

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

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24 **What this study adds.**

25 No systematic review and meta-analysis has examined the association between weight loss and cancer in
26 primary care populations. The sensitivity of unexpected weight loss for cancer is low, demonstrating that many
27 primary care patients with cancer do not experience weight loss. Conversely, the specificity is high. Patients
28 aged 60 years and older with unexpected weight loss have >3% chance of having cancer in one of ten cancer
29 sites. Investment in rapid diagnostic pathways to urgently investigate weight loss across a number of cancer
30 sites is justified.

31

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Abstract

Background

Weight loss (WL) 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 WL as a clinical feature of cancer in patients presenting to primary care.

Design

A diagnostic test accuracy review and meta-analysis.

Methods

Studies reporting 2 x 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

25 studies were included, with 23 (92%) using primary care records. 20 (80%) defined weight loss as a physician's coding of the symptom; the remainder collected data directly. One defined UWL using objective measurements. Positive associations between WL and cancer were found for ten cancer sites: prostate, colorectal, lung, gastro-oesophageal, pancreatic, non-Hodgkins 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 WL for all age groups over 60 years exceeded the 3% risk threshold that current UK guidance proposes for further investigation.

Conclusions

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

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Introduction

Weight loss (WL) 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 or investigate patients who present with WL, although several clinical reviews have suggested different approaches, most commonly in elderly populations (1, 3-6). In the UK, the National Institute of Health and Clinical Excellence (NICE) guidance for suspected cancer reported WL to be a feature of seven cancers in primary care, citing positive predictive values (PPVs) of 0.4-3%, and a cumulative positive predictive value (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 WL as 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, WL has been previously considered as a feature of advanced cancer only, though reports about WL 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 WL (9-11), and yet other data show no relationship between WL and stage or mortality from colorectal cancer (12).

It is also unclear whether WL 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 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 WL as a potential symptom of cancer and omit investigation until other symptoms occur. Patients with pancreatic cancer with WL as their first symptom had the longest time to diagnosis and poorest survival (16). This may reflect the lack of guidelines on investigating WL and the lack of a clear pathway to refer patients with isolated WL for investigation.

The objectives of this systematic review were: first to examine the diagnostic value of WL, alone and in combination with other clinical features for cancer in primary care patients; and second to examine how the predictive value of WL varies by cancer type, cancer stage, gender, and age.

Methods

Protocol and Registration

A protocol was registered with PROSPERO (17). We followed standard *Cochrane* methodology (18). Reporting followed PRISMA, adapted to suit a systematic review and meta-analysis of diagnostic studies (19).

Patient involvement

A survey of patients with experience of a cancer diagnosis informed the choice of methodology.

Eligibility Criteria

Studies were included if 2 x 2 diagnostic accuracy data could be extracted for the symptom of WL and cancer in adults (18yrs or over) presenting to primary care. No restrictions were placed on the definition of WL. A cancer diagnosis of any type or stage was included if confirmed by the cancer registry, histology, the general practice (GP) electronic record, or by another reliable source judged appropriate by the researchers (20-24). A cancer diagnosis within five years of the WL was permitted, though only one study extended beyond two years.

Information sources and search strategy

The electronic databases Embase (OvidSP) [1974-23/10/2015], the Science Citation Index & Conference Proceedings Citation Index (Web of Science Core Collection) [1946-present], and Medline (OvidSP) [1946-present] were searched on the 25/10/2015. Weight loss terms, general symptom terms, and cancer terms were used along with primary care setting terms to identify potentially relevant studies (Appendix 1). Duplicates, studies in non-human animals, case reports, letters, comment articles, and editorials were excluded. No language limits were applied. The reference lists of retrieved reviews and all included studies were checked and a 'Related articles' Pubmed search conducted. All principal investigators were contacted to request additional relevant data.

Study selection and data extraction

Two review authors (BDN and JO) independently screened all titles and abstracts, assessed full-text articles for those (1) deemed relevant based on title and abstract and (2) where a decision could not be made at screening, and extracted data from eligible studies using an extraction guide refined after initial piloting. A third review author (WH) resolved any discrepancies. Figure 1 summarises study selection and the 59 exclusions following full-text review.

Quality assessment.

QUADAS-2 was used to assess methodological quality (25). QUADAS-2 items were weighted to address key potential biases (Appendix 2).

Analyses

Sensitivity, specificity, positive likelihood ratios (PLRs), and diagnostic odds ratios (DOR) were calculated with corresponding 95% confidence intervals (CIs) (18, 26). Review Manager 5.3 was used to (1) produce forest plots to visually show the heterogeneity in sensitivity and specificity across primary studies, and (2) to plot sensitivity and specificity estimates from each study in ROC space. A bivariate meta-analysis model was used to calculate pooled estimates for sensitivity, specificity, and PLRs (27) for subgroups including four or more studies, using Stata (28-33).

Positive predictive values (PPVs) were calculated using Bayes theorem by multiplying the PLR by the prior odds (32). Prior odds were derived using the cancer incidence (the pre-test probability) for the age-ranges included in each study (7, 34). To give a percentage risk of any cancer, cumulative PPVs were calculated by adding together PPVs for each tumour site, and presented by age-group and gender (7). The highest and lowest cumulative PPVs were calculated by adding the PPVs calculated with the highest and lowest LRs respectively.

We conducted a planned bivariate meta-analysis of the predictive value of weight loss by: (1) individual cancer site; (2) cancer stage; (3) gender; (4) age-group. Two sensitivity analyses were pre-specified based on QUADAS-2 assessment: one including studies with a low risk of bias and, a second including studies where the risk of bias in only one domain was high. Investigation of publication bias in diagnostic accuracy studies is not recommended by Cochrane, and so this was not assessed (35-37).

Results

Study Characteristics

Figure 1 summarises study selection. The 25 included studies were published between 1994 and 2015. One study was conducted in the USA and all others in the UK. The sample size ranged from 398 to 2,140,194 participants, median 43,791 (Inter-Quartile Range, 8,476-1,013,262). Table 1 details each included study.

Data source

Eight studies used routinely collected electronic health record data from The Health Improvement Network (THIN) database (8, 38-44), seven from the QCancer database (22, 23, 45-49), and four from the Clinical Practice Research Datalink (CRPD) (50-53). 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 electronic GP records, coded using the International Classification of Primary Care-2, blinded to the cancer outcome (54-56). Two used structured patient questionnaires (57, 58). One included data from three sources: patient questionnaire, patient telephone interview, and the GP record (59).

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 (8, 43, 44, 50-59). Control patients were matched for age (8, 44, 50-58), sex (8, 44, 50-58), GP practice (8, 43, 44, 50-56), consultation year (44) by using adjacency on the GP register (57), using Health Care Financing Administration lists (58), at random using the electronic record (8, 43, 44, 50-56), after attending ovarian screening or being referred for a suspected benign adnexal mass (59). 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 (22, 23, 38-42, 45-49). One study, at high risk of ascertainment bias, used five years (58).

Weight loss

There was marked heterogeneity in the definition of WL. One study used objective weight measurements, calculating the change between the weight measurement nearest to the date of diagnosis and the highest weight in the previous two years (8). All other database studies defined WL using a coded entry in the electronic GP record (22, 23, 38-53, 59). The code lists used to define WL were not published, and no study described the method used to discriminate WL from planned weight loss (e.g. through dieting or exercise). In three studies “any mention of weight loss” was coded after review of the entire coded and non-coded GP record (54-56). Questionnaire studies defined weight loss as “subjective weight loss” (57), “weight loss (unplanned) or the appearance of weight loss” (59), and “unintended weight loss \geq 6 weeks duration” (58).

Cancer type and stage.

The studies reported WL in association with ten cancer types: colorectal (8, 38, 48, 55, 57); pancreatic (40, 49, 52, 58); gastro-oesophageal (41, 45, 53); ovarian (42, 46, 59); lung (43, 54); renal tract (39, 47); myeloma (50), non-Hodgkins lymphoma (51), pancreatic or biliary tree (44), and prostate (56). Two studies identified all cancer types in each of the two sexes (22, 23) Several methods were used to confirm the diagnosis of cancer. The THIN and CRPD used UK Diagnostic Read codes inputted by primary care physicians (38-44, 50-53, 59). The QCancer studies used diagnostic codes and Office of National Statistics (ONS) cause-of-death codes (22, 23, 45-49). Four studies used regional cancer registry and hospital records (54-56, 58) and two only hospital records (57, 59). Three studies, in colorectal, pancreatic and ovarian cancer, reported cancer stage (55, 58, 59).

Risk of bias

Figure 2 and Appendix 2 summarise the QUADAS-2 assessment. Fifteen studies were classified as high risk of bias in one domain (8, 38-56). Three studies were classified as high risk of bias in more than one domain (57-59). The main potential sources of bias were: (a) applicability concerns when secondary care cases were matched either with primary care controls (57), using health care financing lists (58), or with outpatients or attendees at screening programmes (59); (b) selection bias in studies using the case-control design, which exaggerates measures of test accuracy (8, 18, 43, 44, 50-59); (c) inclusion bias because eight studies did not describe why all participants were not included in the analysis; and (d) recall bias in three studies using a retrospective questionnaire (57-59).

Measures of diagnostic accuracy

WL was a presenting feature of 1 in 14 cancers overall. This varied by cancer site: 1 in 5 prostate; 1 in 10 colorectal, gastro-oesophageal and pancreatic; 1 in 16 biliary tree; 1 in 25 myeloma, non-Hodgkins lymphoma and ovarian; and 1 in 33 lung and renal tract cancers. Table 2 presents demographic and diagnostic accuracy data for each study. Appendix 3 details the diagnostic value of WL with other clinical and demographic features. Forest plots are shown in Appendix 4. Figure 3 plots each study in ROC space using coloured symbols to denote subgroups of cancer site and gender.

Cancer type and stage.

Sensitivity ranged from 2% to 47% across cancer types; specificity from 92% to 99% (Table 2 and Appendix 4). Only colorectal and pancreatic cancer had sufficient studies for separate analyses (Table 2 and Appendix 4). The pooled sensitivity for colorectal cancer was 14% (CI 6-30%) and pooled specificity 97% (CI 94-99%). The pooled sensitivity for pancreatic cancer was 13% (CI 8-20%) and pooled specificity 99% (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.

Twenty studies adjusted for other covariates. These included potential confounders, such as age, but mainly symptoms known to be predictors of each cancer, for example rectal bleeding in colorectal cancer (Appendix 3). Adjustment left the DORs unchanged in all but three case-control studies in which they were significantly reduced (8, 43, 55). Hazard Ratios (HRs) ranged from 1.6 for ovarian cancer to 12.5 for pancreatic cancer across the cohort studies. In all cases, adjustment for other symptoms of cancer did not abolish the association between WL and a diagnosis of cancer.

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

Gender and age

Five studies examined diagnostic accuracy by sex. In one study, the sensitivity and specificity for any cancer in males was 3% (CI 3-4%) and 99% (CI 99-99%), respectively (22). In another, the sensitivity and specificity for any cancer in females was 5% (CI 5-6%) and 99% (CI 99-99%), respectively (23). However, there was no significant difference between HRs for men and women after adjustment for age, BMI, and other clinical features (Appendix 4). We were not able to calculate summary estimates for age-groups because studies reporting the same age-range and cancer type were too few.

Positive predictive values

PPVs for WL ranged from 0.0% for biliary tract cancer to 3.3% for prostate cancer (Appendix 5). One study reported higher PPVs for colorectal cancer in people aged >70 years old (1.7%) compared to <70 years old (0.4%) (57). Six studies reported the PPV for WL paired with another clinical feature ranging from 0.1% for chest pain for myeloma to 31.6% for jaundice in pancreatic cancer (Appendix 4). WL with another clinical feature yielded a PPV greater than: WL alone; the paired clinical feature alone; or by adding together the individual PPVs.

We calculated cumulative PPVs by age-group (Table 3). The more conservative estimates using the lowest LRs had a cumulative PPV of 3.0% in females >60years and 10.5% in males >60yrs, reaching the threshold for investigation (3%) used in the 2015 NICE guidelines (7). The more liberal estimate using the highest reported LRs for each cancer site resulted in females (6.7%) and males (14.2%) >60 years. The excess in males was largely the contribution of prostate cancer due to the relatively high LR and incidence. After removing prostate cancer from the analysis, the male PPV >60yrs (7.8%) still reached the threshold for investigation (Appendix 6).

Discussion

Summary of findings

Patients presenting to primary care with WL are at higher risk of having cancer than patients without recorded WL. The ten cancers were prostate, colorectal, lung, gastro-oesophageal, pancreatic, non-Hodgkins 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 PPV of cancer in male and female patients with WL aged 60-79yrs and 80+yrs exceeds the risk threshold for urgent investigation set out in NICE guidelines (7). The risk with WL increases when it presents alongside another clinical feature suggesting an individual cancer site, and with increasing age.

Strengths and weaknesses

To our knowledge, this is the only review of WL as a feature of cancer in non-specialist settings. We used a broad search strategy to interrogate large electronic databases. We have calculated cumulative PPVs for the first time for WL across ten cancer sites by using high quality national cancer incidence data.

There are important weaknesses, however. Foremost, we can provide no clarification about how much WL is required to make cancer possible. Most studies defined WL using coding but no studies reported the codelists used by the authors to define WL so we are unable to report with confidence whether WL was unexpected or expected (following diet or exercise). It seems likely that a WL code represents unexpected WL as a person who achieves weight loss intentionally is unlikely to report this to their GP. Similarly, a GP is unlikely to think that intentional WL is diagnostically relevant enough to code: we know that GP coding has been shown to be prone to recording bias, which occurs when GPs preferentially code the “alarm” features they consider to support their working diagnosis (61, 62). For example, the inclusion of free-text data in one study reduced the PPV of jaundice for pancreatic cancer from 12.8% (7.3 to 21.6) to 6.3% (4.5 to 8.7), and visible haematuria for bladder cancer from 4.0% (3.5 to 4.6) to 2.9% (2.6 to 3.2) (61). GPs commonly use free-text to amplify the clinical narrative after coding “alarm” symptoms, meaning that for some patients the entire details of a clinical feature remain hidden, invisible to analyses solely using symptom codes (61). Low-risk-but-not-no-risk vague symptoms of cancer, such as abdominal pain or cough, have high prevalence in primary care, are coded less, and patients with them are less likely to prompt clinicians to refer patients with these symptoms for urgent investigation (61, 63). However, we have found no reports investigating the influence of recording bias on the prevalence of WL. From the colorectal cancer studies in this review, the prevalence of WL 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%) (8, 48, 55). Only one study used objective measurements to define WL leaving studies at risk of misclassification due to missing data on weight (8, 60).

Furthermore there were insufficient data to describe the grade or stage of cancer diagnosed in patients with WL and how this compares with cancer in patients presenting without WL.

Finally, heterogeneity in diagnostic accuracy relates to heterogeneity in study quality: 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 this heterogeneity. One study, for example, showed that weight loss was reported more frequently when data were collected by questionnaire or telephone interview compared to using only a coded entry in the electronic record (59). Collecting data on unexpected weight loss by questionnaire increased the sensitivity and decreased the specificity compared with using only coded GP data. Ascertainment bias is also likely, despite most studies using an index test and reference standard within a two year period. Two studies have reported that within a two year window “serendipitous” asymptomatic cancers are diagnosed when symptoms (not caused by cancer) are investigated (9, 64).

Comparison to existing literature

Others have reviewed the symptoms of single cancer sites (65-70). We have included all of their studies except where concerns existed over study population (65, 66, 69) or inadequate reporting of 2 x 2 data (70), and we included an additional study post-dating their searches (43). We identified no previous review of symptoms presenting to primary care in association with myeloma, non-Hodgkins lymphoma, ovarian, or prostate cancer.

Implications for clinical practice

Our review suggests that patients aged 60 years or older with WL presenting to primary care settings prompting a clinical record entry warrant rapid investigation for possible cancer, potentially across multiple possible sites. Our findings will therefore be of interest to policymakers developing multidisciplinary symptom-based referral pathways to compliment existing site specific routes (71, 72). As a symptom of cancer, recorded WL is the second highest risk after rectal bleeding in colorectal cancer (65), haemoptysis in lung (54), rib pain in myeloma (50), jaundice in pancreatic (69), and haematuria in renal tract (39); and third highest in non-Hodgkins lymphoma (51) and gastro-oesophageal (41, 45, 53). Additional symptoms in combination with WL strengthen these associations.

The low sensitivity for WL reflects the clinical reality for patients that some cancers lead to weight loss whilst many more do not. Understanding the site distribution of cancer in these patients may inform the sequencing of investigation in this patient group. The low sensitivity also demonstrates that the absence of WL cannot be used to rule out cancer. The extremely high specificity for WL has a number of potential and overlapping

331 explanations: (1) patients may only be attending primary care once weight loss is marked; (2) clinicians may
332 only code the symptom after conducting simple investigations to rule out other causes of WL; (3) the number
333 of false positives is artificially low in comparison to the extremely high number of true negatives that represent
334 the low prevalence of cancer in primary care populations.

335
336 It is probable that when GPs choose to code WL this decision reflects that the clinician believes the symptom
337 to be important; this belief may be based on additional symptoms or physical findings which may themselves
338 represent an increased risk for cancer. Thus some of the risk of cancer associated with coded WL represents a
339 broader assessment by the clinician. Arguably this is helpful. Our results clearly show that coded WL warrants
340 investigative action; if clinical systems were designed to prompt the clinician to consider cancer whenever they
341 enter a WL code, this prompting may lead to an expedited diagnosis.

342 343 *Implications for future research*

344 To overcome the limitations outlined above, the ideal methodology to ascertain the diagnostic value of WL (or
345 any other clinical feature relevant to multiple cancer types) in primary care would be a prospective cohort
346 study. The prospective design overcomes biases in the studies in this review. As the prevalence of cancer (and
347 WL) is low in primary care, a study powered to investigate all relevant symptoms to all cancers would have to
348 be prohibitively large. The CANcer Diagnosis Decision Rules (CANDID) study is underway in UK primary care to
349 investigate the clinical features of colorectal and lung cancer including WL, but the prevalence of WL in this
350 cohort is still likely to be low (73).

351
352 There is more to be gained from historical cohort studies using routinely collected electronic record datasets
353 (22, 23, 74-76) that: (1) ascertain a prevalence for WL based on coded, non-coded, and numeric data; (2)
354 confirm cancer utilising the clinical record (coded and non-coded) and linkages to national cancer registries; (3)
355 report 2x2 data for WL in combination with other clinical features; (4) report diagnostic intervals and longer-
356 term outcomes. Research is required to understand the drivers of weight recording in primary care, and the
357 extent of weight loss that prompts a GP to code it. Without these studies we will remain unable to answer
358 fundamental questions of “how much weight loss should I worry about?”

359
360 In the meantime, once a physician considers that weight loss in a patient over 60 warrants a clinical entry,
361 these data indicate that investigation to identify a cancer is then necessary.

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Table 1: Characteristics of the included studies

Author (year) CANCER <i>Population</i>	DESIGN Data Source <i>Recruitment</i> Follow-up	Index Test-Weight loss <i>Reference Standard- Cancer</i>	Inclusion Criteria	Exclusion Criteria
COLORECTAL (Collins and Altman, 2012) <i>Primary Care, UK</i>	COHORT THIN database <i>01/01/00-30/06/08</i> 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 et al., 1994) <i>Primary and secondary care, North-East England</i>	CASE-CONTROL (1:1) Structured patient questionnaire <i>01/1989-30/09/90</i> 1yr pre-diagnosis	Patient reported "subjective weight loss". <i>Histological diagnosis of cancer.</i>	Cases- Consecutive cases identified <2wks 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 et al., 2005b) <i>Primary Care, Exeter, England.</i>	CASE-CONTROL (1:5) GP record (written and electronic) <i>1998-2002 (diagnosis)</i> 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 et al., 2009) <i>Primary Care, UK.</i>	CASE-CONTROL (1:7) THIN Database <i>01/2001-07/2006 (diagnosis)</i> 2yrs pre-diagnosis	Difference between last recorded weight and highest weight in previous 2 years (≥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 years of records before the index date.
COLORECTAL (Hippisley-Cox and Coupland, 2012a) <i>Primary Care, UK</i>	COHORT QResearch Database <i>01/01/00-30/09/10</i> 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, starting latest of, study start date, 12months after practice registration, first recorded loss rectal bleeding, loss of appetite, weight loss, or abdominal pain.	No Townsend score (195305). Prior colorectal cancer (8414). Rectal bleeding, loss of appetite, weight loss, or abdominal pain in prior 12 months (89572).
GASTRO-OESOPHAGEAL (Collins and Altman, 2013a) <i>Primary Care, UK</i>	COHORT THIN database <i>01/01/00-30/06/08</i> 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 and Coupland, 2011) <i>Primary Care, UK</i>	COHORT QResearch Database <i>01/01/00-30/09/10</i> 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, starting latest of, study start date, 12months after practice registration, first recorded dysphagia, haematemesis, appetite loss, weight loss, or abdominal pain.	No Townsend score (195305). Gastro-oesophageal cancer (1377). Dysphagia, haematemesis, loss of appetite, weight loss, and abdominal pain in prior 12m (89572).

GASTRO-OESOPHAGEAL (Stapley et al., 2013) Primary Care, UK	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 (GO) cancer code. Controls- age, sex and practice matched.	No records <1yr before index date (3335), metastatic cancer (10), cases with past GO cancer (28), cases without controls (17), Oesophageal ca used as gastric (131), controls are cases (262), controls without cases (809), duplicate control (427).
LUNG (Hamilton et al., 2005a) Primary Care, Exeter, England.	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 et al., 2013) Primary Care, UK	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 year of records prior to lung cancer diagnosis, <40yrs at index diagnosis (59)
MULTIPLE Male (Hippisley-Cox and Coupland, 2013a) Primary Care, UK	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 (124743). Red flag symptom in the 12 months prior to study entry (91819).
MULTIPLE Female (Hippisley-Cox and Coupland, 2013b) Primary Care, UK	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 (132945). Red flag symptom in the 12 months prior to study entry (165310).
MYELOMA (Shephard et al., 2015a) Primary Care, UK	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 (1201), 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 et al., 2015b) Primary Care, UK	CASE-CONTROL (1:5) CPRD Database 01/2000-12/2009 >1yr pre-diagnosis	GP weight loss Read Code. <i>106 Non-Hodgkin's Lymphoma (NHL) Read codes.</i>	Cases- Non-Hodgkin Lymphoma code. Controls- age, sex, and practice matched.	Hodgkins lymphoma (HL) (283), control of HL (1402), case of mycosis fungoides (MF) or Sézary syndrome (SS) (147), control of MF or SS (719); no records <1yr before index date (2018); cases without controls (7); controls with NHL (70) controls with no record after registration (26).
OVARIAN (Lim et al., 2012)	COHORT THIN database	Weight loss Read Code.	THIN record starting latest of study start date, registration, first red flag symptom of	Prior Ovarian cancer; GP registered <12m, invalid dates, <30/≥85 yrs.

Primary Care, UK	01/01/00-30/06/08 2yrs following entry	Relevant cancer Read Code.	Ovarian cancer.	
OVARIAN (Hippisley-Cox and Coupland, 2012d) Primary Care, UK	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, 12months after practice registration, first recorded loss of appetite, weight loss, abdominal pain, abdominal distension, rectal bleeding, or postmenopausal bleeding.	No Townsend score (98260). Prior bilateral oophorectomy (21099) or ovarian cancer (2079). Loss of appetite, weight loss, abdominal pain, abdominal distension, rectal bleeding, or postmenopausal bleeding in prior 12 months (55824).
OVARIAN (Lim et al., 2012) Ovarian Cancer Population Study, UK	CASE-CONTROL (1:1.2) Questionnaire, telephone interview, "GP notes" 16/02/06-28/02/08 15m pre-diagnosis.	Unplanned weight loss including the appearance of weight loss (Questionnaire, telephone interview, or GP code). <i>Independent review of staging, histology, pathology, and case notes by Gynae-oncologist.</i>	Cases- 50-79yrs, attending preoperative or medical oncology clinic or admitted for surgery for primary ovarian cancer. Controls- attending Ovarian screening (postmenopausal) clinic or surgery for a suspected benign adnexal mass.	Differential agreement to take part in questionnaire and telephone studies.
PANCREATIC (Collins and Altman, 2013b) Primary Care, UK	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 Pancreatic cancer.	Prior Pancreatic cancer; GP registered <12m, invalid dates, <30/≥85 yrs.
PANCREATIC (Hippisley-Cox and Coupland, 2012b) Primary Care, UK	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, 12months after practice registration, first recorded dysphagia, loss of appetite, weight loss, abdominal pain or distension.	No Townsend score (195305). Prior pancreatic cancer (257). Dysphagia, loss of appetite, weight loss, abdominal pain, or abdominal distension in prior 12 months (77071).
PANCREATIC (Holly et al., 2004) San Francisco Bay 'population'	CASE-CONTROL Two questionnaires by interview. 1994-2001 5-years pre-diagnosis	Patient reported weight loss of >6w duration. <i>Surveillance, Epidemiology, and End Results (SEER) database 18–24 months after diagnosis.</i>	Cases- pancreatic cancer identified within 1 month 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 et al., 2014) Primary Care, UK	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 years of data prior to the index date.
PANCREATIC (Stapley et al., 2012)	CASE-CONTROL (1:5) CPRD Database	GP weight loss Read Code. <i>25 Pancreatic cancer Read codes.</i>	Cases- Pancreatic Cancer code.	Cases without controls (2), not a pancreatic primary (10). Controls with

Primary Care, UK	01/2000-12/2009 >1yr pre-diagnosis		Controls- age, sex and practice matched.	pancreatic cancer (64), controls no case (40), controls with no data in the year before diagnosis the index date (1414).
PROSTATE (Hamilton et al., 2006) <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 and Altman, 2013c) <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 and Coupland, 2012c) <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, 12months after practice registration, first recorded loss of haematuria, appetite loss, weight loss, or abdominal pain.	No Townsend score (195305). Prior renal tract cancer (4417). Haematuria, loss of appetite, weight loss, or abdominal pain in prior 12 months (81332).

Year (ref)	Age (yrs)	Male (%)	2x2 for Weight Loss and Cancer				Weight loss Prevalence (%)			DOR (95% CI)	Sens (95% CI)	Spec (95% CI)	PLR (95% CI)
			TP	FP	FN	TN	All	Cases	Non- Cases				
Biliary Tree													
2014 (1)	72avg 12sd	47.1	46	302	783	16890	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 (2)	30-84	49.6	215	28074	3497	2103754	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	12767 ^M	1912 ^M	1044962 ^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	15307 ^F	1585 ^F	1058792 ^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 (3)	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 (4)	>40	50.7	94	92	255	1652	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 (5)	>30	N/R	561	1530	4916	36784	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%}	5267 ^{5-9.9%}	37462 ^{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%}	5126 ^{>10%}	37636 ^{>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 (6)	30-84	50.2	106	13901	2497	1219043	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											13.5 (5.5-29.5)	96.9 (93.9-98.5)	4.4 (3.2-6)
Gastro-Oesophageal													
2013 (7)	30–84	49.6	218	28185	1548	2110243	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	15379 ^M	1052 ^M	1048227 ^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	12806 ^F	496 ^F	1062016 ^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 (8)	≥40	64.2 ^C	615	276	6856	32601	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 (9)	30-84	50.2	107	9063	1236	952634	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 (10)	>40	68.8	67	54	180	1181	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 (11)	>40	49.1	336 ^{4-24m}	739 ^{4-24m}	11738 ^{4-24m}	119992 ^{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}	11877 ^{4-12m}	120408 ^{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}	11935 ^{13-24m}	120315 ^{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 (12)	≥40	52.5	107	86	2596	12071	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 (13)	≥40	51.3	164	115	4198	19353	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 (14)	30–84	0	35	14996	700	1039087	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 (15)	30-84	0	22	5146	516	466430	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 (16)	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 sites													
2013 (17)	25-89	0	421	6453	11871	648858	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)
2013 (18)	25-89	100	636	5224	11277	662037	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 (19)	30-84	49.6	82	15022	536	2120322	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	13428 ^M	275 ^M	1053833 ^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	1594 ^F	261 ^F	1066489 ^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 (20)	30-84	50.2	61	9354	720	961571	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 (21)	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 (1)	71avg 11sd	47.1	294	302	2496	16890	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 (22)	≥40	48.0 ^C	353	105	3282	16354	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)
Pooled estimates for Pancreatic											12.9 (8.2-19.8)	98.6 (97.6-99.2)	9.1 (6.6-12.6)
Prostate													
2005 (23)	>40	100	48 ^{1st}	21 ^{1st}	169 ^{1st}	1059 ^{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}	1069 ^{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 (24)	30-84	49.6	21	16016	577	1065164	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 (25)	30-84	50	38	9243	1584	956816	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)

Table 1: Demographic characteristics of the population and me

asures of diagnostic accuracy for all studies.

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

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Table 3. Cumulative PPVs across all cancer sites.

Shading: 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-hodgkins lymphoma, ovarian, pancreatic, prostate, and renal tract cancer. Prostate cancer is removed from the female analysis, and ovarian from the male.

	Gender	Age-Group (yrs)														
		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	FEMALE	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
	COMBINED	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
	MALE	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	FEMALE	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
	COMBINED	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
	MALE	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

Figure 1: PRISMA flow diagram of study selection

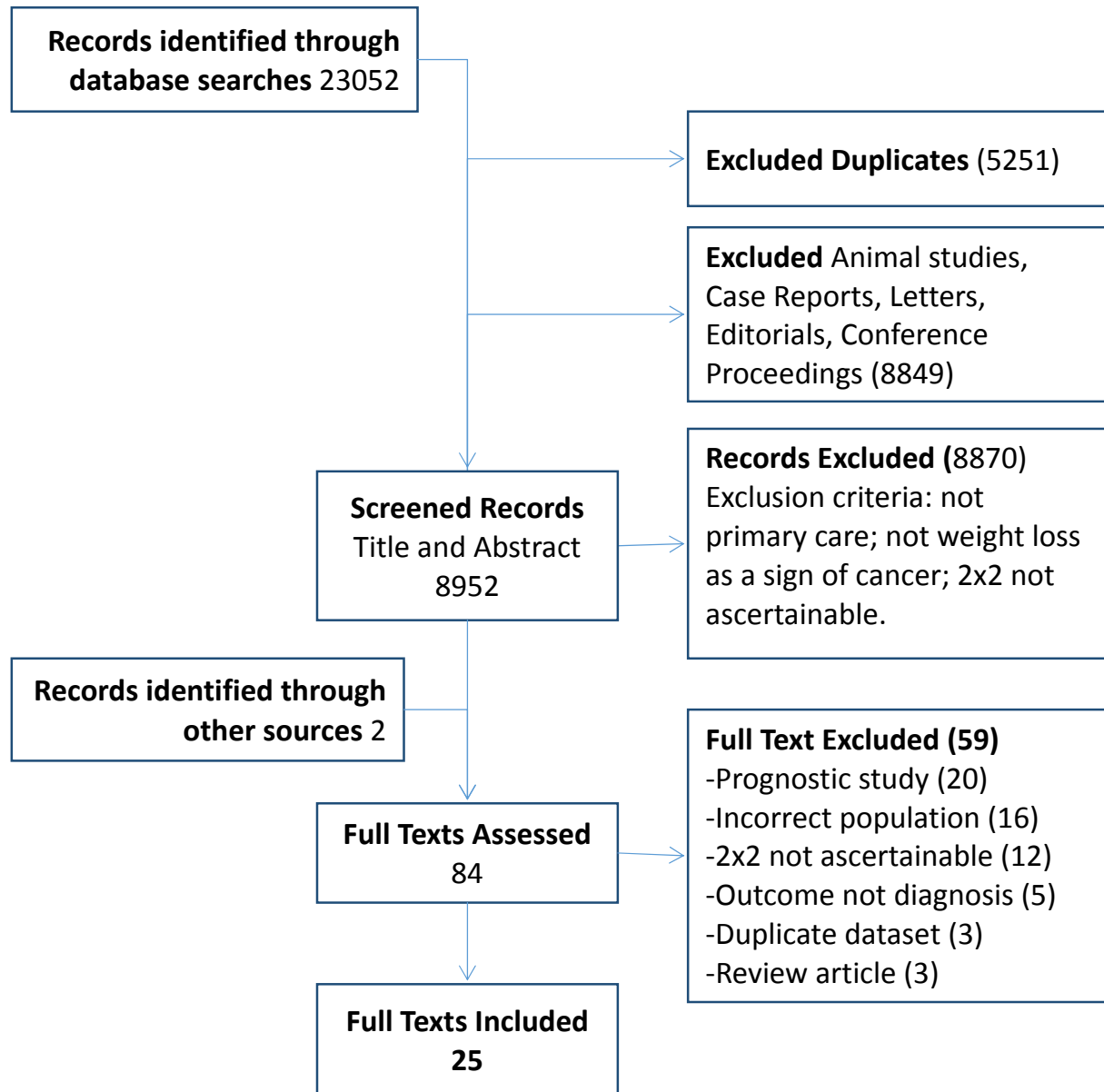


Figure 2: Graphical summary of QUADAS-2 assessment of risk of bias and applicability concerns presented as percentages across all 25 included studies.

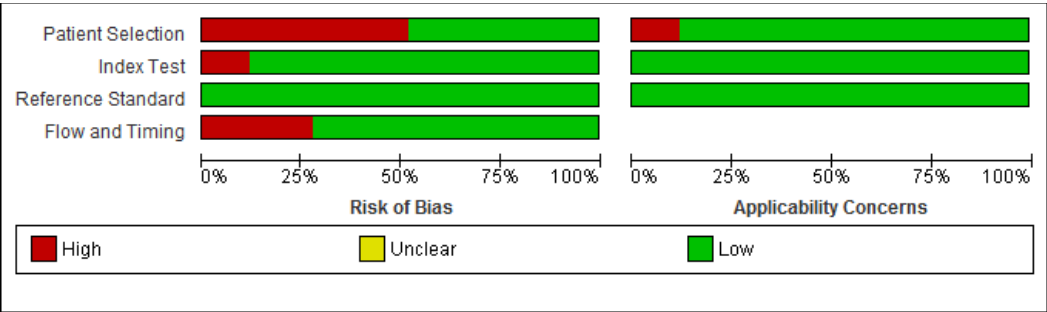
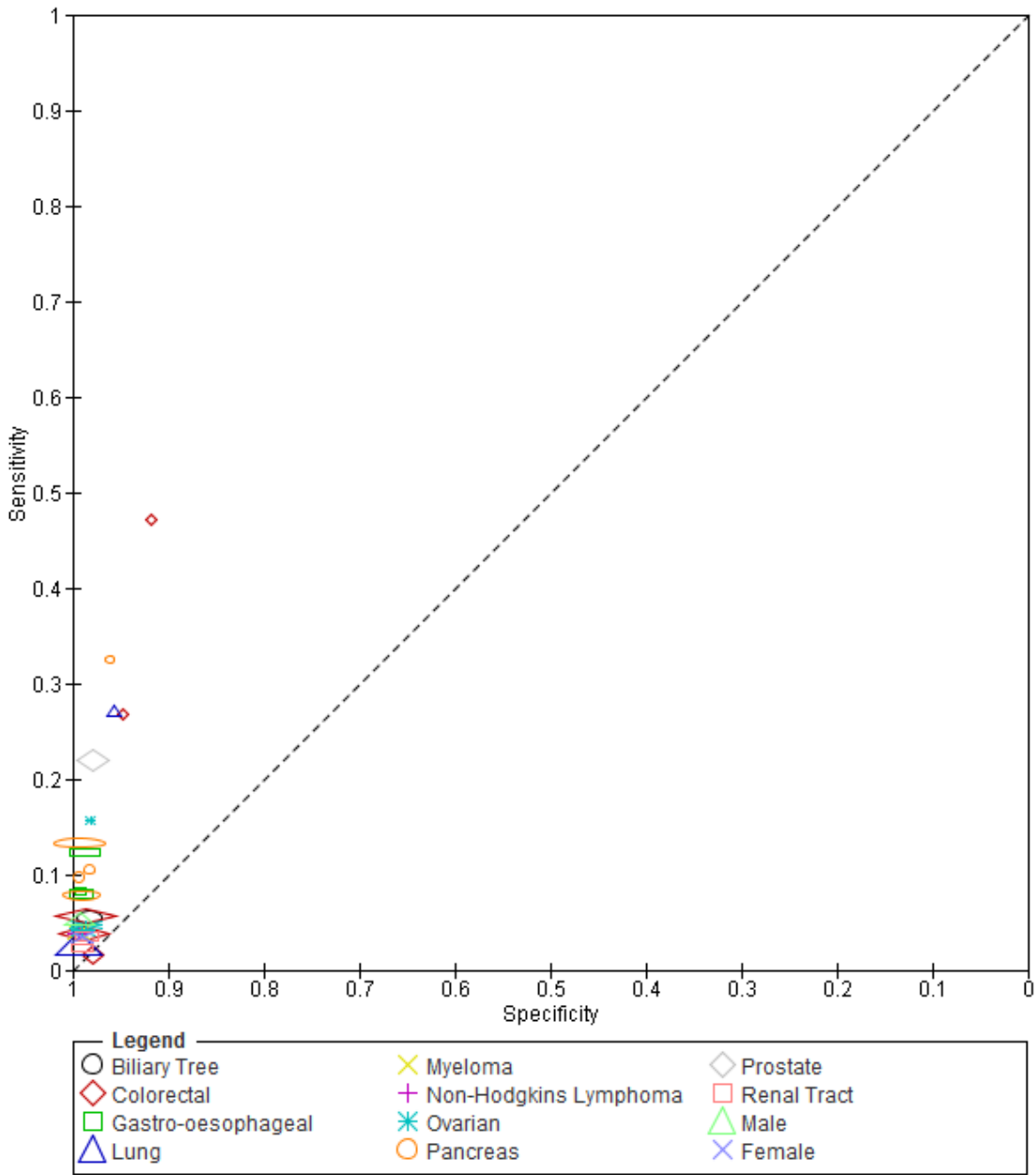


Figure 3. ROC plot of diagnostic value of unexplained weight loss for different cancers.

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 instantly clear that a high specificity comes at the cost of a low sensitivity.



1 Appendix 1. 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.	1224
3	exp neoplasms/	2787539
4	(cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?).ti,ab.	2682980
5	3 or 4	3448016
6	weight loss/	27457
7	body mass index/	92073
8	Body Weight/	169174
9	(weight or bmi or body mass index).ti.	92205
10	(weight adj3 (loss or lose or lost or losing or chang* or reduc*)).ti,ab.	102586
11	((bmi or body mass index) adj3 (chang* or reduc* or low)).ti,ab.	9321
12	6 or 7 or 8 or 9 or 10 or 11	377478
13	*Diagnosis/	13360
14	*early diagnosis/ or "early detection of cancer"/	12811
15	exp *Neoplasms/di [Diagnosis]	246407
16	diagnos*.ti.	486363
17	((cancer* or neoplas* or carcinoma? or malignan* or tumor? or sarcoma? or lymphoma? or leuk?emia?) adj5 (diagnos* or detect*)).ti,ab.	282475
18	(presentation or presenting or feature? or manifest* or symptom*).ti.	321570
19	((clinical or diagnos*) adj2 (feature? or manifest* or symptom* or present*)).ti,ab.	273510
20	"Referral and Consultation"/	54597
21	(referral? or referred or refer).ti,ab.	223637
22	general practitioners/ or physicians, family/ or physicians, primary care/	19302
23	general practice/ or family practice/	66562
24	Office Visits/	5857
25	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.	97966
26	(office? or visit* or clinic or clinics).ti,ab.	407258
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	2027740
28	5 and 12 and 27	7991
29	exp animals/ not humans.sh.	4132479
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.	1712966
31	(exp infant/ or exp child/ or adolescent/) not exp adult/	1606289
32	(child* or infan* or baby or babies or p?ediatric* or preschool* or pre-school* or toddler?).ti.	900861
33	29 or 30 or 31 or 32	6263526
34	28 not 33	6963
35	(case reports or comment or editorial or letter).pt.	3104438
36	34 not 35	5049

2

3

4 **Appendix 2:** Summary of QUADAS-2 assessment.

5 *Blinding was heavily weighted in the index test domain as recall bias could arise if the symptom of UWL was*
6 *elicited after the cancer diagnosis. Highest weighting was given to correct classification of cancer in the*
7 *reference standard domain, as blinding was unnecessary for studies using an objective method. The inclusion of*
8 *all patients in the final analysis was weighted most in the flow and timing domain to address selection bias,*
9 *followed by use of an appropriate interval between UWL and cancer to address ascertainment bias, then*
10 *reference standard consistency, as the same method was used within each study.*

11

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Collins 2012	+	+	+	+	+	+	+
Collins 2013a	+	+	+	+	+	+	+
Collins 2013b	+	+	+	+	+	+	+
Collins 2013c	+	+	+	+	+	+	+
Collins 2013d	+	+	+	+	+	+	+
Curless 1994	-	-	+	+	-	+	+
Hamilton 2005a	-	+	+	+	+	+	+
Hamilton 2005b	-	+	+	+	+	+	+
Hamilton 2005c	-	+	+	+	+	+	+
Hamilton 2009	-	+	+	+	+	+	+
Hippisley-Cox 2011	+	+	+	-	+	+	+
Hippisley-Cox 2012a	+	+	+	-	+	+	+
Hippisley-Cox 2012b	+	+	+	-	+	+	+
Hippisley-Cox 2012c	+	+	+	-	+	+	+
Hippisley-Cox 2012d	+	+	+	-	+	+	+
Hippisley-Cox 2013a	+	+	+	+	+	+	+
Hippisley-Cox 2013b	+	+	+	+	+	+	+
Holly 2004	-	-	+	-	-	+	+
Iyen-Omofoman 2013	-	+	+	+	+	+	+
Keane 2014	-	+	+	+	+	+	+
Lim 2012	-	-	+	-	-	+	+
Shephard 2015a	-	+	+	+	+	+	+
Shephard 2015b	-	+	+	+	+	+	+
Stapley 2012	-	+	+	+	+	+	+
Stapley 2013	-	+	+	+	+	+	+

- High
? Unclear
+ Low

12

13 *Appendix 3: 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, +ve FOB, low haemoglobin
		Constipation	3.0 (1.7-5.4)		
		Diarrhoea	3.1 (1.8-5.5)		
		Rectal bleeding	4.7		
		abdo pain	3.4 (2.1-6.0)		
		abdo tenderness	6.4		
		Abnormal rectal exam	7.4		
		Hb 10-13	1.3 (0.7-2.6)		
		Hb<10	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, CIBH, Abdo 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 GI cancer, Hb <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, haematemesis, Hb<11g/dl in last 12m.
	Stapley (2013)	>55y	Low Hb	OR 8.9 (7.1-11.2)	Dysphagia, epigastric pain, dyspepsia, reflux, nausea or vomiting, abdominal pain, chest pain, constipation, thrombocytosis, low hb, low mcv, leucocytosis, raised inflammatory markers, abnormal liver enzymes, raised cholesterol.
			Raised platelets		
			Constipation		
			Dysphagia		
			Chest pain		
			Abdo pain		
			Nausea + vomiting		
			Dyspepsia		
			Epigastric pain		
			Reflux		
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)					
	Iyen-Omofoman (2013)				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, Hb<12d/dl in last 12m, smoking status, prior cancer diagnosis, COPD, Townsend score.
					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, LRTI, non-specific chest infections, COPD, chest/shoulder pain, hoarse voice, URTI.
MULTIPLE SITES- MALE	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 body mass index, smoking status, previous diagnosis of cancer, anaemia, Townsend deprivation 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- FEMALE	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 body mass index, smoking status, Townsend deprivation score, alcohol, previous Cancer diagnosis, anaemia, 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)	>60y	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, raised mcv, hypercalcaemia.
			Chest Infection	0.3		
			Chest Pain	0.1		
			Low Platelets	0.5		
			Leukopenia	0.5		
			Low Hb	0.4 (0.9-0.7)		
			Fracture	0.3		
			Nausea	0.3		
			Nosebleeds	0.3		
			Back Pain	0.5		
			Raised MCV	0.6		

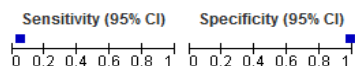
			Raised Infl Markers	0.6 (0.3-1.1)		
			Raised Creatinine	0.5		
			Hypercalcaemia	0.5		
NON-HODGKINS LYMPHOMA	Shephard (2015b)	>60y	infection	0.4 (0.2-0.6)	OR 3.2 (2.3-4.4)	Infection, lymphadenopathy, abdominal pain, mass, shortness of breath, head and neck mass, fatigue, constipation, vomiting and nausea, indigestion, weight loss, second back pain, malaise, low full blood count, raised inflammatory markers, raised liver function tests, leucocytosis, macrocytosis, microcytosis, raise gamma globulin.
			SOB	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)		
			Abdo pain	0.9		
			Mass	2.2		
			Lymphadenopathy	>10		
			Raised LFTs	1.5 (0.8-2.8)		
			Macrocytosis	0.2		
			Raised gamma globulin	3.5		
			Low FBC	0.9 (0.6-1.3)		
			Raised infl 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, Hb <11g/dl in last 12m, abdominal pain, abdominal distension, appetite loss, rectal bleeding, postmenopausal bleeding.
	Lim (2012)				OR 2.9 (0.9-9.9)^d	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 las 12m.
	Holly (2004)				OR 12 (5.2-28)	Age and sex.
	Stapley (2012)	>60y	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		
			Abdo 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, Hb<11g/dl.

- 15 **Appendix 4: Forest plot of sensitivity and specificity of unexplained weight loss for**
- 16 **different types of cancer.** TP = true positive; FP = false positive; FN = false negative; TN = true negative. The blue
- 17 square depicts the sensitivity and specificity for each study and the horizontal line represents the corresponding 95%

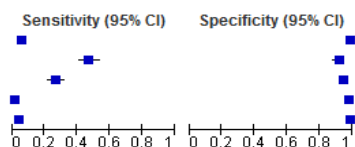
Biliary Tree

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Keane 2014	46	302	783	16890	0.06 [0.04, 0.07]	0.98 [0.98, 0.98]



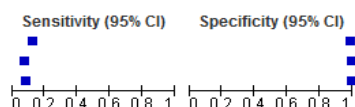
Colorectal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Collins 2012	215	28074	3497	2103754	0.06 [0.05, 0.07]	0.99 [0.99, 0.99]
Curless 1994	129	22	144	251	0.47 [0.41, 0.53]	0.92 [0.88, 0.95]
Hamilton 2005b	94	92	255	1652	0.27 [0.22, 0.32]	0.95 [0.94, 0.96]
Hamilton 2009	690	1530	40393	75098	0.02 [0.02, 0.02]	0.98 [0.98, 0.98]
Hippisley-Cox 2012c	106	13901	2497	1219043	0.04 [0.03, 0.05]	0.99 [0.99, 0.99]



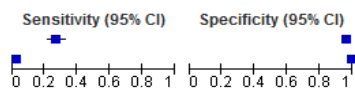
Gastro-oesophageal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Collins 2013d	218	28185	1548	2110243	0.12 [0.11, 0.14]	0.99 [0.99, 0.99]
Hippisley-Cox 2011b	107	9063	1236	952634	0.08 [0.07, 0.10]	0.99 [0.99, 0.99]
Stapley 2013	615	276	6856	32601	0.08 [0.08, 0.09]	0.99 [0.99, 0.99]



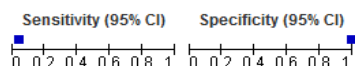
Lung

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hamilton 2005a	67	54	180	1181	0.27 [0.22, 0.33]	0.96 [0.94, 0.97]
Iyen-Omofoman 2013	336	739	11738	119992	0.03 [0.02, 0.03]	0.99 [0.99, 0.99]



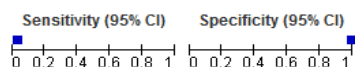
Myeloma

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Shephard 2015a	107	86	2596	12071	0.04 [0.03, 0.05]	0.99 [0.99, 0.99]



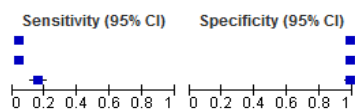
Non-Hodgkins Lymphoma

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Shephard 2015b	164	115	4198	19353	0.04 [0.03, 0.04]	0.99 [0.99, 1.00]



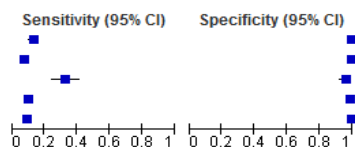
Ovarian

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Collins 2013c	35	14996	700	1039087	0.05 [0.03, 0.07]	0.99 [0.99, 0.99]
Hippisley-Cox 2012a	22	5146	516	466430	0.04 [0.03, 0.06]	0.99 [0.99, 0.99]
Lirn 2012	30	5	161	263	0.16 [0.11, 0.22]	0.98 [0.96, 0.99]



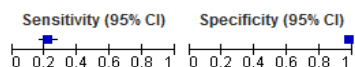
Pancreas

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Collins 2013b	82	15022	536	2120322	0.13 [0.11, 0.16]	0.99 [0.99, 0.99]
Hippisley-Cox 2012d	61	9354	720	961571	0.08 [0.06, 0.10]	0.99 [0.99, 0.99]
Holly 2004	39	7	81	173	0.33 [0.24, 0.42]	0.96 [0.92, 0.98]
Keane 2014	294	302	2496	16890	0.11 [0.09, 0.12]	0.98 [0.98, 0.98]
Stapley 2012	353	105	3282	16354	0.10 [0.09, 0.11]	0.99 [0.99, 0.99]



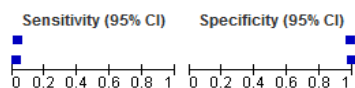
Prostate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hamilton 2005c	48	21	169	1059	0.22 [0.17, 0.28]	0.98 [0.97, 0.99]



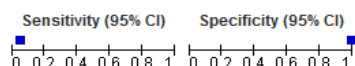
Renal Tract

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Collins 2013a	21	16016	577	1065164	0.04 [0.02, 0.05]	0.99 [0.98, 0.99]
Hippisley-Cox 2012b	38	9243	1584	956816	0.02 [0.02, 0.03]	0.99 [0.99, 0.99]



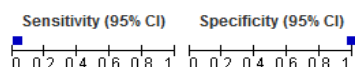
Male

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hippisley-Cox 2013a	636	5224	11277	662037	0.05 [0.05, 0.06]	0.99 [0.99, 0.99]



Female

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hippisley-Cox 2013b	421	6453	11871	648858	0.03 [0.03, 0.04]	0.99 [0.99, 0.99]



19 **Appendix 5: Positive predictive values (PPVs) of unexplained weight loss for a diagnosis of**
20 **cancer.** Prior probability (PrP) is based on the CRUK age-adjusted incidence rates for each cancer for England,
21 2013. The prior odds (PrO) were calculated using $(PrP/(1-PrP))$. The posterior odds (PoO) were calculated using
22 $(PrO*PLR)$. The posterior probability (PoP) was calculated using $(PoO/(1+PoO))$. The Positive Predictive Value
23 (PPV) is the PoP expressed as a proportion. *72avg 12sd, **71avg 11sd.

Cancer	Study	Population (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) All	30-84	0.00106582	0.0010670	4.4	0.004695	0.00467	0.47
	Collins (2012) Male	30-84	0.00111475	0.0011160	5	0.005580	0.00555	0.55
	Collins (2012) Female	30-84	0.00100509	0.0010061	3.8	0.003823	0.00381	0.38
	Curless (1994) All	25-93	0.00101999	0.0010210	5.9	0.006024	0.00599	0.60
	Curless (1994) <70y	25-69	0.00051457	0.0005148	8.6	0.004428	0.00441	0.44
	Curless (1994) >70y	70-89	0.00410450	0.0041214	4.3	0.017722	0.01741	1.74
	Hamilton (2005b)	>40	0.00151671	0.0015190	5.1	0.007747	0.00769	0.77
	Hamilton (2009) All	>30	0.00119001	0.0011914	2.6	0.003098	0.00309	0.31
	Hamilton (2009) 5-9.9%	>30	0.00119001	0.0011914	1.7	0.002025	0.00202	0.20
	Hamilton (2009) >10%	>30	0.00119001	0.0011914	3.6	0.004289	0.00427	0.43
	H-Cox (2012c)	30-84	0.00106582	0.0010670	3.6	0.003841	0.00383	0.38
Gastro-Oesophageal	Collins (2013d) All	30-84	0.00034577	0.0003459	9.4	0.003251	0.00324	0.32
	Collins (2013d) Male	30-84	0.00049279	0.0004930	7.7	0.003796	0.00378	0.38
	Collins (2013d) Female	30-84	0.00020867	0.0002087	12.4	0.002588	0.00258	0.26
	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) 4-24m	>40	0.00142564	0.0014277	4.5	0.006425	0.00638	0.64
	I-Omofoman (2013) 4-12m	>40	0.00142564	0.0014277	6.1	0.008709	0.00863	0.86
	I-Omofoman (2013) 13-24m	>40	0.00142564	0.0014277	3.3	0.004711	0.00469	0.47
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) questionnaire	50-79	0.00046979	0.0004700	8.4	0.003948	0.00393	0.39
	Lim (2012) telephone	50-79	0.00046979	0.0004700	6.8	0.003196	0.00319	0.32
	Lim (2012) e-record	50-79	0.00046979	0.0004700	3.3	0.001551	0.00155	0.15
Pancreatic	Collins (2013b) All	30-84	0.00020084	0.0002009	9.7	0.001949	0.00194	0.19
	Collins (2013b) Male	30-84	0.00022003	0.0002201	13.4	0.002949	0.00294	0.29
	Collins (2013b) Female	30-84	0.00018335	0.0001834	6.1	0.001119	0.00112	0.11
	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) 1st	>40	0.00297681	0.0029857	11.4	0.034037	0.03292	3.29
	Hamilton (2005c) 2nd	>40	0.00297681	0.0029857	4.1	0.012241	0.01209	1.21
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

25 **Appendix 6: Cumulative PPVs across all cancer sites - excluding prostate cancer.**

26 Shading: 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
27 available to the GP. The combined analysis includes: colorectal, gastro-oesophageal, lung, multiple myeloma, non-hodgkins lymphoma, ovarian, pancreatic, and renal tract cancer. Ovarian cancer is
28 removed from the male analysis.

	Gender	Age-Group (yrs)														
		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	FEMALE	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
	COMBINED	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
	MALE	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	FEMALE	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
	COMBINED	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
	MALE	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