-variate (50). I was unable to rely on this option as reporting of the background prevalence was poor.

A fourth option, to understand whether the PPVs derived from each of the above methods were appropriate for clinical use would have been to conduct Internal-External Cross Validation (IECV) to identify whether the predicted PPVs had good calibration with the reported PPVs (48). This method was not possible as only the minority of studies reported PPVs, some of which were adjusted.

Method ii. was therefore used to calculate PPVs in this chapter.

4.3.10.4. Cumulative PPVs

The cumulative PPV represents the overall risk of cancer in a patient presenting to primary care with UWL. The cumulative PPV is calculated by adding together PPVs derived for each cancer site for which an association with weight loss is found. This method was used in the 2015 NICE guidelines for suspected cancer (22). For a cumulative PPV to remain interpretable (below 100%) data must be extracted for a single cancer outcome for each included patient and the background incidence used to calculate the prior odds of disease should originate from the same background population. In this chapter the highest and lowest cumulative PPVs for men and women were calculated by taking the prior probability (new UK cancer cases reported by CRUK in 2013 (49), calculating the prior odds (prior probability/1-prior probability) and multiplying the prior odds by the highest and lowest PLRs for each cancer site included in this review (44).

4.3.10.5. Meta-analysis

As recommended by Cochrane, a bivariate meta-analysis model was built to calculate pooled estimates for sensitivity, specificity, PLR, and NLR (51) using the Stata *metandi* function which utilises the *xtmelogit* command (52, 53). A bivariate meta-analysis was chosen as it produces summary estimates of sensitivity and specificity with their corresponding 95% confidence intervals (95% CIs) that take into account the heterogeneity between studies (a random effects model) (51). Meta-analysis included: (1) studies reporting individual cancer sites; (2) individual cancer sites where there were four or more studies (e.g. colorectal and pancreas); (3) studies reporting results by gender.

4.3.10.6. Investigations of heterogeneity

The quality assessment identified the most likely sources of heterogeneity were: (1) cancer type; (2) gender; (3) definition of weight loss; (4) data source. For each of these subgroups, a bivariate meta-analysis was performed (51).

4.3.10.7. Sensitivity analyses

To explore whether there were differences in the estimates from high and low quality studies, two subgroup analyses were conducted: one to include studies which had a low risk of bias across all four domains, and a second to include studies which had a low risk of bias across three or four domains.

4.3.10.8. Assessment of reporting bias

Investigation of publication bias in diagnostic accuracy studies is known to be problematic, and so this was not attempted (50, 54, 55).

4.4. Results

4.4.1. Study characteristics

Figure 4.4.1-1 summarises the study selection process.

The 25 included studies were published between 1994 and 2015 with one study conducted in the USA and all others in the UK.

The population ranged from 398 to 2,140,194 participants, the median size 43,791 (Inter Quartile Range (IQR) 8,476-1,013,262).

Table 4.4.1-1 details the characteristics of each included study.

Figure 4.4.1-1. PRISMA flow diagram of study selection

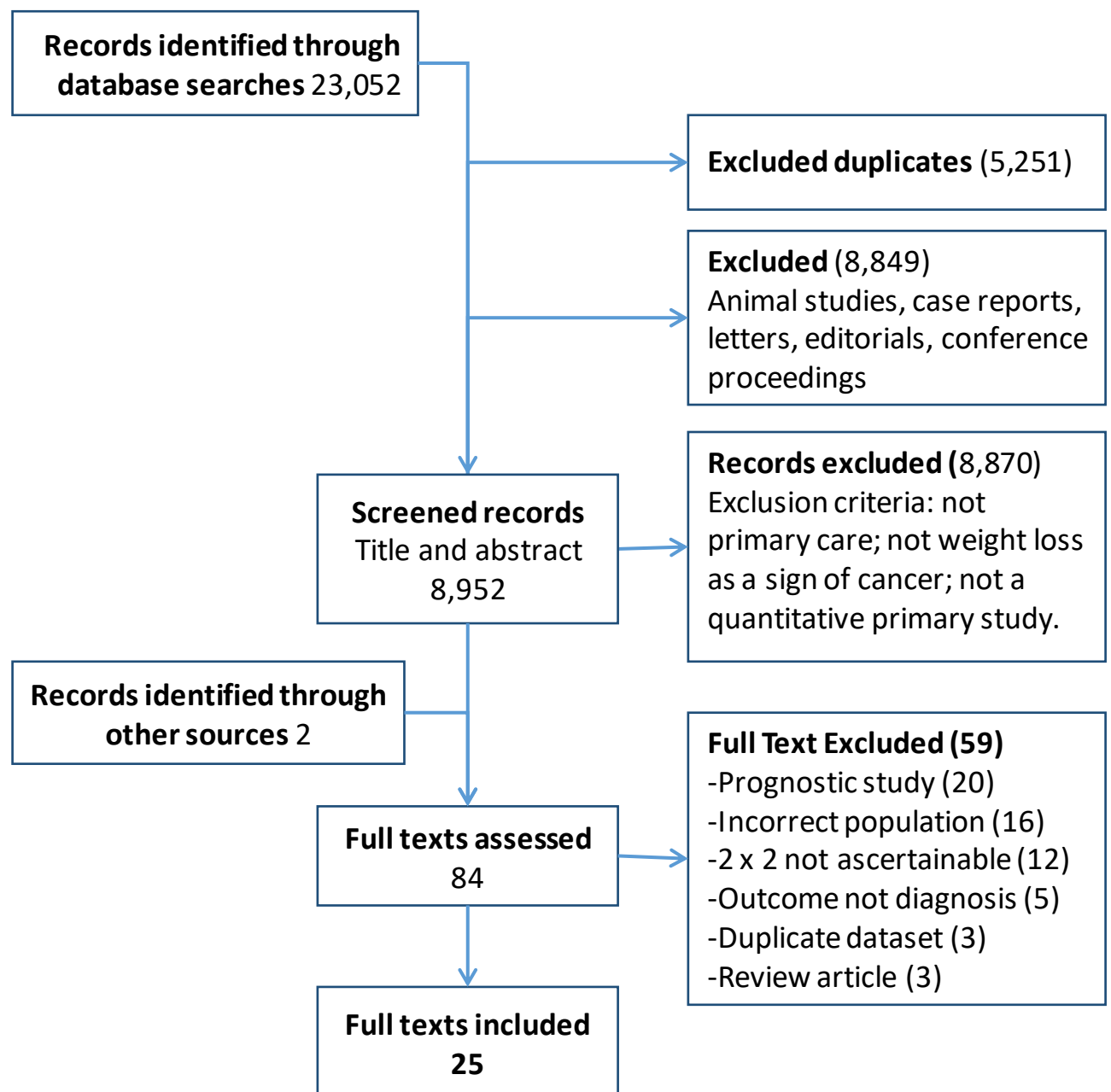


Table 4.4.1-1: Characteristics of the included studies

CANCER Study <i>Population</i>	DESIGN <i>Data Source</i> <i>Recruitment</i> <i>Follow-up</i>	<i>Index Test-Weight loss</i> <i>Reference Standard- Cancer</i>	<i>Inclusion Criteria</i>	<i>Exclusion Criteria (n of participants excluded)</i>
COLORECTAL Collins 2012 (56) <i>Primary care, UK.</i>	COHORT THIN database 01/01/00-30/06/08 2yrs following entry.	Weight loss Read Code. <i>Relevant cancer Read Code.</i>	THIN record starting latest of study start date, registration, first symptom.	Prior colorectal cancer, GP registered <12m, invalid dates, <30/≥85 yrs.
COLORECTAL Curless 1994 (57) <i>Primary and secondary care, North-East England.</i>	CASE-CONTROL (1:1) Structured patient questionnaire 01/1989-30/09/90 1yr pre-diagnosis.	Patient reported "subjective weight loss". <i>Histological diagnosis of cancer.</i>	Cases- consecutive cases identified <2wk of diagnosis by hospital surgical residents. Controls- patients adjacent on GP register for age and sex.	Prior colorectal cancer or inflammatory bowel disease, 'non-white', death (15), outside area (10), no consent (2), unclear diagnosis (1), GP advised against (4), refused (43), unable to contact (6).
COLORECTAL Hamilton 2005 (58) <i>Primary care, Exeter, England.</i>	CASE-CONTROL (1:5) GP record (written and electronic) 1998-2002 (diagnosis) 2yrs pre-diagnosis.	Any mention of weight loss in GP record* <i>Cancer registry, histology reports, and specialist case records.</i>	Cases- identified by local cancer registry, histology reports, or specialist diagnosis. Controls- practice, sex, and age matched to cases, and alive at index diagnosis.	Unobtainable records (96), no entry in the records in 2yrs pre-diagnosis (111), prior colorectal cancer (32), lived outside Exeter at diagnosis (22).
COLORECTAL Hamilton 2009 (59) <i>Primary care, UK.</i>	CASE-CONTROL (1:7) THIN Database 01/2001-07/2006 (diagnosis) 2yrs pre-diagnosis.	Difference between last recorded weight and highest weight in previous 2 yrs. (≥10% or 5-10% weight loss). <i>Cancer recorded in THIN.</i>	Cases- THIN code for colorectal cancer. Controls- practice, sex, year of birth matched.	Prior colorectal cancer, less than 2 yrs. of records before the index date.
COLORECTAL Hippisley-Cox 2012 (60) <i>Primary care, UK</i>	COHORT QResearch Database 01/01/00-30/09/10 2yrs following entry.	Weight loss code. <i>UK diagnostic code in GP record and ONS cause-of-death ICD-9 (153 or 154) or ICD-10 (C18–C21) codes.</i>	EMIS record, latest date of: study start date, 12m after practice registration, first recorded loss rectal bleeding, loss of appetite, weight loss, or abdominal pain.	No Townsend score (195,305), prior colorectal cancer (8,414), rectal bleeding, loss of appetite, weight loss, or abdominal pain in prior 12 m (89,572).

GASTRO-OESOPHAGEAL Collins 2013 (61) <i>Primary care, UK.</i>	COHORT THIN database 01/01/00-30/06/08 2yrs following entry.	Weight loss Read Code. <i>Relevant cancer Read Code.</i>	THIN record starting latest of study start date, registration, first red flag symptom of gastro-oesophageal cancer.	Prior gastro-oesophageal cancer, GP registered <12m, invalid dates, <30/≥85 yrs.
GASTRO-OESOPHAGEAL Hippisley-Cox 2011 (62) <i>Primary care, UK.</i>	COHORT QResearch Database 01/01/00-30/09/10 2yrs following entry.	Weight loss code. <i>UK diagnostic code in GP record and ONS cause-of-death ICD-9 (150 or 151) or ICD-10 (C15 or C16) codes.</i>	EMIS record, latest date of: study start date, 12m after practice registration, first recorded dysphagia, hematemesis, appetite loss, weight loss, or abdominal pain.	No Townsend score (195,305), gastro-oesophageal cancer (1,377), dysphagia, hematemesis, loss of appetite, weight loss, and abdominal pain in prior 12m (89,572).
GASTRO-OESOPHAGEAL Stapley 2013 (63) <i>Primary care, UK.</i>	CASE-CONTROL (1:5) CPRD Database 01/2000-12/2009 >1yr pre-diagnosis.	GP weight loss Read Code. <i>24 gastric & 18 oesophageal Read Codes.</i>	Cases- gastro-oesophageal cancer code. Controls- age, sex and practice matched.	No records <1yr before index date (3,335), metastatic cancer (10), cases with past gastro-oesophageal cancer (28), cases without controls (17), oesophageal cancer used as gastric (131), controls are cases (262), controls without cases (809), duplicate control (427).
LUNG Hamilton 2005 (64) <i>Primary care, Exeter, England.</i>	CASE-CONTROL (1:5) GP record (written and electronic) 1998-2002 (diagnosis) 2yrs pre-diagnosis.	Any mention of weight loss in GP record* <i>Cancer registry, histology reports, and specialist case records.</i>	Cases- identified by local cancer registry, histology reports, or specialist diagnosis. Controls- practice, sex, and age matched to cases, and alive at index diagnosis.	Unobtainable records (77), no records in 2 years pre-diagnosis (98), prior lung cancer (9), lived outside Exeter at diagnosis (15), unconfirmed or atypical (28), metastatic cancer unknown origin (7).
LUNG Iyen-Omofoman 2013 (65) <i>Primary care, UK.</i>	CASE-CONTROL (1:10) THIN database 01/01/00-28/07/09 4-24m pre-diagnosis.	GP weight loss code. <i>Cancer recorded in THIN.</i>	Cases- THIN Code for Lung Cancer. Controls- practice matched to cases.	<1 yr. of records prior to lung cancer diagnosis, <40yrs at index diagnosis (59).
MULTIPLE Men Hippisley-Cox 2013 (66) <i>Primary care, UK.</i>	COHORT QResearch Database 01/01/00-01/04/12 2yrs following entry.	Weight loss code. <i>UK diagnostic code in GP record and ONS cause-of-death ICD-9 or ICD-10 code.</i>	EMIS record for at least a year.	No Townsend score (124,743), red flag symptom in the 12m prior to study entry (91,819).

MULTIPLE Women Hippisley-Cox 2013 (67) <i>Primary care, UK.</i>	COHORT QResearch Database 01/01/00-01/04/12 2yrs following entry.	Weight loss code. <i>UK diagnostic code in GP record and ONS cause-of-death ICD-9 or ICD-10 code.</i>	EMIS record for at least a year.	No Townsend score (132,945), red flag symptom in the 12m prior to study entry (165,310).
MYELOMA Shephard 2015 (68) <i>Primary care, UK.</i>	CASE-CONTROL (1:5) CPRD Database 01/2000-12/2009 >1yr pre-diagnosis.	GP weight loss Read Code. <i>23 Myeloma Read codes.</i>	Cases- multiple myeloma code Controls- age, sex, and practice matched.	No records <1yr before index date (1,201), cases without controls (1), controls with myeloma (8), controls with no record after registration (13), cases with para-proteinaemia >60 days before myeloma code (26), control of para-proteinaemia case (124).
NON-HODGKINS LYMPHOMA Shephard 2015 (69) <i>Primary care, UK.</i>	CASE-CONTROL (1:5) CPRD Database 01/2000-12/2009 >1yr pre-diagnosis.	GP weight loss Read Code. <i>106 Non-Hodgkin's lymphoma Read Code.</i>	Cases- Non-Hodgkin lymphoma code. Controls- age, sex, and practice matched.	Hodgkin's lymphoma (283), control of Hodgkin's lymphoma (1,402), case of mycosis fungoides or Sézary syndrome (147), control of mycosis fungoides or Sézary syndrome (719), no records <1yr before index date (2,018), cases without controls (7), controls with Non-Hodgkin lymphoma (70), controls with no record after registration (26).
OVARIAN Collins 2013 (70) <i>Primary care, UK.</i>	COHORT THIN database 01/01/00-30/06/08 2yrs following entry.	Weight loss Read Code. <i>Relevant cancer Read Code.</i>	THIN record, latest date of: study start date, registration, first red flag symptom of ovarian cancer.	Prior ovarian cancer, GP registered <12m, invalid dates, <30/≥85 yrs.
OVARIAN Hippisley-Cox 2012 (71) <i>Primary care, UK.</i>	COHORT QResearch Database 01/01/00-30/09/10 2yrs following entry.	Weight loss code. <i>UK diagnostic code in GP record and ONS cause-of-death ICD-9 codes (183) or ICD-10 (C56) codes.</i>	EMIS record, starting latest of, study start date, 12m after practice registration, first recorded loss of appetite, weight loss, abdominal pain, abdominal distension, rectal bleeding, or postmenopausal bleeding.	No Townsend score (98,260), prior bilateral oophorectomy (21,099), ovarian cancer (2,079), loss of appetite, weight loss, abdominal pain, abdominal distension, rectal bleeding, or postmenopausal bleeding in prior 12m (55,824).
OVARIAN Lim 2012 (72)	CASE-CONTROL (1:1.2)	Unplanned weight loss including the appearance of weight loss	Cases- 50-79yrs, attending preoperative or medical oncology clinic or admitted for surgery for primary ovarian cancer.	Differential agreement to take part in questionnaire and telephone studies.

<i>Ovarian Cancer Population Study, UK.</i>	Questionnaire, telephone interview, "GP notes" 16/02/06-28/02/08 15m pre-diagnosis.	(questionnaire, telephone interview, or GP code). <i>Independent review of staging, histology, pathology, and case notes by gynae-oncologist.</i>	Controls- attending ovarian screening (postmenopausal) clinic or surgery for a suspected benign adnexal mass.	
PANCREATIC Collins 2013 (73) <i>Primary care, UK.</i>	COHORT THIN database 01/01/00-30/06/08 2yrs following entry.	Weight loss Read Code. <i>Relevant cancer Read Code.</i>	THIN record, starting date latest of: study start date, registration, and first red flag symptom of pancreatic cancer.	Prior pancreatic cancer; GP registered <12m, invalid dates, <30/≥85 yrs.
PANCREATIC Hippisley-Cox 2012 (74) <i>Primary care, UK.</i>	COHORT QResearch Database 01/01/00-30/09/10 2yrs following entry.	Weight loss code. <i>UK diagnostic code in GP record and ONS cause-of-death ICD-9 (157) or ICD-10 (C25) codes.</i>	EMIS record, starting latest of: study start date, 12m after practice registration, first recorded dysphagia, loss of appetite, weight loss, abdominal pain or distension.	No Townsend score (195,305), prior pancreatic cancer (257), dysphagia, loss of appetite, weight loss, abdominal pain, or abdominal distension in prior 12m (77,071).
PANCREATIC Holly 2004 (75) <i>San Francisco Bay 'population'.</i>	CASE-CONTROL Two questionnaires by interview. 1994-2001 5-ys pre-diagnosis.	Patient reported weight loss of >6wk duration. <i>Surveillance, Epidemiology, and End Results database 18–24m after diagnosis.</i>	Cases- pancreatic cancer identified within 1m of diagnosis by North California cancer centre rapid case ascertainment. Controls- random digit dial age (+/- 5yrs) and sex matched (Health Care Financing data supplemented recruitment >65yrs).	Incomplete second questionnaire, non-English speaker, deceased.
PANCREATIC & BILIARY TREE Keane 2014 (76) <i>Primary care, UK.</i>	CASE-CONTROL (1:6) THIN Database 01/01/00-31/12/10 2yrs pre-diagnosis.	GP weight loss code. <i>Cancer recorded in THIN.</i>	Cases- GP practices with acceptable mortality recording and computer usage. Controls- stratified sampling within practice matched by age, sex, year of consultation (controls) or diagnosis (cancer).	<2 yrs. of data prior to the index date.
PANCREATIC Stapley 2012 (77) <i>Primary care, UK.</i>	CASE-CONTROL (1:5) CPRD Database 01/2000-12/2009 >1yr pre-diagnosis.	GP weight loss Read Code. <i>25 Pancreatic cancer Read codes.</i>	Cases- pancreatic cancer code. Controls- age, sex and practice matched.	Cases without controls (2), not a pancreatic primary (10). Controls with pancreatic cancer (64), controls with no case (40), and controls with no data in the year before diagnosis the index date (1,414).

PROSTATE Hamilton 2005 (78) <i>Primary care, Exeter, England.</i>	CASE-CONTROL (1:5) GP record (written and electronic) 1998-2002 (diagnosis) 2yrs pre-diagnosis.	Any mention of weight loss in GP record <i>Cancer registry, histology reports, and specialist case records.</i>	Cases- identified by local cancer registry, histology reports, or specialist diagnosis. Controls- practice, sex, and age matched, and alive at index diagnosis.	Unobtainable records (82), no entry in the records in 2yrs pre-diagnosis (83), prior prostate cancer (27), lived outside Exeter at diagnosis (26), other/unconfirmed (5).
RENAL TRACT Collins 2013 (79) <i>Primary care, UK.</i>	COHORT THIN database 01/01/00-30/06/08 2yrs following entry.	Weight loss Read Code. <i>Relevant cancer Read Code.</i>	THIN record starting latest of study start date, registration, first red flag symptom of renal tract cancer.	Prior renal tract cancer, GP registered <12m, invalid dates, <30/≥85 yrs.
RENAL TRACT Hippisley-Cox 2012 (80) <i>Primary care, UK.</i>	COHORT QResearch Database 01/01/00-30/09/10 2yrs following entry.	Weight loss code. <i>UK diagnostic code in GP record and ONS cause-of-death ICD-9 (188 or 189) or ICD-10 (C64–67) codes.</i>	EMIS record, starting latest of, study start date, 12m after practice registration, first recorded loss of haematuria, appetite loss, weight loss, or abdominal pain.	No Townsend score (195,305), prior renal tract cancer (4,417), haematuria, loss of appetite, weight loss, or abdominal pain in prior 12m (81,332).

UK: United Kingdom; THIN: The Health Improvement Network database; yrs.: years; GP: General Practitioner; m: months; wks: weeks; ONS: Office of National Statistics; ICD: International Classification of Disease; EMIS: Egton Medical Information Systems.; CPRD: Clinical Practice Research Datalink.

4.4.2. Study data sources

Eight studies used routinely collected EHR data from The Health Improvement Network (THIN) database (56, 59, 61, 65, 70, 73, 76, 79), seven from the QCancer database (60, 62, 66, 67, 71, 74, 80), and four from the Clinical Practice Research Datalink (CRPD) (63, 68, 69, 77). These studies utilised the symptom and diagnosis codes physicians use: uncoded “free text” information from the notes was not accessed. Three studies used a combination of written and primary care EHR data coded using the International Classification of Primary Care-2 (58, 64, 78), blinded to the cancer outcome (58, 64, 78). Two used structured patient questionnaires (57, 75) whilst one included data from three sources: patient questionnaire, patient telephone interview, and the primary care EHR (72).

4.4.3. Study design

Thirteen case-control studies and twelve cohort studies were included.

The ratio of cases to controls ranged from 1:1 to 1:10 (57-59, 63-65, 68, 69, 72, 75-78).

Control patients were matched for age (57-59, 63, 64, 68, 69, 75-78), sex (57-59, 63, 64, 68, 69, 75-78), GP practice (58, 59, 63-65, 68, 69, 76-78), consultation year (76) by using adjacency on the GP register (57), using Health Care Financing Administration lists (75), at random using the electronic record (58, 59, 63-65, 68, 69, 76-78), after attending ovarian screening or being referred for a suspected benign adnexal mass (72).

Cohort entry was defined as the first occurrence of weight loss for the exposed group or, for the unexposed, study entry or 12 months after registering with the practice if this was later (56, 60-62, 66, 67, 70, 71, 73, 74, 79, 80). One case-control study, at high risk of ascertainment bias, allowed the occurrence of UWL to occur up to five years prior to the diagnosis of cancer (75).

4.4.4. Unexplained weight loss

There was marked variation in the definitions of UWL used. One study used objective measurements, calculating the difference between in the weight measurement nearest to the cancer diagnosis date and the highest weight in the previous two years (59) – this was the same as the study included in the NICE guidance.

All other database studies defined UWL using a coded entry in the GP EHR (56, 60-63, 65-74, 76, 77, 79, 80). The code lists used to define UWL were not published, and no study described the method used to discriminate UWL from planned weight loss. In three studies “*any mention of weight loss*” was coded by researchers after review of the entire coded and non-coded GP record (58, 64, 78).

Questionnaire studies defined weight loss as “*subjective weight loss*” (57), “*weight loss (unplanned) or the appearance of weight loss*” (72), and “*unintended weight loss ≥ 6 weeks duration*” (75).

4.4.5. Cancer type and stage

I identified positive associations between UWL and ten cancer types: colorectal (56-60); pancreatic (73-75, 77); gastro-oesophageal (61-63); ovarian (70-72); lung (64, 65); renal tract (79, 80); myeloma (68), non-Hodgkins lymphoma (69), pancreatic or biliary tree (76), and prostate (78). Two studies investigated UWL for all cancer types, in men and women (66, 67)

Several methods were used to confirm the diagnosis of cancer. The THIN database and Clinical Practice Research Datalink (CRPD) studies used UK diagnostic Read Codes inputted by GPs (56, 61, 63, 65, 68-70, 72, 73, 76, 77, 79). The QCancer studies used diagnostic codes and Office of National Statistics (ONS) cause-of-death codes (60, 62, 66, 67, 71, 74, 80). Four studies used

regional cancer registry and hospital records (58, 64, 75, 78) and two relied on hospital records only (57, 72). Three studies, in colorectal, pancreatic and ovarian cancer, reported cancer stage (58, 72, 75).

4.4.6. Risk of bias

Figure **4.4.6-1** summarises the QUADAS-2 assessment. Fifteen studies were classified as high risk of bias in one domain (56, 58-65, 68-71, 73, 74, 76-80). Three studies were classified as high risk of bias in more than one domain (57, 72, 75). The main sources of potential bias were: (a) applicability concerns when secondary care cases were matched either with primary care controls (57), using health care financing lists (75), or with outpatients or attendees at screening programmes (72); (b) selection bias in studies using a case-control design, which exaggerates measures of test accuracy (43, 57-59, 63-65, 68, 69, 72, 75-78); (c) inclusion bias as eight studies did not report why not all participants were included in the analyses; and (d) recall bias in three studies using a retrospective questionnaire (57, 72, 75).

Figure 4.4.6-1: Graphical summary of QUADAS-2 assessment of risk of bias and applicability concerns presented as percentages across included studies (n = 25).

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Collins 2012 (56)	+	+	+	+	+	+	+
Collins 2013 (61)	+	+	+	+	+	+	+
Collins 2013 (70)	+	+	+	+	+	+	+
Collins 2013 (73)	+	+	+	+	+	+	+
Collins 2013 (79)	+	+	+	+	+	+	+
Curless 1994 (57)	-	-	+	+	-	+	+
Hamilton 2005 (58)	-	+	+	+	+	+	+
Hamilton 2005 (64)	-	+	+	+	+	+	+
Hamilton 2005 (78)	-	+	+	+	+	+	+
Hamilton 2009 (59)	-	+	+	+	+	+	+
Hippisley-Cox 2011 (62)	+	+	+	+	+	+	+
Hippisley-Cox 2012 (60)	+	+	+	-	+	+	+
Hippisley-Cox 2012 (71)	+	+	+	-	+	+	+
Hippisley-Cox 2012 (74)	+	+	+	-	+	+	+
Hippisley-Cox 2012 (80)	+	+	+	-	+	+	+
Hippisley-Cox 2013 (66)	+	+	+	+	+	+	+
Hippisley-Cox 2013 (67)	+	+	+	+	+	+	+
Holly 2004 (75)	-	-	+	-	-	+	+
Iyen-Omofoman 2013 (65)	-	+	+	+	+	+	+
Keane 2014 (76)	-	+	+	+	+	+	+
Lim 2012 (72)	-	-	+	-	-	+	+
Shephard 2015 (68)	-	+	+	+	+	+	+
Shephard 2015 (69)	-	+	+	+	+	+	+
Stapley 2012 (77)	-	+	+	+	+	+	+
Stapley 2013 (63)	-	+	+	+	+	+	+

 High	 Unclear	 Low

4.4.7. Measures of diagnostic accuracy

Overall, UWL was a primary presenting feature of one in 14 cancer cases. This varied by cancer site ranging from one in five prostate cancers through one in 10 for colorectal, gastro-oesophageal and pancreatic cancers; decreasing to one in 16 biliary tree cancers and one in 25 for myeloma, non-Hodgkins lymphoma and ovarian cancers. One in 33 lung and renal tract cancers had UWL as a presenting symptom. T

Table 4.4.7-1 presents demographic and diagnostic accuracy data for each study. Figure 4.4.7-1 plots each study in Receiver Operator Characteristic (ROC) space using coloured symbols to denote subgroups of cancer site and gender. Table 4.4.7-2 details the diagnostic value of UWL with other clinical and demographic features.

I was unable calculate summary estimates by age-group due to a lack of primary data. Five studies examined diagnostic accuracy by sex. However, there was no significant difference between hazard ratios (HRs) for men and women after adjustment for age, body mass index (BMI) and other clinical features (Table 6).

Table 4.4.7-1: Demographic characteristics of the study population and measures of diagnostic accuracy

Legend: ^c=cases, ^{con}=controls, ^m=mean, ^{sd}=standard deviation, ^M=male, ^F=female, ^{1st}=1st occurrence of weight loss, ^{2nd}=2nd occurrence of weight loss, ^{5-9.9%}=5-9.9% weight loss, ^{>10%}=>10% weight loss, ^{qu}=data collected by questionnaire, ^{tel}=data collected by telephone interview, ^{notes}=data from GP record, ^{4-24m}=4-24 months follow-up, ^{4-12m}=4-12 months follow-up, ^{13-24m}=13-24 months follow-up

Cancer	Year (ref)	Age (yrs.)	Male (%)	2x2 for Weight Loss and Cancer				Weight Loss Prevalence (%)			Diagnostic Odds Ratio (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio (95% CI)
				TP	FP	FN	TN	All	Cases	Non-Cases				
Biliary Tree	2014 (76)	72avg 12sd	47.1	46	302	783	16,890	1.9	5.5	1.8	3.3 (2.4-4.5)	5.5 (3.1-8)	98.2 (98-98.4)	3.2 (2.4-4.2)
Colorectal	2012 (56)	30-84	49.6	215	28,074	3,497	210,3754	1.3	5.8	1.3	4.6 (4-5.3)	5.8 (5.5-6.1)	98.7 (98.7-98.7)	4.4 (3.8-5)
				124 ^M	12,767 ^M	1,912 ^M	104,4962 ^M	1.2	6.1	1.2	5.3 (4.4-6.4)	6.1 (5.7-6.5)	98.8 (98.8-98.8)	5 (4.2-6)
				91 ^F	15,307 ^F	1,585 ^F	1058,792 ^F	1.4	5.4	1.4	4 (3.2-4.9)	5.4 (5.1-5.8)	98.6 (98.6-98.6)	3.8 (3.1-4.7)
	1994 (57)	25-93	56	129	22	144	251	27.7	47.3	8.1	10.2 (6.2-16.8)	47.3 (39.3-55.2)	91.9 (89.3-94.6)	5.9 (5-6.9)
				70<70y	8<70y	80<70y	140<70y	26.2	46.7	5.4	15.3 (7-33.4)	46.7 (35.6-57.7)	94.6 (91.6-97.6)	8.6 (6.9-10.8)
				59>70y	14>70y	64>70y	111>70y	29.4	48.0	11.2	7.3 (3.8-14.1)	48 (36.5-59.4)	88.8 (84.1-93.5)	4.3 (3.3-5.5)
	2005 (58)	>40	50.7	94	92	255	1,652	8.9	26.9	5.3	6.6 (4.8-9.1)	26.9 (20.6-33.3)	94.7 (93.7-95.7)	5.1 (4.2-6.3)
	2009 (59)	>30	N/R	561	1,530	4,916	36,784	4.8	10.2	4.0	2.7 (2.5-3)	10.2 (8.9-11.5)	96 (95.8-96.2)	2.6 (2.4-2.8)
				210 ^{5-9.9%}	852 ^{5-9.9%}	5,267 ^{5-9.9%}	37,462 ^{5-9.9%}	2.4	3.8	2.2	1.8 (1.5-2)	3.8 (2.7-5)	97.8 (97.6-97.9)	1.7 (1.5-2)
				351 ^{>10%}	678 ^{>10%}	5,126 ^{>10%}	37,636 ^{>10%}	2.3	6.4	1.8	3.8 (3.3-4.3)	6.4 (4.9-7.9)	98.2 (98.1-98.4)	3.6 (3.3-4)
	2012 (60)	30-84	50.2	106	13,901	2,497	1,219,043	1.1	4.1	1.1	3.7 (3.1-4.5)	4.1 (3.7-4.4)	98.9 (98.9-98.9)	3.6 (3-4.4)
Pooled estimates for colorectal cancer												13.5 (5.5-29.5)	96.9 (93.9-98.5)	4.4 (3.2-6)
Gastro-oesophageal	2013 (61)	30-84	49.6	218	28,185	1,548	2,110,243	1.3	12.3	1.3	10.5 (9.1-12.2)	12.3 (12-12.7)	98.7 (98.7-98.7)	9.4 (8.2-10.7)
				132 ^M	15,379 ^M	1,052 ^M	1,048,227 ^M	1.5	11.1	1.4	8.6 (7.1-10.3)	11.1 (10.7-11.6)	98.6 (98.5-98.6)	7.7 (6.5-9.2)
				86 ^F	12,806 ^F	496 ^F	1,062,016 ^F	1.2	14.8	1.2	14.4 (11.4-18.1)	14.8 (14.2-15.4)	98.8 (98.8-98.8)	12.4 (10-15.4)
	2013 (63)	≥40	64.2 ^c	615	276	6,856	32,601	2.2	8.2	0.8	10.6 (9.2-12.2)	8.2 (6.4-10)	99.2 (99.1-99.3)	9.8 (9.1-10.6)
	2011 (62)	30-84	50.2	107	9,063	1,236	952,634	1.0	8.0	0.9	9.1 (7.5-11.1)	8 (7.4-8.5)	99.1 (99-99.1)	8.5 (7-10.2)
Lung	2005 (64)	>40	68.8	67	54	180	1,181	8.2	27.1	4.4	8.1 (5.5-12)	27.1 (19.2-35)	95.6 (94.5-96.7)	6.2 (4.9-7.9)
	2013 (65)	>40	49.1	336^{4-24m}	739^{4-24m}	11,738^{4-24m}	119,992^{4-24m}	0.8	2.8	0.6	4.6 (4.1-5.3)	2.8 (1.8-3.8)	99.4 (99.3-99.4)	4.5 (4.1-5.1)
				197 ^{4-12m}	323 ^{4-12m}	11,877 ^{4-12m}	120,408 ^{4-12m}	0.4	1.6	0.3	6.2 (5.2-7.4)	1.6 (0.5-2.7)	99.7 (99.7-99.8)	6.1 (5.3-7)

				139 ^{13-24m}	416 ^{13-24m}	11,935 ^{13-24m}	120,315 ^{13-24m}	0.4	1.2	0.3	3.4 (2.8-4.1)	1.2 (0.3-2)	99.7 (99.6-99.7)	3.3 (2.8-3.9)
Myeloma	2015 (68)	≥40	52.5	107	86	2,596	12,071	1.3	4.0	0.7	5.8 (4.3-7.7)	4 (1.2-6.7)	99.3 (99.2-99.4)	5.6 (4.6-6.8)
NHL	2015 (69)	≥40	51.3	164	115	4,198	1,9353	1.2	3.8	0.6	6.6 (5.2-8.4)	3.8 (1.5-6)	99.4 (99.3-99.5)	6.4 (5.5-7.4)
Ovarian	2013 (70)	30–84	0	35	14,996	700	1,039,087	1.4	4.8	1.4	3.5 (2.5-4.9)	4.8 (4.4-5.1)	98.6 (98.6-98.6)	3.3 (2.4-4.7)
	2012 (71)	30-84	0	22	5,146	516	466,430	1.1	4.1	1.1	3.9 (2.5-5.9)	4.1 (3.5-4.6)	98.9 (98.9-98.9)	3.7 (2.5-5.7)
	2012 (72)	50-78	0	30 ^{qu}	5 ^{qu}	161 ^{qu}	263 ^{qu}	7.6	15.7	1.9	9.8 (3.7-25.8)	15.7 (3.7-27.8)	98.1 (96.8-99.4)	8.4 (6-11.9)
				18 ^{tel}	3 ^{tel}	93 ^{tel}	122 ^{tel}	8.9	16.2	2.4	7.9 (2.3-27.5)	16.2 (0.5-32)	97.6 (95.6-99.6)	6.8 (4.4-10.4)
				5^{notes}	2^{notes}	166^{notes}	225^{notes}	1.8	2.9	0.9	3.4 (0.6-17.7)	2.9 (-9.6-15.4)	99.1 (98.2-100)	3.3 (1.4-7.9)
Multiple	2013 (67)	25-89	0	421	6,453	11,871	648,858	1.0	3.4	1.0	3.6 (3.2-3.9)	3.4 (3-3.9)	99 (99-99)	3.5 (3.2-3.8)
Multiple	2013 (66)	25-89	100	636	5,224	11,277	662,037	0.9	5.3	0.8	7.1 (6.6-7.8)	5.3 (4.8-5.9)	99.2 (99.2-99.2)	6.8 (6.3-7.4)
Pancreatic	2013 (73)	30-84	49.6	82	15,022	536	2,120,322	0.7	13.3	0.7	11 (8.7-13.9)	13.3 (12.9-13.7)	98.6 (98.6-98.6)	9.7 (7.8-12.1)
				56 ^M	13,428 ^M	275 ^M	1,053,833 ^M	1.3	16.9	1.3	16 (12-21.3)	16.9 (16.3-17.6)	98.7 (98.7-98.8)	13.4 (10.3-17.6)
				26 ^F	1,594 ^F	261 ^F	1,066,489 ^F	0.2	9.1	0.1	6.7 (4.4-10)	9.1 (8.6-9.5)	98.5 (98.5-98.5)	6.1 (4.2-9)
	2012 (74)	30–84	50.2	61	9,354	720	961,571	1.0	7.8	1.0	8.7 (6.7-11.3)	7.8 (7.3-8.4)	99 (99-99.1)	8.1 (6.3-10.4)
	2004 (75)	21-85	54	39	7	81	173	15.3	32.5	3.9	11.9 (5.1-27.7)	32.5 (19-46)	96.1 (93.7-98.5)	8.4 (6.2-11.3)
	2014 (76)	71avg 11sd	47.1	294	302	2,496	16,890	3.0	10.5	1.8	6.6 (5.6-7.8)	10.5 (8.1-13)	98.2 (98.1-98.4)	6 (5.4-6.7)
	2012 (77)	≥40	48.0 ^c	353	105	3,282	16,354	2.3	9.7	0.6	16.8 (13.4-20.9)	9.7 (7-12.4)	99.4 (99.3-99.5)	15.2 (13.7-16.9)
<i>Pooled estimates for pancreatic cancer</i>												12.9 (8.2-19.8)	98.6 (97.6-99.2)	9.1 (6.6-12.6)
Prostate	2005 (78)	>40	100	48 ^{1st}	21 ^{1st}	169 ^{1st}	1,059 ^{1st}	5.3	22.1	1.9	14.3 (8.4-24.5)	22.1 (12.3-31.9)	98.1 (97.3-98.8)	11.4 (8.6-15.1)
				9 ^{2nd}	11 ^{2nd}	208 ^{2nd}	1,069 ^{2nd}	1.5	4.1	1.0	4.2 (1.7-10.3)	4.1 (-4.6-12.9)	99 (98.4-99.5)	4.1 (2.1-7.8)
Renal Tract	2013 (79)	30-84	49.6	21	16,016	577	1,065,164	1.5	3.5	1.5	2.4 (1.6-3.7)	3.5 (3.2-3.8)	98.5 (98.5-98.5)	2.4 (1.5-3.6)
	2012 (80)	30–84	50	38	9,243	1,584	956,816	1.0	2.3	1.0	2.5 (1.8-3.4)	2.3 (2-2.7)	99 (99-99.1)	2.4 (1.8-3.4)
Pooled estimates for all cancer sites combined												9 (6.4-12.6)	98.5 (98-98.8)	5.9 (4.8-7.3)

Figure 4.4.7-1: Receiver Operating Characteristic (ROC) plot of diagnostic value of unexplained weight loss for different cancers.

The size of each symbol is proportional to the sample size with the height proportional to the number of patients with cancer and the width to those without. It is clear that a high specificity comes at the cost of a low sensitivity.

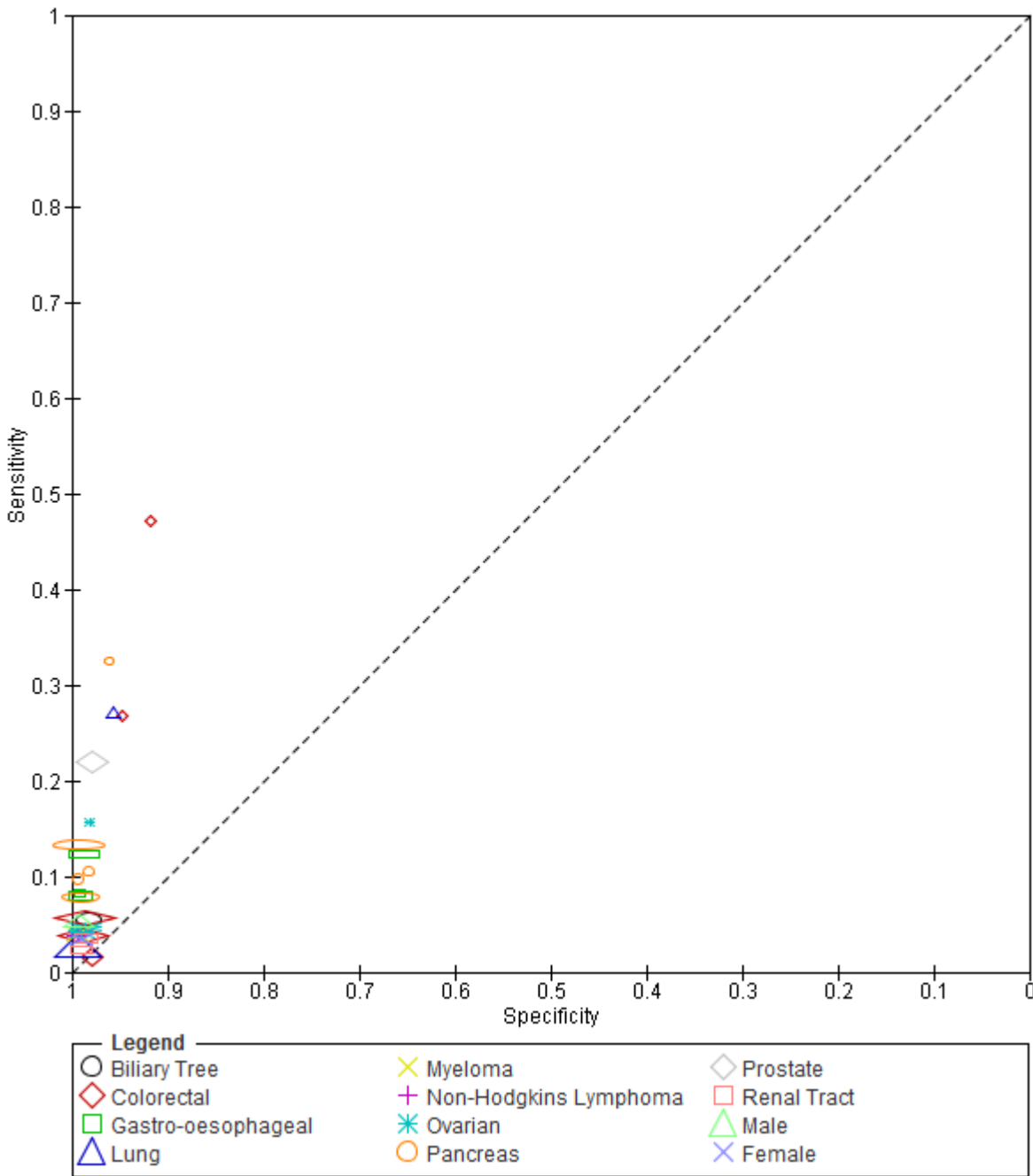


Table 4.4.7-2: Measures of diagnostic association between unexpected weight loss and cancer after adjustment for other predictors.

Cancer	Author (year)	SYMPTOM PAIRS		MULTIIVARIATE ANALYSIS		
		Weight loss combined with:	PPV % (95% CI)	OR/HR (95% CI)	Included variables	
COLORECTAL	Hamilton (2005b)	Second weight loss	1.4 (0.8-2.6)	OR 2.7 (1.7-4.6, p<0.001)	Rectal bleeding, abdominal pain, constipation, diarrhoea, abnormal rectal exam, tender abdomen, positive faecal occult blood test, low haemoglobin.	
		Constipation	3.0 (1.7-5.4)			
		Diarrhoea	3.1 (1.8-5.5)			
		Rectal bleeding	4.7			
		Abdominal pain	3.4 (2.1-6.0)			
		Abdominal tenderness	6.4			
		Abnormal rectal exam	7.4			
		Haemoglobin 10-13g/dl	1.3 (0.7-2.6)			
	Haemoglobin <10g/dl	4.7				
	Hamilton (2009)			OR 1.2 (0.99-1.5) - 5-.9.9% WL OR 2.5 (2.1-3.0) - >10% WL	Rectal bleeding, change in bowel habit, abdominal pain, diarrhoea, constipation.	
Hippisley-Cox (2012c)			HR 7.70 (5.32-1.1) - Female ^d HR 4.07 (3.42-4.85) - Male ^d	Age, alcohol intake, family history of gastrointestinal cancer, haemoglobin <11 in last 12m, rectal bleeding, abdominal, pain, appetite loss, change in bowel habit.		
GASTRO-OESOPHAGEAL	Hippisley-Cox (2011b)			HR 3.97 (3.06 to 5.16) - Female ^d HR 5.64 (4.67 to 6.81) - Male ^d	Age, smoking status, dysphagia, abdominal pain, appetite loss, hematemesis, haemoglobin <11g/dl in last 12m.	
	Stapley (2013)	>55yrs	Low Haemoglobin	1.0 (3.4-1.3)	OR 8.9 (7.1-11.2)	Dysphagia, epigastric pain, dyspepsia, reflux, nausea or vomiting, abdominal pain, chest pain, constipation, thrombocytosis, low haemoglobin, low mean cell volume, leucocytosis, raised inflammatory markers, abnormal liver enzymes, raised cholesterol.
			Raised platelets	1.8 (1.1-3.0)		
			Constipation	1.1 (0.8-1.7)		
			Dysphagia	9.2 (4.4-22.7)		
			Chest pain	1.1 (0.7-1,8)		
			Abdominal pain	1.4 (0.9-2.2)		
			Nausea vomiting	2.8 (1.7-4.8)		
			Dyspepsia	2.1 (1.3-3.5)		
			Epigastric pain	4.2 (1.8-11.0)		
Reflux	3.1 (1.5-6.7)					
LUNG	Hamilton (2005)	Second weight loss	1.2 (0.7-2.3)	OR 4.3 (2.2-8.2, p<0.001)	Loss of appetite, haemoptysis, dyspnoea, fatigue, chest pain, second attendance with cough, finger clubbing, thrombocytosis, abnormal spirometry, smoking status	
		Cough	1.8 (1.1-2.9)			
		Fatigue	1.0 (0.6-1.7)			
		Dyspnoea	2.0 (1.2-3.8)			
		Chest pain	1.8 (1.0-3.4)			
		Appetite loss	2.3 (1.2-4.4)			
		Thrombocytosis	6.1			
		Abnormal spirometry	1.5			
		Haemoptysis	9.2			

	Hippisley-Cox (2011)			HR 4.52 (3.8-5.38)- Female ^d HR 6.09 (5.33-6.95)- Male ^d	Age, BMI, haemoptysis, appetite loss, new cough in last 12m, haemoglobin<12g/dl in last 12m, smoking status, prior cancer diagnosis, COPD, Townsend score.	
	Iyen-Omofoman (2013)			OR 2.66 (2.16-3.29, p<0.001)- 4-12m	Age, sex, Townsend quintile, smoking, number of other GP consults, cough, haemoptysis, dyspnoea, lower respiratory tract infection, non-specific chest infections, COPD, chest/shoulder pain, hoarse voice, upper respiratory tract infection..	
MULTIPLE SITES- MEN	Hippisley-Cox (2013)			HR 2.12 (1.81-2.49)- Prostate HR 3.4 (2.72-4.24)- Blood HR 3.03 (2.52-3.63)- Colorectal HR 4.35 (3.61-5.24)- GastrOesph HR 3.95 (3.46-4.51)- Lung HR 2.87 (2.45-3.37)- Other HR 7.74 (6.00-9.99)- Pancreatic HR 1.98 (1.46-2.68)- Renal tract	Symptoms for each cancer and fractional polynomial terms for age and BMI, smoking status, previous diagnosis of cancer, a naemia, Townsend score, alcohol, family history of prostate cancer, family history of gastrointestinal cancer, chronic Pancreatitis, chronic obstructive airways disease and type 1 and type 2 diabetes.	
MULTIPLE SITES- WOMEN	Hippisley-Cox (2013b)			HR 1.61 (1.1-2.36)- Ovarian HR 2.45 (1.88-3.19)- Blood HR 2.89 (2.3-3.41)- Colorectal HR 3.42 (2.65-4.41)- GastrOesph HR 3.12 (2.64-3.69)- Lung HR 3.02 (2.57-3.55)- Other HR 4.85 (3.68-6.39)- Pancreatic HR 2.16 (1.49-3.14)- Renal tract	Symptoms for each cancer and fractional polynomial terms for age and BMI, smoking status, Townsend score, alcohol, previous Cancer diagnosis, a naemia, family history of breast cancer, family history of gastrointestinal cancer, family history of ovarian cancer, benign breast disease, chronic pancreatitis, type 1 diabetes, type 2 diabetes, endometriosis, endometrial hyperplasia or polyps, fibroids, polycystic ovarian disease, rheumatoid arthritis, systemic lupus erythematosus, HIV or AIDS, oral contraceptive use, and hormone replacement therapy.	
MYELOMA	Shephard (2105)	>60yrs	Shortness of breath	0.1 (0.1-0.3)	OR 3.0 (2.0-4.5)	Back pain, chest pain, chest infection, shortness of breath, nausea, fracture, joint pain, combined bone pain, rib pain, nosebleeds, cytopaenia, raised inflammatory markers, raised creatinine, and raised mean cell volume, hypercalcaemia.
	Chest Infection		0.3			
	Chest Pain		0.1			
	Low Platelets		0.5			
	Leukopenia		0.5			
	Low Haemoglobin		0.4 (0.9-0.7)			
	Fracture		0.3			
	Nausea		0.3			
	Nosebleeds		0.3			
	Back pain		0.5			
	Raised Mean Cell Volume		0.6			
	Raised Inflammatory Markers		0.6 (0.3-1.1)			

			Raised creatinine	0.5		
			Hypercalcaemia	0.5		
NON-HODGKINS LYMPHOMA	Shephard (2015b)	>60yrs	Infection	0.4 (0.2-0.6)	OR 3.2 (2.3-4.4)	Infection, lymphadenopathy, abdominal pain, mass, shortness of breath, head and neck mass, fatigue, constipation, vomiting and nausea, indigestion, weight loss, second back pain, malaise, low full blood count, raised inflammatory markers, raised liver function tests, leucocytosis, macrocytosis, microcytosis, raised gamma globulin.
			Shortness of breath	0.4 (0.2-0.8)		
			Indigestion	0.3 (0.1-0.7)		
			Constipation	0.4 (0.2-0.9)		
			Back pain x2	2.3		
			Fatigue	0.9		
			Nausea	0.6 (0.3-1.3)		
			Vomiting + nausea	0.6 (0.4-1.1)		
			Microcytosis	1.4		
			Leucocytosis	1.0 (0.5-2.0)		
			Abdominal pain	0.9		
			Mass	2.2		
			Lymphadenopathy	>10		
			Raised liver function tests	1.5 (0.8-2.8)		
			Macrocytosis	0.2		
			Raised gamma globulin	3.5		
			Low Faecal blood count	0.9 (0.6-1.3)		
			Raised inflammatory markers	0.8 (0.6-1.3)		
OVARIAN	Hippisley-Cox (2012)				HR 2.0 (1.3-3.1)^d	Age, family history of ovarian cancer, haemoglobin <11g/dl in last 12m, abdominal pain, abdominal distension, appetite loss, rectal bleeding, postmenopausal bleeding.
	Lim (2012)				OR 2.9 (0.9-9.9)^a	All other symptoms
PANCREATIC	Hippisley-Cox (2012d)				HR 3.27 (2.35-4.56) - Female^d HR 12.5 (7.84-19.9) - Male^d	Age, smoking status, type II diabetes, chronic pancreatitis, appetite loss, abdominal pain, abdominal distension, dysphagia, constipation in last 12m.
	Holly (2004)				OR 12 (5.2-28)	Age and sex.
	Stapley (2012)	>60yrs	Weight loss	>10	OR 15.0 (11-22, p<0.001)	Abdominal pain, nausea and vomiting, constipation, malaise, diarrhoea, back pain, jaundice, diabetes.
			Jaundice	31.6		
			Abdominal pain	2.5 (1.5-4.4)		
			Nausea + vomiting	2.2 (1.1-4.6)		
			Malaise	0.9 (0.4-2.1)		
			Constipation	1.5 (0.8-3.0)		
			Diarrhoea	2.7		

			New diabetes	1.6 (1.0-2.9)		
			Back pain	2.0 (1.0-4.3)		
PANCREATIC AND BILIARY	Keane (2014)				OR 6.6 (5.54-7.86, p<0.001) - Panc OR 3.17 (2.32-4.34, p<0.001) - BTC	Age, gender, time period, social deprivation.
PROSTATE	Hamilton (2006)	Second weight loss	2.1		OR 9.2 (2.7-31, p<0.001) - second WL OR 4.5 (1.2-17, p=0.029) – excluding days 1-180 pre-diagnosis	Urinary retention, impotence, frequency, hesitancy, nocturia, haematuria, rectal examination.
		Nocturia	12			
		Benign rectal exam	9.4			
		Frequency/urgency	1.8			
RENAL-TRACT	Hippisley-Cox (2012b)				HR 2.56 (1.75-3.74) - Female ^d HR 5.67 (3.2-10) - Male ^d	Age, smoking status, history of cancer at another site, haematuria, appetite loss, abdominal pain, haemoglobin<11g/dl.

PPV: Positive predictive value; 95%CI: 95% confidence interval; OR: Odds ratio; HR: Hazard ratio; WL: Weight loss; m: months; yrs.: years; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; GP: General practitioner; GastrOesph: Gastro-Oesophageal; Panc: Pancreatic; BTC: Biliary tree cancer.

4.4.7.1. Cancer type and cancer stage

The sensitivity of UWL to detect cancer ranged from 2% to 47% across cancer types with specificity spanning 92% to 99% (Table 4.4.7-1 & Figure 4.4.7-1). Pooled sensitivity was 9% (95% CI 6-13%) and pooled specificity was 99% (95% CI 98-99%). Removing the studies at high risk of bias in more than one QUADAS-2 domain did not significantly alter the pooled results in any of the analyses.

Only colorectal and pancreatic cancer had sufficient data for separate analyses (Table 4.4.7-1). The pooled sensitivity for colorectal cancer was 14% (95% CI 6-30%) and pooled specificity 97% (95% CI 94-99%). The pooled sensitivity for pancreatic cancer was 13% (95% CI 8-20%) and pooled specificity 99% (95% CI 98-99%).

Twenty studies adjusted for covariates including potential confounders, such as age, and symptoms known to be predictors of cancer, for example rectal bleeding in colorectal cancer (Table 4.4.7-2). Adjustment left the diagnostic odds ratios of cancer diagnosis (DORs) unchanged in all but three case-control studies in which they were statistically significantly reduced (58, 59, 65). HRs ranged from 1.6 for ovarian cancer to 12.5 for pancreatic cancer across the cohort studies. For all studies with data available, adjustment for other symptoms of cancer did not remove the statistically significant association between UWL and cancer diagnosis.

No study reported the diagnostic value of UWL according to cancer stage.

4.4.7.2. Positive predictive values

PPVs for UWL ranged from 0.0% for biliary tract cancer to 3.3% for prostate cancer (Table 4.4.7.2-1). One study reported higher PPVs for colorectal cancer in people aged over 70 years old (1.7%) compared to those younger than 70 years old (0.4%) (57).

Six studies reported the PPV for UWL paired with another clinical feature with values spanning 0.1% for chest pain in myeloma to 31.6% for jaundice in pancreatic cancer (Table 4.4.7-2).

UWL with another clinical feature yielded a PPV greater than: UWL alone; the paired clinical feature alone; or by adding together the individual PPVs.

Cumulative PPVs were calculated by age-group (Table 4.4.7.2-2). The more conservative estimates, using the lowest PLRs, produced a cumulative PPV of 3.0% in women aged over 60 years old and 10.5% for men in the same age group, meeting the threshold for investigation used in the 2015 NICE guidelines (3%) (22). Using the highest reported PLRs for each cancer site produced cumulative PPVs of 6.7 % and 14.2% for those aged over 60 years old (women and men respectively). The excess in men was largely due to the contribution of prostate cancer with its relatively high PLR and incidence.

After removing prostate cancer from the analysis, the PPV for men aged over 60 years fell to 7.8%, still exceeding the threshold for investigation (Table 4.4.7.2-3).

Table 4.4.7.2-1: Positive predictive values (PPVs) of unexplained weight loss for cancer diagnosis

Cancer	Study	Age (yrs.)	Prior probability	Prior Odds	PLR	Posterior Odds	Posterior probability	PPV (%)
Biliary Tract	Keane (2014)	60-85*	0.00003580	0.0000358	3.2	0.000115	0.00011	0.01
Colorectal	Collins (2012)	30-84	0.00106582	0.0010670	4.4	0.004695	0.00467	0.47
	Curless (1994)	25-93	0.00101999	0.0010210	5.9	0.006024	0.00599	0.60
	Hamilton (2005b)	>40	0.00151671	0.0015190	5.1	0.007747	0.00769	0.77
	Hamilton (2009)	>30	0.00119001	0.0011914	2.6	0.003098	0.00309	0.31
	H-Cox (2012c)	30-84	0.00106582	0.0010670	3.6	0.003841	0.00383	0.38
Gastro-Oesophageal	Collins (2013d)	30-84	0.00034577	0.0003459	9.4	0.003251	0.00324	0.32
	Stapley (2013)	≥40	0.00049300	0.0004932	9.8	0.004834	0.00481	0.48
	H-Cox (2011b)	30-84	0.00034577	0.0003459	8.5	0.002940	0.00293	0.29
Lung	Hamilton (2005a)	>40	0.00142564	0.0014277	6.2	0.008852	0.00877	0.88
	I-Omofoman (2013)	>40	0.00142564	0.0014277	4.5	0.006425	0.00638	0.64
Myeloma	Shephard (2015a)	≥40	0.00016262	0.0001627	5.6	0.000911	0.00091	0.09
NHL	Shephard (2015b)	≥40	0.00039494	0.0003951	6.4	0.002529	0.00252	0.25
Ovarian	Collins (2013c)	30-84	0.00032507	0.0003252	3.3	0.001073	0.00107	0.11
	H-Cox (2012a)	30-84	0.00032507	0.0003252	3.7	0.001203	0.00120	0.12
	Lim (2012)	50-79	0.00046979	0.0004700	3.3	0.001551	0.00155	0.15
Pancreatic	Collins (2013b)	30-84	0.00020084	0.0002009	9.7	0.001949	0.00194	0.19
	H-Cox (2012d)	30-84	0.00020084	0.0002009	8.1	0.001627	0.00162	0.16
	Holly (2004)	30-85	0.00020084	0.0002009	8.4	0.001687	0.00168	0.17
	Keane (2014)	60-84**	0.00049668	0.0004969	6	0.002982	0.00297	0.30
	Stapley (2012)	≥40	0.00028846	0.0002885	15.2	0.004386	0.00437	0.44
Prostate	Hamilton (2005c)	>40	0.00297681	0.0029857	11.4	0.034037	0.03292	3.29
Renal Tract	Collins (2013a)	30-84	0.00047394	0.0004742	2.4	0.001138	0.00114	0.11
	H-Cox (2012b)	30-84	0.00047394	0.0004742	2.4	0.001138	0.00114	0.11

*Mean: 72years (standard deviation 12 years), **Mean 71 years (standard deviation 11 years) PLR: Positive likelihood ratio; PPV: positive predictive value; Yrs.: years.

Table 4.4.7.2-2: Cumulative Positive Predictive Values (PPVs) across all cancer sites

	Gender	Age-Group (years)														
		40+	50+	60+	70+	80+	90+	40-49	50-59	60-69	70-79	80-89	90+	40-59	60-79	80+
LOWEST LRs from SR	<i>FEMALE</i>	1.6	2.2	3.0	3.9	4.4	4.0	0.2	0.8	1.9	3.5	4.6	4.0	0.7	2.5	4.4
	<i>COMBINED</i>	5.2	7.2	10.0	12.7	13.5	13.9	0.4	2.2	7.2	12.2	13.5	13.9	1.2	9.2	13.5
	<i>MALE</i>	5.4	7.5	10.5	13.7	15.0	16.1	0.4	2.2	7.5	13.0	14.9	16.1	1.3	9.6	15.0
HIGHEST LRs from SR	<i>FEMALE</i>	3.6	5.0	6.7	8.7	9.9	8.4	0.5	1.7	4.2	7.8	10.5	8.4	1.3	5.7	9.9
	<i>COMBINED</i>	7.3	10.1	14.0	18.1	19.6	19.1	0.7	3.2	9.8	17.0	19.9	19.1	1.8	12.6	19.6
	<i>MALE</i>	7.3	10.1	14.2	18.8	21.3	22.3	0.6	3.1	9.8	17.5	21.1	22.3	1.8	12.8	21.3

Table 4.4.7.2-3: Cumulative Positive Predictive values (PPVs) across all cancer sites excluding prostate cancer

	Gender	Age-Group (years)														
		40+	50+	60+	70+	80+	90+	40-49	50-59	60-69	70-79	80-89	90+	40-59	60-79	80+
LOWEST LRs from SR	<i>FEMALE</i>	1.6	2.2	3.0	3.9	4.4	4.0	0.2	0.8	1.9	3.5	4.6	4.0	0.7	2.5	4.4
	<i>COMBINED</i>	1.9	2.6	3.5	4.7	5.4	4.8	0.3	0.9	2.3	4.2	5.6	4.8	0.6	3.0	5.4
	<i>MALE</i>	2.1	2.9	4.1	5.7	7.0	7.0	0.3	0.9	2.5	4.9	7.0	7.0	0.6	3.5	7.0
HIGHEST LRs from SR	<i>FEMALE</i>	3.6	5.0	6.7	8.7	9.9	8.4	0.5	1.7	4.2	7.8	10.5	8.4	1.3	5.7	9.9
	<i>COMBINED</i>	4.1	5.5	7.6	10.0	11.6	10.0	0.6	1.9	4.8	9.0	12.0	10.0	1.2	6.5	11.6
	<i>MALE</i>	4.0	5.6	7.8	10.8	13.3	13.2	0.5	1.8	4.9	9.5	13.3	13.2	1.1	6.6	13.3

PPV 1-2% (yellow) and 2-3% (amber) NICE suggests GPs consider primary care testing, >3% (red) NICE recommend referral for specialist review or definitive investigation if the investigation is available to the GP. The combined analysis includes: colorectal, gastro-oesophageal, lung, multiple myeloma, non-Hodgkin lymphoma, ovarian, pancreatic, prostate and renal tract cancer. LR: likelihood ratio; SR: systematic review

4.5. Discussion

4.5.1. Summary of findings

This review has confirmed that patients presenting to primary care with UWL are at higher risk of having cancer than patients without recorded weight loss. The ten cancers found to be positively associated with UWL were prostate, colorectal, lung, gastro-oesophageal, pancreatic, non-Hodgkin's lymphoma, ovarian, multiple myeloma, renal tract, and biliary tree. Across these cancer sites, sensitivity ranged from 2% to 47% and specificity from 92% to 99%. The pooled sensitivity was 9% (95% CI 6-13%) and the pooled specificity 99% (95% CI 98-99%). The cumulative risk of cancer in men and women with UWL aged between 60-79 years and over 80years old exceeds the risk threshold for urgent investigation set out in NICE guidelines (22). The risk of cancer associated with UWL increases with age and when it presents alongside another clinical feature suggestive of cancer.

4.5.2. Strengths & weaknesses

This is the only review of UWL as a feature of cancer in non-specialist settings. A broad search strategy interrogated large electronic databases. Cumulative PPVs were calculated for the first time for UWL across ten cancer sites by using high quality national cancer incidence data.

There are important weaknesses, however. Foremost, no clarification can be made about the magnitude of UWL associated with cancer diagnosis. Only one study used objective measurements to define UWL and it may suffer from misclassification due to missing weight measurement data (59, 81).

Most other studies defined UWL using coding, which is prone to recording bias. This occurs when GPs preferentially code the "alarm" features they consider to support their working

diagnosis, resulting in inflated PPVs (82, 83). For example, the inclusion of free-text data in a study by Price et al. reduced the PPV of jaundice for pancreatic cancer from 12.8% (95%CI 7.3-21.6) to 6.3% (95%CI 4.5 - 8.7), and visible haematuria for bladder cancer from 4.0% (95%CI 3.5 - 4.6) to 2.9% (2.6 - 3.2) (82). GPs use free-text to amplify the clinical narrative after coding “alarm” symptoms, meaning that for some patients the complete details of a clinical feature can remain hidden, invisible to analyses solely using symptom codes (82). Low-risk-but-not-no-risk vague symptoms of cancer, such as abdominal pain or cough, have high prevalence in primary care. However they are coded less frequently in the EHR and are less likely to prompt clinicians to refer patients with these symptoms for urgent investigation (82, 84). However, no reports were found investigating the influence of recording bias on the prevalence of UWL. From the colorectal cancer studies included in this review, the prevalence of UWL was highest when defined as *“any mention of weight loss”* in the GP record (8.9%), intermediate when objective weight measurements were used (4.8%), and lowest when defined by read coding alone (1.1%) (58-60).

There were insufficient data to describe the grade or stage of cancer diagnosed in patients with UWL and how this compares with cancer in patients presenting without UWL. These important questions remain to be addressed.

It is clear from this review that the methodological quality of a study impacts the estimates of diagnostic accuracy it produces: sensitivity was higher in studies at risk of recall bias; PPVs were higher in case-control studies compared to cohort studies reporting the same tumour site; and the calculation and interpretation of pooled estimates was limited by the heterogeneity in study quality. One study, for example, showed that UWL was reported more frequently when data were collected by questionnaire or telephone interview compared to using only a coded entry in the electronic record (72). Collecting data on UWL by

questionnaire increased the sensitivity and decreased specificity compared to using only coded GP data.

All but one study used English data. This is likely as a result of the sustained focus from major cancer research funders in England on diagnosing cancer earlier in symptomatic patients attending primary care to improve national cancer outcomes. The focus in other developed nations, such as the US, has been to invest in cancer screening for asymptomatic people. Due to the aforementioned biases, without repeating these studies using EHR data from other countries, it is unclear how generalisable these results are to other primary care settings.

An important limitation to explore later in this thesis is the extent to which ascertainment bias is a limitation of the study designs used to investigate the association between UWL and cancer diagnosis. Most studies included in this review used an index test and reference standard within a two-year period. Two studies have previously reported that “serendipitous” asymptomatic cancers are diagnosed within a two year window when symptoms (not caused by cancer) are investigated (40, 41). Furthermore the assumption that, *“a 2-year period represents the period of time during which existing cancers are likely to become clinically manifest”* (16, 85) does not allow that the predictive value of a given symptom may temporally vary before diagnosis.

4.5.3. Findings in context

Other investigators have reviewed the symptoms of single cancer sites (86-91). All of these studies were included in this review except where concerns existed over the study population (86, 87, 90) or inadequate reporting of 2 x 2 data (91) and additional studies were included post-dating their searches (65). No previous reviews of symptoms presenting to primary care

in association with myeloma, non-Hodgkin's lymphoma, ovarian, or prostate cancer were identified.

4.5.4. Implications for research

To overcome the limitations outlined above, the ideal method to ascertain the diagnostic value of UWL (or any other clinical feature relevant to multiple cancer types) in primary care would be a prospective cohort study. The prospective design would overcome the biases observed in the studies included in this review. However, as the incidence of cancer (and UWL) is low in primary care, a study powered to investigate all symptoms relevant to all cancers would have to be prohibitively large.

There is more insight to be gained from conducting historical cohort studies using routinely collected EHR datasets (66, 67, 92-94). Such studies could (1) ascertain a prevalence for UWL based on coded, non-coded, and numeric data; (2) confirm cancer utilising the clinical record (coded and non-coded) and linkages to national cancer registries; (3) report 2 x 2 data for UWL in combination with other clinical features; (4) report diagnostic intervals and longer-term outcomes. Research is also required to understand the drivers of weight recording in primary care, and the extent of UWL that prompts a GP to code it.

4.5.5. Clinical Implications

This review suggests that patients aged 60 years or older presenting to primary care with UWL that prompts a clinical record entry warrant rapid investigation for possible cancer, potentially across multiple possible sites. As a symptom of cancer, recorded UWL has the second highest risk after rectal bleeding in colorectal cancer (86), haemoptysis in lung (64), rib pain in myeloma (68), jaundice in pancreatic (90), and haematuria in renal tract (79); and third

highest in non-Hodgkin's lymphoma (69) and gastro-oesophageal cancer (61-63). Additional symptoms in combination with UWL strengthen these associations.

The low sensitivity for UWL reflects the clinical reality that some cancers lead to weight loss whilst many more do not. Understanding the distribution of cancer sites in patients with UWL and cancer may inform the sequencing of investigations in this group. The low sensitivity also demonstrates that the absence of UWL cannot be used to rule out cancer. The high specificity for UWL suggests that there are very few false positives by the time a GP suspects cancer enough to record it. This may reflect patients only attending primary care once UWL is marked. Alternatively, it may represent clinicians only coding the symptom after conducting simple investigations to rule out other causes of UWL.

It is probable that when GPs choose to code weight loss this decision reflects their belief that the symptom is important. This may be based on additional symptoms or physical findings which may themselves represent an increased risk for cancer. Thus, some of the risk of cancer associated with coded loss of weight may represent a broader clinical assessment. Arguably this is helpful as my results clearly show that coded weight loss warrants investigative action. If EHR clinical systems were designed to prompt the clinician to consider cancer whenever they enter a weight loss code, this may lead to an expedited diagnosis.

4.6. Conclusion and next steps.

In this chapter I have reported the findings from a review of the published literature about UWL as a predictor of cancer in primary care. In Chapter Five I aim to understand whether weight measurements are recorded sufficiently enough in NHS primary care to allow them to be used to define weight loss instead of weight loss being defined using coding that gives no sense of the magnitude of UWL.

5. Determinants and extent of weight recording in UK primary care: an analysis of five million adults' electronic health records from 2000 to 2017

5.1. Background to this chapter

In Chapter Four, the majority of studies using electronic health records (EHR) data to study the association between unexpected weight loss (UWL) in primary care and cancer diagnosis used clinical codes to define weight loss. Only one study used weight measurements, comparing the current weight to the highest recorded in the preceding two years. This time interval could mean the change in weight could be an under- or over-estimate (95). No source of comprehensive data on weight recording in primary care could be identified to understand whether weight recordings could be reliably used to define UWL.

5.2. Objectives

The objectives of Chapter Five are to characterise:

- which patients attending UK primary care have had their weight recorded,
- how frequently weight measurements are recorded and this process is repeated,
- by whom, and in relation to which clinical events, symptoms, and diagnoses is weight recorded.

5.3. Method

5.3.1. Clinical Practice Research Datalink

The Clinical Practice Research Datalink (CPRD) GOLD database was accessed for this analysis. The CPRD is an ongoing primary care database of anonymised EHR data covering 6.9% of the UK population and representative in terms of age, sex and ethnicity (96). To gain access to the datalink, a structured protocol was submitted that also covered all of the CPRD studies included in this thesis to the Independent Scientific Advisory Committee (ISAC) of CPRD. After being granted approval, the protocol was published in BMC Diagnostic and Prognostic Research (34).

5.3.2. Stata software training

I was unfamiliar with using the statistical software Stata to analyse large CPRD datasets as this was the first study of this type I had conducted. I was therefore grateful to work with Dr Sarah Lay-Flurrie (SLF), a statistician experienced at using this statistical software to manage and analyse CPRD datasets. I designed and project managed the study, and developed the code lists used to define covariates. I learnt from discussions with SLF and her Stata code as she managed and analysed the data. By also conducting smaller CPRD analyses and attending several courses on the analysis of large datasets, I progressed to being able to conduct the data management and statistical analysis reported in the following chapters alone.

5.3.3. Study Population

Adult patients (aged ≥ 18 years) were included for the study period of January 1st 2000 and December 31st 2017. Patients were eligible for inclusion in this analysis if they had at least one day of research quality registration as defined by the CPRD, at least one face-to-face

consultation with a healthcare professional during the study period, and were eligible for linkage to the National Cancer Registration and Analysis Service (NCRAS) cancer registry, practice and patient level Index of Multiple Deprivation (IMD) data and Office of National Statistics (ONS) mortality data. Patients entered the study on the latest of either: their date of registration with the GP practice, the date their GP's practice data were assessed to be up-to-standard, and the date study start date. Patients left the study on the earliest of: the date of de-registration with the GP practice, their date of death, the last date of their GP practice's data download to CRPD or the study end date.

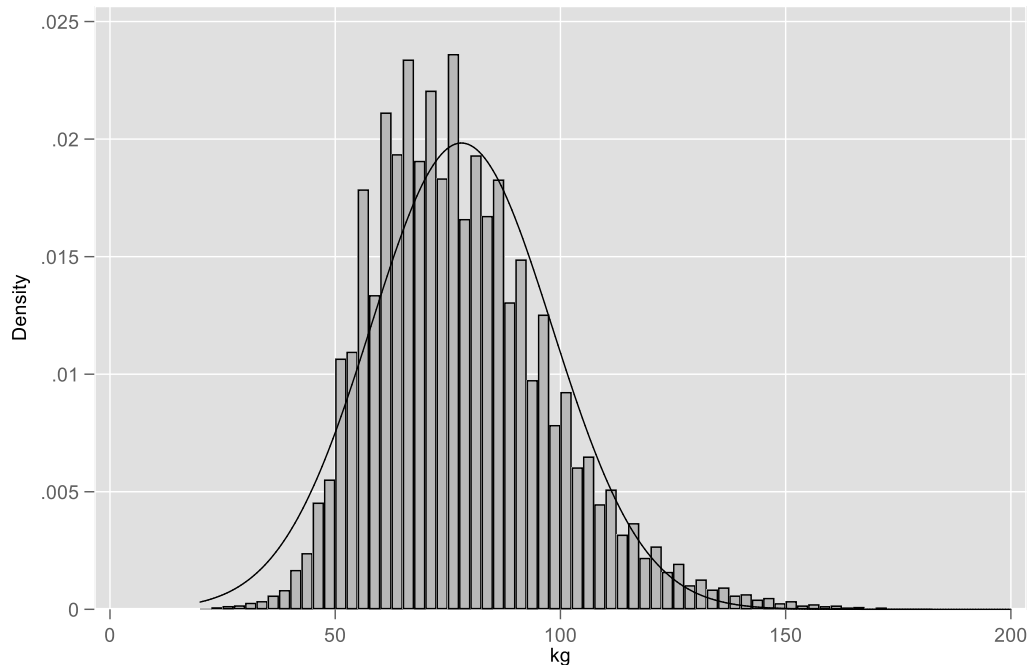
5.3.4. Weight records

The weight measurement value associated with every weight measurement code was extracted for the cohort. A bespoke approach was developed to mitigate the possibility of recording error at the time of weight data entry by the GP into the EHR. Implausible kilogram (kg) weight values were converted into plausible kg values using the following steps:

- i. Weight values were initially assumed to be measured in kg and the median weight (in kg) for each patient was calculated.
- ii. Weight values were then assumed to be recorded in stones and pounds, or pounds alone, and converted into kg.
- iii. Original kg values that were less than half or more than one and a half times the individual's median kg value were replaced by the converted value if the converted value fell within this range.
- iv. Any remaining measurements under 20kg or over 200kg were considered implausible and excluded.

As previously described in large population based cohorts (97), the distribution of the remaining weight measurements was slightly positively skewed (Figure 5.3.4-1).

Figure 5.3.4-1: Distribution of weight values in kilograms (kg) (n =14,049,871)



5.3.5. Baseline characteristics

Baseline characteristics (at study entry) were determined for the closest record prior to each patient’s study entry date. These were gender, age-group, smoking status, alcohol intake, ethnicity, body mass index (BMI) group, index of multiple deprivation (IMD) quintile, and consultation rate in the year before study entry (Table 5.4-1).

5.3.6. Comorbidity

I drew on existing approaches to develop a method to classify comorbidities (98-101). I identified the most common comorbidities reported in primary care (98, 99, 102) and those related to weight change (1, 18). As well as including codes that directly defined these conditions, I also included indirect indicators, for example “hypertension review” as a marker

for hypertension. These comorbidities are listed in Box 5.3.6. The code lists for these comorbidities are included in the Appendix (page 268).

Box 5.3.6: Comorbidities included in the comorbidity variable.

Adrenal insufficiency, atrial fibrillation, alcohol dependence, anxiety, asthma, coronary heart disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular accident, deafness, dementia, depression, diabetes, diverticular disease, drug addiction, dyspepsia, eating disorders, epilepsy, hypertension, inflammatory bowel disease, irritable bowel syndrome, learning disability, malabsorption, multiple sclerosis, obesity, renal failure, rheumatoid arthritis and the spondyloarthropathies, thyroid disease, and tuberculosis.

5.3.7. Clinical events and health professionals' roles

I wanted to assess whether particular clinical events were related to weight recording. *A priori*, I developed and discussed a list of clinical events with SLF and my supervisors, and checked the relevant clinical event codes were available in CPRD Codebrowser. These events were: registration, health check, chronic disease monitoring, medication review, contraception, pregnancy, weight monitoring, and lifestyle advice. The profession of the staff member recording the weight was categorised as: GP, nurse, midwife/health visitor, pharmacist, administrator and dietician.

5.3.8. Diagnosis and symptom codes

Codelists developed for another project were used to define the symptoms, complaints and diagnoses associated with weight recording. I was the clinical lead for an initiative seeking to catalogue EHR codes related to symptoms or complaints and diagnoses according to the second International Classification of Primary Care (ICPC) (103). ICPC-2 classifies patient data

and clinical activity in the domains of general or family practice and primary care, accounting for the frequency of problems seen in these settings (104). It enables classification of the patient's reason for attending, the problems and or diagnoses discussed, interventions, and the ordering of these data in an episode of care structure within the EHR. To illustrate the ICPC structure, the domains are listed below with the respiratory symptom codes expanded:

ICPC Domains
A (general)
B (blood)
D (digest)
F (eye)
H (ear)
K (cardiovascular)
L (musculoskeletal)
N (neurological)
P (psychological)
R (respiratory)
R01 Pain respiratory system
R02 Shortness of breath/dyspnoea
R03 Wheezing
R04 Breathing problem, other
R05 Cough
R06 Nosebleed/epistaxis
R07 Sneezing/nasal congestion
R08 Nose symptom/complaint other
R09 Sinus symptom/complaint
R21 Throat symptom/complaint
R23 Voice symptom/complaint
R24 Haemoptysis
R25 Sputum/phlegm abnormal
R26 Fear of cancer respiratory system
R27 Fear of respiratory disease, other
R28 Limited function/disability (r)
R29 Respiratory symptom/complaint other
S (skin)
T (endocrine)
U (urological)
W (pregnancy etc.)
X (female genitals)
Y (male genitals)
Z (social)

5.3.9. Statistical analysis

5.3.9.1. Number of weights recorded

Firstly, the proportion of patients with a weight record in each calendar year was calculated and it was assessed whether this differed by patient characteristics and over time. As not all patients had a weight record each calendar year, and the sample of patients with a weight record varied by year, each year's sample was not discrete and considered overlapping. Ninety-five percent confidence intervals (95% CIs) were calculated allowing for partial overlapping samples (105). Differences between staff profession type, clinical events and the presenting clinical condition were examined.

5.3.9.2. Likelihood of weight recording

Negative binomial regression (NBR) was used to model the number of weight measurements recorded for each patient in each calendar year. Compared to Poisson regression, NBR is appropriate in cases of overdispersion, particularly when important covariates have been omitted, or there are outliers or marked population heterogeneity (106). In this dataset, the variance was greater than the mean and most patients had no weight measurement per year (median 0; mean 0.47; variance 0.85). A mixed effects NBR model with an offset term for log-person-years of follow-up was used to derive the incident rate ratio (IRR) for the relative likelihood of having a weight recording whilst allowing differing follow-up periods. Patient sociodemographic characteristics, including consultation rate in the previous year, were included as fixed effects with the patient identifier included as a random effect. All characteristics were included in both univariable and multivariable models without selection.

The large dataset meant that the computer available was unable to complete the analysis for the full cohort. Instead, the model could only be fitted for a 10% random subset of the original data set comprising of 491,171 patients.

5.3.9.3. Likelihood of repeat weight recording

To examine the likelihood of patients having a repeat weight record, the time from first weight recording during the study period until repeat measurement or study exit (censored) was recorded. Adjusted hazard ratios (HRs) were derived for all patients using multivariable Cox regression. Cox regression (or proportional hazards regression) is a method used to investigate the effect of several variables upon the time a specified event takes to happen. The hazard is the risk of the event taking place at an individual time-point. The hazard ratio in this analysis represents the likelihood that a repeat weight recording occurs during the follow-up period in one group compared to another group. In order to understand which groups were most likely to have multiple weight records, models included sociodemographic characteristics, ICPC symptom and diagnostic characteristics related to the consultation in which the first weight record occurred and the consultation rate in the previous year. Consultation rate was included so that the adjusted estimates for repeat weight recording accounted for more frequently consulting patients having greater opportunity to be weighed, which could possibly be due to improved access to care and greater health care provision.

5.4. Results

Table 5.4-1 outlines the baseline characteristics of the study cohort.

Table 5.4-1: Baseline Characteristics

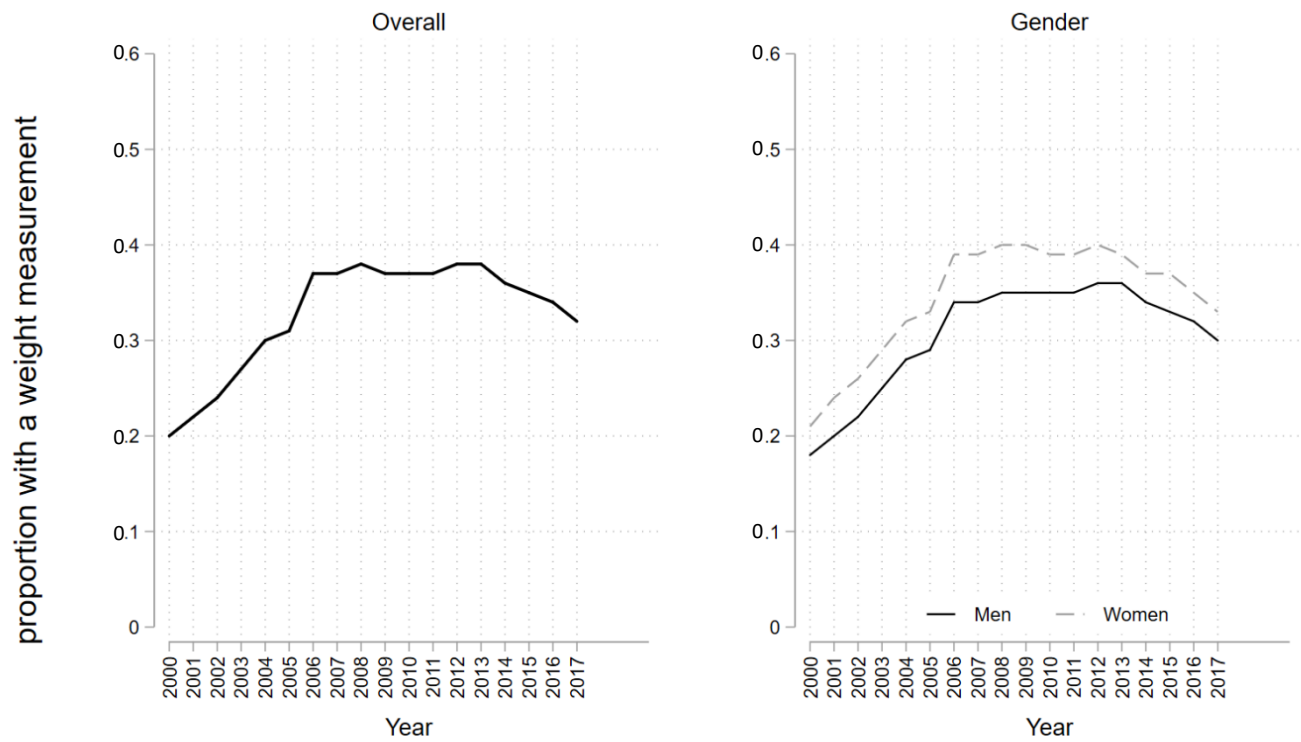
Characteristic	N / mean	% / SD
Male	2,287,850	46.51%
Age (years)	42.09	19.22
Body mass index		
Underweight	76,912	1.56%
Normal	1,223,523	24.87%
Overweight	816,364	16.60%
Obese	292,391	5.94%
Severely obese	128,872	2.62%
Unknown	2,380,684	48.41%
Smoking status		
Non-smoker	1,872,051	38.06%
Current-smoker	848,082	17.24%
Ex-smoker	456,338	9.28%
Unknown	1,742,275	35.42%
Alcohol intake		
Non-drinker	631,693	12.84%
Drinker	1,952,790	39.70%
Unknown	2,334,263	47.46%
Number of comorbidities		
0	2,752,156	55.95%
1	1,189,963	24.19%
2	531,271	10.80%
3	247,220	5.03%
4	112,323	2.28%
5+	85,813	1.74%
Index of Multiple Deprivation Quintile		
I (least deprived)	1,085,515	22.07%
II	1,095,121	22.26%
III	995,658	20.24%
IV	962,126	19.56%
V (most deprived)	775,114	15.76%
Unknown	5,212	0.11%
Ethnicity		
White	1,903,113	38.69%
Indian	64,336	1.31%
Bangladeshi	10,430	0.21%
Pakistani	29,563	0.60%
Chinese	14,982	0.30%
Other Asian	43,373	0.88%
Black African	65,379	1.33%
Black Caribbean	22,525	0.46%
Other Black	13,209	0.27%
Mixed race	40,550	0.82%
Other	26,184	0.53%
Unknown	2,685,102	54.6%
Total patients	4,918,746	

5.4.1. Proportion of patients with a weight record

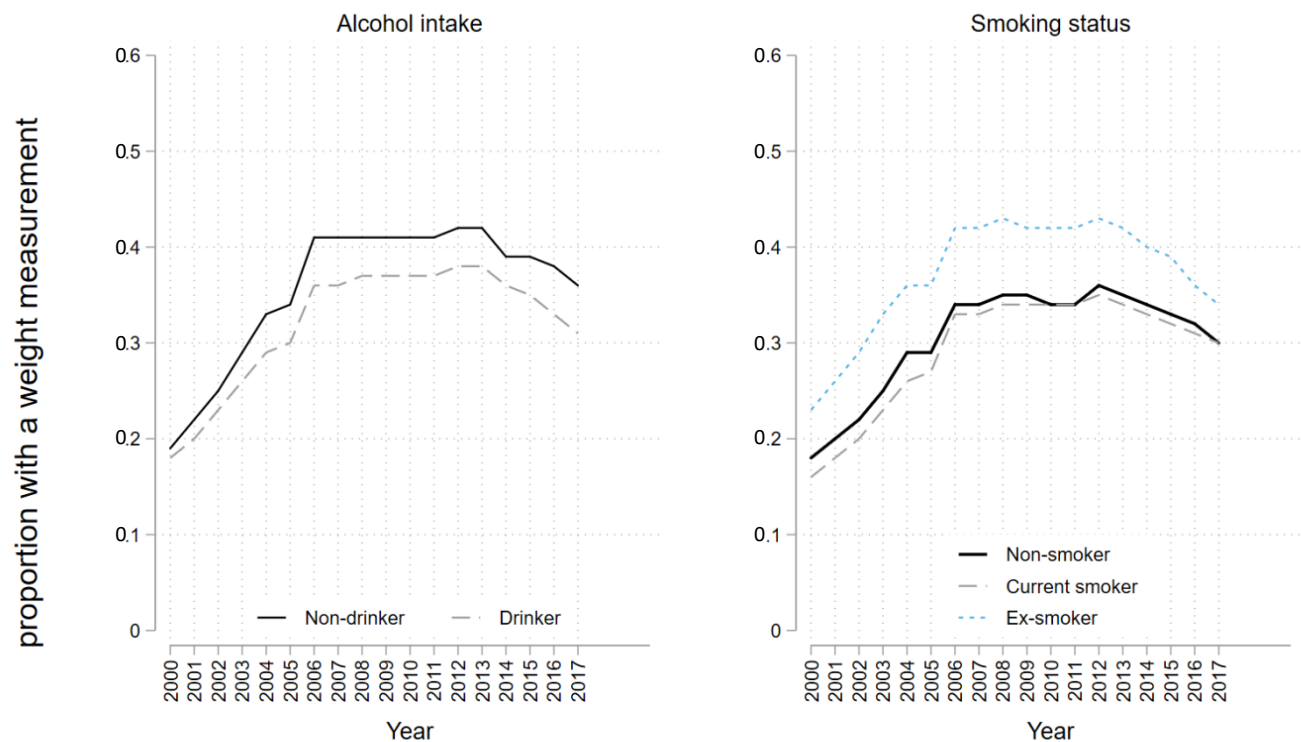
Of the 4,918,746 adults in CPRD during the study period, 3,372,536 (68.6%) had at least one weight record, representing 62.7% of men and 73.6% of women. By year, the proportion of patients with at least one weight record increased from 19.9% (95% CI, 19.8-19.9%) in the year 2000 to 38.5% (38.4-38.6%) in 2012, falling back to 31.5% (31.4-31.7%) in 2017 (Figure 5.4.1-1a). This trend was similar for all sociodemographic subgroups (Figure 5.4.1-1b-h).

Figure 5.4.1-1 (a-h).

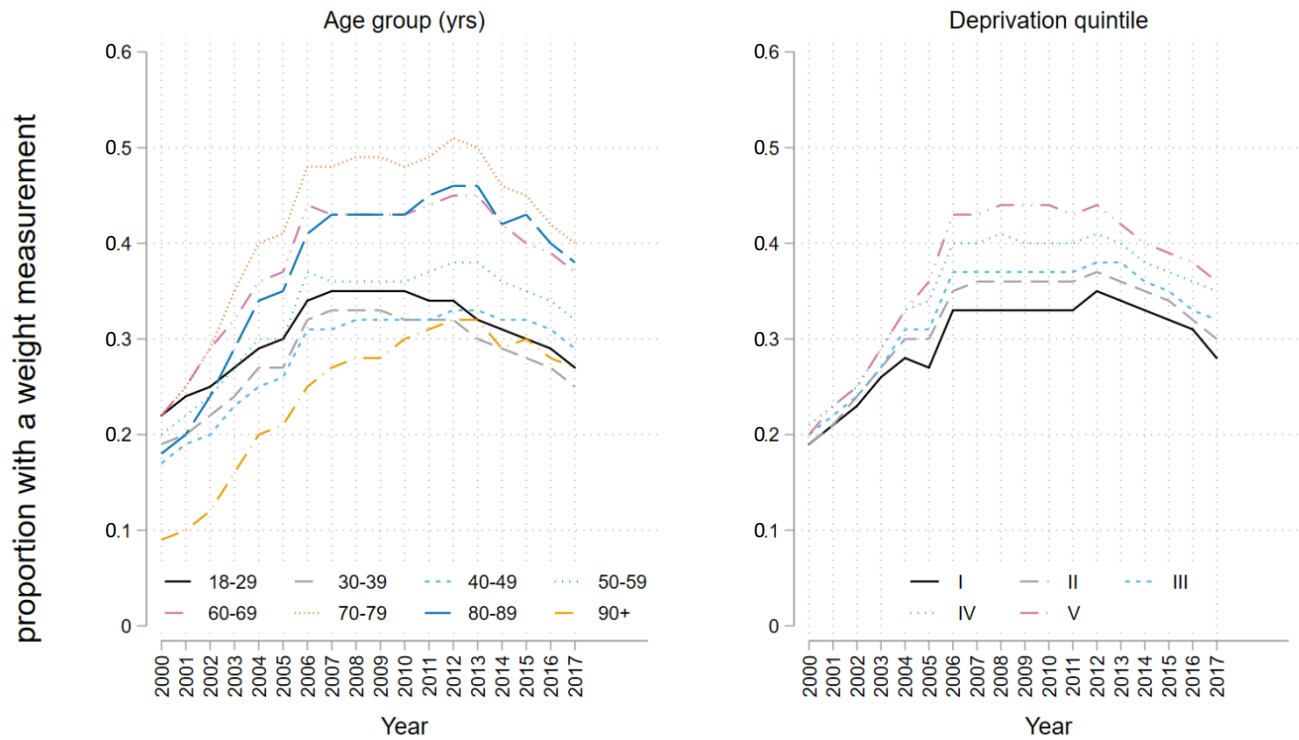
Proportion of patients with one or more weight measurement overall and by gender



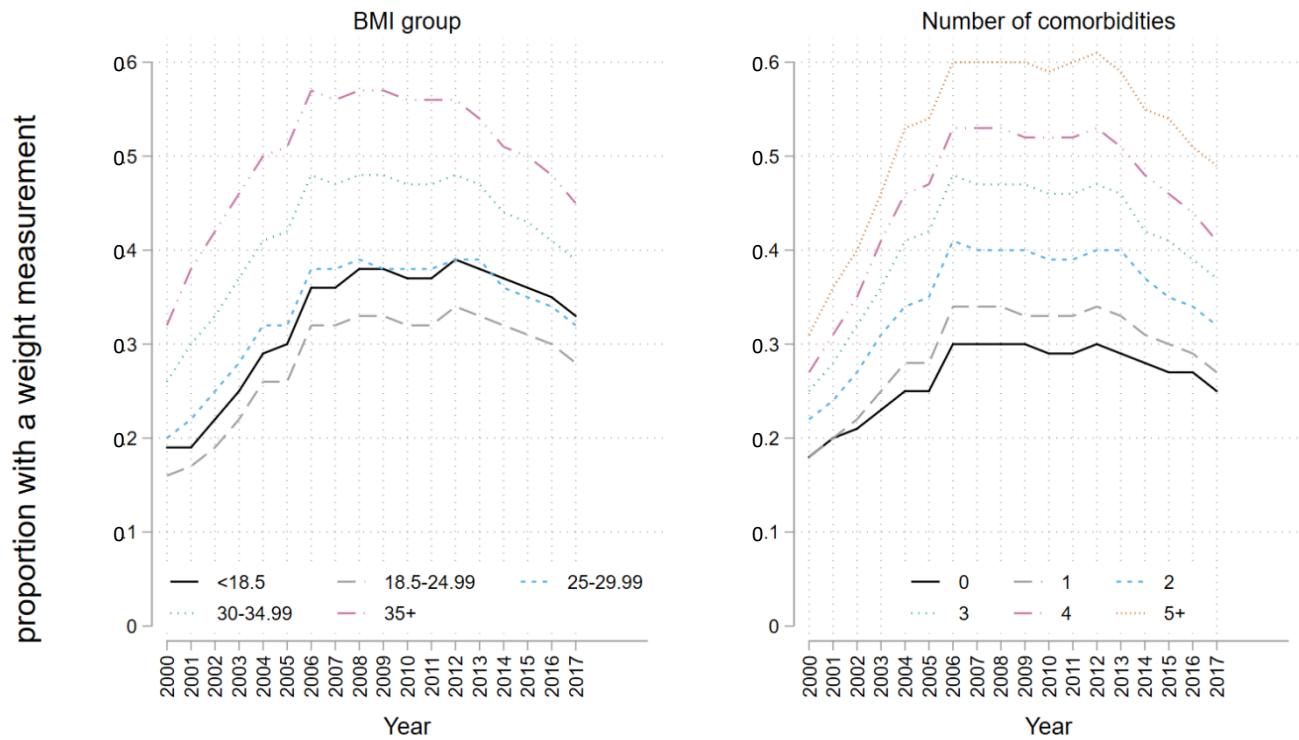
Proportion of patients with one or more weight measurement by alcohol intake and smoking status



Proportion of patients with one or more weight measurement
by age group and by deprivation quintile



Proportion of patients with one or more weight measurement
by BMI group and by number of comorbidities



5.4.2. Repeat weight records

There were 14,049,871 weight records found for 3,372,536 unique patients who had a total of 26,998,591 person-years of observation. Nearly half of weight records (6,908,894, 49.2%) were repeated within a year, whilst 2,126,504 (15.1%) were repeated between one to two years. One in ten measurements (1,429,614, 10.2%) were repeated in between two and six years, whilst 1.5% (212,323) records were not repeated for over six years. Approximately a quarter of weight records (3,372,536, 24.0%) were never repeated. For those with at least one measurement, the average rate of weight recording was one every 1.92 years (initial and repeat measurements). This interval was shorter for women (1.77 years); those aged 70-79 years (1.58 years) and 60-69 years (1.62 years); those with low BMI (1.81 years), or obesity (1.55 years) or morbid obesity (1.08). Weight measurements were also recorded more frequently in patients with lower deprivation and increasing comorbidity (Table 5.4.2-1).

Table 5.4.2-1: Total number of weight measurements and mean time to next measurement

Patient characteristic		Total number of measurements (% of total)	Person-years of follow-up (pyrs)	Mean time to next measure (yrs.)
Gender	Male	5518150 (39.3)	11,904,908	2.16
	Female	8531721 (60.7)	15,093,683	1.77
Age-group (yrs.)	18-29	2484950 (17.7)	4,708,394	1.89
	30-39	2138757 (15.2)	4,705,467	2.20
	40-49	2237814 (15.9)	5,038,093	2.25
	50-59	2556267 (18.2)	4,905,338	1.92
	60-69	2457632 (17.5)	3,969,977	1.62
	70-79	1612986 (11.5)	2,549,141	1.58
	80-89	506102 (3.6)	990,228	1.96
	90+	55363 (0.4)	131,952	2.38
BMI group (kg/m²)	<18.5	320133 (2.3)	577,964	1.81
	18.5-24.99	4408222 (31.4)	10,090,299	2.29
	25-29.99	4492563 (32)	9,241,932	2.06
	30-34.99	2644284 (18.8)	4,111,140	1.55
	35+	1841303 (13.1)	1,988,110	1.08
Smoking status	Non-smoker	7183175 (51.1)	14,373,892	2.00
	Current smoker	3225927 (23)	6,234,614	1.93
	Ex-smoker	3073954 (21.9)	5,510,816	1.79
Alcohol intake	Non-drinker	2994256 (21.3)	4,877,072	1.63
	Drinker	9097148 (64.7)	18,360,952	2.02
IMD quintile	I (least deprived)	2851431 (20.3)	6,383,099	2.24
	II	3074380 (21.9)	6,230,728	2.03
	III	2822249 (20.1)	5,372,371	1.90
	IV	2858074 (20.3)	5,029,158	1.76
	V (most deprived)	2434544 (17.3)	3,964,040	1.63
Comorbidities	0	4466926 (31.8)	10,975,377	2.46
	1	3886327 (27.7)	7,660,234	1.97
	2	2670180 (19)	4,348,982	1.63
	3	1567840 (11.2)	2,230,399	1.42
	4	802685 (5.7)	1,035,466	1.29
	5+	655913 (4.7)	748,134	1.14
Ethnicity	White	6956482 (49.5)	12,463,968	1.79
	Indian	185039 (1.3)	303,332	1.64
	Bangladeshi	29569 (0.2)	42,745	1.45
	Pakistani	84399 (0.6)	120,923	1.43
	Chinese	26037 (0.2)	55,801	2.14
	Other Asian	93638 (0.7)	162,136	1.73
	Black African	143453 (1)	231,100	1.61
	Black Caribbean	89514 (0.6)	128,434	1.43
	Other Black	33707 (0.2)	56,913	1.69
	Mixed race	78337 (0.6)	142,532	1.82
	Other	50834 (0.4)	89,964	1.77
Total measurements		14,049,871 (100)	26,998,590	1.92

Yrs: years; pyrs: person-years; IMD: Index of Multiple Deprivation

5.4.3. Clinical events and staff role

The proportion of weight records made up of clinical events and staff role varied. For example, of the 254,045 weight measurements recorded in 2017, the greatest proportion occurred on the same day as a chronic disease review (16.4%). The recording of weight measurements also coincided with lifestyle advice (10.4% of weight records); a contraception consultation (10.3%); a health check (6.2%); a medication review (6.1%); and practice registration (2.1%). GPs (38.8%), nurses (37.9%), and other healthcare professional group (most likely healthcare assistants) (12.2%) recorded weight most often. Similar patterns were observed in previous years, although it appears that nurses provided a declining proportion of weight recording over time (Table 5.4.3-1).

Table 5.4.3-1: Proportion of weight measurements taken in 2015-2017 by clinical event and staff professional group.

Year	2015	2016	2017
<i>Total weight measurements</i>	<i>587,324</i>	<i>389,319</i>	<i>254,045</i>
Proportion of weight measurements by clinical event			
Chronic disease review	16.65%	16.68%	16.40%
Contraception	9.46%	9.73%	10.32%
Health check	7.04%	5.81%	6.24%
Lifestyle advice	10.83%	10.79%	10.39%
Medication review	8.22%	7.18%	6.09%
Pregnancy	1.42%	1.31%	1.19%
Registration	3.20%	3.23%	2.10%
Weight monitoring	0.49%	0.53%	0.55%
Proportion of weight measurements by staff role			
Administrator	2.31%	3.33%	4.59%
Dietician	0.18%	0.15%	0.70%
GP	36.78%	38.73%	38.84%
Midwife/ health visitor	0.66%	0.60%	0.69%
Nurse	42.49%	39.17%	37.89%
Other health professional	12.34%	12.03%	12.16%
Pharmacist	0.12%	0.42%	0.61%

5.4.4. ICPC symptoms or complaints

The ICPC symptom or complaint group associated with the greatest proportion of weight records in 2017 was “W- Pregnancy, Childbearing, Family Planning” (11.3%), within which the most common items “W14 Contraception other” (7.8%) and “W11 Contraception oral” (5.2%). This was followed by “R – Respiratory” (5.0%) within which the most common items were “R02 Shortness of breath/dyspnoea” (3.0%) and “R05 – Cough” (1.6%); The next most frequent group was “A – General and Unspecified” (4.6%), including “A23 Risk factor NOS[(not otherwise specified)]” (2.2%) and “A29 General symptom/complaint other” (0.35%). Other common ICPC categories were “K- Cardiovascular” (4.3%); “D – Digestive” (2.6%); and “L – Musculoskeletal” (2.5%) (Table 5.4.4-1). The proportion of coded symptoms increases year on year.

Table 5.4.4-1: Detailed breakdown of weight recording by International Classification of Primary Care (ICPC) symptom coding with the most common groups expanded to subgroups

Year	2015 (n = 587,324)	2016 (n = 389,319)	2017 (n = 254,045)
Proportion of measurements occurring on same day as recorded symptom (%)			
A (general/ unspecified)	1.57	2.55	4.55
A01 Pain general/multiple sites	0.10	0.14	0.21
A02 Chills	0.00	0.00	0.00
A03 Fever	0.01	0.01	0.03
A04 Weakness/tiredness general	0.28	0.44	0.74
A05 Feeling ill	0.02	0.04	0.07
A06 Fainting/syncope	0.02	0.04	0.07
A07 Coma	0.00	0.00	0.00
A08 Swelling	0.05	0.08	0.13
A09 Sweating problem	0.02	0.04	0.08
A10 Bleeding/haemorrhage NOS	0.00	0.00	0.00
A11 Chest pain NOS	0.12	0.17	0.30
A13 Concern/fear medical treatment	0.00	0.00	0.00
A16 Irritable infant	0.00	0.00	0.00
A18 Concern about appearance	0.00	0.00	0.00
A20 Euthanasia request/discussion	0.00	0.00	0.00
A21 Risk factor for malignancy	0.19	0.37	0.64

A23 Risk factor NOS	0.66	1.15	2.17
A25 Fear of death/dying	0.00	0.00	0.00
A26 Fear of cancer NOS	0.00	0.00	0.00
A27 Fear of other disease NOS	0.00	0.00	0.00
A28 Limited function/disability NOS	0.07	0.11	0.16
A29 General symptom/complaint other	0.14	0.20	0.35
B (blood)	0.04	0.07	0.12
D (digestive)	1.00	1.55	2.64
F (eye)	0.15	0.13	0.17
H (ear)	0.17	0.24	0.35
K (cardiovascular)	1.47	2.39	4.26
L (musculoskeletal)	1.06	1.61	2.51
N (neurological)	0.98	1.58	2.43
P (psychological)	0.93	1.34	2.14
R (respiratory)	2.08	3.26	4.96
R01 Pain respiratory system	0.00	0.00	0.00
R02 Shortness of breath/dyspnoea	1.28	2.08	3.04
R03 Wheezing	0.05	0.06	0.12
R04 Breathing problem, other	0.01	0.02	0.05
R05 Cough	0.71	1.05	1.60
R06 Nosebleed/epistaxis	0.01	0.02	0.03
R07 Sneezing/nasal congestion	0.01	0.01	0.03
R08 Nose symptom/complaint other	0.04	0.05	0.09
R09 Sinus symptom/complaint	0.01	0.01	0.02
R21 Throat symptom/complaint	0.08	0.11	0.19
R23 Voice symptom/complaint	0.01	0.02	0.03
R24 Haemoptysis	0.01	0.01	0.02
R25 Sputum/phlegm abnormal	0.00	0.00	0.00
R26 Fear of cancer respiratory system	0.00	0.00	0.00
R27 Fear of respiratory disease, other	0.02	0.04	0.07
R28 Limited function/disability (r)	0.00	0.00	0.00
R29 Respiratory symptom/complaint other	0.03	0.04	0.09
S (skin)	0.31	0.49	0.81
T (endocrine)	0.55	1.03	1.52
U (urological)	0.19	0.33	0.53
W (pregnancy etc)	4.17	6.94	11.34
W01 Question of pregnancy	0.00	0.00	0.01
W02 Fear of pregnancy	0.00	0.00	0.00
W03 Antepartum bleeding	0.00	0.00	0.00
W05 Pregnancy vomiting/nausea	0.00	0.00	0.00
W10 Contraception postcoital	0.01	0.02	0.03
W11 Contraception oral	1.80	3.07	5.20
W12 Contraception intrauterine	0.05	0.08	0.14
W13 Sterilization	0.00	0.00	0.00
W14 Contraception other	2.97	4.87	7.75
W15 Infertility/subfertility	0.01	0.02	0.05
W17 Post-partum bleeding	0.00	0.00	0.00

W18 Post-partum symptom/complaint other	0.00	0.00	0.00
W19 Breast/lactation symptom/complaint	0.00	0.00	0.00
W21 Concern body image in pregnancy	0.00	0.00	0.00
W27 Fear complications of pregnancy	0.00	0.00	0.00
W28 Limited function/disability (w)	0.00	0.00	0.00
W29 Pregnancy symptom/complaint other	0.06	0.08	0.12
X (female genital)	0.35	0.54	0.89
Y (male genital)	0.17	0.23	0.37
Z (social problems)	0.00	0.00	0.00
No recorded symptom or complaints	85.12	76.21	61.22

NOS: Not otherwise specified

5.4.5. ICPC diagnoses

The ICPC diagnostic group with the greatest proportion of weight records in 2017 was “T - Endocrine/Metabolic and Nutritional” (14.3%) within which the most common items being “T99 Endocrine/metab[olic]/nutrit[ional] Dis[ease] other” (12.8%), “T90 Diabetes non-insulin dependent” (1.9%), and “T82 Obesity” (0.9%). The next most frequent diagnostic group was “A – General and Unspecified” (8.1%), comprising of “A98 Health maintenance/prevention” (6.8%), “A92 Allergy/allergic reaction NOS” (1.0%) and “A99 General disease NOS” (0.8%). Next was “R – Respiratory” (5.3%) made up of “R96 Asthma” (3.7%), “R95 Chronic obstructive pulmonary dis[ease]” (1.0%) and “R74 Upper respiratory infection acute” (0.2%). Other common codes were “S – Skin” (1.5%); “K – Cardiovascular” (1.2%) and “L – Musculoskeletal” (0.8%) (Table 5.4.5-1). As with the symptom codes, the proportion of coded diagnoses increase year on year.

Table 5.4.5-1: Detailed breakdown of weight recording by International Classification of Primary Care (ICPC) diagnosis coding group with the most common groups expanded to subgroups

Year	2015 (n = 587,324)	2016 (n = 389,319)	2017 (n = 254,045)
Proportion of measurements occurring on same day as a recorded diagnosis (%)			
A (general/ unspecified)	3.03	4.85	8.06

A70 Tuberculosis	0.00	0.00	0.00
A71 Measles	0.00	0.00	0.00
A72 Chickenpox	0.00	0.00	0.00
A73 Malaria	0.00	0.00	0.00
A74 Rubella	0.00	0.00	0.00
A75 Infectious mononucleosis	0.00	0.00	0.00
A76 Viral exanthem other	0.00	0.00	0.00
A77 Viral disease other/NOS	0.01	0.02	0.02
A78 Infectious disease other/NOS	0.02	0.03	0.05
A79 Malignancy NOS	0.00	0.01	0.01
A80 Trauma/injury NOS	0.03	0.05	0.09
A81 Multiple trauma/injuries	0.00	0.00	0.00
A82 Secondary effect of trauma	0.00	0.00	0.00
A84 Poisoning by medical agent	0.00	0.00	0.00
A85 Adverse effect medical agent	0.02	0.03	0.05
A86 Toxic effect non-medicinal substance	0.00	0.00	0.00
A87 Complication of medical treatment	0.00	0.00	0.01
A88 Adverse effect physical factor	0.00	0.00	0.00
A89 Effect prosthetic device	0.00	0.00	0.00
A90 Congenital anomaly OS/multiple	0.00	0.00	0.00
A91 Abnormal result investigation NOS	0.02	0.03	0.06
A92 Allergy/allergic reaction NOS	0.39	0.61	0.96
A93 Premature newborn	0.00	0.00	0.00
A94 Perinatal morbidity other	0.01	0.01	0.01
A95 Perinatal mortality	0.00	0.00	0.00
A96 Death	0.00	0.00	0.01
A97 No disease	0.00	0.00	0.00
A98 Health maintenance/prevention	2.53	4.08	6.78
A99 General disease NOS	0.26	0.48	0.83
B (blood)	0.06	0.11	0.16
D (digestive)	0.26	0.38	0.69
F (eye)	0.10	0.16	0.26
H (ear)	0.18	0.22	0.37
K (cardiovascular)	0.49	0.79	1.18
L (musculoskeletal)	0.34	0.53	0.83
N (neurological)	0.10	0.15	0.25
P (psychological)	0.22	0.37	0.65
R (respiratory)	2.07	3.30	5.27
R71 Whooping cough	0.00	0.00	0.00
R72 Streptococcus throat	0.00	0.00	0.00
R73 Boil/abscess nose	0.00	0.00	0.00
R74 Upper respiratory infection acute	0.08	0.13	0.19
R75 Sinusitis acute/chronic	0.02	0.05	0.06
R76 Tonsillitis acute	0.02	0.03	0.05
R77 Laryngitis/tracheitis acute	0.01	0.01	0.01
R78 Acute bronchitis/bronchiolitis	0.04	0.06	0.07
R79 Chronic bronchitis	0.00	0.00	0.00

R80 Influenza	0.01	0.01	0.01
R81 Pneumonia	0.00	0.00	0.01
R82 Pleurisy/pleural effusion	0.00	0.00	0.01
R83 Respiratory infection other	0.06	0.10	0.17
R84 Malignant neoplasm bronchus/lung	0.00	0.00	0.00
R85 Malignant neoplasm respiratory, other	0.00	0.00	0.00
R86 Benign neoplasm respiratory	0.00	0.00	0.00
R87 Foreign body nose/larynx/bronch	0.00	0.00	0.00
R88 Injury respiratory other	0.00	0.00	0.00
R89 Congenital anomaly respiratory	0.00	0.00	0.00
R90 Hypertrophy tonsils/adenoids	0.00	0.00	0.00
R92 Neoplasm respiratory unspecified	0.00	0.00	0.00
R95 Chronic obstructive pulmonary disease	0.43	0.73	0.95
R96 Asthma	1.41	2.21	3.74
R97 Allergic rhinitis	0.04	0.06	0.13
R98 Hyperventilation syndrome	0.00	0.00	0.00
R99 Respiratory disease other	0.05	0.06	0.12
S (skin)	0.61	0.95	1.51
T (endocrine)	5.70	9.49	14.25
T70 Endocrine infection	0.00	0.00	0.00
T71 Malignant neoplasm thyroid	0.00	0.00	0.00
T72 Benign neoplasm thyroid	0.00	0.00	0.00
T73 Neoplasm endocrine other/unspecified	0.00	0.00	0.00
T78 Thyroglossal duct/cyst	0.00	0.00	0.00
T80 Congenital anomaly endocrine/metabolic.	0.00	0.00	0.00
T81 Goitre	0.00	0.00	0.00
T82 Obesity	0.33	0.48	0.87
T83 Overweight	0.03	0.07	0.10
T85 Hyperthyroidism/thyrotoxicosis	0.01	0.01	0.02
T86 Hypothyroidism/myxoedema	0.03	0.04	0.07
T87 Hypoglycaemia	0.01	0.02	0.03
T89 Diabetes insulin dependent	0.06	0.09	0.16
T90 Diabetes non-insulin dependent	0.71	1.31	1.91
T91 Vitamin/nutritional deficiency	0.03	0.05	0.10
T92 Gout	0.02	0.03	0.05
T93 Lipid disorder	0.06	0.09	0.16
T99 Endocrine/metabolic/nutritional. disease Other	5.10	8.62	12.80
U (urological)	0.25	0.36	0.62
W (pregnancy etc.)	0.11	0.18	0.29
X (female genital)	0.12	0.18	0.26
Y (male genital)	0.03	0.05	0.07
Z (social problems)	0.25	0.38	0.61
No recorded diagnoses	86.08	77.55	64.67

NOS: Not otherwise specified

5.4.6. Likelihood of weight recording and repeat weight recording

In the multivariable analysis, women were more likely than men to have a weight record (IRR 1.30 (95%CI 1.29-1.31)) and a repeat weight record (HR 1.30 (95%CI 1.29-1.30) (Table 5.4.6-1). Ex-smokers were more likely to have a repeat weight record (HR 1.09 (95%CI 1.08-1.09)) than never smokers, but there was no evidence of an association for current smokers. The likelihood of weight recording increased over time from 2000 (IRR reference category) to 2009 (IRR 1.93 (1.91-1.96) reducing slightly to 2017 (IRR 1.64 (1.61-1.67)) but there was little change in the likelihood of a repeat record over time (Table 5.4.6-1). Repeat weight records were positively associated with pregnancy, endocrine, digestive, and cardiovascular complaints (Table 5.4.6-1).

The likelihood of weight recording and repeat weight recording for the remaining ordinal covariates (age-group, IMD quintile, BMI group, number of comorbidities, and number of consultations/year) each demonstrated a distinct pattern of association (Figure 5.4.6-1). Compared with adults aged 18-29 years, adults in their 30s and 40s were less likely to have weight recorded, while those aged 60 years and older were more likely to have weight recorded (Figure 5.4.6-1). People who were underweight and obese were more likely to have weight recorded. People who were more deprived were more likely to have weight recorded as were people with more comorbidities. People in the white ethnic group were less likely to have their weight recorded. People who had consulted more frequently in the year prior to the index were more likely to have weight recorded.

Table 5.4.6-1: Univariable and multivariable negative binomial regression and Cox regression to estimate the unadjusted and adjusted likelihood of weight measurement (incident rate ratio) and repeat weight measurement (hazard ratio)

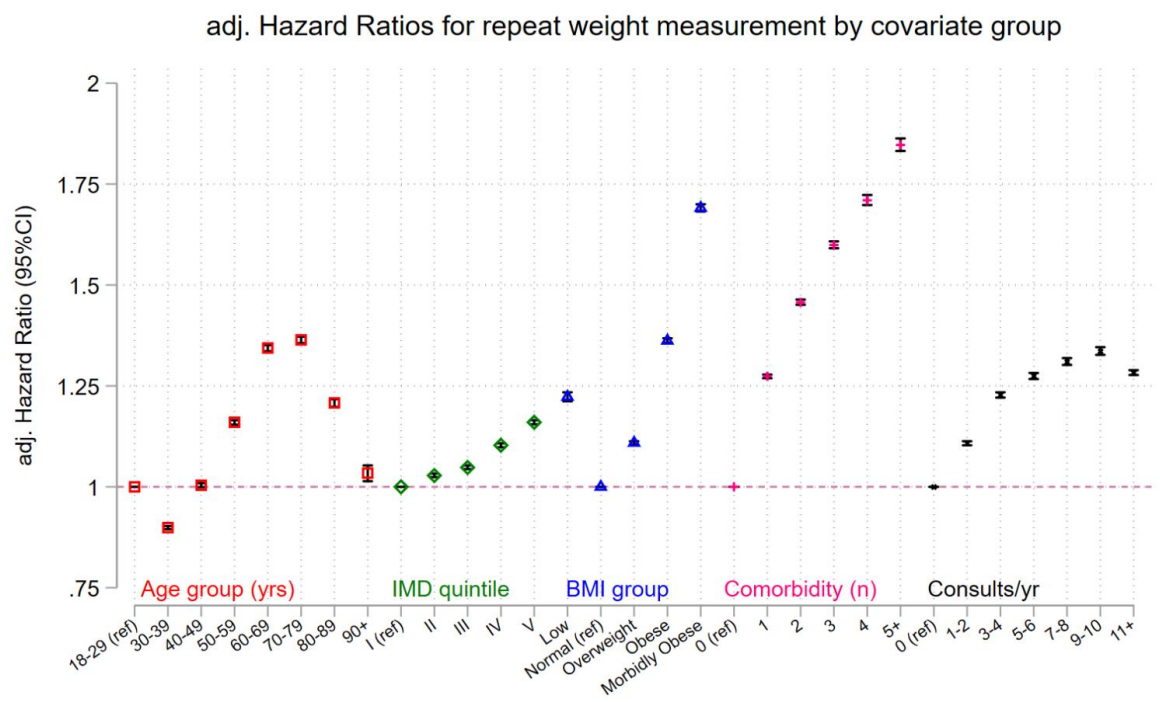
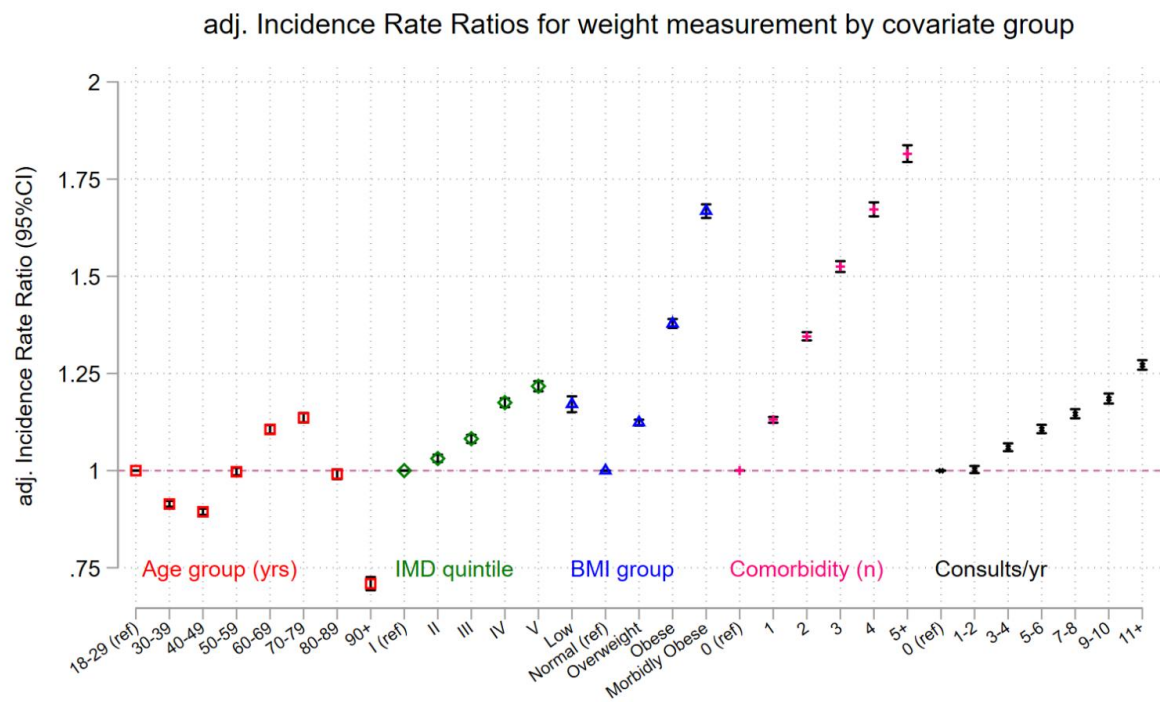
Covariate	Likelihood of weight measurement		Likelihood of repeat measurement	
	Incidence Rate Ratio (95% CI)		Hazard Ratio (95% CI)	
	Univariate	Multivariable	Univariate	Multivariable
Gender (ref = Men)				
Women	1.32 (1.31-1.33)	1.30 (1.29-1.31)	1.46 (1.46-1.47)	1.30 (1.29-1.30)
Age group, years (ref = 18-29 years)				
30-39	0.86 (0.86-0.87)	0.91 (0.91-0.92)	0.91 (0.91-0.92)	0.90 (0.89-0.90)
40-49	0.87 (0.86-0.88)	0.89 (0.89-0.90)	1.05 (1.05-1.06)	1.00 (1.00-1.01)
50-59	1.01 (1.00-1.02)	1.00 (0.99-1.01)	1.27 (1.26-1.27)	1.16 (1.15-1.17)
60-69	1.23 (1.22-1.24)	1.11 (1.10-1.12)	1.58 (1.57-1.58)	1.34 (1.34-1.35)
70-79	1.40 (1.39-1.41)	1.14 (1.12-1.15)	1.74 (1.73-1.75)	1.36 (1.36-1.37)
80-89	1.36 (1.35-1.38)	0.99 (0.98-1.00)	1.57 (1.56-1.58)	1.21 (1.20-1.22)
90+	1.01 (0.99-1.04)	0.71 (0.69-0.73)	1.30 (1.27-1.32)	1.03 (1.01-1.05)
IMD Quintile (ref = quintile I, least deprived)				
II	1.09 (1.08-1.10)	1.03 (1.02-1.04)	1.08 (1.07-1.08)	1.03 (1.02-1.03)
III	1.17 (1.16-1.19)	1.08 (1.07-1.09)	1.10 (1.09-1.10)	1.05 (1.04-1.05)
IV	1.31 (1.30-1.33)	1.17 (1.16-1.19)	1.15 (1.15-1.16)	1.10 (1.10-1.11)
V	1.41 (1.40-1.43)	1.22 (1.20-1.23)	1.24 (1.23-1.24)	1.16 (1.15-1.17)
Unknown	1.06 (0.95-1.19)	1.08 (0.98-1.20)	0.95 (0.90-0.99)	0.94 (0.90-0.99)
BMI group, kg/m² (ref = 18.5 -24.99)				
<18.5	1.24 (1.22-1.27)	1.17 (1.15-1.19)	1.31 (1.29-1.32)	1.22 (1.21-1.23)
25-29.99	1.19 (1.18-1.20)	1.12 (1.12-1.13)	1.13 (1.13-1.14)	1.11 (1.11-1.11)
30-34.99	1.59 (1.58-1.60)	1.38 (1.37-1.39)	1.52 (1.51-1.52)	1.36 (1.36-1.37)
35+	2.09 (2.07-2.11)	1.67 (1.65-1.68)	2.07 (2.05-2.08)	1.69 (1.68-1.70)
Unknown	1.58 (1.57-1.59)	1.08 (1.07-1.09)	0.83 (0.83-0.84)	0.73 (0.73-0.74)
Smoking status (ref = non-smoker)				
Current	0.96 (0.95-0.96)	1.02 (1.01-1.02)	0.96 (0.96-0.96)	1.01 (1.01-1.02)
Ex-smoker	1.23 (1.22-1.24)	1.10 (1.09-1.10)	1.17 (1.16-1.17)	1.09 (1.08-1.09)
Unknown	1.88 (1.86-1.89)	2.60 (2.57-2.62)	1.16 (1.15-1.17)	1.13 (1.12-1.14)
Drinking status (ref = non-drinker)				
Drinker	0.91 (0.90-0.91)	N/E	0.83 (0.83-0.84)	N/E
Unknown	1.33 (1.32-1.34)	1.16 (1.14-1.17)	0.96 (0.95-0.96)	1.06 (1.05-1.06)
Comorbidities, n (ref = 0)				
1	1.11 (1.10-1.12)	1.13 (1.12-1.14)	1.43 (1.42-1.43)	1.27 (1.27-1.28)
2	1.40 (1.38-1.41)	1.35 (1.33-1.36)	1.80 (1.79-1.81)	1.46 (1.45-1.46)
3	1.68 (1.67-1.69)	1.52 (1.51-1.54)	2.12 (2.11-2.13)	1.60 (1.59-1.61)
4	1.95 (1.93-1.97)	1.67 (1.65-1.69)	2.42 (2.40-2.43)	1.71 (1.70-1.72)
5+	2.27 (2.24-2.29)	1.82 (1.79-1.84)	2.82 (2.80-2.85)	1.85 (1.83-1.86)
Ethnic group (ref = White)				
Indian	1.17 (1.14-1.21)	1.25 (1.22-1.29)	0.90 (0.89-0.91)	1.08 (1.07-1.10)
Bangladeshi	1.24 (1.16-1.34)	1.28 (1.20-1.37)	0.98 (0.95-1.00)	1.18 (1.14-1.21)
Pakistani	1.23 (1.18-1.29)	1.21 (1.17-1.26)	1.03 (1.02-1.05)	1.20 (1.18-1.22)
Chinese	1.07 (1.00-1.15)	1.18 (1.11-1.26)	0.63 (0.61-0.65)	0.81 (0.79-0.84)
Other Asian	1.17 (1.13-1.22)	1.23 (1.19-1.27)	0.78 (0.77-0.80)	0.99 (0.97-1.00)

Black African	1.24 (1.20-1.28)	1.24 (1.20-1.28)	0.93 (0.92-0.94)	1.06 (1.05-1.07)
Black Caribbean	1.27 (1.21-1.34)	1.18 (1.13-1.23)	1.14 (1.12-1.16)	1.11 (1.09-1.13)
Other Black	1.08 (1.01-1.16)	1.08 (1.02-1.15)	0.95 (0.93-0.98)	1.04 (1.02-1.07)
Other	1.17 (1.11-1.23)	1.17 (1.12-1.23)	0.77 (0.75-0.78)	0.91 (0.89-0.93)
Mixed Race	1.10 (1.06-1.14)	1.11 (1.07-1.15)	0.75 (0.74-0.77)	0.89 (0.87-0.91)
Unknown	0.67 (0.66-0.67)	0.76 (0.76-0.77)	0.82 (0.82-0.82)	0.82 (0.81-0.82)
Year of initial measurement (ref = 2000)				
2001	1.12 (1.11-1.14)	1.11 (1.10-1.13)	0.89 (0.89-0.90)	0.93 (0.93-0.94)
2002	1.25 (1.24-1.27)	1.21 (1.20-1.23)	0.91 (0.91-0.92)	0.96 (0.96-0.97)
2003	1.40 (1.38-1.42)	1.35 (1.33-1.36)	0.89 (0.89-0.90)	0.95 (0.94-0.95)
2004	1.56 (1.54-1.58)	1.51 (1.49-1.53)	0.93 (0.92-0.93)	0.99 (0.99-1.00)
2005	1.61 (1.59-1.64)	1.63 (1.61-1.65)	0.94 (0.94-0.95)	1.03 (1.03-1.04)
2006	1.91 (1.88-1.93)	1.90 (1.87-1.92)	0.91 (0.90-0.91)	0.96 (0.96-0.97)
2007	1.95 (1.92-1.97)	1.89 (1.87-1.92)	0.88 (0.87-0.88)	0.95 (0.94-0.95)
2008	1.97 (1.94-2.00)	1.91 (1.88-1.93)	0.86 (0.86-0.87)	0.94 (0.93-0.95)
2009	1.99 (1.96-2.01)	1.93 (1.91-1.96)	0.88 (0.87-0.88)	0.95 (0.94-0.96)
2010	1.95 (1.93-1.98)	1.85 (1.83-1.88)	0.88 (0.87-0.89)	0.95 (0.94-0.95)
2011	1.96 (1.93-1.99)	1.84 (1.82-1.86)	0.91 (0.90-0.91)	0.96 (0.96-0.97)
2012	1.99 (1.97-2.02)	1.86 (1.83-1.88)	0.89 (0.89-0.90)	0.95 (0.94-0.96)
2013	2.02 (2.00-2.05)	1.89 (1.87-1.92)	0.90 (0.89-0.91)	0.96 (0.96-0.97)
2014	1.92 (1.89-1.94)	1.77 (1.74-1.79)	0.88 (0.88-0.89)	0.96 (0.95-0.97)
2015	1.86 (1.83-1.89)	1.70 (1.68-1.73)	0.91 (0.90-0.92)	0.98 (0.97-0.99)
2016	1.80 (1.77-1.82)	1.62 (1.60-1.65)	0.95 (0.93-0.96)	0.99 (0.98-1.01)
2017	1.81 (1.78-1.84)	1.64 (1.61-1.67)	1.00 (0.97-1.02)	1.04 (1.01-1.06)
Consultation rate in prior year (ref = 0)				
1-2	0.98 (0.97-0.99)	1.00 (0.99-1.01)	1.25 (1.25-1.26)	1.11 (1.10-1.11)
3-4	1.07 (1.06-1.08)	1.06 (1.05-1.07)	1.55 (1.54-1.56)	1.23 (1.22-1.23)
5-6	1.15 (1.14-1.16)	1.11 (1.10-1.12)	1.70 (1.69-1.71)	1.27 (1.27-1.28)
7-8	1.21 (1.20-1.23)	1.15 (1.13-1.16)	1.82 (1.81-1.83)	1.31 (1.30-1.32)
9-10	1.28 (1.27-1.29)	1.19 (1.17-1.20)	1.91 (1.90-1.93)	1.34 (1.33-1.35)
11+	1.42 (1.41-1.43)	1.27 (1.26-1.28)	1.73 (1.72-1.74)	1.28 (1.28-1.29)
New patient	1.22 (1.21-1.23)	0.83 (0.82-0.84)	1.10 (1.10-1.11)	1.09 (1.09-1.10)
ICPC Diagnosis group				
A (general)		0.90 (0.90-0.90)	0.94 (0.93-0.94)	
B (blood)		1.08 (1.04-1.13)	0.97 (0.94-1.01)	
D (digestive)		0.98 (0.97-1.00)	0.95 (0.94-0.96)	
F (eye)		0.96 (0.94-0.98)	0.94 (0.92-0.96)	
H (ear)		0.87 (0.86-0.89)	0.89 (0.87-0.90)	
K (cardiovascular)		1.50 (1.49-1.51)	1.14 (1.14-1.15)	
L (muscular skeletal)		0.93 (0.92-0.94)	0.89 (0.88-0.90)	
N (neurological)		0.99 (0.97-1.01)	0.98 (0.96-1.00)	
P (psychological)		1.14 (1.13-1.16)	1.00 (0.99-1.02)	
R (respiratory)		0.98 (0.97-0.99)	0.96 (0.95-0.97)	
S (skin)		0.83 (0.82-0.84)	0.93 (0.92-0.94)	
T (endocrine)		2.31 (2.30-2.32)	1.63 (1.62-1.64)	
U (urological)		1.06 (1.04-1.07)	1.00 (0.98-1.01)	
W (pregnancy etc.)		1.23 (1.21-1.25)	1.34 (1.31-1.36)	

X (female genitals)	1.10 (1.08-1.12)	1.03 (1.01-1.05)
Y (male genitals)	0.79 (0.76-0.82)	1.00 (0.96-1.03)
Z (social)	0.96 (0.94-0.97)	0.95 (0.94-0.96)
ICPC Symptom group		
A (general)	0.84 (0.84-0.85)	0.94 (0.93-0.94)
B (blood)	0.91 (0.88-0.94)	0.96 (0.93-0.99)
D (digest)	1.04 (1.03-1.05)	1.02 (1.01-1.03)
F (eye)	0.97 (0.95-1.00)	0.92 (0.90-0.95)
H (ear)	0.86 (0.84-0.88)	0.90 (0.88-0.92)
K (cardiovascular)	0.86 (0.86-0.86)	0.94 (0.93-0.94)
L (muscularskeletal)	0.95 (0.94-0.96)	0.95 (0.94-0.96)
N (neurological)	1.08 (1.06-1.09)	1.01 (0.99-1.02)
P (psychological)	1.00 (0.99-1.01)	0.97 (0.96-0.98)
R (respiratory)	1.08 (1.07-1.09)	1.00 (1.00-1.01)
S (skin)	0.89 (0.88-0.90)	0.95 (0.94-0.97)
T (endocrine)	1.46 (1.44-1.48)	1.37 (1.35-1.38)
U (urological)	1.09 (1.07-1.11)	1.01 (0.99-1.03)
W (pregnancy etc.)	1.34 (1.34-1.35)	1.55 (1.54-1.56)
X (female genitals)	1.14 (1.12-1.15)	1.04 (1.02-1.05)
Y (male genitals)	0.86 (0.84-0.88)	1.01 (0.99-1.04)
Z (social)	N/E	N/E

95%CI: 95% confidence interval; ref: reference; ICPC: International Classification of Primary Care; N/E: Not Estimable.

Figure 5.4.6-1: Adjusted (adj) Incidence Rate Ratios for weight measurement and adjusted Hazard Ratios for repeat weight measurement by covariate group



5.5. Discussion

5.5.1. Summary of findings

This analysis of over 14 million weight records in the EHRs of 5 million patients reveals only a third of UK adult patients have a weight recorded in primary care in any given year. Patients with a weight record had it repeated, on average, within two years. These findings help explain why extant studies have not used weight measurements to define UWL when investigating its association with cancer.

Even if there were sufficient recorded measurements available to define weight loss, investigation reveals that measurements are recorded for patients groups unrepresentative of the primary care population as a whole. Patient characteristics found to be independently associated with an increased likelihood of weight recording were: female, younger and older age groups, almost all minority ethnic groups, non-drinkers, ex-smokers, patients with a low or high BMI, being from a more deprived neighbourhood, having a greater number of diagnosed comorbidities, and consulting more frequently.

Weight records were most often taken by GPs and nursing staff as part of health checks and chronic disease or medication reviews. They were also associated with consultations for contraception, obesity, and respiratory disease.

5.5.2. Strengths and Limitations

This is the largest and most comprehensive analysis of the determinants of weight recording and repeat weight recording in primary care to date. No other study has adjusted for consultation rate, which enabled the reporting of independent associations with repeat weight recording.

A limitation of this study was that this dataset was restricted to recorded weights that were coded within the structured EHR because access to the free text data is not possible within the CPRD. However, based on my own clinical experience, I know that chronic disease reviews and health checks, and less frequently contraception and medication reviews, are completed using EHR templates that facilitate structured data entry. Whilst there may be few additional weight data hidden in the free text, it cannot be ruled out that such entries may be clinically significant. For example, weight recording outside of templates may be associated with symptoms and diagnoses that prompt the GP to think about weight, such as possible cancer. By including only coded weight measurements, this analysis may overemphasise clinical events whose template require the recording of a weight measurement. An increase in the proportion of weight records with an associated ICPC code was also observed over the final three years of the study period. Over the same period, the number of patients included in the analysis decreased. The explanation for this is unclear but may represent increases in structured template entry over time related to chronic disease and a reduction in the number of practices contributing data to CPRD as they switch from the Vision EHR to other providers. To acknowledge variation in clinical practice, a broad and inclusive approach was adopted, based on the ICPC classification, for capturing symptoms and diagnoses associated with weight recording. *“General and unspecified”* was one of the most common ICPC categories representing some overlap with chronic disease review, health check, and registration events. Furthermore, the characteristics selected for investigation were based on experience of working in NHS primary care and research experience using UK EHR data, but other researchers may have chosen different ones. The code lists used were adapted from pre-existing published schedules developed by consensus between clinical and non-clinical researchers.

A final key issue is this method can only confirmed that a weight was recorded, but not whether it was measured. Similarly it cannot analyse the measurements that GPs took but did not record, as they were similar to previous recordings. For example, many UK GP practices ask patients to complete a short registration questionnaire on joining, which asks for their weight and height. Whilst this method did exclude records likely to relate to registration, it is impossible to separate reported from measured weights in this study.

5.5.3. Findings in context

A systematic review from 2017 reported that within UK primary care, a third of adults had their BMI recorded within a year, half within three years, and two-thirds within five years (107). Overall, two-thirds of adults reported in this chapter had a weight record - with notable variation by year.

The UK NHS's Quality and Outcomes Framework (QOF) was introduced in 2004, linking remuneration for general practices to recorded quality of care for chronic conditions (108). QOF indicators have incentivised weight recording for patients with diabetes, obesity, serious mental health conditions, and cardiovascular disease (100). For example, OB002 stated "The contractor establishes and maintains a register of patients aged 18 years or over with a recorded BMI of ≥ 30 in the preceding 12 months" (109). There were three indicators incentivising weight recording between 2006 and 2013, increasing to four from 2013 to 2014, then falling to two from 2014 to 2018. These results demonstrate an overall rise and fall in weight recording activity that tracks the number of QOF indicators supporting the hypothesis that weight recording is more frequent when incentivised but declines when the incentives are removed. An increase in weight recording in the early years of the UK QOF has previously been noted (81, 108). However, I am unaware of other reports of the decrease in weight recording after the partial removal of these incentives. The same close link between

inducements and weight recording has been described in the Netherlands as part of chronic condition management (110)

Although not the primary aim of my study it suggests that ongoing incentives for weight recording did not fully cover those that were removed. More detailed methods, such as interrupted time-series analysis would be required to investigate this more thoroughly with a separate application to the ISAC of CPRD required.

It is notable that whilst QOF may have encouraged weight recording in UK primary care, there are concerns that this was amongst selected patient groups. For example, in one UK study in 2015, 97% of people with diabetes had a weight recording in their EHR compared to 54% of people without diabetes (111), a finding replicated elsewhere (9, 32). Other studies have reported that weight recording was more common in young (define) adults (112), older (define) adults (107, 110), women (107, 112), those with a higher BMI (107, 110), those living in more deprived neighbourhoods (107, 112), patients with chronic obstructive pulmonary disease (COPD) (110), cardiovascular disease (110, 112), or stroke (112). In addition, I have shown associations between recorded weight and low BMI (define) and increasing comorbidities.

5.5.4. Implications for clinical practice

The findings of this chapter emphasise that, although it is a simple low-cost biometric, weight recording is not routine in NHS primary care. It seems to occur when incentivised for existing disease by QOF and is included in population level health screening (e.g. NHS Health Checks). The evidence of improved outcome associated with the latter is mixed: (113-115). In 2009, to reduce inequalities in care, the NHS Health Check programme was introduced, offering individuals aged 40–74 years without pre-existing cardiovascular disease (CVD), kidney

disease, type 2 diabetes, or dementia an assessment of their risk of developing such conditions and access to behavioural health advice to reduce that risk (116).

Qualitative research has identified concerns about alienating patients, limited time, and a poor understanding about obesity care prevent GP clinicians from broaching the topic of weight (117). For patients with a lower BMI, increased weight recording may represent ongoing monitoring or be an opportunistic weight measurement when a patient attends primary care. Little is published about the acceptability of weighing underweight patients in primary care – either from a patient, GP or nurse perspective, but I feel that this is an important area to understand if weighing is to become a routine activity in this setting.

I have shown that patients with a healthy BMI were less likely to have weight recorded. If all patients were routinely weighed this may lessen concerns about damaging the patient relationship as patients expect it and clinicians may become more comfortable raising the topic. If weight measurement occurred as part of check-in or as routine observations prior to the clinical encounter, weight data could enter the clinical record without interrupting the consultation. In a recent trial of an opportunistic brief intervention for obesity, patients were weighed before their consultation, handing the results to the GP (118). GPs reported this made it easier to discuss weight, and the trial showed the brief intervention was effective in motivating and supporting weight loss. Blood pressure measurement in GP waiting rooms is acceptable to patients, and in some cases preferable to home monitoring, but very little research has been conducted into the acceptability and feasibility of weight measurement in the waiting room (119-121). As it is perhaps unlikely that a seismic shift in UK clinical practice will occur that results in the primary care EHR containing at least one annual weight record for all patients, it seems more likely that progress will be made by developing mechanisms to capture weight measurements taken at home, using patient self-reports or smart devices that are able to feed data into the EHR remotely and securely.

5.5.5. Implications for research

Previous authors have suggested that patterns of weight recording could be used in prediction modelling as recording weight is an informative process (not missing at random) if careful attention is given to developing appropriate methods to avoid bias (122). It has been noted that any multiple imputation of missing weight records should be carefully implemented with accompanying sensitivity analyses to explore alternative missing data assumptions (112).

Recording of weight measurements in the EHR would have to become a regular activity to become a helpful resource in defining EWL. Increasing the number of records could allow systems to be developed that signal important deviations from an underlying weight trend. However, research is necessary to establish how (in)frequently weight should be measured in primary care to identify meaningful deviations from an individual's weight trajectory. This sort of signal could be useful in consultations for a clinical problem, such as undiagnosed cancer, in which detecting a weight change would be informative but visually difficult due to its gradual nature or being masked by obesity.

5.6. Conclusions and next steps

From conducting this analysis it has become clear that weight recording is not routine in UK primary care as it is recorded for only around a third of patients each year and is repeated on average every two years for these patients.

In Chapter Six, I aim to understand whether there are sufficient weight records prior to codes for weight loss to define how much weight loss, over how much time, leads a primary care clinician to enter a weight loss code. By conducting this analysis, I intended to identify the codes that most reliably signal weight loss codes for use in studies using EHR data in preparation for Chapters Seven to Nine.

6. The internal validation of weight change coding using weight measurement data within the UK primary care electronic health record

6.1. Background to this chapter

Out of the 25 studies included in the systematic review in Chapter Four, none of the 19 studies that defined weight loss using a code published their code lists, making it impossible to replicate these studies. Guidelines recommend that code-lists are published to promote transparency and to allow external validation studies in other datasets (31). As there is no accepted method for code list generation researchers develop their own strategies and collate existing lists (101, 123, 124).

The REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guideline recommends that authors conduct both external and internal validation studies to ensure the accuracy and credibility of coding used in EHR studies (125). External questionnaire or linked secondary care data can be used as sources of external validation data (126-128). Validation studies of symptom codes are relatively uncommon, probably due to the scarcity of external datasets holding detailed symptom information (129, 130). Internal validation uses corroborative data from the source dataset, such as blood pressure measurement data to verify hypertension coding (129).

6.2. Objectives

The objectives of the study detailed in this chapter were to:

- investigate the degree of recorded weight change prior to the application of weight change codes in the primary care EHR,
- compare approaches to assessing the internal validity of weight-change coding.

6.3. Method

6.3.1. Study Population

The dataset from Chapter Five was used for this analysis. To recap, the source population included adult patients (aged 18 years and over) recorded in CPRD during the period of January 1st 2000 to December 31st 2017.

6.3.2. Weight-related codes

A long list of candidate weight-related codes was generated by searches of the Read terms in the medical dictionary of the CPRD code browser using: *weight*, *body mass index*, *BMI*, *fat*, *thin*, *cachexi*. The Read code hierarchies were then explored around the candidate codes to identify potential related terms not picked up by the initial searching. Read codes are entered by GPs into the EHR as part of routine clinical practice and not primarily for research purposes. Due to there being a number of Read codes that pertain to each clinical presentation or diagnosis, and no standardisation of which codes are used, great variation is observed in the Read codes entered into the EHR between individual GPs.

6.3.3. Code categorisation

Due to the inherent variation in Read coding, all candidate codes were categorised into four emergent groups with two other clinical researchers and two methodologists to reach consensus (Table 6.3.4-1 & Figure 6.3.4-1). These were:

- Abnormal Weight - codes that reported a weight outside of normality;
- Weight Change - codes that suggested weight change;
- Weight “Symptom” - codes that reported a weight “symptom” without further clarification;

- Weight Other - codes that reported weight measurement, weight related advice, or a normal weight.

All codes were then extracted from CPRD together with the associated date, the patient's gender, their age at the time of the weight code and all available height values.

6.3.4. Weight measurements

I then extracted weight measurement values for every patient with a weight related code and used the method developed in Chapter Five to convert implausible kilogram (kg) values.

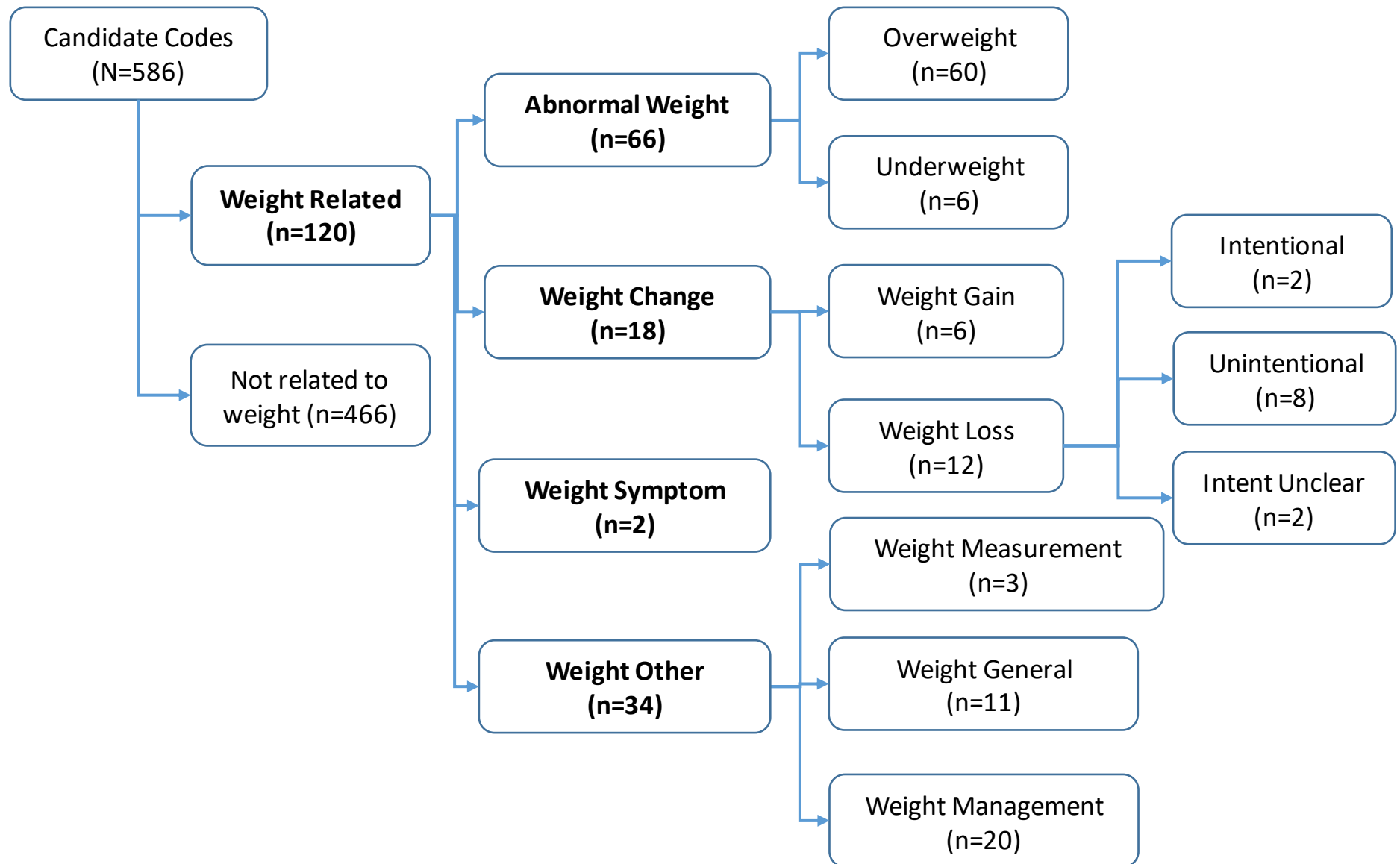
Table 6.3.4-1: Categorised Read code-list

Category	Read Code	Code Description
Abnormal Weight		
Overweight		
	1444	H/O: obesity
	6878	Obesity screen
	13A3.00	Weight reducing diet
	222A.00	O/E - obese
	22A4.00	O/E - weight 10-20% over ideal
	22A4.11	O/E - overweight
	22A5.00	O/E - weight > 20% over ideal
	22A5.11	O/E - obese
	22AA.00	Overweight
	22K2.00	Body Mass Index high K/M2
	22K4.00	Body mass index index 25-29 - overweight
	22K5.00	Body mass index 30+ - obesity
	22K7.00	Body mass index 40+ - severely obese
	22KC.00	Obese class I (body mass index 30.0 - 34.9)
	22KD.00	Obese class II (body mass index 35.0 - 39.9)
	22KE.00	Obese class III (BMI equal to or greater than 40.0)
	66C..00	Obesity monitoring
	66C1.00	Initial obesity assessment
	66C2.00	Follow-up obesity assessment
	66C4.00	Has seen dietician - obesity
	66C6.00	Treatment of obesity started
	66C9.11	Weight loss advised
	66CC.00	Wants to lose weight
	66CG.00	Weight management programme offered
	66CH.00	Weight management plan started
	66CJ.00	Weight management plan completed
	66CX.00	Obesity multidisciplinary case review
	66CZ.00	Obesity monitoring NOS
	6B4..00	Counterweight weight management programme
	8B57.00	Weight reducing diet

8CA4011	Patient advised to lose weight
8CdC.00	Weight management service opportunity signposted
8CP5.00	Discussion about weight management programme
8CV7.00	Anti-obesity drug therapy commenced
8HHH.00	Refer to weight management programme
8IAM.00	Referral to weight management service declined
8IAu.00	Weight management advice declined
9N1yK00	Seen in weight management clinic
9NS0300	Referral to weight management service offered
9OK..00	Obesity monitoring admin.
9OK1.00	Attends obesity monitoring
9OK2.00	Refuses obesity monitoring
9OK3.00	Obesity monitoring default
9OKA.00	Obesity monitoring check done
9OKZ.00	Obesity monitoring admin.NOS
C38..00	Obesity and other hyperalimentation
C380.00	Obesity
C380000	Obesity due to excess calories
C380200	Extreme obesity with alveolar hypoventilation
C380300	Morbid obesity
C380400	Central obesity
C380500	Generalised obesity
C38y011	Obesity hypoventilation syndrome
C38z.00	Obesity and other hyperalimentation NOS
C38z000	Simple obesity NOS
Cyu7.00	[X]Obesity and other hyperalimentation
ZC2C711	Dietary advice for weight reduction
ZC2CM00	Dietary advice for obesity
ZG53100	Patient advised to lose weight
ZV65319	[V]Dietary counselling in obesity
Underweight	
2287	Abnormally thin
22A1.00	O/E - weight > 20% below ideal
22A6.00	O/E - Underweight
22K3.00	Body Mass Index low K/M ²
22K6.00	Body mass index less than 20
R034800	[D]Underweight
Weight Symptom	
162..00	Weight symptom
162Z.00	Weight symptom NOS
Weight Change	
Weight Gain	
1622	Weight increasing
1624	Abnormal weight gain
1628	Pattern of weight gain
1629	Unintentional weight gain
L161.11	Excessive weight gain in pregnancy
R031.00	[D]Abnormal weight gain
Weight Loss	
1625.11	Abnormal weight loss - symptom
1623	Weight decreasing
1625	Abnormal weight loss
1626	Intentional weight loss

1627	Unintentional weight loss
2224	O/E - cachexic
14f..00	H/O: attempted weight loss
1D1A.00	Complaining of weight loss
22A8.00	Weight loss from baseline weight
R032.00	[D]Abnormal loss of weight
R2y4.00	[D]Cachexia
R2y4z00	[D]Cachexia NOS
Weight Other	
Weight Measurement	
22A..00	O/E - weight
22AZ.00	O/E - weight NOS
22K..00	Body Mass Index
Weight General	
1621	Weight steady
1621.11	Weight static
2286	Thin build
6878.11	Weight screen
22A7.00	Baseline weight
22K1.00	Body Mass Index normal K/M2
22K8.00	Body mass index 20-24 - normal
66C..11	Weight monitoring
66CB.00	Ideal weight
66CF.00	Target weight
66CK.00	Target weight reached
Weight Management	
13AC.00	Diabetic weight reducing diet
1F1..00	Dietary fat intake
212Q.00	Obesity resolved
22A3.00	O/E - weight within 10% ideal
22Z..00	Height and Weight
66C7.00	Treatment of obesity stopped
66C9.00	Target weight discussed
66CA.00	Ideal weight discussed
66Cc.00	Intensive weight management programme ended
679P.00	Health education - weight management
67I9.00	Advice about weight
8B5B.00	Weight gain diet
8Cd7.00	Advice given about weight management
ZC1..00	Actions to lose weight
ZC17.00	Exercising to lose weight
ZC1A.00	Excessive exercising to lose weight
ZC2C700	Patient advised about weight-reducing diet
ZC2CN00	Dietary advice for weight gain
ZC2CO00	Dietary advice for weight loss
ZG53.00	Advice about weight

Figure 6.3.4-1: Flowchart of candidate code categorisation.



6.3.5. Statistical Analysis

6.3.5.1. Assessing weight change

Weight measurement values were ordered by date leading up to the first Weight Change code for each patient. Weight Symptom codes were also included in this analysis to understand their use. Weight change was estimated as the percentage (%) difference between the kg value at the time of the code and baseline weight calculated by three different methods:

- previous weight value within a two year period;
- predicted weight value for the time of the weight code, estimated by fitting a linear regression model for each patient through three-monthly means of all weight values recorded in the preceding five years (131)
- historic mean weight of each patient using values recorded in the preceding five years.

For the second and third methods, if there was no weight measurement on the day of the weight code, the nearest measurement within the preceding month was classified as the weight value at the time of the weight code. For all three methods, weight change less than the first percentile or greater than the ninety-ninth percentile was regarded as implausible and excluded. This approach was developed to balance minimising data loss whilst excluding implausible extreme changes to increase the likelihood that weight change would be captured where present.

The mean weight change (95% confidence interval, 95%CI) and median weight change (interquartile-range, IQR) were calculated for each weight code for each method.

Estimates of the absolute difference between these three methods were also calculated.

6.3.5.2. Weight loss code validation

Codes were validated as weight loss codes when the IQR remained below zero for at least two of the three methods. In doing so, the influence of outliers was reduced and by ensuring that at least 75% of values accurately represented weight loss. All analyses were conducted in Stata version 15

6.4. Results

During the study period, 8,108,481 weight-related codes were recorded in CPRD (Table 6.4-1). Twice as many weight-related codes were recorded in women (n = 5,208,593, 64%) than in men. They were most commonly recorded in individuals aged in their fifties (1,533,516, 19%); forties (1,470,111, 18%); and sixties (1,425,102, 18%). The three most commonly used codes were “O/E [On examination] – weight” (5,378,411, 66%) which usually accompanies a weight measurement value, “Body Mass Index” (1,023,792, 13%), and “Ideal Weight” (314,499, 4%).

Table 6.4-1: The patient characteristics of electronic health records with recorded weight related codes (n = 8,108,481).

Characteristic		n (%)	Mean (SD)
Gender	Male	2,899,888 (35.8)	
	Female	5,208,593 (64.2)	
Age (years)	18-29	1,149,079 (14.2)	
	30-39	1,246,907 (15.4)	
	40-49s	1,470,111 (18.1)	
	50-59s	1,533,516 (18.9)	
	60-69s	1,425,102 (17.6)	
	70-79s	922,554 (11.4)	
	80+	361,212 (4.5)	
Weight measurement	Yes	5,378,411 (66.3)	84.2 (22.4)
	No	2,370,070 (33.6)	

Abbreviations: n, Numerator; SD, Standard Deviation.

6.4.1. Internal validity of weight loss coding

Table 6.4.1-1 shows the percentage weight change expressed as the median (IQR) weight change for each estimation method and each Weight Change or Weight Symptom code. Ten codes met the criterion for validation. Two Weight Symptom codes could not be confidently reclassified as weight loss codes and were retained as Weight Symptom codes.

Table 6.4.1-1: Internal validation of weight change read codes using three methods.

Weight Change Code	Method of Percentage Weight Change Estimation					
	Current vs Last		Current vs Predicted		Current vs Mean	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
[D]Abnormal loss of weight	13,126	-5.3 (-9.1 to -2.0)	8,641	-6 (-10.7 to -1.9)	13,189	-8.5 (-12.8 to -4.8)
Abnormal weight loss – symptom	21,603	-5.1 (-8.9 to -1.8)	14,007	-5.9 (-10.4 to -1.8)	22,448	-8.1 (-12.4 to -4.5)
Unintentional weight loss	168	-5.2 (-9.6 to -1.7)	109	-7 (-11.4 to -2.5)	152	-8.6 (-12.2 to -5.4)
Abnormal weight loss	1,962	-4.7 (-9 to -1.1)	1,170	-5.8 (-10.8 to -1.6)	1,910	-7.9 (-12.6 to -3.7)
Complaining of weight loss	5,397	-4.3 (-7.9 to -1.3)	3,773	-5 (-9.4 to -1)	5,702	-7 (-11.3 to -3.4)
Weight decreasing	7,089	-3.9 (-7.4 to -1.3)	4,419	-4.8 (-9.2 to -1.5)	6,881	-6 (-10.2 to -2.3)
O/E - cachexic	31	-3.6 (-10 to 0.2)*	13	-7.6 (-8.4 to -4.9)	15	-13.7 (-22.2 to -3.5)
Intentional weight loss	238	-3.9 (-7.6 to -1.5)	168	-5.4 (-9.7 to -2.8)	213	-5.1 (-8.8 to -1.5)
[D]Cachexia	175	-2.9 (-7.2 to 0)*	48	-5.5 (-10.6 to -0.9)	73	-10.7 (-15.2 to -7.1)
Weight loss from baseline weight	3,013	-2.7 (-5.1 to -1.1)	2,465	-3.3 (-6.5 to -0.7)	3,058	-2.6 (-6.2 to 0.6)*
Pattern of weight gain	3	-0.4 (-7.1 to 0)*	2	2 (-6.4 to 10.4)*	2	11.8 (9.7 to 14)
H/O: attempted weight loss	8	-1.7 (-4 to -0.2)*	8	-0.7 (-4.3 to 6)*	9	-0.2 (-7 to 0.7)*
History of attempted weight loss	1349	-0.5 (-3.9 to 2.5)*	1,031	-2.1 (-6.4 to 1.8)*	1,303	0.7 (-5.6 to 5.2)*
Weight symptom NOS	163	0 (-2.8 to 3.3)*	80	-1.4 (-6.1 to 2.4)*	137	0.3 (-4.8 to 4.3)*
Weight symptom	27925	0.6 (-2.0 to 4.0)*	18,135	-0.1 (-4 to 4.2)*	27,385	2.4 (-2.2 to 7.3)*
Excessive weight gain in pregnancy	22	0.2 (-1.7 to 6.0)*	22	0.8 (-5.6 to 20.7)*	28	9.6 (-2.3 to 18)*
Weight increasing	9,401	2.9 (0.5 to 6.3)	5,831	3 (-0.4 to 7.7)*	8,601	5.9 (2.2 to 10.3)
[D]Abnormal weight gain	8,210	4.2 (1.1 to 7.9)	4,782	3.9 (0 to 9.2)	7,876	7.8 (4 to 12.7)
Abnormal weight gain	346	4.4 (0.8 to 8.1)	215	4.6 (0.3 to 9)	354	7.9 (4.2 to 13.2)
Unintentional weight gain	1	7.1 (7.1 to 7.1)	1	12 (12 to 12)	1	2.6 (2.6 to 2.6)

*denotes the IQR incorporates 0. Orange shading denotes validated weight loss codes. Blue shading denotes weight symptom codes which can be classified as neither weight gain nor weight loss codes. Green shading denotes validated weight gain codes. Abbreviations: IQR, Inter-Quartile Range; vs, versus.

6.4.2. Amount of weight change

The mean weight loss prior to a validated weight loss code ranged from - 5.2% (95%CI -5.2% to -5.2%) to -7.9% (95%CI -8.0% to -7.8%), dependent on the calculation method (Table 6.4.2-1). For women, the amount of weight loss ranged from -5.4% (95%CI -5.5% to -5.3%) to -8.3% (95%CI -8.4% to -8.2%), and in men from -4.8% (95%CI -4.9% to -4.7%) to -7.4kg (95%-7.5% to -7.3%). Within each method, there was little variation in the mean weight loss across age-groups although there was a slight trend towards greater weight loss being observed in the oldest age-groups: mean weight loss for the trend method ranged from -5.2% (95%CI -5.7% to -4.7%) to -5.8% (95%CI -6.0 to -5.6%) across age-groups and from -6.3% (95%CI -6.5% to -6.1%) to -10.2% (95%CI -10.3% to -10.1%) using the historic mean.

The mean weight gain prior to a validated weight gain code ranged from 4.2% (95%CI, 4.1% to 4.3%) to 7.9% (7.8% to 8.0kg), dependent on the calculation method used (Table 6.4.2-1).

Weight gain codes were 3.5 times more likely to be recorded in women than men. For women, the amount of weight gain ranged from 4.5% (95%CI 4.4% to 4.6%) to 8.4% (95%CI 8.3% to 8.5%), and in men from 3.3% (95%CI 3.2% to 3.4%) to 6.4% (95%CI 6.2% to 6.6%).

Each calculation method produced a different pattern in weight gain coding across age-groups: the trend method suggested a similar pattern of weight gain across age-groups whilst the previous and historic mean methods suggested a decreasing amount of weight gain triggered a code with increasing age.

The mean weight change associated with a weight symptom code ranged from 0.7% (95% CI 0.6% to 0.8%) to 2.7% (95%CI 2.6% to 2.8%), depending on the method used (Table 6.4.2-1). For women with a weight symptom code, weight change ranged from 1.0% (95%CI 0.8% to 1.2%) to 3.2% (95%CI 3.1% to 3.3%), and for men from -0.3% (95%CI -0.5% to -0.1%) to 0.9% (95%CI 0.7% to -1.1%). Whichever method was used to assess change in weight, weight

symptom codes were more commonly used after weight loss in older people, with weight change ranging from -2.3% (95%CI -3.0 to -1.6%) to -6.7% (95%CI -7.2% to -6.2%) in the over 80 years old age-group, while the same weight symptom code ranged from 1.0% (95%CI 0.6% to 1.4%) to 4.5% (95%CI 4.2% to 4.8%) in the 18 to 29 year age-group.

Table 6.4.2-1: Weight change by weight change group, gender, and age-group for each of the three methods of percentage weight change estimation.

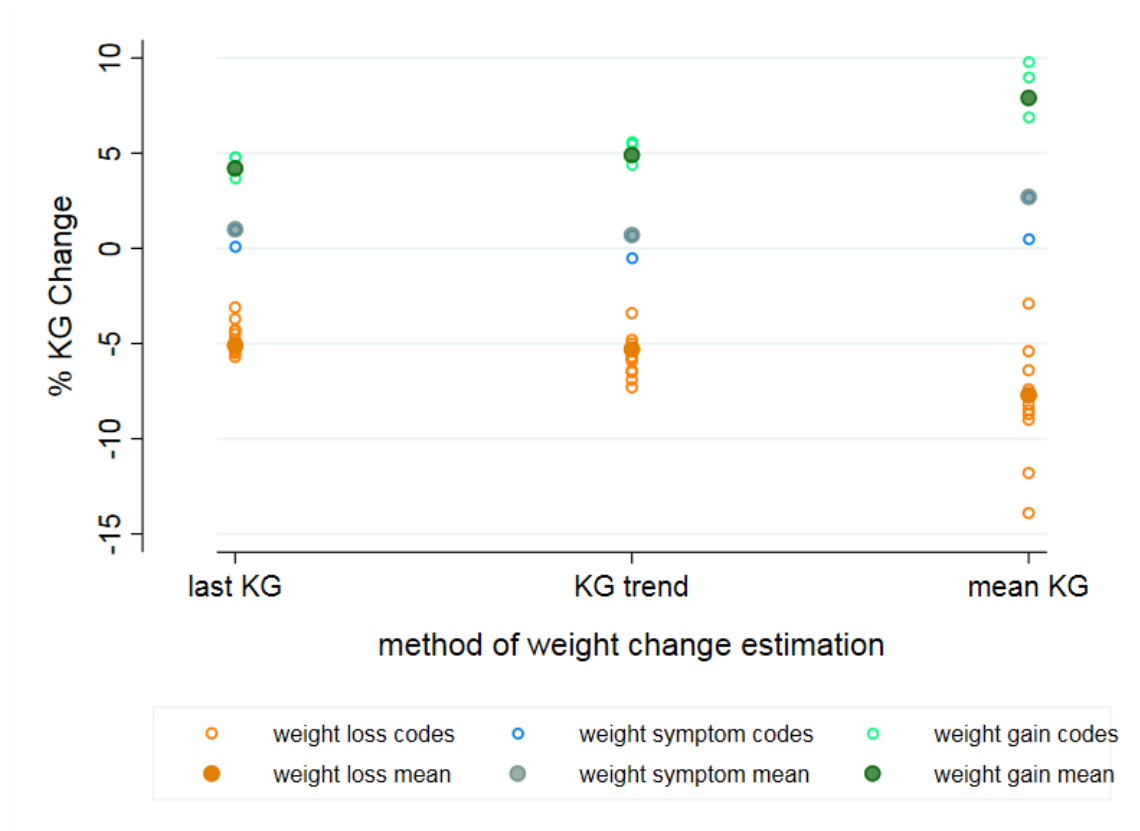
	Method of Percentage Weight Change Estimation					
	Current vs Last		Current vs Trend		Current vs Mean	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Weight loss						
Overall	52,802	-5.2 (-5.2 to -5.2)	34,813	-5.4 (-5.5 to -5.3)	53,641	-7.9 (-8 to -7.8)
Male	21,785	-4.8 (-4.9 to -4.7)	14,048	-5.2 (-5.3 to -5.1)	22,292	-7.4 (-7.5 to -7.3)
Female	31,017	-5.4 (-5.5 to -5.3)	20,765	-5.6 (-5.8 to -5.4)	31,349	-8.3 (-8.4 to -8.2)
18-29 years	5,903	-5.0 (-5.2 to -4.8)	3,097	-5.2 (-5.7 to -4.7)	6,313	-6.3 (-6.5 to -6.1)
30-39 years	4,379	-4.9 (-5.1 to -4.7)	2,678	-5.4 (-5.9 to -4.9)	5,089	-6.5 (-6.7 to -6.3)
40-49 years	5,150	-5.0 (-5.2 to -4.8)	3,354	-5.2 (-5.5 to -4.9)	5,977	-6.8 (-7.0 to -6.6)
50-59 years	6,478	-4.9 (-5.0 to -4.8)	4,367	-5.0 (-5.3 to -4.7)	7,108	-7.0 (-7.2 to -6.8)
60-69 years	8,267	-5.0 (-5.1 to -4.9)	5,663	-5.2 (-5.4 to -5.0)	8,327	-7.7 (-7.8 to -7.6)
70-79 years	11,618	-5.3 (-5.4 to -5.2)	8,130	-5.7 (-5.9 to -5.5)	10,859	-8.9 (-9.0 to -8.8)
80+ years	11,007	-5.7 (-5.8 to -5.6)	7,524	-5.8 (-6.0 to -5.6)	9,968	-10.2 (-10.3 to -10.1)
Weight symptom						
Overall	28,088	1.0 (0.9 to 1.1)	18,215	0.7 (0.6 to 0.8)	27,522	2.7 (2.6 to 2.8)
Male	6,628	0.1 (0.0 to 0.2)	4,120	-0.3 (-0.5 to -0.1)	6,537	0.9 (0.7 to 1.1)
Female	21,460	1.3 (1.2 to 1.4)	14,095	1.0 (0.8 to 1.2)	20,985	3.2 (3.1 to 3.3)
18-29 years	5,931	1.7 (1.5 to 1.9)	3,427	1.0 (0.6 to 1.4)	5,875	4.5 (4.2 to 4.8)
30-39 years	5,600	1.7 (1.6 to 1.8)	3,659	1.4 (1.1 to 1.7)	5,761	4.1 (3.9 to 4.3)
40-49 years	5,226	1.4 (1.3 to 1.5)	3,413	1.2 (0.9 to 1.5)	5,340	3.5 (3.3 to 3.7)
50-59 years	4,489	1.0 (0.9 to 1.1)	3,106	1.1 (0.8 to 1.4)	4,440	2.6 (2.4 to 2.8)
60-69 years	3,400	0.5 (0.3 to 0.7)	2,338	0.2 (-0.1 to 0.5)	3,126	1.4 (1.1 to 1.7)
70-79 years	2,162	-0.9 (-1.1 to -0.7)	1,448	-1.0 (-1.4 to -0.6)	1,896	-2.1 (-2.5 to -1.7)
80+ years	1,280	-3.0 (-3.4 to -2.6)	824	-2.3 (-3.0 to -1.6)	1,084	-6.7 (-7.2 to -6.2)
Weight gain						
Overall	17,957	4.2 (4.1 to 4.3)	10,828	4.9 (4.7 to 5.1)	16,831	7.9 (7.8 to 8)
Male	4,006	3.3 (3.2 to 3.4)	2,473	4.0 (3.7 to 4.3)	3,707	6.4 (6.2 to 6.6)
Female	13,951	4.5 (4.4 to 4.6)	8,355	5.0 (4.8 to 5.2)	13,124	8.4 (8.3 to 8.5)
18-29 years	3,320	5.4 (5.2 to 5.6)	1,806	4.9 (4.4 to 5.4)	3,155	10.3 (10.0 to 10.6)
30-39 years	3,284	4.7 (4.5 to 4.9)	1,999	5.2 (4.7 to 5.7)	3,236	9.1 (8.8 to 9.4)
40-49 years	3,409	4.3 (4.1 to 4.5)	2,093	5.0 (4.6 to 5.4)	3,488	7.9 (7.6 to 8.2)
50-59 years	3,294	3.7 (3.5 to 3.9)	2,078	5.0 (4.6 to 5.4)	3,115	7 (6.8 to 7.2)
60-69 years	2,592	3.4 (3.2 to 3.6)	1,644	4.5 (4.1 to 4.9)	2,243	6 (5.7 to 6.3)
70-79 years	1,544	3.3 (3.1 to 3.5)	935	4.5 (4.0 to 5.0)	1,240	5.6 (5 to 6)
80+ years	514	3.3 (2.8 to 3.8)	273	5.4 (4.3 to 6.5)	354	4.9 (4.0 to 5.8)

Abbreviations: CI, Confidence Interval; N, Denominator; vs, versus.

6.4.3. Method consistency

For the validated weight change codes, there was greater consistency between the method using the previous weight measurement value and the predicted measurement method compared with the historic mean (Figure 6.4.3-1). In addition, the time between the last weight measurement and the weight code and the weight change were positively associated (Table 6.4.3-1).

Figure 6.4.3-1: Comparison of the mean percentage weight change estimated using three methods for each weight change code (hollow circles) and combined by weight change group (full circles).



Abbreviations: KG, Kilogram.

Table 6.4.3-1: Association between time from previous weight measurement and estimated weight change.

	Current vs Last (%)		
	N	Mean (95% CI)	Median (IQR)
Weight loss			
0-2 weeks	3,278	-1.1 (-1.2 to -1.0)	-1.1 (-2.9 to 0.3)
2-4 weeks	3,853	-2.3 (-2.4 to -2.2)	-2.1 (-4 to -0.3)
1-2 months	5,401	-3.4 (-3.5 to -3.3)	-3.1 (-5.5 to -1.1)
2-6 months	15,272	-4.9 (-5.0 to -4.8)	-4.7 (-7.8 to -1.9)
6-12 months	13,572	-6.3 (-6.4 to -6.2)	-6.1 (-9.9 to -2.7)
12-24 months	11,426	-7.2 (-7.3 to -7.1)	-7.1 (-11.3 to -3.3)
Weight symptom			
0-2 week	1,704	-0.3 (-0.4 to -0.2)	-0.1 (-1.7 to 1.0)
2-4 weeks	2,209	-0.5 (-0.6 to -0.4)	-0.5 (-2.2 to 1.0)
1-2 months	3,217	-0.3 (-0.4 to -0.2)	0 (-2.3 to 1.6)
2-6 months	8,331	0.5 (0.4 to 0.6)	0.6 (-2.2 to 3.4)
6-12 months	6,755	1.7 (1.5 to 1.9)	1.9 (-1.9 to 5.6)
12-24 months	5,872	2.4 (2.2 to 2.6)	2.7 (-1.8 to 7.1)
Weight gain			
0-2 weeks	738	0.6 (0.4 to -0.8)	0.0 (-0.9 to 1.8)
2-4 weeks	9,23	1 (0.8 to 1.2)	0.8 (-0.9 to 2.5)
1-2 months	1,499	1.7 (1.5 to 1.9)	1.4 (-0.2 to 3.3)
2-6 months	5,552	3.4 (3.3 to -3.5)	2.9 (0.6 to 5.7)
6-12 months	4,983	5 (4.8 to 5.2)	4.6 (1.5 to 8.2)
12-24 months	4,262	6.6 (6.4 to 6.8)	6.2 (2.7 to 10.3)

Abbreviations: KG, Kilogram; CI, Confidence Interval; N, Denominator; IQR, Inter-Quartile Range; vs, versus.

To evaluate the potential bias of modelling only individuals with valid BMI measures, I compared information on age and gender for those with and without a valid measure. The proportion of individuals with weight measured was consistent across age-group and gender (Table 6.4.3-2).

Table 6.4.3-2: Characteristics of individuals with and without weight measurements stratified by weight change grouping.

	With weight measurement n (%)	Without weight measurement n (%)
Weight loss		
Overall	95,866 (42.1)	131,958 (57.9)
Male	40,897 (41.8)	56,876 (58.2)
Female	54,969 (42.3)	75,082 (57.7)
18-29 years	13,195 (41.8)	18,355 (58.2)
30-39 years	9,588 (41.1)	13,741 (58.9)
40-49 years	10,847 (41.3)	15,391 (58.7)
50-59 years	12,407 (42)	17,134 (58)
60-69 years	14,177 (42.7)	18,988 (57.3)
70-79 years	18,026 (43.1)	23,776 (56.9)
80+ years	17,626 (41.8)	24,573 (58.2)
Weight symptom		
Overall	48,643 (44.9)	59,740 (55.1)
Male	12,061 (45)	14,756 (55)
Female	36,582 (44.8)	44,984 (55.2)
18-29 years	11,232 (45.4)	13,484 (54.6)
30-39 years	9,937 (44.9)	12,194 (55.1)
40-49 years	9,255 (44.6)	11,511 (55.4)
50-59 years	7,619 (44.6)	9,459 (55.4)
60-69 years	5,263 (45.2)	6,383 (54.8)
70-79 years	3,297 (45)	4,024 (55)
80+ years	2,040 (43.2)	2,685 (56.8)
Weight gain		
Overall	35,854 (42.7)	48,102 (57.3)
Male	8,012 (44.7)	9,919 (55.3)
Female	27,842 (42.2)	38,183 (57.8)
18-29 years	6,925 (43.7)	8,929 (56.3)
30-39 years	6,892 (42.5)	9,326 (57.5)
40-49 years	7,436 (41.8)	10,349 (58.2)
50-59 years	6,408 (42.4)	8,723 (57.6)
60-69 years	4,647 (43.3)	6,073 (56.7)
70-79 years	2,651 (43.2)	3,479 (56.8)
80+ years	895 (42.3)	1,223 (57.7)

Abbreviation: n, Numerator.

6.5. Discussion

6.5.1. Summary of findings

This chapter has reported compared methods to assess the extent of weight change prior to a weight change code and findings of the first internal EHR validation study. A degree of correlation would be expected when using one dataset for all three analyses. Of the three methods investigated, the estimates of weight change were most alike when produced using the difference from the preceding weight measurement and the predicted weight based on linear trend. Weight Loss codes were typically employed when weight loss was $\geq 5\%$, especially when the previous weight measurement was over six months ago. Weight Symptom codes were not commonly used by GPs to record weight change and were used variably depending on patient age. These findings have important implications for code list development.

6.5.2. Comparison with existing literature

No directly comparable studies were found. As mentioned in the previous chapters, only one English study has used weight measurement data to define weight loss (95). Weight loss was defined by using the highest recorded weight in the preceding two years, leading to the possibility of under-or over-estimation of weight change.

6.5.3. Strengths and limitations

The previous chapter demonstrated that weight is not recorded routinely in UK primary care and is an example of informative observation: comorbid or sicker patients (potentially with a weight-related problem) are more likely to attend and to have their weight measured (132) or a weight related code (133). Sperrin and colleagues (2017) modelled the time to next BMI

measurement as a recurrent event using anonymised UK primary care data in patients with type 2 diabetes (134). They showed that the higher the previous BMI measurement the higher the likelihood of repeat BMI measurement, that an increasing trend in BMI lowered the likelihood of repeat BMI measurement, and that the presence of comorbidity increased the likelihood of BMI measurement. To minimise the impact of weight coding on subsequent weight measurement patterns, this analysis was restricted to measurements prior to the first weight change code.

Body weight typically increases slowly throughout adulthood, via gains in adiposity, and then slowly decreases from the seventh decade of life as muscle mass is slowly lost (13). Deviations from this underlying trend are unusual without an identifiable pathological or behavioural explanation (1). The slight trend observed in this study towards greater weight loss in the oldest age-groups may represent expected muscle loss or alternatively underlying serious disease in the frail elderly. Information about disease status was not extracted from CPRD for this study meaning that these possibilities could not be investigated as part of this analysis.

To account for expected weight loss, a simple linear regression modelling approach was used in preference to more sophisticated modelling techniques such as regression with restricted cubic splines (135). Weight change was measured over short periods of up to five years and three-monthly means generated to reduce the effect of measurement error in patients with multiple measurements after cleaning the data for outliers.

Nonetheless, each method may have led to inaccuracies in the amount of weight loss estimated. Comparing the current with the last recorded weight may underestimate the extent of weight loss in patients being monitored by their GP for rapid weight loss or in patients without a recent measure who have gained then lost weight since the last recorded measurement. Linear regression may under- or over-estimate weight loss by failing to capture

a curved trajectory. Whereas, as observed, using the historic mean is more likely to overestimate recent weight loss if there are no recent measurements recorded.

6.5.4. Implications for research

Although this study has specific relevance to epidemiologists utilising read coded data derived from the UK general practice EHR, the methods developed are transferrable to any EHR that includes weight measurement data and weight related coding in other healthcare systems.

A cross-sectional analysis examining diabetes coding between 1995 and 2014 showed that code selection made a significant difference to the incidence of diabetes (136). As mentioned in the chapter's introduction, the reporting guideline for this type of the study (the RECORD statement) (31) recommends that the validation steps used when choosing codes or algorithms to select the study population should be provided or referenced, together with a complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers. To this end, this study has validated weight change Read codes for use in primary care EHR research. Such codes will be valuable for epidemiological studies interested in weight as a covariate and, in particular, disease areas with links between weight change and clinical outcomes. Extant studies assessing whether the presence of cancer is predicted by weight loss have mostly defined such loss using read codes without publishing the code lists. Without understanding which codes have been used, and their internal validity, it has been impossible to ascertain the accuracy of the prevalence and the predictive value of weight loss. Having established this for the first time in this chapter, further research should investigate whether estimates of the predicted value of weight loss are modified when using the codes found here to classify weight loss with greater confidence. Din and colleagues recently reported the code lists they used to define symptoms when investigating differences in the interval between symptomatic presentation and a diagnosis of cancer (the diagnostic interval)

(29). They included Weight Symptom codes to define weight loss. This analysis has shown that codes categorised as Weight Symptom codes do not represent weight loss.

6.5.5. Implications for clinical practice

The NICE guidelines for suspected cancer recommend that UWL in combination with other clinical features should prompt further investigation for cancer (22). The systematic review in Chapter Four suggested that UWL alone should prompt investigation for cancer in patients over the age of 60 years. However, neither of these recommendations defined the degree of weight loss, or the time period of loss, that should prompt action. The improved transparency made possible by the consistent use of validated code-lists could inform clinical practice by allowing studies to identify how much weight change is predictive of cancer or other serious disease in primary care. This chapter provides first evidence from primary care that a read code for UWL represents a mean loss of $\geq 5\%$ of body weight in a six-month period. This is a finding that is broadly consistent across age-groups and gender.

6.6. Conclusions and next steps

In this chapter, I have established for the first time the read codes that can be used with confidence to define weight loss in epidemiological studies using CPRD. Upon this basis, I can use Read codes to define weight loss in chapters seven to nine, although some refinement in these chapters will be necessary to maximise the likelihood of including patients with UWL. In Chapter Seven I will conduct a matched-cohort analysis to investigate the association between UWL and cancer across all cancer sites including data on cancer stage to identify the time period of greatest risk of a cancer diagnosis following a presentation of UWL in primary care.

7. The association between unexpected weight loss and cancer diagnosis in patients attending primary care: a matched cohort analysis of 65,000 presentations over 14 years using routinely collected electronic health record data

7.1. Background to this chapter

The systematic review in Chapter Four found 25 primary care studies reporting a positive association between presenting to primary care with unexpected weight loss (UWL) and a subsequent diagnosis of 10 different cancers. No study reported the association between UWL and cancer across all cancer sites or reported UWL in relation to cancer stage. Most studies examined the association between UWL and cancer diagnosis within two years. However the association between UWL and cancer diagnosis is likely to change over time (137).

7.2. Objectives

The objectives of the study detailed in this chapter were to examine:

- the predictive value of UWL for a diagnosis of cancer for all cancers combined;
- the predictive value of UWL for a diagnosis of cancer by cancer site and cancer stage;
- whether any observed association between UWL and cancer varies over time.

7.3. Method

7.3.1. Study design and population

This retrospective matched cohort study used electronic health records (EHR) data from the Clinical Practice Research Datalink (CPRD) with linkage to cancer outcomes data from the National Cancer Registration Analysis Service (NCRAS) (96).

The codes identified in Chapter Six (Table 7.3.1-1) to identify adults aged 18 years or older with coded UWL between the 1st January 2000 to 31st December 2012. I chose to define UWL with a read code as my analysis in Chapter Three demonstrated that relying on weight measurement data to define weight loss would very likely lead to an unrepresentative study population and bias.

Table 7.3.1-1: Validated Read codes used to define unexpected weight loss

medcode	Read term	n (%)
654	Weight Decreasing	6,439 (10.1)
3647	[D]Abnormal loss of weight	15,738 (24.6)
4663	Abnormal weight loss	2,551 (4.0)
5812	Abnormal weight loss - symptom	31,562 (49.3)
12398	Complaining of weight loss	4,809 (7.5)
22005	O/E - cachexic	45 (0.1)
24068	[D]Cachexia	249 (0.4)
37937	Weight loss from baseline weight	2,537 (4.0)
102563	Unintentional weight loss	43 (0.1)
Total		63,973 (100)

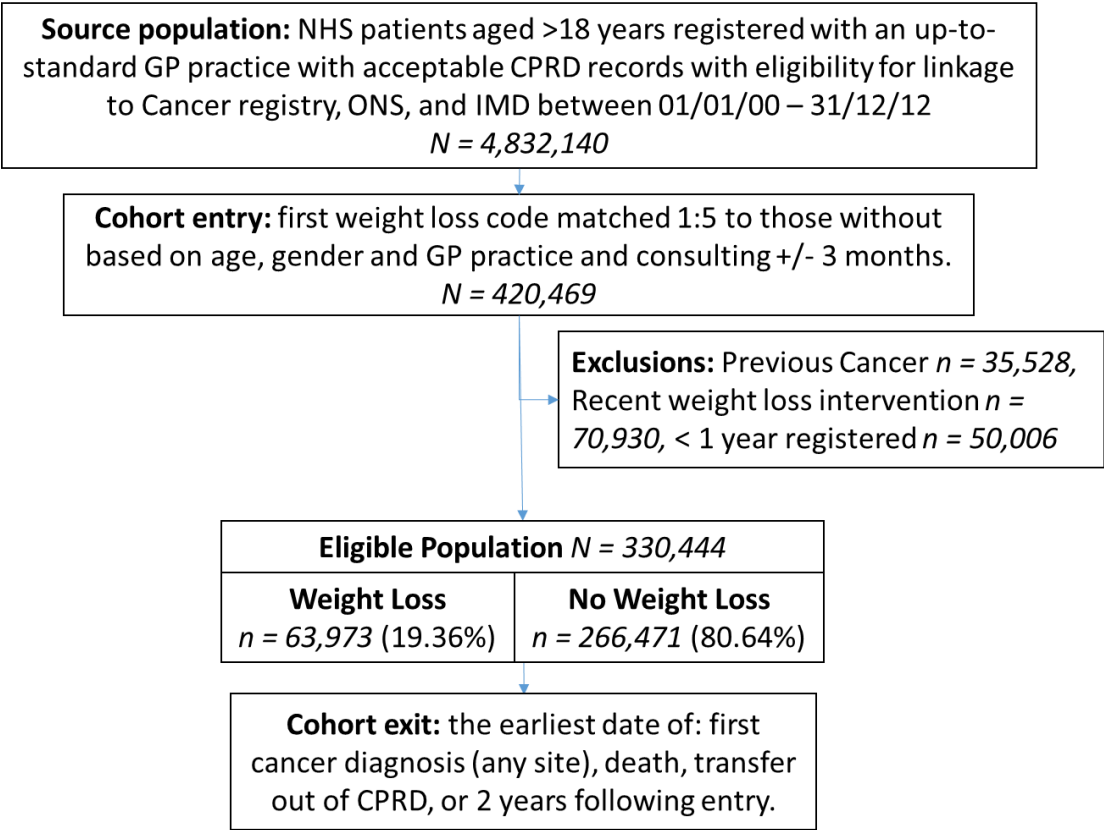
D: Diagnosis; O/E: Observation / Examination

For inclusion, records were required to be of acceptable data quality as judged by CPRD and eligible for linkage to the NCRAS cancer registry, Office for National Statistics (ONS) mortality, and index of multiple deprivation (IMD) data.

The study inclusion date was truncated at the 31st December 2012 as CPRD data were applied for in 2016 and two years of follow-up was required for each included patient to identify

cancer diagnoses following an UWL presentation (2012-2014). It then takes two years for NCRAS to release validated cancer registry data (2014-2016). Cohort entry, exclusions and exit are summarised in Figure 7.3.1-1.

Figure 7.3.1-1: Study flow diagram



To each patient coded with UWL, five patients who had never had a coded entry for UWL were matched if they had consulted within six months (3 months before or after) of the UWL code date, and also matched on their age, gender and GP practice. Age and sex were chosen to ensure sufficient patients in each age and sex strata, and GP practice to account for practice level clustering of GP coding behaviour.

A matched cohort study design was chosen over an open cohort as this is an efficient study design that limits confounding by forcing the baseline distribution of matching variables to be identical between patients with and without UWL. Age, sex and practice are known

confounders of the association between UWL and cancer for which there would be very little missing data.

When I received the dataset from CPRD, who had mandated that they performed this data cut due to information governance reasons as it was linked to NCRAS data, I realised that CPRD had not matched patients with and without UWL using age and sex. This resulted in a large proportion of the non-UWL group being under the age of 18 years and there being insufficient patients without UWL in each age and sex strata to perform a meaningful analysis of the association with cancer in adults. Although, my CPRD protocol had been approved in September 2016 it was not until March 2018 that I received a second dataset: however this too contained errors in the non-UWL group: 50,006 of these patients had not been registered for at least one year prior to the index date. Whilst I was lucky to have identified this prior to conducting any time-consuming data management or analysis, the delay in getting started provided me with a lesson in building in contingencies when working with external data providers. Due to the time constraints of my degree, I was unable to wait for CPRD to provide a further dataset and therefore adapted my methods to exclude the patients with inadequate registration time after matching.

Additional steps were taken to ensure the accurate definition of the cohort with UWL. Firstly, unlike several previous studies (17, 47), patients with a past history of cancer were excluded as they are at higher risk of cancer than the primary care population (21). Other studies have attempted to adjust for previous cancer, however this was without considering how long ago that cancer was diagnosed in relation to the UWL (16, 85). Secondly, unlike earlier studies, patients with evidence of intentional weight loss were excluded by searching prescription records and identifying recent bariatric surgery. Thirdly, patients who had been registered with the CPRD general practice for less than a year prior to the data cut date to ensure that there was no cancer diagnosis or previous UWL codes within this period. The CPRD had not

implemented this exclusion criterion in the non-UWL comparators when preparing the dataset.

If a patient with UWL was excluded, all of their matched controls were excluded. If a control patient without UWL was excluded, only that one control was excluded.

7.3.2. Identifying cancers diagnosed

A library of cancer Read codes developed by Hamilton and colleagues was reviewed (34), and updated by searching the Read code hierarchy to include all high-level ICD-O categories.

Cancer codes were grouped to represent the most common sites reported in the UK (49) and those that would be investigated together to ensure our findings could inform clinical guidance. For example: renal, ureteric and bladder cancer were combined as renal tract; and liver, gallbladder and biliary tree as hepatobiliary (HPB). Haematological cancers were investigated in combination and separately as previous reports have shown a greater association between weight loss and lymphoma compared to myeloma or leukaemia (68, 69, 138).

All new cancer diagnoses in the 24 months following the index date were identified in CPRD using the code lists and the linked cancer registry data using International Classification of Diseases for Oncology (ICD-O) categories. A two-year period was used to align with the existing literature (16, 85). When more than one incident cancer occurred, the first cancer was included in the analysis. Cancer of unknown primary (CUP) was classified if patients' records indicated secondary cancer with no primary site. Data on cancer stage, grade, tumour size, and histology were received from NCRAS but the extent of missing data meant that only cancer stage could be included. Cancer stage was analysed by individual stage, and then grouped as early-stage (I and II) and late-stage (III and IV).

7.3.3. Additional covariates

Potential confounders were taken from the dataset before the index date and are defined in Table 7.4.1-1.

7.3.4. Statistical analysis

A series of time-to-event analyses were conducted to investigate the association between a patient presenting to UK primary care with UWL and a subsequent diagnosis of cancer, for all cancers combined and separately by cancer type, cancer stage, by gender and by age-group. All analyses were conducted in Stata version 15. I developed the statistical analysis plan, wrote the code and conducted the analyses based on my own reading and by attending targeted short courses, only asking for advice from statistician colleagues to discuss emerging results and to confirm that the approach taken was appropriate and robust.

The diagnostic interval (DI) was summarised using the median (inter-quartile range, IQR) and mean (standard deviation, SD) and differences between medians assessed using the k-sample test (Table 1). For the UWL group, the DI is the number of days between the index date of the UWL consultation and the cancer diagnosis (139). For the comparator group without UWL, the DI represents the time between index consultation for something other than UWL and the cancer diagnosis.

Smoothed hazard rates and cumulative hazard rates were then plotted over time from the index consultation, stratified by gender, age-group, and cancer type and cancer stage. A hazard rate is the proportion of patients at each time point who have the event (140). The cumulative hazard is the proportion of patients who have had the event up to and including each time point (140). Differences between groups were assessed using the Wilcoxon rank test in preference to the logrank test as the event distribution was right-skewed (there were

more events early in the follow-up period for patients with UWL) (141). A p-value of less than 0.05 was used to identify a statistically significant difference between curves.

Stata's *stcox* command was used to implement multivariable Cox models to derive hazard ratios (HRs) and corresponding 95% confidence intervals (95%CI) for cancer for each six-month period of follow-up, adjusted for all covariates. HRs derived using Cox regression summarises how much a covariate increases or decreases the risk of an event (hazard) rate during a specified follow-up period (140). The basic assumption required for Cox modelling is that the difference between groups does not change over time or that the difference remains proportional over time (the proportional hazards assumption).

A priori, "heaviside" functions using the *stsplit* command in Stata were used to split the follow-up period into six-month intervals in order to investigate the time varying nature of the association between UWL and cancer (142). Within each interval, the validity of the proportional hazards assumption was assessed using the Schoenfeld residuals test (SRT) (142). The SRT failed for all cancers combined in men and women and lung cancer in men (Table 7.4.9-1 & Table 7.4.9-2). After refitting the Cox models with an initial three-month interval and stratifying the analyses by comorbidity, all cancer groupings passed the SRT (Table 7.4.9-1 & Table 7.4.9-2).

Adjusted HRs for zero to three months and zero to six months intervals were plotted in order of magnitude and by gender.

7.3.5. Sensitivity analyses

Three sensitivity analyses were conducted to further explore the association between UWL and cancer diagnosis.

Firstly, flexible parametric Royston-Palmar (RP) models were fitted to assess how the HR changed over time for all cancers combined, adjusted for all covariates. RP models do not require the HR to remain proportional over time and so the follow-up period does not need to be split using the heaviside function. RP models allow changes in the HR by using restricted cubic splines to model the baseline log cumulative hazard function on the log timescale (135, 140, 142). Restricted cubic splines are a series of (cubic) curves that, when pieced together and the joins smoothed, produce a curve that is a similar shape to a more complex curve. Each curve is joined by a “knot”: $X \text{ knots} = X+1 \text{ degrees of freedom}$. The HR was modelled for cancer overall using restricted cubic splines with 4 degrees of freedom (140). It was not possible to fit RP models for most individual cancer sites due to the low numbers of events, despite reducing the degrees of freedom to address this.

Secondly, HRs were calculated from Cox models that included a variable to denote each matched group of UWL and non-UWL patients to assess its effect on HR precision.

Thirdly, the probability that a person with UWL is diagnosed with cancer in the next three months was calculated based on their age and gender by substituting age-group with age as a continuous variable in the zero to three months Cox models, centering age at 60 years and including interactions between UWL, age and gender. Marginal effects at representative values (MERS) were calculated as a type of population level prediction (143, 144). Similar to the RP models, small event numbers for some cancers meant the analysis was not stratified by cancer site or stage.

7.4. Results

7.4.1. Summary of cohort.

63,973 patients had UWL recorded in CPRD, a prevalence of 1.3% (63,973 of 4,832,140) during the study period. Table 4.4.1-1 details how patients with UWL compared to controls.

1,375 of 63,973 patients (2.2%) with UWL and 8,285 of 266,471 patients (3.1%) without UWL were diagnosed with cancer over two-years of follow-up (Table 4.4.7-2). There was only a minority (n=1103, 11.4%) of cancers with cancer staging reported precluding stratification by cancer site (Table 4). Of staged cancers, 260 (23.6%) were Stage I, 227 (20.6%) Stage II, 180 (16.3%) Stage III, 436 (39.5%) stage IV.

The DI was significantly shorter in patients with UWL (median 80 days, IQR 26- to 290 days), with a positive skew (mean 181 days, SD205), compared to patients without (median 353 days, IQR 181 to 541days), $p<0.01$).

Table 7.4.1-1: Baseline demographics of the study population by Unexplained Weight Loss (UWL) status

		UWL	No UWL	Chi²
	N	n (%)	n (%)	p-value
Total	330,444	63,973 (19.4)	266,471 (80.6)	n/a
Gender				
Men	140,002	26,758 (41.8)	113,244 (42.5)	<0.001
Women	190,442	37,215 (58.2)	153,227 (57.5)	<0.001
Age-group (years)				
18-39	69,837	14,290 (22.3)	55,547 (20.9)	<0.001
40-49	42,159	8,016 (12.5)	34,143 (12.8)	0.155
50-59	45,229	8,511 (13.3)	36,718 (13.8)	0.018
60-69	48,292	9,017 (14.1)	39,275 (14.7)	0.003
70-79	61,125	11,565 (18.1)	49,560 (18.6)	0.023
80+	63,828	12,574 (19.7)	51,254 (19.2)	0.067
Smoking				
Current	33,440	9,629 (15.1)	23,811 (9.0)	<0.001
Ex-Smoker	38,153	7,164 (11.1)	30,989 (11.6)	<0.001
Non-Smoker	84,913	14,457 (22.6)	70,456 (26.4)	0.410
Missing	173,938	32,723 (51.2)	141,215 (53.0)	<0.001
Alcohol				
Current	99,340	18,435 (28.8)	80,905 (30.4)	<0.001
Non-Drinker	35,950	8,095 (12.7)	27,855 (10.5)	<0.001
Past-Drinker	4,015	1,087 (1.7)	2,928 (1.1)	<0.001
Missing	191,139	36,356 (56.8)	154,783 (58.1)	<0.001
Family history cancer				
Yes	19,491	4,119 (6.4)	15,372 (5.8)	<0.001
No	310,953	59,854 (93.6)	251,099 (94.2)	<0.001
IMD quintile				
I (least deprived)	72,623	12,552 (19.6)	60,071 (22.6)	<0.001
II	72,525	13,212 (20.7)	59,313 (22.3)	<0.001
III	70,486	13,507 (21.1)	56,979 (21.4)	0.135
IV	59,757	12,156 (19.2)	47,601 (17.9)	<0.001
V (most deprived)	54,694	12,417 (19.4)	42,277 (15.9)	<0.001
Comorbidity				
0	82,373	8,870 (13.9)	73,503 (27.6)	<0.001
1	74,057	12,765 (20.0)	61,292 (23.0)	<0.001
2	59,361	12,641 (19.8)	46,720 (17.5)	<0.001
3	43,747	10,378 (16.2)	33,369 (12.5)	<0.001
4	29,756	7,638 (12.0)	22,118 (8.3)	<0.001
5+	44,153	11,684 (18.3)	29,469 (11.1)	<0.001
BMI group				
Underweight	11,294	6,691 (10.9)	4,603 (1.7)	<0.001
Normal	122,298	33,846 (52.9)	88,452 (33.2)	<0.001
Overweight	95,490	10,790 (16.9)	84,700 (31.8)	<0.001
Obese	56,968	5,141 (8.0)	51,827 (19.5)	<0.001
Missing	44,124	7,235 (11.3)	36,889 (13.8)	<0.001

N/A: not applicable; IMD: index of multiple deprivation; BMI: body mass index

Table 7.4.1-2: Distribution and diagnostic intervals for cancers diagnosed in the two years following the index date stratified by unexplained weight loss (UWL) status. IQR: Interquartile range; SD: standard deviation

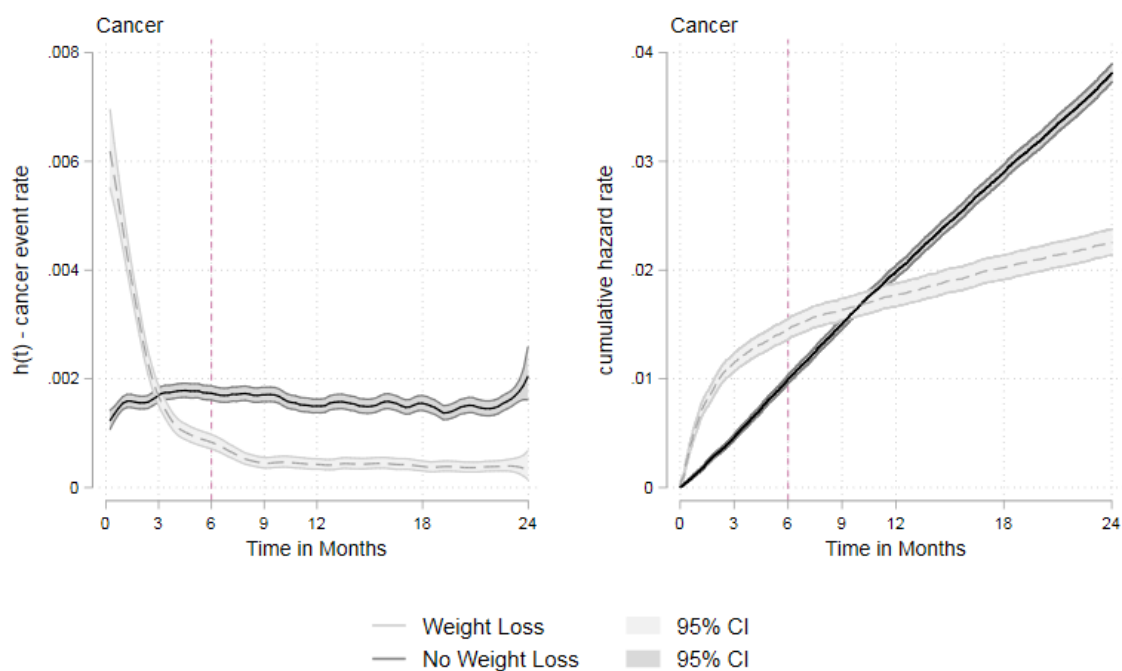
Cancer	UWL				No UWL			K-Sample Test
	All	Cancers	Diagnostic Interval (days)		Cancers	Diagnostic Interval (days)		
	<i>n</i> (% of All)	<i>n</i> (% of UWL)	Median (IQR)	Mean (SD)	<i>n</i> (% of no UWL)	Median (IQR)	Mean (SD)	<i>p</i> -value
Overall	9,660 (2.92)	1375 (2.15)	80 (26-290)	181 (205)	8285 (3.11)	353 (181-541)	361 (209)	<0.01
Stage 1	260 (0.08)	41 (0.06)	404 (194-551)	372 (224)	219 (0.08)	395 (201-525)	375 (202)	1.00
Stage 2	227 (0.07)	35 (0.05)	314 (24-607)	314 (270)	192 (0.07)	463 (240-610)	427 (213)	0.08
Stage 3	180 (0.05)	34 (0.05)	166 (17-341)	210 (213)	146 (0.05)	432 (214-652)	418 (231)	<0.01
Stage 4	436 (0.13)	139 (0.22)	76 (25-416)	202 (230)	297 (0.11)	404 (203-580)	391 (218)	<0.01
Lung	1,417 (0.43)	309 (0.48)	63 (24-210)	155 (187)	1,108 (0.42)	362 (190-541)	368 (207)	<0.01
Bowel	1,394 (0.42)	180 (0.28)	89 (30-311)	190 (203)	1,214 (0.46)	351 (188-535)	358 (208)	<0.01
Prostate	1,260 (0.38)	76 (0.12)	142 (42-438)	247 (227)	1,184 (0.44)	366 (184-552)	370 (209)	<0.01
Breast	1,183 (0.36)	26 (0.04)	426 (188-593)	400 (237)	1,157 (0.43)	341 (173-532)	353 (209)	0.16
Renal tract	703 (0.21)	96 (0.15)	111 (30-277)	177 (183)	607 (0.23)	346 (188-532)	358 (207)	<0.01
Gastro-oesophageal	562 (0.17)	141 (0.22)	42 (16-195)	138 (189)	421 (0.16)	350 (196-533)	361 (207)	<0.01
Lymphoma	407 (0.12)	94 (0.15)	80 (23-205)	146 (166)	313 (0.12)	363 (187-533)	368 (212)	<0.01
Pancreatic	348 (0.11)	111 (0.17)	56 (17-219)	158 (203)	237 (0.09)	379 (179-556)	372 (215)	<0.01
Cancer of unknown primary	325 (0.10)	87 (0.14)	58 (15-223)	152 (200)	238 (0.09)	314 (157-514)	339 (211)	<0.01
Leukaemia	280 (0.08)	18 (0.03)	141 (63-302)	208 (200)	262 (0.10)	371 (189-584)	376 (217)	0.03
Melanoma	278 (0.08)	10 (0.02)	184 (68-612)	299 (261)	268 (0.10)	386 (189-567)	382 (211)	0.75
Ovary	210 (0.06)	32 (0.05)	114 (44-540)	257 (254)	178 (0.07)	342 (174-555)	355 (213)	0.18
Head & neck	202 (0.06)	19 (0.03)	186 (106-557)	297 (250)	183 (0.07)	329 (168-497)	342 (206)	0.63
Uterine	195 (0.06)	20 (0.03)	149 (42-528)	273 (266)	175 (0.07)	335 (152-521)	342 (215)	0.49
Hepatobiliary	192 (0.06)	55 (0.09)	61 (20-161)	166 (223)	137 (0.05)	345 (173-532)	363 (210)	<0.01
Bone, connective soft tissue	190 (0.06)	30 (0.05)	95 (32-288)	180 (202)	160 (0.06)	320 (136-526)	336 (216)	0.01
Other	182 (0.06)	22 (0.03)	149 (36-319)	206 (209)	160 (0.06)	374 (205-566)	371 (213)	0.01
Myeloma	164 (0.05)	24 (0.04)	218 (127-449)	268 (198)	140 (0.05)	379 (219-584)	390 (207)	0.05
Central nervous system	155 (0.05)	19 (0.03)	133 (58-295)	194 (162)	136 (0.05)	306 (130-534)	328 (218)	0.05

7.4.2. Hazard rates and cumulative hazard

The risk of a cancer diagnosis was higher in patients with UWL than patients without UWL in the three months after the index consultation. However, for the remainder of the two-year follow up period, the risk of cancer was higher in the patients without UWL (Figure 7.4.2-1 – left panel).

Expressed as the cumulative hazard of cancer, 1.2% of patients with UWL and 0.5% without UWL had been diagnosed with cancer in the first three months after the index consultation, a difference that narrowed to 1.6% and 1.5% by nine months and then inverted to 1.8% and 2.0% by 12 months (Figure 7.4.2-1 – right panel).

Figure 7.4.2-1: Univariate smoothed hazard rate and cumulative hazard of cancer diagnosis by unexpected weight loss status



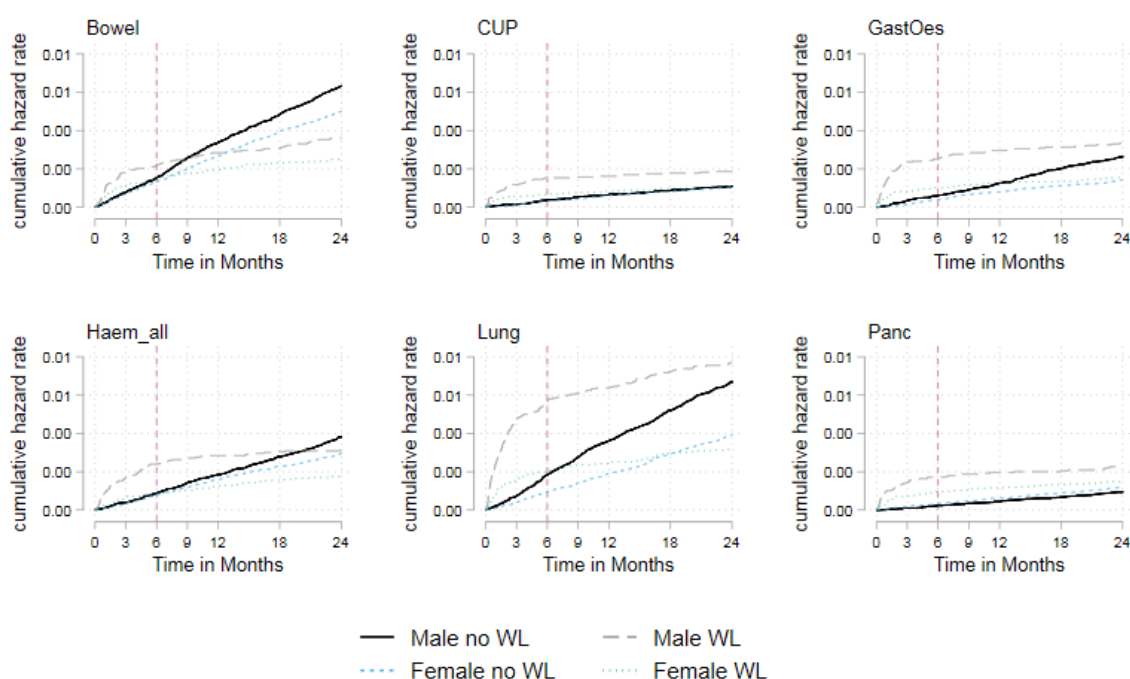
CI: confidence interval; $h(t)$: hazard at time t

7.4.3. Stronger association cancer sites

Figure 7.4.3-1 illustrates the cancer sites with a stronger association with UWL based on the shape of the cumulative hazard curve. They exhibited a rapid acceleration in the cumulative hazard during the first three months that levelled out by six months.

The increased cumulative hazard in patients with UWL was sustained for at least the first year of follow-up in CUP, gastro-oesophageal and pancreatic cancer. For lung, bowel and haematological cancer, the increased cumulative incidence was not sustained: the cumulative incidence of patients without UWL overtook patients with UWL throughout follow-up although this occurred later in men reflecting their greater initial acceleration of cumulative hazard.

Figure 7.4.3-1: Cumulative hazard rates for cancer sites with a stronger association with unexpected weight loss



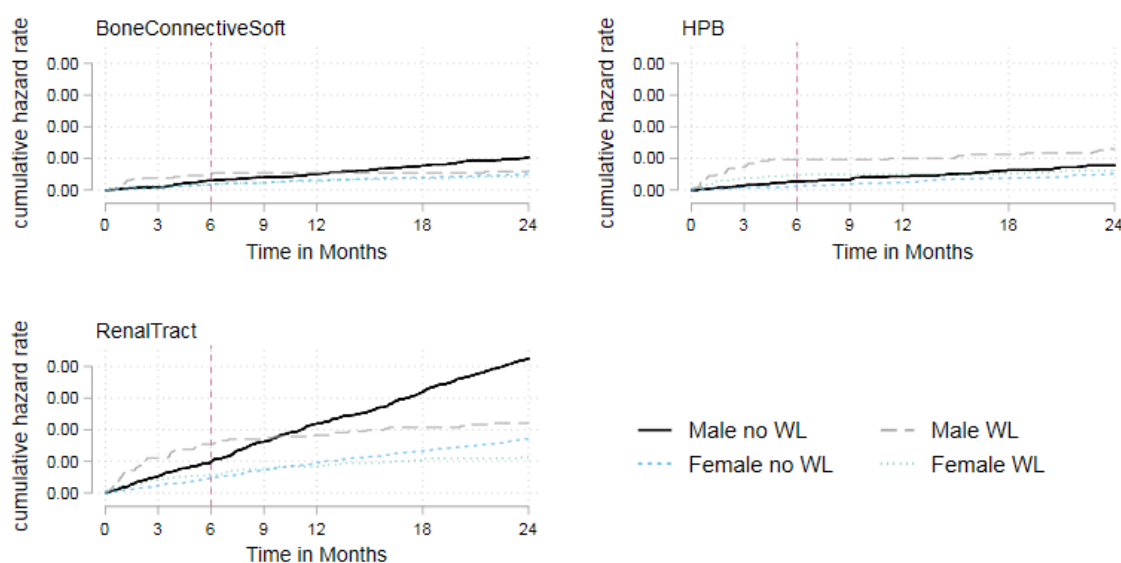
(CUP: cancer of unknown primary; GastOes: gastro-oesophageal; Haem_all: combined haematological; Panc: pancreatic; WL: weight loss)

7.4.4. Moderate association cancer sites

Figure 7.4.4-1 presents the cancers observed to have a moderate association between UWL and a cancer diagnosis. These are bone, connective and soft tissue cancer, HPB cancer and cancer of the renal tract.

The initial acceleration in cumulative incidence is less marked than in the 'stronger association' cancers (Figure 3) but an initial separation is still observed. Due to the slower early acceleration, the cumulative hazard rates typically lie closer together and crossover sooner. Exceptions are UWL in men diagnosed with HPB cancer, for whom a sustained greater cumulative incidence is seen, and men with renal tract cancer who, compared to women, have a greater cumulative incidence

Figure 7.4.4-1: Cumulative hazard ratios for cancers sites with a moderate association with unexpected weight loss



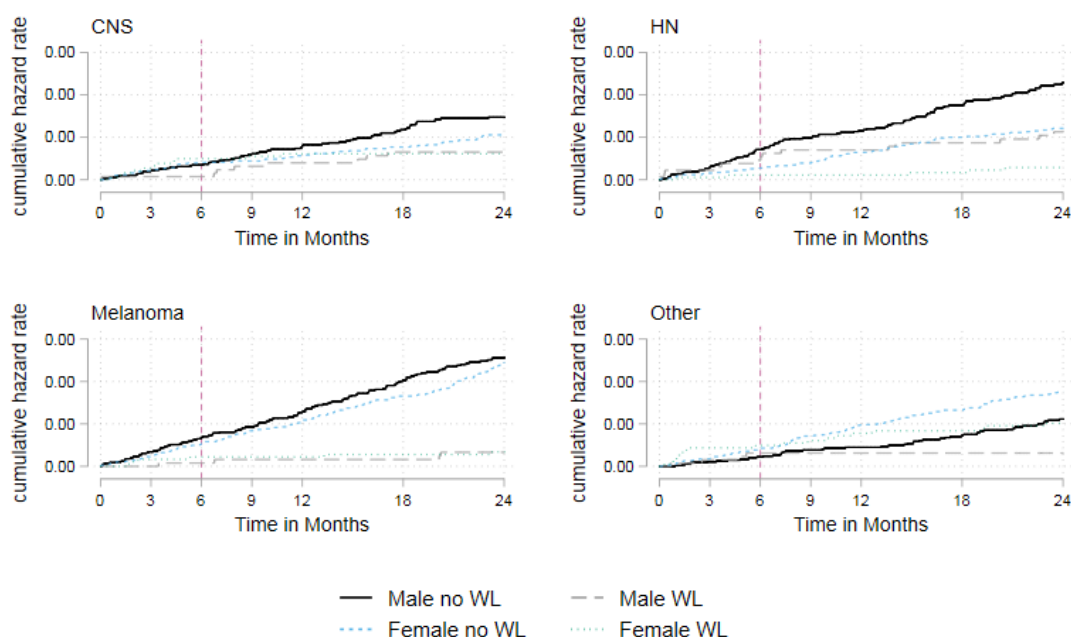
HPB: hepatobiliary; WL: weight loss

7.4.5. Weaker association cancer sites

Figure 7.4.5-1 reports the cancer sites that did not demonstrate a strong or moderate association with UWL. These are central nervous system tumours, head and neck cancers, melanoma and other cancers.

The cumulative hazard rate observed for men and women with UWL remained below the rate for patients without UWL for central nervous system tumours and melanoma. For head and neck cancer, there was a very early acceleration in hazard rates in men that was soon overtaken by patients without UWL in the first month. No such difference was observed in women. The opposite effect is seen for other cancers (made up of x and y) in which there was an increase in cancer incidence in women with UWL initially but not in men.

Figure 7.4.5-1: Cumulative hazard rates for cancer sites with a weaker association with unexpected weight loss



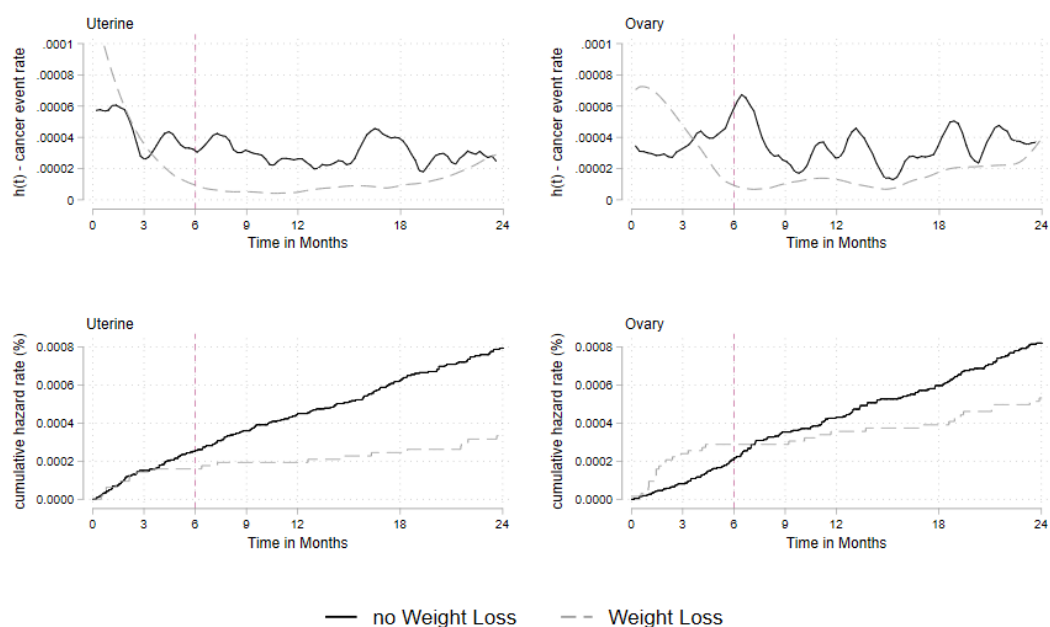
CNS: central nervous service; HN: head and neck

7.4.6. Female cancer sites

The cumulative hazard curve for ovarian cancer was similar to a stronger association cancer. However, the initially increased cumulative hazard was not sustained throughout the follow-up period with the cumulative incidence of patients without UWL overtaking patients with UWL between six and nine months...

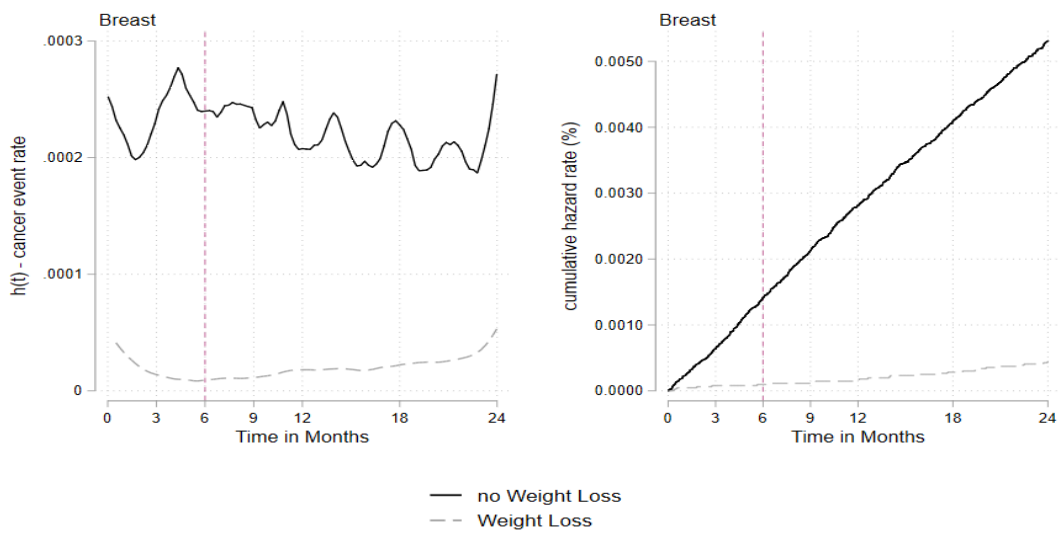
For uterine cancer, the association with UWL appeared to be much weaker resembling the pattern seen in men with head and neck cancer: a very early acceleration in hazard was overtaken by patients without UWL in the first month (Figure 7.4.6-1).

Figure 7.4.6-1: Hazard rate and cumulative hazard of uterine and ovarian cancer diagnosis by weight loss status ($h(t)$ hazard at time t)



There appeared to be no association between UWL and breast cancer with the hazard rate and cumulative hazard in women without UWL exceeding those in women with UWL (Figure 7.4.6-2).

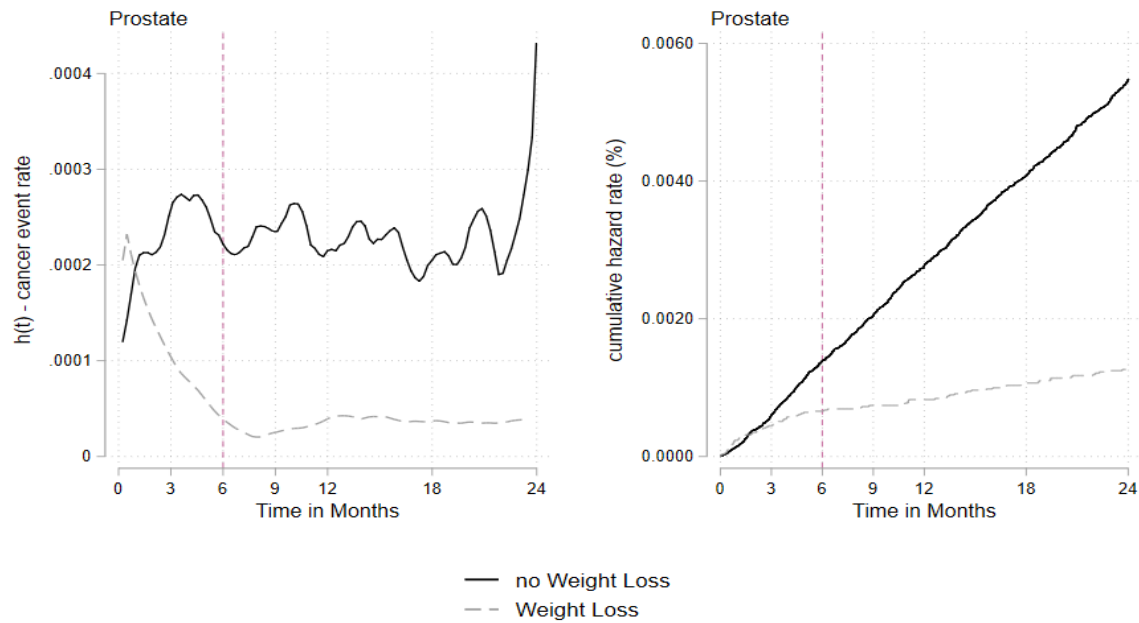
Figure 7.4.6-2: Hazard rate and cumulative hazard of breast cancer by unexpected weight loss status



7.4.7. Prostate cancer

The association between prostate cancer and UWL was weak with a slightly increased hazard in the UWL group that was quickly overtaken by the cumulative hazard for cancer in the group without UWL (Figure 7.4.7-1).

Figure 7.4.7-1: Hazard rate and cumulative hazard of prostate cancer by unexpected weight loss status ($h(t)$: hazard at time t)



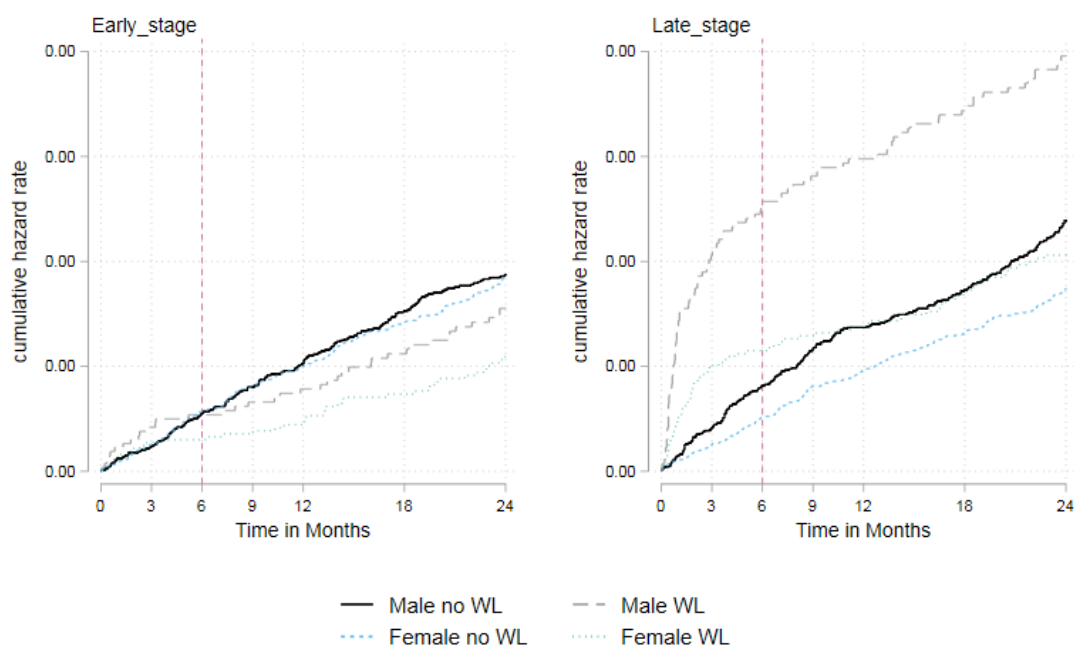
7.4.8. Cancer stage

The risk of early stage cancer was similar between UWL and non-UWL groups: the cumulative hazard of early-stage cancer in the non-UWL group quickly overtook the UWL group. 21

(0.03%) of 61,608 patients with UWL were diagnosed in the first 3 months rising to 25 (0.04%) by 6-months, compared to 64 (0.02%) of 252,909 patients without UWL rising to 141 (0.06%).

UWL was associated with late-stage cancer diagnoses (Figure 7.4.8-1). The cumulative hazard remained persistently greater in patients with UWL following a sharp acceleration during the first 3-6 months. By six months, the cumulative hazard was over three times greater in patients with UWL. 54 (0.20%) were diagnosed in 25,551 men with UWL in the first three months, rising to 66 (0.30%) by six months. This compared to 46 (0.04%) of 10,706 men without UWL in the first three months rising to 88 (0.08%) by six. In the first three months, 37 (0.10%) were diagnosed in 36,057 women with UWL rising to 52 (0.10%) by six. 38 (0.02%) were diagnosed in 145,203 women without UWL over three months rising to 75 (0.05%).

Figure 7.4.8-1: Univariate smoothed hazard rate and cumulative hazard by cancer stage in patients with and without unexpected weight loss by gender



7.4.9. Multivariable models

The Cox models showed that in the first three months, men with UWL had more than a three-fold likelihood of being diagnosed with cancer compared to their matched controls (HR 3.28, 95%CI 2.88-3.73) (Table 7.4.9-1). For women, the HR was less (1.85, 95% CI 1.6-2.14) (Table 7.4.9-2). A similar pattern was observed when considering HRs for the first six months (Table 7.4.9-1, Table 7.4.9-2, Figure 7.4.9-1, Figure 7.4.9-2).

UWL was associated with an increased likelihood of pancreatic cancer, CUP, gastro-oesophageal, lymphoma, HPB, lung, bowel and renal tract compared with controls Table 7.4.9-1, Table 7.4.9-2, Figure 7.4.9-1, Figure 7.4.9-2). UWL was associated with a decreased likelihood of breast in women and prostate cancer compared to the controls. The HR for bone, connective and soft tissue cancers and myeloma in men, and ovarian in women were statistically significantly increased over three months in patients with UWL but not over six months (Table 7.4.9-1, Table 7.4.9-2, Figure 7.4.9-1, Figure 7.4.9-2).

The RP models allowed closer inspection of how the HR changed over time for men and women (

Figure 7.4.9-3). The HR for all cancer types combined was initially much higher in men and women with UWL. However, at approximately three months of follow-up, it fell below the probability of cancer in patients without UWL and remained lower thereafter.

This pattern was most frequently seen in Stage IV cancers but there was also an increased likelihood of Stage III cancer diagnosis in men with UWL (Table 7.4.9-1). An increased probability of Stage II cancer was observed for men (HR 3.38, 95%CI 1.3-8.82) although there was no difference in likelihood for earlier stage cancers combined.

Table 7.4.9-1: Hazard ratios (HRs) for a diagnosis of cancer in men patients presenting to primary care with unexpected weight loss for 0-3 months and 0-6 months models.

Each model is adjusted for age-group, smoking status, alcohol intake, ethnicity, deprivation, BMI-group, and family history of cancer.

	Men						
	0-3 months			0-6 months			
	HR (95% CI)	<i>p-value</i>	SRT	HR (95% CI)	<i>p-value</i>	SRT	
All cancers	3.28 (2.88-3.73)	<0.01	0.2	1.87 (1.68-2.08)	<0.01	<0.01	
Stage I	0.73 (0.21-2.58)	0.63	0.9	0.53 (0.18-1.54)	0.24	0.97	
Stage II	3.38 (1.3-8.82)	0.01	0.98	1.39 (0.66-2.91)	0.39	0.56	
Stage III	2.53 (1.12-5.69)	0.03	0.9	2.11 (1.05-4.22)	0.04	0.79	
Stage IV4	6.89 (4.22-11.24)	<0.01	0.8	3.79 (2.57-5.61)	<0.01	0.34	
Early Stage (I & II)	1.72 (0.83-3.55)	0.14	0.98	0.95 (0.52-1.73)	0.87	0.58	
Late Stage (III & IV)	5.22 (3.46-7.88)	<0.01	0.79	3.26 (2.32-4.58)	<0.01	0.34	
Bone connective & soft tissue	4.58 (1.87-11.18)	<0.01	0.79	1.97 (1.01-3.87)	0.05	0.4	
Bowel	2.56 (1.78-3.67)	<0.01	0.97	1.49 (1.09-2.03)	0.01	0.33	
Cancer of unknown primary	8.20 (4.41-15.26)	<0.01	0.69	4.29 (2.69-6.83)	<0.01	0.17	
Central nervous system	0.32 (0.04-2.53)	0.28	0.76	0.23 (0.03-1.71)	0.15	0.67	
Gastro-oesophageal	7.10 (4.66-10.81)	<0.01	0.52	4.26 (2.97-6.1)	<0.01	0.14	
Head & neck	0.58 (0.17-2.02)	0.39	0.85	0.51 (0.21-1.23)	0.13	0.88	
Hepatobiliary	5.26 (2.63-10.52)	<0.01	0.92	3.85 (2.19-6.76)	<0.01	0.67	
Leukaemia	1.25 (0.49-3.22)	0.64	0.88	1.03 (0.48-2.19)	0.95	0.97	
Lung	5.93 (4.43-7.94)	<0.01	0.23	2.74 (2.18-3.43)	<0.01	<0.01	
Lymphoma	6.69 (3.82-11.73)	<0.01	0.92	4.22 (2.72-6.55)	<0.01	0.96	
Melanoma	N/E	N/E	N/E	0.13 (0.02-0.95)	0.04	0.95	
Myeloma	6.44 (1.16-35.86)	0.03	0.9	1.42 (0.53-3.77)	0.48	0.65	
Other	1.79 (0.35-9.22)	0.48	0.93	1.95 (0.6-6.31)	0.26	0.94	
Pancreas	13.31 (6.79-26.1)	<0.01	0.83	6.86 (4.11-11.43)	<0.01	0.31	
Prostate	0.79 (0.53-1.19)	0.27	0.74	0.51 (0.37-0.71)	<0.01	0.32	
Renal tract	2.16 (1.36-3.43)	<0.01	0.75	1.61 (1.1-2.35)	0.01	0.44	

CI confidence interval; SRT: Schoenfeld residuals test, <0.05 indicates non-proportionality. N/E: not estimable.

Table 7.4.9-2: Hazard ratios (HRs) for a diagnosis of cancer in women patients presenting to primary care with unexpected weight loss (UWL) for 0-3m and 0-6m models.

Each model is adjusted for age-group, smoking status, alcohol intake, ethnicity, deprivation, BMI-group, and family history of cancer.

	Women						
	0-3 months			0-6 months			
	HR (95% CI)	<i>p-value</i>	SRT	HR (95% CI)	<i>p-value</i>	SRT	
Cancer	1.85 (1.6-2.14)	<0.01	0.28	1.12 (0.99-1.26)	0.08	<0.01	
Stage I	1.31 (0.52-3.3)	0.57	0.95	0.61 (0.26-1.45)	0.26	0.69	
Stage II2	1.31 (0.42-4.03)	0.64	0.7	0.86 (0.33-2.26)	0.76	0.5	
Stage III3	1.54 (0.54-4.37)	0.42	0.86	0.85 (0.32-2.27)	0.75	0.81	
Stage IV4	5.32 (3.06-9.24)	<0.01	0.94	2.93 (1.86-4.59)	<0.01	0.48	
Early Stage (I & II)	1.31 (0.64-2.68)	0.46	0.83	0.71 (0.37-1.34)	0.29	0.46	
Late Stage (III & IV)	3.96 (2.47-6.34)	<0.01	0.86	2.25 (1.51-3.34)	<0.01	0.48	
Bone connective & soft tissue	1.96 (0.66-5.82)	0.22	0.94	0.92 (0.37-2.28)	0.85	0.6	
Bowel	1.55 (1.07-2.25)	0.02	0.73	1.10 (0.81-1.50)	0.53	0.37	
Breast	0.13 (0.05-0.31)	<0.01	0.09	0.07 (0.03-0.16)	<0.01	0.62	
Cancer of unknown primary	4.22 (2.24-7.96)	<0.01	0.55	2.10 (1.26-3.50)	<0.01	0.19	
Central nervous system	1.34 (0.48-3.75)	0.57	0.97	1.27 (0.59-2.76)	0.54	0.96	
Gastro-oesophageal	5.45 (3.09-9.63)	<0.01	0.44	2.66 (1.72-4.13)	<0.01	0.12	
Head & neck	0.29 (0.04-2.28)	0.24	0.95	0.35 (0.08-1.53)	0.16	0.94	
Hepatobiliary	5.36 (2.4-11.95)	<0.01	0.8	4.27 (2.13-8.55)	<0.01	0.62	
Leukaemia	0.20 (0.03-1.48)	0.11	0.88	0.29 (0.09-0.96)	0.04	0.84	
Lung	3.59 (2.47-5.21)	<0.01	0.54	1.82 (1.36-2.44)	<0.01	0.07	
Lymphoma	3.21 (1.75-5.88)	<0.01	0.91	1.75 (1.06-2.91)	0.03	0.37	
Melanoma	0.75 (0.22-2.58)	0.65	0.94	0.52 (0.19-1.48)	0.22	0.96	
Myeloma	0.80 (0.09-6.78)	0.84	0.81	0.56 (0.16-1.90)	0.35	0.89	
Other	2.59 (1.06-6.34)	0.04	0.99	1.28 (0.59-2.75)	0.53	0.63	
Ovary	3.47 (1.75-6.91)	<0.01	0.87	1.59 (0.91-2.76)	0.10	0.33	
Pancreas	4.30 (2.47-7.50)	<0.01	0.84	2.92 (1.85-4.60)	<0.01	0.55	
Renal Tract	1.85 (1.01-3.39)	0.05	0.9	1.26 (0.76-2.08)	0.37	0.79	
Uterine	1.29 (0.61-2.70)	0.51	0.95	0.84 (0.43-1.67)	0.62	0.71	

CI confidence interval; SRT: Schoenfeld residuals test, <0.05 indicates non-proportionality.

Figure 7.4.9-1: Adjusted hazard ratios for cancer in men with unexpected weight loss in the six months following presentation derived using cox regression adjusted for all covariates.

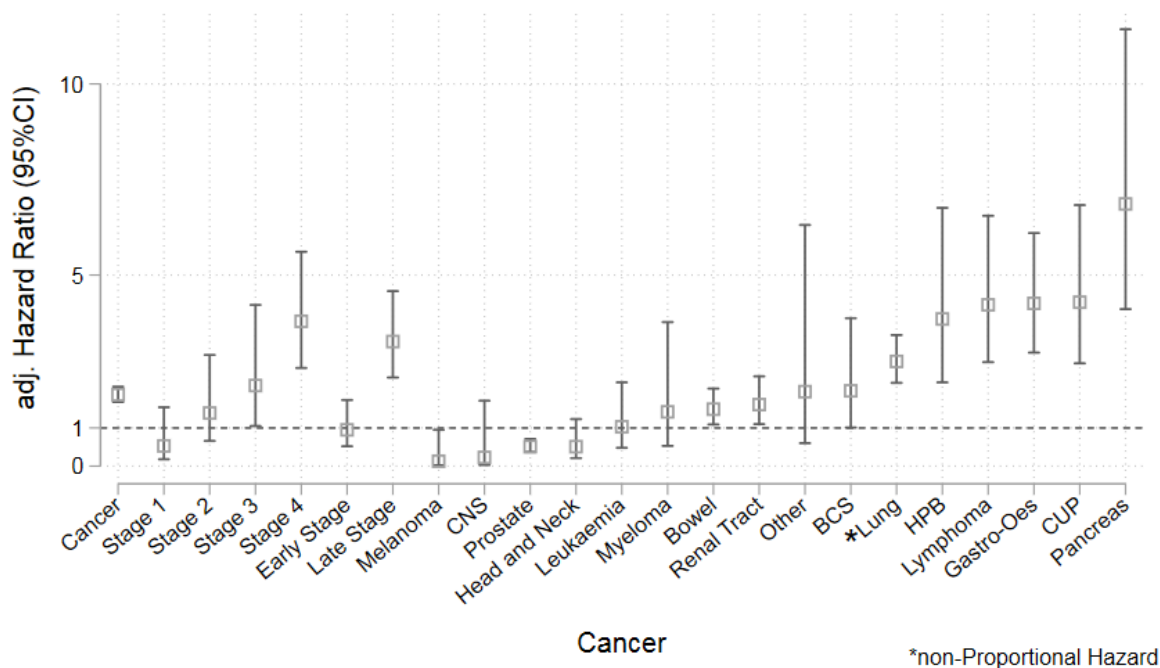
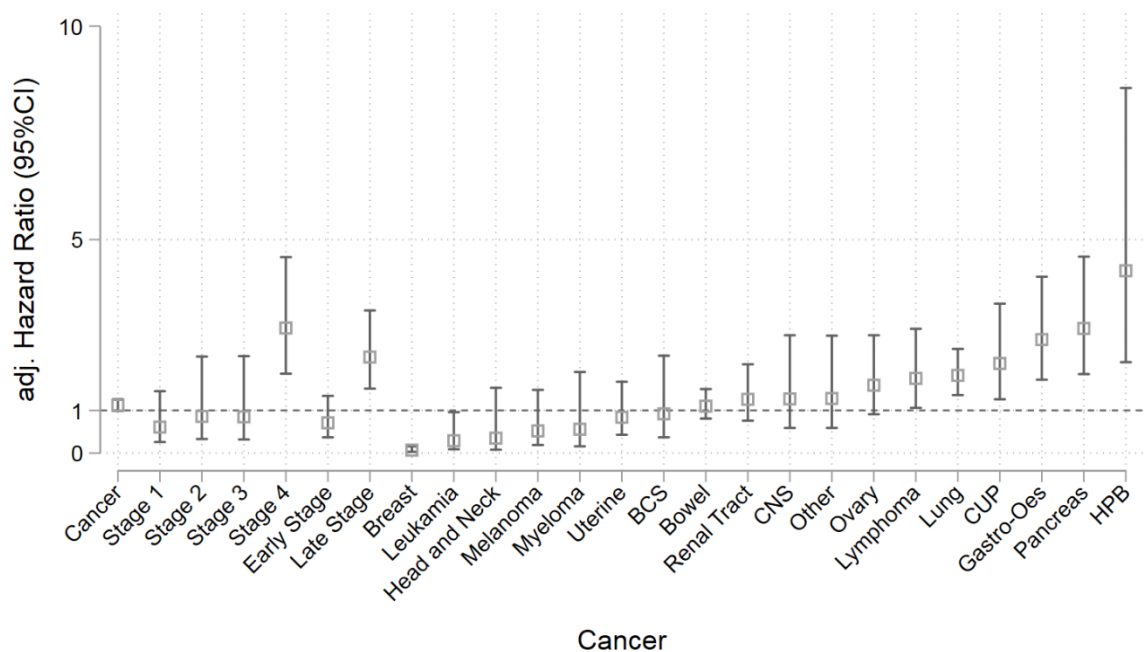


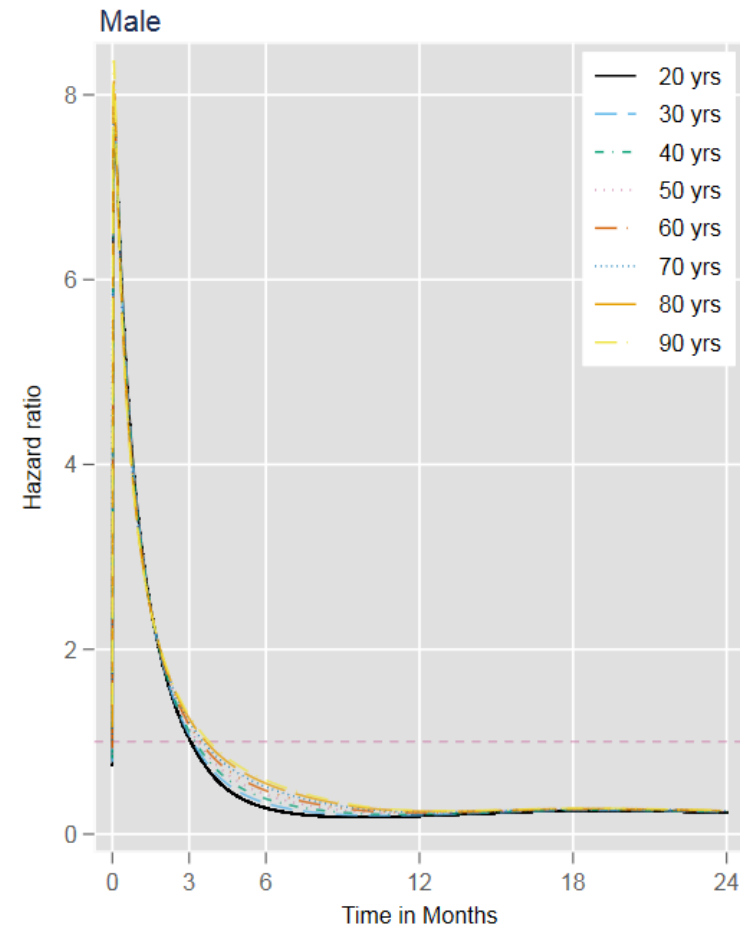
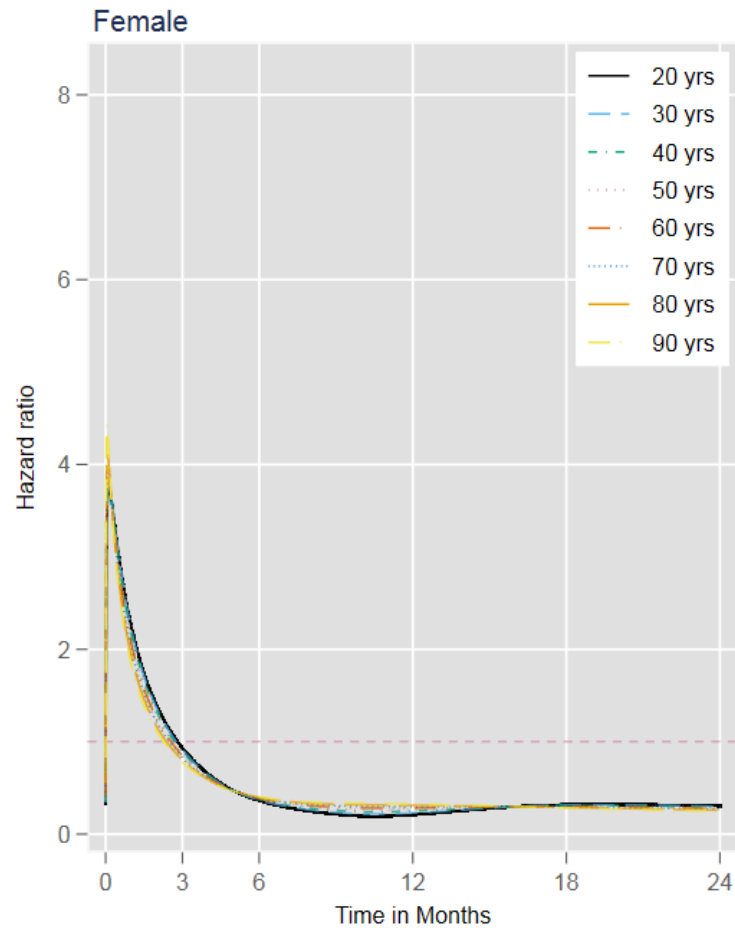
Figure 7.4.9-2: Adjusted hazard ratios for cancer in women with unexpected weight loss in the six months following presentation derived using cox regression adjusted for all covariates.



CI: confidence interval; BCS: bone connective and soft tissue, CNS: central nervous system; CUP: cancer of unknown primary; Gastro-Oes: gastro-oesophageal; HPB: hepato-biliary

Figure 7.4.9-3: Royston-Palmar flexible parametric survival models showing the dynamic hazard ration for cancer in patients with unexpected weight loss by age and gender.

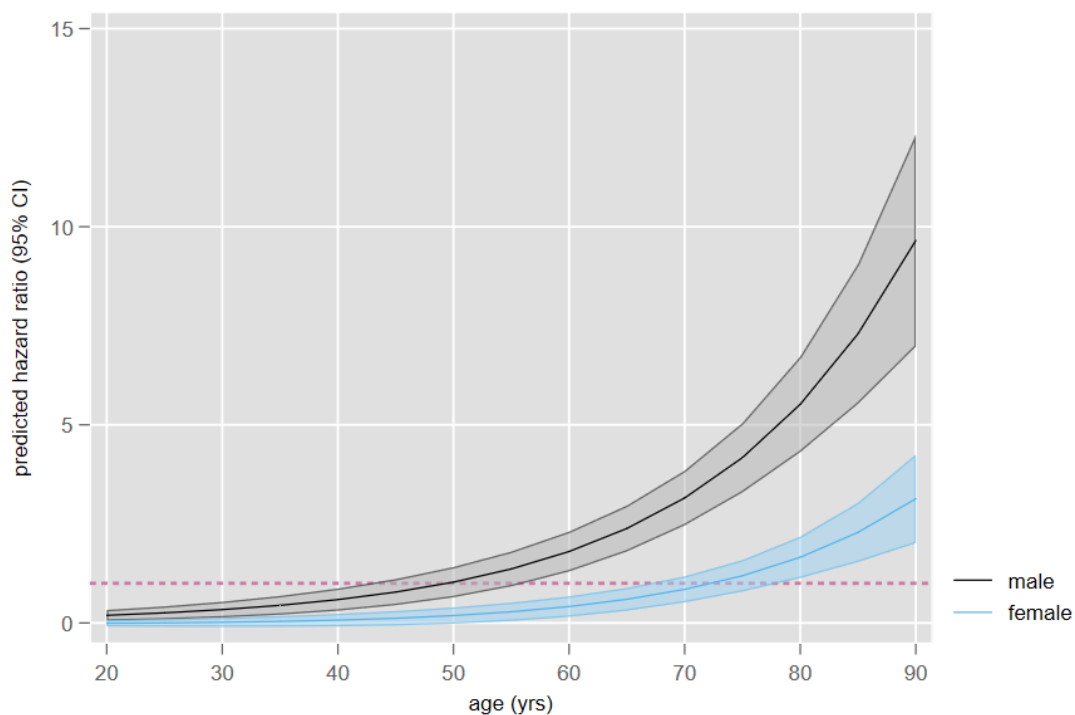
Models are adjusted for all covariates. yrs.: years



7.4.10. Population level predictions

For men under the age of 40 years, UWL was associated with a decreased likelihood of cancer diagnosis in the following three months compared to those without UWL (Figure 7.4.10-1). In older men, between 40-59 years, there was no evidence of an association, whilst for those aged above 60 years, UWL was associated with an increasing likelihood of cancer (for example HR 1.80, 95%CI 1.30-2.30 at 60 years). For women with UWL, the likelihood of cancer did not increase until aged 80 years and over (HR 1.66, 95%CI 1.13-2.18 at 80 years)

Figure 7.4.10-1: Hazard ratio predictions for cancer in the next three months with unexpected weight loss using marginal effects at representative values, by gender



CI: confidence interval; yrs.: years

7.5. Discussion

7.5.1. Summary of findings

Patients with a record of UWL in their GP electronic health record (EHR) are at increased risk of being diagnosed with the following cancers in the next three months: pancreatic, CUP, gastro-oesophageal, lymphoma, HPB, lung, bowel and renal tract. The association is greatest in men aged 60 years and above and in women aged 80 years and above. Conversely, the risks of breast cancer and prostate cancer diagnosis are less likely in patients with UWL compared to controls. Most cancers associated with UWL are diagnosed at a late stage (stage IV), but there was some evidence for a positive association between presence diagnosis of UWL and the diagnosis of Stage II and Stage III cancers. Three-months after the UWL being recorded, the risk of a cancer diagnosis dropped below the risk of cancer in patients without UWL, and this reduction is sustained for the following 21 months.

7.5.2. Strengths and limitations

This analysis represents the largest study to examine the association between UWL and subsequent cancer diagnosis in primary care. The period with the greatest probability of a cancer diagnosis could be identified by using a matched-cohort design and time-to-event methods. By utilising cancer-registry linked data, the association between UWL and cancer stage could be investigated.

Most previous studies have used a one to two year pre-diagnostic period to examine the association between UWL and cancer (137). A common justification is, *“a 2-year period was used, since this represents the period of time during which existing cancers are likely to become clinically manifest”* (16, 85). This approach does not allow that the predictive

value of a symptom may temporally vary before diagnosis. This analysis shows that the probability of cancer diagnosis, some of which may represent earlier diagnosis of cancers that would have been found later, is initially much higher in patients with newly recorded UWL, after which it falls below the probability observed in control patients without UWL. This highlights the mechanism by which associations between symptoms and cancer diagnoses could be inaccurately estimated if the hazard of cancer is not proportional throughout the follow-up period. For example, by setting too long a follow-up period, the probability of cancer could be underestimated as initially high probabilities are counterbalanced by later lower probabilities, attenuating the hazard ratio to the null. Similarly, predictive values could be overestimated if the follow-up period was too long, as cancers occurring after the “at-risk” period associated with UWL would be incorrectly classified as true positives. However, by restricting our analysis to the period of greatest probability resulted in low event numbers for some cancer sites and uncertainty of the estimates of association. Collapsing categories to overcome this would have countered our intent to define clinically sensible groups of cancers that are diagnosed via a common pathway. To assess whether the results were robust, different statistical models were used and the strengths of association between cancer site and stage over the first three and first six months after presenting with UWL and found similar results whichever analysis was used.

A proportion of the people in the non-UWL comparator group are likely to have consulted with another symptom associated with cancer. This group would be at an increased risk of cancer compared to other people in this group attending for a routine health check or medication review. As cancer symptoms cluster, the prevalence of cancer symptoms co-occurring with UWL is likely to be higher than the prevalence of cancer symptoms in the comparator cohort. However, the likelihood of these symptoms

being coded at the same time as UWL is less likely than when they present in isolation giving the biases in symptom coding noted in the systematic review chapter (Chapter 4). Due to these conflicting biases, this analysis selects people for inclusion and matching solely on the presence or absence of the UWL code without taking into consideration other coded clinical features.

In addition to the steps outlined in the methods section to increase the likelihood that the weight loss codes identified in Chapter Six represented UWL rather than expected weight loss, patients with any medical condition plausibly related to weight loss could also have been excluded. This was not done as in these situations UWL usually represents a deterioration or complication, such as end-stage Chronic Obstructive Pulmonary Disorder (COPD) or wasting in dementia (1). The prevalence of these conditions is high, and it is challenging to identify disease severity in EHRs. Instead, the multivariable analysis adjusted for comorbidity.

7.5.3. Findings in context

Chapter Four found evidence that UWL was associated with ten different cancers: prostate, colorectal, lung, gastro-oesophageal, pancreatic, non-Hodgkin's lymphoma, ovarian, myeloma, renal tract, and HPB cancers. Since that review was conducted, English and Swedish case-control studies have reported that UWL is associated with the presence of acute and chronic leukaemia and non-metastatic colorectal cancer (10, 138). However, for some cancer sites there have been no studies on the association with UWL in primary care. This analysis is the first to focus on the association between UWL and across all sites of cancer, identifying eight cancer sites with a strong positive association and two with a strong negative association.

The finding that breast cancer is negatively associated with the recording of UWL has not been reported before. Previously, a case-control study excluded UWL as it was present in less than one percent of presenting primary care patients who were diagnosed with breast cancer, reflecting that other symptoms are more common in such situations (145). A negative association means that breast cancer may still be diagnosed following UWL, but this is less likely than in patients without UWL. The finding that prostate cancer is negatively associated with UWL conflicts with two previous primary care studies reporting positive associations (16, 146). This difference could be as a consequence of the longer follow-up period they used without consideration of non-proportional hazards. The estimate of association between UWL and myeloma was imprecise as there were few cases. A previous case-control study found an increased risk of myeloma in the three months following present to primary care with UWL (147).

Few studies have reported the association between UWL and cancer stage in primary care (35). A recent cross-sectional study using data from the English National Cancer Diagnosis Audit (NCDA) of reported that 49% of 584 cancers associated with UWL were diagnosed at stage IV (148). In this study, 66-70% of staged cancers were diagnosed at stage IV, depending on gender and the period of follow-up. Cancers diagnosed at early stage are more likely to be treated with curative intent and to survive for longer than late stage cancers. However, diagnosing late stage cancer earlier, through a controlled investigative process rather than as an emergency, is also associated with improved survival also allowing for better symptom control or palliation.

7.5.4. Implications for research

There are important implications for future research. The National Institute of Health and Care Excellence (NICE) recommends urgent cancer investigation for patients with

clinical features with a positive predictive value of three percent or greater (22). This analysis demonstrates that estimates of association derived from observational studies may be incorrect if a longer (or shorter) follow-up period is used compared to the time period of increased risk of a cancer diagnosis that is associated with that symptom. Studies seeking to inform policy should therefore report association estimates for the appropriate period of increased risk, which will likely vary by symptom and cancer site. Most patients with UWL will not have cancer: for example, only 0.2% of patients with UWL and aged under 60 years old in this study were diagnosed with cancer in the following 24 months. In many countries efforts are underway to reduce unnecessary medical intervention that does benefit patients and may even cause harm (149). In the United States, the Institute of Medicine estimates that \$105 billion could be saved annually by reducing unnecessary intervention by half (150). In the UK, increased diagnostic activity related to 'alarm' symptoms is already stretching capacity (151, 152). Research is urgently required to inform evidence-based guidelines about which patients with UWL are at high risk of cancer and should be investigated by using additional risk factors, clinical features, and primary care testing. These tests would have to be easily accessible to GPs with results available promptly to avoid delaying onward referral for definitive diagnosis.

7.5.5. Implications for clinical practice

Previous studies have suggested that a health-care system that focusses on investigating individual cancer sites based on alarm symptoms may underperform for most patients with non-specific symptoms (153). A Danish study showed that 6.0% of patients who received a negative result after investigation for a single cancer site were re-referred within six months for another site, 4.4% of whom were diagnosed with cancer (154).

These results show that UWL is associated with several cancer sites suggesting a broader investigative strategy may be better suited than one focussed on ruling-out a single site. In Northern Europe attention has shifted to the role of multidisciplinary diagnostic centres (MDCs) to achieve this (36, 153, 155, 156) with emerging evidence from pilot sites in the UK showing that UWL is the most common reason for referral (155, 156). Insights gained from the ongoing evaluation of MDCs may inform the optimal diagnostic process for patients referred with UWL.

For patients with UWL who are not initially investigated for cancer, or for those with ongoing UWL for whom initial investigation does not identify malignancy, primary care clinicians could employ a policy of watchful waiting over the subsequent three months when the risk of a cancer being detected is greatest. During this time, repeat evaluation may consider the necessity of further investigation and referral.

7.6. Conclusions and next steps

Presentation and recording of UWL is uncommon in primary care, with an incidence of 1.3% over a 14 year period. However, UWL may be a presenting feature of cancer in primary care that, when recorded in older people, warrants early investigation across a broad range of cancer sites. This recommendation is reinforced by my finding that the associated cancer risk occurs within three months of the UWL recording.

The analyses detailed in Chapters Eight and Nine will establish the role of risk factors and accompanying symptoms, signs and simple primary care tests that could safely be used to rule-in and rule-out patients with UWL for further intensive cancer investigation.

8. Prioritising patients with unexpected weight loss for cancer investigation in primary care: a diagnostic accuracy study using routinely collected electronic health records data from 65,000 presentations

8.1. Background to this chapter

Chapter Five showed that unexplained weight loss (UWL) in patients attending primary care is associated with a subsequent diagnosis of cancer. More specifically that a first presentation of UWL is associated with an increased likelihood of a diagnosis of lymphoma, cancer of unknown primary, pancreatic, gastro-oesophageal, hepatobiliary, lung, bowel or renal-tract cancers.

Chapter Four demonstrated that existing studies have investigated UWL together with other symptoms and signs occurring within a one to two-year period preceding the cancer diagnosis. However these studies did not acknowledge that the positive predictive value (PPV) of individual symptoms will vary over time(137). In this context, PPV's could have been reported for pairs of clinical features that occur months or up to two years apart, potentially with different aetiologies unrelated to the eventual cancer diagnosis.

Simple blood tests are often used to investigate people with non-specific symptoms in primary care (157-159) but their role in helping GPs select patients with UWL for cancer investigation is poorly understood. In some cases abnormal test findings may facilitate patient triage (147, 160), may be poor predictors of cancer (161, 162) or be predictive across several cancer sites (163).

8.2. Objectives

The objectives of the study detailed in this chapter were to:

- establish the predictive value of UWL for cancer given risk factors (age, gender, smoking status).
- calculate the predictive value for cancer of concurrent clinical features (symptoms, signs and blood test results) in patients with UWL.
- consider the predictive value of risk factors and clinical features for cancer overall and by cancer site to identify the clinical investigations appropriate for patients with UWL.

8.3. Methods

8.3.1. Study design and population

This cross-sectional diagnostic accuracy study included the cohort of patients with UWL detailed in Chapter Seven.

8.3.2. Cancer (reference standard)

To identify cancers, the same method was used as in Chapter Seven. However, based on the results of that study, only on the cancers diagnosed in the six months following the date of the UWL record (the index date) were included. This was the period I ascertained was the “at-risk” period for a cancer diagnosis associated with a presentation of UWL. Whilst the association was greater in the three months following the UWL presentation, the risk was also increased over a six month period.

8.3.3. Sociodemographic and clinical features

Sociodemographic details recorded on or before the index date were extracted (Table 8.4.1-1). Body mass index (BMI) was categorised as underweight ($<18.5\text{kg/m}^2$), normal (18.5 to 24.9 kg/m^2), overweight (25 and 29.9kg/m^2) or obese (30kg/m^2 and over). Symptoms, signs and blood test results (clinical features) recorded in the period of three months before the index date of UWL to one month after this date were identified (Appendix). A candidate list of symptoms and signs associated with cancer was developed either through inclusion in the NICE NG12 guidance for suspected cancer or based on studies published subsequently (for symptoms and signs of central nervous system malignancies and head and neck cancers) (Table 8.4.2-1). For blood tests, the results of tests used commonly in primary care were identified based on clinical experience, and outliers and erroneous test results dropped. Test results were dichotomised as abnormal/normal using standard laboratory ranges (Table 8.4.3-1) (164).

8.3.4. Statistical analysis

All analyses were conducted in Stata version 15. For combinations of UWL and age-group, gender, smoking status, clinical features and blood test abnormalities, diagnostic accuracy statistics were estimated for the cancer outcome using the *diagt* Stata module. These were sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), negative predictive value (NPV) and the diagnostic odds ratios (DOR) with 95% confidence intervals (95%CI). There are details of how these are calculated in the methods section of Chapter Four. The analysis was conducted for cancer overall and by cancer site.

To select clinical features, multivariable backwards stepwise logistic regression was used starting with all clinical features and sociodemographic factors as independent covariates, using a p-value ≤ 0.05 for retention. The main advantage of using an objective automated stepwise selection procedure is that it results in a parsimonious model following a procedure that may be replicated, for example in an external validation exercise. Stepwise selection procedures may be problematic when the numbers of events are low leading to: instability of the selected variables, estimated regression coefficients that are too extreme, and overestimation of model performance.

Diagnostic accuracy statistics were calculated for each of the ten most commonly recorded blood tests including only patients with a blood test result. When tests were components of a “parent” test, for example white cell subtypes as components of the total white cell count, the “parent” test was used.

The results are presented in relation to the $\geq 3\%$ PPV threshold used to recommend further cancer investigation by NICE (22).

8.3.5. Sensitivity analysis

The selection process was repeated for clinical features using an interval of three months before the index date to the soonest of either i) three months after the index date or ii) the cancer diagnosis date. The objective was to explore whether broadening the window for clinical feature inclusion made a meaningful difference to the findings.

8.4. Results

8.4.1. Baseline characteristics

To recap, of the 63,973 patients with an UWL code, 37,215 (58.2%) were women; 33,156 (51.8%) were aged 60 years or older, 33,846 (52.9%) had a normal body mass index (BMI), and 16,793 (26.3%) were ever-smokers (Table 8.4.1-1).

Table 8.4.1-1: Baseline demographics of study population (n= 63,973)

Characteristic		n (%)
Gender	<i>Male</i>	26,758 (41.83)
	<i>Female</i>	37,215 (58.17)
Age (years)	<i>18-39</i>	14,290 (22.34)
	<i>40-49</i>	8,016 (12.53)
	<i>50-59</i>	8,511 (13.30)
	<i>60-69</i>	9,017 (14.10)
	<i>70-79</i>	11,565 (18.08)
	<i>80+</i>	12,574 (19.66)
Smoking	<i>Current</i>	9,629 (15.05)
	<i>Ex-Smoker</i>	7,164 (11.10)
	<i>Non-Smoker</i>	14,457 (22.60)
	<i>Missing</i>	32,723 (51.15)
Alcohol	<i>Current</i>	18,435 (28.82)
	<i>Non-Drinker</i>	8,095 (12.65)
	<i>Past-Drinker</i>	1,087 (1.70)
	<i>Missing</i>	36,356 (56.83)
BMI	<i>Underweight</i>	6,691 (10.88)
	<i>Normal</i>	33,846 (52.91)
	<i>Overweight</i>	10,790 (16.87)
	<i>Obese</i>	5,141 (8.04)
	<i>Missing</i>	7,235 (11.31)
Cancer	<i>Yes</i>	908 (1.42)
	<i>No</i>	63,065 (98.58)

BMI: Body Mass Index

8.4.2. Co-occurring clinical features

The most common features recorded alongside the UWL were cough (7.6%), abdominal pain (5.9%), back pain (5.1%), chest infection (4.7%) and fatigue (4.5%) (Table 8.4.2-1).

Table 8.4.2-1: Clinical features with a prevalence $\geq 1\%$ in a four-month window around the unexpected weight loss record (three months before to one month after)

Clinical feature	Weight loss <i>n (%)</i>
Cough	4,861 (7.6)
Abdominal pain	3,762 (5.9)
Pain - back	3,277 (5.1)
Infection - chest	2,975 (4.7)
Fatigue	2,872 (4.5)
Shortness of breath	2,671 (4.2)
Diarrhoea	2,496 (3.9)
Constipation	2,381 (3.7)
Urinary tract infection	2,113 (3.3)
Pain - chest	1,866 (2.9)
Dyspepsia	1,776 (2.8)
Appetite loss	1,592 (2.5)
Diabetes	1,529 (2.4)
Dizziness	1,505 (2.4)
Nausea	1,457 (2.3)
Vomiting	1,401 (2.2)
Lower urinary tract symptoms	1,311 (2.1)
Headache	1,051 (1.6)
Sore throat	1,038 (1.6)
Reflux	972 (1.5)
Pain - shoulder	910 (1.4)
Iron deficiency anaemia	780 (1.2)
Oral symptoms	771 (1.2)
Dysphagia	717 (1.1)
Pruritus	649 (1.0)
Change in bowel habit	641 (1.0)
Lump	629 (1.0)
Rectal bleeding	606 (1.0)

8.4.3. Blood testing

The most commonly recorded test was the full blood count, the most frequent components of which were haemoglobin (72.1%), platelets (70.7%), total white cell count (69.9%), and creatinine (69.7%). Liver function tests were the next most common test, namely bilirubin (65.5%), albumin (65.1%) and alkaline phosphatase (64.5%) (Table 8.4.3-1).

Table 8.4.3-1: The ten most commonly reported laboratory tests in a four-month window around the unexpected weight loss record (three months before to one month after)

Blood test	Normal range	n (%) tested	Abnormal	n (%) abnormal
<i>Full Blood Count</i>				
Haemoglobin	130-180 g/L (male) 115-160 g/L (female)	46,129 (72.1)	Low	7440 (16.1)
Total white cell count	4.0-11.00 x10 ⁹ /L	44,714 (69.9)	Raised	3245 (13.8)
Platelets	150-400 x10 ⁹ /L	45,239 (70.7)	Raised	1903 (4.2)
<i>Liver function tests</i>				
Albumin	35-50 g/L	41,622 (65.1)	Low	2867 (6.9)
Alkaline Phosphatase	30-130 iu/L	41,278 (64.5)	Raised	7024 (17)
Bilirubin	3-17 umol/L	41,895 (65.5)	Raised	2075 (5.0)
<i>Inflammatory markers</i>				
C-reactive protein	0-10 mg/L	14,703 (23.0)	Raised	3085 (21.0)
Erythrocyte sedimentation rate	0-10 mm/h (aged <65 years, male) 0-15 mm/h (aged <65 years, female) 0-20 mm/h (aged ≥65 years, male) 0-25 mm/h (aged ≥65 years, female)	22,931 (35.9)	Raised	6785 (33.6)
<i>Biochemistry</i>				
Calcium	2.12-2.60 mmol/L	20,214 (31.6)	Raised	429 (2.1)
Creatinine	60-106 umol/L (male) 45- 80 umol/L (female)	44,671 (69.8)	Raised	13225 (29.6)

g/L; grams per litre, iu: international units, umol: micromole, mm/h: millimetre per hour, mmol: millimole.

8.4.4. Age, gender and smoking status

The PPV for a cancer diagnosis was higher in people who were older and those who smoked (Table 8.4.4-1). It was more than two percent in patients aged 50 years and above. Analysis by gender showed that the PPV was over three percent for men aged 50 years and older who had smoked whereas the PPV remained under two percent for women, except in smokers aged 70 years and over.

Table 8.4.4-1: Positive predictive values for cancer by gender, age-group and smoking status

	PPV for cancer diagnosis in the next six months.			
Age (years)	UWL	UWL in smokers~	UWL in non-smokers	Isolated UWL*
Overall				
N	63,973	16,793	14,457	54,080
≥40	1.82 (1.70-1.94)	1.98 (1.75-2.23)	1.01 (0.85-1.19)	1.44 (1.32-1.55)
≥50	2.12 (1.98-2.26)	2.35 (2.07-2.65)	1.26 (1.06-1.48)	1.69 (1.56-1.83)
≥60s	2.52 (2.35-2.69)	2.83 (2.48-3.21)	1.46 (1.23-1.72)	2.02 (1.86-2.20)
≥70s	2.83 (2.62-3.04)	3.23 (2.79-3.73)	1.64 (1.38-1.94)	2.32 (2.11-2.54)
≥80	2.78 (2.50-3.09)	3.31 (2.66-4.06)	1.77 (1.46-2.13)	2.36 (2.08-2.67)
Male				
N	26,758	7,974	4,819	23,365
≥40	2.54 (2.34-2.76)	2.64 (2.26-3.06)	1.58 (1.24-1.97)	2.05 (1.85-2.26)
≥50	2.98 (2.74-3.24)	3.06 (2.62-3.55)	1.97 (1.56-2.46)	2.43 (2.19-2.68)
≥60	3.65 (3.34-3.98)	3.70 (3.15-4.31)	2.38 (1.88-2.96)	3.00 (2.70-3.33)
≥70	4.35 (3.94-4.78)	4.34 (3.62-5.16)	2.78 (2.17-3.50)	3.63 (3.23-4.07)
≥80	4.58 (3.98-5.25)	4.60 (3.51-5.91)	3.38 (2.59-4.34)	3.98 (3.37-4.66)
Female				
N	37,215	8,819	9,638	30,715
≥40	1.26 (1.14-1.40)	1.31 (1.04-1.61)	0.73 (0.57-0.92)	0.94 (0.82-1.07)
≥50	1.47 (1.32-1.63)	1.59 (1.27-1.97)	0.90 (0.7-1.14)	1.10 (0.96-1.26)
≥60	1.71 (1.53-1.90)	1.90 (1.50-2.37)	1.02 (0.79-1.29)	1.29 (1.12-1.48)
≥70	1.86 (1.65-2.09)	2.10 (1.59-2.70)	1.15 (0.89-1.46)	1.45 (1.24-1.68)
≥80	1.83 (1.56-2.15)	2.12 (1.42-3.03)	1.16 (0.87-1.51)	1.48 (1.21-1.80)

PPV: positive predictive values; UWL: unexpected weight loss; ~: current and ex-smokers; *: UWL without concurrent symptoms and signs in Table 3. Red shading represents a positive predictive value (PPV) ≥3%, the threshold above which NICE recommend investigation for cancer. Yellow shading represents a PPV of ≥2-<3%.

8.4.5. Signs and symptoms

In multivariable analysis, features selected to be positively associated with cancer diagnosis in patients with UWL were: abdominal pain, appetite loss, abdominal mass, iron deficiency anaemia, jaundice, chest signs and lymphadenopathy (Table 8.4.6-1). Dysphagia, haemoptysis and non-cardiac chest pain were associated with cancer for men only, and back pain, change in bowel habit, dyspepsia and venous thromboembolism in women only. PLRs ranged from 1.86 (95%CI 1.32-2.62) for non-cardiac chest pain to 6.10 (95%CI 3.44-10.80) for abdominal mass in men. In women, PLRs spanned 1.62 (95%CI 1.15-2.29) for back pain to 20.9 (95%CI 10.7-40.9) for jaundice. NLRs ranged from 0.94 to 1.00 (Table 6). For most patients over the age of 60 years, and particularly men, UWL and the co-occurrence of selected symptoms and signs gave PPVs greater than three percent (Table 8.4.6-2 & Table 8.4.6-3).

8.4.6. Blood tests

The following abnormal blood tests, in combination with UWL, had the highest PLR values for cancer diagnosis (Table 8.4.6-1): low albumin (PLR 4.67, 95%CI 4.14-5.27), raised platelets (4.57, 95%CI 3.88-5.38), a raised calcium level (4.28, 95%CI 3.05-6.02), a raised total white cell count (3.76, 95%CI 3.3-4.28), and a raised C-reactive protein (3.59, 95%CI 3.31-3.89) (Table 8.4.6-1). Normal inflammatory markers had the lowest NLRs: C-reactive protein (0.35, 95%CI 0.29-0.43) and erythrocyte sedimentation rate (0.4, 95%CI 0.35-0.47). In men and women aged 60 years and older, all single-test abnormalities had a PPV of over three percent, except for raised creatinine (Table 8.4.6-4 & Table 8.4.6-5). For patients aged between 40 and 59 years, PPV values of $\geq 3\%$ were observed for thrombocytosis (both sexes) and, in men only, for low albumin, raised alkaline phosphatase and raised calcium.

Table 8.4.6-1: Predictive value of clinical features and blood tests in combination with unexpected weight loss for cancer diagnosis in the 6 months following index date.

	TP	FP	FN	TN	PLR (95%CI)	NLR (95%CI)
Male						
<i>Symptoms</i>						
Abdominal pain	61	1,336	487	24,874	2.18 (1.71-2.78)	0.94 (0.91-0.96)
Appetite loss	38	615	510	25,595	2.96 (2.15-4.06)	0.95 (0.93-0.98)
Dysphagia	21	290	527	25,920	3.46 (2.24-5.35)	0.97 (0.96-0.99)
Haemoptysis	9	101	539	26,109	4.26 (2.17-8.38)	0.99 (0.98-1.00)
Non-cardiac chest pain	32	823	516	25,387	1.86 (1.32-2.62)	0.97 (0.95-0.99)
<i>Signs</i>						
Abdominal mass	13	102	535	26,108	6.10 (3.44-10.8)	0.98 (0.97-0.99)
Chest signs	6	53	542	26,157	5.41 (2.34-12.5)	0.99 (0.98-1.00)
Iron deficiency anaemia	22	212	526	25,998	4.96 (3.23-7.64)	0.97 (0.95-0.98)
Jaundice	7	59	541	26,151	5.67 (2.60-12.4)	0.99 (0.98-1.00)
Lymphadenopathy	4	73	544	26,137	2.62 (0.96-7.14)	1.00 (0.99-1.00)
Female						
<i>Symptoms</i>						
Abdominal pain	52	2,313	308	34,542	2.30 (1.78-2.97)	0.91 (0.87-0.95)
Appetite loss	23	916	337	35,939	2.57 (1.72-3.84)	0.96 (0.93-0.99)
Back pain	30	1,895	330	34,960	1.62 (1.15-2.29)	0.97 (0.94-1.00)
Change in bowel habit	12	347	348	36,508	3.54 (2.01-6.24)	0.98 (0.96-0.99)
Dyspepsia	25	1,004	335	35,851	2.55 (1.74-3.74)	0.96 (0.93-0.98)
<i>Signs</i>						
Abdominal mass	6	112	354	36,743	5.48 (2.43-12.4)	0.99 (0.97-1.00)
Chest signs	3	26	357	36,829	11.8 (3.59-38.9)	0.99 (0.98-1.00)
Iron deficiency anaemia	19	526	341	36,329	3.70 (2.37-5.78)	0.96 (0.94-0.98)
Jaundice	10	49	350	36,806	20.9 (10.7-40.9)	0.97 (0.96-0.99)
Lymphadenopathy	3	129	357	36,726	2.38 (0.76-7.44)	1.00 (0.99-1.00)
Venous Thromboembolism	7	112	353	36,743	6.40 (3.00-13.6)	0.98 (0.97-1.00)
Overall						
<i>Liver function tests</i>						
Low albumin	202	2,665	463	38,292	4.67 (4.14-5.27)	0.74 (0.71-0.78)
Raised alkaline phosphatase	271	6,753	372	33,882	2.54 (2.31-2.78)	0.69 (0.65-0.74)
Raised bilirubin	47	2,028	598	39,222	1.48 (1.12-1.96)	0.98 (0.95-1.00)
<i>Full blood count</i>						
Low haemoglobin	341	7,099	374	38,315	3.05 (2.82-3.30)	0.62 (0.58-0.67)
Raised total white cell count	179	3,066	505	40,964	3.76 (3.30-4.28)	0.79 (0.76-0.83)
Raised platelets	127	1,776	570	42,766	4.57 (3.88-5.38)	0.85 (0.82-0.88)
<i>Inflammatory markers</i>						
Raised c-reactive protein	194	2,891	76	11,542	3.59 (3.31-3.89)	0.35 (0.29-0.43)
Raised erythrocyte sedimentation rate	274	6,511	116	16,030	2.43 (2.27-2.60)	0.42 (0.36-0.49)
<i>Biochemistry</i>						
Raised calcium	31	398	351	19,432	4.28 (3.05-6.02)	0.93 (0.90-0.96)
Raised creatinine	254	12,971	445	31,001	1.23 (1.12-1.36)	0.90 (0.85-0.96)

TP: true positive; FP: false positive; FN: false negative; TN: true negative; PLR: positive likelihood ratio; NLR: negative likelihood ratio; 95% CI: 95% confidence interval.

Table 8.4.6-2: Positive predictive values for symptoms and signs selected to be predictive of a cancer diagnosis within six months in men with unexpected weight loss by age-group.

	Positive predictive value (95%CI)			
	Age-group, years			
	40-59	60-79	80+	
UWL	0.56 (0.40-0.75)	3.22 (2.88-3.6)	4.58 (3.98-5.25)	Cancer sites in rank order of risk
UWL plus:				
Symptoms				
Abdominal pain	2.02 (0.87-3.93)	7.03 (5.00-9.57)	7.58 (4.4-12.02)	Bowel, Panc, Lung, CUP, Lymph, GOS, Renal-tract, HPB, Prostate, BCS
Appetite loss	2.14 (0.44-6.13)	8.4 (5.27-12.55)	8.19 (4.55-13.36)	Lung, GOS, Bowel, Panc, Renal-tract, CUP, Lymph, Leuk, BCS, Myeloma, Prostate
Dysphagia	1.59 (0.04-8.53)	10.42 (5.95-16.6)	6.17 (2.03-13.82)	GOS, Lung, H&N, Bowel, Myeloma
Haemoptysis	3.57 (0.09-18.35)	13.33 (5.05-26.79)	9.52 (1.17-30.38)	Lung, Lymph, CUP,
Non-cardiac chest pain	0.79 (0.10-2.82)	6.19 (3.82-9.40)	7.30 (3.56-13.01)	Lung, GOS, Lymph, Bowel, CUP, Prostate, HPB, Panc, Myeloma, Leuk
Signs				
Abdominal mass	7.69 (0.95-25.13)	9.62 (3.2-21.03)	20.00 (7.71-38.57)	Bowel, GOS, Lung, Lymph, CUP
Chest signs	0.00 (0.00-45.93)	12.5 (3.51-28.99)	9.52 (1.17-30.38)	BCS, Lung, Bowel, GOS, Other
Iron deficiency anaemia	0.00 (0.00-12.77)	12.8 (7.50-19.95)	8.57 (3.21-17.73)	Bowel, GOS, Lung, Renal-tract, Panc, HPB, Lymph, BCS
Jaundice	11.76 (1.46-36.44)	7.41 (0.91-24.29)	30.00 (6.67-65.25)	Panc, HPB, Lung, BCS
Lymphadenopathy	8.33 (1.03-27)	7.14 (0.18-33.87)	16.67 (0.42-64.12)	Lymph, Renal-tract, CUP

UWL: unexpected weight loss; 95%CI: 95% confidence interval; Panc: pancreas CUP: cancer of unknown primary; GOS: gastro-oesophageal; HPB: hepatobiliary; Lymph: lymphoma; BCS: bowel connective and soft tissue; Leuk: leukaemia; H&N: head and neck; CNS: central nervous system. Red shading represents a PPV $\geq 3\%$; orange shading represents PPV of ≥ 2 - $<3\%$.

Table 8.4.6-3: Positive predictive values for symptoms and signs selected to be predictive of a cancer diagnosis within six months in women with unexplained weight loss by age-group.

	Positive predictive value (95%CI)			Cancer sites in rank order of risk
	Age-group, years			
	40-59	60-79	80+	
UWL	0.29 (0.19-0.43)	1.61 (1.38-1.86)	1.83 (1.56-2.15)	
UWL plus:				
Symptoms				
Abdominal pain	1.22 (0.49-2.5)	3.99 (2.69-5.68)	3.55 (2.00-5.79)	Panc, Bowel, HPB, CUP, GOS, Lymph, Lung, Ovary, CNS, Renal-tract, Myeloma, Uterine, Leuk, Other
Appetite loss	0.00 (0.00-2.09)	3.43 (1.72-6.05)	3.69 (1.86-6.51)	Bowel, Lung, Panc, GOS, H&N, HPB, CUP, Lymph, Other
Back pain	0.88 (0.24-2.23)	2.54 (1.51-3.98)	1.64 (0.66-3.35)	Lung, Panc, CUP, Renal-tract, Bowel, GOS, Breast, Myeloma, Other, HPB, BCS, Ovary, Lymph
Change in bowel habit	1.10 (0.03-5.97)	2.86 (0.78-7.15)	7.37 (3.01-14.6)	Bowel, Lymph, Panc, HPB, GOS, Renal-tract, Ovary, Uterine
Dyspepsia	1.06 (0.22-3.07)	3.21 (1.67-5.54)	4.05 (1.87-7.56)	GOS, Bowel, Panc, Lung, BCS, Lymph, CUP, Other, Breast, CNS, Leuk
Signs				
Abdominal mass	3.03 (0.08-15.8)	8.89 (2.48-21.2)	2.86 (0.07-14.9)	Bowel, GOS, Lung, H&N, Renal-tract
Chest signs	0.00 (0.00-52.2)	10.0 (0.25-44.5)	14.3 (1.78-42.8)	Lung, Bowel, CUP
Iron deficiency anaemia	1.83 (0.22-6.47)	5.70 (2.64-10.5)	4.02 (1.63-8.11)	Bowel, GOS, Lung, Renal-tract, BCS, Uterine, Ovary, CUP, Other
Jaundice	0.00 (0.00-21.8)	33.3 (14.6-57.0)	15.0 (3.21-37.9)	HPB, Panc, Bowel, GOS
Lymphadenopathy	0.00 (0.00-10.3)	0.00 (0.00-14.8)	27.3 (6.02-61.0)	Lymph
Thromboembolism	0.00 (0.00-18.5)	8.00 (2.22-19.2)	6.98 (1.46-19.1)	Lung, CUP, Panc, Lymph, Ovary

UWL: unexpected weight loss; 95%CI: 95% confidence interval; Panc: pancreas; CUP: cancer of unknown primary; GOS: gastro-oesophageal; HPB: hepatobiliary; Lymph: lymphoma; BCS: bowel connective and soft tissue; Leuk: leukaemia; H&N: head and neck; CNS: central nervous system. Red shading represents PPV $\geq$ 3%; orange shading represents PPV of ≥ 2 -<3%.

Table 8.4.6-4: Positive predictive values of simple blood test abnormalities in combination with unexpected weight loss for a cancer diagnosis within six months in men, by age-group.

	Positive predictive value (95%CI)			
	Age-group, years			
	40-59	60-79	80+	
UWL	0.56 (0.40-0.75)	3.22 (2.88-3.6)	4.58 (3.98-5.25)	Cancer sites in rank order of risk
UWL plus:				
Full blood count				
Haemoglobin (low)	2.09 (1.05-3.7)	6.76 (5.68-7.97)	6.34 (5.21-7.6)	Lung, Lymph, Bowel, GOS, Renal-tract, Prostate, CUP, Panc, HPB, BCS, Myeloma, Leuk, H&N, Other
Total white cell count (raised)	2.49 (1.25-4.41)	9.85 (7.56-12.5)	11.7 (8.06-16.1)	Lung, Bowel, GOS, Prostate, Renal-tract, Lymph, Panc, CUP, HPB, BCS, H&N, Leuk
Platelets (raised)	4.71 (2.05-9.06)	12.6 (9.22-16.6)	15.3 (9.75-22.5)	Lung, Bowel, Renal-tract, Lymph, GOS, CUP, Prostate, Panc, BCS, HPB, H&N
Liver function tests				
Albumin (low)	3.81 (1.66-7.37)	12.0 (9.53-14.7)	9.20 (6.84-12.0)	Lung, Bowel, GOS, Renal-tract, Lymph HPB, CUP, Panc, Prostate, Leuk, BCS, H&N, CNS, Myeloma
Alkaline phosphatase (raised)	3.01 (1.73-4.85)	8.25 (6.61-10.1)	8.30 (6.17-10.9)	Lung, Panc, CUP, HPB, Bowel, Lymph, Prostate, Renal-tract, GOS, BCS, Other, Melanoma, Myeloma, Leuk
Bilirubin (raised)	0.54 (0.07-1.95)	3.71 (2.21-5.8)	6.13 (3.31-10.3)	HPB, Panc, Lung, Bowel, Lymph, CUP, GOS, Renal-tract, Prostate, Leuk
Inflammatory markers				
C-reactive protein (raised)	3.58 (1.8-6.32)	10.11 (8-12.57)	8.82 (6.26-12.0)	Lung, Lymph, Renal-tract, Bowel, Panc, CUP, GOS, HPB, Prostate, BCS, H&N
Erythrocyte sedimentation rate (raised)	0.83 (0.33-1.7)	7.01 (5.81-8.36)	6.94 (5.33-8.84)	Lung, GOS, Bowel, Lymph, Renal-tract, Prostate, CUP, Panc, HPB, Myeloma, BCS, H&N, Leuk
Biochemistry				
Calcium (raised)	8.00 (0.98-26.0)	17.9 (8.91-30.4)	10.7 (2.27-28.2)	Lung, Lymph, Renal-tract, CUP, GOS, HPB, Other
Creatinine (raised)	0.67 (0.14-1.94)	3.44 (2.64-4.41)	4.41 (3.43-5.56)	Lung, Prostate, GOS, Renal-tract, Lymph, Bowel, CUP, Panc, HPB, Leuk, BCS, Myeloma, Other

UWL: unexpected weight loss; 95%CI: 95% confidence interval; Panc: pancreas; CUP: cancer of unknown primary; GOS: gastro-oesophageal; HPB: hepatobiliary; Lymph: lymphoma; BCS: bowel connective and soft tissue; Leuk: leukaemia; H&N: head and neck; CNS: central nervous system. Red represents a PPV $\geq$ 3%, yellow represents a PPV of $\geq$ 2- <3%.

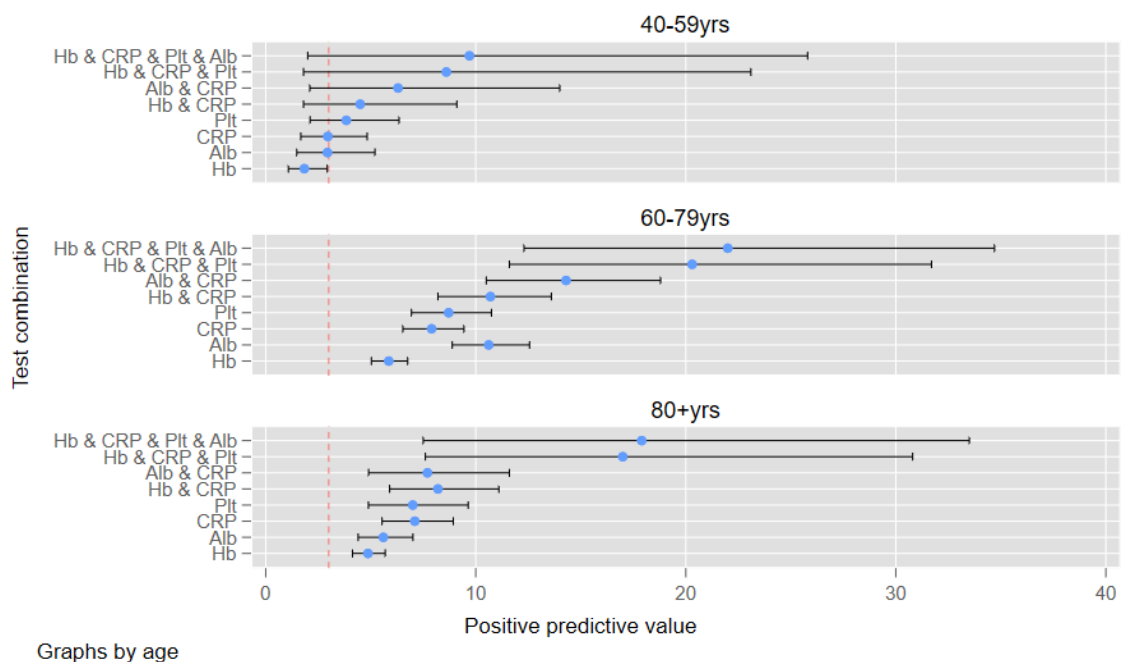
Table 8.4.6-5 Positive predictive values of simple blood test abnormalities in combination with unexpected weight loss for a cancer diagnosis within six months in women, by age-group.

	Positive predictive value (95%CI)			Cancer sites in rank order of risk
	Age-group, years			
	40-59	60-79	80+	
UWL	0.29 (0.19-0.43)	1.61 (1.38-1.86)	1.83 (1.56-2.15)	
UWL plus:				
Full blood count				
Haemoglobin (low)	1.52 (0.56-3.27)	4.16 (3.03-5.57)	3.17 (2.32-4.21)	Lung, Bowel, Lymph, GOS, CUP, Renal-tract, HPB, Panc, Ovary, Uterine, Breast, BCS CNS, Myeloma, Leuk, Other, H&N
Total white cell count (raised)	2.29 (1.05-4.30)	5.86 (4.18-7.96)	6.92 (4.75-9.68)	Lung, Bowel, CUP, GOS, Panc, Lymph, HPB, Renal-tract, Uterine, Ovary, Breast, Other, BCS, H&N
Platelets (raised)	3.08 (1.14-6.58)	6.41 (4.53-8.76)	3.72 (2.00-6.29)	Bowel, Lung, Renal-tract, CUP, HPB, GOS, Ovary, Lymph, Other, Panc, BCS, Breast, Uterine
Liver function tests				
Albumin (low)	1.83 (0.38-5.25)	8.91 (6.55-11.8)	3.17 (2.04-4.68)	Lung, Lymph, Bowel, CUP, Renal-tract, GOS, Ovary, HPB, Uterine, Other, Panc, CNS, Breast, Myeloma, Leuk
Alkaline phosphatase (raised)	1.07 (0.49-2.03)	3.35 (2.60-4.25)	3.12 (2.31-4.10)	Lung, Bowel, Lymph, GOS, Panc, HPB, CUP, Renal-tract, CNS, Ovary, Uterine, Other, Breast, Melanoma, BCS, H&N, Myeloma
Bilirubin (raised)	0.00 (0.00-20.1)	4.64 (2.34-8.15)	1.83 (0.38-5.25)	HPB, Panc, Lung, GOS, Bowel, Breast
Inflammatory markers				
C-reactive protein (raised)	2.00 (0.55-5.04)	5.58 (3.98-7.58)	5.78 (3.96-8.11)	Lung, CUP, Lymph, Bowel, GOS, Renal-tract, Panc, Ovary, Uterine, Breast, HPB, BCS, CNS, Melanoma, H&N, Leuk
Erythrocyte sedimentation rate (raised)	1.24 (0.50-2.53)	4.10 (3.10-5.30)	2.91 (1.97-4.13)	Lung, Lymph, Bowel, GOS, CUP, Panc, Renal-tract, HPB, Ovary, Uterine, Other, CNS, Breast, H&N, CNS, Melanoma, Leuk
Biochemistry				
Calcium (raised)	2.50 (0.06-13.2)	8.63 (4.54-14.59)	4.90 (1.61-11.1)	Lung, Renal-tract, Lymph, CUP, Bowel, BCS, Myeloma
Creatinine (raised)	0.15 (0.02-0.53)	1.74 (1.32-2.25)	1.79 (1.38-2.28)	Lung, Bowel, Renal-tract, Lymph, CUP, Panc, GOS, HPB, Ovary, Other, Uterine, Breast, BCS, CNS, Melanoma, Mveloma, H&N

UWL: unexpected weight loss; 95%CI: 95% confidence interval; Panc: pancreas; CUP: cancer of unknown primary; GOS: gastro-oesophageal; HPB: hepatobiliary; Lymph: lymphoma; BCS: bowel connective and soft tissue; Leuk: leukaemia; H&N: head and neck; CNS: central nervous system; Red represents PPV ≥ 3%; yellow a PPV of ≥2-<3%.

Some combinations of abnormal results in younger age-groups had PPVs over three percent but there was less precision in these estimates because not all patients had all tests (Figure 8.4.6-1).

Figure 8.4.6-1: Positive predictive values for cancer for combinations of abnormal laboratory tests in patients with unexpected weight loss by age.



Hb: low haemoglobin; CRP: raised C-reactive protein; Plt: raised platelets; Alb: low albumin.

8.4.7. Cancer outcomes

Cancer was diagnosed in 908 out of 63,973 (1.4%) patients within six months of the index date. Of these patients, 882 (97.1%) were aged 50 years and over almost all ((902, 99.3%) were aged 40 years and above. The most commonly diagnosed cancers were lung (220, 24.2%), bowel (114, 12.6%), gastro-oesophageal (103, 11.3%), pancreatic (80, 8.8%) and lymphoma (68, 7.5%).

Individually, some clinical features are generally considered to be associated with a single cancer site; however, when they co-occurred with UWL, they were associated with several cancer types. For example, patients with dyspepsia and UWL were diagnosed with the following cancers (in rank order): stomach or oesophagus, bowel, pancreas, lung, bone connective or soft tissues, lymphoma, unknown primary, other, breast, central nervous system and leukaemia (Table 8.4.6-2 & Table 8.4.6-3).

Similarly, test abnormalities in patients with UWL were also associated with multiple cancer sites. For example, women aged between 60 and 79 years with low albumin were diagnosed with following cancers (in rank order): lung, lymphoma, bowel, unknown primary, renal-tract, stomach or oesophagus, ovary, hepatobiliary, uterus, other, pancreas, central nervous system, breast, myeloma and leukaemia (Table 8.4.6-4 & Table 8.4.6-5).

8.4.8. Isolated UWL

The PPVs for cancer in patients without any of the selected clinical features were lower across every age range compared to the full cohort (Table 8.4.4-1). In addition, 13,941 (21.8%) patients had no record of a blood test, 142 (1.0%) of whom were diagnosed with cancer. Eighty-nine patients (57 men and 32 women) with UWL and cancer had neither a clinical feature nor blood test on record. Almost all of this group were aged 60 years or above (52, 91.2% of men; 27, 84.3% of women).

8.4.9. Sensitivity analysis

Widening the time window for inclusion in the final analysis made almost no difference to the clinical features selected as predictive for cancer in combination with UWL.

8.5. Discussion

8.5.1. Summary of findings

This diagnostic accuracy study shows that the risk of undiagnosed cancer in adults with recorded UWL alone is below the UK's current three percent threshold for urgent investigation. However, in men aged 50 years and over who have smoked and in all patients with concurrent clinical features the probability of undiagnosed cancer rises above this threshold. These features are: abdominal mass, abdominal pain, appetite loss, chest signs, iron deficiency anaemia, jaundice and lymphadenopathy in both men and women; dysphagia, haemoptysis and non-cardiac chest pain in men; and back pain, change in bowel habit, dyspepsia and venous thromboembolism in women. The abnormal blood test results in all patients are: low albumin, and raised white cell count, calcium levels, platelets and inflammatory markers. The absence of individual clinical features or the presence of individual normal blood tests does not confidently rule-out cancer in patients with UWL.

8.5.2. Strengths and weaknesses

This study used the codes validated to be associated with observed weight loss in Chapter Six. Furthermore, the size of the study allowed separate estimates for each age group, smoking status, and gender to be produced.

Clinical features were considered to occur with UWL if they were coded in a four month window surrounding the index date (the three months prior to the date and one month after). This was a clinical decision, based on clinical experience that a GP is likely to review recent notes and investigate UWL within a month of presentation, as the

epidemiology on this topic is limited. Symptoms occurring more than three months before the index date may well be unlinked to the UWL. Some case-control studies have reported the frequency of individual clinical features before a cancer diagnosis, with very few symptoms more prevalent in cases than controls earlier than six months before cancer diagnosis (64, 146, 147). However, none of these studies reported the timing of multiple symptoms leading up to such a diagnosis. Chapter Seven showed that cancers are likely to be diagnosed within three months of presenting with UWL. The sensitivity analysis extending the inclusion period for co-occurring symptoms and signs up to the day of diagnosis did not change the findings significantly.

Individual analyses were conducted for each blood test, only including patients with a result for that assay. Previous studies have replaced missing blood tests with negative results to allow full-case multivariable analysis that included all patients in the cohort. There were two main reasons why this was not done here. Firstly, patients who have been tested may represent a higher risk population than untested patients (162, 165), meaning that people with a normal result may not have the same likelihood of undiagnosed cancer as people who have not been tested. It is unclear how this testing bias may relate to patients with UWL, for whom the blood test date and the index date were close enough to be confident that they were clinically linked. Secondly, classifying absent tests as negative tests inflates the number of 'true' negatives and misestimates diagnostic accuracy making NLRs and NPVs difficult to interpret.

Finally, people were classified as having cancer if a code was entered within six months of presenting with UWL. This was based on the findings of Chapter Seven that

demonstrated beyond this time point there is a low risk of cancer being the cause of UWL (42).

8.5.3. Findings in context

The PPVs reported in this chapter are lower than those estimated in Chapter Four, possibly due to the heterogeneity of studies included in that analysis. For example, sensitivity was higher in the studies in Chapter Four at risk of recall bias due to including retrospective patient reported symptoms. The PPVs also varied by study design in the systematic review and were higher in case–control studies than cohort studies reporting on the same tumour site. Chapter Four also found that seventeen symptoms, signs and test results had a PPV for cancer over three percent in combination with UWL. These estimates were taken from case-control studies using primary care records that included clinical features occurring up to two years prior to cancer diagnosis. This study used a much shorter interval around the presentation with UWL to ensure symptoms were contemporaneous with UWL.

This study presents evidence for some clinical features and blood test abnormalities in combination with UWL not previously reported as predictive of cancer: abdominal pain, appetite loss, non-cardiac chest pain, chest signs, dyspepsia, raised alkaline phosphatase, low albumin and a raised white cell count. In addition, this study confirms the importance of jaundice, lymphadenopathy, haemoptysis, dysphagia, thrombocytosis and anaemia reported in Chapter Four.

8.5.4. Implications for future research

As described in Chapter Two, a pro-inflammatory state underpins cancer cachexia (4, 166) and prognostic scores composed of markers of the systemic inflammatory response are used in cachectic patients to predict survival and response to treatment in secondary care (167-169). A potential avenue for future research, building on the research reported in this chapter, is to investigate the utility of inflammatory marker scores and combinations of negative tests in selecting who should (and who should not) undergo invasive cancer testing.

Women presenting with UWL were at markedly lower risk of having cancer than men with UWL. Different, but interrelated, mechanisms may underpin this finding. Firstly, women may be more likely to attend their GP to discuss their weight and Chapter Five showed that they are more likely to have a weight measurement recorded in UK primary care. Secondly, women may be more likely to report symptoms of cancer earlier to prompt investigation before weight loss occurs. Thirdly, cancers that are only (or mostly) diagnosed in females may present with more readily identifiable symptoms at an earlier stage, with established rapid routes to diagnosis. This is especially plausible for breast lumps in breast cancer, the cancer of highest incidence in females, and for post-menopausal vaginal bleeding in endometrial cancer. Fourth, men may delay presentation until weight loss is marked (170). This study could not examine these possibilities. An avenue for future research is to study these gender differences further.

8.5.5. Implications for clinical practice

Patients who have not smoked presenting with UWL alone, with the exception of men over 80 years of age, have a risk of having cancer that is below the referral threshold for urgent investigation set by NICE (22). However, in combination with the symptoms and

signs highlighted in this chapter, cancer risk increases such that referral for urgent invasive investigation becomes justified. In the absence of these features, GPs might arrange simple “routine” blood tests, in particular, full blood count, liver function tests, erythrocyte sedimentation rate, C-reactive protein and calcium. Almost any abnormal result increases the risk of cancer sufficiently to trigger invasive testing.

However, whilst normal blood test results may reassure patients with UWL, as NLRs were never lower than 0.2 (the threshold below which is regarded a good rule-out test (45, 46)), clinicians should be aware that in isolation a normal blood test result does not reduce the probability sufficiently to rule-out cancer (45).

In concordance with the conclusions of Chapter Five, these findings may have implications for cancer referral pathways. Clinical features thought to be specific to an individual cancer site are markers of several different types of cancer when they co-occur with UWL, meaning that new, broader, investigative approaches are needed for patients with UWL. For example, NICE guidelines suggest that patients with UWL and abdominal pain should be investigated for colorectal cancer (22). In this study, over ten further cancers that presented in this way would be missed by colonoscopy. Likewise, some non-alarm symptoms, such as loss of appetite and non-cardiac chest pain, indicated a probability of cancer that was above the threshold for invasive investigation in the presence of UWL.

8.6. Conclusions and next steps

In men who have smoked and are aged 50 years and above, urgent referral may be justified with UWL and no additional clinical features. Some further clinical

characteristics increase the risk of cancer substantially over the three percent threshold warranting more urgent intensive cancer investigation. Clinical features thought to be specific to an individual cancer site are markers of several different types of cancer when they co-occur with UWL. The recording of UWL alone in people who do not smoke is unlikely to be due to cancer and urgent referral for invasive testing may not be justified.

However, the absence of individual clinical features does not sufficiently rule-out the need for further cancer investigation. In Chapter Nine, the final analysis chapter, I will use multiple imputation to replace missing data and explore whether a prediction model can be derived that identifies combinations of normal blood test results and absent clinical features that could sufficiently rule-out the need for urgent cancer investigation. Conversely, combinations of test results and the presence of features that do warrant urgent referral for investigation will be explored.

9. Derivation, internal cross-validation, and net-benefit analysis of a risk score to select primary care patients with unexpected weight loss for cancer investigation

9.1. Background to this chapter

Chapters Seven and Eight confirmed that most patients presenting to primary care with unexpected weight loss (UWL) will not have cancer. Diagnostic strategies that avoid the harms of unnecessary invasive and costly investigation are therefore required for patients with UWL who are at a low-risk of cancer. Chapter Eight showed that the absence of individual co-occurring clinical features does not reduce the likelihood of cancer enough to sufficiently rule-out patients from further cancer investigations. It also identified that primary care clinicians commonly request multiple blood tests when patients present with UWL. When baseline investigations are normal, a watchful waiting approach including periodic review of patients with UWL in primary care may be more appropriate than invasive testing.

Prediction models have been developed to identify the most helpful combinations of clinical features to estimate cancer risk in patients with UWL (171, 172). However, these studies were based on small cohorts from secondary care and recommended conflicting approaches. Their recommendations are difficult to implement in primary care as they include some investigations uncommon in this setting. The models also require external validation in primary care populations as estimates derived from secondary care are likely to be biased due to the spectrum effect discussed in the introductory chapter.

9.2. Objectives

The objectives of the study detailed in this chapter were to:

- derive prediction models using co-occurring risk factors, symptoms, signs and blood test data that could be used to stratify cancer risk in patients attending primary care with UWL.
- assess the clinical utility of the prediction models and conduct internal validation.
- present simple risk scores that could be used by GPs to stratify patients with UWL for referral for invasive cancer investigation.

9.3. Methods

9.3.1. Study design

This derivation cohort for this study was the same group of patients included in Chapters Seven and Eight. UWL, cancer diagnosis, sociodemographic features and pre-existing co-morbidities were defined using identical methods. Clinical features were included if shown to be associated with cancer in Chapter Eight if recorded in a four month window around the index date (the three months before to one month after the UWL recording).

The results of blood test commonly requested within this time period were also included.

9.3.2. Multiple imputation

Multiple imputation was used to replace missing values for smoking status, alcohol intake, body mass index (BMI), and blood tests using the *mi* suite of commands in Stata so that prediction models could be developed that included all patients with UWL (173,

174). Multiple imputation is considered a relatively flexible, general purpose approach to dealing with missing data (175). It assumes that the data are missing at random (MAR), meaning that any systematic difference between the missing values and the observed values can be explained (or predicted) by differences in observed data.

The imputation model for this chapter included the outcome (cancer diagnosis), all candidate variables to be included in the final prediction models, and auxiliary variables to increase the likelihood that the MAR assumption was satisfied. The latter were a combination of variables found to predict missingness (age and sex were most predictive), personal characteristics, comorbidities, risk factors, markers of inflammation and other components of the full blood count. The imputation model can be found in Box 9.3.2-1.

First fifty copies of the derivation dataset were created and the missing values of all variables replaced with randomly selected values taken from the observed data. Then, starting with the variable with the least missing data, using a method called “chained equations”, the appropriate regression model was fitted in the entire dataset using all other variables to predict (and then replace) the missing values (175). For continuous variables, linear regression is sometimes used but can lead to predictions that are out of range, for example replacing blood test values with results below zero. Predictive mean matching (PMM) is preferred as it preserves the observed distribution of values. It uses linear regression to create predictions for each patient and then, for each person with missing data, it selects the neighbouring patients with the closest linear predictions and randomly selects a value to impute from these donors. Two to ten donor patient are commonly used (176). Multinomial logistic regression was used to impute categorical

variables and PMM with five donors was used to impute continuous variables (176). The appropriateness of each imputation was assessed by tabulating (for categorical variables) or plotting (for continuous variables) the observed and the imputed data for comparison. This process is known as imputation diagnostics.

Each prediction model was derived in each imputed dataset. Rubin's rules were used to average the results across the imputed datasets and to calculate standard errors taking into account of the variability in results between the imputed datasets, reflecting the uncertainty associated with the missing values (173).

Box 9.3.2-1. Multiple imputation model

```
use "C:\Users\bnicholson\Weight Loss\full_for_analysis_labs_wcc_mi2.dta", replace
set more off, permanently
set matsize 800
mi set mlong
```

**register the regular (complete) variables to include in the imputation model*

**this is a combination of variables for use in the final models and auxiliary variables*

```
mi register regular age gender cancer_6m apanc_m3p1m appetiteloss_m3p1m
ascites_m3p1m bleedrectal_m3p1m chestsign_m3p1m cough_m3p1m dyspepsia_m3p1m
dysphagia_m3p1m fatigue_m3p1m fever_m3p1m haematemesis_m3p1m haematuria_m3p1m
haemoptysis_m3p1m infectchest_m3p1m infectrecur_m3p1m ida_m3p1m jaundice_m3p1m
lymphaden_m3p1m massabdo_any_m3p1m nausea_m3p1m nightsweat_m3p1m vomit_m3p1m
painback_m3p1m painabdo_any_m3p1m painbone_m3p1m painchestnc_m3p1m painpelvic_m3p1m
painshoulder_m3p1m painthroat_m3p1m pmb_m3p1m reflux_m3p1m sob_m3p1m
steatorrhoea_m3p1m uti_m3p1m headache_m3p1m sore_throat_m3p1m vte_m3p1m prev_ckd
prev_cpnc prev_diabetes prev_eating_disorders prev_ibd prev_malabs prev_obesity prev_ren_fail
prev_rheum prev_thyroid
```

**register the incomplete variables with missing data to include in the imputation model*

**this is a combination of variables for use in the final models and auxiliary variables*

```
mi register imputed smoking_fc albumin_value lympho_value monocyte_value neutrophil_value
platelets_value haemoglobin_value BMI_group_fc alcohol_fc alp_value ast_value bili_value esr_value
haematocrit_value mcv_value pv_value twcc_value crp_value eosin_value baso_value
```

**this is the imputation model*

```
mi impute chained (mlogit, aug) smoking_fc BMI_group_fc alcohol_fc (pmm, knn(5)) albumin_value
lympho_value monocyte_value neutrophil_value platelets_value haemoglobin_value alp_value ast_value
bili_value esr_value haematocrit_value mcv_value pv_value twcc_value crp_value eosin_value baso_value
= age gender cancer_6m apanc_m3p1m appetiteloss_m3p1m ascites_m3p1m bleedrectal_m3p1m
chestsign_m3p1m cough_m3p1m dyspepsia_m3p1m dysphagia_m3p1m fatigue_m3p1m fever_m3p1m
haematemesis_m3p1m haematuria_m3p1m haemoptysis_m3p1m infectchest_m3p1m
infectrecur_m3p1m ida_m3p1m jaundice_m3p1m lymphaden_m3p1m massabdo_any_m3p1m
nausea_m3p1m nightsweat_m3p1m vomit_m3p1m painback_m3p1m painabdo_any_m3p1m
painbone_m3p1m painchestnc_m3p1m painpelvic_m3p1m painshoulder_m3p1m painthroat_m3p1m
pmb_m3p1m reflux_m3p1m sob_m3p1m steatorrhoea_m3p1m uti_m3p1m headache_m3p1m
sore_throat_m3p1m vte_m3p1m prev_ckd prev_cpnc prev_diabetes prev_eating_disorders prev_ibd
prev_malabs prev_obesity prev_ren_fail prev_rheum prev_thyroid, rseed(278) add(50)
```

```
compress
```

```
save "Desktop\cont_mi.dta"
```

```
save "C:\Users\bnicholson\Weight Loss\ro_tests_mi_cont.dta", replace
```

9.3.3. Model derivation

Three prediction models were derived: a symptoms only model (Sm), a symptoms and tests model (STm), and a simple tests only model (Tm). All models had an appropriate sample size with at least 15 events per variable (177). For each model, the *mim* Stata command was used to select variables using backwards stepwise logistic regression with cancer (yes/no) as a binary outcome, using a p-value of <0.01 for inclusion.

Candidate variables for Sm included risk factors and clinical features found to be associated with a cancer diagnosis within six months in men and women. These were gender, age-group, smoking status, abdominal mass, abdominal pain, appetite loss, back pain, chest pain (non-cardiac), chest signs, change in bowel habit, dyspepsia, dysphagia, iron deficiency anaemia, jaundice, lymphadenopathy and venous.

Candidate variables for the STm also included the blood tests most commonly requested by general practitioners (GPs) in patients with UWL and tests used in prognostic scores for patients with cancer (4, 7). For the primary analysis, continuous test results were dichotomised as abnormal/normal in each imputed dataset using standard laboratory ranges (Table 9.3.3-1). The candidate variables were as per Sm plus albumin, alkaline phosphatase, bilirubin, C-reactive protein, erythrocyte sedimentation rate, haemoglobin, liver enzymes, lymphocytes, mean cell volume, monocytes, neutrophils and platelets.

For the Tm, candidate variables included risk factors and blood tests. As I intended to derive a parsimonious model, in this case I chose the quantum over component tests; for example, the total white cell count was included rather than the white cell subtypes.

The candidate variables were gender, age-group, smoking status, albumin, alkaline phosphatase, bilirubin, C-reactive protein, erythrocyte sedimentation rate, haemoglobin, liver enzymes, platelets and total white cell count.

Table 9.3.3-1: Common laboratory test ranges in general practice (164)

Blood test group	Blood test (units)	Normal range / threshold	Abnormality associated with cancer diagnosis
Liver function tests	Albumin (g/L)	35-50	Low (161)
	Alkaline Phosphatase (iu/L)	30-130	Raised (178, 179)
	Liver enzymes (AST /ALT) (iu/L)	5-35	Raised (178, 179)
	Bilirubin (umol/L)	3-17	Raised (178, 179)
Full blood count	Haemoglobin (g/L)	130-180 (men) 115-160 (women)	Low (160)
	Lymphocytes (x10 ⁹ /L)	1.0-4.5	Low (169)
	Mean cell volume (fL)	76-96	Low
	Monocytes (x10 ⁹ /L)	0.2-0.8	Raised (169)
	Neutrophils (x10 ⁹ /L)	2.0-7.5	Raised (169)
	Platelets (x10 ⁹ /L)	150-400	Raised (163)
	Total white cell count (x10 ⁹ /L)	4.0-11.00	Raised
Inflammatory markers	CRP (mg/L)	<10	Raised (162)
	Erythrocyte Sedimentation Rate (mm/h)	0-10 (aged <65 years, men) 0-15 (aged <65 years, women) 0-20 (aged ≥65 years, men) 0-25 (aged ≥65 years, women)	Raised (162)

g/L; grams per litre, iu: international units, umol: micromole, mm/h: millimetre per hour, mmol: millimole.

9.3.4. Internal cross-validation

Ten-fold internal cross-validation was used to assess overall model performance using the mean predicted probability for each patient across all 50 imputation datasets with the *cvauroc* command in Stata (180). In 10-fold cross-validation, the dataset is split into 10 (near to) equal sized samples. The model is developed in a dataset made up of nine samples and then tested in the remaining sample. This process is repeated until all ten combinations of nine and one have been used. The performance of the model is then averaged across the ten combinations (181).

Model performance was assessed using discrimination and calibration statistics.

Discrimination is a measure of how well the model can discriminate between patients who will be diagnosed with cancer and those who will not. It was quantified using the area under the curve (AUC) and 95% confidence intervals (95%) calculated using bootstrap resampling. An AUC of 0.5 represents the discriminatory value of model is no better than chance, whilst an AUC of 1 indicates the model has perfect ability to discriminate (182).

Calibration plots were generated using Stata's *pmcalplot* command to assess how the predicted probabilities derived by each model correspond to the observed proportion of patients diagnosed with cancer (183). On calibration plots, predictions are plotted on the x-axis and the observed cancers on the y-axis. A calibration slope is created by applying smoothing techniques to visualise the association between the observed and predicted values (184). The calibration slope of a perfectly calibrated model sits on the straight diagonal line between the bottom left to the top right of the square calibration plot. Calibration is summarised by a number of metrics: the intercept of the calibration

slope (called the calibration-in the-large (CITL), the slope (or beta) of the calibration slope (called the calibration slope), and by the ratio of the observed and expected values (the O:E ratio) (185). A perfectly calibrated model has a CITL of 0, a calibration slope of 1, and an O:E ratio of 1. The extent of miscalibration, or of model over- or under-prediction, can be assessed by the magnitude of deviation, positive or negative, of these metrics from perfect calibration. Visual inspection of the calibration slope affords greater appreciation of whether the degree of miscalibration varies at different levels of predicted risk.

9.3.5. Decision curve analysis

Decision curve analysis (DCA) was used to compare the net benefit and proportion of investigations avoided by Sm, STm and Tm with scenarios where no prediction model was used (i.e. treat everyone or treat nobody), across a range of risk thresholds (threshold probabilities) using the *dca* command in Stata (186). In general, the strategy with the highest net benefit (the highest plotted curve) is considered to have the greatest clinical utility at any given risk threshold (187). Net benefit represents the proportion of the studied population with true positive results minus the proportion with false positives multiplied by the odds of cancer at each risk threshold. An alternative, perhaps more intuitive presentation of DCA, is the proportion of patients who would avoid further investigation without missing a cancer diagnosis at each risk threshold (188).

9.3.6. Clinical risk scores

Finally, to demonstrate how these models could be used in clinical practice, established methods were followed to develop two simple clinical risk scores for the STm and Tm (189). The risk score associated with each variable is the coefficient of each variable multiplied by a conversion factor rounded to the nearest whole number. The calculated the mean point score for each patient was averaged across the imputation datasets and a constructed a 2x2 table using each total score as the cut-off. To understand the diagnostic performance of each risk threshold the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV) and negative predictive (NPV) values were calculated for each score (see Chapter Four for an explanation of these tests).

9.3.7. Sensitivity analysis

The models were refitted using continuous blood test results to explore the impact on discrimination and calibration statistics. Stata's *mfpmi* command was used to select the most appropriate functional linear or fractional polynomial (FP) form for each continuous covariate in relation to the outcome (190).

9.4. Results

9.4.1. Study participants

In the derivation cohort of 63,973 adults (aged 18 years and over) with UWL recorded, 908 (1.4%) were diagnosed with cancer within six months of the index date, of whom 902 (99.3%) were aged 40 years or older. Table 9.4.2-1 summarises the baseline characteristics of the study population. Patients with UWL were more commonly women (58.2%), aged ≥ 60 years (51.8%) and of normal BMI (52.9%). The most commonly recorded clinical features were abdominal pain (5.9%), back pain (5.1%), non-cardiac chest pain (2.9%) and dyspepsia (2.8%) (Table 9.4.2-2). The most commonly recorded tests were haemoglobin (72.1%), platelets (70.7%), and total white cell count (69.9%) (Table 9.4.2-2).

9.4.2. Missing data

Smoking status was missing for 32,723 (51.15%) of patients, whilst 36,356 (56.8%) were without data on alcohol consumption and 7,235 (11.3%) had no BMI recorded (Table 9.4.2-1). The most common missing blood tests were liver enzymes (53,062, 82.9%), C-reactive protein (49,270, 77.0%) and erythrocyte sedimentation rate (41,042, 64.1%) (Table 9.4.2-2).

Imputation diagnostics were deemed satisfactory for all imputed variables. Figure 9.4.2-1 illustrates the diagnostics for the first twenty imputed datasets for C-reactive protein.

Table 9.4.2-1: Baseline characteristics of the derivation cohort (n = 63,973) and imputation dataset (n = 50*63973)

	Derivation cohort	Imputation dataset
	n (%)	%
Gender		
<i>Men</i>	26,758 (41.8)	41.8
<i>Women</i>	37,215 (58.2)	58.2
Age-group (years)		
<i>18-39</i>	14,290 (22.3)	22.3
<i>40-49</i>	8,016 (12.5)	12.5
<i>50-59</i>	8,511 (13.3)	13.3
<i>60-69</i>	9,017 (14.1)	14.1
<i>70-79</i>	11,565 (18.1)	18.1
<i>80+</i>	12,574 (19.7)	19.7
Smoking status		
<i>Current</i>	9,629 (15.1)	31.0*
<i>Ex-Smoker</i>	7,164 (11.1)	22.9*
<i>Non-Smoker</i>	14,457 (22.6)	46.0*
<i>Missing</i>	32,723 (51.2)	-
Alcohol consumption		
<i>Current</i>	18,435 (28.8)	66.9*
<i>Non-Drinker</i>	8,095 (12.7)	29.1*
<i>Past-Drinker</i>	1,087 (1.7)	4.0*
<i>Missing</i>	36,356 (56.8)	-
Body Mass Index		
<i>Underweight</i>	6,691 (10.9)	12.4*
<i>Normal</i>	33,846 (52.9)	60.0*
<i>Overweight</i>	10,790 (16.9)	18.8*
<i>Obese</i>	5,141 (8.0)	8.8*
<i>Missing</i>	7,235 (11.3)	-
Comorbidities		
<i>0</i>	8,870 (13.9)	13.9
<i>1</i>	12,762 (20.0)	20.0
<i>2</i>	12,641 (19.8)	19.8
<i>3</i>	10,378 (16.2)	16.2
<i>4</i>	7,638 (11.9)	11.9
<i>5+</i>	11,684 (18.3)	18.3

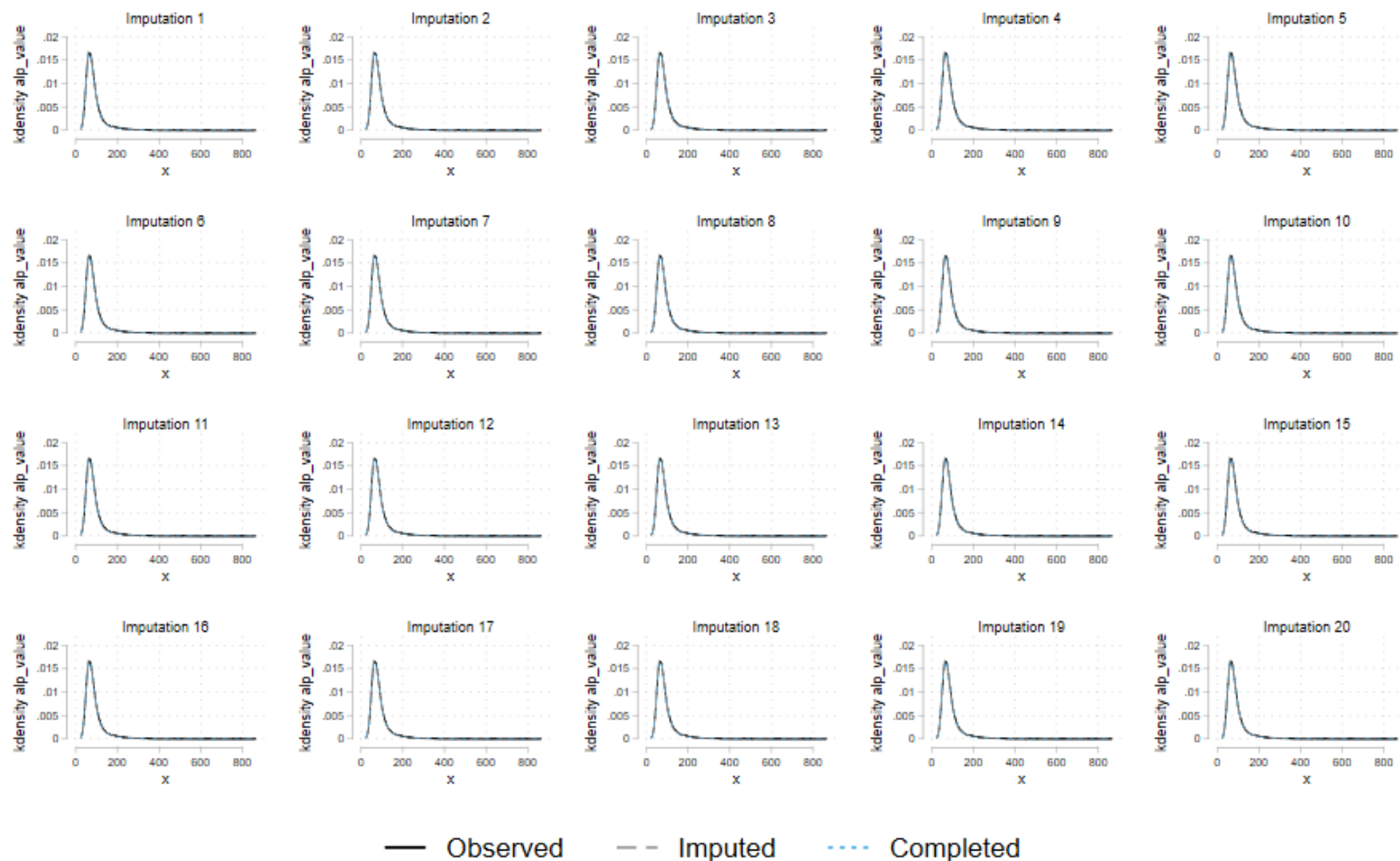
*=imputed data

Table 9.4.2-2: Co-occurring clinical features and blood tests in the derivation cohort.

	Derivation cohort		Imputation dataset
	n (%)	mean (sd)	% / mean (sd)
Co-occurring clinical features			
Appetite loss	1,592 (2.5)		2.5
Abdominal mass	233 (0.4)		0.4
Abdominal pain	3,762 (5.9)		5.9
Back pain	3,277 (5.1)		5.1
Change in bowel habit	641 (1.0)		1.0
Chest pain (non-cardiac)	1,866 (2.9)		2.9
Chest signs	90 (0.1)		0.1
Dyspepsia	1,776 (2.8)		2.8
Dysphagia	717 (1.1)		1.1
Haemoptysis	181 (0.3)		0.3
Iron deficiency anaemia	780 (1.2)		1.2
Jaundice	126 (0.2)		0.2
Lymphadenopathy	209 (0.3)		0.3
Venous thromboembolism	201 (0.3)		0.3
Liver function tests			
Albumin (g/L)	41,622 (65.1)	41.1 (4.8)	41.2 (4.8)*
Alkaline Phosphatase (iu/L)	41,278 (64.5)	90.8 (57.5)	89.9 (56.8)*
AST /ALT (iu/L)	10,911 (17.1)	25.9 (20.7)	25.4 (18.9)*
Bilirubin (umol/L)	41,895 (65.5)	11.1 (6.9)	11.1 (6.8)*
Full blood count			
Haemoglobin (g/L)	46,129 (72.1)	13.5 (1.6)	13.5 (1.6)*
Lymphocytes (x10 ⁹ /L)	42,502 (66.5)	1.9 (0.7)	1.9 (0.8)*
Mean cell volume (fL)	45,010 (70.4)	91.1 (6.2)	91.1 (6.2)*
Monocytes (x10 ⁹ /L)	42,607 (66.6)	0.6 (0.4)	0.6 (0.4)*
Neutrophils (x10 ⁹ /L)	40,592 (63.5)	4.6 (2.1)	4.6 (2.1)*
Platelets (x10 ⁹ /L)	45,239 (70.7)	272.5 (88.5)	272.2 (88.3)*
Total white cell count (x10 ⁹ /L)	44,714 (69.9)	7.3 (2.5)	7.3 (2.5)*
Inflammatory markers			
C-reactive protein (mg/L)	14,703 (23.0)	13.3 (30.1)	11.7 (27.3)*
Erythrocyte sedimentation rate (mm/h)	22,931 (35.9)	17.4 (21.4)	17.6 (21.0)*
Cancer diagnosis within six months			
Yes	908 (1.4)		1.4
No	63,065 (98.6)		98.6

*=imputed data; sd: standard deviation

Figure 9.4.2-1: Imputation diagnostics for C-reactive protein for the first twenty imputed datasets



9.4.3. The prediction models

Table 9.4.3-1 shows the final symptoms only model (Sm) in which 12 of the 17 candidate variables were associated with cancer (Table 9.4.3-1). Jaundice (adjusted odds ratio (aOR) 6.62, 95%CI 3.77 to 11.63), lymphadenopathy (aOR 4.67, 95%CI 2.08 to 10.47) and chest signs (aOR 3.73, 95%CI 1.81 to 7.68) were most predictive of cancer.

Table 9.4.3-1: Symptoms only model (Sm)

Covariate		Coefficient (95%CI)	Odds Ratio (95%CI)	p-value
Demographics				
Age-group (ref: 60-69 years)	18-39	-3.85 (-4.75 to -2.96)	0.02 (0.01 to 0.05)	<0.01
	40-49	-1.93 (-2.40 to -1.46)	0.14 (0.09 to 0.23)	<0.01
	50-59	-1.11 (-1.43 to -0.78)	0.33 (0.24 to 0.46)	<0.01
	70-79	0.63 (0.43 to 0.82)	1.87 (1.53 to 2.28)	<0.01
	80+	0.72 (0.52 to 0.93)	2.06 (1.69 to 2.52)	<0.01
Gender (ref: women)	male	0.77 (0.63 to 0.91)	2.16 (1.87 to 2.48)	<0.01
Risk factors				
Smoking status (ref: never)	current	0.61 (0.37 to 0.84)	1.84 (1.45 to 2.32)	<0.01
	ex	0.21 (-0.02 to 0.43)	1.23 (0.98 to 1.54)	0.07
Symptoms				
	Abdominal pain	0.77 (0.56 to 0.98)	2.17 (1.76 to 2.67)	<0.01
	Appetite loss	0.61 (0.33 to 0.89)	1.84 (1.39 to 2.43)	<0.01
	Dyspepsia	0.46 (0.16 to 0.75)	1.58 (1.18 to 2.12)	<0.01
Signs				
	Abdominal mass	1.09 (0.59 to 1.59)	2.98 (1.81 to 4.93)	<0.01
	Chest signs	1.32 (0.60 to 2.04)	3.73 (1.81 to 7.68)	<0.01
	Iron deficiency anaemia	1.15 (0.82 to 1.48)	3.16 (2.27 to 4.41)	<0.01
	Jaundice	1.89 (1.33 to 2.45)	6.62 (3.77 to 11.6)	<0.01
	Lymphadenopathy	1.54 (0.73 to 2.35)	4.67 (2.08 to 10.5)	<0.01
	Venous thromboembolism	1.10 (0.47 to 1.73)	3.00 (1.60 to 5.64)	<0.01
Constant		-4.97 (-5.2 to -4.75)		<0.01

CI: confidence interval; ref: reference group

Table 9.4.3-1 shows the final symptoms and tests model (STm) in which 17 out of 29 candidate variables were retained. A raised C-reactive protein (aOR 4.09, 95%CI 3.24 to 5.16), concurrent jaundice (aOR 2.33, 95%CI 1.27 to 4.28) and a concurrent change in bowel habit (aOR 2.03, 95%CI 1.26 to 3.26) were most predictive. The risk scores derived for each covariate included in the final STm ranged from -10 to four.

Table 9.4.3-2: Symptoms and test model (STm).

Covariate		Coefficient (95% CI)	Odds Ratio (95% CI)	p-value	Risk score*
Demographics					
Age-group (ref: 60-69 years)	18-39	-3.34 (-4.24 to -2.44)	0.04 (0.01 to 0.09)	<0.01	-10
	40-49	-1.61 (-2.09 to -1.13)	0.20 (0.12 to 0.32)	<0.01	-5
	50-59	-0.96 (-1.3 to -0.63)	0.38 (0.27 to 0.53)	<0.01	-3
	70-79	0.36 (0.16 to 0.57)	1.44 (1.17 to 1.77)	<0.01	1
	80+	0.33 (0.11 to 0.54)	1.38 (1.12 to 1.72)	<0.01	1
Gender (ref: women)	Male	0.53 (0.38 to 0.69)	1.70 (1.46 to 1.99)	<0.01	2
Smoking status (ref: never)	Current	0.60 (0.35 to 0.85)	1.82 (1.41 to 2.34)	<0.01	2
	Ex	0.18 (-0.06 to 0.42)	1.20 (0.94 to 1.53)	0.14	1
Symptoms					
	Abdominal pain	0.64 (0.42 to 0.86)	1.90 (1.52 to 2.37)	<0.01	2
	Change in bowel habit	0.71 (0.23 to 1.18)	2.03 (1.26 to 3.26)	<0.01	2
	Dyspepsia	0.47 (0.16 to 0.77)	1.59 (1.17 to 2.17)	<0.01	1
Signs					
	Iron deficiency anaemia	0.51 (0.15 to 0.88)	1.67 (1.16 to 2.41)	0.01	2
	Jaundice	0.85 (0.24 to 1.45)	2.33 (1.27 to 4.28)	0.01	3
Blood tests					
	Low albumin	0.36 (0.17 to 0.55)	1.43 (1.18 to 1.73)	<0.01	1
	Raised alk phos	0.67 (0.48 to 0.86)	1.95 (1.61 to 2.36)	<0.01	2
	Raised liver enzymes	0.69 (0.39 to 0.99)	1.99 (1.47 to 2.70)	<0.01	2
	Raised CRP (>10)	1.41 (1.18 to 1.64)	4.09 (3.24 to 5.16)	<0.01	4
	Low haemoglobin	0.37 (0.19 to 0.55)	1.45 (1.21 to 1.74)	<0.01	1
	Low MCV	-0.47 (-0.68 to -0.25)	0.63 (0.50 to 0.78)	<0.01	-1
	Raised platelets	0.50 (0.31 to 0.70)	1.65 (1.36 to 2.02)	<0.01	2
	Raised monocytes	0.68 (0.50 to 0.86)	1.97 (1.65 to 2.36)	<0.01	2
	Low lymphocytes	0.36 (0.18 to 0.53)	1.43 (1.20 to 1.70)	<0.01	1
Constant		-6.09 (-6.36 to 5.81)		<0.01	

*conversion factor = 0.32. The conversion factor is used to translate coefficients into the risk score, rounded to the nearest integer. CI: Confidence interval; ref: reference group; alk phos: alkaline phosphatase; CRP: C-reactive protein MCV: mean cell volume.

Table 9.4.3-3 shows the final tests only model (Tm) in which nine of 12 candidate predictor variables were retained. Raised C-reactive protein (aOR 4.50, 95%CI 3.60 to 5.64) and raised liver enzymes (aOR 2.02, 95%CI 1.51 to 2.71) were most predictive. The risk scores derived for each covariate included in the final Tm ranged from -10 to five.

Table 9.4.3-3: Tests only model (Tm)

Covariate		Coefficient (95%CI)	Odds Ratio (95%CI)	p-value	Risk score*
Demographics					
Age-group (ref: 60-69 years)	18-39	-3.31 (-4.20 to -2.41)	0.04 (0.01 to 0.09)	<0.01	-10
	40-49	-1.61 (-2.08 to -1.14)	0.20 (0.12 to 0.32)	<0.01	-5
	50-59	-0.94 (-1.28 to -0.61)	0.39 (0.28 to 0.54)	<0.01	-3
	70-79	0.36 (0.15 to 0.56)	1.43 (1.17 to 1.75)	<0.01	1
	80+	0.26 (0.06 to 0.47)	1.30 (1.06 to 1.60)	0.01	1
Gender (ref: women)	male	0.61 (0.46 to 0.76)	1.84 (1.59 to 2.14)	<0.01	2
Blood tests					
	Low albumin	0.38 (0.19 to 0.57)	1.47 (1.21 to 1.78)	<0.01	1
	Raised alkaline phosphatase	0.70 (0.51 to 0.89)	2.01 (1.66 to 2.43)	<0.01	2
	Raised liver enzymes	0.70 (0.41 to 1.00)	2.02 (1.51 to 2.71)	<0.01	2
	Raised CRP (>10)	1.50 (1.28 to 1.73)	4.50 (3.60 to 5.64)	<0.01	5
	Raised total white cell count	0.60 (0.40 to 0.79)	1.82 (1.50 to 2.20)	<0.01	2
	Raised platelets	0.52 (0.32 to 0.72)	1.68 (1.38 to 2.04)	<0.01	2
	Low haemoglobin	0.44 (0.26 to 0.61)	1.55 (1.30 to 1.85)	<0.01	1
Constant		-5.69 (-5.93 to -5.46)		<0.01	

*conversion factor = 0.32. The conversion factor is used to translate coefficients into the risk score, rounded to the nearest integer. CI: confidence interval; ref: reference group; CRP: C-reactive protein.

9.4.4. Internal validation

The AUC for both the STm (0.92, 95%CI 0.91 to 0.93) and the Tm (0.91, 95%CI 0.90 to 0.92) showed excellent discrimination, which was superior to the Sm (0.79, 95%CI 0.78 to -0.81) (Table 9.4.4-1). However, the calibration statistics showed that the Sm performed better overall compared to the STm and Tm. Plots revealed that the difference in overall calibration statistics was mainly due to under-prediction in the highest decile of risk for the STm and Tm models that was not seen for the Sm (Figure 9.4.5-1).

Table 9.4.4-1: Prediction model discrimination and calibration statistics

Models	Discrimination	Calibration		
	AUC (95% CI)	E:O	CITL	Slope
Sm	0.79 (0.78-0.81)	0.995	0.005	0.993
STm - dichotomous primary analysis	0.92 (0.91-0.93)	0.825	0.210	1.197
<i>STm - continuous sensitivity analysis</i>	0.92 (0.91-0.93)	0.820	0.220	1.199
Tm - dichotomous primary analysis	0.91 (0.90- 0.92)	0.824	0.209	1.213
<i>Tm - continuous sensitivity analysis</i>	0.92 (0.91-0.93)	0.826	0.211	1.199

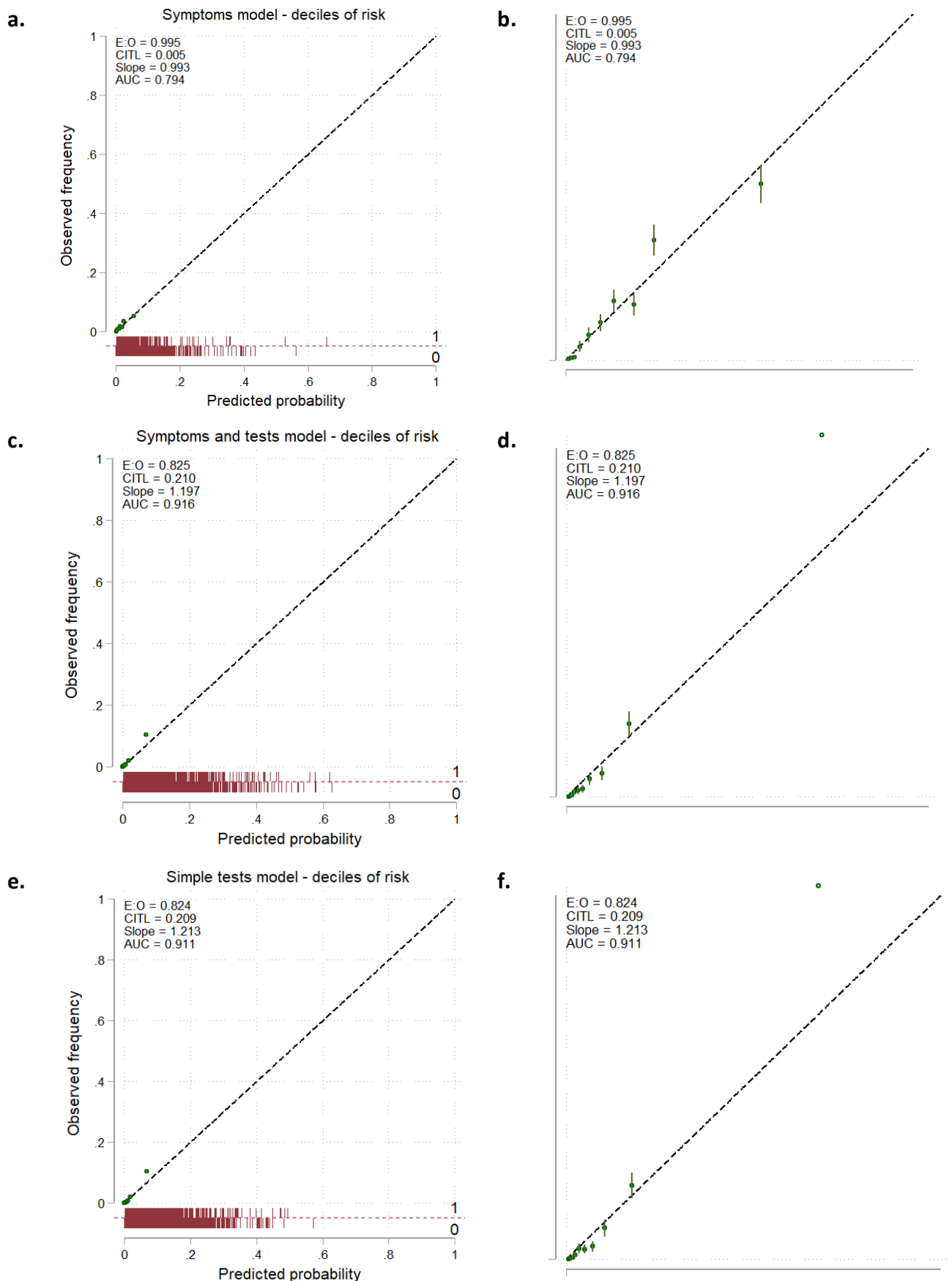
AUC: area under the curve; E:O: ratio of expected (predicted) probability versus observed frequency of the outcome; CITL: calibration in the large; Sm: symptoms only model; STm: symptoms and test model; Tm: test only model.

9.4.5. Sensitivity analysis

In the sensitivity analyses, a linear form was selected for most continuous blood tests except for alkaline phosphatase (FP1, -0.5), C-reactive protein (FP1, 0), lymphocytes (FP1, 3) and monocytes (FP1, 0) (

Table 9.4.5-1 & Table 9.4.5-2). Refitting the STm and Tm with continuous blood test results in place of dichotomised blood test results made negligible difference to model performance in terms of discrimination (Table 9.4.4-1) and calibration (Figure 9.4.5-2).

Figure 9.4.5-1: Calibration plots for the Sm (a-b) STm (c-d) and Tm (e-f).



E:O: ratio of expected (predicted) probability versus observed frequency of the outcome; CITL: calibration in the large; AUC: area under the curve. Green points are deciles of predicted probability with error bars. The right hand panels (2b, 2d, 2e) are zoomed in to show in detail the first 0.1% of predicted probability and observed frequency.

Table 9.4.5-1: Symptoms and tests model containing continuous variables (sensitivity analysis)

Covariate	Category /form.	Coefficient (95% CI)	Odds Ratio (95% CI)	p-value
Demographics				
Age-group (ref:60-69 years)	18-39	-3.31 (-4.21 to -2.41)	0.04 (0.02 to 0.09)	<0.01
	40-49	-1.62 (-2.10 to -1.13)	0.20 (0.12 to 0.32)	<0.01
	50-59	-0.94 (-1.28 to -0.60)	0.40 (0.28 to 0.55)	<0.01
	70-79	0.40 (0.18 to 0.61)	1.49 (1.20 to 1.84)	<0.01
	80+	0.40 (0.18 to 0.62)	1.50 (1.20 to 1.87)	<0.01
Gender (ref: women)	Male	0.67 (0.51 to 0.83)	1.96 (1.67 to 2.30)	<0.01
Smoking status (ref: never)	Current	0.62 (0.37 to 0.88)	1.86 (1.45 to 2.40)	<0.01
	Ex	0.20 (-0.04 to 0.45)	1.22 (0.96 to 1.56)	0.12
Symptoms				
Abdominal pain		0.62 (0.39 to 0.85)	1.86 (1.47 to 2.34)	<0.01
Change in bowel habit		0.69 (0.21 to 1.17)	1.99 (1.23 to 3.29)	<0.01
Dyspepsia		0.51 (0.20 to 0.83)	1.67 (1.22 to 2.30)	<0.01
Signs				
Iron deficiency anaemia		0.07 (-0.32 to 0.47)	1.08 (0.73 to 1.60)	0.71
Jaundice		0.51 (-0.16 to 1.19)	1.67 (0.86 to 3.27)	0.13
Blood tests (continuous)				
Albumin	linear	-0.03 (-0.04 to -0.01)	0.98 (0.96 to 0.99)	<0.01
Alkaline phosphatase	FP1(-0.5)	-1.54 (-1.94 to -1.15)	0.21 (0.14 to 0.32)	<0.01
Liver enzymes	linear	0.61 (0.30 to 0.91)	1.83 (1.35 to 2.45)	<0.01
C-reactive protein	FP1(0)	0.53 (0.43 to 0.62)	1.69 (1.54 to 1.85)	<0.01
Haemoglobin	linear	-0.06 (-0.12 to -0.01)	0.94 (0.89 to 0.99)	0.02
MCV	linear	-0.05 (-0.06 to -0.04)	0.96 (0.94 to 0.96)	<0.01
Platelets	linear	0.05 (0.02-0.13)	1.05 (0.98 to 1.13)	0.16
Monocytes	FP1(0)	0.36 (0.18 to 0.53)	1.43 (1.12 to 1.70)	<0.01
Lymphocytes	FP1(3)	1.37 (-0.87 to 3.61)	3.96 (0.42 to 36.91)	0.23
Constant		1.12 (-0.21 to 2.60)		0.09

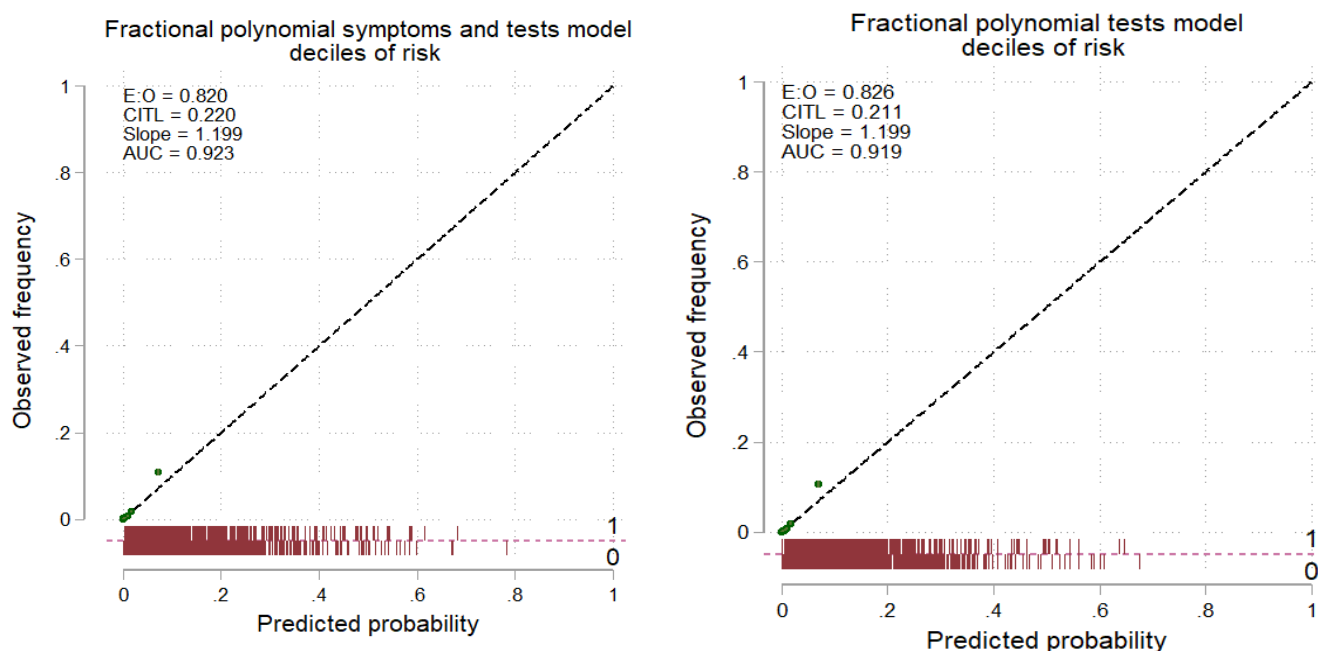
CI: confidence interval; ref: reference group; FP1: first order fractional polynomial; MCV: mean cell volume. The platelets and liver enzymes coefficients represents a per 100 unit increase

Table 9.4.5-2: Continuous Tests only model

Covariate		Coefficient (95% CI)	Odds Ratio (95% CI)	p-value
Demographics				
Age-group (ref: 60-69 years)	18-39	-3.14 (-4.03 to -2.24)	0.04 (0.02 to 0.11)	<0.01
	40-49	-1.53 (-2.01 to -1.05)	0.22 (0.14 to 0.35)	<0.01
	50-59	-0.90 (-1.23 to -0.56)	0.41 (0.29 to 0.57)	<0.01
	70-79	0.32 (0.11 to 0.52)	1.37 (1.11 to 1.69)	<0.01
	80+	0.23 (0.02 to 0.44)	1.25 (1.02 to 1.55)	0.04
Gender (ref: women)	male	-3.14 (-4.03 to -2.24)	0.04 (0.02 to 0.11)	<0.01
Blood tests				
	Albumin Linear	-0.02 (-0.04 to -0.00)	0.98 (0.96 to 1.00)	0.02
	Alkaline phosphatase FP1(-0.5)	-1.60 (-1.99 to -1.21)	0.20 (0.14 to 0.30)	<0.01
	Liver enzymes Linear	0.01 (0.00 to 0.01)	1.01 (1.00 to 1.01)	<0.01
	C-reactive protein FP1(0)	0.53 (0.44 to 0.62)	1.70 (1.55 to 1.87)	<0.01
	Total white cell count Linear	0.05 (0.03 to 0.08)	1.05 (1.03 to 1.08)	<0.01
	Platelets Linear	0.01 (0.02 to 0.17)	1.10 (1.03 to 1.18)	0.01
	Haemoglobin Linear	-0.11 (-0.16 to -0.06)	0.90 (0.85 to 0.94)	<0.01
Constant		-2.93 (-3.85 to -2.01)		<0.01

CI: confidence interval; ref: reference group; FP1: first order fractional polynomial. The platelets coefficient represents a per 100 unit increase

Figure 9.4.5-2: Cross-validation plots for continuous models (left panel: STm; right panel: Tm tests model)



E:O: ratio of expected (predicted) probability versus observed frequency of the outcome; CITL: calibration in the large; AUC: area under the curve.

9.4.6. Decision curve analysis

The STm and Tm were found to have the greatest clinical utility when DCA was used to investigate differences in the performance of the models (Figure 9.4.7-1). The STm had higher net benefit than the Sm for risk thresholds of 0.4% to 18.0% whilst the Tm had greater net benefit compared to the Sm for risk thresholds of 0.5% to 15.0% (Figure 9.4.7-1a). Compared to a strategy of testing all patients with UWL, at a cancer risk threshold of 1.0%, the STm translates into a 55.0% reduction in the number of people undergoing further investigation for cancers, the Tm a 53.0% reduction, and the Sm a 36.0% reduction (Figure 9.4.7-1b).

9.4.7. Clinical risk score examples

As the STm and Tm were the models with the greatest clinical utility, the diagnostic accuracy statistics corresponding to each possible point score are presented (Table 9.4.7-1 & Table 9.4.7-3). The numbers of primary care patients with UWL with and without cancer referred for invasive cancer investigation, those without cancer who would be spared referral, and those with cancer who would not be referred are reported in Table 9.4.7-2 and Table 9.4.7-4 based on the STm and the Tm, respectively. These tables also report the ratio of i) the total number referred for investigation against the total with cancer and ii) the total without cancer spared referral for investigation against the total with cancer who were not referred. Box 9.4.7-1 combines the insight provided by Table 9.4.7-1 and Table 9.4.7-2 by giving clinical examples of how the STm score might be used in practice. an example of a threshold that might sufficiently rule-out the need for referral for further cancer investigation, one that balances ruling-in and ruling-out the need for referral, and one derived from using the threshold closest to 3% PPV (the threshold used by the National Institute of Health and Clinical Excellence (NICE).

Figure 9.4.7-1: Decision curve analysis comparing the three models in terms of net benefit (a) and investigations avoided (b)

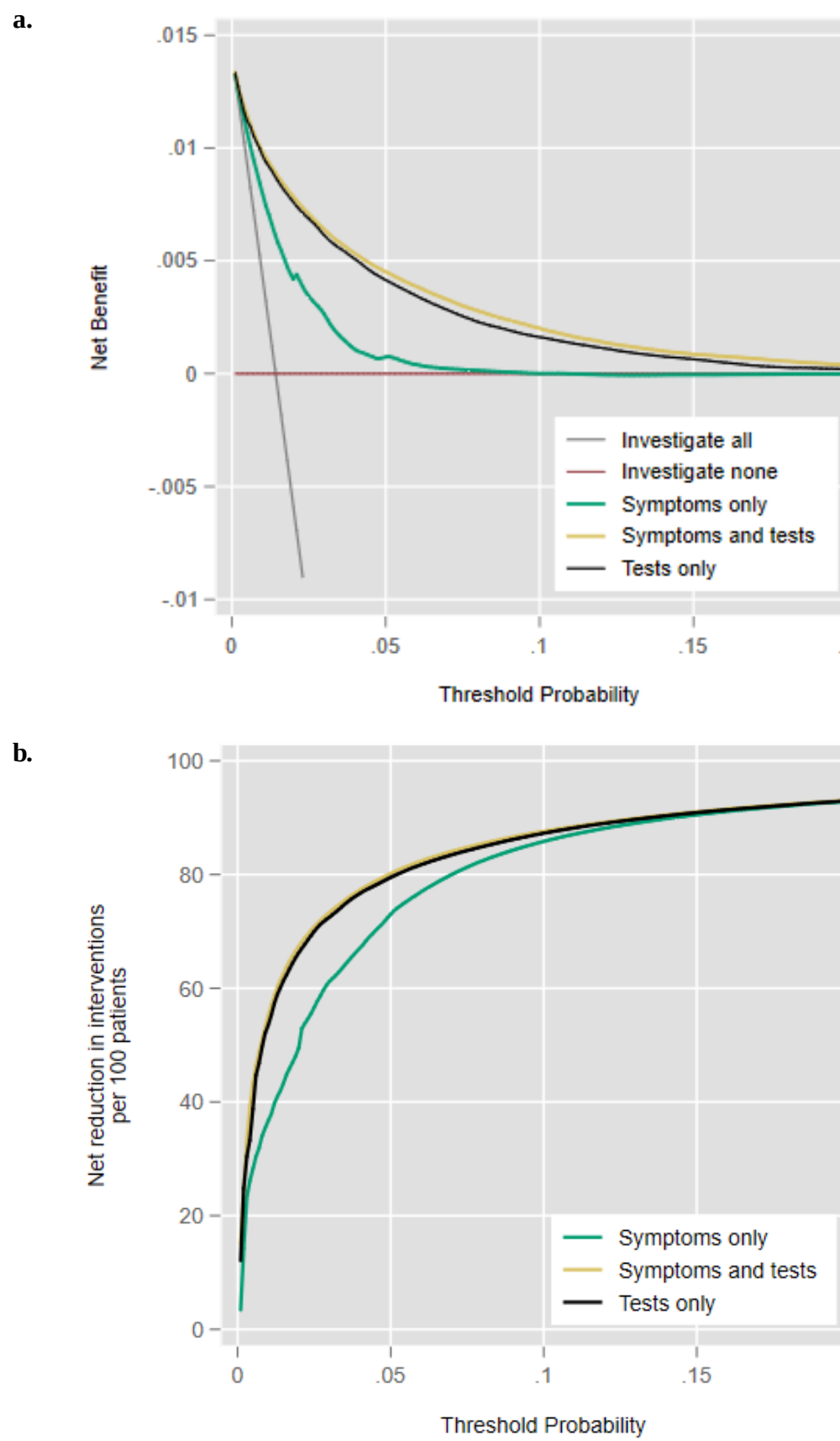


Table 9.4.7-1: Diagnostic accuracy statistics for each point score total calculated using the symptoms and tests model (STm).

Score	TP	FP	FN	TN	Sn (%)	Sp (%)	PLR	NLR	PPV (%)	NPV (%)
-11	908	63065	0	0	100	N/E	N/E	N/E	1.42	100
-10	908	63011	0	54	100	0.09	1.00	0	1.42	100
-9	908	61640	0	1425	100	2.26	1.02	0	1.45	100
-8	908	58467	0	4598	100	7.29	1.08	0	1.53	100
-7	908	55344	0	7721	100	12.2	1.14	0	1.61	100
-6	908	53119	0	9946	100	15.8	1.19	0	1.68	100
-5	908	50735	0	12330	100	19.6	1.24	0	1.76	100
-4	907	49186	1	13879	99.9	22.0	1.28	0	1.81	100
-3	906	47187	2	15878	99.8	25.2	1.33	0.01	1.88	100
-2	904	44756	4	18309	99.6	29.0	1.40	0.02	1.98	100
-1	902	41821	6	21244	99.3	33.7	1.50	0.02	2.11	100
0	900	38919	8	24146	99.1	38.3	1.61	0.02	2.26	100
1	895	35673	13	27392	98.6	43.4	1.74	0.03	2.45	100
2	889	30976	19	30089	97.9	50.9	1.99	0.04	2.79	99.9
3	875	25753	33	37312	96.4	59.2	2.36	0.06	3.29	99.9
4	853	19938	55	43127	93.9	68.4	2.97	0.09	4.10	99.9
5	822	14710	86	48355	90.5	76.7	3.88	0.12	5.29	99.8
6	784	10706	124	52359	86.3	83.0	5.09	0.16	6.82	99.8
7	729	7439	179	55626	80.3	88.2	6.81	0.22	8.93	99.7
8	667	5207	241	57858	73.5	91.7	8.90	0.29	11.4	99.6
9	583	3654	325	59411	64.2	94.2	11.1	0.38	13.8	99.5
10	487	2475	421	60590	53.6	96.1	13.7	0.48	16.4	99.3
11	389	1591	519	61474	42.8	97.5	17.0	0.59	19.6	99.2
12	262	996	646	62069	28.9	98.4	18.3	0.72	20.8	99.0
13	186	575	722	62490	20.5	99.1	22.5	0.80	24.4	98.9
14	125	324	783	62741	13.8	99.5	26.8	0.87	27.8	98.8
15	71	159	837	62906	7.82	99.7	31.0	0.92	30.9	98.7
16	45	77	863	62988	4.96	99.9	40.6	0.95	36.9	98.6
17	19	27	889	63038	2.09	100	48.9	0.98	41.3	98.6
18+	10	17	898	63048	1.10	100	40.9	0.99	37.0	98.6

TP: true positive; FP: false positive; FN: false positive; TN: true negative; Sn: sensitivity; Sp: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; N/E: not estimable.

Table 9.4.7-2: Symptoms and test model (STm) risk score thresholds expressed per 100,000 patients referred with unexpected weight loss (UWL)

STm Score	Per 100,000 patients with UWL referred				Ratio of patients referred without cancer to patients with cancer referred	Ratio of patients not referred without cancer to each patient with cancer not referred
	Patients referred with cancer	Patients referred without cancer	Patients with cancer not referred	Patients not referred without cancer		
-11	1,419	98,581	0	0	69:1	N/E
-10	1,419	98,482	0	99	69:1	N/E
-9	1,419	96,314	0	2,267	68:1	N/E
-8	1,419	91,385	0	7,196	64:1	N/E
-7	1,419	86,554	0	12,027	61:1	N/E
-6	1,419	83,005	0	15,576	58:1	N/E
-5	1,419	79,259	0	19,322	56:1	N/E
-4	1,418	76,893	1	21,688	54:1	21688:1
-3	1,417	73,739	2	24,842	52:1	12421:1
-2	1,414	69,993	5	28,588	50:1	5718:1
-1	1,409	65,359	10	33,222	46:1	3322:1
0	1,407	60,825	12	37,756	43:1	3146:1
1	1,399	55,797	20	42,784	40:1	2139:1
2	1,390	48,403	29	50,178	35:1	1730:1
3	1,368	40,221	51	58,360	29:1	1144:1
4	1,333	31,152	86	67,429	23:1	784:1
5	1,285	22,970	134	75,611	18:1	564:1
6	1,225	16,759	194	81,822	14:1	422:1
7	1,140	11,633	279	86,948	10:1	312:1
8	1,043	8,183	376	90,398	8:1	240:1
9	911	5,718	508	92,863	6:1	183:1
10	761	3,845	658	94,736	5:1	144:1
11	607	2,465	812	96,116	4:1	118:1
12	410	1,578	1,009	97,003	4:1	96:1
13	291	888	1,128	97,693	3:1	87:1
14	196	493	1,223	98,088	3:1	80:1
15	111	296	1,308	98,285	3:1	75:1
16	71	99	1,348	98,482	1:1	73:1
17	30	0	1,389	98,581	0:1	71:1
18	16	0	1,403	98,581	0:1	70:1
19	3	0	1,416	98,581	0:1	70:1
20+	0	0	1,419	98,581	N/E	69:1

N/E: not estimable.

Table 9.4.7-3: Diagnostic accuracy statistics for each point score total calculated using the tests only model (Tm)

Score	TP	FP	FN	TN	Sn (%)	Sp (%)	PLR	NLR	PPV (%)	NPV (%)
-10	908	63065	0	0	100	N/E	N/E	N/E	1.42	100
-9	908	57861	0	5204	100	8.25	1.09	0	1.55	100
-8	908	55062	0	8003	100	12.7	1.15	0	1.62	100
-7	908	51801	0	11264	100	17.9	1.22	0	1.72	100
-6	908	49986	0	13079	100	20.7	1.26	0	1.78	100
-5	907	49539	1	13526	99.9	21.4	1.27	0.01	1.80	100
-4	905	46990	3	16075	99.7	25.5	1.34	0.01	1.89	100
-3	905	45476	3	17589	99.7	27.9	1.38	0.01	1.95	100
-2	899	41089	9	21976	99.0	34.8	1.52	0.03	2.14	100
-1	896	38674	12	24391	98.7	38.7	1.61	0.03	2.26	100
0	895	35884	13	27181	98.6	43.1	1.73	0.03	2.43	100
1	885	32309	23	30756	97.5	48.8	1.90	0.05	2.67	99.9
2	861	25792	47	37273	94.8	59.1	2.32	0.09	3.23	99.9
3	844	20112	64	42953	93.0	68.1	2.91	0.10	4.03	99.9
4	805	13840	103	49225	88.7	78.1	4.04	0.15	5.50	99.8
5	763	9879	145	53186	84.0	84.3	5.36	0.19	7.17	99.7
6	708	6882	200	56183	78.0	89.1	7.15	0.25	9.33	99.6
7	638	4985	270	58080	70.3	92.1	8.89	0.32	11.3	99.5
8	555	3649	353	59416	61.1	94.2	10.6	0.41	13.2	99.4
9	450	2618	458	60447	49.6	95.8	11.9	0.53	14.7	99.2
10	351	1755	557	61310	38.7	97.2	13.9	0.63	16.7	99.1
11	239	1143	669	61922	26.3	98.2	14.5	0.75	17.3	98.9
12	170	721	738	62344	18.7	98.9	16.4	0.82	19.1	98.8
13	111	419	797	62646	12.2	99.3	18.4	0.88	20.9	98.7
14	58	205	850	62860	6.39	99.7	19.7	0.94	22.1	98.7
15	29	93	879	62972	3.19	99.9	21.7	0.97	23.8	98.6
16	15	38	893	63027	1.65	99.9	27.4	0.98	28.3	98.6
17	7	7	901	63058	0.77	100	69.5	0.99	50.0	98.6
18	2	0	906	63065	0.22	100	N/E	1.00	100	98.6

TP: true positive; FP: false positive; FN: false positive; TN: true negative; Sn: sensitivity; Sp: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; N/E: not estimable.

Table 9.4.7-4: Test only model (Tm) risk score thresholds expressed per 100,000 referred patients with unexpected weight loss (UWL)

Tm Score	Per 100,000 referred patients with UWL				Ratio of patients referred without cancer to patients with cancer referred	Ratio of patients not referred without cancer to each patient with cancer not referred
	Patients referred with cancer	Patients referred without cancer	Patients with cancer not referred	Patients not referred without cancer		
-10	1,419	98,581	0	0	69:1	N/E
-9	1,419	90,399	0	8,182	64:1	N/E
-8	1,419	86,061	0	12,520	61:1	N/E
-7	1,419	80,935	0	17,646	57:1	N/E
-6	1,419	78,175	0	20,406	55:1	N/E
-5	1,418	77,485	1	21,096	55:1	21,096:1
-4	1,415	73,443	4	25,138	52:1	6,285:1
-3	1,415	71,077	4	27,504	50:1	6,876:1
-2	1,405	64,275	14	34,306	46:1	2,450:1
-1	1,401	60,430	18	38,151	43:1	2,120:1
0	1,399	56,093	20	42,488	40:1	2,124:1
1	1,384	50,474	35	48,107	36:1	1,374:1
2	1,346	40,320	73	58,261	30:1	798:1
3	1,320	31,448	99	67,133	24:1	678:1
4	1,259	21,590	160	76,991	17:1	481:1
5	1,192	15,478	227	83,103	13:1	366:1
6	1,107	10,746	312	87,835	10:1	282:1
7	998	7,788	421	90,793	8:1	216:1
8	867	5,718	552	92,863	7:1	168:1
9	704	4,141	715	94,440	6:1	132:1
10	549	2,761	870	95,820	5:1	110:1
11	373	1,775	1,046	96,806	5:1	93:1
12	265	1,085	1,154	97,496	4:1	84:1
13	173	690	1,246	97,891	4:1	79:1
14	91	296	1,328	98,285	3:1	74:1
15	45	99	1,374	98,482	2:1	72:1
16	24	99	1,395	98,482	4:1	71:1
17	11	0	1,408	98,581	0:1	70:1
18	3	0	1,416	98,581	0:1	70:1

N/E: not estimable

Box 9.4.7-1: Consequences of applying the STm score in clinical practice

i) A clinical example

A 52-year-old woman with UWL but no other clinical features, a low albumin, high alkaline phosphatase and a raised C-reactive protein corresponds to a STm score of four. This cut-off achieves a sensitivity of 93.9% and a specificity of 68.4% (Table 9.4.7-1). At this threshold, 23 people would be referred for each person with cancer referred and 784 people would be spared investigation for each person with cancer not referred (Table 9.4.7-2). Per 100,000 people with UWL, 1,333 with cancer would be referred, 31,152 would be referred unnecessarily, 67,429 correctly spared referral and 86 with cancer would not be referred.

ii) Example of maximising sensitivity to rule-out cancer

A STm score of one prioritises ruling-out cancer by maximising sensitivity (98.6%) to the detriment of specificity (43.4%) (Table 9.4.7-1). At this threshold, 40 people with UWL would be referred for each person with cancer referred and 2,139 people with UWL spared referral for each person with cancer not referred (Table 9.4.7-2). Per 100,000 people with UWL, 1,399 people with cancer would be referred, 55,797 people would be unnecessarily referred, and 42,784 correctly spared referral and 20 people with cancer not referred.

iii) Example of a threshold to balance ruling-in and ruling-out cancer

A STm score of six would balance ruling-in (PLR 5.09) and ruling-out (NLR 0.16) achieving a sensitivity of 86.3% and a specificity 83.0% (Table 9.4.7-1). At this threshold, there would be 14 people referred for investigation for each person with cancer referred, 422 people would be spared investigation for each person with cancer not referred (Table 9.4.7-2). Per 100,000 people with UWL, 1,225 people with cancer would be referred, 16,759 patients would be unnecessarily referred, and 81,822 correctly spared referral and 194 people with cancer not referred.

iv) Example of a threshold close to the NICE PPV threshold of 3%

A STm score of two is the closest to a PPV to 3%, the threshold chosen by NICE to warrant further investigation. This cut-off achieves a sensitivity of 97.9% and a specificity of 50.9% (Table 9.4.7-1). At this threshold, 35 people would be referred for each person with cancer referred and 1,730 patients would be spared investigation for each person with cancer not referred (Table 9.4.7-2). Per 100,000 patients with UWL, 1,390 people with cancer would be referred, 48,403 patients would be unnecessarily referred, 50,178 would be correctly spared referral and 29 people with cancer not referred.

9.5. Discussion

9.5.1. Summary of findings

This chapter reports the derivation and internal validation of three prediction models to estimate the risk of undiagnosed cancer in patients presenting to primary care with UWL that could be used to select patients who do not – or conversely those that do - warrant further cancer investigation. The models including test results discriminated excellently between patients with and without cancer, were well calibrated at the levels of risk that decisions to investigate are made in primary care, and showed superior clinical utility when compared to the symptoms-based model. These models are presented as stand-alone risk scores that could be used by GPs away from the electronic health record (EHR). The simplest includes age-group, gender and seven primary care blood tests (alkaline phosphatase, liver enzymes, albumin, C-reactive protein, haemoglobin, platelets and total white cell count).

9.5.2. Strengths and limitations

The same steps were taken as those used in the previous chapters to minimise bias in relation to the definition of UWL and cancer. By utilising multiple imputation to replace missing risk factor and continuous test result data, precise estimates were produced for combinations of multiple covariates. Chapter Four showed us that previous studies have focused on single or pairs of blood test abnormalities. Auxiliary variables were included to increase the likelihood that missing values could be accurately predicted by the observed data (the MAR assumption) (173). However, there is no established method to formally evaluate whether this was successful. Imputation allowed the combination of multiple blood test results and to show that once blood tests are modelled with gender and age, the resulting more parsimonious model performed almost equivalently to the model also including clinical features.

Each blood test was dichotomised for the primary analysis to produce a simple risk score for use in clinical practice using the upper or lower boundary of the normal reference range. This approach has imitations. Firstly, by reducing a continuous data into a binary form, information is lost by grouping slightly and extremely abnormal results together. Secondly, choosing raised values to define abnormal might be unhelpful for cancer sites associated with low values (and vice versa). Thirdly, for blood tests where there is no consensus on how to define abnormal (for example raised liver enzymes can be defined by two to three times the upper limit of normal), the upper limit of the normal range was chosen. Refitting the models to include continuous linear and fractional polynomial terms made no meaningful difference to model performance.

The intention was to develop a testing strategy appropriate for a composite of all cancer types. The literature reports that the direction of blood test abnormalities is similar for most cancers and that a pro-inflammatory state underpins many cancers and cancer cachexia (4, 7, 160-163, 167, 168, 179, 191). It is likely that the composite cancer outcome is partly responsible for the under-prediction observed at the highest decile of risk. It is unlikely that this would have adverse clinical consequences because GPs' decisions to refer patients for invasive testing is likely to be triggered at thresholds lower than this.

Ten-fold internal cross-validation was used to derive estimates of predictive performance (192). However, such internal validation can produce over-optimistic estimates (185) and external validation is still required. Furthermore, a health economic (impact) evaluation is needed to identify the most appropriate risk score thresholds to identify patients who do not – or do - warrant further cancer investigation.

9.5.3. Findings in context

One previous study developed a risk score to predict cancer in a cohort of 256 patients referred for the investigation of UWL. The score included the following variables: age of 80 years and over, white blood cell count, and levels of albumin, alkaline phosphatase and lactate dehydrogenase (172). The AUC from internal validation was 0.90 (95% CI 0.88 to 0.92). The AUC was lower (AUC 0.70, 95%CI 0.61 to 0.78) when the model was externally validated in a cohort of 290 consecutive patients referred to hospital with UWL (171). This study also developed a simpler three-variable score that included age ≥ 60 years and over, alkaline phosphatase and albumin levels. This model had an AUC of 0.74 (95% CI 0.66 to 0.81) but was not internally or externally validated (171). The models in this chapter produced higher AUCs than these and, more importantly, include a cohort of all patients presenting to primary care with UWL, not just those referred to hospital for further investigation.

Two existing primary care prediction models incorporate multiple symptoms and risk factors to estimate cancer risk over a two year period for 1.24 million women (AUC 0.85 (95% CI 0.84 to 0.85)) and 1.26 million men (0.87 (0.88 to 0.89)) aged 25-89 years (16, 85). They also demonstrate good calibration at the lower deciles of risk but worse calibration at the highest decile of risk. The relative timing of symptoms was not reported. Blood tests were not included, except haemoglobin results in the 12 months before to two months after study entry were used to define anaemia as a baseline risk factor. Consequently, the design and reporting of these models make it impossible to understand the diagnostic value of symptoms and blood tests co-occurring with UWL.

9.5.4. Implications for clinical practice

DCA was used to describe the probable 'yield' of cancer diagnoses through hospital-based invasive investigations at different risk thresholds (187). However, DCA cannot define the acceptable balance between the total number of people referred to the cases of cancer diagnosed or between the number of people spared referral to the cases of cancer missed. The examples shown in Box 9.4.7-1 illustrate how a risk score could inform these decisions. Moreover, these scenarios could help GPs develop watchful waiting strategies for patients with intermediate cancer risk, perhaps scheduling periodic review and blood test re-evaluation to examine whether the risk has changed. However, these trade-offs are for patients, clinicians and society at large to decide and require health economic evaluation.

9.5.1. Implications for research

There is a dearth of research on how risk scores for cancer are best adopted into clinical practice. The intention of this analysis was to derive an intuitive risk score that mirrors clinical practice by focussing on simple combinations of clinical features including commonly used blood tests. Each score could be completed by GPs by hand, used as an online calculator or integrated into the EHR. However, the available literature suggests that risk scores are underused with GPs finding predictions difficult to interpret or trust, especially when they conflict with intuitive clinical judgement (193, 194). Further research is therefore required to optimise their uptake and to assess whether their use improves on cancer outcomes.

9.6. Conclusion and next steps

These internally validated clinical risk scores identify patients with UWL who warrant further urgent cancer investigation, while recognising that many with UWL and normal blood test results can be exempted from such a referral.

Having succeeded in developing these prediction models and risk scores, I had neared my goal of developing the evidence base to inform GPs about which patients with UWL to refer for further investigation of cancer.

In the next, and final, chapter I will summarise my thesis findings and consider future avenues for research that follow from what I have learned.

10. Discussion

My motivation to study unexplained weight loss (UWL) as a predictor of cancer in primary care grew from encounters with three of my own patients, as detailed in Chapter One. In each case, I was uncertain about whether, and to what extent, to investigate for cancer. I referred to the existing evidence base and clinical guidance for assistance but they lacked clarity on the optimal investigative strategy.

During my DPhil, I have sought to conduct the research necessary to enable general practitioners (GPs) like me to identify which patients presenting with UWL should be offered testing for cancer. From a starting point of having no experience in electronic health record (EHR) research or large-scale statistical computing, I have developed the methodological expertise necessary to conduct complex prediction modelling using datasets comprising of millions of patient records. This was a significant undertaking and learning curve.

10.1. Summary of findings

10.1.1. Evidence gaps

The diagnostic test accuracy review reported in Chapter Four formally identified the gaps in the existing evidence base and provided the foundations for the subsequent five chapters. Of the 25 studies located, none reported the association between UWL and cancer across all cancer sites or cancer stage. A mixture of study designs led to bias and heterogeneity in the reported estimates of association between UWL and cancer. For some cancer sites, there had been no published research and so it remained unclear what the overall predictive value of UWL was for cancer. The majority of studies used codes to define UWL but none reported the code lists making it difficult to understand who was included and replicate their methods. No

data were reported about the timing of UWL in relation to the cancer diagnosis date. It was also unclear how the timing of clinical features, reported as co-occurring with UWL, compared to the UWL date. This made it difficult to elucidate the temporal sequence of events.

10.1.2. Weight recording

In Chapters Five and Six, I hoped to understand why there had been a reliance on coding to define UWL in the studies included in my systematic review. I identified that: i) approximately two thirds of patients in the UK primary care EHR did not have a weight recording each year; ii) for the third of patients with a weight record, an average of two years passed before a repeat measurement; and iii) that weight records were clustered in groups of patients not representative of the primary care population as a whole. Whilst it appeared that incentivising weight recording increased this activity and the proportion of patients with a record, this effect was not sustained after the incentive was removed. Through conducting this analysis, it became clear that I would not be able to rely on weight records from UK primary care to define UWL in a representative sample of primary care patients.

10.1.3. Weight loss coding

In Chapter Six, I used the available weight records to calculate the magnitude of recorded weight change that prompted weight loss codes to be added to the EHR. Of the three techniques I developed, I found that a complex method using linear regression to compare the predicted (expected) current weight with the actual (recorded) current weight led to broadly similar estimates of weight loss as a simple difference between current weight and previous weight. I also ascertained that there was a great deal of variation in the magnitude of weight change recorded prior to a primary care clinician entering a weight loss code. I identified the codes that can be used with greatest confidence to define weight loss in the EHR and

reported, for the first time, that such codes represent a mean loss of five percent or greater over a six-month period..

10.1.4. Cancers associated with weight loss

I used the weight loss codes identified in Chapter Six in Chapter Seven to define UWL in a matched cohort study investigating its association with cancer across all cancer sites and cancer stages. As noted in Chapter Four, previous studies had been uncomprehensive in their approach to answering this question. By using time-to event analysis, I found that the association between UWL and cancer diagnosis to be greatest in the three months after the first UWL code. This association was strongest in men aged 60 years and above and in women aged 80 years and above. Positive associations were observed for the following cancers: pancreatic, cancer of unknown primary, gastro-oesophageal, lymphoma, hepatobiliary, lung, bowel and renal tract. Strong negative associations were found for cancers of the breast and prostate. Whilst a positive association was more pronounced with late stage cancer, there was some evidence that UWL is also positively associated with earlier Stage II and Stage III cancers. Interestingly, and of use when devising an investigative strategy for primary care, the risk of a cancer diagnosis dropped below the risk of cancer in patients without UWL three months after the UWL presentation.

10.1.5. Identifying which patients with UWL should be investigated

Building on the results from Chapter Seven, I conducted a diagnostic accuracy study for patients with UWL that is reported in Chapter Eight. I investigated which clinical features (risk factors, symptoms, signs and blood test abnormalities) were most predictive of cancer when

co-occurring with UWL. This was necessary as I was concerned that an investigative strategy based on the findings of Chapter Seven would result in all men aged 60 years or over and all women aged 80 years or over being referred on for further investigation. This approach might lead to the over-investigation of UWL in men and its under-investigation in women.

Current UK National Institute of Health and Care Excellence (NICE) guidelines recommend further investigation when a patient's risk of cancer is three percent or greater. I found that the risk amongst adults with UWL presenting to primary care is two percent or less. However, I also identified groups of patients whose risk was above the NICE threshold. These were men who smoke or previously smoked aged 50 years or over and those with concurrent clinical features. This analysis also showed that clinical features that typically trigger investigation for a specific cancer site were found to be markers of several cancer types when they co-occur with UWL.

10.1.6. Identifying patients with UWL who do not warrant further investigation

In Chapter Eight, I found no combinations of UWL and clinical features that lowered the risk of cancer to sufficiently rule-out the need for further referrals. Identifying such combinations would be valuable to save people undergoing unnecessary invasive investigations. I suspected this finding was a consequence of missing data, in particular blood test data. In order to explore this further, as reported in Chapter Nine, I learnt how to develop and internally validate a clinical prediction model. I view this as a vital component of my research training as there is a strong and growing emphasis on informing clinical practice based on the wealth of insight provided by analysing big data. By using multiple imputation to replace missing data, I was able to develop prediction models to estimate the cancer risk of each individual patient based on combinations of multiple (present or absent, normal or abnormal) clinical features. I

present these models as simple risk scores that GPs could use in everyday practice to inform decisions about which adult patients with UWL warrant referral for further investigation for cancer. In doing so, I have achieved the goal of my thesis.

10.2. Overall strengths

My thesis presents the most comprehensive series of studies investigating the predictive value of UWL for cancer in primary care patients to date. I have reported the strengths of each study in each chapter. The key strengths are summarised here.

10.2.1. Robust evidence synthesis

Chapter Four examined the existing evidence base by following Cochrane methods, commonly regarded as the most robust approaches for evidence synthesis. It was the first, and currently only, review to examine the evidence for the predictive value of UWL across all cancer sites and stages and, importantly to summarise the weaknesses of the previous literature in this field.

10.2.2. Epidemiology of weight recording

Chapter Five included the largest and most up-to-date analysis of weight recording in UK primary care EHRs. It was also the first investigation of repeat weight recording in NHS general practice. The study confirmed my clinical observation that weight recording is not a routine activity in this setting. This chapter provided clarity that it is more appropriate to focus on coding within EHRs to define weight loss rather than to develop methods based on recorded weight measurements.

10.2.3. Weight loss code validation

Chapter Four identified that studies investigating the association between UWL and cancer diagnosis have not published the code lists used to define UWL making it impossible to replicate and validate their findings. Available, published code lists for UWL include the Weight Symptom codes however, in Chapter Six, I provided evidence that such codes are not associated with recorded weight loss and should not be used to define weight change in epidemiological studies. I report the codes I have identified which define UWL with greatest confidence, thus making them available to other researchers helping to ensure future UWL cohorts are comparable.

10.2.4. Temporal association of UWL and cancer diagnosis

Chapter Seven addressed a major limitation of the current evidence base, as highlighted in Chapter Four, by investigating the timing of UWL before an associated cancer diagnosis. I selected study participants based on their UWL status, arranging the dataset so that day 0 represented the date of UWL. Using this design, I was able to establish that the increased risk of a cancer diagnosis was confined to the three to six months following a first presentation of UWL. Previous studies have included a longer time span reporting, *“a 2-year period [...] represents the period of time during which existing cancers are likely to become clinically manifest”* (16). My findings indicate that such approaches derive inaccurate estimates of association by including cancers from outside this window. Unfortunately, this justification had been used by the majority of the studies included in Chapter Four.

10.2.5. Identifying associated clinical features

The major strengths of Chapters Eight and Nine also relate to timing. I restricted the follow-up period for cancer diagnosis to the “at-risk” period identified in Chapter Seven. Based on my experience as a GP, I included clinical features (symptoms, signs and blood test results) recorded in a four-month window around the UWL date (the three months before to one month after). These decisions increased the likelihood that the diagnosed cancer was associated with the UWL and the clinical features co-occurred with the UWL. Previous studies have included clinical features from a longer period; however in clinical practice such timing would not be considered as co-occurring.

10.2.6. Incorporating blood test results

The design of Chapters Eight and Nine allowed a robust investigation of the role of blood tests in the triage of patients with UWL. This has not been researched before despite clinicians often requesting blood tests to investigate UWL. I focussed on understanding the predictive value of tests commonly used in primary care so that my findings were clinically relevant. I built prediction models incorporating multiple blood test results for patients with UWL. The blood tests included in the final prediction models were consistent with our understanding from secondary care about blood test abnormalities associated UWL or cachexia (7, 167, 168). The prediction models including blood test results performed extremely well in internal validation.

10.3. Overall limitations

As with the strengths, I have detailed the study limitations in each chapter. The key overall limitations of the thesis are outlined here.

10.3.1. Reliance on coding

The most disappointing limitation of my thesis is that I have not been able to clarify the magnitude of weight loss, over how much time, is most predictive of cancer in primary care. This was a criticism I received when submitting the literature review reported in Chapter Four for journal publication and, furthermore, is important information for practising GPs. In Chapter Six, I go some way to addressing this by estimating the amount of recorded weight loss prior to a UWL code being applied (five percent or more over six months). This amount and duration of UWL is consistent with the secondary care literature (1). Even so, the estimates are imprecise with variation observed according to age-group. This is a major weakness of my thesis that provides an avenue for post-doctoral research into the feasibility of routine weight measurement in NHS primary care to increase the number patients with weight records in their EHR.

10.3.2. Coding bias

GPs are known to preferentially code clinical features they are most concerned about, noting features of less concern in the unstructured free text, a phenomenon known as recording or coding bias (82). By not including free text, it is probable that there are patients with UWL that are not included in my analyses. Furthermore, the predictive value of coded UWL will be overstated if only patients considered high risk are coded. However, the studies in Chapter

Four that included only coded EHR data led to more conservative estimates of association than those identifying UWL via other methods.

To partially address variability in coding, I used GP practice as a matching criterion between cases and controls in Chapter Seven as it is possible GPs working in the same surgery are more likely to code in a similar way, although I have found no direct evidence that this occurs. I excluded patients with evidence of intentional weight loss and those who had not been registered for at least a year in Chapters Five to Seven to increase the likelihood that the weight loss was unexpected. I also chose not to investigate a second UWL code as I wanted to investigate how a GP should respond when faced with a first presentation of UWL.

10.3.3. Calculation of cumulative positive predictive values

The design of diagnostic accuracy study reported in Chapter Eight would have met the inclusion criteria for the review reported in Chapter Four. A noticeable discrepancy is observed between the cumulative positive predictive values (PPVs) reported in Chapters Four and Eight. However, after removing prostate cancer as part of the sensitivity analysis in the systematic review, the estimates are closer. In Chapter Seven, prostate cancer was found to be less likely in patients with UWL, in disagreement with the strong positive association reported in Chapter Four. A possible explanation for this difference is that the prostate cancer study in Chapter Four used a follow-up period longer than the “at-risk” period identified in Chapter Seven, leading to a relatively high positive likelihood ratio (PLR) of 11. Multiplying this figure by the prior odds of prostate cancer resulted in a large PPV for prostate cancer in Chapter Four. This cancer is common in older men but it is commonly early stage and indolent (195). However, the prior odds were determined using national cancer incidence data that did not incorporate cancer stage. It may be more appropriate to use the prior odds for each stage

of each cancer associated with UWL; however I could not access sufficient staging data to investigate this.

10.3.4. Limited cancer stage data

I did not include cancer stage in the studies reported in Chapters Eight and Nine because only 10% of cancers had complete stage information in the data provided by NCRAS via CPRD. I attempted to supplement the staging data available in the “best stage” variable by utilising the TNM Classification of Malignant Tumours to stage additional cancers (6). I increased the proportion of patients with cancer stage to almost a half; however, after discussing this time consuming approach with colleagues and NCRAS, I decided not to pursue it any further as part of this thesis. In the future, I hope to work more closely with NCRAS and collaborate with the International Union Against Cancer to improve the accessibility of staging data and better understand cancer registration. I also hope to repeat my analysis in a newer dataset with more complete stage data.

10.4. Implications for clinical practice

The clinical implications of my thesis centre on three topics: detecting weight change, assessing cancer risk in patients attending primary care with UWL and investigating patients with UWL for possible cancer.

10.4.1. Detecting weight loss in primary care

Although the literature clearly demonstrates that cachexia can occur at any stage of cancer, clinical opinion considers UWL is a sign of late stage disease with poor prognosis (7). In my introductory chapter, I highlighted a number of mechanisms that may perpetuate this

disconnection between basic science and clinical practice. In Chapter Five, I elucidated that we, as NHS primary care practitioners, do not routinely record our patient's weight. In Chapter Six, I show this is often the case even when a weight related code is present in the EHR. Due to infrequent or absent weight monitoring we are reliant on our patients to identify their UWL and present themselves to primary care. If we were to monitor weight (and biomarkers for cachexia) more proactively we might catch clinically significant UWL before it is marked and more likely to be associated with late stage cancer.

As discussed in Chapter Two, Fearon et al defined pre-cachexia where clinical and biochemical signs precede significant UWL (4). Although this pre-cachectic stage is disputed, it could present an opportunity to detect the beginning of cachexia in primary care. I have been collaborating on a systematic review about the screening and assessment of cachexia with palliative care colleagues from Hull York Medical School. The most striking finding was the paucity of studies assessing cachexia risk with none set in primary care. Without a greater understanding of how best to identify patients at the pre-cachectic stage in general practice, UWL will inevitably continue to be the first clinical sign of cachexia that prompts a referral for further investigation. Our review suggests that body impedance analysis could be used in clinical practice to detect early markers of cachexic weight loss when accompanied by appropriate malnutrition screening questionnaires tools or inflammatory markers (5). However, these strategies are yet to be researched in primary care.

10.4.2. Selecting patients with UWL for intensive cancer investigation

Table 10.4.2.1-1 to Table 10.4.2.4-3 present different strategies to select primary care patients with UWL for cancer investigation based on the current NICE guidelines and the analyses in this thesis. To enable comparisons of the diagnostic strategies I developed, I calculated the

diagnostic accuracy statistics for the decision rules developed in Chapters Seven and Eight using Chapter Nine's imputed data.

10.4.2.1. The NICE strategy

One of the key clinical implications of my thesis is that UWL is associated with a broad range of cancers even when co-occurring with clinical features that would normally point to a single cancer site. It is unhelpful and problematic to directly compare the diagnostic accuracy of the NICE guidelines (Table 10.4.2.1-1) with the strategies derived in my thesis. Each NICE recommendation relates to a single cancer site whereas the strategies developed in my thesis are based on all cancers combined.

I will now illustrate why a new strategy is required to replace the current approach recommended by NICE, that was collated based on an incomplete evidence base. For example, a 65 year-old patient with UWL and thrombocytosis qualifies for a non-urgent gastroscopy if following NICE guidance. In Chapter Six, I identified that a man with these characteristics has a PPV of approximately 13% spread across eleven cancer sites, ten of which would not be diagnosed with a gastroscopy. A woman with this phenotype has a PPV of approximately 6% spread over thirteen cancer sites, twelve of which would not be diagnosed with gastroscopy. I suggest that the current NICE guidelines are incomplete and require updating. The analyses reported in Chapters Seven to Nine provide important evidence to inform their revision.

Table 10.4.2.1-1: NICE recommendations for the investigation of unexplained weight loss. (22)

Age (years)	Unexplained weight loss AND:	Action	Cancer
N/A	lymphadenopathy or splenomegaly	Urgent specialist referral*	Lymphoma
N/A	female	CA125 test in primary care	Ovarian
≥40	abdominal pain	Urgent specialist referral*	Colorectal
	ever-smoker / asbestos exposure	Urgent Chest X-Ray	Lung
	never-smoker AND cough / fatigue / shortness of breath / chest pain / appetite loss		
<50	rectal bleeding	Consider urgent specialist referral	Colorectal
≥50		Faecal Occult Blood Test	
≥55	upper abdominal pain / reflux / dyspepsia	Urgent gastroscopy	Gastro-oesophageal
	thrombocytosis / nausea and vomiting	Non-urgent gastroscopy	
≥60	Diarrhoea / back pain / abdominal pain / nausea / vomiting / constipation / new onset diabetes.	Consider urgent CT abdomen	Pancreas

**to be assessed within 2 weeks. N/A: not applicable; CT: computed tomography.*

10.4.2.2. The selection strategy from Chapter Seven

Table 10.4.2.2-1 shows the diagnostic accuracy statistics corresponding to a decision rule based on the time-to-event analysis reported in Chapter Seven. A strategy combining investigating all men aged 60 years or over with UWL and all women aged 80 years or over with UWL across all cancer sites has an overall sensitivity of 72% and specificity of 66%. This decision rule has a PPV of 3%, similar to that intended for the NICE guidelines. Using this strategy, 33 patients presenting with UWL in primary care would be referred for investigation for each patient with cancer referred and 165 patients would be spared invasive investigation for each patient with cancer not referred (Table 10.4.2.4-3). The ability of the strategy to rule-

out the need for further investigation, denoted by the ratio between investigations spared and cancers not investigated, would increase if the sensitivity increased.

Table 10.4.2.2-1: Summary of the decision rule derived from Chapter Seven

	TP	FP	FN	TN	Sens	Spec	AUC	PLR	NLR	PPV	NPV
Men $\geq$ 60 yrs.	504	13,303	404	49,762	55.5	78.9	0.67	2.63	0.56	3.65	99.2
Women $\geq$ 80 yrs.	151	8,082	757	54,983	16.6	87.2	0.52	1.30	0.96	1.83	98.6
Chapter 7 overall	655	21,385	253	41,680	72.1	66.1	0.69	2.13	0.42	2.97	99.4

TP: true positive; FP: false positive; FN: false positive; TN: true negative; Sens: sensitivity; Spec: specificity; AUC: area under curve; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; yrs.: years.

10.4.2.3. The selection strategy from Chapter Eight

Table 10.4.2.4-1 and Table 10.4.2.4-2 highlight the complexity of the decision rule derived by the diagnostic accuracy study presented in Chapter Eight in men and women, respectively. They report the diagnostic accuracy of each of the 36 individual decision rules and overall summary statistics.

Whilst the overall specificity (67%) is similar to Chapter Seven's rule, the sensitivity (80%) has improved with a corresponding improvement in the area under curve (AUC) from 0.69 to 0.74 and a reduction in the negative likelihood ratio (NLR) from 0.42 to 0.29. Using this strategy, five fewer patients ($n = 28$) presenting with UWL to primary care would be referred for investigation for each patient with cancer referred and 75 additional ($n = 240$) patients would be spared referral for each patient with cancer not referred (Table 10.4.2.4-3). Whilst this strategy improves on the performance of the rule from Chapter Seven, the negative likelihood ratio (NLR) remains above the threshold of 0.2 (below which is considered a good rule-out

test, and, at 2.44, the positive likelihood ratio (PLR) remains under 5 (above which is considered a good rule-in test) (45, 46).

10.4.2.4. The selection strategies arising from Chapter Nine

I present the incremental value of using a prediction modelling approach to patient selection in Table 10.4.2.4-3. These models (STm, symptoms and test model; Tm, tests only model) derive a cancer prediction for individual patients rather than using a strategy based on population level summary statistics.

I illustrate the gains in sensitivity made by utilising this approach by identifying the risk score closest to the specificity reported by Chapter Five (66.1%) and Chapter Six (67.0%). At this specificity, both prediction models (STm and Tm) performed similarly. A STm risk score of four had a specificity of 68.4%, a sensitivity of 93.9%, an AUC of 0.81 and a negative likelihood ratio (NLR) of 0.09. A risk score of four could be used to rule-out further investigation sufficiently: In other words, twenty three patients presenting with UWL in primary care would be referred for investigation for each cancer diagnosed and 784 patients would be spared invasive investigation for each person with cancer not referred (Table 10.4.2.4-3).

A STm threshold of six, corresponded to a PLR of 5.09 and a NLR of 0.16, could be chosen if the priority was to balance ruling-in and ruling-out cancer referral. This would result in seven fewer people (n = 14) presenting with UWL being referred for each person with cancer referred and fewer (n = 422) patients would be spared invasive investigation for each patient with cancer not referred (Table 10.4.2.4-3).

By working through these decision rules and comparing risk score thresholds, I have clearly illustrated the clinical implications of each strategy and their incremental benefit over and above the current NICE guidelines. If the performance of the prediction models is maintained in external validation, they offer an alternative to the current approach used to select patients with UWL for referral for cancer investigation. They could be used as a paper based decision rule, integrated into the EHR as a calculator for the GP to activate, or as an automatic prompt based on data entered.

Table 10.4.2.4-1: Summary of the decision rules derived for men from Chapter Eight

Chapter 8 decision rules for men	TP	FP	FN	TN	Sens	Spec	AUC	PLR	NLR	PPV	NPV
≥ 50 yrs. ever-smokers	169	5,349	739	57,716	18.6	91.5	0.55	2.19	0.89	3.06	98.7
≥ 60 yrs. with abdominal pain	53	684	855	62,381	5.8	98.9	0.52	5.27	0.95	7.19	98.6
≥ 60 yrs. with appetite loss	35	386	873	62,679	3.9	99.4	0.52	6.50	0.97	8.31	98.6
≥ 60 yrs. with non-cardiac chest pain	30	430	878	62,635	3.3	99.3	0.51	4.71	0.97	6.52	98.6
≥ 40 yrs. with haemoptysis	9	85	899	62,980	1.0	99.9	0.50	10.0	0.99	9.57	98.6
≥ 40 yrs. with an abdominal mass	13	95	895	62,970	1.4	99.8	0.51	7.0	0.99	12.04	98.6
≥ 60 yrs. with chest signs	6	47	902	63,018	0.7	99.9	0.50	7.0	0.99	11.32	98.6
≥ 60 yrs. with iron deficiency anaemia	22	173	886	62,892	2.4	99.7	0.51	8.0	0.98	11.28	98.6
≥ 40 yrs. with jaundice	7	47	901	63,018	0.8	99.9	0.50	8.0	0.99	12.96	98.6
≥ 40 yrs. with lymphadenopathy	4	40	904	63,025	0.4	99.9	0.50	4.0	1.00	9.09	98.6
≥ 40 yrs. with low albumin	156	1,602	752	61,463	17.2	97.5	0.57	6.88	0.85	8.87	98.8
≥ 40 yrs. with raised alkaline phosphatase	150	1,978	758	61,087	16.5	96.9	0.57	5.32	0.86	7.05	98.8
≥ 60 yrs. with raised bilirubin	60	1,735	848	61,330	6.6	97.2	0.52	2.36	0.96	3.34	98.6
≥ 60 yrs. with a low haemoglobin	234	3,330	674	59,735	25.8	94.7	0.60	4.87	0.78	6.57	98.9
≥ 60 yrs. with a raised total white cell count	92	803	816	62,262	10.1	98.7	0.54	7.77	0.91	10.28	98.7
≥ 40 yrs. with raised platelets	108	999	800	62,066	11.9	98.4	0.55	7.44	0.90	9.76	98.7
≥ 40 yrs. with raised C-reactive protein	122	1,434	786	61,631	13.4	97.7	0.56	5.83	0.89	7.84	98.7
≥ 60 yrs. with a raised erythrocyte sedimentation rate	181	3,158	727	59,907	19.9	95.0	0.57	3.98	0.84	5.42	98.8
Chapter 8 overall rule (for men and women)	732	20,781	176	42,284	80.6	67.0	0.74	2.44	0.29	3.4	99.6

TP: true positive; FP: false positive; FN: false positive; TN: true negative; Sens: sensitivity; Spec: specificity; AUC: area under curve; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; yrs.: years.

Table 10.4.2.4-2: Summary of the decision rules derived for women from Chapter Eight

Chapter 8 decision rules for women	TP	FP	FN	TN	Sens	Spec	AUC	PLR	NLR	PPV	NPV
≥ 60 yrs. with abdominal pain	44	1,105	864	61,960	4.8	98.2	0.52	2.67	0.97	3.83	98.6
≥ 60 yrs. with appetite loss	22	597	886	62,468	2.4	99.1	0.51	2.67	0.98	3.55	98.6
≥ 80 yrs. with a change in bowel habit	7	88	901	62,977	0.8	99.9	0.50	8.0	0.99	7.37	98.6
≥ 60 yrs. with dyspepsia	21	575	887	62,490	2.3	99.1	0.51	2.56	0.99	3.52	98.6
≥ 40 yrs. with an abdominal mass	6	107	902	62,958	0.7	99.8	0.50	3.5	0.99	5.31	98.6
≥ 60 yrs. with chest signs	3	21	905	63,044	0.3	100.0	0.50	N/E	1.00	12.5	98.6
≥ 60 yrs. with iron deficiency anaemia	16	316	892	62,749	1.8	99.5	0.51	3.6	0.99	4.82	98.6
≥ 60 yrs. with jaundice	10	46	898	63,019	1.1	99.9	0.51	11	0.99	17.86	98.6
≥ 80 yrs. with lymphadenopathy	3	8	905	63,057	0.3	100	0.50	N/E	1.00	27.27	98.6
≥ 60 yrs. with a venous thromboembolism	7	104	901	62,961	0.8	99.8	0.50	4.0	0.99	6.31	98.6
≥ 60 yrs. with low albumin	81	1,547	827	61,518	8.9	97.5	0.53	3.56	0.93	4.98	98.7
≥ 60 yrs. with raised alkaline phosphatase	86	1,849	822	61,216	9.5	97.1	0.53	3.28	0.93	4.44	98.7
60-79 yrs. with raised bilirubin	21	645	887	62,420	2.3	99.0	0.51	2.3	0.99	3.15	98.6
≥ 60 yrs. with a low haemoglobin	88	2,366	820	60,699	9.7	96.2	0.53	2.55	0.94	3.59	98.7
≥ 60 yrs. with a raised total white cell count	71	1,062	837	62,003	7.8	98.3	0.53	4.59	0.94	6.27	98.7
≥ 40 yrs. with raised platelets	88	1,953	820	61,112	9.7	96.9	0.53	3.13	0.93	4.31	98.7
≥ 60 yrs. with raised C-reactive protein	71	1,265	837	61,800	7.8	98.0	0.53	3.9	0.94	5.31	98.7
≥ 60 yrs. with a raised erythrocyte sedimentation rate	85	2,289	823	60,776	9.4	96.4	0.53	2.61	0.94	3.58	98.7
Chapter 8 overall rule (for men and women)	732	20,781	176	42,284	80.6	67.0	0.74	2.44	0.29	3.4	99.6

TP: true positive; FP: false positive; FN: false positive; TN: true negative; Sens: sensitivity; Spec: specificity; AUC: area under curve; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; yrs.: years; NE: not estimable.

Table 10.4.2.4-3: Comparison of diagnostic strategies reported in Chapters Seven Eight and Nine expressed as diagnostic accuracy measures.

Decision rule	Sens	Spec	AUC	PLR	NLR	PPV	NPV	Ratio of patients referred without cancer to patients with cancer referred	Ratio of patients not referred without cancer to each patient with cancer not referred
Fixing sensitivity to explore differences in specificity (rule-in)									
Chapter 7 overall rule (men ≥60yrs, women ≥80yrs)	72.1	66.1	0.69	2.13	0.42	2.97	99.4	33:1	165:1
STm threshold (=8) with closest sensitivity to Chapter 7 sensitivity	73.5	91.7	0.83	8.86	0.29	11.36	99.6	8:1	240:1
Tm threshold (=7) with closest sensitivity to Chapter 7 sensitivity	70.3	92.1	0.81	8.90	0.32	11.35	99.5	8:1	216:1
Chapter 8 overall rule (all the combinations reported in the chapter)	80.6	67.0	0.74	2.44	0.29	3.40	99.6	28:1	240:1
STm threshold (=7) with closest sensitivity to Chapter 8 sensitivity	80.3	88.2	0.84	6.81	0.22	8.93	99.7	10:1	312:1
Tm threshold (=6) with closest sensitivity to Chapter 8 sensitivity	78.0	89.1	0.84	7.16	0.25	9.33	99.6	10:1	282:1
Fixing specificity to explore differences in sensitivity (rule-out)									
Chapter 7 overall rule (men ≥60yrs, women ≥80yrs)	72.1	66.1	0.69	2.13	0.42	2.97	99.4	33:1	165:1
Chapter 8 overall rule (all the combinations reported in the chapter)	80.6	67.0	0.74	2.44	0.29	3.40	99.6	28:1	240:1
STm threshold (=4) with closest specificity to Chapters 7 & 8 specificity	93.9	68.4	0.81	2.97	0.09	4.10	99.9	23:1	784:1
Tm threshold (=3) with closest specificity to Chapters 7 & 8 specificity	93.0	68.1	0.81	2.92	0.10	4.03	99.9	24:1	678:1
Balancing sensitivity and specificity									
STm threshold (=6), balance of PLR (5.09) and NLR (0.16)	86.3	83.0	0.85	5.08	0.17	6.82	99.8	14:1	422:1
Tm threshold (=5), balance of PLR (5.36) and NLR (0.19)	84.0	84.3	0.84	5.35	0.19	7.17	99.7	13:1	366:1

Sens: sensitivity; Spec: specificity; AUC: area under curve; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; yrs.: years; STm: symptoms and test model; Tm: test only model.

10.4.1. Investigating patients with UWL

After deciding that a patient with UWL needs further investigation for cancer, the next question is what is the most appropriate investigative strategy to cover the broad range of cancer sites I have found to be associated with UWL?

Whilst my thesis was not specifically designed to answer this question, the Suspected CANcer (SCAN) pathway in Oxfordshire aims to develop and pilot a new service to investigate patients with UWL referred from primary care. It is part of the Accelerate Coordinate Evaluate (ACE) Programme that was established by Cancer Research UK, Macmillan Cancer Support and NHS England to pilot rapid diagnostic pathways to detect cancer in patients with non-specific symptoms (196, 197).

All 70 GP practices in Oxfordshire (covering approx. 748,000 patients) now have access to the SCAN pathway. GPs refer patients aged 40 years or older if they are concerned about cancer or serious disease, or if their patient has a non-specific symptom such as UWL, severe unexplained fatigue, persistent nausea or appetite loss, or new atypical pain. Patients undergo laboratory testing (blood, urine, and stool samples) and cross sectional diagnostic imaging (thorax, abdomen, and pelvis computed tomography with structured reporting) within two weeks of the referral. Following these tests, onward referral is made to the SCAN Multidisciplinary Diagnostic Centre (MDC) for further investigation if no cancer is diagnosed but it or another serious disease is suspected. The MDC has access to a broad range of investigations and specialist expertise in managing patients with non-specific cancer symptoms. At all points along the pathway, patients are in contact with the SCAN navigator, a radiographer who offers support and continuity of care.

By May 2019, 1,182 patients (58% female, mean age 69 years) had been accepted by the SCAN pathway. The most common reason for referral was UWL (63%). Over one hundred patients (114, 10%) were confirmed to have cancer, approximately 75% at a late stage. The most commonly diagnosed cancers were lung, pancreatic and bowel,

As academic lead for SCAN I have ensured that consecutive patients accepted onto the pathway are entered into the SCAN database. All patients are also asked to consent for their primary and secondary care records being reviewed by the SCAN team, if necessary, with only 14 (1.2%) declining. The SCAN database is a unique resource that collates information from a range of sources. Data is collected retrospectively from the primary care record, prospectively using bespoke radiology and clinic templates, and from the integrated hospital EHR (198). It includes demographic characteristics, comorbidities, the timing of each clinical encounter, symptoms prior to referral, tests and referrals, primary and secondary care contacts and diagnoses. Each patient is followed-up for at least two years to identify short-term and long-term outcomes. The evaluation of the SCAN pathway will directly inform the rollout of Rapid Diagnostic Centres across the NHS.

As well as having clinical implications for patients in Oxfordshire and further afield, I intend to use this prospective cohort to externally validate my UWL prediction models in a population of patients referred for UWL and to investigate the following research questions:

- How does the route to cancer diagnosis compare for NHS patients with and without access to a dedicated non-specific symptoms pathway?
- What are the characteristics of incidental and non-cancer diagnoses detected by a non-specific symptoms pathway requiring further investigation and / or management?
- What are the clinical consequences and long-term experiences of NHS patients referred to a non-specific symptoms pathway?

- What are the likely costs and consequences with and without a dedicated non-specific symptoms pathway?

10.5. Further implications for research

In this penultimate section, I will outline future areas of work that follow from the research I have conducted during my DPhil.

10.5.1. Why do patients attend their GP with UWL?

Now that I have established that NHS GPs are reliant on patients detecting their UWL and then consulting about it, investigating why patients decide to present to their GP with UWL is an important step in understanding if we can detect UWL associated cancer earlier. I have been unable to identify any existing literature reporting the pre-diagnostic experience of patients with UWL later found to have cancer. I have been collaborating with colleagues from the Health Experiences Research Group in my Department (the Nuffield Department of Primary Care Health Sciences) on a secondary analysis of pre-diagnostic narratives using transcripts from a video archive (healthtalkonline). The results, which are currently being written up, reveal that patients present when their UWL interrupts daily life, is rapid and alarming, is accompanied by pain, or draws comment from friends and family. In contrast, UWL that is slow, in the context of planned weight loss (even if previous attempts to lose weight have failed), another explanatory diagnosis, or that draws positive comment from friends and family, can lead to delays in consulting their GP. Conducting more qualitative research such as this is essential to understand why patients with UWL choose to (not) attend their GP and to inform the design of public health campaigns to encourage patients with UWL to attend for assessment.

10.5.2. Is it feasible to increase weight recording in NHS primary care?

As outlined in Chapter Three, the finding that weight is not recorded routinely in UK primary care leads to a number of research questions. During my time as a DPhil candidate, I gained ethical approval with a fellow DPhil candidate for a study assessing the feasibility of routine weighing in NHS primary care. Fundamentally, we want to understand why weight is currently recorded in only a subset of patients and whether it could feasibly be recorded more widely. In the US, where a physician's assistant records a routine set of observations before every primary care contact, there are many weight measurements available alongside other basic clinical observations such as blood pressure, pulse, respiratory rate (ref). It is unclear, however, whether these weights would be recorded without a physician assistant being present, for example in the NHS setting. A UK qualitative study found that GPs believed it was up to the patient whether they wanted to be weighed or not (199) whilst an Australian feasibility study of routine weighing found that patients felt it disrupted their passage through the GP surgery. In our study, patients attending their GP will be asked to weigh themselves before their appointment. We will conduct an ethnographic study to observe patient flow around the scales and interactions between patients and also staff. Semi-structured interviews will be conducted with patients and their GP to assess the acceptability of routine weighing, the impact on the subsequent consultation and any unintended consequences.

10.5.3. Is measured UWL more predictive of cancer than coded UWL in primary care?

I have developed a collaboration with the University of Washington and Kaiser Permanente (KP), a not for profit healthcare provider, in Seattle and now have access to a KP primary care

EHR dataset. This includes weight measurement data for a random sample of 50,000 patients age 40 years and over with linkage to cancer outcomes from the Surveillance Epidemiology and End Results Programme database. On average, there are a median of three weight records per year (inter-quartile range, two to five). Following completion of this DPhil, I intend to work with colleagues in the UK and United States to investigate outstanding research questions such as:

- What is the most appropriate method for detecting weight change using serial weight measurement data?
- How much weight change is predictive of cancer in primary care?
- Is cancer associated with UWL diagnosed at an earlier stage when UWL is detected using serial weight measurements compared to UWL volunteered or elicited as a symptom in primary care?

This area of work may well become the focus of my postdoctoral research. I am motivated to develop the expertise to understand existing methods and to develop new approaches for the interpretation of temporal weight trends and to understand how to translate these metrics into a clinically useful tools. I would be keen to progress this work to a point where I can understand how to interpret co-occurring changes in multiple biomarkers, such as weight and blood test data, and to comprehend how these data could be incorporated into prediction models. For example, it would be valuable to investigate whether a binary variable representing a single threshold of weight loss is more or less predictive than a continuous covariate utilising the expertise and interest I developed when comparing dichotomous and continuous blood test model performance in Chapter Seven.

10.6. Concluding remarks

I opened my thesis by recalling three patient encounters that sparked my interest in UWL as an indication for cancer investigation in primary care. It later transpired that all of these patients had normal blood test results and none were subsequently diagnosed with cancer. Using the STm model, the slim man in his forties with appetite loss and abdominal pain would have scored minus one, the woman in her late fifties who was an ex-smoker minus two, and the sixty-five year old man with urinary frequency zero. These scores have excellent rule-out statistics (sensitivities ranging from 99.1% to 99.6% and NLRs of 0.02). Correspondingly, three to six thousand patients would be spared invasive investigation for each patient with cancer not referred for investigation using these thresholds.

If I had had access to such a simple tool to assess the risk of cancer in each of these patients with UWL, they may have been spared unnecessary anxiety and invasive cancer investigation. I wonder how many other NHS patients in similar circumstances could have been too.

I hope my thesis findings will offer reassurance and guidance to GPs and patients.

11. Appendix

Papers published at the time of submission arising from this thesis.

Nicholson et al (2018). The British Journal of General Practice.

Research

Brian D Nicholson, William Hamilton, Jack O'Sullivan, Paul Aveyard and FD Richard Hobbs

Weight loss as a predictor of cancer in primary care:

a systematic review and meta-analysis

Abstract

Background

Weight loss is a non-specific cancer symptom for which there are no clinical guidelines about investigation in primary care.

Aim

To summarise the available evidence on weight loss as a clinical feature of cancer in patients presenting to primary care.

Design and setting

A diagnostic test accuracy review and meta-analysis.

Method

Studies reporting 2 × 2 diagnostic accuracy data for weight loss (index test) in adults presenting to primary care and a subsequent diagnosis of cancer (reference standard) were included. QUADAS-2 was used to assess study quality. Sensitivity, specificity, positive likelihood ratios, and positive predictive values were calculated, and a bivariate meta-analysis performed.

Results

A total of 25 studies were included, with 23 (92%) using primary care records. Of these, 20 (80%) defined weight loss as a physician's coding of the symptom; the remainder collected data directly. One defined unexplained weight loss using objective measurements. Positive associations between weight loss and cancer were found for 10 cancer sites: prostate, colorectal, lung, gastro-oesophageal, pancreatic, non-Hodgkin's lymphoma, ovarian, myeloma, renal tract, and biliary tree. Sensitivity ranged from 2% to 47%, and specificity from 92% to 99%, across cancer sites. The positive predictive value for cancer in male and female patients with weight loss for all age groups ≥60 years exceeded the 3% risk threshold that current UK guidance proposes for further investigation.

Conclusion

A primary care clinician's decision to code for weight loss is highly predictive of cancer. For such patients, urgent referral pathways are justified to investigate for cancer across multiple sites.

Keywords

cancer; diagnosis; primary care; systematic review; weight loss.

INTRODUCTION

Weight loss is a non-specific symptom posing a diagnostic challenge to clinicians in non-specialist settings such as primary care. It can be associated with several cancer and non-cancer conditions.¹ In relation to cancer, two main diagnostic groupings exist: patients with additional clinical features, such as haemoptysis, which can focus diagnostic efforts; and patients without such a pointer in whom, if cancer is suspected, the clinician must consider several possible sites.²

There are no international or national clinical guidelines to support primary care physicians in how to respond to or investigate patients who present with weight loss, although several clinical reviews have suggested different approaches, most commonly in older populations.^{1,3-6} In the UK, guidance for suspected cancer from the National Institute for Health and Care Excellence (NICE) reported weight loss to be a feature of seven cancers in primary care, citing positive predictive values (PPVs) of 0.4–3.0%, and a cumulative PPV of 7.1% across all cancer sites, a figure considerably above the 3% threshold used by NICE in formulating their urgent investigation guidance.⁷ The methods used by NICE will have incorrectly estimated the true PPV for weight loss, because for several cancer sites no evidence could be found: summary PPVs for each cancer site were added together, meaning any possible

contribution to the total PPV from a cancer site as yet unreported was omitted.

People who have lost more weight are more likely to have cancer than those who have lost less,⁸ but almost all evidence on this comes from specialist care.¹ Furthermore, weight loss has been previously considered as a feature of advanced cancer only, although reports about weight loss and stage at diagnosis give conflicting results. Studies of colorectal, pancreatic, and lung cancer have reported that even people with early-stage cancer may present with weight loss,⁹⁻¹¹ and yet other data show no relationship between weight loss and stage or mortality from colorectal cancer.¹²

It is also unclear whether weight loss might occur in the period immediately before a diagnosis is established, or be a symptom that occurs well before cancer is manifest. In one study, patients with pancreatic cancer had a similar body mass index (BMI) to controls without cancer, suggesting weight loss has not continued for long.¹³ Other evidence, however, suggests that some patients experience symptoms for some time before consulting with insidious weight loss, misattributed to normal weight fluctuations due to changes in diet and exercise.^{14,15}

It is possible that non-specialist doctors do not recognise weight loss as a potential symptom of cancer and omit investigation until other symptoms occur. Patients with pancreatic cancer with weight loss

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PROTOCOL

Open Access



Weight loss as a predictor of cancer and serious disease in primary care: an ISAC-approved CPRD protocol for a retrospective cohort study using routinely collected primary care data from the UK

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Abstract

Background: Unexpected weight loss is a symptom of serious disease in primary care, for example between 1 in 200 and 1 in 30 patients with unexpected weight loss go on to develop cancer. However, it remains unclear how and when general practitioners (GPs) should investigate unexpected weight loss. Without clarification, GPs may wait too long before referring (choosing to watch and wait and potentially missing a diagnosis) or not long enough (overburdening hospital services and exposing patients to the risks of investigation). The overall aim of this study is to provide the evidence necessary to allow GPs to more effectively manage patients with unexpected weight loss.

Methods: A retrospective cohort analysis of UK Clinical Practice Research Datalink (CPRD) data to: (1) describe how often in UK primary care the symptom of reported weight loss is coded, when weight is measured, and how GPs respond to a patient attending with unexpected weight loss; (2) identify the predictive value of recorded weight loss for cancer and serious disease in primary care, using cumulative incidence plots to compare outcomes between subgroups and Cox regression to explore and adjust for covariates. Preliminary work in CPRD estimates that weight loss as a symptom is recorded for approximately 148,000 eligible patients > 18 years and is distributed evenly across decades of age, providing adequate statistical power and precision in relation to cancer overall and common cancers individually. Further stratification by cancer stage will be attempted but may not be possible as not all practices within CPRD are eligible for cancer registry linkage, and staging information is often incomplete. The feasibility of using multiple imputation to address missing covariate values will be explored.

Discussion: This will be the largest reported retrospective cohort of primary care patients with weight measurements and unexpected weight loss codes used to understand the association between weight measurement, unexpected weight loss, and serious disease including cancer. Our findings will directly inform international guidelines for the management of unexpected weight loss in primary care populations.

Keywords: Weight loss, Early detection of cancer, Serious disease, Primary care, Cohort study

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Editorials

The elusive diagnosis of cancer:

testing times

In this issue of the *BJGP*, Just and colleagues question PSA testing in men with lower urinary tract symptoms (LUTS).¹ Like others, they propose that the majority of cancers detected will be indolent and unrelated to the LUTS, basing their judgement on PSA screening trial data and general population LUTS surveys.² Danish primary care data, not included by Just and colleagues, indicates that indolent prostate cancer detection increases as PSA testing increases without a corresponding change in advanced disease detection or mortality.³ Over half of UK hospitals now use multiparametric-MRI to protect men from the harms of unnecessary biopsy and treatment for indolent prostate cancer.⁴ The important question Just and colleagues raise is not which test should be performed once a patient is referred for suspected prostate cancer, but rather should patients with non-specific symptoms be tested in primary care and are there harms of testing them?

The myriad of urgent referral pathways, complex referral criteria, and regional variations in test and specialist access have created a complex bureaucracy for UK cancer diagnosis that has favoured patients with 'alarm' symptoms. Within this context, cancers with non-specific symptom signatures such as myeloma and pancreatic cancer have become associated with longer intervals between presentation and diagnosis, they are less likely to be diagnosed via urgent GP referral and more likely to be diagnosed as an emergency.^{5,6}

But general practice is dominated by common non-specific cancer symptoms such as LUTS, abdominal pain, back pain, and fatigue. Like cancer, these symptoms increase in incidence with age and comorbidity. Our conundrum as specialist generalists has always been how to efficiently differentiate benign or self-limiting causes from more serious diseases, such as cancer, without subjecting patients to the harms of unnecessary testing or overburdening secondary care. Given the high prevalence of non-specific symptoms and the low prevalence of cancer in primary care, different approaches are necessary for patients with these symptoms.

RULING OUT CANCER NOT RULING IN CANCER

As GPs we are familiar with using tests to triage patients into further cancer

"There are surprisingly few simple triage tests or test combinations that GPs can use to rule out cancer and avoid the need for further investigation."

investigation rather than away from it. Low haemoglobin, for example, rules-in patients for urgent colorectal investigation but a normal haemoglobin does not rule it out.⁷ Raised platelets are of interest to rule-in patients for investigation across a number of cancers, but normal platelets do not rule-out cancer.⁸ There are surprisingly few simple triage tests or test combinations that GPs can use to rule out cancer and avoid the need for further investigation, but the evidence is building.

The combination of normal inflammatory marker (ESR or plasma viscosity) and normal haemoglobin confidently rules-out myeloma in patients tested in primary care without necessitating the GP to think myeloma when requesting the test.⁹ Faecal immunochemical testing (FIT) shows promise as a rule-out test for colorectal cancer in patients with non-specific abdominal symptoms, but access to FIT (a cheap and simple test) remains patchy in the UK, its suggested use as both a rule-in and rule-out test is confusing,¹⁰ and the optimum analytical threshold to minimise false negatives in primary care is unclear.¹¹

Transferring testing strategies from settings with higher (secondary care) or lower (screening) cancer prevalence should be avoided as this leads to inaccurate predictions of test performance.¹² In cancer screening, for example, testing is calibrated to minimise referrals for false positive results rather than minimising false negatives. Continued analysis of primary care data should focus on identifying clusters of symptomatic and at-risk patients for whom a cancer rule-out strategy could be confidently employed. It is unlikely, though, that currently available laboratory tests will advance GPs' rule-out ability significantly enough, and uncertainty for many cancers will remain.

EXPLAINING SYMPTOMS NOT JUST RULING IN CANCER

There is limited but increasing evidence for a move away from linear pathways to rule-

in individual cancers, to more sophisticated multidisciplinary diagnostic centres (MDCs) equipped to explain the cause of non-specific symptoms. As complex healthcare interventions, MDCs intend to avoid multiple cancer site specific referrals for a heterogeneous group of patients. Reports from Danish MDCs show that cancer is diagnosed following 11% to 21% of referrals, exceeding the 8% achieved by the UK's 2-week-wait referral pathways, and serious other disease is diagnosed in 22% to 34% of patients.¹³

A range of MDC models are under evaluation in the UK, some with stringent pre-referral triage testing (akin to the Danish MDCs), others with an MDC triage step following referral and prior to investigation, and some with up-front imaging then triage. MDCs have the potential to be a step beyond 'one-stop-shop' clinics as multiple assessments and investigations may occur in series over time and across multiple body sites, and serious or non-serious disease may be diagnosed.¹⁴ MDCs that retain responsibility for the patient until their symptoms are explained and managed are distinct from GP direct access (cancer) testing which leaves these actions to the GP.¹⁵

After years of investment in cancer site-specific urgent referral pathways, this change in thinking appeals to generalists and specialists interested in explaining symptom causation and frustrated with subspecialist silos restricted to one cancer site. But for these MDCs to function, their positioning must become established within local healthcare systems, and test access and patient flow must be liberated to allow cross-speciality referrals and shared multidisciplinary clinical responsibility. Ongoing evaluation of the optimal constellation of patient characteristics, symptoms, and pre-referral triage testing will facilitate adoption by ensuring that MDCs only accept patients who will benefit from intense investigation. One might also ask whether MDCs are filling

The internal validation of weight and weight change coding using weight measurement data within the UK primary care Electronic Health Record

This article was published in the following Dove Medical Press journal:
Clinical Epidemiology

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Purpose: To use recorded weight values to internally validate weight status and weight change coding in the primary care Electronic Health Record (EHR).

Patients and methods: We included adult patients with weight-related Read codes recorded in the UK's Clinical Practice Research Datalink EHR between 2000 and 2017. Weight status codes were compared to weight values recorded on the same day and positive predictive values (PPVs) were calculated for commonly used codes. Weight change codes were validated using three methods: the percentage (%) difference in kilograms at the time of the code and 1) the previous weight measurement, 2) the weight predicted using linear regression, and 3) the historic mean weight. Weight change codes were validated if estimates were consistent across two out of three methods.

Results: A total of 8,108,481 weight codes were recorded in 1,000,002 patients' EHR. Twice as many were recorded in females (n=5,208,593, 64%). The mean body mass index for "overweight" codes ranged from 31.9 kg/m² to 46.9 kg/m² and from 17.4 kg/m² to 19.2 kg/m² for "underweight" codes. PPVs for the most commonly used weight status codes ranged from 81.3% (80%–82.5%) to 99.3% (99.2%–99.4%). Across the estimation methods, and using only validated weight change codes, mean weight loss ranged from – 5.2% (SD 5.8%) to –7.9% (SD 7.3%) and mean weight gain from 4.2 % (SD 5.5%) to 7.9 % (SD 8.2%). The previous and predicted weight methods were most consistent.

Conclusion: We have developed an internationally applicable methodology to internally validate weight-related EHR coding by using available weight measurement data. We demonstrate the UK Read codes that can be confidently used to classify weight status and weight change in the absence of weight values. We provide the first evidence from primary care that a Read code for unexpected weight loss represents a mean loss of ≥ 5 % in a 6-month period, which was broadly consistent across age groups and gender.

Keywords: validation studies, electronic health records, body weight, weight loss, weight gain, primary health care, data quality

Introduction

Extremes of weight and unexpected weight change are associated with multiple disease states such as cancer and cardiovascular disease, with increased morbidity and mortality.^{1–3} Although weight is a simple low-cost biometric retained in multiple clinical prediction models,^{4–7} weight measurements are commonly missing (not at random) from Electronic Health Records (EHRs) in primary care.^{8,9} In clinical settings where weight

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PRACTICE

UNCERTAINTIES

When should unexpected weight loss warrant further investigation to exclude cancer?

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What you need to know

- Unexpected weight loss can be associated with cancer, but also with a range of other conditions
- Weight loss codes in primary care typically represent $\geq 5\%$ loss within a 6 month period, but there is a lack of evidence on how much weight loss and over what time period increase the likelihood of a cancer diagnosis in primary care
- Urgently refer people over the age of 60 years with unexpected weight loss for investigations to exclude cancer
- The optimal diagnostic strategy to detect cancer in patients with weight loss remains unclear

Unexpected weight loss presents a diagnostic challenge in primary care. It is associated with a wide range of benign and serious conditions (box 1).¹

Box 1: Differential diagnosis for patients with unexpected weight loss¹

Cardiovascular—End stage heart failure (cardiac cachexia)
Endocrine—Adrenal insufficiency, diabetes, hyperthyroidism
Gastrointestinal—Diarrhoea, colitis, malabsorption, mesenteric ischaemia
Infection—Chronic infection (such as HIV, tuberculosis)
Malignancy—Solid tumours more likely than haematological malignancies
Medication—Antidepressants, antiepileptics, anxiolytics, diuretics, laxatives, stimulants
Neurological—Dementia, multiple sclerosis, neuromuscular disease, Parkinson's disease, stroke
Psychiatric—Anorexia nervosa, anxiety, bulimia, depression
Renal—End stage renal failure (uraemic cachexia)
Respiratory—Chronic obstructive pulmonary disease (COPD), interstitial lung disease, vasculitis
Rheumatologic—Rheumatoid arthritis
Social—Excess alcohol consumption, neglect, use of opiates, poor oral health, poverty, smoking

Weight loss may be missed or misattributed because of several factors (see box 2). Once it is detected, the uncertainty for clinicians is not about whether unexpected weight loss is a symptom of concern, it is about who should be investigated further and who can be spared unnecessary investigation. Specifically, how much weight loss, over how much time, in combination with what other clinical features makes cancer sufficiently likely to warrant urgent investigation?

Box 2: Challenges in detecting weight loss in primary care

Physiological factors

- Being overweight both increases the risk of cancer and the challenge of detecting weight loss²
- Gradual decline in muscle mass is expected from the sixth decade of life³
- Diurnal fluctuations in body weight of ± 2 kg occur from changes in fluid balance and gut contents⁴

Measurement factors

- Weight measurement is not routine practice in many health systems; it is most commonly measured in people with particular clinical problems⁵
- Clinicians record weight status in kg, pounds, or body mass index (BMI), making detection of weight loss slower⁶
- Patients delay attending their clinician with weight loss for longer than other symptoms of cancer⁷
- Intentional weight loss and exercise complicate the interpretation of weight change⁸

Sources and selection criteria

We searched Embase, Medline, Web of Science, and the Cochrane Library for systematic reviews and primary studies using the following terms and related terms: neoplasia, weight loss, symptoms, diagnosis, general practice, family practice, primary care.

Correspondence to: B D Nicholson brian.nicholson@phc.ox.ac.uk This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at uncertainties@bmj.com

CPRD Code list for cancer outcome.

readcode	readterm	Cancer group	
B21..00	Malignant neoplasm of larynx		1
B550.00	Malignant neoplasm of head, neck and face		1
B01..00	Malignant neoplasm of tongue		1
B060.00	Malignant neoplasm of tonsil		1
B020.00	Malignant neoplasm of parotid gland		1
B0...00	Malignant neoplasm of lip, oral cavity and pharynx		1
B05..00	Malignant neoplasm of other and unspecified parts of mouth		1
B0z0.00	Malignant neoplasm of pharynx unspecified		1
B21z.00	Malignant neoplasm of larynx NOS		1
B04..00	Malignant neoplasm of floor of mouth		1
B00..00	Malignant neoplasm of lip		1
B0...11	Carcinoma of lip, oral cavity and pharynx		1
B06..00	Malignant neoplasm of oropharynx		1
B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS		1
B07..00	Malignant neoplasm of nasopharynx		1
B210.00	Malignant neoplasm of glottis		1
B0z2.00	Malignant neoplasm of laryngopharynx		1
B211.00	Malignant neoplasm of supraglottis		1
B02..00	Malignant neoplasm of major salivary glands		1
B200.00	Malignant neoplasm of nasal cavities		1
B010.00	Malignant neoplasm of base of tongue		1
B08..00	Malignant neoplasm of hypopharynx		1
B053.00	Malignant neoplasm of soft palate		1
B00..11	Carcinoma of lip		1
B550400	Malignant neoplasm of neck NOS		1
B061.00	Malignant neoplasm of tonsillar fossa		1
B01z.00	Malignant neoplasm of tongue NOS		1
B03..00	Malignant neoplasm of gum		1
B060z00	Malignant neoplasm tonsil NOS		1
B05z.00	Malignant neoplasm of mouth NOS		1
B050.00	Malignant neoplasm of cheek mucosa		1
B081.00	Malignant neoplasm of pyriform sinus		1
B021.00	Malignant neoplasm of submandibular gland		1
B016.00	Malignant neoplasm of lingual tonsil		1
B213300	Malignant neoplasm of thyroid cartilage		1
B052.00	Malignant neoplasm of hard palate		1
B550100	Malignant neoplasm of cheek NOS		1
B215.00	Malignant neoplasm of epiglottis NOS		1

B202.00	Malignant neoplasm of maxillary sinus	1
B050.11	Malignant neoplasm of buccal mucosa	1
B21y.00	Malignant neoplasm of larynx, other specified site	1
B550200	Malignant neoplasm of nose NOS	1
B550000	Malignant neoplasm of head NOS	1
B213.00	Malignant neoplasm of laryngeal cartilage	1
B06z.00	Malignant neoplasm of oropharynx NOS	1
B04z.00	Malignant neoplasm of floor of mouth NOS	1
B056.00	Malignant neoplasm of retromolar area	1
B072000	Malignant neoplasm of pharyngeal recess	1
B203.00	Malignant neoplasm of ethmoid sinus	1
B071100	Malignant neoplasm of pharyngeal tonsil	1
B07z.00	Malignant neoplasm of nasopharynx NOS	1
B064.00	Malignant neoplasm of anterior epiglottis	1
B012.00	Malignant neoplasm of tongue, tip and lateral border	1
B040.00	Malignant neoplasm of anterior portion of floor of mouth	1
B062000	Malignant neoplasm of faucial pillar	1
B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx	1
B204.00	Malignant neoplasm of frontal sinus	1
B550z00	Malignant neoplasm of head, neck and face NOS	1
B054.00	Malignant neoplasm of uvula	1
B05y.00	Malignant neoplasm of other specified mouth parts	1
B031.00	Malignant neoplasm of lower gum	1
B08z.00	Malignant neoplasm of hypopharynx NOS	1
B212.00	Malignant neoplasm of subglottis	1
B006.00	Malignant neoplasm of overlapping lesion of lip	1
B200z00	Malignant neoplasm of nasal cavities NOS	1
B550300	Malignant neoplasm of jaw NOS	1
B001000	Malignant neoplasm of lower lip, external	1
B055.00	Malignant neoplasm of palate unspecified	1
B06y.00	Malignant neoplasm of oropharynx, other specified sites	1
B080.00	Malignant neoplasm of postcricoid region	1
B042.00	Malignant neoplasm, overlapping lesion of floor of mouth	1
B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx	1
B213100	Malignant neoplasm of cricoid cartilage	1
B200200	Malignant neoplasm of septum of nose	1
B062.00	Malignant neoplasm of tonsillar pillar	1
B063.00	Malignant neoplasm of vallecula	1
B013.00	Malignant neoplasm of ventral surface of tongue	1
B055z00	Malignant neoplasm of palate NOS	1
B20..00	Malig neop nasal cavities, middle ear and accessory sinuses	1
B007.00	Malignant neoplasm of lip, unspecified	1
B017.00	Malignant overlapping lesion of tongue	1
B083.00	Malignant neoplasm of posterior pharynx	1
B205.00	Malignant neoplasm of sphenoidal sinus	1
B200300	Malignant neoplasm of vestibule of nose	1
B030.00	Malignant neoplasm of upper gum	1
B071000	Malignant neoplasm of adenoid	1

B041.00	Malignant neoplasm of lateral portion of floor of mouth	1
B000000	Malignant neoplasm of upper lip, external	1
B201.00	Malig neop auditory tube, middle ear and mastoid air cells	1
B213z00	Malignant neoplasm of laryngeal cartilage NOS	1
B001.00	Malignant neoplasm of lower lip, vermilion border	1
B011.00	Malignant neoplasm of dorsal surface of tongue	1
B064000	Malignant neoplasm of epiglottis, free border	1
B001100	Malignant neoplasm of lower lip, lipstick area	1
B003100	Malignant neoplasm of lower lip, frenulum	1
B003200	Malignant neoplasm of lower lip, mucosa	1
B02z.00	Malignant neoplasm of major salivary gland NOS	1
B051000	Malignant neoplasm of upper buccal sulcus	1
B550500	Malignant neoplasm of supraclavicular fossa NOS	1
B004000	Malignant neoplasm of lip unspecified, buccal aspect	1
B011z00	Malignant neoplasm of dorsum of tongue NOS	1
B05z000	Kaposi's sarcoma of palate	1
B064z00	Malignant neoplasm of anterior epiglottis NOS	1
B066.00	Malignant neoplasm of lateral wall of oropharynx	1
B001z00	Malignant neoplasm of lower lip, vermilion border NOS	1
B002300	Malignant neoplasm of upper lip, oral aspect	1
B01y.00	Malignant neoplasm of other sites of tongue	1
B051100	Malignant neoplasm of lower buccal sulcus	1
B062z00	Malignant neoplasm of tonsillar fossa NOS	1
B071.00	Malignant neoplasm of posterior wall of nasopharynx	1
B07y.00	Malignant neoplasm of other specified site of nasopharynx	1
B62x400	Malignant reticulosis	1
B004300	Malignant neoplasm of lip, oral aspect	1
B013100	Malignant neoplasm of frenulum linguae	1
B014.00	Malignant neoplasm of anterior 2/3 of tongue unspecified	1
B015.00	Malignant neoplasm of tongue, junctional zone	1
	Malignant neoplasm of other specified site of oropharynx	
B06yz00	NOS	1
	Malignant neoplasm aryepiglottic fold, hypopharyngeal	
B082.00	aspect	1
B20z.00	Malignant neoplasm of accessory sinus NOS	1
B022.00	Malignant neoplasm of sublingual gland	1
B04y.00	Malignant neoplasm of other sites of floor of mouth	1
B055100	Malignant neoplasm of roof of mouth	1
B065.00	Malignant neoplasm of junctional region of epiglottis	1
B067.00	Malignant neoplasm of posterior wall of oropharynx	1
B201z00	Malig neop auditory tube, middle ear, mastoid air cells NOS	1
B213000	Malignant neoplasm of arytenoid cartilage	1
B000.00	Malignant neoplasm of upper lip, vermilion border	1
B000z00	Malignant neoplasm of upper lip, vermilion border NOS	1
B002100	Malignant neoplasm of upper lip, frenulum	1
B002200	Malignant neoplasm of upper lip, mucosa	1
B003.00	Malignant neoplasm of lower lip, inner aspect	1
B003000	Malignant neoplasm of lower lip, buccal aspect	1

B003z00	Malignant neoplasm of lower lip, inner aspect NOS	1
B00zz00	Malignant neoplasm of lip, vermilion border NOS	1
B010000	Malignant neoplasm of base of tongue dorsal surface	1
B055000	Malignant neoplasm of junction of hard and soft palate	1
B060000	Malignant neoplasm of faucial tonsil	1
B064100	Malignant neoplasm of glossoepiglottic fold	1
B071z00	Malignant neoplasm of posterior wall of nasopharynx NOS	1
B08y.00	Malignant neoplasm of other specified hypopharyngeal site	1
B200000	Malignant neoplasm of cartilage of nose	1
B000100	Malignant neoplasm of upper lip, lipstick area	1
B003300	Malignant neoplasm of lower lip, oral aspect	1
B005.00	Malignant neoplasm of commissure of lip	1
B013z00	Malignant neoplasm of ventral tongue surface NOS	1
B070.00	Malignant neoplasm of roof of nasopharynx	1
B072.00	Malignant neoplasm of lateral wall of nasopharynx	1
	Malignant neoplasm posterior margin nasal septum and	
B073200	choanae	1
B201200	Malignant neoplasm of tympanic antrum	1
B201300	Malignant neoplasm of mastoid air cells	1
B206.00	Malignant neoplasm, overlapping lesion of accessory sinuses	1
B20y.00	Malig neop other site nasal cavity, middle ear and sinuses	1
B214.00	Malignant neoplasm, overlapping lesion of larynx	1
B002.00	Malignant neoplasm of upper lip, inner aspect	1
B004.00	Malignant neoplasm of lip unspecified, inner aspect	1
B00z100	Malignant neoplasm of lip, unspecified, lipstick area	1
B010.11	Malignant neoplasm of posterior third of tongue	1
B010z00	Malignant neoplasm of fixed part of tongue NOS	1
B013000	Malignant neoplasm of anterior 2/3 of tongue ventral surface	1
B02y.00	Malignant neoplasm of other major salivary glands	1
B03z.00	Malignant neoplasm of gum NOS	1
B051.00	Malignant neoplasm of vestibule of mouth	1
B062200	Malignant neoplasm of palatoglossal arch	1
B072z00	Malignant neoplasm of lateral wall of nasopharynx NOS	1
B0z1.00	Malignant neoplasm of Waldeyer's ring	1
B200100	Malignant neoplasm of nasal conchae	1
B002z00	Malignant neoplasm of upper lip, inner aspect NOS	1
B004200	Malignant neoplasm of lip unspecified, mucosa	1
B00z000	Malignant neoplasm of lip, unspecified, external	1
B011100	Malignant neoplasm of midline of tongue	1
B03y.00	Malignant neoplasm of other sites of gum	1
B060100	Malignant neoplasm of palatine tonsil	1
B060200	Malignant neoplasm of overlapping lesion of tonsil	1
B062100	Malignant neoplasm of glossopalatine fold	1
B062300	Malignant neoplasm of palatopharyngeal arch	1
B073.00	Malignant neoplasm of anterior wall of nasopharynx	1
B073100	Malignant neoplasm of nasopharyngeal soft palate surface	1
B073z00	Malignant neoplasm of anterior wall of nasopharynx NOS	1
B074.00	Malignant neoplasm, overlapping lesion of nasopharynx	1

B201000	Malignant neoplasm of auditory (Eustachian) tube	1
B213200	Malignant neoplasm of cuneiform cartilage	1
B201100	Malignant neoplasm of tympanic cavity	1
Byu0.00	[X]Malignant neoplasm of lip, oral cavity and pharynx	1
B10..00	Malignant neoplasm of oesophagus	2
B10z.11	Oesophageal cancer	2
B10z.00	Malignant neoplasm of oesophagus NOS	2
B105.00	Malignant neoplasm of lower third of oesophagus	2
B104.00	Malignant neoplasm of middle third of oesophagus	2
B103.00	Malignant neoplasm of upper third of oesophagus	2
B10y.00	Malignant neoplasm of other specified part of oesophagus	2
B101.00	Malignant neoplasm of thoracic oesophagus	2
B102.00	Malignant neoplasm of abdominal oesophagus	2
B107.00	Siewert type I adenocarcinoma	2
B100.00	Malignant neoplasm of cervical oesophagus	2
B106.00	Malignant neoplasm, overlapping lesion of oesophagus	2
B11..00	Malignant neoplasm of stomach	3
B11z.00	Malignant neoplasm of stomach NOS	3
B11..11	Gastric neoplasm	3
B110.00	Malignant neoplasm of cardia of stomach	3
	Malignant neoplasm of cardio-oesophageal junction of stomach	3
B110100		3
B114.00	Malignant neoplasm of body of stomach	3
B111100	Malignant neoplasm of pyloric canal of stomach	3
B112.00	Malignant neoplasm of pyloric antrum of stomach	3
B115.00	Malignant neoplasm of lesser curve of stomach unspecified	3
B111.00	Malignant neoplasm of pylorus of stomach	3
B113.00	Malignant neoplasm of fundus of stomach	3
B118.00	Siewert type II adenocarcinoma	3
B116.00	Malignant neoplasm of greater curve of stomach unspecified	3
B119.00	Siewert type III adenocarcinoma	3
B110z00	Malignant neoplasm of cardia of stomach NOS	3
B111000	Malignant neoplasm of prepylorus of stomach	3
B110111	Malignant neoplasm of gastro-oesophageal junction	3
B111z00	Malignant neoplasm of pylorus of stomach NOS	3
B11y.00	Malignant neoplasm of other specified site of stomach	3
B11yz00	Malignant neoplasm of other specified site of stomach NOS	3
B11y100	Malignant neoplasm of posterior wall of stomach NEC	3
B11y000	Malignant neoplasm of anterior wall of stomach NEC	3
B110000	Malignant neoplasm of cardiac orifice of stomach	3
B117.00	Malignant neoplasm, overlapping lesion of stomach	3
B120.00	Malignant neoplasm of duodenum	4
B12..00	Malignant neoplasm of small intestine and duodenum	4
B12z.00	Malignant neoplasm of small intestine NOS	4
B122.00	Malignant neoplasm of ileum	4
B121.00	Malignant neoplasm of jejunum	4
B123.00	Malignant neoplasm of Meckel's diverticulum	4
B12y.00	Malignant neoplasm of other specified site small intestine	4

B13..00	Malignant neoplasm of colon	5
B13z.11	Colonic cancer	5
B134.00	Malignant neoplasm of caecum	5
B133.00	Malignant neoplasm of sigmoid colon	5
B1z0.11	Cancer of bowel	5
B13z.00	Malignant neoplasm of colon NOS	5
B136.00	Malignant neoplasm of ascending colon	5
B140.00	Malignant neoplasm of rectosigmoid junction	5
B142.00	Malignant neoplasm of anal canal	5
B131.00	Malignant neoplasm of transverse colon	5
B134.11	Carcinoma of caecum	5
B132.00	Malignant neoplasm of descending colon	5
B130.00	Malignant neoplasm of hepatic flexure of colon	5
B137.00	Malignant neoplasm of splenic flexure of colon	5
B135.00	Malignant neoplasm of appendix	5
B13y.00	Malignant neoplasm of other specified sites of colon	5
B138.00	Malignant neoplasm, overlapping lesion of colon	5
B141.00	Malignant neoplasm of rectum	6
B141.12	Rectal carcinoma	6
B141.11	Carcinoma of rectum	6
	Malignant neoplasm of rectum, rectosigmoid junction and	
B14..00	anus	6
	Malignant neoplasm rectum,rectosigmoid junction and anus	
B14z.00	NOS	6
B14y.00	Malig neop other site rectum, rectosigmoid junction and anus	6
B142.11	Anal carcinoma	7
B143.00	Malignant neoplasm of anus unspecified	7
B142000	Malignant neoplasm of cloacogenic zone	7
B150300	Hepatocellular carcinoma	8
B152.00	Malignant neoplasm of liver unspecified	8
B150.00	Primary malignant neoplasm of liver	8
B150000	Primary carcinoma of liver	8
B15..00	Malignant neoplasm of liver and intrahepatic bile ducts	8
B150100	Hepatoblastoma of liver	8
B150z00	Primary malignant neoplasm of liver NOS	8
B150200	Primary angiosarcoma of liver	8
Byu1100	[X]Other specified carcinomas of liver	8
B160.00	Malignant neoplasm of gallbladder	9
B160.11	Carcinoma gallbladder	9
B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS	9
B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts	9
B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct	9
B162.00	Malignant neoplasm of ampulla of Vater	10
B161200	Malignant neoplasm of common bile duct	10
B161.00	Malignant neoplasm of extrahepatic bile ducts	10
B151.00	Malignant neoplasm of intrahepatic bile ducts	10
B161211	Carcinoma common bile duct	10
B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS	10

B161100	Malignant neoplasm of hepatic duct	10
B161z00	Malignant neoplasm of extrahepatic bile ducts NOS	10
B151z00	Malignant neoplasm of intrahepatic bile ducts NOS	10
B163.00	Malignant neoplasm, overlapping lesion of biliary tract	10
B151400	Malignant neoplasm of intrahepatic gall duct	10
B151200	Malignant neoplasm of intrahepatic biliary passages	10
B151000	Malignant neoplasm of interlobular bile ducts	10
B161000	Malignant neoplasm of cystic duct	10
B161300	Malignant neoplasm of sphincter of Oddi	10
B151100	Malignant neoplasm of interlobular biliary canals	10
B17..00	Malignant neoplasm of pancreas	11
B17z.00	Malignant neoplasm of pancreas NOS	11
B170.00	Malignant neoplasm of head of pancreas	11
B173.00	Malignant neoplasm of pancreatic duct	11
B172.00	Malignant neoplasm of tail of pancreas	11
B171.00	Malignant neoplasm of body of pancreas	11
B717011	Endocrine tumour of pancreas	11
B17yz00	Malignant neoplasm of specified site of pancreas NOS	11
B17y.00	Malignant neoplasm of other specified sites of pancreas	11
B174.00	Malignant neoplasm of Islets of Langerhans	11
B17y000	Malignant neoplasm of ectopic pancreatic tissue	11
B181.00	Mesothelioma of peritoneum	12
B18y.00	Malignant neoplasm of specified parts of peritoneum	12
B180.00	Malignant neoplasm of retroperitoneum	12
B18y300	Malignant neoplasm of omentum	12
B18y500	Malignant neoplasm of pelvic peritoneum	12
B18..00	Malignant neoplasm of retroperitoneum and peritoneum	12
B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS	12
B18yz00	Malignant neoplasm of specified parts of peritoneum NOS	12
B18y700	Malignant neoplasm of mesentery	12
B180z00	Malignant neoplasm of retroperitoneum NOS	12
B180200	Malignant neoplasm of retrocaecal tissue	12
B18y600	Malignant neoplasm of the pouch of Douglas	12
B18y400	Malignant neoplasm of parietal peritoneum	12
B180100	Malignant neoplasm of perinephric tissue	12
B18y200	Malignant neoplasm of mesorectum	12
B18y100	Malignant neoplasm of mesocaecum	12
B1z1.00	Malignant neoplasm of spleen NEC	12
B1z1000	Angiosarcoma of spleen	12
B1z1100	Fibrosarcoma of spleen	12
B1z1z00	Malignant neoplasm of spleen NOS	12
B22z.11	Lung cancer	13
B22z.00	Malignant neoplasm of bronchus or lung NOS	13
B22..00	Malignant neoplasm of trachea, bronchus and lung	13
B221.00	Malignant neoplasm of main bronchus	13
B222100	Malignant neoplasm of upper lobe of lung	13
B222.00	Malignant neoplasm of upper lobe, bronchus or lung	13
B224100	Malignant neoplasm of lower lobe of lung	13

B224.00	Malignant neoplasm of lower lobe, bronchus or lung	13
B221z00	Malignant neoplasm of main bronchus NOS	13
B222000	Malignant neoplasm of upper lobe bronchus	13
B22y.00	Malignant neoplasm of other sites of bronchus or lung	13
B222.11	Pancoast's syndrome	13
B221100	Malignant neoplasm of hilus of lung	13
B223.00	Malignant neoplasm of middle lobe, bronchus or lung	13
B223100	Malignant neoplasm of middle lobe of lung	13
B224000	Malignant neoplasm of lower lobe bronchus	13
B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS	13
B220.00	Malignant neoplasm of trachea	13
B23..00	Malignant neoplasm of pleura	13
B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS	13
B221000	Malignant neoplasm of carina of bronchus	13
B223000	Malignant neoplasm of middle lobe bronchus	13
B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS	13
B220z00	Malignant neoplasm of trachea NOS	13
B230.00	Malignant neoplasm of parietal pleura	13
B220100	Malignant neoplasm of mucosa of trachea	13
B231.00	Malignant neoplasm of visceral pleura	13
B240.00	Malignant neoplasm of thymus	14
B24X.00	Malignant neoplasm of mediastinum, part unspecified	14
B242.00	Malignant neoplasm of anterior mediastinum	14
B24..00	Malignant neoplasm of thymus, heart and mediastinum	14
B241000	Malignant neoplasm of endocardium	14
B241.00	Malignant neoplasm of heart	14
B241300	Malignant neoplasm of pericardium	14
B241400	Mesothelioma of pericardium	14
B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS	14
B243.00	Malignant neoplasm of posterior mediastinum	14
B241200	Malignant neoplasm of myocardium	14
B241z00	Malignant neoplasm of heart NOS	14
B24y.00	Malig neop of other site of heart, thymus and mediastinum	14
B23y.00	Malignant neoplasm of other specified pleura	14
B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung	15
B3...12	Sarcoma of bone and connective tissue	16
BBX..00	[M]Giant cell tumours	16
BBY0.00	[M]Ewing's sarcoma	16
B30z000	Osteosarcoma	16
B30z.00	Malignant neoplasm of bone and articular cartilage NOS	16
BBV1.13	[M]Osteogenic sarcoma NOS	16
B30..00	Malignant neoplasm of bone and articular cartilage	16
BBXz.00	[M]Giant cell tumour NOS	16
B301.00	Malignant neoplasm of mandible	16
BBV4.00	[M]Telangiectatic osteosarcoma	16
BBV1.00	[M]Osteosarcoma NOS	16
B300A00	Malignant neoplasm of maxilla	16
BBY..00	[M]Miscellaneous bone tumours	16

B307000	Malignant neoplasm of femur	16
BBX0.00	[M]Giant cell tumour of bone NOS	16
BBVA.00	[M] Small cell osteosarcoma	16
B302.00	Malignant neoplasm of vertebral column	16
B303000	Malignant neoplasm of rib	16
B306500	Malignant sacral teratoma	16
B302200	Malignant neoplasm of lumbar vertebra	16
BBV2.00	[M]Chondroblastic osteosarcoma	16
B304200	Malignant neoplasm of humerus	16
BBV8.00	[M]Osteoblastoma	16
B302100	Malignant neoplasm of thoracic vertebra	16
BBV1.11	[M]Osteoblastic sarcoma	16
B306.00	Malignant neoplasm of pelvic bones, sacrum and coccyx	16
B307200	Malignant neoplasm of tibia	16
B303100	Malignant neoplasm of sternum	16
B306z00	Malignant neoplasm of pelvis, sacrum or coccyx NOS	16
B304000	Malignant neoplasm of scapula	16
B307.00	Malignant neoplasm of long bones of leg	16
B306300	Malignant neoplasm of sacral vertebra	16
B302000	Malignant neoplasm of cervical vertebra	16
B300.00	Malignant neoplasm of bones of skull and face	16
B302z00	Malignant neoplasm of vertebral column NOS	16
BBYz.00	[M]Miscellaneous bone tumour NOS	16
B306000	Malignant neoplasm of ilium	16
BBV1.12	[M]Osteochondrosarcoma	16
BBVz.00	[M]Osteoma or osteosarcoma NOS	16
B303200	Malignant neoplasm of clavicle	16
BBV3.00	[M]Fibroblastic osteosarcoma	16
B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd	16
BBV5.00	[M]Osteosarcoma in Paget's disease of bone	16
B303.00	Malignant neoplasm of ribs, sternum and clavicle	16
B305D00	Malignant neoplasm of phalanges of hand	16
B304.00	Malignant neoplasm of scapula and long bones of upper arm	16
BBY0.11	[M]Endothelial bone sarcoma	16
B300100	Malignant neoplasm of frontal bone	16
B300300	Malignant neoplasm of nasal bone	16
B300800	Malignant neoplasm of temporal bone	16
B303300	Malignant neoplasm of costal cartilage	16
B308D00	Malignant neoplasm of phalanges of foot	16
BBX1.00	[M]Giant cell tumour of bone, malignant	16
B300000	Malignant neoplasm of ethmoid bone	16
B300700	Malignant neoplasm of sphenoid bone	16
B300z00	Malignant neoplasm of bones of skull and face NOS	16
B303500	Malignant neoplasm of xiphoid process	16
B305.00	Malignant neoplasm of hand bones	16
B306200	Malignant neoplasm of pubis	16
B307100	Malignant neoplasm of fibula	16
B300C00	Malignant neoplasm of vomer	16

B306100	Malignant neoplasm of ischium	16
BBX1.11	[M]Giant cell bone sarcoma	16
B300400	Malignant neoplasm of occipital bone	16
B300500	Malignant neoplasm of orbital bone	16
B303z00	Malignant neoplasm of rib, sternum and clavicle NOS	16
B305100	Malignant neoplasm of carpal bone - lunate	16
B305z00	Malignant neoplasm of hand bones NOS	16
B306400	Malignant neoplasm of coccygeal vertebra	16
B300600	Malignant neoplasm of parietal bone	16
B304300	Malignant neoplasm of radius	16
B304400	Malignant neoplasm of ulna	16
B305.12	Malignant neoplasm of metacarpal bones	16
BBX1.12	[M]Osteoclastoma, malignant	16
BBZG.11	[M]Adamantinoma, malignant	16
B308100	Malignant neoplasm of talus	16
B308200	Malignant neoplasm of calcaneum	16
BBV..11	[M]Juxtacortical osteogenic sarcoma	16
B300200	Malignant neoplasm of malar bone	16
B300900	Malignant neoplasm of zygomatic bone	16
B303400	Malignant neoplasm of costo-vertebral joint	16
B304z00	Malig neop of scapula and long bones of upper arm NOS	16
B305000	Malignant neoplasm of carpal bone - scaphoid	16
B307z00	Malignant neoplasm of long bones of leg NOS	16
B308300	Malignant neoplasm of medial cuneiform	16
B308z00	Malignant neoplasm of short bones of leg NOS	16
B30W.00	Malignant neoplasm/overlap lesion/bone+articulr cartilage	16
BBZ2.11	[M]Intraosseous carcinoma	16
B304100	Malignant neoplasm of acromion	16
B305.11	Malignant neoplasm of carpal bones	16
B305800	Malignant neoplasm of first metacarpal bone	16
B305A00	Malignant neoplasm of third metacarpal bone	16
B305C00	Malignant neoplasm of fifth metacarpal bone	16
B308.00	Malignant neoplasm of short bones of leg	16
B308800	Malignant neoplasm of first metatarsal bone	16
B308B00	Malignant neoplasm of fourth metatarsal bone	16
BBV..13	[M]Periosteal osteogenic sarcoma	16
B300B00	Malignant neoplasm of turbinate	16
B600.00	Reticulosarcoma	16
B600000	Reticulosarcoma of unspecified site	16
B32..00	Malignant melanoma of skin	17
B32z.00	Malignant melanoma of skin NOS	17
B325100	Malignant melanoma of breast	17
B325700	Malignant melanoma of back	17
B327400	Malignant melanoma of lower leg	17
B327.00	Malignant melanoma of lower limb and hip	17
B325.00	Malignant melanoma of trunk (excluding scrotum)	17
B327100	Malignant melanoma of thigh	17
B324.00	Malignant melanoma of scalp and neck	17

B326100	Malignant melanoma of upper arm	17
B326.00	Malignant melanoma of upper limb and shoulder	17
B326200	Malignant melanoma of fore-arm	17
B326000	Malignant melanoma of shoulder	17
B323000	Malignant melanoma of external surface of cheek	17
B324100	Malignant melanoma of neck	17
B324000	Malignant melanoma of scalp	17
B325800	Malignant melanoma of chest wall	17
B327700	Malignant melanoma of foot	17
B323z00	Malignant melanoma of face NOS	17
B327200	Malignant melanoma of knee	17
B323.00	Malignant melanoma of other and unspecified parts of face	17
B325300	Malignant melanoma of groin	17
B32y.00	Malignant melanoma of other specified skin site	17
B325000	Malignant melanoma of axilla	17
B325z00	Malignant melanoma of trunk, excluding scrotum, NOS	17
B327500	Malignant melanoma of ankle	17
B323400	Malignant melanoma of external surface of nose	17
B322.00	Malignant melanoma of ear and external auricular canal	17
B327800	Malignant melanoma of toe	17
B327z00	Malignant melanoma of lower limb or hip NOS	17
B322000	Malignant melanoma of auricle (ear)	17
B321.00	Malignant melanoma of eyelid including canthus	17
B323500	Malignant melanoma of temple	17
B323300	Malignant melanoma of forehead	17
B326300	Malignant melanoma of hand	17
B326500	Malignant melanoma of thumb	17
B327600	Malignant melanoma of heel	17
B326400	Malignant melanoma of finger	17
B327900	Malignant melanoma of great toe	17
B320.00	Malignant melanoma of lip	17
B325200	Malignant melanoma of buttock	17
B326z00	Malignant melanoma of upper limb or shoulder NOS	17
B323100	Malignant melanoma of chin	17
B327300	Malignant melanoma of popliteal fossa area	17
B325500	Malignant melanoma of perineum	17
B325600	Malignant melanoma of umbilicus	17
B322z00	Malignant melanoma of ear and external auricular canal NOS	17
B327000	Malignant melanoma of hip	17
B323200	Malignant melanoma of eyebrow	17
B324z00	Malignant melanoma of scalp and neck NOS	17
B329.00	Malignant melanoma stage IB	17
B32A.00	Malignant melanoma stage IIA	17
B322100	Malignant melanoma of external auditory meatus	17
B325400	Malignant melanoma of perianal skin	17
B32G.00	Malignant melanoma stage IV M1a	17
B32H.00	Malignant melanoma stage IV M1b	17
B328.00	Malignant melanoma stage IA	17

B32B.00	Malignant melanoma stage IIB	17
B32F.00	Malignant melanoma stage IIIC	17
B32J.00	Malignant melanoma stage IV M1c	17
B32y000	Overlapping malignant melanoma of skin	17
B31..00	Malignant neoplasm of connective and other soft tissue	19
B31z.00	Malignant neoplasm of connective and soft tissue, site NOS	19
BBV9.00	[M]Myxoid chondrosarcoma	19
BBTA.00	[M]Kaposi's sarcoma	19
BBT1.11	[M]Angiosarcoma	19
BBW4.00	[M]Chondrosarcoma NOS	19
B310100	Malignant neoplasm of soft tissue of face	19
B312100	Malig neop of connective and soft tissue thigh and upper leg	19
B310200	Malignant neoplasm of soft tissue of neck	19
B310000	Malignant neoplasm of soft tissue of head	19
B312300	Malig neop of connective and soft tissue of lower leg	19
B314.00	Malignant neoplasm of connective and soft tissue of abdomen	19
BBW..00	[M]Chondromatous neoplasms	19
BBW7.00	[M]Chondroblastoma NOS	19
B310.00	Malig neop of connective and soft tissue head, face and neck	19
B311200	Malignant neoplasm of connective and soft tissue of fore-arm	19
B313000	Malignant neoplasm of connective and soft tissue of axilla	19
B313.00	Malignant neoplasm of connective and soft tissue of thorax	19
B315.00	Malignant neoplasm of connective and soft tissue of pelvis	19
B312.00	Malig neop of connective and soft tissue of hip and leg	19
B311300	Malignant neoplasm of connective and soft tissue of hand	19
B311100	Malignant neoplasm of connective and soft tissue, upper arm	19
B310300	Malignant neoplasm of cartilage of ear	19
B310z00	Malig neop connective and soft tissue head, face, neck NOS	19
B31y.00	Malig neop connective and soft tissue other specified site	19
B314z00	Malig neop of connective and soft tissue of abdomen NOS	19
B315000	Malignant neoplasm of connective and soft tissue of buttock	19
B311000	Malignant neoplasm of connective and soft tissue of shoulder	19
BBW7.11	[M]Chondromatous giant cell tumour	19
BBW9.00	[M]Mesenchymal chondrosarcoma	19
B311.00	Malig neop connective and soft tissue upper limb/shoulder	19
B62D.00	Histiocytic sarcoma	19
B312400	Malignant neoplasm of connective and soft tissue of foot	19
B316.00	Malig neop of connective and soft tissue trunk unspecified	19
B310400	Malignant neoplasm of tarsus of eyelid	19
B311500	Malignant neoplasm of connective and soft tissue of thumb	19
B314000	Malig neop of connective and soft tissue of abdominal wall	19
B311400	Malignant neoplasm of connective and soft tissue of finger	19
B315200	Malignant neoplasm of connective and soft tissue of perineum	19
B313z00	Malig neop of connective and soft tissue of thorax NOS	19
B315z00	Malig neop of connective and soft tissue of pelvis NOS	19
B653.00	Myeloid sarcoma	19

B312000	Malignant neoplasm of connective and soft tissue of hip	19
B312z00	Malig neop connective and soft tissue hip and leg NOS	19
B315100	Malig neop of connective and soft tissue of inguinal region	19
B31z000	Kaposi's sarcoma of soft tissue	19
B311z00	Malig neop connective soft tissue upper limb/shoulder NOS	19
B312200	Malig neop connective and soft tissue of popliteal space	19
B313100	Malignant neoplasm of diaphragm	19
BBWz.00	[M]Chondromatous neoplasm NOS	19
BBrA300	[M]Myeloid sarcoma	19
BBTD200	[M]Haemangiopericytoma, malignant	19
B313200	Malignant neoplasm of great vessels	19
B313300	Malig neoplasm of connective and soft tissues of thor spine	19
B314100	Malig neoplasm of connective and soft tissues of lumb spine	19
BBW4.11	[M]Fibrochondrosarcoma	19
B310500	Malignant neoplasm soft tissues of cervical spine	19
B312500	Malignant neoplasm of connective and soft tissue of toe	19
B315300	Malig neopl of connective and soft tissue - sacrum or coccyx	19
BBW6.00	[M]Juxtacortical chondrosarcoma	19
BBW8.00	[M]Chondroblastoma, malignant	19
BBrA312	[M]Granulocytic sarcoma	19
B524400	Malignant neoplasm of peripheral nerve of abdomen	19
B524000	Malignant neoplasm of peripheral nerves of head, face & neck	19
B524500	Malignant neoplasm of peripheral nerve of pelvis	19
B524200	Malignant neoplasm of peripheral nerve of low limb, incl hip	19
B524100	Malignant neoplasm of peripheral nerve, upp limb, incl should	19
B524300	Malignant neoplasm of peripheral nerve of thorax	19
B226.00	Mesothelioma	19
B232.00	Mesothelioma of pleura	19
Byu5011	[X]Mesothelioma of lung	19
B23z.00	Malignant neoplasm of pleura NOS	19
Byu5100	[X]Mesothelioma, unspecified	19
Byu5000	[X]Mesothelioma of other sites	19
B34..00	Malignant neoplasm of female breast	20
B34..11	Ca female breast	20
B34z.00	Malignant neoplasm of female breast NOS	20
Byu6.00	[X]Malignant neoplasm of breast	20
B344.00	Malignant neoplasm of upper-outer quadrant of female breast	20
B35..00	Malignant neoplasm of male breast	20
B340.00	Malignant neoplasm of nipple and areola of female breast	20
B342.00	Malignant neoplasm of upper-inner quadrant of female breast	20
B341.00	Malignant neoplasm of central part of female breast	20
B345.00	Malignant neoplasm of lower-outer quadrant of female breast	20
B340000	Malignant neoplasm of nipple of female breast	20
B343.00	Malignant neoplasm of lower-inner quadrant of female breast	20

B346.00	Malignant neoplasm of axillary tail of female breast	20
B34y.00	Malignant neoplasm of other site of female breast	20
B34yz00	Malignant neoplasm of other site of female breast NOS	20
B35zz00	Malignant neoplasm of male breast NOS	20
B340100	Malignant neoplasm of areola of female breast	20
B340z00	Malignant neoplasm of nipple or areola of female breast NOS	20
B347.00	Malignant neoplasm, overlapping lesion of breast	20
B350000	Malignant neoplasm of nipple of male breast	20
B35z.00	Malignant neoplasm of other site of male breast	20
B350.00	Malignant neoplasm of nipple and areola of male breast	20
B350100	Malignant neoplasm of areola of male breast	20
B34y000	Malignant neoplasm of ectopic site of female breast	20
B35z000	Malignant neoplasm of ectopic site of male breast	20
B450.00	Malignant neoplasm of vagina	21
B450100	Malignant neoplasm of vaginal vault	21
B450z00	Malignant neoplasm of vagina NOS	21
B454.00	Malignant neoplasm of vulva unspecified	21
B454.11	Primary vulval cancer	21
B451.00	Malignant neoplasm of labia majora	21
B453.00	Malignant neoplasm of clitoris	21
B451000	Malignant neoplasm of greater vestibular (Bartholin's) gland	21
B452.00	Malignant neoplasm of labia minora	21
B451z00	Malignant neoplasm of labia majora NOS	21
B41z.00	Malignant neoplasm of cervix uteri NOS	22
B410.00	Malignant neoplasm of endocervix	22
B41y.00	Malignant neoplasm of other site of cervix	22
B410z00	Malignant neoplasm of endocervix NOS	22
B411.00	Malignant neoplasm of exocervix	22
B41yz00	Malignant neoplasm of other site of cervix NOS	22
B410000	Malignant neoplasm of endocervical canal	22
B412.00	Malignant neoplasm, overlapping lesion of cervix uteri	22
B410100	Malignant neoplasm of endocervical gland	22
B41y000	Malignant neoplasm of cervical stump	22
B41y100	Malignant neoplasm of squamocolumnar junction of cervix	22
B430200	Malignant neoplasm of endometrium of corpus uteri	23
B41..00	Malignant neoplasm of cervix uteri	23
B41..11	Cervical carcinoma (uterus)	23
B40..00	Malignant neoplasm of uterus, part unspecified	23
B43..00	Malignant neoplasm of body of uterus	23
B43z.00	Malignant neoplasm of body of uterus NOS	23
B430.00	Malignant neoplasm of corpus uteri, excluding isthmus	23
B430211	Malignant neoplasm of endometrium	23
B430z00	Malignant neoplasm of corpus uteri NOS	23
B43y.00	Malignant neoplasm of other site of uterine body	23
B430300	Malignant neoplasm of myometrium of corpus uteri	23
B431.00	Malignant neoplasm of isthmus of uterine body	23
B430100	Malignant neoplasm of fundus of corpus uteri	23
B430000	Malignant neoplasm of cornu of corpus uteri	23

B431000	Malignant neoplasm of lower uterine segment	23
B431z00	Malignant neoplasm of isthmus of uterine body NOS	23
B441.00	Malignant neoplasm of fallopian tube	23
Byu7000	[X]Malignant neoplasm of uterine adnexa, unspecified	23
B44z.00	Malignant neoplasm of uterine adnexa NOS	23
B440.11	Cancer of ovary	24
B440.00	Malignant neoplasm of ovary	24
B420.00	Choriocarcinoma	25
B48..00	Malignant neoplasm of penis and other male genital organs	26
B483.00	Malignant neoplasm of penis, part unspecified	26
B481.00	Malignant neoplasm of glans penis	26
B482.00	Malignant neoplasm of body of penis	26
B480.00	Malignant neoplasm of prepuce (foreskin)	26
B46..00	Malignant neoplasm of prostate	27
B47..00	Malignant neoplasm of testis	28
B47z.11	Seminoma of testis	28
B471000	Seminoma of descended testis	28
B47z.12	Teratoma of testis	28
B47z.00	Malignant neoplasm of testis NOS	28
B471100	Teratoma of descended testis	28
B470200	Seminoma of undescended testis	28
B470300	Teratoma of undescended testis	28
B471.00	Malignant neoplasm of descended testis	28
B470.00	Malignant neoplasm of undescended testis	28
B471z00	Malignant neoplasm of descended testis NOS	28
B470z00	Malignant neoplasm of undescended testis NOS	28
B484.00	Malignant neoplasm of epididymis	29
B485.00	Malignant neoplasm of spermatic cord	29
B48y100	Malignant neoplasm of tunica vaginalis	29
B4A0.00	Malignant neoplasm of kidney parenchyma	30
B4A..00	Malig neop of kidney and other unspecified urinary organs	30
B4A..11	Renal malignant neoplasm	30
B4Az.00	Malignant neoplasm of kidney or urinary organs NOS	30
B4A0000	Hypernephroma	30
B4A2.00	Malignant neoplasm of ureter	30
B4A1.00	Malignant neoplasm of renal pelvis	30
B4A3.00	Malignant neoplasm of urethra	30
B4A1z00	Malignant neoplasm of renal pelvis NOS	30
B4A1000	Malignant neoplasm of renal calyces	30
B4A1100	Malignant neoplasm of ureteropelvic junction	30
B49..00	Malignant neoplasm of urinary bladder	31
B49z.00	Malignant neoplasm of urinary bladder NOS	31
B492.00	Malignant neoplasm of lateral wall of urinary bladder	31
B496.00	Malignant neoplasm of ureteric orifice	31
B494.00	Malignant neoplasm of posterior wall of urinary bladder	31
B495.00	Malignant neoplasm of bladder neck	31
B49y.00	Malignant neoplasm of other site of urinary bladder	31
B490.00	Malignant neoplasm of trigone of urinary bladder	31

B493.00	Malignant neoplasm of anterior wall of urinary bladder	31
B491.00	Malignant neoplasm of dome of urinary bladder	31
B497.00	Malignant neoplasm of urachus	31
B506.00	Malignant neoplasm of choroid	33
B50..00	Malignant neoplasm of eye	33
B509.00	Malignant melanoma of eye	33
B505.00	Malignant neoplasm of retina	33
B503.00	Malignant neoplasm of conjunctiva	33
B500000	Malignant neoplasm of ciliary body	33
B501.00	Malignant neoplasm of orbit	33
B50z.00	Malignant neoplasm of eye NOS	33
B500100	Malignant neoplasm of iris	33
B50y.00	Malignant neoplasm of other specified site of eye	33
B500z00	Malignant neoplasm of eyeball NOS	33
B508.00	Malignant neoplasm, overlapping lesion of eye and adnexa	33
B501z00	Malignant neoplasm of orbit NOS	33
B502.00	Malignant neoplasm of lacrimal gland	33
B504.00	Malignant neoplasm of cornea	33
B507.00	Malignant neoplasm of lacrimal duct	33
B501000	Malignant neoplasm of connective tissue of orbit	33
B500200	Malignant neoplasm of crystalline lens	33
B507000	Malignant neoplasm of lacrimal sac	33
B500.00	Malig neop eyeball excl conjunctiva, cornea, retina, choroid	33
B507100	Malignant neoplasm of nasolacrimal duct	33
BBbG.12	[M]Piloid astrocytoma	34
B521.00	Malignant neoplasm of cerebral meninges	34
B52X.00	Malignant neoplasm of meninges, unspecified	34
B523.00	Malignant neoplasm of spinal meninges	34
B521z00	Malignant neoplasm of cerebral meninges NOS	34
B521000	Malignant neoplasm of cerebral dura mater	34
B523z00	Malignant neoplasm of spinal meninges NOS	34
B521200	Malignant neoplasm of cerebral pia mater	34
ByuA200	[X]Malignant neoplasm of meninges, unspecified	34
B51..00	Malignant neoplasm of brain	35
B51..11	Cerebral tumour - malignant	35
B51z.00	Malignant neoplasm of brain NOS	35
BBTF.00	[M]Haemangioblastoma	35
B511.00	Malignant neoplasm of frontal lobe	35
B513.00	Malignant neoplasm of parietal lobe	35
B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)	35
B546.00	Neuroblastoma	35
B516.00	Malignant neoplasm of cerebellum	35
B512.00	Malignant neoplasm of temporal lobe	35
B510z00	Malignant neoplasm of cerebrum NOS	35
B543.00	Malignant neoplasm of pineal gland	35
B545.00	Malignant neoplasm of aortic body and other paraganglia	35
B542100	Malignant neoplasm of craniopharyngeal duct	35

B514.00	Malignant neoplasm of occipital lobe	35
B545000	Malignant neoplasm of glomus jugulare	35
B510100	Malignant neoplasm of cerebral cortex	35
B512z00	Malignant neoplasm of temporal lobe NOS	35
B517.00	Malignant neoplasm of brain stem	35
B51y.00	Malignant neoplasm of other parts of brain	35
B510000	Malignant neoplasm of basal ganglia	35
B510500	Malignant neoplasm of thalamus	35
B51y000	Malignant neoplasm of corpus callosum	35
B517300	Malignant neoplasm of pons	35
B52..00	Malig neop of other and unspecified parts of nervous system	35
B515000	Malignant neoplasm of choroid plexus	35
B544.00	Malignant neoplasm of carotid body	35
BBTF.11	[M]Angioblastoma	35
B517z00	Malignant neoplasm of brain stem NOS	35
B510400	Malignant neoplasm of hypothalamus	35
B515.00	Malignant neoplasm of cerebral ventricles	35
B517100	Malignant neoplasm of medulla oblongata	35
B517000	Malignant neoplasm of cerebral peduncle	35
B517200	Malignant neoplasm of midbrain	35
B51yz00	Malignant neoplasm of other part of brain NOS	35
B512000	Malignant neoplasm of hippocampus	35
B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS	35
B510300	Malignant neoplasm of globus pallidus	35
BBbL.11	[M]Glioblastoma multiforme	35
BBbB.00	[M]Astrocytoma NOS	35
BBbQ.00	[M]Oligodendroglioma NOS	35
BBbL.00	[M]Glioblastoma NOS	35
BBb7.00	[M]Ependymoma NOS	35
BBbT.00	[M]Medulloblastoma NOS	35
BBbG.00	[M]Pilocytic astrocytoma	35
BBbC.00	[M]Astrocytoma, anaplastic type	35
BBbR.00	[M]Oligodendroglioma, anaplastic type	35
BBba.00	[M]Primitive neuroectodermal tumour	35
BBb3.12	[M]Subependymal astrocytoma NOS	35
BBbA.00	[M]Myxopapillary ependymoma	35
BBbF.00	[M]Fibrillary astrocytoma	35
BBb3.13	[M]Subependymoma	35
BBb8.00	[M]Ependymoma, anaplastic type	35
BBbE.00	[M]Gemistocytic astrocytoma	35
BBbG.11	[M]Juvenile astrocytoma	35
BBbS.00	[M]Oligodendroblastoma	35
BBbZ.00	[M]Pleomorphic xanthoastrocytoma	35
BBb4.00	[M]Subependymal giant cell astrocytoma	35
BBbM.00	[M]Giant cell glioblastoma	35
BBbU.00	[M]Desmoplastic medulloblastoma	35
BBb3.11	[M]Subependymal astrocytoma NOS	35
BBb9.00	[M]Papillary ependymoma	35

BBc7.11	[M]Neuroastrocytoma	35
B522.00	Malignant neoplasm of spinal cord	36
B525.00	Malignant neoplasm of cauda equina	36
B520200	Malignant neoplasm of acoustic nerve	36
B520100	Malignant neoplasm of optic nerve	36
B51y200	Malignant neoplasm, overlapping lesion of brain	36
B520.00	Malignant neoplasm of cranial nerves	36
B520000	Malignant neoplasm of olfactory bulb	36
B520z00	Malignant neoplasm of cranial nerves NOS	36
B53..00	Malignant neoplasm of thyroid gland	37
B540.11	Phaeochromocytoma	37
B540.00	Malignant neoplasm of adrenal gland	37
B540z00	Malignant neoplasm of adrenal gland NOS	37
B540000	Malignant neoplasm of adrenal cortex	37
B540100	Malignant neoplasm of adrenal medulla	37
B541.00	Malignant neoplasm of parathyroid gland	37
B542000	Malignant neoplasm of pituitary gland	37
B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct	37
B590.00	Disseminated malignancy NOS	38
B590.11	Carcinomatosis	38
BB03.00	[M]Neoplasm, metastatic	38
B577.11	Liver metastases	38
BB13.00	[M]Carcinoma, metastatic, NOS	38
B585.00	Secondary malignant neoplasm of bone and bone marrow	38
B58..00	Secondary malignant neoplasm of other specified sites	38
B583200	Cerebral metastasis	38
B570.00	Secondary malignant neoplasm of lung	38
B577.00	Secondary malignant neoplasm of liver	38
B583000	Secondary malignant neoplasm of brain	38
1D18.00	Pain from metastases	38
BB53.00	[M]Adenocarcinoma, metastatic, NOS	38
B56..11	Lymph node metastases	38
B57..11	Metastases of respiratory and/or digestive systems	38
BB2B.00	[M]Squamous cell carcinoma, metastatic NOS	38
B585000	Pathological fracture due to metastatic bone disease	38
B58z.00	Secondary malignant neoplasm of other specified site NOS	38
B56..00	Secondary and unspecified malignant neoplasm of lymph nodes	38
B153.00	Secondary malignant neoplasm of liver	38
B583.00	Secondary malignant neoplasm of brain and spinal cord	38
B58y000	Secondary malignant neoplasm of breast	38
B58y500	Secondary malignant neoplasm of prostate	38
B582.00	Secondary malignant neoplasm of skin	38
B572.00	Secondary malignant neoplasm of pleura	38
B58yz00	Secondary malignant neoplasm of other specified site NOS	38
B58y.00	Secondary malignant neoplasm of other specified sites	38
B576100	Secondary malignant neoplasm of peritoneum	38

ByuC700	[X]Secondary malignant neoplasm of other specified sites	38
B56z.00	Secondary and unspec malig neop lymph nodes NOS	38
C354A00	Metastatic calcification	38
BB04.00	[M]Neoplasm, malig, uncertain whether primary or metastatic	38
B57..00	Secondary malig neop of respiratory and digestive systems	38
BB03.11	[M]Secondary neoplasm	38
B580.00	Secondary malignant neoplasm of kidney	38
B587.00	Secondary malignant neoplasm of adrenal gland	38
B583100	Secondary malignant neoplasm of spinal cord	38
B563000	Secondary and unspec malig neop axillary lymph nodes	38
B575000	Secondary malignant neoplasm of colon	38
B586.00	Secondary malignant neoplasm of ovary	38
B581100	Secondary malignant neoplasm of bladder	38
B594.00	Secondary malignant neoplasm of unknown site	38
B582600	Secondary malignant neoplasm of skin of breast	38
B560.00	Secondary and unspec malig neop lymph nodes head/face/neck	38
B561900	Secondary and unspec malig neop pulmonary lymph nodes	38
B57y.00	Secondary malignant neoplasm of other digestive organ	38
B571.00	Secondary malignant neoplasm of mediastinum	38
ByuC300	[X]Secondary malignant neoplasm/oth+unspc respiratory organs	38
B575.00	Secondary malignant neoplasm of large intestine and rectum	38
ByuC.00	[X]Malignant neoplasm of ill-defined, secondary and unspeci	38
B582z00	Secondary malignant neoplasm of skin NOS	38
B561300	Secondary and unspec malig neop ant mediastinal lymph nodes	38
B582300	Secondary malignant neoplasm of skin of trunk	38
B573.00	Secondary malignant neoplasm of other respiratory organs	38
B562.00	Secondary and unspec malig neop intra-abdominal lymph nodes	38
B576000	Secondary malignant neoplasm of retroperitoneum	38
B563.00	Secondary and unspec malig neop axilla and upper limb LN	38
ByuC400	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs	38
B583z00	Secondary malignant neoplasm of brain or spinal cord NOS	38
B575100	Secondary malignant neoplasm of rectum	38
B56y.00	Secondary and unspec malig neop lymph nodes multiple sites	38
B57z.00	Secondary malig neop of respiratory or digestive system NOS	38
B58y400	Secondary malignant neoplasm of vulva	38
B565.00	Secondary and unspec malig neop intrapelvic lymph nodes	38
B58y100	Secondary malignant neoplasm of uterus	38
B561.00	Secondary and unspec malig neop intrathoracic lymph nodes	38
B576.00	Secondary malig neop of retroperitoneum and peritoneum	38
B564.00	Secondary and unspec malig neop inguinal and lower limb LN	38
B562z00	Secondary and unspec malig neop intra-abdominal LN NOS	38
B560200	Secondary and unspec malig neop superficial cervical LN	38

B58y200	Secondary malignant neoplasm of cervix uteri	38
B582500	Secondary malignant neoplasm of skin of hip and leg	38
B581.00	Secondary malignant neoplasm of other urinary organs	38
B582200	Secondary malignant neoplasm of skin of neck	38
B582000	Secondary malignant neoplasm of skin of head	38
B564000	Secondary and unspec malig neop superficial inguinal LN	38
G240000	Secondary malignant renovascular hypertension	38
B560500	Secondary and unspec malig neop submandibular lymph nodes	38
B582100	Secondary malignant neoplasm of skin of face	38
B581z00	Secondary malignant neoplasm of other urinary organ NOS	38
B561500	Secondary and unspec malig neop paratracheal lymph nodes	38
B560900	Secondary and unspec malig neop deep cervical LN	38
B564z00	Secondary and unspec malig neop of inguinal and leg LN NOS	38
B58y700	Secondary malignant neoplasm of penis	38
B574000	Secondary malignant neoplasm of duodenum	38
B575z00	Secondary malig neop of large intestine or rectum NOS	38
B581200	Secondary malignant neoplasm of urethra	38
B560000	Secondary and unspec malig neop of superficial parotid LN	38
B560800	Secondary and unspec malig neop anterior cervical LN	38
B58y900	Secondary malignant neoplasm of tongue	38
B58y300	Secondary malignant neoplasm of vagina	38
B574z00	Secondary malig neop of small intestine or duodenum NOS	38
B574.00	Secondary malignant neoplasm of small intestine and duodenum	38
B561400	Secondary and unspec malig neop post mediastinal lymph nodes	38
B563300	Secondary and unspec malig neop pectoral lymph nodes	38
B561000	Secondary and unspec malig neop internal mammary lymph nodes	38
B562000	Secondary and unspec malig neop coeliac lymph nodes	38
B561800	Secondary and unspec malig neop bronchopulmonary lymph nodes	38
B563z00	Secondary and unspec malig neop axilla and upper limb LN NOS	38
B563200	Secondary and unspec malig neop infraclavicular lymph nodes	38
B560400	Secondary and unspec malig neop deep parotid lymph nodes	38
B562300	Secondary and unspec malig neop common iliac lymph nodes	38
B582400	Secondary malignant neoplasm of skin of shoulder and arm	38
B584.00	Secondary malignant neoplasm of other part of nervous system	38
B58y600	Secondary malignant neoplasm of testis	38
B560700	Secondary and unspec malig neop submental lymph nodes	38
B565000	Secondary and unspec malig neop internal iliac lymph nodes	38
B562400	Secondary and unspec malig neop external iliac lymph nodes	38
B561z00	Secondary and unspec malig neop intrathoracic LN NOS	38
B565z00	Secondary and unspec malig neop intrapelvic LN NOS	38
B58y211	Secondary cancer of the cervix	38

B576z00	Secondary malig neop of retroperitoneum or peritoneum NOS	38
B562200	Secondary and unspec malig neop inferior mesenteric LN	38
B564100	Secondary and unspec malig neop deep inguinal lymph nodes	38
B562100	Secondary and unspec malig neop superficial mesenteric LN	38
B561200	Secondary and unspec malig neop diaphragmatic lymph nodes	38
BBy2.00	[M]No microscopic confirmation tumour, clinically metastatic	38
BB85100	[M]Metastatic signet ring cell carcinoma	38
B560600	Secondary and unspec malig neop of facial lymph nodes	38
B560300	Secondary and unspec malignant neoplasm occipital lymph node	38
B581000	Secondary malignant neoplasm of ureter	38
B565300	Secondary and unspec malig neop sacral lymph nodes	38
B563100	Secondary and unspec malig neop supratrochlear lymph nodes	38
B561600	Secondary and unspec malig neop superfic tracheobronchial LN	38
B58y411	Secondary cancer of the vulva	38
B574100	Secondary malignant neoplasm of jejunum	38
B58y800	Secondary malignant neoplasm of epididymis and vas deferens	38
B574200	Secondary malignant neoplasm of ileum	38
B565200	Secondary and unspec malig neop circumflex iliac LN	38
B561700	Secondary and unspec malig neop inferior tracheobronchial LN	38
B561100	Secondary and unspec malig neop intercostal lymph nodes	38
B560100	Secondary and unspec malignant neoplasm mastoid lymph nodes	38
B627.00	Non - Hodgkin's lymphoma	39
B61..00	Hodgkin's disease	39
B62y.00	Malignant lymphoma NOS	39
B621.00	Mycosis fungoides	39
B627C11	Follicular lymphoma NOS	39
B62x.00	Malignant lymphoma otherwise specified	39
B62yz00	Malignant lymphoma NOS	39
B627C00	Follicular non-Hodgkin's lymphoma	39
B628.00	Follicular lymphoma	39
B627W00	Unspecified B-cell non-Hodgkin's lymphoma	39
B627E00	Diffuse large B-cell lymphoma	39
B614.00	Hodgkin's disease, nodular sclerosis	39
ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type	39
ByuDF11	[X]Non-Hodgkin's lymphoma NOS	39
B602.00	Burkitt's lymphoma	39
B61..11	Hodgkin lymphoma	39
B62F100	Mantle cell lymphoma	39
B620.00	Nodular lymphoma (Brill - Symmers disease)	39
B61z.00	Hodgkin's disease NOS	39
B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites	39

B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas	39
B61zz00	Hodgkin's disease NOS	39
B62x200	Peripheral T-cell lymphoma	39
B627.11	Non-Hodgkin lymphoma	39
B627X00	Diffuse non-Hodgkin's lymphoma, unspecified	39
B627000	Follicular non-Hodgkin's small cleaved cell lymphoma	39
B62F000	Small cell B-cell lymphoma	39
B627A00	Diffuse non-Hodgkin's large cell lymphoma	39
B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma	39
B622.00	Sezary's disease	39
B627B00	Other types of follicular non-Hodgkin's lymphoma	39
B627200	Follicular non-Hodgkin's large cell lymphoma	39
B614z00	Hodgkin's disease, nodular sclerosis NOS	39
ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma	39
B615.00	Hodgkin's disease, mixed cellularity	39
B615z00	Hodgkin's disease, mixed cellularity NOS	39
B62E.00	T/NK-cell lymphoma	39
B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck	39
B621z00	Mycosis fungoides NOS	39
B620z00	Nodular lymphoma NOS	39
B627900	Mucosa-associated lymphoma	39
B62y000	Malignant lymphoma NOS of unspecified site	39
B61z100	Hodgkin's disease NOS of lymph nodes of head, face and neck	39
B614100	Hodgkin's nodular sclerosis of head, face and neck	39
BBv2.00	[M]AngiocentricT-cell lymphoma	39
B620100	Nodular lymphoma of lymph nodes of head, face and neck	39
ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma	39
B61z200	Hodgkin's disease NOS of intrathoracic lymph nodes	39
B62E300	Cutaneous T-cell lymphoma	39
BBv0.00	[M]Monocytoid B-cell lymphoma	39
ByuD300	[X]Other specified types of non-Hodgkin's lymphoma	39
B628100	Follicular lymphoma grade 2	39
B62E100	Anaplastic large cell lymphoma, ALK-positive	39
B62E900	Angioimmunoblastic T-cell lymphoma	39
B62y700	Malignant lymphoma NOS of spleen	39
B617.00	Nodular lymphocyte predominant Hodgkin lymphoma	39
B618.00	Nodular sclerosis classical Hodgkin lymphoma	39
B621000	Mycosis fungoides of unspecified site	39
B627G00	Mediastinal (thymic) large B-cell lymphoma	39
B602z00	Burkitt's lymphoma NOS	39
B61C.00	Other classical Hodgkin lymphoma	39
B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma	39
B628000	Follicular lymphoma grade 1	39
B620000	Nodular lymphoma of unspecified site	39
B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)	39
B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes	39
ByuD000	[X]Other Hodgkin's disease	39

B61z000	Hodgkin's disease NOS, unspecified site	39
B62E200	Anaplastic large cell lymphoma, ALK-negative	39
B611.00	Hodgkin's granuloma	39
B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg	39
B614200	Hodgkin's nodular sclerosis of intrathoracic lymph nodes	39
B616z00	Hodgkin's disease, lymphocytic depletion NOS	39
B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma	39
B616.00	Hodgkin's disease, lymphocytic depletion	39
B61z800	Hodgkin's disease NOS of lymph nodes of multiple sites	39
B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma	39
B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes	39
B614000	Hodgkin's disease, nodular sclerosis of unspecified site	39
B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma	39
B62F200	Lymphoblastic (diffuse) lymphoma	39
B62x000	T-zone lymphoma	39
B628300	Follicular lymphoma grade 3a	39
B628600	Cutaneous follicle centre lymphoma	39
B62F.00	Nonfollicular lymphoma	39
B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm	39
B61z400	Hodgkin's disease NOS of lymph nodes of axilla and arm	39
B620300	Nodular lymphoma of intra-abdominal lymph nodes	39
B620500	Nodular lymphoma of lymph nodes of inguinal region and leg	39
B620800	Nodular lymphoma of lymph nodes of multiple sites	39
B627D00	Diffuse non-Hodgkin's centroblastic lymphoma	39
B628200	Follicular lymphoma grade 3	39
B628400	Follicular lymphoma grade 3b	39
B62x100	Lymphoepithelioid lymphoma	39
B602100	Burkitt's lymphoma of lymph nodes of head, face and neck	39
B616000	Hodgkin's lymphocytic depletion of unspecified site	39
B621500	Mycosis fungoides of lymph nodes of inguinal region and leg	39
B62F.11	Non-follicular lymphoma	39
B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes	39
ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma	39
B602200	Burkitt's lymphoma of intrathoracic lymph nodes	39
B610.00	Hodgkin's paraganuloma	39
B612.00	Hodgkin's sarcoma	39
B614300	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes	39
B614400	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm	39
B614800	Hodgkin's nodular sclerosis of lymph nodes of multiple sites	39
B615100	Hodgkin's mixed cellularity of lymph nodes head, face, neck	39
B61B.00	Lymphocyte-rich classical Hodgkin lymphoma	39
B61z.11	Hodgkin lymphoma NOS	39
B62E800	Blastic NK-cell lymphoma	39
ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified	39
B622z00	Sezary's disease NOS	39
BBI1.00	[M]Sezary's disease	39
B611100	Hodgkin's granuloma of lymph nodes of head, face and neck	39

B615000	Hodgkin's disease, mixed cellularity of unspecified site	39
B615200	Hodgkin's mixed cellularity of intrathoracic lymph nodes	39
B621800	Mycosis fungoides of lymph nodes of multiple sites	39
B628500	Diffuse follicle centre lymphoma	39
B628700	Other types of follicular lymphoma	39
B62E500	Hepatosplenic T-cell lymphoma	39
B62E600	Enteropathy-associated T-cell lymphoma	39
B62Ew00	Other mature T/NK-cell lymphoma	39
B602300	Burkitt's lymphoma of intra-abdominal lymph nodes	39
B602500	Burkitt's lymphoma of lymph nodes of inguinal region and leg	39
B610100	Hodgkin's paraganuloma of lymph nodes of head, face, neck	39
B610300	Hodgkin's paraganuloma of intra-abdominal lymph nodes	39
B614700	Hodgkin's disease, nodular sclerosis of spleen	39
B615500	Hodgkin's mixed cellularity of lymph nodes inguinal and leg	39
B616500	Hodgkin's lymphocytic depletion lymph nodes inguinal and leg	39
B616700	Hodgkin's disease, lymphocytic depletion of spleen	39
B616800	Hodgkin's lymphocytic depletion lymph nodes multiple sites	39
B619.00	Mixed cellularity classical Hodgkin lymphoma	39
B61z300	Hodgkin's disease NOS of intra-abdominal lymph nodes	39
B61z500	Hodgkin's disease NOS of lymph nodes inguinal region and leg	39
B61z700	Hodgkin's disease NOS of spleen	39
B620200	Nodular lymphoma of intrathoracic lymph nodes	39
B621300	Mycosis fungoides of intra-abdominal lymph nodes	39
B621400	Mycosis fungoides of lymph nodes of axilla and upper limb	39
B627400	Diffuse non-Hodgkin's small cleaved cell (diffuse) lymphoma	39
B62E400	Extranodal NK/T-cell lymphoma, nasal type	39
B62E700	Subcutaneous panniculitic T-cell lymphoma	39
B62x600	True histiocytic lymphoma	39
ByuDD00	[X]Oth and unspecif peripheral & cutaneous T-cell lymphomas	39
B616400	Hodgkin's lymphocytic depletion lymph nodes axilla and arm	39
B601200	Lymphosarcoma of intrathoracic lymph nodes	39
B601z00	Lymphosarcoma NOS	39
B601300	Lymphosarcoma of intra-abdominal lymph nodes	39
B612400	Hodgkin's sarcoma of lymph nodes of axilla and upper limb	39
B601700	Lymphosarcoma of spleen	39
B62x500	Malignant immunoproliferative small intestinal disease	40
B62A.00	Sarcoma of dendritic cells	40
B62..00	Other malignant neoplasm of lymphoid and histiocytic tissue	40
B613.00	Hodgkin's disease, lymphocytic-histiocytic predominance	40
B613100	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck	40
B613z00	Hodgkin's, lymphocytic-histiocytic predominance NOS	40
B613000	Hodgkin's, lymphocytic-histiocytic predominance unspec site	40
B613500	Hodgkin's, lymphocytic-histiocytic pred inguinal and leg	40
B613600	Hodgkin's, lymphocytic-histiocytic pred intrapelvic nodes	40
B613200	Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes	40
B613300	Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node	40
B613700	Hodgkin's, lymphocytic-histiocytic predominance of spleen	40

B613800	Hodgkin's, lymphocytic-histiocytic pred of multiple sites	40
B627911	Maltoma	40
B630.00	Multiple myeloma	41
B630200	Plasmacytoma NOS	41
B630.12	Myelomatosis	41
B630100	Solitary myeloma	41
B630300	Lambda light chain myeloma	41
	Malignant plasma cell neoplasm, extramedullary	
B630000	plasmacytoma	41
B630400	Solitary plasmacytoma	41
B630.11	Kahler's disease	41
B641.00	Chronic lymphoid leukaemia	42
B650.00	Acute myeloid leukaemia	42
B651.00	Chronic myeloid leukaemia	42
B68z.00	Leukaemia NOS	42
B640.00	Acute lymphoid leukaemia	42
B65..00	Myeloid leukaemia	42
B64..11	Lymphatic leukaemia	42
B64..00	Lymphoid leukaemia	42
B641.11	Chronic lymphatic leukaemia	42
BBr..00	[M]Leukaemias	42
B680.00	Acute leukaemia NOS	42
BBrA400	[M]Hairy cell leukaemia	42
B68..00	Leukaemia of unspecified cell type	42
B691.00	Chronic myelomonocytic leukaemia	42
B681.00	Chronic leukaemia NOS	42
B624.12	Hairy cell leukaemia	42
B65y100	Acute promyelocytic leukaemia	42
BBr0100	[M]Acute leukaemia NOS	42
B69..00	Myelomonocytic leukaemia	42
B651.11	Chronic granulocytic leukaemia	42
B661.00	Chronic monocytic leukaemia	42
B67..00	Other specified leukaemia	42
B641000	B-cell chronic lymphocytic leukaemia	42
BBr2700	[M]Adult T-cell leukaemia/lymphoma	42
B640000	B-cell acute lymphoblastic leukaemia	42
B631.00	Plasma cell leukaemia	42
B64y100	Prolymphocytic leukaemia	42
BBr0300	[M]Chronic leukaemia NOS	42
BBrz.00	[M]Leukaemia NOS	42
B651z00	Chronic myeloid leukaemia NOS	42
BBr6700	[M]Acute myelomonocytic leukaemia	42
BBr2100	[M]Acute lymphoid leukaemia	42
BBr2300	[M]Chronic lymphoid leukaemia	42
B64z.00	Lymphoid leukaemia NOS	42
B670.00	Acute erythraemia and erythroleukaemia	42
BBr6100	[M]Acute myeloid leukaemia	42
BBr6011	[M]Granulocytic leukaemia NOS	42

B64y200	Adult T-cell leukaemia	42
BBr6.00	[M]Myeloid leukaemias	42
B67z.00	Other specified leukaemia NOS	42
B660.00	Acute monocytic leukaemia	42
B641100	Clinical stage A chronic lymphocytic leukaemia	42
B66..00	Monocytic leukaemia	42
BBr6600	[M]Acute promyelocytic leukaemia	42
B65z.00	Myeloid leukaemia NOS	42
BBr2011	[M]Lymphatic leukaemia	42
B68y.00	Other leukaemia of unspecified cell type	42
BBr6800	[M]Chronic myelomonocytic leukaemia	42
BBr6300	[M]Chronic myeloid leukaemia	42
B64y.00	Other lymphoid leukaemia	42
B64yz00	Other lymphoid leukaemia NOS	42
BBr4.00	[M]Erythroleukaemias	42
BBr0000	[M]Leukaemia NOS	42
BBr2.00	[M]Lymphoid leukaemias	42
BBr2000	[M]Lymphoid leukaemia NOS	42
B653100	Granulocytic sarcoma	42
ByuD600	[X]Other myeloid leukaemia	42
ByuD500	[X]Other lymphoid leukaemia	42
BBr0112	[M]Blastic leukaemia	42
B64y500	Adult T-cell lymphoma/leukaemia (HTLV-1-associated)	42
B641011	Chronic lymphocytic leukaemia of B-cell type	42
B654.00	Acute myeloblastic leukaemia	42
B67y.00	Other and unspecified leukaemia	42
B690.00	Acute myelomonocytic leukaemia	42
BBr2600	[M]Burkitt's cell leukaemia	42
B641200	Clinical stage B chronic lymphocytic leukaemia	42
B672.11	Thrombocytic leukaemia	42
BBr0111	[M]Blast cell leukaemia	42
BBrA500	[M]Acute megakaryoblastic leukaemia	42
B672.00	Megakaryocytic leukaemia	42
BBr6000	[M]Myeloid leukaemia NOS	42
ByuD800	[X]Other specified leukaemias	42
B651100	Chronic myeloid leukaemia, BCR/ABL positive	42
B651300	Atypical chronic myeloid leukaemia, BCR/ABL negative	42
B65yz00	Other myeloid leukaemia NOS	42
B651000	Chronic eosinophilic leukaemia	42
B67yz00	Other and unspecified leukaemia NOS	42
BBr0.00	[M]Leukaemias unspecified	42
BBr2500	[M]Prolymphocytic leukaemia	42
B64y400	T-cell prolymphocytic leukaemia	42
B652.00	Subacute myeloid leukaemia	42
B66..12	Monoblastic leukaemia	42
B66z.00	Monocytic leukaemia NOS	42
BBr3.00	[M]Plasma cell leukaemias	42
B641300	Clinical stage C chronic lymphocytic leukaemia	42

B64y300	B-cell prolymphocytic leukaemia	42
B663.00	Acute monoblastic leukaemia	42
B682.00	Subacute leukaemia NOS	42
B693.00	Juvenile myelomonocytic leukaemia	42
BBr0113	[M]Stem cell leukaemia	42
BBr0z00	[M]Leukaemia unspecified, NOS	42
BBr8.00	[M]Eosinophilic leukaemias	42
B642.00	Subacute lymphoid leukaemia	42
B673.00	Mast cell leukaemia	42
B67y000	Lymphosarcoma cell leukaemia	42
BBr6900	[M]Juvenile myelomonocytic leukaemia	42
BBr6z00	[M]Other myeloid leukaemia NOS	42
BBr9000	[M]Monocytic leukaemia NOS	42
BBrAz00	[M]Miscellaneous leukaemia NOS	42
B651200	Chronic neutrophilic leukaemia	42
B66..11	Histiocytic leukaemia	42
B662.00	Subacute monocytic leukaemia	42
B66y.00	Other monocytic leukaemia	42
B66yz00	Other monocytic leukaemia NOS	42
B676.00	Acute erythroid leukaemia	42
B692.00	Subacute myelomonocytic leukaemia	42
BBr0200	[M]Subacute leukaemia NOS	42
BBr0400	[M]Aleukaemic leukaemia NOS	42
BBr3z00	[M]Plasma cell leukaemia NOS	42
BBr4000	[M]Erythroleukaemia	42
BBr4z00	[M]Erythroleukaemia NOS	42
BBr6200	[M]Subacute myeloid leukaemia	42
BBr6311	[M]Naegeli-type monocytic leukaemia	42
BBr7000	[M]Basophilic leukaemia	42
BBr8000	[M]Eosinophilic leukaemia	42
BBr8z00	[M]Eosinophilic leukaemia NOS	42
BBrA.00	[M]Miscellaneous leukaemias	42
BBrA100	[M]Megakaryocytic leukaemia	42
BBrA111	[M]Thrombocytic leukaemia	42
ByuD700	[X]Other monocytic leukaemia	42
ByuD900	[X]Other leukaemia of unspecified cell type	42
B624.11	Leukaemic reticuloendotheliosis	42
B624.00	Leukaemic reticuloendotheliosis	42
B670.11	Di Guglielmo's disease	42
B675.00	Acute myelofibrosis	42
B674.00	Acute panmyelosis	42
B653000	Chloroma	42
B624z00	Leukaemic reticuloendotheliosis NOS	42

CPRD code lists for comorbidity.

Adrenal insufficiency

medcode	desc
3113	Corticoadrenal insufficiency
4042	Addisonian crisis
4481	Addison's disease
12227	Addisonian crisis
12396	Corticoadrenal insufficiency NOS
20786	Adrenal insufficiency NEC
21539	Acute adrenal insufficiency
21594	Hypoaldosteronism
28896	Adrenal hypofunction
40154	Drug-induced adrenocortical insufficiency
42873	Adrenal crisis
55153	Adrenal haemorrhage
56634	Postprocedural adrenocortical(-medullary) hypofunction
101824	Adrenocortical haemorrhage
108019	Hyporeninaemic hypoaldosteronism

Atrial Fibrillation

medcode	desc
1268	Paroxysmal atrial fibrillation
1664	Atrial fibrillation
2212	Atrial fibrillation and flutter
23437	Atrial fibrillation and flutter NOS
35127	Non-rheumatic atrial fibrillation
45773	Atrial fibrillation annual review
84152	Perc transluminal ablation of atrial wall for atrial flutter
96076	Persistent atrial fibrillation
96277	Permanent atrial fibrillation
105554	Atrial fibrillation care pathway

Alcoholism

medcode	desc
669	Nondependent alcohol abuse, unspecified
1399	Alcohol problem drinking
1618	Heavy drinker - 7-9 u/day
2081	Alcoholism
2082	Alcohol withdrawal syndrome
2084	Alcohol dependence syndrome
3216	Acute alcoholic hepatitis
4500	Korsakov's alcoholic psychosis
4506	Alcoholic gastritis
5740	Acute alcoholic intoxication in alcoholism
5758	[X]Chronic alcoholism
6169	Alcohol dependence syndrome NOS

7885	Alcoholic liver damage
10691	Alcoholic fatty liver
11106	Korsakov's alcoholic psychosis with peripheral neuritis
	Mental & behav disorders due to use of alcohol: psychotic
12353	disorder
12442	Alcohol disorder monitoring
12974	Nondependent alcohol abuse, episodic
12977	Very heavy drinker - >9u/day
12984	Very heavy drinker
16225	Alcohol withdrawal delirium
16237	Alcoholic psychosis
18636	Wernicke-Korsakov syndrome
24064	Continuous chronic alcoholism
24485	Chronic alcoholism in remission
25110	Alcohol withdrawal hallucinosis
26106	Episodic chronic alcoholism
29691	Aversion therapy - alcoholism
31443	Chronic alcoholism
32964	Alcohol abuse monitoring
33635	Chronic alcoholism NOS
33670	Other alcoholic psychosis
33839	Cerebellar ataxia due to alcoholism
36296	Acute alcoholic intoxication in alcoholism NOS
	Mental & behavioural dis due to use of alcohol: dependence
39327	syndrome
40530	Acute alcoholic intoxication, unspecified, in alcoholism
41983	Alcohol detoxification
43193	Unspecified chronic alcoholism
47555	Cerebral degeneration due to alcoholism
56947	Continuous acute alcoholic intoxication in alcoholism
57939	Pathological alcohol intoxication
59574	Acute alcoholic intoxication in remission, in alcoholism
62000	Mental & behav dis due alcoh: resid & late-onset psychotic dis
64101	Men & behav dis due alcoh: withdrawal state with delirium
67651	Alcoholic psychosis NOS
68111	Other alcoholic psychosis NOS
104611	Alcohol-induced acute pancreatitis

Anxiety

medcode	desc
636	Anxiety states
655	Anxiety with depression
1758	Chronic anxiety
2030	Obsessional neurosis
3076	Agoraphobia with panic attacks
4069	Panic disorder
4534	Anxiety state NOS
4634	Recurrent anxiety

4659	Generalised anxiety disorder
5385	[X]Other anxiety disorders
6939	Anxiety state unspecified
8205	[X]Panic disorder [episodic paroxysmal anxiety]
9125	Anxiety management training
10344	[X]Generalized anxiety disorder
11913	[X]Mixed anxiety and depressive disorder
23838	[X]Anxiety disorder, unspecified
24066	[X]Other specified anxiety disorders
27685	[X]Other phobic anxiety disorders
44321	[X]Other mixed anxiety disorders

Asthma

medcode	desc
78	Asthma
81	Asthma monitoring
185	Acute exacerbation of asthma
232	Asthma attack
233	Severe asthma attack
719	H/O: asthma
1555	Bronchial asthma
2290	Allergic asthma
3018	Mild asthma
3366	Severe asthma
3458	Occasional asthma
3665	Late onset asthma
4442	Asthma unspecified
4606	Exercise induced asthma
4892	Status asthmaticus NOS
5267	Intrinsic asthma
5627	Hay fever with asthma
5798	Chronic asthmatic bronchitis
5867	Exercise induced asthma
5909	Chronic wheezy bronchitis
6707	Extrinsic asthma with asthma attack
7058	Emergency admission, asthma
7146	Extrinsic (atopic) asthma
7191	Asthma limiting activities
7378	Asthma management plan given
7416	Asthma disturbing sleep
7731	Pollen asthma
8335	Asthma attack NOS
8355	Asthma monitored
9552	Change in asthma management plan
10043	Asthma annual review
10274	Asthma medication review
10487	Asthma - currently active
11022	Asthma trigger

11370 Asthma confirmed
12987 Late-onset asthma
13065 Moderate asthma
13066 Asthma - currently dormant
13173 Asthma not disturbing sleep
13174 Asthma not limiting activities
13175 Asthma disturbs sleep frequently
13176 Asthma follow-up
14777 Extrinsic asthma without status asthmaticus
15248 Hay fever with asthma
16070 Asthma NOS
16667 Asthma control step 2
16785 Asthma control step 1
18223 Step down change in asthma management plan
18224 Asthma control step 3
18323 Intrinsic asthma with asthma attack
19167 Asthma monitoring by nurse
19519 Asthma treatment compliance unsatisfactory
19520 Asthma treatment compliance satisfactory
20860 Asthma control step 5
20886 Asthma control step 4
21232 Allergic asthma NEC
24479 Emergency asthma admission since last appointment
24506 Further asthma - drug prevent.
24884 Asthma causes daytime symptoms 1 to 2 times per week
25181 Asthma restricts exercise
25791 Asthma clinical management plan
25796 Mixed asthma
26501 Asthma never causes daytime symptoms
26503 Asthma causes daytime symptoms most days
26504 Asthma never restricts exercise
26506 Asthma severely restricts exercise
26861 Asthma sometimes restricts exercise
27926 Extrinsic asthma with status asthmaticus
29325 Intrinsic asthma without status asthmaticus
29645 Asthma control step 0
30815 Asthma causing night waking
31167 Asthma night-time symptoms
31225 Asthma causes daytime symptoms 1 to 2 times per month
32727 Hyperreactive airways disease
38143 Asthma never disturbs sleep
38144 Asthma limits walking up hills or stairs
38145 Asthma limits walking on the flat
38146 Asthma disturbs sleep weekly
39570 Asthma causes night symptoms 1 to 2 times per month
40823 Brittle asthma
42824 Asthma daytime symptoms
45073 Intrinsic asthma NOS

45782	Extrinsic asthma NOS
58196	Intrinsic asthma with status asthmaticus
73522	Work aggravated asthma
99793	Patient has a written asthma personal action plan
100107	Health education - asthma self management
100509	Under care of asthma specialist nurse
100740	Health education - structured asthma discussion
102170	Asthma review using Roy Colleg of Physicians three questions
102301	Asthma trigger - seasonal
102341	Asthma trigger - pollen
102395	Asthma causes symptoms most nights
102400	Asthma causes night time symptoms 1 to 2 times per week
102449	Asthma trigger - respiratory infection
102713	Asthma limits activities 1 to 2 times per month
102871	Asthma trigger - exercise
102888	Asthma limits activities 1 to 2 times per week
102952	Asthma trigger - warm air
103318	Health education - structured patient focused asthma discuss
103321	Asthma trigger - animals
103612	Asthma never causes night symptoms
103631	Royal College Physician asthma assessment 3 question score
103813	Asthma trigger - cold air
103944	Asthma trigger - airborne dust
103945	Asthma trigger - damp
103952	Asthma trigger - emotion
103955	Asthma trigger - tobacco smoke
103998	Asthma limits activities most days
105420	Asthma self-management plan review
105674	Asthma self-management plan agreed
	Number days absent from school due to asthma in past 6
107167	month

Coronary heart disease

medcode	desc
240	Ischaemic heart disease
241	Acute myocardial infarction
1204	Heart attack
1344	Coronary artery disease
1414	Angina on effort
1430	Angina pectoris
1431	Unstable angina
1655	Triple vessel disease of the heart
1676	Ischaemic heart disease NOS
1677	MI - acute myocardial infarction
1678	Inferior myocardial infarction NOS
1792	IHD - Ischaemic heart disease
2491	Coronary thrombosis
3704	Acute subendocardial infarction

3999 Single coronary vessel disease
 4017 Old myocardial infarction
 4656 Crescendo angina
 5030 [V]Presence of coronary artery bypass graft
 5254 Double coronary vessel disease
 5387 Other specified anterior myocardial infarction
 5413 Coronary atherosclerosis
 5674 [V]Presence of coronary artery bypass graft - CABG
 6336 H/O: angina pectoris
 6980 [V]Status following coronary angioplasty NOS
 7320 Ischaemic cardiomyopathy
 7347 Unstable angina
 7696 Syncope anginosa
 8935 Acute inferolateral infarction
 9276 Acute coronary insufficiency
 9412 Other acute and subacute ischaemic heart disease
 9507 Acute non-Q wave infarction
 9555 Post infarct angina
 10562 Acute non-ST segment elevation myocardial infarction
 11048 Variant angina pectoris
 11983 Acute coronary syndrome
 12139 Acute anterolateral infarction
 12229 Acute ST segment elevation myocardial infarction
 12734 Coronary artery bypass graft occlusion
 12804 Stable angina
 12986 Prinzmetal's angina
 13566 Attack - heart
 13571 Thrombosis - coronary
 14658 Acute myocardial infarction NOS
 14897 Anterior myocardial infarction NOS
 14898 Lateral myocardial infarction NOS
 15661 Dressler's syndrome
 15754 Other chronic ischaemic heart disease NOS
 16408 Healed myocardial infarction
 17307 Angina at rest
 17464 Personal history of myocardial infarction
 17689 Silent myocardial infarction
 17872 Acute anteroseptal infarction
 18118 Worsening angina
 18125 Nocturnal angina
 18643 [V]Presence of coronary angioplasty implant and graft
 18842 Subsequent myocardial infarction
 18889 Asymptomatic coronary heart disease
 18913 [V]Presence of aortocoronary bypass graft
 19655 Angina at rest
 20095 Angina decubitus
 21844 Transient myocardial ischaemia
 22383 Other specified ischaemic heart disease

23078 Chronic myocardial ischaemia
 23579 Postmyocardial infarction syndrome
 23708 Atrial septal defect/curr comp folow acut myocardal infarct
 23892 Posterior myocardial infarction NOS
 24126 Haemopericardium/current comp folow acut myocardi infarct
 24540 Chronic coronary insufficiency
 24783 Arteriosclerotic heart disease
 25842 Angina pectoris NOS
 26863 New onset angina
 27951 Other acute and subacute ischaemic heart disease
 27977 Other acute and subacute ischaemic heart disease NOS
 28138 Other chronic ischaemic heart disease
 28554 Angina pectoris NOS
 28736 Acute atrial infarction
 29421 Silent myocardial ischaemia
 29643 Acute inferoposterior infarction
 29758 Acute transmural myocardial infarction of unspecif site
 29902 Angina decubitus NOS
 30330 Acute Q-wave infarct
 30421 Cardiac rupture following myocardial infarction (MI)
 32272 Postoperative myocardial infarction
 32450 Ischaemic chest pain
 32854 Acute posterolateral myocardial infarction
 34328 Refractory angina
 34633 Other specified chronic ischaemic heart disease
 34803 Other acute myocardial infarction
 35674 H/O: myocardial infarct <60
 35713 Other specified chronic ischaemic heart disease NOS
 36423 Certain current complication follow acute myocardial infarct
 36523 Preinfarction syndrome
 36609 Atherosclerotic cardiovascular disease
 36854 Coronary artery spasm
 37657 Ventric septal defect/curr comp fol acut myocardal infarctn
 38609 Subsequent myocardial infarction of inferior wall
 39449 Coronary thrombosis not resulting in myocardial infarction
 39546 [X]Other forms of angina pectoris
 39655 Impending infarction
 39693 Subendocardial ischaemia
 40399 H/O: myocardial infarct >60
 40429 Acute anteroapical infarction
 41221 Acute septal infarction
 41835 Postoperative subendocardial myocardial infarction
 45809 Subsequent myocardial infarction of anterior wall
 46017 Other acute myocardial infarction NOS
 46112 Postoperative transmural myocardial infarction anterior wall
 46166 Subsequent myocardial infarction of unspecified site
 46276 Postoperative transmural myocardial infarction inferior wall
 47637 [X]Other forms of chronic ischaemic heart disease

50372	H/O: Myocardial infarction in last year
52517	[X]Ischaemic heart diseases
54251	Preinfarction syndrome NOS
54535	Stenocardia
55137	MI - myocardial infarction aborted
57062	H/O: Angina in last year
59189	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	Ruptur chordae tendinae/curr comp fol acute myocard infarct
61072	Myocardial infarction aborted
62626	Acute papillary muscle infarction
63467	True posterior myocardial infarction
66388	Status anginosus
68357	Microinfarction of heart
68401	[X]Other forms of acute ischaemic heart disease
68748	Postoperative myocardial infarction; unspecified
69474	Rupture papillary muscle/curr comp fol acute myocard infarct
72562	Subsequent myocardial infarction of other sites
96838	[X]Acute transmural myocardial infarction of unspecif site
99991	[X]Subsequent myocardial infarction of unspecified site
109035	[X]Subsequent myocardial infarction of other sites

Cardiac failure

medcode	desc
398	Congestive heart failure
884	Left ventricular failure
1223	Cardiac failure
2062	Heart failure
2906	Congestive cardiac failure
4024	Heart failure NOS
5942	Impaired left ventricular function
8966	Left ventricular systolic dysfunction
9524	Biventricular failure
9913	Heart failure confirmed
10079	Right heart failure
10154	Right ventricular failure
11284	Echocardiogram shows left ventricular systolic dysfunction
11424	Compensated cardiac failure
12550	Left ventricular diastolic dysfunction
13189	New York Heart Association classification - class II
17278	Cardiac failure NOS
18853	New York Heart Association classification - class I
19066	New York Heart Association classification - class III
20822	Congenital cardiac failure
21837	Hypertensive heart&renal dis with (congestv) failure
22262	Rheumatic left ventricular failure
27884	Decompensated cardiac failure
30779	Heart failure annual review
32671	Chronic congestive heart failure

51214	New York Heart Association classification - class IV
57987	Hyperten heart&renal did+both(congestv)heart and renal fail
94870	Congestive heart failure due to valvular disease
101137	HFNEF - heart failure with normal ejection fraction
101138	Heart failure with normal ejection fraction
104275	Right ventricular failure
106897	Heart failure with preserved ejection fraction
107397	Left ventricular cardiac dysfunction

Chronic kidney disease

medcode	desc
12479	Chronic kidney disease stage 4
12566	Chronic kidney disease stage 3
12586	Chronic Kidney disease stage 2
19473	Chronic kidney disease monitoring
30735	Chronic kidney disease annual review
94793	Chronic kidney disease stage 3 with proteinuria
94965	Chronic kidney disease stage 3A
95121	Chronic kidney disease stage 2 without proteinuria
95122	Chronic kidney disease stage 4 with proteinuria
95123	Chronic kidney disease stage 3 without proteinuria
95146	Chronic kidney disease stage 2 with proteinuria
95175	Chronic kidney disease stage 3A without proteinuria
95177	Chronic kidney disease stage 3B without proteinuria
95179	Chronic kidney disease stage 3B
95406	Chronic kidney disease stage 4 without proteinuria
95408	Chronic kidney disease stage 3A with proteinuria
104619	Chronic kidney disease stage 3
104963	Chronic kidney disease stage 4

Chronic obstructive pulmonary disease

mecode	desc
794	Emphysema
998	Chronic obstructive airways disease
1001	Chronic obstructive pulmonary disease
1446	Acute exacerbation of chronic obstructive airways disease
3243	Chronic bronchitis
5710	Chronic obstructive airways disease NOS
5798	Chronic asthmatic bronchitis
5909	Chronic wheezy bronchitis
7884	Chron obstruct pulmonary dis wth acute exacerbation, unspec
9520	Chronic obstructive pulmonary disease monitoring
9876	Severe chronic obstructive pulmonary disease
10802	Moderate chronic obstructive pulmonary disease
10863	Mild chronic obstructive pulmonary disease
10980	Centrilobular emphysema
11019	Admit COPD emergency
11026	Excepted from COPD quality indicators: Patient unsuitable

11150 Mucopurulent chronic bronchitis
 11266 Excepted from COPD quality indicators: Informed dissent
 11287 Chronic obstructive pulmonary disease annual review
 12166 Other specified chronic obstructive airways disease
 14798 Emphysematous bronchitis
 15157 Chronic bronchitis NOS
 15626 Chronic catarrhal bronchitis
 16410 Other emphysema NOS
 18476 COPD follow-up
 18501 COPD self-management plan given
 18621 Chronic obstructive pulmonary disease follow-up
 18717 Exception reporting: COPD quality indicators
 18792 Chronic obstructive pulmonary disease monitoring admin
 19003 Emergency COPD admission since last appointment
 19106 COPD accident and emergency attendance since last visit
 21061 Chronic obstruct pulmonary dis with acute lower resp infectn
 23492 Chronic bullous emphysema NOS
 24248 Mixed simple and mucopurulent chronic bronchitis
 25603 Simple chronic bronchitis
 26018 Chronic obstructive pulmonary disease monitoring by nurse
 26306 Chronic bullous emphysema
 27819 Obstructive chronic bronchitis
 28743 Number of COPD exacerbations in past year
 28755 Chronic obstructive pulmonary disease monitoring 1st letter
 33450 Emphysema NOS
 34202 Chronic obstructive pulmonary disease monitoring 2nd letter
 34215 Chronic obstructive pulmonary disease monitoring 3rd letter
 37247 Chronic obstructive pulmonary disease NOS
 37371 Chronic obstructive pulmonary disease monitoring due
 40159 Purulent chronic bronchitis
 40788 Other emphysema
 44525 Obstructive chronic bronchitis NOS
 45089 Chronic tracheobronchitis
 45770 Chronic obstructive pulmonary disease disturbs sleep
 45771 Chronic obstructive pulmonary disease does not disturb sleep
 45777 Chronic obstructive pulmonary disease clini management plan
 45998 Chronic obstructive pulmonary disease monitoring by doctor
 46036 Multiple COPD emergency hospital admissions
 46578 Panlobular emphysema
 56860 Segmental bullous emphysema
 59263 Acute interstitial emphysema
 60188 Giant bullous emphysema
 61118 Simple chronic bronchitis NOS
 61513 Mucopurulent chronic bronchitis NOS
 63479 MacLeod's unilateral emphysema
 64721 Chronic emphysema due to chemical fumes
 65733 [X]Other specified chronic obstructive pulmonary disease
 66043 Other chronic bronchitis

66058	[X]Other emphysema
67040	Other specified chronic obstructive pulmonary disease
68066	Other chronic bronchitis NOS
68662	Zonal bullous emphysema
70787	Atrophic (senile) emphysema
92955	Acute vesicular emphysema
93568	Very severe chronic obstructive pulmonary disease
96931	At risk of chronic obstructive pulmonary disease exacerbation
97800	COPD - enhanced services administration
	COPD structured smoking assessment declined - enh serv
98283	admin
	Refer COPD structured smoking assessment - enhanc serv
98284	admin
99948	COPD patient unsuitable for pulmonary rehab - enh serv admin
101042	Issue of chronic obstructive pulmonary disease rescue pack
102685	Chronic obstructive pulmonary disease 3 monthly review
103007	Chronic obstructive pulmonary disease 6 monthly review
103400	Referred for COPD structured smoking assessment
103494	History of chronic obstructive pulmonary disease
103558	Preferred place of care for next exacerbation of COPD
103758	Referral to COPD community nursing team
103760	COPD structured smoking assessment declined
104117	COPD self-management plan agreed
104169	COPD self-management plan review
104608	End stage chronic obstructive airways disease
	On COPD (chr obstruc pulmonary disease) supportv cre
104710	pathway
104985	On chronic obstructive pulmonary disease supprtv cre pathway
105457	Chronic obstructive pulmonary disease care pathway
106637	Seen in chronic obstructive pulmonary disease clinic
106945	Chronic obstructive pulmonary disease rescue pack declined
107877	Chronic obstructive pulmon dis wr self managem plan declined

Chronic pancreatitis

medcode	desc
1419	Chronic pancreatitis

Cerebrovascular disease

medcode	desc
504	Transient cerebral ischaemia
569	Infarction - cerebral
1298	CVA unspecified
1433	Transient ischaemic attack
1469	Stroke and cerebrovascular accident unspecified
1895	Transient cerebral ischaemia NOS
3149	Cerebral infarction NOS
3535	Intracerebral haemorrhage NOS
5051	Intracerebral haemorrhage

5185 Lateral medullary syndrome
 5363 CVA - cerebral artery occlusion
 5602 Cerebellar infarction
 5871 H/O: stroke
 6116 CVA - Cerebrovascular accident unspecified
 6155 Stroke due to cerebral arterial occlusion
 6228 Sequelae of stroke, not spec'd as h'morrhage or infarction
 6253 Stroke unspecified
 6960 CVA - cerebrovascular accid due to intracerebral haemorrhage
 7780 Left sided CVA
 7912 Pontine haemorrhage
 8443 Brain stem stroke syndrome
 8837 Cerebral arterial occlusion
 9985 Left sided cerebral infarction
 10504 Right sided cerebral infarction
 12833 Right sided CVA
 13564 Cerebellar haemorrhage
 13707 Stroke / transient ischaemic attack referral
 15019 Cerebral embolism
 15252 Brainstem infarction NOS
 15788 Transient cerebral ischaemia NOS
 16507 Intermittent cerebral ischaemia
 16517 Cerebral thrombosis
 17322 Cerebellar stroke syndrome
 18604 Stroke due to intracerebral haemorrhage
 18686 Stroke/CVA annual review
 18689 Middle cerebral artery syndrome
 19201 Right sided intracerebral haemorrhage, unspecified
 19348 [V]Personal history of stroke
 19354 Other transient cerebral ischaemia
 23671 Cerebral infarct due to thrombosis of precerebral arteries
 24446 Cerebral infarction due to embolism of precerebral arteries
 25615 Brainstem infarction
 26424 Infarction of basal ganglia
 27975 Cerebral infarction due to embolism of cerebral arteries
 28314 Left sided intracerebral haemorrhage, unspecified
 28914 Haemorrhagic stroke monitoring
 30045 External capsule haemorrhage
 30202 Intracerebral haemorrhage, intraventricular
 31060 Intracerebral haemorrhage in hemisphere, unspecified
 31595 Cortical haemorrhage
 31805 Other and unspecified intracranial haemorrhage
 33543 Cerebral infarctn due/unspcf occlusn or sten/cerebral artrs
 34135 H/O: CVA/stroke
 34758 Cerebral embolus
 36717 Cerebral infarction due to thrombosis of cerebral arteries
 39344 Cerebral infarct due cerebral venous thrombosis, nonpyogenic
 39403 Sequelae of cerebral infarction

40338	Internal capsule haemorrhage
40758	Cereb infarct due unsp occlus/stenos precerebr arteries
46316	Basal nucleus haemorrhage
48149	Sequelae of intracerebral haemorrhage
53745	[X]Other cerebral infarction
53810	[X]Other intracerebral haemorrhage
55247	Impending cerebral ischaemia
57315	Intracerebral haemorrhage, multiple localized
62342	Bulbar haemorrhage
63746	[X]Other transnt cerebral ischaemic attacks+related syndroms
66873	H/O: Stroke in last year
91627	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artr
92036	[X]Occlusion and stenosis of other cerebral arteries
94482	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
96630	[X]Intracerebral haemorrhage in hemisphere, unspecified
100639	Central post-stroke pain
101251	[V]Personal history of transient ischaemic attack
104505	Stroke initial post discharge review
104638	Ref multidisciplinary stroke function improvement declined
105100	Stroke 6 month review
105520	Admission to stroke unit
105738	Carotid territory transient ischaemic attack
107195	Stroke self-management plan agreed
107440	Lobar cerebral haemorrhage
107886	Stroke annual review

Deafnesss

medcode	desc
412	Hearing loss
467	Deafness
536	Sensorineural hearing loss
626	Ear fitting hearing aid
686	Deafness NOS
1151	Unspecified conductive hearing loss
1681	Unilateral deafness
1752	Presbycusis
1774	Partial deafness
2061	Unspecified perceptive hearing loss
2348	Perceptive deafness
2552	Noise induced deafness
2625	High frequency deafness
2876	[V]Fitting or adjustment of hearing aid
3171	Nerve deafness
3747	Deaf mutism, NEC
3912	Hearing aid provision
4035	Bilateral deafness
5016	Ear anomalies with hearing impairment
5149	O/E - very deaf

5967 Hearing difficulty
 6082 Unspecified sudden hearing loss
 6641 Deafness symptom
 6846 Neural hearing loss
 7085 O/E - conductive deafness
 7301 Mixed conductive and sensorineural hearing loss, bilateral
 7344 Fit hearing aid
 7825 O/E - perceptive deafness
 7891 HOH - Hard of hearing
 8033 Low frequency deafness
 8941 Conductive hearing loss
 9830 Hearing loss
 9882 Mixed hearing loss
 10112 Sensorineural hearing loss, bilateral
 10170 Hearing aid worn
 10367 Deafness
 10665 Congenital sensorineural deafness
 11619 Hearing aid provision
 12324 HL - Hearing loss
 12339 Deafness - traumatic - NOS
 12692 HI - Hearing impairment
 13113 O/E - significantly deaf
 13114 O/E - deaf
 13115 O/E - slightly deaf
 14805 Deafness
 14893 Rubella deafness
 14983 Mixed conductive and sensorineural deafness
 15723 [V]Problems with hearing
 15940 Noise-induced hearing loss
 16393 Perceptive hearing loss NOS
 16648 Chronic deafness
 17407 Difficulty using hearing aid
 17699 Deteriorating hearing
 18008 Hearing impairment
 18375 Uses hearing aid
 18520 Sensory hearing loss
 18945 Conductive hearing loss, bilateral
 19068 Hearing impaired
 19084 High frequency deafness
 19417 Does use hearing aid
 19666 Difficulty hearing
 19694 Insertn bone anchors subcutaneous bone anchored hearing aid
 20715 O/E - High tone deafness
 22102 Hard of hearing
 26539 O/E - completely deaf
 27901 Mix cond/sensneurl hear loss,unlat unrestrict hear/contrlat sd
 29191 Sensorineurl hear loss,unilat unrestrict hear/contralat side
 30206 Hearing aid procedure

30394	Checking hearing aid
31374	Deafness due to congenital anomaly NEC
31748	Conductive hearing loss due to disorder of middle ear
33583	Conductive hearing loss NOS
36660	Conductive hearing loss due to disorder of external ear
38563	Other specified forms of hearing loss
39022	Difficulty hearing with background noise
43581	Conduct hear loss,unilat+unrestric hearing on contralat side
44282	Low frequency deafness
45751	Conductive deafness
47440	Ototoxicity - deafness
	Conductive hearing loss due to disorder of tympanic
52758	membrane
53800	[X]Other specified hearing loss
54116	Combined perceptive hearing loss
58602	Provide head worn hearing aid
62906	Combined conductive hearing loss
69894	Central hearing loss
71827	[X]Deaf mutism, not elsewhere classified
94782	Conductive hearing loss due to disorder of inner ear
96245	Hearing impairment
96803	[V]Bone anchored hearing aid in situ
98253	Maternally inherited deafness

Dementia

medcode	desc
1350	Senile/presenile dementia
1916	Senile dementia
1917	Alzheimer's disease
4357	[X] Senile dementia NOS
4693	[X] Unspecified dementia
5931	H/O dementia
6578	[X]Vascular dementia
7323	Uncomplicated senile dementia
7572	Lewy body disease
7664	[X]Dementia in Alzheimer's disease
8195	[X]Alzheimer's dementia unspec
8634	Multi infarct dementia
8934	[X]Subcortical vascular dementia
9509	[X]Dementia in Parkinson's disease
9565	[X]Arteriosclerotic dementia
11136	Pick's disease
11175	[X]Multi-infarct dementia
11379	[X]Senile dementia,Alzheimer's type
12621	[X]Dementia in other diseases classified elsewhere
12710	Dementia annual review
15165	Presenile dementia
16797	Alzheimer's disease with early onset

18386 Senile dementia with paranoia
 19393 [X]Vascular dementia, unspecified
 19477 Arteriosclerotic dementia
 21887 Senile dementia with depression
 25386 Dementia in conditions EC
 25704 [X]Presenile dementia,Alzheimer's type
 26270 [X]Lewy body dementia
 26323 [X]Alcoholic dementia NOS
 27342 Alcoholic dementia NOS
 27677 Presenile dementia with depression
 27759 [X] Senile dementia, depressed or paranoid type
 28402 [X]Dementia in Pick's disease
 29386 [X]Dementia in Alzheimer's disease, unspecified
 29512 Senile degeneration of brain
 30032 Presenile dementia with paranoia
 30706 [X]Dementia in Alzheimer's dis, atypical or mixed type
 31016 [X]Mixed cortical and subcortical vascular dementia
 32057 Alzheimer's disease with late onset
 33707 Senile and presenile organic psychotic conditions
 34944 [X] Primary degenerative dementia NOS
 37014 [X]Dementia in Huntington's disease
 37015 Senile dementia with delirium
 38438 Presenile dementia NOS
 38678 [X]Dementia in Alzheimer's disease with late onset
 41089 Senile dementia with depressive or paranoid features NOS
 41185 [X]Dementia in human immunodef virus [HIV] disease
 42279 Arteriosclerotic dementia NOS
 42602 Uncomplicated presenile dementia
 43089 Uncomplicated arteriosclerotic dementia
 43292 Arteriosclerotic dementia with depression
 43346 [X]Primary degen dementia of Alzheimer's type, senile onset
 44674 Senile dementia with depressive or paranoid features
 46488 [X]Vascular dementia of acute onset
 46762 [X]Alzheimer's disease type 1
 48501 [X] Presenile dementia NOS
 49263 [X]Dementia in Alzheimer's disease with early onset
 49513 Presenile dementia with delirium
 53446 [X]Delirium superimposed on dementia
 54106 [X]Dementia in Creutzfeldt-Jakob disease
 54505 Other alcoholic dementia
 55023 Dementia monitoring
 55222 Language disorder of dementia
 55313 [X]Other vascular dementia
 55467 Arteriosclerotic dementia with paranoia
 55838 [X]Predominantly cortical dementia
 56912 Arteriosclerotic dementia with delirium
 59122 [X]Other Alzheimer's disease
 60059 [X]Primary degen dementia, Alzheimer's type, presenile onset

61528	[X]Alzheimer's disease type 2
62132	Drug-induced dementia
64267	[X]Dementia in other specified diseases classif elsewhere
68125	[X]Delirium not superimposed on dementia, so described
101999	[X]Dementia infantilis

Depression

medcode	desc
324	Depressive disorder NEC
543	[X]Depression NOS
595	Endogenous depression
655	Anxiety with depression
1055	Agitated depression
1131	Neurotic depression reactive type
1855	Psychotic reactive depression
1996	Depressed
2716	H/O: depression
3291	[X]Depressive disorder NOS
3292	[X]Recurrent depressive disorder
4323	Chronic depression
5879	Agitated depression
5987	[X] Reactive depression NOS
6482	Recurrent depression
6546	Endogenous depression first episode
6932	Endogenous depression - recurrent
7737	[X]Neurotic depression
7749	[X]Mild anxiety depression
7953	[X]Dysthymia
8851	[X]Recurrent episodes of depressive reaction
9183	Masked depression
9796	Symptoms of depression
10667	[X]Mild depression
10720	[X]Atypical depression
11055	[X]Schizoaffective disorder, depressive type
11252	[X]Major depression, recurrent without psychotic symptoms
11329	[X]Endogenous depression without psychotic symptoms
11913	[X]Mixed anxiety and depressive disorder
12099	[X]Severe depressive episode with psychotic symptoms
12122	Depression medication review
12399	Depression annual review
14709	Recurrent major depressive episodes, moderate
15099	Recurrent major depressive episode
16861	[X]Recurrent severe episodes of psychotic depression
19054	[X]Recurrent brief depressive episodes
19696	[X]Recurrent episodes of psychogenic depression
20785	[X]Post-schizophrenic depression
21887	Senile dementia with depression
22116	[X]Recurrent depressive disorder, currently in remission

23731 [X]Endogenous depression with psychotic symptoms
 24171 Recurrent major depressive episodes, severe, with psychosis
 25563 Recurrent major depressive episode NOS
 25697 Recurrent major depressive episodes, severe, no psychosis
 27491 Atypical depressive disorder
 27677 Presenile dementia with depression
 29342 Recurrent major depressive episodes, mild
 29520 [X]Recurrent depressive disorder, current episode moderate
 29784 [X]Recurrent depressive disorder, current episode mild
 30405 Depression interim review
 31757 [X]Recurr severe episodes/psychogenic depressive psychosis
 32841 Referral for guided self-help for depression
 32845 [X]Depressive conduct disorder
 [X]Recurr severe episodes/major depression+psychotic
 32941 symptom
 33469 [X]Recurr depress disorder cur epi severe without psyc sympt
 35274 [X]Schizoaffective psychosis, depressive type
 35671 Recurrent major depressive episodes, unspecified
 36616 [X]Monopolar depression NOS
 37764 [X]Recurrent severe episodes/reactive depressive psychosis
 41022 [X]Schizophreniform psychosis, depressive type
 42931 On depression register
 43292 Arteriosclerotic dementia with depression
 44300 [X]Recurrent depressive disorder, unspecified
 47009 [X]Recurrent depress disorder cur epi severe with psyc symp
 55384 Recurrent major depressive episodes, in full remission
 56273 Recurrent major depressive episodes,partial/unspec remission
 73991 [X]Vital depression, recurrent without psychotic symptoms
 98252 [X]Major depression, moderately severe
 98346 [X]Major depression, mild
 98414 [X]Major depression, severe without psychotic symptoms
 98417 [X]Major depression, severe with psychotic symptoms

Diabetes

medcode	desc
506	Non-insulin dependent diabetes mellitus
711	Diabetes mellitus
758	Type 2 diabetes mellitus
1038	Insulin dependent diabetes mellitus
1323	Diabetic retinopathy
1407	Insulin treated Type 2 diabetes mellitus
1549	Type 1 diabetes mellitus
1647	Insulin dependent diabetes mellitus
1682	Diabetes mellitus with ketoacidosis
1684	Diabetic on oral treatment
2340	Diabetic amyotrophy
2342	Diabetic neuropathy
2378	Diabetic - poor control

2471 Nephrotic syndrome in diabetes mellitus
 2475 Diabetic nephropathy
 2478 Brittle diabetes
 2986 Proliferative diabetic retinopathy
 3286 Proliferative diabetic retinopathy
 3550 Diabetic monitoring
 3837 Diabetic maculopathy
 4513 Non-insulin dependent diabetes mellitus
 5002 Diabetic polyneuropathy
 5884 NIDDM - Non-insulin dependent diabetes mellitus
 6125 Diabetic annual review
 6430 Attending diabetes clinic
 6509 Insulin dependent diabetes mellitus with retinopathy
 6791 Insulin dependent diabetes mellitus - poor control
 6813 H/O: diabetes mellitus
 7045 H/O: Admission in last year for diabetes foot problem
 7059 Admit diabetic emergency
 7069 Background diabetic retinopathy
 7328 Cellulitis in diabetic foot
 7563 Diabetic on diet only
 7795 Diabetes mellitus with neuropathy
 8403 Non-insulin dependent diabetes mellitus - poor control
 8842 Diabetic on insulin
 9013 Unstable diabetes
 9835 O/E - diabetic maculopathy present both eyes
 9881 Mixed diabetic ulcer - foot
 9974 Seen in diabetic eye clinic
 10098 Other specified diabetes mellitus with other spec comps
 10099 Advanced diabetic maculopathy
 10418 Type 1 diabetes mellitus with nephropathy
 10642 Dietary advice for diabetes mellitus
 10659 Diabetic cataract
 10692 Type 1 diabetes mellitus with ketoacidosis
 10755 Non proliferative diabetic retinopathy
 10824 Seen in diabetic foot clinic
 10977 Diabetic peripheral neuropathy screening
 11018 Diabetic retinopathy 12 month review
 11129 O/E - left eye background diabetic retinopathy
 11348 Excepted from diabetes qual indicators; informed dissent
 11433 O/E - right eye background diabetic retinopathy
 11471 Diabetes medication review
 11551 Diabetes mellitus induced by steroids
 11599 Pan retinal photocoagulation for diabetes
 11626 Diabetic retinopathy NOS
 11663 Neuropathic diabetic ulcer - foot
 11930 Under care of diabetes specialist nurse
 12213 Patient on maximal tolerated therapy for diabetes
 12307 Diabetes care by hospital only

12455 Type I diabetes mellitus
 12640 Type 2 diabetes mellitus with nephropathy
 12675 Diabetes: shared care programme
 12736 Type 2 diabetes mellitus with gangrene
 13067 Diabetic monitoring NOS
 13071 Diabetic - good control
 13097 O/E - right eye proliferative diabetic retinopathy
 13099 O/E - right eye preproliferative diabetic retinopathy
 13101 O/E - left eye proliferative diabetic retinopathy
 13102 O/E - right eye diabetic maculopathy
 13103 O/E - left eye preproliferative diabetic retinopathy
 13108 O/E - left eye diabetic maculopathy
 13192 Diabetes monitor. check done
 13279 Other specified diabetes mellitus with renal complications
 14803 Diabetes mellitus, adult onset, no mention of complication
 14889 Maturity onset diabetes
 15690 Diabetes mellitus with ketoacidotic coma
 16490 Diabetic treatment changed
 16491 Diabetes mellitus with polyneuropathy
 16502 Diabetes mellitus with renal manifestation
 17247 Diabetic mononeuritis NOS
 17262 Non-insulin-dependent diabetes mellitus with retinopathy
 17313 Diabetic iritis
 17545 Type I diabetes mellitus with diabetic cataract
 17858 Type 1 diabetes mellitus
 17859 Type 2 diabetes mellitus
 17869 Diabetic-uncooperative patient
 17886 Diabetic - follow-up default
 18142 Diabetic cheiroarthropathy
 18143 Type II diabetes mellitus with arthropathy
 18167 Annual diabetic blood test
 18209 Type 2 diabetes mellitus with renal complications
 18219 Type II diabetes mellitus
 18230 Type 1 diabetes mellitus with neuropathic arthropathy
 18264 Insulin treated Type II diabetes mellitus
 18278 Insulin treated Type 2 diabetes mellitus
 18387 Type 1 diabetes mellitus with retinopathy
 18390 Type 2 diabetes mellitus with persistent microalbuminuria
 18425 Type 2 diabetes mellitus with polyneuropathy
 18496 Type 2 diabetes mellitus with retinopathy
 18505 IDDM-Insulin dependent diabetes mellitus
 18642 Type 1 diabetes mellitus with arthropathy
 18683 Type 1 diabetes mellitus with ulcer
 18777 Type 2 diabetes mellitus with renal complications
 20900 Diabetes monitored
 21482 Diabetes mellitus with hyperosmolar coma
 21983 Type 1 diabetes mellitus with renal complications
 22023 Diabetic - poor control NOS

22487 Secondary diabetes mellitus
 22573 Diabetes mellitus NOS with neurological manifestation
 22871 Type 1 diabetes mellitus with exudative maculopathy
 22884 Type II diabetes mellitus
 22967 Retinal abnormality - diabetes related
 24423 Type I diabetes mellitus
 24458 Type II diabetes mellitus - poor control
 24490 Diabetes mellitus, juvenile type, no mention of complication
 24571 Asymptomatic diabetic neuropathy
 24693 Non-insulin dependent diabetes mellitus with arthropathy
 24694 Insulin dependent diabetes mellitus with mononeuropathy
 24836 Type 2 diabetes mellitus with nephropathy
 25591 Type 2 diabetes mellitus with exudative maculopathy
 25627 Type 2 diabetes mellitus - poor control
 26054 Type 2 diabetes mellitus with persistent proteinuria
 26108 Steroid induced diabetes mellitus without complication
 26664 O/E - Left diabetic foot at risk
 26666 O/E - Right diabetic foot at low risk
 26667 O/E - Left diabetic foot at low risk
 26855 Unstable insulin dependent diabetes mellitus
 27891 Diabetic Charcot arthropathy
 27921 Foot abnormality - diabetes related
 28574 Exception reporting: diabetes quality indicators
 28769 Diabetic on insulin and oral treatment
 28856 Transition of diabetes care options discussed
 28873 Diabetic 6 month review
 29041 Date diabetic treatment start
 29979 Non-insulin-dependent diabetes mellitus without complication
 30294 Type 1 diabetes mellitus with persistent microalbuminuria
 30323 Type 1 diabetes mellitus with persistent proteinuria
 31156 O/E - Left diabetic foot at moderate risk
 31157 O/E - Right diabetic foot at moderate risk
 31171 O/E - Right diabetic foot at high risk
 31172 O/E - Left diabetic foot at high risk
 31310 Insulin dependent diabetes maturity onset
 31790 Polyneuropathy in diabetes
 32403 Diabetes mellitus with gangrene
 32556 Diabetes with gangrene
 32627 Type 2 diabetes mellitus with ketoacidosis
 32739 Seen in community diabetes specialist clinic
 33254 Diabetes mellitus with ophthalmic manifestation
 33343 Diabetes mellitus with other specified manifestation
 33807 Diabetes mellitus, adult with gangrene
 33969 Malnutrition-related diabetes mellitus with ketoacidosis
 34152 Diabetic peripheral angiopathy
 34268 Type 2 diabetes mellitus with neurological complications
 34283 Diabetes mellitus NOS with ophthalmic manifestation
 34450 Hyperosmolar non-ketotic state in type 2 diabetes mellitus

34912 Non-insulin dependent diabetes mellitus with ulcer
 35105 Diabetes mellitus, adult onset, with renal manifestation
 35107 Diabetes mellitus with nephropathy NOS
 35116 O/E - Left diabetic foot - ulcerated
 35288 Type 1 diabetes mellitus - poor control
 35316 O/E - Right diabetic foot - ulcerated
 35383 Diabetic patient unsuitable for digital retinal photography
 35385 Type 2 diabetes mellitus with neuropathic arthropathy
 35399 Diabetes mellitus with peripheral circulatory disorder
 36633 Hyperosmolar non-ketotic state in type 2 diabetes mellitus
 36695 Diabetes mellitus autosomal dominant type 2
 37315 Diabetic mononeuropathy
 37648 Insulin treated non-insulin dependent diabetes mellitus
 37806 Type 2 diabetes mellitus with peripheral angiopathy
 37957 Type A insulin resistance
 38161 Type I diabetes mellitus with retinopathy
 38617 Other specified diabetes mellitus with ketoacidosis
 38986 Diabetes mellitus with no mention of complication
 39070 Type 1 diabetes mellitus with hypoglycaemic coma
 39317 Diabetes mellitus, adult onset, + neurological manifestation
 39406 Reaven's syndrome
 39420 Myasthenic syndrome due to diabetic amyotrophy
 39809 Insulin dependent diab mell with neuropathic arthropathy
 40023 Diabetes mellitus, juvenile type, with hyperosmolar coma
 40401 Non-insulin dependent diabetes mellitus with gangrene
 40682 Type 1 diabetes mellitus maturity onset
 40837 Type 1 diabetes mellitus with ketoacidotic coma
 40962 Non-insulin dependent d m with neuropathic arthropathy
 41049 Type 1 diabetes mellitus with retinopathy
 41389 Diabetes mellitus, adult onset, + ophthalmic manifestation
 41686 [X]Other specified diabetes mellitus
 41716 Insulin dependent diabetes mellitus with polyneuropathy
 42505 Diabetes mellitus NOS with ketoacidosis
 42567 Diabetes mellitus, juvenile type, with ketoacidotic coma
 42729 Type I diabetes mellitus with hypoglycaemic coma
 42762 Type 2 diabetes mellitus with retinopathy
 42831 Type 1 diabetes mellitus with neurological complications
 43139 Diabetes mellitus, adult onset, with hyperosmolar coma
 43227 Type II diabetes mellitus with multiple complications
 43453 Diabetes mellitus autosomal dominant
 43785 Non-insulin dependent diabetes mellitus with hypoglyca coma
 43857 Lipoatrophic diabetes mellitus
 43921 Unstable type 1 diabetes mellitus
 44033 Diabetic mononeuritis multiplex
 44260 Insulin dependent diabetes mellitus with diabetic cataract
 44440 Insulin dependent diabetes mellitus with hypoglycaemic coma
 44443 Insulin dependent diabetes mellitus with ulcer
 44779 Type 2 diabetes mellitus with diabetic cataract

44982 Type 2 diabetes mellitus with diabetic cataract
 45276 Insulin dependent diabetes mellitus with multiple complicat
 45467 Non-insulin dependent diabetes mellitus with polyneuropathy
 45491 Diabetes mellitus with unspecified complication
 45913 Type 2 diabetes mellitus - poor control
 45914 Type 1 diabetes mellitus - poor control
 45919 Type 2 diabetes mellitus with neurological complications
 46150 Type 2 diabetes mellitus with gangrene
 46290 Other specified diabetes mellitus with multiple comps
 46301 Type 1 diabetes mellitus with polyneuropathy
 46850 Type I diabetes mellitus - poor control
 46917 Type 2 diabetes mellitus with hypoglycaemic coma
 46963 Insulin-dependent diabetes mellitus with renal complications
 47315 Type II diabetes mellitus - poor control
 47321 Type 2 diabetes mellitus with ophthalmic complications
 47377 Other specified diabetes mellitus with ophthalmic complicatn
 47409 Type II diabetes mellitus with polyneuropathy
 47582 Type 1 diabetes mellitus with renal complications
 47584 Advanced diabetic retinal disease
 47649 Type 1 diabetes mellitus with ophthalmic complications
 47650 Type 1 diabetes mellitus with multiple complications
 47816 Type II diabetes mellitus with neuropathic arthropathy
 47954 Type 2 diabetes mellitus without complication
 48078 Acute painful diabetic neuropathy
 48192 Type II diabetes mellitus with diabetic cataract
 49074 Type 2 diabetes mellitus with ulcer
 49146 Type I diabetes mellitus with neurological complications
 49276 Insulin-dependent diabetes mellitus with ophthalmic comps
 49554 Type 1 diabetes mellitus with diabetic cataract
 49640 O/E - left chronic diabetic foot ulcer
 49655 Type II diabetes mellitus with retinopathy
 49869 Type 2 diabetes mellitus with arthropathy
 49884 Diabetic pre-pregnancy counselling
 49949 Unstable type I diabetes mellitus
 50225 Type II diabetes mellitus with renal complications
 50429 Non-insulin-dependent diabetes mellitus with ophthalm comps
 50527 Type II diabetes mellitus with polyneuropathy
 50609 Pre-existing diabetes mellitus, non-insulin dependent
 50813 Type II diabetes mellitus with mononeuropathy
 50937 Referral to diabetes preconception counselling clinic
 50960 Pre-existing diabetes mellitus, insulin dependent
 50972 Diabetes mellitus NOS with no mention of complication
 51261 Insulin dependent diabetes mellitus
 51697 Secondary pancreatic diabetes mellitus
 51756 Type 2 diabetes mellitus with ketoacidotic coma
 51957 Type I diabetes mellitus with ulcer
 52041 O/E - left eye stable treated prolifer diabetic retinopathy
 52104 Insulin dependent diabetes mellitus with multiple complicatn

52212 [X]Diabetes mellitus
 52303 Non-insulin-dependent diabetes mellitus with renal comps
 52630 O/E - sight threatening diabetic retinopathy
 53200 Diabetes mellitus, juvenile type, with ketoacidosis
 53392 Type II diabetes mellitus without complication
 54008 Type 1 diabetes mellitus with neuropathic arthropathy
 54212 Non-insulin-dependent d m with peripheral angiopath
 54600 Unstable insulin dependent diabetes mellitus
 54856 Diabetes mellitus, adult onset, with ketoacidosis
 54899 Type II diabetes mellitus with peripheral angiopathy
 55075 Type II diabetes mellitus with ulcer
 55239 Type 1 diabetes mellitus with gastroparesis
 55431 Pre-existing diabetes mellitus, unspecified
 55842 Non-insulin-dependent diabetes mellitus with neuro comps
 56268 Type II diabetes mellitus with hypoglycaemic coma
 56448 Insulin-dependent diabetes without complication
 56803 NIDDM with peripheral circulatory disorder
 56885 Type A insulin resistance without complication
 57278 Type II diabetes mellitus with renal complications
 57333 Diabetic cheiropathy
 57621 Insulin dependent diabetes mellitus with nephropathy
 58604 Type II diabetes mellitus with retinopathy
 59253 Type 2 diabetes mellitus with arthropathy
 59288 Other specified diabetes mellitus with coma
 59365 Non-insulin dependent diabetes mellitus with nephropathy
 59725 Type II diabetes mellitus with ophthalmic complications
 59903 Diabetic amyotrophy
 59991 Maturity onset diabetes in youth type 2
 60107 Unstable type I diabetes mellitus
 60208 Type I diabetes mellitus with neuropathic arthropathy
 60499 Insulin dependent diabetes mellitus with gangrene
 60699 Type 2 diabetes mellitus with peripheral angiopathy
 60796 Type II diabetes mellitus with persistent proteinuria
 61071 Type 2 diabetes mellitus with hypoglycaemic coma
 61122 Diabetes mellitus induced by non-steroid drugs
 61344 Type I diabetes mellitus with renal complications
 61523 Other specified diabetes mellitus with neurological comps
 61829 Type 1 diabetes mellitus with neurological complications
 62107 Type II diabetes mellitus with gangrene
 62146 Non-insulin-dependent diabetes mellitus with multiple comps
 62209 Type I diabetes mellitus with ketoacidosis
 62352 Type I diabetes mellitus with arthropathy
 62613 Type I diabetes mellitus without complication
 62674 Type 2 diabetes mellitus with mononeuropathy
 63017 Type I diabetes mellitus maturity onset
 63357 Diabetes mellitus, adult, + peripheral circulatory disorder
 63371 Diabetes mellitus, adult, + other specified manifestation
 63412 Diabetes clinical management plan

63690 Type 2 diabetes mellitus with gastroparesis
 63762 Diabetes mellitus, adult onset, + unspecified complication
 64283 Other specified diabetes mellitus with unspecified comps
 64357 Diabetes mellitus NOS with unspecified complication
 64446 Insulin dependent diab mell with peripheral angiopathy
 64449 Unspecified diabetes mellitus with multiple complications
 64571 Type II diabetes mellitus with nephropathy
 64668 Insulin treated Type II diabetes mellitus
 65025 Diabetes mellitus NOS with peripheral circulatory disorder
 65062 Diabetes mellitus NOS with ketoacidotic coma
 65267 Type 2 diabetes mellitus with multiple complications
 65463 High risk non proliferative diabetic retinopathy
 65616 Insulin dependent diabetes mellitus with arthropathy
 65704 Type 2 diabetes mellitus with ulcer
 66145 Type I diabetes mellitus with ketoacidotic coma
 66872 Type I diabetes mellitus with nephropathy
 66965 Type 2 diabetes mellitus with neuropathic arthropathy
 67212 DM induced by non-steroid drugs without complication
 67853 Diabetes mellitus, juvenile, + neurological manifestation
 67905 Type II diabetes mellitus with neurological complications
 68105 Type 1 diabetes mellitus with mononeuropathy
 68390 Type 1 diabetes mellitus with ulcer
 68792 Diabetes mellitus, juvenile type, + unspecified complication
 68843 Diabetes mellitus, adult onset, with ketoacidotic coma
 69278 Non-insulin depend diabetes mellitus with diabetic cataract
 69676 Type 1 diabetes mellitus without complication
 69748 Diabetes mellitus, juvenile type, + ophthalmic manifestation
 69993 Type 1 diabetes mellitus with gangrene
 70316 Type 2 diabetes mellitus with ophthalmic complications
 70448 Diabetes mellitus, juvenile +peripheral circulatory disorder
 70766 Type 1 diabetes mellitus with hypoglycaemic coma
 70821 Diabetes mellitus NOS with other specified manifestation
 Non-insulin dependent diabetes mellitus with
 72320 mononeuropathy
 72345 Diabetes mellitus NOS with hyperosmolar coma
 72702 Insulin dependent diabetes mellitus - poor control
 83532 Diabetes type 2 review
 85660 Diabetes type 1 review
 85991 Type II diabetes mellitus with persistent microalbuminuria
 91646 Type II diabetes mellitus with ulcer
 91942 Type I diabetes mellitus with multiple complications
 91943 Type I diabetes mellitus with polyneuropathy
 93380 Cystic fibrosis related diabetes mellitus
 93468 Type 1 diabetes mellitus with peripheral angiopathy
 93727 Type II diabetes mellitus with diabetic cataract
 93875 Insulin dependent diabetes mellitus with retinopathy
 93878 Type I diabetes mellitus with ulcer
 93922 Diabetes mellitus, juvenile type, with renal manifestation

94383 Secondary diabetes mellitus without complication
 95343 Type I diabetes mellitus with retinopathy
 95351 Type II diabetes mellitus with mononeuropathy
 95539 Maternally inherited diabetes mellitus
 95992 Type I diabetes mellitus without complication
 96235 Type I diabetes mellitus maturity onset
 96506 Secondary pancreatic diabetes mellitus without complication
 97446 Type 1 diabetes mellitus maturity onset
 97474 Unstable type 1 diabetes mellitus
 97894 Type I diabetes mellitus with exudative maculopathy
 98071 Insulin-dependent diabetes mellitus with ophthalmic comps
 98392 Maturity onset diabetes in youth type 1
 98616 Type II diabetes mellitus with neurological complications
 98704 Insulin dependent diabetes mellitus with ulcer
 98723 Type II diabetes mellitus with hypoglycaemic coma
 99231 Type I diabetes mellitus with mononeuropathy
 99311 Type I diabetes mellitus with ophthalmic complications
 99628 [X]Glomerular disorders in diabetes mellitus
 99716 Insulin dependent diabetes mellitus with hypoglycaemic coma
 99719 Insulin-dependent diabetes without complication
 100292 [X]Unspecified diabetes mellitus with renal complications
 100770 Insulin dependent diabetes mellitus with diabetic cataract
 100964 Type II diabetes mellitus with ophthalmic complications
 101311 Insulin dependent diabetes mellitus with polyneuropathy
 101735 Insulin-dependent diabetes mellitus with neurological comps
 102112 Type I diabetes mellitus with gangrene
 102163 Insulin dependent diabetes mellitus with nephropathy
 102201 Type II diabetes mellitus with nephropathy
 102611 Type 2 diabetic dietary review
 102620 Type I diabetes mellitus with persistent microalbuminuria
 102704 Type I diabetic dietary review
 102740 Type 1 diabetes mellitus with ophthalmic complications
 102946 Insulin-dependent diabetes mellitus with renal complications
 103902 Type II diabetes mellitus with arthropathy
 103935 No evidence of diabetic nephropathy
 104323 Type II diabetes mellitus with gangrene
 104453 Type 1 diabetic dietary review
 104639 Type II diabetes mellitus with peripheral angiopathy
 105337 Type I diabetes mellitus - poor control
 105740 O/E - Left diabetic foot at increased risk
 105741 O/E - Right diabetic foot at increased risk
 105784 Type 2 diabetes mellitus without complication
 106061 Type II diabetes mellitus with ketoacidotic coma
 106360 Erectile dysfunction due to diabetes mellitus
 106528 Type II diabetes mellitus with ketoacidosis
 106927 Diab insipidus, diab mell, optic atrophy and deafness
 107361 Education about diabetes and driving
 107452 Further diabetic monitoring

107603	Diabetes mellitus in remission
107701	Hyperosmolar non-ketotic state in type II diabetes mellitus
107824	Type II diabetes mellitus in remission
107881	Clinical diabetic nephropathy
108005	Type 2 diabetes mellitus with multiple complications
108007	Type I diabetes mellitus with multiple complications
108360	Type I diabetes mellitus in remission
108724	Type I diabetes mellitus with gastroparesis
109051	Insulin dependent diabetes mellitus with gangrene
109103	Type II diabetes mellitus without complication
109197	Type II diabetes mellitus with neuropathic arthropathy
109628	Type 1 diabetes mellitus in remission
109837	Type I diabetes mellitus with renal complications
109865	Type 2 diabetes mellitus with polyneuropathy
110400	Type 1 diabetes mellitus with diabetic cataract
110611	Type 2 diabetes mellitus in remission
110997	Diabetes mellitus, juvenile, + other specified manifestation
111106	Type 1 diabetes mellitus without complication

Diverticular disease

medcode	desc
347	Diverticulitis
1101	Diverticulosis of the colon
2044	Bleeding diverticulosis
2536	Diverticulosis of the large intestine NOS
3538	Diverticulosis of the duodenum
3593	Diverticulosis
5686	Diverticular abscess
5857	Diverticular disease
7662	Diverticulosis NOS
8322	Diverticula of intestine
9511	Diverticula of the intestine NOS
10437	Diverticulitis NOS
10483	Diverticulitis of the colon
12345	Diverticulitis of the duodenum
14942	Perforated diverticulum
17105	Divertic dis/both sml+lge intestin without perfor or abscess
19935	Diverticulitis unspecified
27444	Diverticulosis of the jejunum
31365	Diverticulitis of the small intestine unspecified
37588	Perforated diverticulum of duodenum
37813	Perforated diverticulum of colon
38941	Divertic disease/both sml+lge intestin with perforat+abscess
42866	Perforated diverticulum of ileum
44647	Diverticulosis of the ileum
47924	Diverticulosis of the small intestine unspecified
48173	Perforated diverticulum of jejunum
48589	Perforated diverticulum of large intestine unspecified

49066	Perforated diverticulum unspecified
49084	Diverticulosis unspecified
50313	Perforated diverticulum of large intestine NOS
51511	Diverticulitis of the large intestine unspecified
53092	Diverticulosis of the large intestine unspecified
61664	Diverticulitis of the ileum
61722	Diverticulitis of the jejunum
62979	Diverticulitis of the large intestine NOS
69918	Perforated diverticulum of intestine NOS
71130	Perforated diverticulum of small intestine unspecified
72590	Diverticulitis of the small intestine NOS
73334	Diverticulosis of the small intestine NOS
106340	Perforated diverticulum of small intestine NOS

Drug addiction

medcode	desc
689	Heroin dependence
1588	Misuse of drugs NOS
3519	Drug addiction
4564	[X]Heroin addiction
5105	Drug dependence
5203	Glue sniffing dependence
6111	Drug addictn therap-methadone
7496	Drug addiction therapy
8284	Cannabis type drug dependence
8490	Drug user
9024	Drug dependence therapy
9615	[X]Drug addiction NOS
10045	[X]Drug addiction-other stimul
10538	[X]Drug addiction - opioids
11746	[X]Drug addiction - cocaine
11840	Cocaine type drug dependence
14809	Combined drug dependence, excluding opioids
16243	Opioid type drug dependence
16374	Methadone dependence
20962	Episodic opioid dependence
21087	Ecstasy type drug dependence
21662	[X]Drug addiction - cannabis
21683	LSD dependence
22079	Injecting drug user
24441	Opioid drug dependence NOS
24616	Cannabis dependence, unspecified
24849	Drug addict notific to CMO
24998	Other specified drug dependence, continuous
25527	[X]Cold turkey, opiate withdrawal
25646	Amphetamine or psychostimulant dependence NOS
25670	Stimulant dependence
25748	Cocaine dependence, continuous

25808 Cocaine dependence, unspecified
 25925 Prolonged high dose use of cannabis
 26061 Combined opioid with other drug dependence
 28766 Persistent substance misuse
 28976 Drug addiction detoxification therapy - methadone
 29446 Drug dependence NOS
 29728 Drug addiction notification
 30251 Intravenous drug user
 30565 Failed heroin detoxification
 30679 Drug dependence home detoxification
 30694 Drug addiction maintenance therapy - methadone
 32653 Drug dependence self detoxification
 32804 Opium dependence
 32887 Hallucinogen dependence
 33462 Cannabis drug dependence NOS
 33585 [X]Drug addiction - solvent
 33774 Glue sniffing dependence, episodic
 33942 Cocaine drug dependence NOS
 34249 [X]Mental and behav dis due to use opioids: dependence syndr
 37316 Marihuana dependence
 37472 Amphetamine or psychostimulant dependence, unspecified
 38034 Unspecified opioid dependence
 38072 Glue sniffing dependence, unspecified
 38360 Amphetamine or psychostimulant dependence, continuous
 39836 Cocaine dependence, episodic
 40720 Hashish dependence
 40781 Other specified drug dependence NOS
 41473 Drug dependence in pregnancy, childbirth and the puerperium
 41476 Psychostimulant dependence
 42923 Cannabis dependence, continuous
 43075 Continuous opioid dependence
 44991 Cannabis dependence in remission
 45208 [X]Mental and behav dis mlti/oth psych sbs: dependence syndr
 46732 Stimulant abuse
 47784 [X]Drug addiction - hallucinogen
 49585 Amphetamine or psychostimulant dependence, episodic
 49618 Current drug user
 50302 [X]Mental and behav dis due to use cocaine: dependence syndr
 50778 Hypnotic or anxiolytic dependence, episodic
 51052 Drug addiction detoxification therapy - buprenorphine
 51197 Other specified drug dependence
 52794 Cannabis dependence, episodic
 52815 [X]Mental and behav dis due to vol solvents: dependence synd
 53678 Combined drug dependence, excluding opioid, continuous
 56194 Combined opioid with other drug dependence, unspecified
 [X]Mental and behav dis due to cannabinoids: dependence
 56504 synd
 58743 Drug addiction notif NOS

59184 Glue sniffing dependence NOS
 59676 Other specified drug dependence, unspecified
 60355 Methadone maintenance
 60372 Drug addict re-notif to CMO
 60985 Drug dependence home detoxification contraindicated
 62717 Combined drug dependence, excluding opioid, episodic
 63379 Drug dependence during pregnancy - baby delivered
 64265 Combined opioid with other drug dependence, continuous
 64277 Combined opioid with other drug dependence, episodic
 64500 Pregnancy and drug dependence
 65826 [X]Mental and behav dis due to hallucinogens: dependence syn
 65927 Drug addict-notify local SMR22
 67098 Drug dependence during pregnancy - baby not yet delivered
 68150 Hallucinogen dependence NOS
 69963 Drug addict re-notific due
 71086 Hallucinogen dependence, continuous
 72342 Combined drug dependence, excluding opioid, NOS
 72371 Lysergic acid diethylamide dependence
 72564 Other specified drug dependence, episodic
 72663 Substance misuse clinical management plan reviewed
 73448 Hallucinogen dependence, episodic
 73737 Combined opioid with other drug dependence NOS
 91260 Combined drug dependence, excluding opioid, unspecified
 92353 Hallucinogen dependence, unspecified
 93850 Referral to substance misuse service
 95460 Heroin maintenance
 Drug dependence during pregnancy/childbirth/puerperium
 96004 NOS
 96925 Heroin misuse
 97000 Drug injection behaviour
 97028 Illicit drug use
 97375 Glue sniffing dependence, continuous
 97578 Misuses drugs
 98221 Seen in substance misuse clinic
 98528 Long-term drug misuser
 98914 Drug addict
 100178 Admission to substance misuse detoxification centre
 100632 Methadone therapy
 101697 Notified addict
 102440 Amfetamine or psychostimulant dependence NOS
 103241 Shared care drug misuse treatment
 103726 Shares drug equipment
 103844 Sniffs drugs
 105104 Chases the dragon
 107355 Seen in drug misuse clinic
 107593 Smokes drugs through a pipe
 109077 Amfetamine or psychostimulant dependence, unspecified
 109558 Injects drugs subcutaneously

Dyspepsia

medcode	desc
257	Dyspepsia
290	Epigastric pain
542	[D]Epigastric pain
592	Oesophagitis
984	Gastro-oesophageal reflux
1327	Oesophageal reflux
2281	Acid reflux
2535	Reflux oesophagitis
3869	Psychogenic dyspepsia
5370	Hyperacidity
7104	Gastro-oesophageal reflux with oesophagitis
7623	Indigestion NOS
8697	Flatulent dyspepsia
15054	Acid reflux
16605	Oesophageal reflux with oesophagitis
16714	[X]Psychogenic dyspepsia
25610	Oesophageal reflux without mention of oesophagitis
43233	Undiagnosed dyspepsia
47048	Discharged from care of dyspepsia specialist nurse
64004	Under care of dyspepsia specialist nurse
88289	Referral to dyspepsia specialist nurse
109682	Functional dyspepsia
109725	Non-ulcer dyspepsia

Eating disorders

medcode	desc
605	Bulimia NOS
912	Anorexia
2135	Anorexia nervosa
4377	Bulimia (non-organic overeating)
6159	[X]Eating disorders
6583	Bulimia NOS
7743	Other and unspecified non-organic eating disorders
8027	H/O: anorexia nervosa
9581	Bulimia nervosa
11608	Compulsive eating disorder
30570	Anorexia nervosa
32892	Non-organic eating disorder NOS
33863	Atypical bulimia nervosa
34929	Atypical anorexia nervosa
53746	Anorexia NOS

Epilepsy

medcode	desc
573	Epilepsy

988 Grand mal (major) epilepsy
 1715 Epileptic absences
 2907 Petit mal (minor) epilepsy
 3175 Temporal lobe epilepsy
 3607 Fit (in known epileptic) NOS
 4093 Status epilepticus
 4109 Traumatic epilepsy
 4602 Nocturnal epilepsy
 4801 Epileptic seizures - myoclonic
 5117 Grand mal status
 5152 Epileptic seizures - tonic
 5525 Focal epilepsy
 6271 Status epilepticus, unspecified
 6709 [X]Epileptic psychosis NOS
 6983 Epilepsy monitoring
 8187 Tonic-clonic epilepsy
 9747 Epilepsy NOS
 9886 Petit mal status
 9979 Other forms of epilepsy NOS
 11186 Generalised nonconvulsive epilepsy
 11394 Complex partial epileptic seizure
 13220 Epilepsy control poor
 17399 Juvenile absence epilepsy
 18471 Epileptic seizures - clonic
 19550 Epilepsy control good
 19551 Epilepsy care arrangement
 19552 Epilepsy does not limit activities
 20566 Epilepsy treatment stopped
 22341 Epilepsy confirmed
 22804 Tonic-clonic epilepsy
 22991 Epilepsy severity
 24309 Epileptic seizures - atonic
 25330 Complex partial status epilepticus
 26015 Partial epilepsy without impairment of consciousness
 26144 Generalised convulsive epilepsy
 26512 Epilepsy treatment changed
 26619 Epilepsy limits activities
 26620 Epilepsy restricts employment
 26733 Partial epilepsy without impairment of consciousness OS
 27526 Partial epilepsy without impairment of consciousness NOS
 30604 Alcohol-induced epilepsy
 30635 Photosensitive epilepsy
 30816 Drug-induced epilepsy
 31830 Epileptic seizures - akinetic
 31920 Partial epilepsy with impairment of consciousness NOS
 32288 Partial epilepsy with impairment of consciousness
 34079 Epileptic automatism
 34792 Lennox-Gastaut syndrome

36203	Psychosensory epilepsy
37592	Somatosensory epilepsy
37644	Progressive myoclonic epilepsy
38307	Other forms of epilepsy
38919	Transient epileptic amnesia
40105	Simple partial epileptic seizure
40806	Generalised convulsive epilepsy NOS
43679	[X]Acquired aphasia with epilepsy [Landau - Kleffner]
44252	Generalised nonconvulsive epilepsy NOS
45927	Other specified generalised convulsive epilepsy
46603	Emergency epilepsy treatment since last appointment
48134	Sensory induced epilepsy
50012	Epilepsy associated problems
50702	Epilepsy prevents employment
53483	Gelastic epilepsy
55260	Cursive (running) epilepsy
55665	Limbic system epilepsy
55739	Visual reflex epilepsy
56359	Menstrual epilepsy
59120	[X]Other status epilepticus
59185	Other specified generalised nonconvulsive epilepsy
63826	Unverricht - Lundborg disease
65673	Stress-induced epilepsy
65699	Motor epilepsy
68946	Unilateral epilepsy
69831	[X]Other epilepsy
71719	Kojevnikov's epilepsy
71801	[X]Status epilepticus, unspecified
73542	Visceral reflex epilepsy
98870	Partial epilepsy with autonomic symptoms
100652	Contraceptive advice for patients with epilepsy
100920	Pre-conception advice for patients with epilepsy
101143	Contraceptiv advice for patients with epilepsy not indicated
102359	Pregnancy advice for patients with epilepsy

Hypertension

medcode	desc
204	Hypertensive disease
351	High blood pressure
799	Essential hypertension
1894	Benign essential hypertension
2666	H/O: hypertension
3425	On treatment for hypertension
3712	Hypertension NOS
4372	Systolic hypertension
4444	Hypertension monitoring
7057	Hypertensive disease NOS
7329	Secondary hypertension

8732	BP - hypertensive disease
10818	Essential hypertension NOS
11056	Patient on maximal tolerated antihypertensive therapy
12680	Hypertension clinical management plan
13186	Hypertension monitoring
13188	Hypertensive treatm.changed
15377	Malignant essential hypertension
16059	Secondary hypertension NOS
16565	Good hypertension control
18057	Antihypertensive therapy
18482	Hypertension six month review
18590	Moderate hypertension control
18765	Other specified hypertensive disease
19070	Hypertension annual review
25371	Secondary benign renovascular hypertension
27511	Poor hypertension control
31387	Secondary renovascular hypertension NOS
31755	Secondary malignant hypertension
34744	Hypertension secondary to endocrine disorders
42229	Secondary hypertension NOS
51635	Secondary benign hypertension NOS
57288	Secondary benign hypertension
59383	Secondary benign renovascular hypertension
69753	[X]Hypertensive diseases
73293	Secondary malignant hypertension NOS
83473	Diastolic hypertension
97533	[X]Hypertension secondary to other renal disorders
99259	Trial reduction of antihypertensive therapy
102406	Hypertension 9 month review
102458	[X]Other secondary hypertension
105274	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105316	Stage 1 hypertension
105371	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105480	Hypertension resistant to drug therapy
105487	Severe hypertension
105989	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
107704	Primary hypertension
	Stage 1 hyperten (NICE 2011) without evidnce end organ
108136	damge
109771	Telehealth hypertension monitoring
109797	Stage 1 hyperten (NICE 2011) with evidnce end organ damge

Inflammatory bowel disease

medcode	desc
593	Crohn's disease
704	Ulcerative colitis
1784	Ulcerative colitis and/or proctitis
5133	Idiopathic proctocolitis

6538	Crohn's colitis
6650	Ulcerative proctocolitis
8347	Ulcerative proctitis
9359	Crohn's disease of the small bowel NOS
11286	Regional enteritis - Crohn's disease
15207	Idiopathic proctocolitis NOS
15773	Regional ileocolitis
20688	Crohn's disease of the large bowel NOS
22516	Exacerbation of ulcerative colitis
23950	Mucous colitis and/or proctitis
24550	Other idiopathic proctocolitis
24858	Ulcerative rectosigmoiditis
28476	Crohn's disease of the terminal ileum
29616	Orofacial Crohn's disease
30433	Ulcerative (chronic) enterocolitis
33456	Ulcerative proctocolitis NOS
36913	Exacerbation of Crohn's disease of small intestine
39037	Exacerbation of Crohn's disease of large intestine
39278	Crohn's disease of the ileum NOS
42822	Ulcerative (chronic) ileocolitis
43090	Other idiopathic proctocolitis NOS
44426	Regional enteritis of the large bowel
48732	Ulcerative ileocolitis
51576	Regional enteritis of the small bowel
51578	Granulomatous enteritis
52449	Regional enteritis NOS
53743	[X]Other ulcerative colitis
59994	Crohn's disease NOS
62628	Regional enteritis of the colon
63036	Regional enteritis of the jejunum
64773	Regional enteritis of the rectum
66238	Crohn's disease of the ileum unspecified
69959	[X]Other Crohn's disease
71945	Regional enteritis of the duodenum
104259	Ulcerative pancolitis

Irritable bowel syndrome

medcode	desc
451	irritable bowel syndrome
923	irritable colon - IBS
30630	History of irritable bowel syndrome

Learning disability

medcode	desc
302	Moderate mental retardation, IQ in range 35-49
1278	Imbecile
1362	Mental retardation
1543	Down's syndrome - trisomy 21

1680 Educationally subnormal
 1787 Mild mental retardation, IQ in range 50-70
 4477 [X]Learning disability NOS
 4825 Severe mental retardation, IQ in range 20-34
 6123 [X]Moderate mental retardation
 6516 [X]Developmental disorder of scholastic skills, unspecified
 7226 Pervasive developmental disorders
 10628 Fragile X chromosome
 10759 Down's syndrome NOS
 16855 [X]Learning disorder NOS
 18415 Trisomy 21
 19436 Learning disability
 22760 On learning disability register
 23489 Mongolism
 27691 [X]Severe mental subnormality
 28740 [X]Mild mental retardation
 28962 [X]Mental retardation
 32603 Fragile X syndrome
 [X]Unsp mental retardation without mention impairment
 32820 behav
 33949 [X]Mild mental subnormality
 34174 Mental retardation with autistic features
 34734 [X]Moderate mental subnormality
 36143 [X]Severe mental retardation
 37867 Mental retardation NOS
 37887 [X]Mental deficiency NOS
 37911 [X]Mental subnormality NOS
 39016 [X]Mild mental retardation, other impairments of behaviour
 39412 [X]Mld mental retard sig impairment behav req attent/treatmt
 42520 [X]Other mental retardation, other impairments of behaviour
 42589 [X]Unspecified mental retardation
 [X]Unsp mental retard with statement no or min impair
 42886 behav
 44327 Pervasive developmental disorder, unspecified
 45133 Profound mental retardation with IQ less than 20
 46504 [X]Mld mental retard with statement no or min impair behav
 47948 Other pervasive developmental disorders
 50606 [X]Mild mental retardation without mention impairment behav
 50751 [X]Sev mental retard sig impairment behav req attent/treatmt
 50947 [X]Sev mental retard with statement no or min impair behav
 51268 [X]Profound mental retardation
 52602 Overactive disorder assoc mental retard/stereotype movts
 54179 Other specified mental retardation NOS
 [X]Mod mental retard sig impairment behav req
 54881 attent/treatmt
 55560 [X]Sev mental retardation without mention impairment behav
 55848 [X]Severe mental retardation, other impairments of behaviour
 56547 [X]Oth mental retard sig impairment behav req attent/treatmt

56577	Other specified mental retardation
57199	Other specified mental retardation
59407	[X]Mod retard oth behav impair
	[X]Prfnd mental retardation without mention impairment
60062	behav
	[X]Mod mental retardation without mention impairment
60473	behav
	[X]Mod mental retard with statement no or min impairm
60913	behav
61627	Trisomy 21 NOS
	[X]Other mental retardation without mention impairment
63273	behav
65468	[X]Profound mental subnormality
66383	[X]Unspecified mental retardatn, other impairments of behav
66783	[X]Unsp mentl retard sig impairment behav req attent/treatmt
70008	[X]Oth mental retard with statement no or min impairm behav
	[X]Profound ment retrd wth statement no or min impairm
70102	behav
71196	[X]Other mental retardation
90276	[X]Profound mental retardation, other impairments of behavr
98100	[X]Profound ment retard sig impairmnt behav req attent/treat
98293	[X]Severe learning disability
98342	[X]Moderate learning disability
99774	[X]Mild learning disability
100648	[X]Profound learning disability
107968	[X]Specific learning disability

Malabsorption

medcode	desc
1515	Coeliac disease
2678	Fat intolerance NEC
3509	Gluten enteropathy
3626	Food intolerance NEC
4787	Steatorrhea - idiopathic
5088	Other gastrointestinal tract malabsorption NOS
6663	Other intestinal malabsorption
7790	Cow's milk intolerance
9355	Intestinal malabsorption
9741	Villous atrophy
10203	Pancreatic steatorrhoea
11916	Soya protein intolerance
11934	Malabsorption syndrome NOS
12217	Gluten intolerance
16019	Protein-losing enteropathy
16365	Sprue - nontropical
17374	Milk intolerance NEC
21565	Chronic steatorrhoea
23498	Blind loop syndrome

29513	Malabsorption due to intolerance to fat
31392	Intestinal malabsorption of fat
31419	Malabsorption - iron
31471	Tropical sprue
37440	Postsurgical malabsorption - other
42715	Intestinal malabsorption NOS
44310	Coeliac disease NOS
49191	Intestinal malabsorption of protein
49739	Intestinal malabsorption of carbohydrate
50718	Partial villous atrophy
52278	Post gastrointestinal tract surgery hypoglycaemia
57647	Post gastrointestinal tract surgery malnutrition
57966	Gee - Herter disease
62397	Congenital coeliac disease
63195	Acquired coeliac disease
68113	Postsurgical nonabsorption NOS
68680	Coeliac rickets
72885	Other postsurgical nonabsorption
97008	Non-coeliac gluten sensitivity
97144	Non-coeliac gluten intolerance

Multiple sclerosis

medcode	desc
684	Multiple sclerosis
2298	Exacerbation of multiple sclerosis
3440	Disseminated sclerosis
20493	Multiple sclerosis NOS
23730	Generalised multiple sclerosis
40344	Multiple sclerosis of the brain stem
43232	Multiple sclerosis multidisciplinary review
44985	Multiple sclerosis review
50161	Multiple sclerosis care plan agreed
69886	Multiple sclerosis of the spinal cord
95864	Management of multiple sclerosis in stable disability phase
95972	Relapsing and remitting multiple sclerosis
96246	Secondary progressive multiple sclerosis
96291	Benign multiple sclerosis
96607	Primary progressive multiple sclerosis
97487	Management of multiple sclerosis in early disease phase
98521	Management of multiple sclerosis in palliative phase
98835	Management of multiple sclerosis in onset phase

Obesity

medcode	desc
430	Obesity
3176	Has seen dietician - obesity
8854	Morbid obesity
10728	Dietary advice for obesity

11401	Simple obesity NOS
11461	Obesity monitoring
13278	Body mass index 30+ - obesity
17444	Reason for obesity therapy - occupational
17477	[V]Dietary counselling in obesity
22695	Central obesity
25968	Generalised obesity
38059	Extreme obesity with alveolar hypoventilation
38632	Treatment of obesity started
38658	Initial obesity assessment
38799	Obesity due to excess calories
40153	Obesity monitoring NOS
47439	Obesity monitoring check done
52735	Obesity monitoring admin.NOS
52782	[X]Obesity and other hyperalimentation
64712	Treatment of obesity changed
66406	Obesity and other hyperalimentation
67516	Refuses obesity monitoring
69757	[X]Other obesity
70898	Obesity and other hyperalimentation NOS
103574	Obesity hypoventilation syndrome
104129	Adult-onset obesity
104421	Lifelong obesity
108147	Referral to multidisciplinary obesity clinic
108478	Obese class III (BMI equal to or greater than 40.0)
108610	Obese class II (body mass index 35.0 - 39.9)
108694	Obese class I (body mass index 30.0 - 34.9)
110415	Obesity multidisciplinary case review

Renal failure

medcode	desc
2994	Peritoneal dialysis
2996	Haemodialysis NEC
6712	End stage renal failure
11773	Dialysis for renal failure
20073	Renal dialysis
30756	Continuous ambulatory peritoneal dialysis
31549	Compensation for renal failure
48022	Other specified compensation for renal failure
53852	End stage renal failure
64636	Compensation for renal failure NOS
64828	Peritoneal dialysis NEC
71124	Haemofiltration
88597	Automated peritoneal dialysis
101756	Thomas intravascular shunt for dialysis
105151	Chronic kidney disease stage 5

Rheumatoid and connective tissue disorders

medcode	desc
476	psoriatic arthropathy
844	Rheumatoid arthritis
1408	Polymyalgia rheumatica
2667	discoid lupus erythematosus
3944	Chronic post-rheumatic arthropathy
4125	Lupus erythematosus
4186	Juvenile rheumatoid arthritis - Still's disease
4578	Sero negative arthritis
4908	Dermatomyositis
5723	Rheumatoid nodule
6639	H/O: rheumatoid arthritis
6916	Seronegative rheumatoid arthritis
7196	Other juvenile arthritis
7522	Lupus erythematosus NOS
7871	Systemic lupus erythematosus
8350	Flare of rheumatoid arthritis
9707	Seropositive erosive rheumatoid arthritis
12019	Seropositive rheumatoid arthritis, unspecified
12500	Psoriatic arthropathy NOS
15511	Polymyositis
17412	Rheumatoid arthrit. monitoring
17675	CREST syndrome
18155	Rheumatoid bursitis
20615	Inflammatory polyarthropathy
21358	Rheumatoid arthritis of shoulder
21533	Pauciarticular juvenile rheumatoid arthritis
23552	Felty's syndrome
23833	other specified inflammatory polyarthropathy NOS
23834	adult Still's disease
24747	Inflammatory polyarthropathy NOS
25020	Unspecified polyarthropathy or polyarthritis
25390	subacute cutaneous lupus erythematosus
26368	Psoriasis spondylitica
27557	Juvenile rheumatoid arthritis NOS
27603	Rheumatoid arthritis and other inflammatory polyarthropathy
28316	Dermatopolymyositis, unspecified
28417	Systemic sclerosis
28456	Juvenile arthritis in psoriasis
28853	Fibrosing alveolitis associated with rheumatoid arthritis
30548	Rheumatoid vasculitis
31054	Rheumatoid arthritis - multiple joint
31181	Juvenile seronegative polyarthritis
31209	Myopathy due to rheumatoid arthritis
31360	Juvenile rheumatoid arthritis
31724	Rheumatoid lung
32001	Adult-onset Still's disease
32649	Juvenile dermatomyositis

34880 Inflammatory spondylopathies
 36276 Monarticular juvenile rheumatoid arthritis
 36597 Other specified inflammatory polyarthropathy
 37418 Fibromyositis
 37431 Rheumatoid arthropathy + visceral/systemic involvement NOS
 41941 Rheumatoid arthritis of PIP joint of finger
 42299 Rheumatoid arthritis of MCP joint
 42405 Juvenile ankylosing spondylitis
 43816 Rheumatoid carditis
 44141 Progressive systemic sclerosis
 44203 Other rheumatoid arthritis of spine
 44743 Rheumatoid arthritis of cervical spine
 46436 Rheumatoid lung disease
 46622 Pauciarticular onset juvenile chronic arthritis
 47831 Acute polyarticular juvenile rheumatoid arthritis
 48832 Rheumatoid arthritis of wrist
 49067 Rheumatoid arthritis of hip
 49227 Other rheumatoid arthropathy + visceral/systemic involvement
 49787 Rheumatoid myocarditis
 50644 Juvenile rheumatoid arthropathy unspecified
 50863 Rheumatoid arthritis of knee
 51238 Rheumatoid arthritis of 1st MTP joint
 51239 Rheumatoid arthritis of ankle
 53621 Rheumatoid nodule
 56202 [X]Seropositive rheumatoid arthritis, unspecified
 56838 Caplan's syndrome
 59658 Community DMARD monitoring appointment
 59738 Rheumatoid arthritis of elbow
 62401 Polyneuropathy in rheumatoid arthritis
 63198 Rheumatoid arthritis of DIP joint of finger
 63365 Rheumatoid arthritis of distal radio-ulnar joint
 70221 [X]Other specified rheumatoid arthritis
 70658 Rheumatoid arthritis of talonavicular joint
 71083 Juvenile arthritis in ulcerative colitis
 71784 Rheumatoid arthritis of other tarsal joint
 73619 Rheumatoid arthritis of subtalar joint
 93715 [X]Other seropositive rheumatoid arthritis
 94854 Other juvenile arthritis
 96202 seen in GP DMARD monitoring clinic
 96880 Psoriatic arthritis
 99414 Rheumatoid arthritis of lesser MTP joint
 100187 Disease activity score in rheumatoid arthritis
 100776 Rheumatoid arthritis of sacro-iliac joint
 100789 Seen in community DMARD monitoring clinic
 100914 Rheumatoid arthritis of acromioclavicular joint
 102088 Delivery of rehabilitation for rheumatoid arthritis
 103829 Disease activity score 28 joint in rheumatoid arthritis
 105507 Rheumatoid arthritis annual review

106440	[X]Rheumatoid arthritis+involvement/other organs or systems
107112	Rheumatoid arthritis of IP joint of toe
107791	Rheumatoid arthritis of tibio-fibular joint
107963	Rheumatoid arthritis of sternoclavicular joint

Tuberculosis

medcode	desc
635	Pulmonary tuberculosis
1840	Tuberculosis
2193	Tuberculosis of intestines, peritoneum and mesenteric glands
2208	Tuberculosis of hip
3273	Tuberculosis of vertebral column - Pott's
3303	Tuberculosis of kidney
3596	Tuberculosis of bones and joints
3720	Tuberculous - cervical lymphadenitis
3830	Tuberculosis of bladder
4256	Tuberculosis of peripheral lymph nodes
4621	Tuberculosis lichenoides
4907	Tuberculosis limb bones - Tuberculous dactylitis
5101	Tuberculous adenitis
5145	Tuberculosis of hilar lymph nodes
7133	Respiratory TB not confirmed bact or histologically
9953	Tuberculous pneumonia
11975	Tuberculous meningitis
12448	Tuberculous endometritis
14913	Tuberculous hydrothorax
15158	Tuberculosis NOS
15693	Tuberculous bronchiectasis
16265	Primary tuberculous complex
16331	Tuberculosis of lung with cavitation
16367	Tuberculosis - lupus vulgaris
16414	Miliary tuberculosis
16741	Tuberculous fibrosis of lung
17153	Tuberculous mastoiditis
18950	Other specified pulmonary tuberculosis
19652	Tuberculous episcleritis
20333	Tuberculous laryngitis
22011	Primary tuberculous infection
22572	Tuberculous osteomyelitis
23451	Tuberculosis of knee
23472	Tuberculous pleurisy
23940	Renal tuberculosis
23962	Bazin's disease - erythema induratum - TB hypersensitivity
24413	TB lung confirm sputum microscopy with or without culture
24517	Primary respiratory TB confirm bact and histologically
24626	Tuberculous arthritis
26344	Tuberculosis of peripheral lymph nodes NOS
27399	Tuberculosis of epididymis

29482 Tuberculosis of mesenteric lymph glands
 30358 Tuberculous keratoconjunctivitis
 30687 Tuberculosis of skin and subcutaneous tissue NOS
 30945 Tuberculosis of testis
 31349 Fallopian tube tuberculosis
 31409 Tuberculous peritonitis
 31436 Tuberculosis of small intestine
 31445 Tuberculosis verrucosa cutis
 31670 Resp TB bacteriologically and histologically confirmed
 31680 Tuberculous myelitis
 31844 Acute miliary tuberculosis of a single specified site
 32459 Other specified miliary tuberculosis
 33372 Other gastrointestinal tract tuberculosis NOS
 34430 Other specified tuberculosis
 34640 Tuberculous erythema nodosum
 34657 Tuberculosis of other urinary organs
 35443 Tuberculous pleurisy, conf bacteriologically/histologically
 35760 Tuberculosis of adrenal glands - Addison's disease
 37329 Tuberculous chorioretinitis
 37422 Tuberculosis of genitourinary system
 37492 Tuberculosis - lupus NOS
 37598 Tuberculosis of mediastinum
 37694 Primary tuberculous infection NOS
 37834 Tuberculosis of pleura
 37886 Tuberculosis of other specified bones
 38110 Pulmonary tuberculosis NOS
 38342 Tuberculous chronic iridocyclitis
 38920 Tuberculous salpingitis
 39279 Tuberculosis of large intestine
 39512 Tuberculous empyema
 40231 Tuberculosis pericardium
 40522 Scrofula - tuberculous cervical lymph nodes
 40605 Prim respiratory TB without mention of bact or hist confirm
 41051 Tuberculosis lung bact and histological examin not done
 41208 Tuberculosis of meninges and central nervous system
 41383 Other specified tuberculosis of central nervous system
 42201 Tuberculosis of other specified joint
 42479 Acute miliary tuberculosis of multiple sites
 42630 Other primary progressive tuberculosis
 43791 Tuberculous meningoencephalitis
 43976 Tuberculosis of eye
 44039 Tuberculosis of larynx, trachea & bronchus conf bact/hist'y
 44128 Tuberculosis of bones or joints NOS
 44129 Tuberculosis of mediastinal lymph nodes
 44573 Tuberculosis with erythema nodosum hypersensitivity reaction
 44655 TB intrathoracic lymph nodes confirm bact histologically
 45318 Tuberculous synovitis
 45861 Tuberculosis of nasal sinus

45932 Tuberculosis of other organs NOS
 46019 Tuberculosis of stomach
 46039 Tuberculoma of spinal cord
 46044 Tuberculous abscess of spinal cord
 46147 Tuberculosis of liver
 46272 Tuberculous pleurisy in primary progressive tuberculosis
 46383 Tuberculosis of other specified organs NOS
 46675 Lupus - tuberculous
 46727 Tuberculosis of other specified organs
 46802 Tuberculosis of spinal meninges
 46926 Tuberculosis of intrathoracic lymph nodes NOS
 47336 Lung tuberculosis
 47430 Tuberculosis - scrofuloderma
 47832 Tuberculosis of lung, bacteriologically & histolog'y neg
 47881 Tuberculosis of skin and subcutaneous tissue
 48580 Nodular lung tuberculosis
 49112 Tuberculous cervicitis
 49235 Tuberculous pyelonephritis
 49433 Tuberculosis of retroperitoneal lymph nodes
 49481 Tuberculosis seminal vesicle
 49503 Tuberculosis of tracheobronchial lymph nodes
 50147 Other specified respiratory tuberculosis NOS
 50261 Genitourinary tuberculosis NOS
 50489 Tuberculosis of urinary tract
 50837 Tuberculous pyelitis
 50869 Tuberculosis myocardium
 50902 Other specified respiratory tuberculosis
 51110 Scrofulous tuberculous abscess
 52199 Tuberculoma of brain
 52272 Tuberculous nephropathy
 53331 Miliary tuberculosis NOS
 53473 Isolated tracheal or bronchial tuberculosis NOS
 53548 Tuberculosis of ureter
 53701 Infiltrative lung tuberculosis
 54570 Other gastrointestinal tract tuberculosis
 54579 Tuberculosis of gastrointestinal tract NOS
 54840 Tuberculosis of cerebral meninges
 55629 Tuberculous interstitial keratitis
 55835 Tuberculosis of other organs
 56670 Tuberculosis oesophagus
 56833 Erythema nodosum with tuberculosis NOS
 56890 Tuberculous pleurisy NOS
 57398 Tuberculous abscess of brain
 57417 Tuberculoma of meninges
 57466 Tuberculous oophoritis or salpingitis
 58588 Tuberculosis of lung, confirmed by unspecified means
 58673 Tuberculosis of ear
 58827 Tuberculosis of intrathoracic lymph nodes

59087	Tuberculosis of rectum
59202	Tuberculous encephalitis or myelitis
60040	Tuberculosis of prostate
62033	Tuberculosis papulonecrotica
62468	Tuberculosis of bronchus
62530	Tuberculosis of lung, confirmed histologically
63351	Tuberculosis cutis
63796	Tuberculous oophoritis or salpingitis NOS
63959	Other respiratory tuberculosis
66441	Tuberculous pneumothorax
66584	Tuberculosis of other female genital organs
66976	Tuberculosis spleen
67292	Tuberculosis of kidney NOS
67637	Tuberculosis - lupus exedens
68821	Tuberculosis of other male genital organs
68973	Tuberculosis of other female genital organs NOS
69154	Tuberculosis of other male genital organs NOS
69260	Isolated tracheal or bronchial tuberculosis
69322	Tuberculous meningitis NOS
69471	Resp TB unspcf,w/out mention/bacterial or histol confrmtn
70140	Tuberculosis of central nervous system NOS
70491	Tuberculosis of eye NOS
72008	Acute miliary tuberculosis
72072	Tuberculous encephalitis or myelitis NOS
72402	Tuberculosis of nasopharynx
72743	Tuberculous oophoritis
73590	Tuberculosis of thyroid gland
93015	Isolated tracheal tuberculosis
93071	Tuberculosis of lung, confirmed by culture only
93360	Tuberculous encephalitis
93948	Isolated bronchial tuberculosis
96668	Tuberculosis endocardium
97658	Tuberculosis of nasal septum
110373	Disseminated tuberculosis
111299	Multidrug resistant tuberculosis

Thyroid disease

medcode	desc
273	Hypothyroidism
677	Thyrotoxicosis
1472	Hyperthyroidism
1619	Myxoedema
1882	Disorders of thyroid gland
3290	Acquired hypothyroidism
3436	Hashimoto's disease
3857	Aytiunnyne thyroiditis
3941	Hypothyroidism NOS
5257	Grave's disease

10097	Congenital hypothyroidism
10760	Toxic goitre
11322	Irradiation hypothyroidism
14704	Thyroid deficiency
15743	Hypothyroidism resulting from para-aminosalicylic acid
18282	Hypothyroid goitre, acquired
20310	Pretibial myxoedema - hypothyroid
23014	Thyroid insufficiency
24748	Other acquired hypothyroidism
27533	Cretinism
28852	Postsurgical hypothyroidism
31612	Congenital hypothyroidism with diffuse goitre
31971	Autoimmune myxoedema
34221	Iodine hypothyroidism
38976	Iatrogenic hypothyroidism NOS
47449	Goitrous cretin
47521	Post ablative hypothyroidism
50275	Other postablative hypothyroidism
50860	Postinfectious hypothyroidism
51481	Congenital hypothyroidism NOS
51706	Postablative hypothyroidism NOS
56722	Premature puberty due to hypothyroidism
59702	Myxoedema coma
67513	Cretinism
69290	Other specified congenital hypothyroidism
93159	Congenital hypothyroidism without goitre
93323	Congenital thyroid insufficiency
94915	Hypothyroidism resulting from resorcinol
97090	Hypothyroidism resulting from phenylbutazone

CPRD code lists for family history of cancer

Family History

medcode	readterm
6179	FH: * - breast
6230	H/O: * skin
6473	FH: Breast cancer
6781	FH: Cancer - *
6963	FH: Bowel cancer
8559	FH: Ovarian carcinoma
8815	FH: Neoplasm - *
9076	FH: Stomach cancer
12079	[V]Family history of malignant neoplasm
13242	FH: * - trachea/bronchus/lung
13251	FH: * - male genital organ
13255	FH: * - female genital organ

18133	FH: Bowel cancer
18577	FH: neoplasm of ovary
19568	FH: * - skin
19569	FH: * - gastrointestinal tract
19662	FH: Malignant disease
20619	FH: * - ears, nose, throat
22624	[V]Family history of malignant neoplasm of genital organ
22630	FH: neoplasm of cervix
26629	FH: * - NOS
26655	Family history of prostate cancer
26656	FH: * - urinary organ
29069	FH: Neoplasm of CNS
30788	FH: neoplasm of uterus

CPRD code lists for weight reduction interventions.

Bariatric surgery

medcode	readterm
93378	Sleeve gastrectomy and duodenal switch
89259	Sleeve gastrectomy NEC
89148	Laparoscopic sleeve gastrectomy
18863	Laparoscopic adjustable gastric banding
88474	Partitioning of stomach using band
56926	Partitioning of stomach using staples
90600	Partitioning of stomach NEC
95929	Laparoscopic gastric bypass
90517	Duodenal switch

Weight loss medication

prodcode	productname
525	Orlistat 120mg capsules
3020	Xenical 120mg capsules (Cheplapharm Arzneimittel GmbH)
22792	ORLISTAT
39843	Orlistat 60mg capsules
40337	Alli 60mg capsules (GlaxoSmithKline Consumer Healthcare)
47158	Orlistat 27mg chewable tablets
47193	Alli 27mg chewable tablets (GlaxoSmithKline Consumer Healthcare)
53469	Xenical 120mg capsules (Waymade Healthcare Plc)
56456	Orlistat 120mg capsules (A H Pharmaceuticals Ltd)
64912	Beacita 120mg capsules (Actavis UK Ltd)
70741	Orlistat 120mg capsules (Almus Pharmaceuticals Ltd)

CPRD code lists for clinical features

Acute pancreatitis

medcode	desc
1113	Acute pancreatitis
1506	Acute recurrent pancreatitis
14905	Acute pancreatitis NOS
31395	Acute haemorrhagic pancreatitis
48685	Subacute pancreatitis
49499	Acute pancreatitis unspecified
105194	Idiopathic acute pancreatitis
105066	Other acute pancreatitis
104385	Biliary acute pancreatitis

Appetite loss

medcode	desc
912	[D]Anorexia
1855	[D]Appetite loss
6607	Loss of appetite - symptom
7608	Appetite loss - anorexia
7744	Anorexia symptom
13081	Reduced appetite
17203	[X]Psychogenic loss of appetite
22820	Non-organic loss of appetite
25189	Restricting food intake
53746	[D]Anorexia NOS

Ascites

medcode	desc
1508	[D]Ascites
3503	Drainage of ascites NEC
8154	Malignant ascites
13575	Ascitic fluid: malignant cells
14274	Ascitic fluid exam. normal
14275	Ascitic fluid examination
16113	O/E - ascites
19438	Paracentesis abdominis for ascites
25337	Chylous ascites
29009	[D]Fluid in peritoneal cavity
37930	[D]Ascites NOS
41858	Ascitic fluid microscopy
44222	Peritoneal to venous drainage for ascites
48138	Insertion of peritoneal to venous shunt for ascites
50130	Chronic peritoneal effusion
50376	[D]Peritoneal fluid abnormal
52567	Ascitic fluid for C/S
52838	O/E -ascites-shifting dullness
58736	O/E - ascites NOS
61782	Ascitic fluid for organism
62393	Peritoneal fluid for organism

63281	Ascitic fluid cell count
65129	Ascitic fluid gen. exam. NOS
72677	Ascitic fluid exam. - general
73004	Ascitic fluid exam. NOS
73305	O/E-ascites-fluid thrill shown
94678	Ascitic fluid appearance NOS
95845	Ascitic fluid lactate dehydrogenase level
95846	Ascitic fluid protein level
98095	Ascitic fluid: organisms
98428	Ascitic fluid sent for exam.
98986	O/E - ascites - dipping shown
99253	Ascitic fluid exam. abnormal
99814	Ascitic fluid chemistry
101413	Ascitic fluid clear
101500	Ascitic fluid appearance
107314	Ascitic fluid glucose level

Bleeding gums

medcode	desc
9395	Bleeding gums
29281	O/E - bleeding gums

Bleeding (rectal)

medcode	desc
621	Rectal bleeding
1642	GIB - Gastrointestinal bleeding
2150	Intestinal haemorrhage NOS
2832	Bleeding haemorrhoids NOS
2873	Blood in stool
3053	Faecal occult blood: positive
3097	Gastrointestinal haemorrhage
3872	Bleeding PR
4636	Gastrointestinal tract haemorrhage NOS
5462	Blood in faeces
6151	Blood in faeces symptom
6554	PRB - Rectal bleeding
6574	Rectal haemorrhage
9968	Blood on toilet paper
11698	Painless rectal bleeding
11718	Painful rectal bleeding
12471	Gastrointestinal haemorrhage unspecified
14256	Blood in faeces
19271	Haemorrhage of rectum and anus
20859	Blood in stools altered
27862	Altered blood in stools
32446	Anal haemorrhage
40901	Faecal occult blood: trace
44004	Faeces: fresh blood present

45911	Blood on pants
46479	Haemorrhage of rectum and anus NOS
61761	Perinatal rectal haemorrhage
104124	Referral to rectal bleeding clinic

Breast symptom

medcode	desc
1730	Disorders of breast
14999	Inflammatory breast disease
17115	Induration of breast
22475	Contour of breast distorted
25021	Deformation of breast
25753	O/E - ulcer on breast
48280	Chronic nonpuerperal breast abscess
54827	O/E - ulcerated breast lesion
72237	Chronic subareolar nonpuerperal abscess
10920	Nipple eczema
12300	[M]Paget's disease, mammary
12480	[M]Paget's disease and intraductal carcinoma of breast
14999	Inflammatory breast disease
17115	Induration of breast
31252	O/E - peau d'orange
42542	[M]Paget's disease and infiltrating breast duct carcinoma
51266	Skin thickening of breast
54827	O/E - ulcerated breast lesion
60803	[M]Paget's disease, breast

Bruising

medcode	desc
1084	Contusion (bruise) with intact skin
1155	Haematoma with intact skin
1372	Spontaneous bruising
3090	Contusion, foot
3170	Subungual haematoma
3555	Contusion, ear
3600	Perianal haematoma
4028	Haematoma NOS
4166	[D]Petechiae
4398	Haematoma of leg
4702	Scrotal haematoma due to nontraumatic cause
4838	Contusion, eye NOS
4883	Contusion of face, scalp and neck NOS
4954	Contusion, chest wall
5018	Male genital haematoma NOS
5130	Leg bruise
5139	Contusion, ankle
5320	Contusion, fingernail (includes subungual haematoma)
5586	Contusion, back

5952 Contusion, knee
 5953 Contusion, nose
 6070 Bruising symptom
 6191 O/E - bruising
 6656 Petechiae
 6711 [D]Spontaneous bruising
 6996 Contusion of face, scalp and neck, excluding eye(s)
 6998 Contusion, buttock
 7096 Perianal haematoma
 7144 Toenail bruise
 7280 O/E - petechiae present
 7402 Contusion, elbow or forearm
 7472 Traumatic haematoma
 7565 Contusion, thigh
 7671 Contusion, lower limb and other unspecified sites
 7928 Contusion, toe
 8197 Bruise, trunk
 8434 Contusion, lip
 8495 Purpura
 8532 Senile purpura
 8670 Contusion, thumb
 8845 Arm bruise
 8896 Contusion of toe(s) with damage to nail
 9209 Contusion, finger, unspecified
 9350 O/E - ecchymoses present
 9459 Contusion, upper limb
 9503 Purpura and other haemorrhagic conditions
 9670 Contusion, lower leg
 9740 Bruise of head
 9926 Contusion, gum
 10616 Contusion, forearm area
 10764 Heel bruise
 10984 Haematoma of rectus sheath
 11254 Contusion, elbow area
 12068 Contusion wrist or hand
 12069 Contusion, shoulder or upper arm
 12142 Bruise of face
 12253 Contusion, hand, excluding finger
 12503 Contusion, breast
 12615 Bruise of eye
 12729 Shoulder bruise
 12796 Contusion, back NOS
 14906 Contusion, abdominal wall
 15188 Contusion, eyelids and periocular tissues
 15238 [D]Spontaneous ecchymoses
 15444 Breast haematoma due to nontraumatic cause
 15860 Contusion, forehead
 16525 Haematoma of vulva

16906 Contusion, eye and adnexa
 16949 Haematoma of pinna
 17087 Contusion of coccyx
 17214 Contusion, wrist
 17491 Contusion, trunk
 17870 Contusion, eyeball
 17978 Contusion, cheek
 18086 Contusion of pelvic region
 18295 Contusion, penis
 18589 Contusion, hip
 19962 Contusion, trunk NOS
 20117 Other contusion neck
 20281 Contusion, genital organs
 20326 Perineal haematoma
 20411 Contusion, orbital tissues
 20946 Bruise of scrotum
 21161 Bruise of eyelids
 21263 Bruise of ear
 22308 Contusion of lower back
 23695 Bruising symptom NOS
 23771 Contusion, scalp
 24349 Testicular haematoma due to nontraumatic cause
 24981 Post-traumatic bruising
 25560 Contusion with skin intact, NOS
 25669 Contusion, upper arm
 27517 Contusion, groin
 27711 Bruises easily
 27731 Vulval and perineal haematoma during delivery
 27745 Contusion, finger
 28015 Contusion, site NOS
 28038 Contusion, anterior abdominal wall
 28142 Contusion, lower limb NOS
 28280 Contusion, finger NOS
 28434 Contusion of sacral region
 29090 Contusion, ankle and foot NOS
 29126 Contusion of pelvic region
 29889 Contusion hand, dorsum
 29895 Contusion, knee and lower leg NOS
 30087 Contusion, flank
 30204 Contusion hand, palm
 30275 Contusion, vagina
 30347 Contusion, genital organs NOS
 30733 Contusion of lower back
 33792 Contusion, wrist and hand NOS
 34284 Bruise of mandibular joint area
 34453 Contusion, perineum
 34757 Vaginal haematoma
 35318 Black heel

35436	O/E - purpura in mouth
36085	Contusion, vulva
36318	Contusion, scapular area
36395	Contusion, throat
36485	Contusion, multiple sites NEC
36594	Contusion, hip and thigh NOS
37355	Contusion, shoulder area
37479	Contusion, interscapular region
37495	Contusion, abdominal wall NOS
38656	Contusion, finger, multiple
39407	Contusion, multiple sites of trunk
41764	Contusion, lower limb, multiple sites
41856	Contusion, scrotum or testis
42121	Contusion, knee and lower leg
42692	Cerebral laceration and contusion NOS
43606	Contusion, elbow and forearm NOS
44298	Contusion, upper limb, multiple sites
44456	Contusion, upper limb NOS
44522	Contusion, hip and thigh
44597	Contusion, ankle and foot, excluding toe(s)
45488	Contusion wrist, volar
46591	Bruise of periocular tissue
48325	Cerebellar laceration and contusion
48717	[D]Spontaneous ecchymoses NOS
103476	Bleeding symptom

Cervical abnormalities

medcode	desc
18975	Lesion of cervix
19999	Leukoplakia of cervix
23408	Ulcer of cervix
26872	Suspected cervical cancer
29859	Avulsion of lesion of cervix uteri
44580	Excision of lesion of cervix uteri
58094	Malignant neoplasm, overlapping lesion of cervix uteri

Testicular abnormalities

medcode	desc
1475	Testicular swelling NOS
2015	O/E - testicular swelling
4322	O/E - scrotal swelling
6162	O/E - testicular swelling
7289	[D]Swelling of scrotum
16571	O/E -scrotal swelling-transill
24134	O/E - scrotal swelling NOS
31624	Hypertrophy of testis
32658	O/E - right scrotal swelling
40769	O/E - left scrotal swelling

44878	Male genital organ oedema
50437	O/E -scrotal swell.no transill
58737	Hypertrophy of scrotum
59660	Fibrosis of testis
102278	C/O scrotal swelling

Chest signs

medcode	desc
947	Pleural effusion NOS
7593	Malignant pleural effusion
8370	Collapse of lung
9559	Pleural effusion NOS
9855	O/E - collapse - lung
11614	O/E - bronchial breathing
12520	[D]Percussion of chest abnormal
18081	Other pleural effusion
19937	[D]Abnormal chest sounds NOS
20107	[D]Abnormal chest sounds
30065	Other pleural effusion excluding mention of tuberculosis
52850	[X]Pleural effusion in conditions classified elsewhere

Change in bowel habit

medcode	desc
910	Change in bowel habit
16665	[D]Change in bowel habit
19690	Altered bowel habit
62248	GIT symptom changes

Clubbing

medcode	desc
7575	O/E - finger clubbing
14752	[D]Clubbing of fingers
30453	Clubbed nail pachydermoperiostosis
51048	O/E - hands - finger clubbing

Compressed trachea

medcode	desc
741	[D]Shortness of breath
3092	[D]Dyspnoea
3456	[D]Stridor
4084	Airways obstructn irreversible
4229	Choking due to airways obstruction
5896	Dyspnoea - symptom
7000	O/E - dyspnoea
7683	Breathless - lying flat
9089	Orthopnoea symptom
9177	Airways obstruction reversible
9195	O/E - stridor present

11451 [D]Orthopnoea
 18116 Nocturnal dyspnoea
 37704 O/E - orthopnoea

Constipation

medcode	desc
1028	Constipation
1437	[D]Incontinence of faeces
1709	Constipation - functional
2004	Constipation symptom
2264	Manual removal of impacted faeces from rectum
3381	Incontinent of faeces
5803	Constipation NOS
6083	Incontinent of faeces symptom
6364	Chronic constipation with overflow
8541	Painful defaecation
10687	Faecal impaction
15555	[D]Incontinence of faeces NOS
15939	Psychogenic constipation
17652	Constipated
18335	O/E - PR-rectum full of faeces
20450	Constipation NOS
20464	Removal of impacted faeces
21618	[D] Defaecation painful
23641	Acute constipation
24180	Other specified constipation
25797	Chronic constipation without overflow
26022	Drug induced constipation
52085	Faeces consistency: hard
55812	Faeces consistency: dry
63169	Faeces quantity: bulky
97021	Difficulty in ability to defaecate
98785	O/E - defaec.ref.abn.-constip.
99999	Chronic constipation

Cough

medcode	desc
92	Cough
292	Chesty cough
1025	Bronchial cough
1160	[D]Cough
1234	Productive cough NOS
1273	C/O - cough
1612	Chronic cough
3068	Night cough present
3628	Persistent cough
3645	Coughing up phlegm
4070	Morning cough

4836	Nocturnal cough / wheeze
4931	Dry cough
7706	Productive cough -clear sputum
7707	Cough symptom NOS
7708	Productive cough-yellow sputum
7773	Productive cough -green sputum
8239	[D]Cough with haemorrhage
8968	Cough fracture
12715	[X]Psychogenic cough
15483	Psychogenic cough
16717	Smokers' cough
18907	Cough with fever
19470	Reflux cough
26211	Bovine cough
28538	Cough fracture of ribs
29318	Evening cough
43795	Unexplained cough
90332	Barking cough
100333	Cough on exercise
100515	Cough swab
103989	[X]Primary cough headache
104163	[D]Episodic dry cough

Diarrhoea

medcode	desc
192	Diarrhoea
1695	Loose stools
2133	Dysenteric diarrhoea
2182	Diarrhoea & vomiting, symptom
4343	Diarrhoea
4542	Infectious diarrhoea
5036	Functional diarrhoea
5090	Diarrhoea of presumed infectious origin
5134	Diarrhoea symptoms
6007	Diarrhoea due to Campylobacter jejuni
6016	Noninfective diarrhoea
6685	Chronic diarrhoea
7644	Diarrhoea and vomiting
11155	Travellers' diarrhoea
13387	Allergic diarrhoea
14665	Diarrhoea & vomiting -? infect
14695	Diarrhoea symptom NOS
14881	[D] Stools loose
15289	Viral diarrhoea
15371	Psychogenic diarrhoea
17017	Diarrhoea - presumed non-infectious
17162	Dietetic diarrhoea
21294	Spurious (overflow) diarrhoea

29835	Irritable bowel syndrome with diarrhoea
30321	Presumed noninfectious diarrhoea
30684	Faeces consistency: semi-fluid
36613	Epidemic diarrhoea
38163	Neonatal diarrhoea
39233	Faeces consistency: fluid
43316	[X]Psychogenic diarrhoea
48313	Infectious diarrhoea NOS
52750	[X]Diarrhoea+gastroenteritis of presumed infectious origin
53739	Diarrhoea due to staphylococcus
56957	Diarrhoea due to Pseudomonas pyocyanea
61519	Diarrhoea due to staphylococcal toxin

Discharge - vaginal

medcode	desc
449	O/E - vaginal discharge
1170	O/E - blood stained vag. disch
3627	Vaginal discharge symptom
8313	Vaginal discharge present
14668	O/E - vaginal discharge NOS
16119	Vaginal discharge NOS
16189	Vaginal discharge NOS
25866	O/E - white vag. discharge
25898	O/E - frothy vag. discharge
28091	O/E - offensive vag. discharge
48025	O/E - profuse vag. discharge
50107	O/E - creamy vag. discharge
51628	O/E - yellow vag. discharge
52978	O/E - green vag. discharge

Distension / bloating

medcode	desc
2657	Abdomen feels distended
5150	[D]Bloating
5821	Bloating symptom
6229	Abdominal distension symptom
14880	[D]Abdominal distension, gaseous
29567	Abdomen feels bloated
41607	Abd. distension symptom NOS

Dizziness

medcode	desc
132	[D]Dizziness
392	[D]Giddiness
393	[D]Acute vertigo
1114	[D]Vertigo NOS
1957	Benign paroxysmal positional vertigo or nystagmus
5800	Dizziness symptom

5816	Giddiness symptom
5934	H/O: vertigo
6262	Dizziness present
7417	Feels off balance
14681	Other and unspecified peripheral vertigo
15909	[D]Dizziness and giddiness
16214	Vertigo of central origin
18564	Dizziness on standing up
23332	Giddiness present
105212	Benign paroxysmal positional vertigo

Digital rectal examination

medcode	desc
1068	Prostate enlarged on PR
46087	O/E - PR - Prostate median sulcus not preserved

Dyspepsia

medcode	desc
134	Indigestion
257	Dyspepsia
592	Oesophagitis
1008	Regurgitation
2535	Reflux oesophagitis
3869	Psychogenic dyspepsia
4422	Excessive belching
5150	[D]Bloating
5283	Ulcerative oesophagitis
5821	Bloating symptom
5862	Indigestion symptoms
6216	Belching symptom
7623	Indigestion NOS
8697	Flatulent dyspepsia
14760	Oesophagitis NOS
15579	Peptic oesophagitis
16450	Regurgitant oesophagitis
16605	Oesophageal reflux with oesophagitis
34836	Chemical oesophagitis
35037	Other specified oesophagitis
37118	Indigestion symptom NOS
43233	Undiagnosed dyspepsia
64004	Under care of dyspepsia specialist nurse
88289	Referral to dyspepsia specialist nurse

Dysphagia

medcode	desc
727	[D]Difficulty in swallowing
1241	Dysphagia
1360	[D]Choking sensation

3687 [X]Inhalation + ingestion of food causing obstr resp tract
 3805 Massive aspiration syndrome
 3847 Pneumonitis due to inhalation of food or vomitus
 4229 Choking due to airways obstruction
 4281 [D]Dysphagia
 6300 Difficulty swallowing solids
 6722 Choking sensation
 9256 Choked on food
 10360 Swallowing symptoms
 11429 Cardiospasm - oesophagus
 16693 [V]Problems with swallowing
 17726 Inhalation/ingestion of food - resp obstruction/suffocation
 18878 Painful swallowing
 23624 Choked on regurgitated food
 23964 Aspiration of fluid with complication, without blame
 24457 Asphyxia by regurgitated food
 25464 Choked on regurgitated food
 25900 Safe swallow technique
 26042 Difficulty swallowing liquids
 30924 Regurgitates food
 30955 [D]Dysphagia NOS
 32194 Swallowing symptom NOS
 35911 Respiratory obstruction due to food lodged in oesophagus
 37494 Asphyxia by food
 37836 Management of choking
 40441 Obstruction of pharynx by food
 41781 Pneumonitis due to inhalation of regurgitated food
 45560 Dysphagia therapy regime
 55478 Sideropenic dysphagia
 58761 Choked on food NOS
 Respiratory obstruction due to food lodged in oesophagus
 63041 NOS
 64369 Inhalation/ingestion food - resp obstruction/suffocation NOS
 64979 [X]Inhal+ingest food caus obst resp tract occ unspecif place
 65545 Respiratory obstruction due to food lodged in oesophagus
 65840 Tracheal compression due to food lodged in oesophagus
 66528 Massive aspiration syndrome NOS
 70256 [V]Problem with swallowing or mastication
 70519 Suffocation by food
 73627 Aspiration of fluid with complication, without blame NOS
 73808 Interruption of respiration due to food lodged in oesophagus
 73929 Swallowing defect amelioration
 85666 Facilitating initiation of swallowing exercises
 101204 Aspiration pneumonia
 103094 Dysphagia screening completed
 107072 [X]Inhal+ingest food caus obst resp tract occ resid instit'n

Dysuria

medcode	desc
532	Dysuria
4498	[D]Painful urination
5350	[D]Dysuria
15389	[D]Vesical tenesmus
15435	Genitourinary pain NOS
15599	[D]Dysuria NOS
19930	Strangury
45124	[D]Strangury
52859	[X]Painful micturition, unspecified
53122	[X]Psychogenic dysuria
55781	Psychogenic dysuria

Epistaxis

medcode	desc
1557	[D]Nosebleed
501	[D]Epistaxis

Erectile dysfunction

medcode	desc
710	Impotence
3838	Erectile dysfunction
10648	Advice about impotence
12066	[X]Male erectile disorder
12790	Referral to erectile dysfunction clinic
12867	Treatment of erectile dysfunction NEC
17639	[X]Psychogenic impotence
17894	Impotence of organic origin
20833	Penile injection to produce erection
40725	Advice on technique for impotence
41382	Ligation of penile veins for impotence
81439	Operations on penis for erectile dysfunction NEC
92310	Provision of device for impotence
94343	Cannot sustain an erection
94821	Cannot get an erection
102274	C/O erectile dysfunction
102434	Diabetic erectile dysfunction review
102490	Diabetic assessment of erectile dysfunction
102859	Referral to erectile dysfunction clinic declined

Fatigue

medcode	desc
1042	[D]Postviral (asthenic) syndrome
1147	[D]Tiredness
1371	[D]Lethargy
1404	Fatigue
1582	Nervous exhaustion
1688	[D]Fatigue

1900	[D]Debility, unspecified
2855	Weakness present
3361	Neurasthenia - nervous debility
4546	Chronic fatigue syndrome
5049	[D]Asthenia NOS
5583	Lethargy - symptom
5658	[D]Malaise
5751	Tired all the time
5794	Tiredness symptom
5814	[D]Lassitude
6029	Weakness symptoms
6190	Postviral fatigue syndrome
6242	Fatigue - symptom
7235	Tired all the time
7529	CFS - Chronic fatigue syndrome
9127	Post-viral fatigue syndrome
9220	Exhaustion
9435	O/E - apathetic
9656	[X]Fatigue syndrome
9823	C/O - debility - malaise
9889	[D]General weakness
12411	[D]Post viral debility
15516	C/O - 'tired all the time'
16479	O/E - weakness
16561	[X]Neurasthenia
17736	Malaise/lethargy
23932	[D]Malaise and fatigue NOS
24382	[D]Senile exhaustion
27877	PVFS - Postviral fatigue syn
29292	Tiredness symptom NOS
44215	[D]Malaise and fatigue
97284	Moderate chronic fatigue syndrome
98512	Mild chronic fatigue syndrome
98734	Severe chronic fatigue syndrome

Fever

medcode	desc
1020	[D]Fever NOS
2389	[D]Pyrexia of unknown origin
2717	O/E -pyrexia of unknown origin
5859	Feels hot/feverish
5892	O/E - fever
6065	Fever symptoms
6086	Pyrexia symptoms
7118	O/E - pyrexia - ? cause
8950	Feverish cold
9093	Pyrexial cold
14744	O/E - fever - general

15446	O/E - fever examination - NAD
16792	[D]Pyrexial convulsion
17722	O/E - fever - remittent
17989	[D]Fever of unknown origin
18907	Cough with fever
19939	Sweating fever
20119	[D]Hyperpyrexia NOS
20367	[D]Pyrexia of unknown origin NOS
21430	Relapsing fever
22444	[D]Persistent fever
22620	O/E - level of fever
23349	[D]Chills with fever
25311	O/E - hyperpyrexia-> 40.5 oCEL
27231	O/E - temperature elevated
31412	O/E - fever - intermittent
35761	O/E - fever - general NOS
46292	O/E - fever NOS
47246	Fever with sweating
51514	O/E - character of fever
53552	Examination of fever
53952	O/E - fever - acute rise
64688	O/E - level of fever NOS
66310	O/E - fever - continuous
73259	O/E - fever - gradual rise

Fracture (pathological)

medcode	desc
5526	Pathological fracture
18676	Pathological fracture due to metastatic bone disease
29332	Other specified pathological fracture
30352	Pathological fracture of lumbar vertebra
30616	Pathological fracture of thoracic vertebra
37945	Pathological fracture of cervical vertebra
54834	Fracture of bone in neoplastic disease
62343	Pathological fracture NOS

Frequency

medcode	desc
503	[D]Frequency of micturition, unspecified
729	Urinary frequency
4160	Frequency of micturition
6724	Micturition frequency
22278	Frequency of micturition
23662	[D]Micturition frequency and polyuria
28490	Micturition frequency NOS
63898	[D]Frequency of micturition or polyuria NOS

Haematemesis

medcode	desc
1188	Haematemesis
1642	GIB - Gastrointestinal bleeding
2712	Vomiting of blood
3097	Gastrointestinal haemorrhage
4354	Upper gastrointestinal haemorrhage
4636	Gastrointestinal tract haemorrhage NOS
8344	Coffee ground vomit
12471	Gastrointestinal haemorrhage unspecified
15517	Gastric haemorrhage NOS
16617	Blood in vomit - symptom
40165	Occult blood in vomit
43288	Vomit: coffee ground
43534	Blood in vomit O/E
44489	Vomiting blood - fresh
44691	Vomiting blood - coffee ground
53643	Vomit: frank blood present
60151	Vomit occult blood
63244	Vomit occult blood positive
71101	Vomit occult blood NOS
38851	[D]Throat haemorrhage
71829	O/E - throat haemorrhage

Haematuria

medcode	desc
507	Haematuria
6030	Haematuria - symptom
6234	Blood in urine - symptom
6659	Blood in urine - haematuria
6901	Clot haematuria
7164	Recurrent benign haematuria syndrome
7232	Frank haematuria
9651	Painless haematuria
13913	Blood in urine test
13915	RBCs- red blood cells in urine
13929	Urine blood test = +++
13934	Urine blood test = +
17060	Recurrent and persistent haematuria
19361	Traumatic haematuria
19792	Urine blood test = ++
20357	Painful haematuria
35555	Urine: red - blood
44541	Recurrent and persistent haematuria, dense deposit disease
47228	Essential haematuria

Haemoptysis

medcode	desc
1610	Haemoptysis - symptom

2244	[D]Haemoptysis
4135	Blood in sputum - haemoptysis
7285	[D]Pulmonary haemorrhage NOS
8239	[D]Cough with haemorrhage
10013	Blood in sputum - symptom
33742	[D]Haemoptysis NOS

Headache

medcode	desc
129	Headache
130	Frontal headache
1197	[D]Headache
1788	Occipital headache
3340	Temporal headache
5056	pain in head
5110	Vascular headache, not elsewhere classified
5660	Sick headache
5767	C/O - a headache
6139	Chronic post-traumatic headache
9891	Generalised headache
9915	Headache character
9999	Muscular headache
10502	Drug-induced headache, not elsewhere classified
11321	Unilateral headache
16247	Headache site
20932	Aching headache
26450	Medication overuse headache
83480	History of headache
94830	[X]Benign coital headache
98239	[X]Cervicogenic headache
103916	[X]Primary exertional headache

Hoarse voice

medcode	desc
1412	[D]Dysphonia
1921	[D]Hoarseness
2246	Voice hoarseness
5281	[D]Change in voice
5936	Hoarse
6423	[D]Voice disturbance
6517	Hoarseness symptom
7848	O/E - dysphonia
10277	Dysphonia
11627	Hoarseness - throat symptom
16810	O/E - hoarseness
18490	Spasmodic dysphonia
18801	[X]Psychogenic dysphonia
22331	Hyperfunctional dysphonia

35056	Spastic dysphonia
38120	Hoarseness symptom NOS
43769	Hypofunctional dysphonia
97636	[X]Other and unspecified voice disturbances

Iron deficiency anaemia

medcode	desc
539	Microcytic - hypochromic anaemia
795	Iron deficiency anaemias
882	Hypochromic - microcytic anaemia
2743	Acute posthaemorrhagic anaemia
4566	Ferritin level low
4839	Microcytic hypochromic anaemia
4858	[X]Other iron deficiency anaemias
9537	Other specified iron deficiency anaemia NOS
15439	Iron deficiency anaemia NOS
18137	Unspecified iron deficiency anaemia
21127	Iron deficiency anaemia due to dietary causes
27726	Iron deficiency anaemia due to chronic blood loss
33420	Other specified iron deficiency anaemia
40750	Idiopathic hypochromic anaemia
48338	Iron deficiency anaemia due to blood loss
94528	Asiderotic anaemia

Infection - chest

medcode	desc
68	Chest infection
312	Acute bronchitis
572	Pneumonia due to unspecified organism
886	Bronchopneumonia due to unspecified organism
1019	Acute bronchiolitis
1382	Acute viral bronchitis unspecified
1576	Pneumonia due to mycoplasma pneumoniae
1849	Lobar (pneumococcal) pneumonia
2581	Chest infection NOS
3683	Basal pneumonia due to unspecified organism
4019	Congenital pneumonia due to viral agent
4899	Recurrent chest infection
4910	Interstitial pneumonia
4974	O/E - consolidation present
5202	Viral pneumonia
5324	Atypical pneumonia
5612	Pneumonia due to staphylococcus
5978	Acute wheezy bronchitis
6094	Pneumonia or influenza NOS
6124	Acute lower respiratory tract infection
8318	Lung consolidation
9043	Acute pneumococcal bronchitis

9389 Chest infection - viral pneumonia
 9639 Lobar pneumonia due to unspecified organism
 9953 Tuberculous pneumonia
 10086 Pneumonia and influenza
 10321 O/E - consolidation
 11072 Acute purulent bronchitis
 11101 Acute tracheobronchitis
 11833 Hypersensitivity pneumonitis NOS
 11849 Other specified pneumonia or influenza
 12061 Pneumonia - Legionella
 12423 Pneumonia due to streptococcus
 13563 Other aspiration pneumonia as a complication of care
 13573 Influenza with bronchopneumonia
 14308 Mycoplasma pneumoniae antibody level
 14976 Viral pneumonia NOS
 15912 Influenza with pneumonia
 16287 Chest infection - unspecified bronchopneumonia
 17025 Chlamydial pneumonia
 17185 Acute bronchiolitis with bronchospasm
 17359 Chest infection - unspecified bronchitis
 17917 Acute bronchiolitis NOS
 18451 Acute bronchiolitis due to respiratory syncytial virus
 19400 Chest infection - pneumonia due to unspecified organism
 20198 Acute bronchitis NOS
 21145 Acute croupous bronchitis
 21492 Acute haemophilus influenzae bronchitis
 22009 Streptococ pneumonia/cause/disease classified/oth chapters
 22795 Chest infection - other bacterial pneumonia
 22835 Bronchiolitis obliterans organising pneumonia
 23095 Bacterial pneumonia NOS
 23333 Hypostatic pneumonia
 23546 Pneumonia due to klebsiella pneumoniae
 23726 Pneumonia with varicella
 24316 Chest infection with infectious disease EC
 24356 Hypostatic bronchopneumonia
 24800 Acute bacterial bronchitis unspecified
 25054 Aspiration pneumonia due to vomit
 25462 Varicella pneumonitis
 25694 Pneumonia due to other specified organisms
 25895 Septicaemia due to streptococcus pneumoniae
 26278 'Ventilation' pneumonitis
 26287 Klebsiella pneumoniae/cause/disease classified/oth chapters
 27519 Pneumonia with pneumocystis carinii
 27641 HIV disease resulting in Pneumocystis carinii pneumonia
 28634 Other bacterial pneumonia
 29166 Chest infection - pneumococcal pneumonia
 29273 Acute bronchitis due to parainfluenza virus
 29457 Chest infection - influenza with pneumonia

29669 Acute bronchitis and bronchiolitis
 30437 Pneumonia with whooping cough
 30509 Post operative chest infection
 30591 Pneumonia due to pseudomonas
 30653 Chest infection - pneumonia organism OS
 31024 Mycoplasma pneumoniae [PPLO] cause/dis classifd/oth chaptr
 31269 Pneumonia due to respiratory syncytial virus
 31643 Congenital pneumonia
 31886 Acute bronchitis due to mycoplasma pneumoniae
 32172 Postmeasles pneumonia
 33478 Viral pneumonia NEC
 33837 Pneumonitis due to inhalation of food or vomitus NOS
 34251 Pneumonia due to specified organism NOS
 34274 Pneumonia with aspergillosis
 34300 Postoperative pneumonia
 35082 Pneumonia with pertussis
 35189 Abscess of lung with pneumonia
 35745 Influenza with pneumonia NOS
 36015 Nonpneumonic Legionnaires' disease
 36675 Pneumonia due to parainfluenza virus
 37447 Acute lower respiratory tract infection
 37881 Pneumonia due to haemophilus influenzae
 38065 Pneumonitis, unspecified
 38639 Bronchitis and pneumonitis due to chemical fumes
 39382 Chlamydia pneumoniae IgG level
 40299 Pneumonia - candidal
 40498 Pneumonia with infectious diseases EC
 41015 Lipoid pneumonia (exogenous)
 41034 Pneumonia with measles
 41137 Acute bronchitis or bronchiolitis NOS
 41781 Pneumonitis due to inhalation of regurgitated food
 43286 Pneumonia with cytomegalic inclusion disease
 43362 Acute streptococcal bronchitis
 43884 Pneumonia due to bacteria NOS
 45072 Cytomegaloviral pneumonitis
 45425 Pneumonia due to proteus
 46052 Severe acute respiratory syndrome
 46066 Pneumonitis due to inhalation of solid or liquid NOS
 46977 Allergic alveolitis and pneumonitis NOS
 47295 Pneumonic plague, unspecified
 47504 Pneumonitis due to inhalation of other solid or liquid
 47973 Herpes simplex pneumonia
 48593 Acute bronchitis due to respiratory syncytial virus
 48804 Pneumonia due to haemophilus influenzae
 Congenital pneumonia due to group B haemolytic
 48982 streptococcus
 49398 Pneumonia with typhoid fever
 49794 Acute neisseria catarrhalis bronchitis

50396 Acute fibrinous bronchitis
 50408 Ornithosis with pneumonia
 50705 Congenital pneumonia NOS
 50867 Pneumonia due to other specified bacteria
 51372 Pneumonitis due to fetal aspiration
 51398 Pleuropneumonia-like organism (PPLO) infection
 52071 Pneumonia with candidiasis
 52384 Pneumonia due to other aerobic gram-negative bacteria
 52520 [X]Other viral pneumonia
 53095 Allergic alveolitis and pneumonitis NOS
 53753 [X]Other pneumonia, organism unspecified
 53947 [X]Pneumonia in viral diseases classified elsewhere
 53969 Pneumonia with systemic mycosis NOS
 54252 Pneumonitis due to inhalation of solid or liquid NOS
 Congenital pneumonia due to group A haemolytic
 54530 streptococcus
 55162 Chlamydia pneumoniae IgM level
 55391 Subacute bronchitis unspecified
 56762 Toxoplasma pneumonitis
 57213 Chlamydia pneumoniae IgA level
 57667 Gangrenous pneumonia
 58896 Salmonella pneumonia
 59083 Pneumonitis due to inhalation of gastric secretions
 60119 Pneumonia due to Eaton's agent
 60299 E.coli pneumonia
 60482 Pneumonia with Q-fever
 61623 Pneumonia with actinomycosis
 61991 Endogenous lipoid pneumonia
 62623 Pneumonia with ornithosis
 62632 Influenza with pneumonia, influenza virus identified
 63763 [X]Other bacterial pneumonia
 63858 Pneumonia due to streptococcus, group B
 64799 Rheumatic pneumonia
 64890 Acute bronchitis due to rhinovirus
 65419 Pneumonia due to escherichia coli
 65916 Acute bronchitis due to echovirus
 66228 Acute bronchiolitis due to other specified organisms
 66362 Pneumonia with infectious diseases EC NOS
 66397 [X]Other acute lower respiratory infections
 66773 Pneumonitis due to inhalation of oil or essence NOS
 67836 Pneumonia due to adenovirus
 67901 Pneumonia with nocardiasis
 68445 Congenital pneumonia due to Escherichia coli
 69230 Other specified congenital pneumonia
 69782 Pneumonia with other infectious diseases EC
 70559 Pneumonia with other infectious diseases EC NOS
 70710 Primary pneumonic plague
 71370 Acute pseudomembranous bronchitis

72182	Pneumonia with salmonellosis
73100	[X]Acute bronchitis due to other specified organisms
73735	Pneumonia due to pleuropneumonia like organisms
93153	Acute bronchitis due to coxsackievirus
94165	Congenital pneumonia due to Chlamydia
96059	Mycoplasma pneumoniae detected
96583	[X]Klebsiella pneumoniae/cause/disease classifd/oth chapters
97634	Congenital pneumonia due to staphylococcus
98225	Congenital pneumonia due to pseudomonas
98381	[X]Pneumonia due to other specified infectious organisms
98782	Pneumonia with toxoplasmosis
99214	[X]Acute bronchiolitis due to other specified organisms
101204	Aspiration pneumonia
101292	Histoplasma duboisii with pneumonia
101507	Histoplasma capsulatum with pneumonia
103404	Pneumonia with coccidioidomycosis
103475	Cryptogenic organising pneumonia
103559	Usual interstitial pneumonitis
103637	Hypersensitivity pneumonitis
104121	Community acquired pneumonia
104264	Hospital acquired pneumonia
104315	Sepsis due to Streptococcus pneumoniae
104717	HIV disease resulting in Pneumocystis jirovecii pneumonia
105895	Acute bronchiolitis due to human metapneumovirus
	[X]Mycoplasma pneumoniae [PPLO]cause/dis classifd/oth
106031	chaptr
106300	Pneumonia due to human metapneumovirus
106515	[X]Hypersensitivity pneumonitis due to other organic dusts
106908	Pneumonia with tularaemia

Infection - recurrent

medcode	desc
1353	Recurrent cystitis
1572	Recurrent urinary tract infection
1747	Recurrent acute tonsillitis
2985	Recurrent UTI
3628	Persistent cough
4221	Recurrent upper respiratory tract infection
4899	Recurrent chest infection
6202	Recurrent boils
7092	Recurrent wheezy bronchitis
9378	Recurrent urinary tract infections
9973	Recurrent acute otitis media
10515	Recurrent urinary tract infection
12489	Persistent sore throat
15393	Recurrent appendicitis
17173	Recurrent sinusitis
20364	Recurrent bronchiectasis

33831	Recurrent mouth ulcers
95893	History of recurrent tonsillitis
99759	History of recurrent urinary tract infection

Jaundice

medcode	desc
355	[D]Jaundice (not of newborn)
2612	[D]Jaundice
3121	Obstructive jaundice NOS
5300	[D]Cholaemia NOS
5996	O/E - jaundiced
6000	Jaundice - symptom
18019	Yellow - symptom
18574	[D]Icterus NOS
25418	Yellow/jaundiced colour
29488	O/E - jaundiced colour
38877	[D]Jaundice (not of newborn) NOS
39682	Acholuric familial jaundice
73695	O/E: blood looks deep yellow

Lesion - skin

medcode	desc
17232	[M]Amelanotic melanoma
22196	Crusting of pigmented skin lesion
22793	Itching of pigmented skin lesion
24588	Changing colour of pigmented skin lesion
25362	Changing shape of pigmented skin lesion
29499	O/E - skin red over lesion
30562	O/E - skin lesion
46254	Non-healing pigmented skin lesion
54864	Irregular outline of pigmented skin lesion

Limp

medcode	desc
405	[D]Gait abnormality
2582	O/E - limping gait
14714	[D]Gait abnormality NOS
95802	[X]Other and unspecified abnormalities of gait and mobility

Lump

medcode	desc
942	[D]Foot lump
961	[D]Localized swelling, mass and lump, upper limb
1026	[D]Lump on hand
1233	O/E - joint swelling
1461	[D]Localized swelling, mass and lump, neck
1710	[D]Local superficial swelling, mass or lump
1853	[D]Chest lump

1884	[D]Swelling, local and superficial
1935	[D]Mass, localized and superficial
2185	[D]Toe lump
2591	[D]Axillary lump
2615	[D]Shoulder lump
2681	[D]Groin swelling
2718	[D]Finger lump
3006	[D]Groin lump
3074	[D]Swelling in head or neck
3526	[D]Lump on head
3657	[D]Lump, localized and superficial
4154	[D]Lump on leg
4200	[D]Wrist lump
4248	[D]Lump in head or neck
4540	[D]Lump on thigh
5415	Feeling of lump in throat
5601	Swelling of limb
5856	O/E - a lump
5877	O/E - a swelling
6033	C/O: a swelling
6409	[D]Swelling, mass or lump in neck
6756	O/E - soft tissue swelling
6861	[D]Local superficial swelling, mass or lump NOS
7466	[D]Localized swelling, mass and lump, lower limb
8107	[D]Localized swelling, mass and lump, head
8371	[D]Chest mass
8753	Lump on neck
9784	[D]Submental lump
9795	O/E - muscle mass
15285	[D]Chest swelling
16002	[D]Swelling, mass and lump of chest
16842	[D]Lump on shin
21443	[D]Groin mass
21979	[D]Swelling, mass or lump in head
23997	[D]Localized swelling, mass and lump, multiple sites
24465	[D]Swelling, mass or lump in head or neck NOS
27023	US scan of soft tissue mass
29328	[D]Lump on back
32008	O/E-soft tissue swelling-local
49057	O/E - muscle mass NOS
57679	[D]Swelling, mass or lump of chest NOS

Lump - breast

medcode	desc
841	Lump in breast
2149	Breast irregular nodularity
5770	Breast lump symptom
7646	Breast mass

10103	Breast lump present
16551	O/E - breast lump position
17215	O/E - breast lump consistency
17595	O/E - breast lump size
27635	O/E - breast lump tethering
28300	O/E - breast lump - outline
29506	O/E - breast lump palpated
29518	O/E - breast lump regularity
29523	O/E - breast lump-orange size
29607	O/E-breast lump-upper in-quad
29653	O/E-breast lump-upper out-quad
29837	O/E-breast lump-nipple/central
29838	O/E - breast lump - pea size
32819	Breast lump detected by mammogram
35542	Breast lump detected by clinician examination
36141	Breast lump symptom NOS
37366	O/E-breast lump- axillary tail
39091	Breast lump detected by self-examination
45821	O/E - breast lump - plum size
45894	O/E-breast lump-lower out-quad
46086	O/E - breast lump palpated NOS
51819	O/E - breast lump irregular
52747	O/E - breast lump cystic
52777	O/E - breast lump hard
54545	O/E -breast lump-lower in-quad
54546	O/E - breast lump smooth
54547	O/E - breast lump not tethered
56223	O/E - breast lump size NOS
58947	O/E - breast lump soft
59003	O/E -breast lump fixed to skin
61283	O/E - breast lump tethered NOS
61291	Breast lump detected by partner
68736	O/E - breast lump consist. NOS
72764	O/E-breast lump-tangerine size
74003	O/E-breast lump regularity NOS
102282	O/E - breast lump fixed deep

Lower urinary tract symptoms

medcode	desc
503	[D]Frequency of micturition, unspecified
583	Urgency of micturition
667	Urinary symptoms
729	Urinary frequency
840	Nocturia
1052	[D]Retention of urine
3002	[D]Acute retention of urine
4160	Frequency of micturition
4598	[D]Urinary system symptoms

5038	[D]Slowing of urinary stream
5375	Cannot pass urine - retention
5579	[D]Nocturia
5959	Urgency
5994	Retention - symptom
6158	[D]Retention of urine unspecified
6724	Micturition frequency
7487	Hesitancy of micturition
8028	[D] Urgency of micturition
10732	Genitourinary symptoms
15012	[D]Other urinary system symptom
15151	[D]Urinary system symptoms NOS
15243	[D]Vesical pain
16399	[D]Polyuria
20483	[D]Splitting of urinary stream
22278	Frequency of micturition
22339	Genitourinary symptom NOS
23662	[D]Micturition frequency and polyuria
25649	Hesitancy
27529	[D]Urination abnormality NOS
28017	[D]Chronic retention of urine
28490	Micturition frequency NOS
28788	[D]Difficulty with micturition
30703	Genitourinary symptoms NOS
32867	Incomplete emptying of bladder
41605	[D]Poor urinary stream
43634	[D]Other urination abnormality
43707	Urinary symptom change
63898	[D]Frequency of micturition or polyuria NOS
68379	Psychogenic genitourinary tract symptoms
73228	[X]Other difficulties with micturition
73547	Psychogenic genitourinary tract symptom NOS
93952	Urge to pass urine again shortly after finishing voiding
97888	[X]Symptoms and signs involving the urinary system
99784	Lower urinary tract symptoms
104344	Severe lower urinary tract symptoms
104390	Moderate lower urinary tract symptoms
104539	Mild lower urinary tract symptoms
83547	International prostate symptom score

Lymphadenopathy

medcode	desc
523	O/E -cervical lymphadenopathy
1496	[D]Lymphadenopathy
1584	[D]Adenitis NOS
3181	[D]Swollen glands
3446	O/E -axillary lymphadenopathy
4234	[SO]Lymph node

4593	[SO]Cervical lymph node
5226	Swollen glands
6273	[D]Lymph node enlargement
7051	[SO]Axillary lymph node
7182	O/E - inguinal lymphadenopathy
8126	O/E - lymphadenopathy
10490	[SO]Inguinal lymph node
12032	O/E-sub-mental lymphadenopathy
12581	[SO]Mediastinal lymph node
15129	O/E - lymph node character NOS
15737	[D]Lymph node enlargement NOS
15740	O/E - lymph nodes firm
15814	O/E - lymph nodes tender
17458	[D]Generalized enlarged lymph nodes
18146	O/E - enlarged lymph nodes
20897	[D]Localized enlarged lymph nodes
21677	[D]Enlarged submandibular lymph gland
22737	O/E-supraclav.lymphadenopathy
22767	[SO]Paraaortic lymph node
24116	O/E -popliteal lymphadenopathy
25853	O/E - post-auricular lymphadenopathy
29791	[SO]Lymph node NEC
33427	O/E - lymphadenopathy NOS
42517	O/E - lymph nodes discrete
44408	O/E - lymph nodes fluctuant
50087	O/E - lymph nodes hard
50456	[SO]Specified lymph node NEC
62921	[SO]Scalene lymph node
72824	[SO]Retroperitoneal lymph node
86012	[SO]Other lymph node
89366	[SO]Sentinel lymph node
94103	[SO]Other lymph node NEC
94179	[SO]Pelvic lymph node
96220	[SO]Specified other lymph node NEC
101030	[D]Reactive lymphadenopathy
102193	Acute febrile mucocutaneous lymph node syndrome

Lymphadenopathy - neck

medcode	desc
523	O/E -cervical lymphadenopathy
12032	O/E-sub-mental lymphadenopathy
22737	O/E-supraclav.lymphadenopathy

Lymphadenopathy - axilla

3446	O/E -axillary lymphadenopathy

Mass - abdomen

medcode	desc

1780 Hepatosplenomegaly
 3006 [D]Groin lump
 3015 [D]Abdominal mass
 3034 [D]Hepatomegaly
 3125 [D]Splenomegaly
 4800 [D]Abdominal swelling
 5698 [D]Liver enlargement
 5838 [D]Swelling, mass or lump within abdomen or pelvis
 7073 [D]Abdominal lump
 7533 O/E - liver grossly enlarged
 8731 O/E - abdominal mass palpated
 9301 O/E - hepatomegaly
 11442 [D]Umbilical lump
 15857 O/E -liver moderately enlarged
 16370 [D]Swelling, mass or lump within abdomen or pelvis NOS
 16670 [D]Umbilical swelling
 16900 O/E - splenomegaly
 20387 O/E - abdominal mass shape
 20827 Right iliac fossa mass
 21301 O/E-abdominal mass consistency
 21443 [D]Groin mass
 21575 O/E left lower abdominal mass
 21684 O/E -abd.mass fills 1 quadrant
 21686 O/E - abdominal mass - soft
 22499 O/E - spleen enlarged
 24034 [D]Umbilical mass
 24527 Epigastric mass
 29832 [D]Spleen enlargement
 34238 Biopsy of abdominal mass
 42038 [D]Hepatomegaly NOS
 44281 [D]Splenomegaly NOS
 50336 O/E - spleen just palpable
 51626 O/E - abdominal mass - hard
 53736 [D]Lump stomach
 55574 O/E - splenomegaly NOS
 59025 O/E - abd.mass consistency NOS
 59578 O/E - abd.mass movt.with resp.
 63484 O/E - abd. mass fills abdomen
 63706 O/E - gross splenomegaly
 65538 O/E -abd.mass -irregular shape
 67090 O/E -abd.mass-upper border def
 68388 O/E -abd.mass -border def. NOS
 68939 O/E - abd.mass moves with resp
 69694 O/E -abd.mass-lower border def
 72395 O/E - moderate splenomegaly
 72512 O/E - abd.mass still with resp
 93588 O/E - painful splenomegaly
 96439 Chronic congestive splenomegaly

97889 O/E - abdominal mass-very hard
 98951 O/E - abd.mass + respn. NOS
 99958 O/E - abd.mass -border defined

Mass - neck

medcode	desc
523	O/E -cervical lymphadenopathy
1461	[D]Localized swelling, mass and lump, neck
3074	[D]Swelling in head or neck
4248	[D]Lump in head or neck
6409	[D]Swelling, mass or lump in neck
6896	[D]Swelling, mass or lump in head and neck
6910	[D]Mass in head or neck
8753	Lump on neck
20897	[D]Localized enlarged lymph nodes
24465	[D]Swelling, mass or lump in head or neck NOS

Mass - pelvis

medcode	desc
5838	[D]Swelling, mass or lump within abdomen or pelvis
6361	[D]Pelvic mass
7939	O/E - VE - pelvic mass NOS
16370	[D]Swelling, mass or lump within abdomen or pelvis NOS
17585	O/E - pelvic mass palpated
28343	Biopsy of pelvic mass
30075	[D]Pelvic lump
35684	O/E - pelvic mass palpable-LIF
49378	O/E - central pelvic mass
53814	O/E - pelvic mass palpable-RIF
56662	O/E - pelvic mass palpable NOS

Mass - rectum

medcode	desc
1987	O/E - PR - rectal mass

Mass - testis

medcode	desc
1475	Testicular swelling NOS
2015	O/E - testicular swelling
4322	O/E - scrotal swelling
6162	O/E - testicular swelling
7289	[D]Swelling of scrotum
7399	Testicular lump
24134	O/E - scrotal swelling NOS
24885	Benign neoplasm of testis
32658	O/E - right scrotal swelling
35126	Other types of hydrocele
38406	Excision of lesion of testis

40769	O/E - left scrotal swelling
50437	O/E -scrotal swell.no transill
102278	C/O scrotal swelling

Mass - thyroid

medcode	desc
728	O/E - thyroid lump
1881	Thyroid enlargement
2338	Thyroid cyst
2572	Thyroid nodule
2592	Excision of lesion of thyroid gland
15728	O/E - thyroid swelling -unilat
23090	Biopsy of lesion of thyroid gland
26700	Nontoxic uninodular goitre
47120	Adenomatous goitre
62125	Incision of lesion of thyroid gland
24527	Epigastric mass
53736	[D]Lump stomach

Mass - vagina

medcode	desc
5399	Polyp of vagina
15186	Biopsy of lesion of vagina
19148	Vaginal mass
22798	Excision of lesion of vagina
23577	Neoplasm of uncertain behaviour of vagina

Mass - vulva

medcode	desc
2523	Polyp of vulva
7729	Lesion of vulva
9424	Laser destruction of lesion of vulva
17126	Polyp of female genital tract, unspecified
17241	Polyp of labia and vulva
46458	Malignant neoplasm of skin of perineum
95409	[X]Polyp of other parts of female genital tract
98624	[X]Polyp of female genital tract, unspecified

Memory disturbance

medcode	desc
1993	Memory loss - amnesia
2908	Memory disturbance
3639	Amnesia symptom
5777	Memory loss symptom
6061	Organic memory impairment
6387	Mild memory disturbance
6489	Transient global amnesia
7711	[D]Memory deficit

7742	Forgetful
9786	Loss of memory for recent events
10123	Memory loss
10514	Memory impairment
10571	Short-term memory loss
11410	Poor short-term memory
11936	[X]Mild cognitive disorder
12057	Memory problem
12583	Poor memory
12805	Memory loss - amnesia
18996	Transient global amnesia
19004	TGA - Transient global amnesia
19073	Memory lapses
19297	Loss of memory
24952	Forgetful
28278	Transient global amnesia
28406	Amnesia
32367	Impairment of working memory
39507	Poor visual sequential memory
39915	Memory dysfunction
53507	Minor memory lapses
60263	GDS level 3 - mild cognitive decline
103453	Short-term memory loss
107282	Mild cognitive impairment

Nausea

medcode	desc
491	Nausea
1890	[D]Nausea
3416	[D]Nausea and vomiting
5843	Nausea present
6402	Nausea symptoms
7616	Morning nausea
9579	Nausea NOS
15018	[D]Nausea and vomiting NOS
20434	[D]Retching
28493	C/O - nausea

Night sweats

medcode	desc
1740	Night sweats
96946	[D]Night sweats

Nipple discharge

medcode	desc
1148	Nipple discharge
7397	Nipple discharge symptom
17703	Nipple discharge present

24191	O/E - nipple discharge
29478	Nipple discharge NOS
45373	O/E - nipple discharge - milky
52954	O/E-nipple discharge-blood-red
61678	O/E - nipple discharge NOS
62961	O/E - nipple discharge - clear
65842	O/E - nipple discharge - pus

Nipple retraction

medcode	desc
2247	Inversion of nipple
3614	Retraction of nipple
28992	O/E - retracted nipple
39417	O/E - retraction of nipple

Non-visible haematuria

medcode	desc
2784	Microscopic haematuria
13915	RBCs- red blood cells in urine
13919	Urine: trace non-haemol. blood
13929	Urine blood test = +++
13932	Urine: trace haemolysed blood
13934	Urine blood test = +
14561	Urine dipstick for blood
17060	Recurrent and persistent haematuria
19792	Urine blood test = ++

Oral symptoms

medcode	desc
1281	Angular stomatitis and cheilitis
1538	Mouth ulcer
1597	painful tongue
2774	Dry mouth
2921	[SO]Mouth
3123	coated tongue
3207	Sore mouth
3296	Mouth symptoms
3904	Oral aphthae
4300	sore lip
4752	[SO]Lip
4881	O/E - lip swelling
4982	black hairy tongue
5834	[SO]Palate
5852	O/E - angular stomatitis
6113	Tongue symptoms
7760	Excessive salivation - symptom
7769	O/E - glossitis
8341	salivary secretion disturbance

8575 O/E - furred tongue
 9434 O/E - mouth ulcer
 9609 O/E - mouth ulcer present
 9626 Abscess of oral soft tissue unspecified
 9923 [SO]Gingiva
 10297 [SO]Salivary apparatus
 10351 O/E - dry lips
 11083 [D]Saliva abnormal
 12164 O/E - ulcer on tongue
 12456 O/E - cracked lips
 12617 O/E - sublingual swelling
 14715 discomfort in mouth
 14955 mouth infection
 15002 angular cheilitis
 15172 xerostomia
 15849 Sore mouth - symptom
 17044 [SO]Tongue
 17729 Minor aphthous ulceration
 18586 O/E - salivary calculus
 19077 burning mouth syndrome
 23909 O/E - dry/cracked lips
 25672 Mouth symptom NOS
 27631 glossodynia
 29839 O/E - fissured tongue
 33959 Allergic parotitis
 96203 Poor oral hygiene
 104278 Oral mucositis

Pain - abdomen

177 Abdominal pain
 290 Epigastric pain
 421 Iliac fossa pain
 542 [D]Epigastric pain
 628 [D]Hypochondrial pain
 701 Left flank pain
 716 [D]Abdominal cramps
 948 [D]Acute abdomen
 1181 Right iliac fossa pain
 1228 Retrosternal pain
 1239 [D]Colic NOS
 1763 [D]Abdominal pain
 1976 Abdominal pain type
 2056 [D]Abdominal colic
 2234 [D]Recurrent acute abdominal pain
 2383 Abdominal discomfort
 2982 Left iliac fossa pain
 3086 Right flank pain

3338 [D]Abdominal pain NOS
 3978 Upper abdominal pain
 4617 Central abdominal pain
 4771 [D]Umbilical pain
 5691 Non-colicky abdominal pain
 5782 O/E - abdomen tender
 5804 O/E - tenderness
 5899 C/O - lumbar pain
 5960 Site of abdominal pain
 6357 Subcostal pain
 6395 Type of GIT pain - symptom
 7300 Suprapubic pain
 7490 Flank pain
 7726 [D]Right upper quadrant pain
 7812 Colicky abdominal pain
 8362 [D]Left upper quadrant pain
 8436 [D]Upper abdominal pain
 9061 [D]Left lower quadrant pain
 9695 Right upper quadrant pain
 11070 General abdominal pain-symptom
 11647 O/E - abd. pain - R.ilic
 12639 O/E - abd.pain-R.hypochondrium
 13626 Tenderness of epigastrium
 14916 O/E -abd.pain on palpation NOS
 14989 Type of GIT pain
 15180 O/E - abdo. pain on palpation
 15213 O/E - tenderness/pain
 15288 [D]Loin pain
 16402 [D]Abdominal tenderness
 16806 [D]Pain in right iliac fossa
 16868 [D]Pain in left iliac fossa
 17223 O/E - iliac pain on palpation
 17324 Gripping pain
 17451 O/E - rebound tenderness
 17636 O/E - umbilical pain on palp.
 19020 O/E - lumbar pain on palpation
 19223 O/E - abd. pain - epigastrium
 19283 [D]Nonspecific abdominal pain
 19360 [D]Right lower quadrant pain
 20475 [D]Suprapubic pain
 20640 O/E - epigastric pain on palp.
 21583 O/E - abd. pain - L.ilic
 22608 Lower abdominal pain
 23872 Left subcostal pain
 24584 O/E - guarding of abdomen
 24627 O/E - abd. pain - umbilical
 24661 Generalised abdominal pain
 24821 Right subcostal pain

25118	Site of GIT pain
25630	O/E - abd. pain - L.lumbar
28285	[D]Gas pain (abdominal)
29352	Abdominal wall pain
29922	Site of GIT pain NOS
31062	[D]Other specified abdominal pain
34301	O/E - guarding on palpation
35876	O/E - guarding - R.ilic
36558	O/E - abd. pain - R.lumbar
37101	O/E - abd.pain-L.hypochondrium
42195	O/E - guarding-R.hypochondrium
42211	O/E - abd. pain - hypogastrium
42235	O/E - guarding - epigastrium
44484	Type of GIT pain NOS
50590	O/E - abdominal rigidity
50662	[X]Pain localized to other parts of lower abdomen
51337	Shoulder pain from abdomen
52402	[X]Other and unspecified abdominal pain
53766	Psychogenic pain unspecified
54385	[D]Acute abdomen
56084	O/E - guarding - hypogastrium
56085	O/E - guarding - L.ilic
56091	O/E - rebound tenderness NOS
56094	O/E - guarding-L.hypochondrium
62933	O/E - guarding - umbilical
71471	O/E -guarding on palpation NOS
103540	[D]Functional abdominal pain syndrome

Pain after alcohol

medcode	desc
44783	Pain in lymph nodes after alcohol consumption

Pain - back

medcode	desc
153	Backache
154	Low back pain
313	Sciatica
537	Facet joint syndrome
557	Backache, unspecified
1335	Pain in lumbar spine
1720	Lumbago
2786	Backache symptom
3324	Back pain without radiation NOS
3763	C/O - low back pain
4948	Pain in thoracic spine
5023	Acute back pain - lumbar
5476	Acute back pain - disc
5840	Acute back pain with sciatica

5899	C/O - lumbar pain
5916	Acute back pain - thoracic
5923	Acute back pain - unspecified
6226	C/O - upper back ache
6472	Backache symptom NOS
6704	Back pain, unspecified
8241	Backache with radiation
8823	Prolapsed lumbar intervertebral disc with sciatica
9682	Referral to back pain clinic
9801	Exacerbation of backache
10231	Chronic low back pain
12189	Mechanical low back pain
14866	Lumbago with sciatica
15109	Lumbalgia
19020	O/E - lumbar pain on palpation
24796	Back pain worse on sneezing
38521	[X]Psychogenic backache
45205	Psychogenic backache
94797	[X]Other dorsalgia
105661	Low back pain clinical pathway

Pain - bone

medcode	desc
917	Bone pain
1274	Clavicle pain
1335	Pain in lumbar spine
2519	Rib pain
4706	Bony pelvic pain
4948	Pain in thoracic spine
35744	Pain in cervical spine

Pain - breast

medcode	desc
602	Mastodynia - pain in breast
7401	Breast soreness
9117	Persistent mastalgia
10530	Unilateral mastalgia
11506	Breast tenderness
12195	Cyclical mastalgia
17602	Intractable breast pain

Pain - chest

374	Chest pain
544	[D]Chest pain, unspecified
726	Atypical chest pain
1059	Pleuritic pain
1270	[D]Chest tightness
2519	Rib pain

2584	[D]Chest pain
3518	[D]Musculoskeletal chest pain
3796	[D]Chest pain NOS
7346	Central chest pain
7844	[D]Non-cardiac chest pain
7878	[D]Chest discomfort
8349	Costal margin chest pain
9340	[D]Non cardiac chest pain
9698	Anterior chest wall pain
10370	Chest pain NOS
14819	[D]Painful respiration NOS
14823	[D]Anterior chest wall pain
15528	[D]Chest pressure
18134	Chest pain on exertion
18183	[D]Pleuritic pain
19199	[D]Parasternal chest pain
20490	Painful breathing -pleurodynia
21082	[D]Retrosternal chest pain
24321	Chest wall tenderness
24704	Chest wall pain
29490	[D] Retrosternal chest pain
50477	[D]Central chest pain
53806	[X]Other chest pain

Pain - pelvic

medcode	desc
421	Iliac fossa pain
628	[D]Hypochondrial pain
1181	Right iliac fossa pain
1336	[D]Groin pain
2781	C/O pelvic pain
2982	Left iliac fossa pain
4706	Bony pelvic pain
7248	[D] Perineal pain
9061	[D]Left lower quadrant pain
9811	[D] Pelvic pain
9920	[D]Pelvic and perineal pain
11647	O/E - abd. pain - R.ilic
16547	Other pelvic pain - female
16806	[D]Pain in right iliac fossa
16868	[D]Pain in left iliac fossa
17223	O/E - iliac pain on palpation
19360	[D]Right lower quadrant pain
20475	[D]Suprapubic pain
21583	O/E - abd. pain - L.ilic
35876	O/E - guarding - R.ilic
50662	[X]Pain localized to other parts of lower abdomen
56085	O/E - guarding - L.ilic

Pain - shoulder

medcode	desc
198	Shoulder pain
2397	Shoulder joint pain
5787	Shoulder pain
20170	Pancoast's syndrome

Postmenopausal bleeding

medcode	desc
1583	Postmenopausal bleeding
1802	Proteinuria
5451	[D]Albuminuria
10924	[D]Microalbuminuria
11248	[D]Proteinuria
13590	Urine protein test = +
13600	Urine protein test = ++++
13611	Urine protein test = ++
13612	Urine protein test = trace
13613	Urine protein abnormal
13621	Urine protein test = +++
14901	Benign postural proteinuria
16465	Persistent proteinuria, unspecified
27266	Urine protein/creatinine ratio
38284	[D]Proteinuria NOS
43611	Isolated proteinuria with specified morphological lesion
44804	Isolated proteinur/specified morphologic lesion focal+segmental glomerular lesion
56736	Urine protein electr. abnormal
59992	Isolated proteinuria, with unspecified morphologic changes
61811	Isolated proteinur+specified morphologic lesion of mesangiocapillary glomerulonephritis
64030	[X]Persistent proteinuria, unspecified
66613	Isolated proteinur/specified morphologic lesion of mesangial proliferative glomerulonephritis
71964	Isolated proteinur/specified morphologic lesion of membranous glomerulonephritis
94789	Chronic kidney disease stage 1 with proteinuria
94793	Chronic kidney disease stage 3 with proteinuria
95122	Chronic kidney disease stage 4 with proteinuria
95145	CKD stage 3 with proteinuria
95146	Chronic kidney disease stage 2 with proteinuria
95178	Chronic kidney disease stage 3B with proteinuria
95180	CKD stage 3B with proteinuria
95408	Chronic kidney disease stage 3A with proteinuria
95508	Chronic kidney disease stage 5 with proteinuria
95571	CKD stage 3A with proteinuria
97979	CKD stage 2 with proteinuria
97980	CKD stage 1 with proteinuria
99160	CKD stage 5 with proteinuria
99312	CKD stage 4 with proteinuria
101572	Isolated proteinuria, with other specific morphologic changes

Pruritis - itch

medcode	desc
991	Pruritus vulvae
1317	Pruritus ani
1829	Pruritus NOS
1920	Pruritus and related conditions
2311	Itch
3177	Skin irritation
4005	Pruritus of genital organs
5250	Scalp itchy
5784	C/O: itching
5830	Perianal itch
9474	Aquagenic pruritis
10138	Other specified pruritic conditions
12134	Pruritus senilis
15959	Psychogenic pruritus
16679	[X]Psychogenic pruritis
17109	Pruritus scroti
20780	Pruritus vulvae
23442	Pruritus hiemalis
24633	Other pruritic conditions NOS
52818	[X]Pruritus, unspecified
52837	[X]Other pruritus
98178	Brachioradial pruritis
98652	Pruritus aestivalis
99843	Itching of skin lesion
10363	[D]Raised PSA
22598	Prostate specific antigen abnormal

Reflux

medcode	desc
592	Oesophagitis
846	Heartburn
984	Gastro-oesophageal reflux
1008	Regurgitation
1327	Oesophageal reflux
2281	Acid reflux
2535	Reflux oesophagitis
4448	[D]Heartburn
5283	Ulcerative oesophagitis
5370	Hyperacidity
6041	Heartburn symptom
6412	Waterbrash symptom
7104	Gastro-oesophageal reflux with oesophagitis
7577	Gastric reflux
14713	Antireflux fundoplication using thoracic approach
14760	Oesophagitis NOS

14849	[D]Waterbrash
15054	Acid reflux
15579	Peptic oesophagitis
16450	Regurgitant oesophagitis
16605	Oesophageal reflux with oesophagitis
17263	Oesophageal reflux operations
17610	Antireflux fundoplication using abdominal approach
18211	Antireflux operations
19111	Laryngopharyngeal reflux
19470	Reflux cough
25610	Oesophageal reflux without mention of oesophagitis
25805	[D]Heartburn NOS
28619	Antireflux operation NOS
33772	Waterbrash
34005	Other specified antireflux operation
35037	Other specified oesophagitis
39323	Phlegmonous oesophagitis
45360	Antireflux gastropexy
68276	Antireflux procedure using thoracic approach NEC
98929	Gangrenous oesophagitis
103564	Antireflux procedure and gastroplasty HFQ

Spinal cord compression

medcode	desc
5457	Cord compression
8816	Cord compression NOS
12547	Spinal cord compression
16564	Spinal cord compression NOS

Seizure

medcode	desc
614	[D]Convulsions, febrile
1137	convulsions
1306	seizure NOS
1902	Had a fit
3607	Fit (in known epileptic) NOS
3652	Fit - had one, symptom
5668	Grand mal seizure
6063	O/E - febrile convulsion
6721	fit, non epileptic
7275	O/E - a seizure
7807	last fit
7808	Convulsion - symptom
7809	O/E - petit mal fit
8097	Absence seizure
8262	fit frequency
8487	Myoclonic seizure
9085	Had a convulsion

9932	H/O: febrile convulsions
11025	[D]Fit
11394	Complex partial epileptic seizure
11505	Seizures in response to acute event
12662	Febrile convulsion
13221	2 to 4 seizures a month
17136	O/E - a fit
18899	daily seizures
19549	1 to 7 seizures a week
21935	[D]Reflex anoxic seizure
26618	1 to 12 seizures a year
32662	O/E - fit/convulsion
38457	O/E - fit/convulsion NOS
39160	many seizures a day
40105	Simple partial epileptic seizure
99834	[D]Nocturnal seizure

Pain - shoulder

medcode	desc
552	Painful arc syndrome
827	Adhesive capsulitis of the shoulder
874	Frozen shoulder
1230	Scapulohumeral fibrositis
1726	Rotator cuff shoulder syndrome and allied disorders
3823	Subacromial bursitis
4278	Supraspinatus tendinitis
4922	Supraspinatus syndrome
5327	Rotator cuff sprain
5489	Shoulder tendonitis
5647	Bursitis - shoulder
5787	Shoulder pain
5938	Injury of tendon of the rotator cuff of shoulder
6555	[SO]Rotator cuff
8298	Subacromial impingement
8949	Impingement syndrome of shoulder
10457	Subacromial bursitis
10555	Periarthritis of shoulder
10901	Plastic repair of rotator cuff of shoulder
10935	Rotator cuff decompression - open acromioplasty
12828	Biceps tendinitis
16137	Calcifying tendinitis of the shoulder
17285	Bicipital tenosynovitis
17552	Bursitis of shoulder
17603	Subdeltoid bursitis
20427	Rotator cuff syndrome, unspecified
20524	Rotator cuff syndrome NOS
21924	Rotator cuff complete rupture
27844	Partial thickness rotator cuff tear

28211	Triceps tendinitis
28584	Full thickness rotator cuff tear
32154	Open acromioplasty for decompression of rotator cuff
39556	Revision repair of rotator cuff
42610	Other shoulder affections NEC
52110	Coracoid impingement
61440	Kessel rotator cuff decompression
63756	[X]Other shoulder lesions
68569	Watson rotator cuff decompression
96941	Plastic repair of rotator cuff of shoulder NEC
96965	Plastic repair of multiple tears of rotator cuff of shoulder
97024	Revisional repair of rotator cuff NEC
97102	Revisional repair multiple tears of rotator cuff of shoulder
104106	Injury of muscle of rotator cuff of shoulder

Shortness of breath

medcode	desc
735	[D]Breathlessness
741	[D]Shortness of breath
1429	Breathlessness
2563	[D]Respiratory distress
2575	Short of breath on exertion
2931	Difficulty breathing
3092	[D]Dyspnoea
4822	Shortness of breath
5175	Breathlessness symptom
5349	Shortness of breath symptom
5896	Dyspnoea - symptom
6326	Breathless - moderate exertion
6434	Paroxysmal nocturnal dyspnoea
7000	O/E - dyspnoea
7683	Breathless - lying flat
7932	Breathless - mild exertion
9089	Orthopnoea symptom
9297	[D]Respiratory insufficiency
11451	[D]Orthopnoea
12474	SOBOE
18116	Nocturnal dyspnoea
19426	MRC Breathlessness Scale: grade 3
19427	MRC Breathlessness Scale: grade 2
19429	MRC Breathlessness Scale: grade 5
19430	MRC Breathlessness Scale: grade 4
19432	MRC Breathlessness Scale: grade 1
21801	Breathlessness NOS
22094	Short of breath dressing/undressing
24889	Breathless - strenuous exertion
27400	[D]Cheyne-Stokes respiration
31143	Breathless - at rest

37704	O/E - orthopnoea
42287	Borg Breathlessness Score: 6 severe (+)
53771	Dyspnoea on exertion
57193	Borg Breathlessness Score: 3 moderate
57759	Borg Breathlessness Score: 2 slight
57903	CLASP shortness of breath score
59860	Borg Breathlessness Score: 4 somewhat severe
60096	CLASP shortness of breath score
64049	Borg Breathlessness Score: 5 severe
67566	Borg Breathlessness Score: 9 very, very sev (almost maximal)
68707	Borg Breathlessness Score: 1 very slight
70061	Borg Breathlessness Score: 7 very severe
70818	Borg Breathlessness Score: 0.5 very, very slight
72334	Borg Breathlessness Score: 8 very severe (+)
101843	Borg Breathlessness Score: 10 maximal

Sore throat

medcode	desc
386	Throat pain
404	Throat soreness
1499	Throat irritation
5553	Has a sore throat
5755	Sore throat symptom
6014	Sore throat NOS
7366	Pain in throat
8127	Throat symptom NOS
10083	Chronic pharyngitis and nasopharyngitis
12489	Persistent sore throat
14931	Inflamed throat
15039	[D]Throat pain
15287	Sore throat symptom NOS
16814	Sore throat - chronic
18878	Painful swallowing
21060	[D]Throat discomfort

Speech problem

medcode	desc
2107	Speech problem
3537	[D]Dysphasia
4834	[D]Dysarthria
5688	[D]Other speech disturbance NOS
6495	[V]Problems with speech
7081	O/E - dysarthria
7583	O/E - aphasia
8752	slurred speech
9287	Stammer - symptom
9594	[X]Expressive language disorder
9713	Speech problem - symptom

9992	Dysphasia
10091	Stutter - symptom
10110	Expressive dysphasia
11598	Aphasia
18039	[D]Other speech disturbance
19124	Dysarthria
20922	[V]Problems with communication, inclu. Speech
22896	Speech and language disorder
26046	O/E - speech delay
32923	Speech problem
33403	Speech problem NOS
33998	Word finding difficulty
35192	Nominal dysphasia
46539	Bulbar palsy type of dysarthria

Steatorrhoea

medcode	desc
4787	Steatorrhea - idiopathic
3456	[D]Stridor
9195	O/E - stridor present
11541	Suspected skin cancer
85844	Fast track referral for suspected skin cancer
106004	Seen in fast track suspected skin cancer clinic

Superior vena cava obstruction

medcode	desc
744	[D]Swelling face
8273	SVCO - Superior vena cava obstruction
8412	Superior vena cava syndrome
10212	O/E - JVP raised
12144	O/E - arm oedema
29444	O/E - oedema of arms

Testicular symptoms

medcode	desc
1639	Pain in testis
2707	Pain in scrotum
4733	Pain in testis
5966	Testicular pain
6764	O/E - scrotal oedema
14648	Testicular pain
16078	Pain in testicle

Ulcer - vulval

medcode	desc
2008	Ulceration of vulva
14936	Vulval sores
25721	Ulceration of vulva unspecified

37164 Ulceration of vulva NOS
 48043 Pudendal ulcer
 68892 [X]Vulvovaginal ulceration+inflammation in other diseases CE

Urinary tract infection

medcode	desc
150	Urinary tract infection, site not specified NOS
389	Cystitis
898	Urethritis unspecified
1106	Pyelitis unspecified
1289	Urinary tract infection, site not specified
1353	Recurrent cystitis
1572	Recurrent urinary tract infection
1625	Nonspecific urethritis
1899	Pyelonephritis unspecified
2546	Acute pyelonephritis
2650	Chronic urinary tract infection
2725	Urethritis due to non venereal causes
2939	Calculous pyelonephritis
2985	Recurrent UTI
3469	Chronic cystitis unspecified
4370	Urethritis due to non venereal cause NOS
4654	Chronic pyelonephritis
4788	Acute gonococcal urethritis
4993	Bacteriuria, site not specified
9378	Recurrent urinary tract infections
10295	Acute gonococcal cystitis
10515	Recurrent urinary tract infection
10857	Other specified cystitis
11315	Other chronic cystitis NOS
11585	Chronic interstitial cystitis
12484	Cystitis NOS
14828	Acute pyelitis
15074	Acute cystitis
15436	Post menopausal atrophic urethritis
21158	Chronic pyelitis
21999	Trichomonal urethritis
22682	Cystitis cystica
23776	Submucous cystitis
29460	Chronic interstitial cystitis NOS
29497	Prostatocystitis
30068	Subacute cystitis
30964	Cystitis in diseases EC NOS
32787	Other chronic cystitis
34311	Other urethritis NOS
34630	Other cystitis NOS
34652	Irradiation cystitis
35360	Nonobstructive reflux-associated chronic pyelonephritis

36670	Other urethritis
38572	Xanthogranulomatous pyelonephritis
38698	Acute pyelonephritis NOS
39257	Periurethritis
41018	Acute gangrenous cholecystitis
44897	Cystitis in trichomoniasis
48111	Chronic pyelonephritis NOS
48855	Chronic obstructive pyelonephritis
49842	Cystitis in actinomycosis
53944	Pyelonephritis and pyonephrosis unspecified
55168	Cystitis in moniliasis
57568	Chronic pyelonephritis with medullary necrosis
59121	Unspecified pyelonephritis NOS
61319	Periurethritis
64482	Acute pyelonephritis without medullary necrosis
65979	[X]Chlamydial infection of genitourinary tract, unspecified
67410	[X]Other genitourinary tract infections following delivery
67495	Post menopausal urethritis
69832	[X]Other urethritis
70189	[X]Other cystitis
71787	Pyelitis in diseases EC
72686	[X]Other chronic cystitis
93839	Cystitis in diseases EC
95710	Pyelonephritis in diseases EC
97002	Urinary tract infection
99631	Chronic pyelonephritis without medullary necrosis
101832	Advice on avoiding recurrent urinary tract infection
105634	Candida pyelonephritis

Visual disturbance

medcode	desc
567	visual disturbance
568	O/E - hemianopia
570	visual field defects
746	blurred vision
927	Flashing lights seen
1195	amaurosis fugax
1444	Visual loss NOS
1617	Diplopia
1714	Temporary visual disturbance
2954	scotoma
3268	Loss of vision
3553	Double vision
5290	homonymous hemianopia
5991	Diplopia/double vision
6020	Impaired vision
6499	Visual symptoms
6661	[V]Problems with sight

6726	tunnel vision
9875	O/E - homonymous hemianopia
11391	Scintillating scotoma
12194	visual disturbance
15604	Visual symptom NOS
16720	peripheral visual field defect
17670	photopsia
18462	double vision (diplopia)
20736	sudden visual loss
21748	cloudy vision
25881	Oscillopsia
28414	Distortion of visual image
105202	H/O amaurosis fugax

Vomiting

medcode	desc
176	Vomiting
2182	Diarrhoea & vomiting, symptom
2712	Vomiting of blood
2871	Cyclical vomiting - psychogenic
3380	Projectile vomiting
3416	[D]Nausea and vomiting
3422	Psychogenic vomiting NOS
3992	Vomiting symptoms
5164	[D]Vomiting
5881	Vomiting
6101	[D]Projectile vomiting
6752	Persistent vomiting
6796	[X]Psychogenic vomiting
6936	[D]Possetting
7644	Diarrhoea and vomiting
8344	Coffee ground vomit
12117	Winter vomiting disease
12383	Cyclical vomiting NOS
12772	C/O - vomiting
14665	Diarrhoea & vomiting -? infect
15018	[D]Nausea and vomiting NOS
15789	[D]Sickness
15825	[D]Emesis
15933	Viral vomiting
15951	Vomit appearance
15964	Vomit appearance - abnormal
16604	Vomit - O/E, general
16617	Blood in vomit - symptom
16621	Vomit examination
16622	[X]Vomiting associated with other psychological disturbances
17600	Bilious vomit O/E
17882	Air sickness

20358	Mild hyperemesis unspecified
22161	Emesis
22276	[D]Drug induced vomiting
24284	Vomiting - bile stained
24368	Vomiting - infective
25834	Functional vomiting
28305	Vomit: faeculant
30862	Faeculant vomit O/E
33809	Throwing up
35626	Vomit pH NOS
35707	Persistent vomiting NOS
37436	Vomit: excessive acidity
37602	Vomiting NOS
40165	Occult blood in vomit
40410	Vomit: bilious
41463	Epidemic vomiting syndrome
43288	Vomit: coffee ground
43534	Blood in vomit O/E
44489	Vomiting blood - fresh
44691	Vomiting blood - coffee ground
48509	pH of vomit
49061	Habit vomiting
49507	Vomit toxicology
52239	Emesis - persistent
53643	Vomit: frank blood present
53821	Motion sickness NOS
55756	Vomit examination normal
56385	Vomit inhalation pneumonitis
57038	Vomit examination - general
57728	Vomit pH
58104	Vomit appearance - normal
58105	Vomit odour
60151	Vomit occult blood
63244	Vomit occult blood positive
71101	Vomit occult blood NOS
71930	Vomit examination NOS
72676	Vomit exam. general NOS
72861	Vomit: appearance NOS
92271	Vomit sent for examination
92454	Parasite in vomit O/E
97080	Induction of emesis
98827	Vomit: mucous present
100905	Vomit examination abnormal
101965	Vomit occult blood negative

venous thromboembolism

medcode	desc
428	Thrombosis of vein NOS

824 Deep vein thrombosis
 1264 Thrombophlebitis NOS
 1266 Pulmonary embolism
 2198 Embolism of vein NOS
 2199 Embolism and thrombosis NOS
 3392 DVT - Deep vein thrombosis
 3466 Phlebitis and thrombophlebitis of the leg NOS
 3576 Deep vein phlebitis and thrombophlebitis of the leg
 5503 Embolism and thrombosis of the renal vein
 5822 Phlebitis and thrombophlebitis
 8769 Portal vein thrombosis
 9255 Thrombosis of vein of leg
 9701 Pulmonary embolus
 11031 Thrombophlebitis of a superficial leg vein NOS
 14657 Other phlebitis and thrombophlebitis NOS
 14742 Phlebitis and thrombophlebitis NOS
 15382 Thrombophlebitis of the femoral vein
 16446 Thrombophlebitis migrans
 16976 [V] Personal history of pulmonary embolism
 17452 Saphenous vein thrombophlebitis
 17847 [V] Personal history DVT- deep vein thrombosis
 19562 [V] Personal history deep vein thrombosis
 21337 H/O: embolism
 22038 Deep vein thrombosis of lower limb
 23765 Penis vein thrombosis
 24737 Thrombophlebitis of the long saphenous vein
 25478 Deep vein thrombosis, leg
 27284 Deep vein phlebitis and thrombophlebitis of the leg NOS
 27688 Embolism and thrombosis NOS
 28404 Superficial phlebitis and thrombophlebitis of the leg NOS
 32002 Deep vein thrombophlebitis of the leg unspecified
 35297 Other embolism and thrombosis
 37849 Embolus of vein NOS
 38099 Phlebitis and/or thrombophlebitis of iliac vein
 38527 Thrombophlebitis of the short saphenous vein
 42435 Other phlebitis and thrombophlebitis
 42506 Deep vein thrombosis of leg related to air travel
 43555 Embolism and thrombosis of the vena cava
 44100 Phlebitis and thrombophlebitis NOS
 47503 H/O: thrombo-embolism
 48920 Deep vein thrombosis of leg related to intravenous drug use
 55661 Thrombophlebitis of the popliteal vein
 58023 Thrombophlebitis of the external iliac vein
 58166 Thrombophlebitis of the common iliac vein
 59865 Thrombophlebitis of the breast - Mondor's disease
 61760 Thrombophlebitis of the posterior tibial vein
 70467 Phlebitis and thrombophlebitis of the iliac vein NOS
 91282 Thrombophlebitis of the iliac vein unspecified

94496	Thrombophlebitis of the internal iliac vein
95077	Thrombophlebitis of the anterior tibial vein
96209	Recurrent pulmonary embolism
97808	Thrombosis of inferior vena cava
98526	Deep vein thrombosis of peroneal vein
100103	Axillary vein thrombosis
101655	Deep vein thrombosis - enhanced services administration
102776	DVT stage 1 service level - enhanced services administration
102777	DVT stage 2 service level - enhanced services administration
104290	DVT enhanced services administration stage 1 service level
104342	Recurrent deep vein thrombosis
105403	Thrombosis of subclavian vein
106482	Thrombophlebitis of the dorsalis pedis vein
106850	Thrombosis of internal jugular vein
107023	DVT stage 3 service level - enhanced services administration
107851	Thrombosis of external jugular vein
110542	Unprovoked deep vein thrombosis

Weakness

medcode	desc
1749	Hemiplegia
2006	Dystonia, unspecified
2390	Facial weakness
3063	Paraplegia
4174	Meralgia paraesthetica
4494	Abducens (sixth) nerve palsy
5848	C/O paraesthesia
7167	Specified palsy NEC
8459	O/E - spastic gait
8492	Hemiplegia NOS
8862	Left sided weakness
8933	Left hemiplegia
9375	Spastic paraplegia
9385	Progressive supranuclear palsy
12793	Hemiparesis
13017	Paralysis symptoms
16117	Tetraplegia
17392	proximal myopathy
18084	Pseudobulbar palsy
18969	Brachial plexus palsy due to birth trauma
23665	Trochlear (fourth) nerve palsy
24738	O/E - muscle tone spastic
27377	Progressive bulbar palsy
31140	Third nerve palsy - total
40893	Upper limb spasticity
55371	O/E - paraplegic in flexion

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