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Original Article

Prevalence of multimorbidity in survivors of 28 cancer sites: an English nationwide cross-sectional study

Tahania A Ahmad[1], Abu ZM Dayem Ullah[2], Claude Chelala[2], Dipesh P Gopal[1], Fabiola Eto[1], Rafael Henkin[1], Miriam Samuel[1], Sarah Finer[1], Stephanie JC Taylor[1]

[1]*Wolfson Institute of Population Health, Queen Mary University of London, London, The United Kingdom;* [2]*Barts Cancer Institute, Queen Mary University of London, London, The United Kingdom*

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Abstract: Multimorbidity, the presence of a chronic condition in addition to cancer, is of particular importance to cancer survivors. It has an impact on the progression, stage at diagnosis, prognosis, and treatment of cancer patients. Evidence is scarce on the prevalence of specific comorbidities in survivors of different cancers to inform prevention and management of multimorbidity. The objective of this study is to address this evidence gap by using large scale electronic health data from multiple linked UK healthcare databases to examine the prevalence of multimorbidity in 28 cancer sites. For this population-based cross-sectional study, we linked primary and secondary healthcare data from the UK Clinical Research Practice Datalink (CPRD) GOLD dataset and Hospital Episode Statistics (HES). We identified survivors of 28 common cancers aged 18 years or older at diagnosis who survived 2 years of cancer and compared their multimorbidity with matched controls without a history of cancer. To compare prevalence of individual comorbidity, multivariable logistic regression models, adjusted for confounding factors were used. Between January 1, 2010 and December 31, 2020, we identified 347,028 cancer survivors and 804,299 controls matched on age, sex and general practice. Cancer survivors had a higher prevalence of multimorbidity compared to non-cancer controls across all the cancer sites. Hypertension (56.2%), painful conditions (39.8%), osteoarthritis (38.0%), depression (31.8%) and constipation (31.4%) were the five most frequent chronic conditions reported. Compared to the controls, higher odds of constipation were found in survivors of 25 of the 28 cancer sites and higher odds of anaemia were found in 23 cancer sites. Prevalence of constipation, anaemia and painful conditions were higher after cancer diagnosis compared to before diagnosis. Since these comorbidities are not uniformly assessed as part of any of the comorbidity scales, they tend to be underreported among cancer survivors. The elevated risk of certain comorbidities in cancer survivors suggests the potential for preventative efforts in this population to lower disease burden and improve quality of life. Long-term conditions should not be viewed as the inevitable result of cancer diagnosis and treatment. We need to consider integrated management of chronic conditions tailored to specific cancers to improve cancer survivorship.

Keywords: Cancer survivor, cancer survivorship, multimorbidity, comorbidity, prevalence, before and after cancer, living with and beyond cancer, chronic conditions, quantitative study, cancer care, cancer treatment

Introduction

Cancer incidence is rising worldwide, and it is the leading cause of death after cardiovascular disease [1]. About 43% of men and 30% of women aged 65 and above will develop cancer at some point in their lives [2]. The global population is rapidly ageing and by 2030, older people will make up 70% of the cancer cases in high income countries such as the USA [3]. Fortunately, 5-year survival rates are nearly 80% for the most common cancers as cancer diagnosis and treatments are improving [4]. Due to these two complementary trends, the population of cancer survivors is growing rapidly.

Multimorbidity is defined as the co-occurrence of two or more long-term conditions (LTC). Most cancer patients are likely to suffer from multimorbidity [2, 5, 6]. Prevalence of one comorbid condition in cancer patients ranges from 40-69% and prevalence of more than one comorbidity ranges from 12-32% [7, 8]. Pa-

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tterns of multimorbidity vary according to cancer site and stage, as well as other factors such as ethnicity, deprivation, and health status of patients [9]. The number of comorbidities in cancer patients is up to three times greater than age and gender matched controls [6, 10].

There are several definitions of cancer survivorship. The National Cancer Institute (NCI) and National Coalition for Cancer Survivorship (NCCS) defines cancer survivorship as "from the time of diagnosis to the balance of life" [11, 12]. The National Cancer Survivorship Initiative (NCSI) in the UK defines cancer survivors as "Those who are undergoing primary treatment, those who are in remission following treatment, those who are cured and those with active or advanced disease" [13]. Many authors, particularly in European journals define cancer survivors as "patients without evidence of disease and free from specific treatment for a period of at least 5 years" [14-16]. The 5 years period cut off may not be appropriate for some cancers, such as lung cancer and pancreatic cancer where the majority of patients die within 1 year of diagnosis [17]. In any case, cancer survivors have other medical comorbidities to manage in addition to their cancer.

With increasing cancer survivorship, the prevalence of multimorbidity also increases. The detection of cancer may be influenced by multimorbidity, with some people having their cancer diagnosed sooner due to frequent interactions with healthcare providers, and others being diagnosed later if their cancer shares common symptoms with a comorbid disease, as in the case of chronic obstructive pulmonary disease (COPD) and lung cancer [9]. Cancer treatment may also be associated with several long-term sequelae such as chronic pain and fatigue, sexual dysfunction, anxiety, depression, and lymphedema [18-21]. People with multimorbidity are less likely to receive cancer treatment with curative intent [9]. The presence of multimorbidity leads to the increased complexity of health care needs for cancer survivors. A scoping review conducted by the authors recently found that detailed exploration of the epidemiology of multimorbidity in cancer survivors is lacking for most cancers [22]. Previous studies using primary care data have focused on single cancer site or single comorbidity or comorbidities from the same bodily system (e.g., cardiovascular disease) or older age survivors [5, 22-24]. Other studies have explored the prevalence of multimorbidity among cancer patients using secondary care data such as hospital records [5, 25]. Such studies may underestimate the prevalence of multimorbidity that are managed in primary care, as many conditions do not typically require hospital admission. Moreover, only a few studies compared comorbidities in cancer survivors with matched controls for such a large group of cancers.

In this study, we aimed to examine the prevalence of 29 comorbidities in cancer survivors in England using population based electronic health records of patients with linked primary and secondary health care data. We focused on patients from 28 different cancer sites and compared them to age, sex, and general practice matched controls.

Materials and methods

Study population

This study is a sub study of a larger study titled *"Characterisation of multimorbidity clusters and trajectories using data-driven approaches in a nationally representative population"* [26]. Data for this study were obtained from the Clinical Practice Research Datalink GOLD (CPRD GOLD). CPRD prospectively collects primary care records from general practices in the UK that use VISION or EMIS software with coverage of over 11.3 million patients from 674 practices in the UK with 4.4 million active (alive, currently registered) patients [27]. It captures coded diagnoses and care events (using Read codes), prescriptions issued in primary care, and numerical test results (e.g., blood pressure readings). The primary healthcare data were then linked to national data on Hospital Episode Statistics Admitted-Patient Care (HES APC), death registration data - from the Office of National Statistics (ONS) and individual postcode-based index of multiple deprivation data (IMD). Our study population comprises of all acceptable patients permanently registered in any English CPRD General Practice that meet 'up to standard' CPRD GOLD data quality criteria between January 1, 2010, and December 31, 2020, and who ever had a recorded long-term condition (from a set of 204 conditions) during this time frame. Patients are labelled as 'acceptable' if their data meets

acceptable data quality criteria for use in research [27]. The list of long-term conditions was selected after doing a thorough literature search on disease codes that had already been validated in previous UK studies [28-31]. Additional codes which were not validated were added and reviewed by a panel of ten clinicians from a range of specialities. Each panel member independently reviewed the list of conditions and scored them according to relevance to the condition. Any disagreements were further reviewed by a second consensus panel of three clinicians who collaboratively decided on its inclusion/exclusion. The detailed selection procedure is shared on an open GitHub repository [32].

In this population based cross-sectional study, we compared comorbidities in cancer survivors against controls without a history of cancer. From the population described above, we selected patients who had a diagnosis of any of the 28 cancers over the age of 18. Up to three controls were selected based on "no history of cancer", matched on age (±2 years), sex, and general practice. Cancer diagnosis was defined as the first code of cancer at the site of interest in any of the linked databases. Participants with no information on smoking, body mass index (BMI), or index of multiple deprivation (an area-based UK indicator for socio-economic status) were excluded from this analysis.

Procedures

A cancer survivor was defined in this study as any cancer patient who was alive two years after the date of primary cancer diagnosis. Patients who did not have minimum of two years of follow-up data after cancer diagnosis were excluded. Each cancer survivor was matched with up to three controls.

The outcomes of the study were presence or absence of a long-term condition. From the preliminary list of 204 medical conditions (see Supplementary File), 29 conditions were selected for further analysis. These 29 conditions were selected because they were included in one of the following: the Quality Outcomes Framework (QOF) [33]; the Charlson Comorbidity Index (CCI) [34]; the Cambridge Multimorbidity Score (CMS) [30], or they arose from consultation with a patient-public involvement group (PPI) that included cancer patients and their caregivers. Demographic characteristics such as ethnicity, last known smoking status, mean BMI were identified from the CPRD GOLD dataset. Patients were followed up from the date of registration at their GP practice until date of death or end of study period (1st June 2021).

Statistical analysis

The study described the prevalence of multimorbidity in cancer patients, explored the association between multimorbidity and patient characteristics, and examined the prevalence of specific comorbidities across the 28 cancer groups.

Firstly, we described the median, interquartile range (where appropriate) and proportion of cancer survivors compared to matched controls by patient characteristics (age group, sex, ethnicity, IMD, mortality and number of co-morbidities). We calculated prevalence of comorbidity in cancer survivors and matched controls. We did not standardise for age and sex as cancer survivors were matched for age, sex and general practice already. Then, we compared the prevalence of the same comorbidities before and after cancer diagnosis for the cancer survivors. Subsequently, we fitted multivariable logistic regression models initially accounting only for matching factors (age, sex and general practice) and then additionally adjusting for shared risk factors and demographics (BMI, ethnicity, and smoking status) to find the odds of the comorbidity outcome compared to the matched controls. The primary outcome measure for this study is the presence of a long-term condition as a binary outcome (present vs absent). Crude and adjusted odds ratios for each comorbidity were calculated, adjusted odds ratio with 95% CI was presented. The reference groups were controls with no cancer (but with at least one LTC), white ethnicity, least socio-economic deprived quintile group, never smoker. For both the unadjusted and adjusted analyses, Data are presented as mean (SD) and median (IQR) for continuous data, number (%) for binary data, or as adjusted odds ratios (AOR) with 95% confidence intervals. All statistical analyses were performed in R version 4.2.0.

Results

A total of 472,918 cancer patients and 2,495,601 patients without a cancer diagnosis

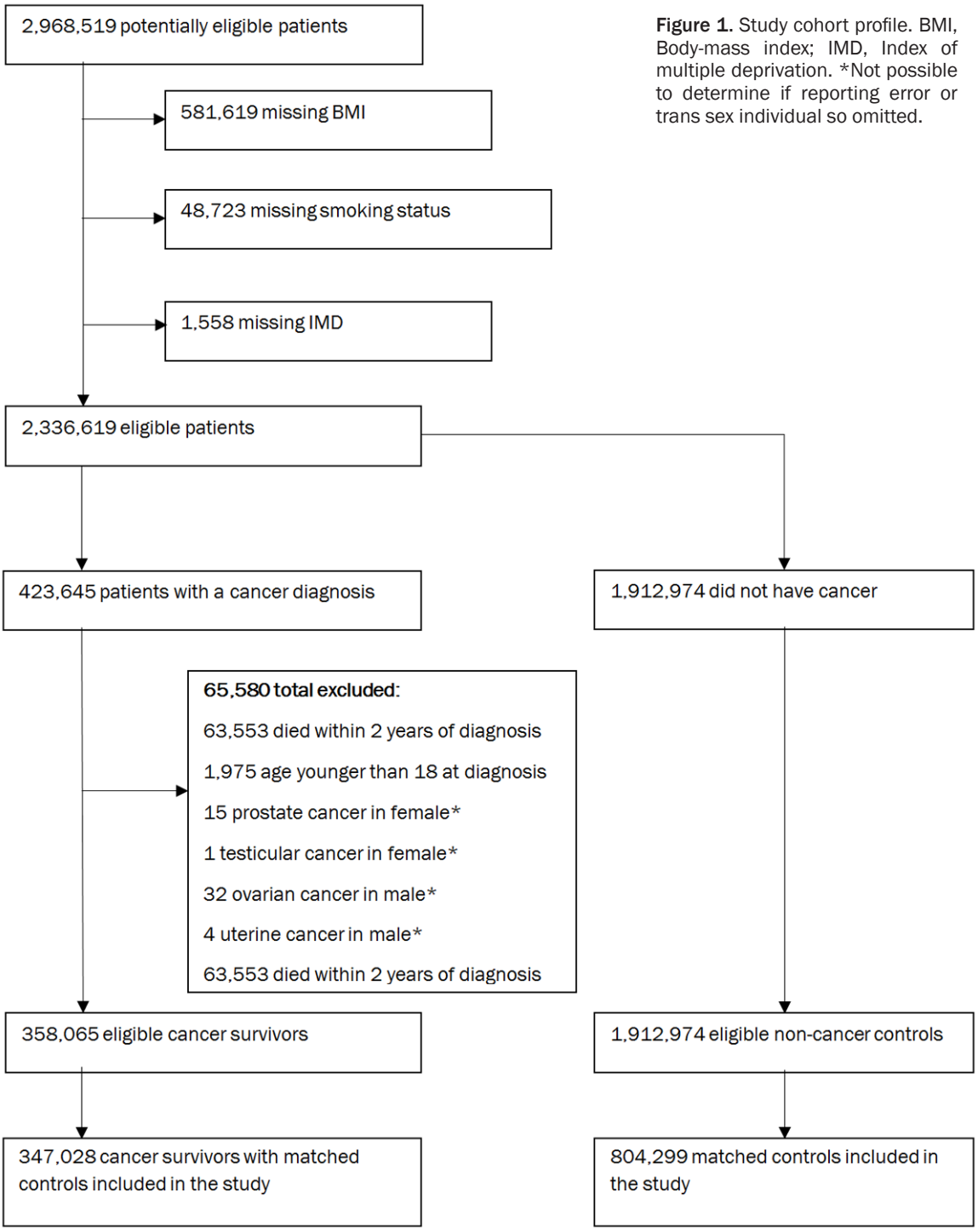


Figure 1. Study cohort profile. BMI, Body-mass index; IMD, Index of multiple deprivation. *Not possible to determine if reporting error or trans sex individual so omitted.

were extracted from the CPRD GOLD dataset. 631,900 (21.3%) participants were excluded due to missing BMI, IMD and/or smoking status. A further 65,580 cancer patients were excluded due to data anomaly, death within 2 years of cancer diagnosis or cancer diagnosis before the age of 18 (**Figure 1**). After matching for age, sex, and general practice, 347,028 cancer survivors and 804,299 non-cancer matched controls were eligible for inclusion in the study.

Table 1 describes the demographics of our study population. White ethnicity was common-

Table 1. Baseline characteristics of cancer survivors and matched controls across all cancer sites

	Cancer survivors	Non-cancer patients*
Total number of patients (n, %)	347,028 (30.1%)	804,299 (69.9%)
Sex		
Male	150951 (43.5%)	318,386 (39.6%)
Female	196077 (56.5%)	485,913 (60.4%)
Age group		
(18, 30)	912 (0.3%)	2,579 (0.3%)
(30, 45)	15,127 (4.4%)	44,122 (5.5%)
(45, 60)	47,947 (13.8%)	138,710 (17.2%)
(60, 75)	112,056 (32.3%)	302,589 (37.6%)
(75, 90)	138,743 (40.0%)	263,682 (32.8%)
>90	32,243 (9.3%)	52,617 (6.5%)
Ethnicity		
White	320,413 (92.3%)	645,164 (80.2%)
Mixed	1,055 (0.3%)	2,663 (0.3%)
Asian or Asian British	4,746 (1.4%)	17,309 (2.2%)
Black or Black British	3,539 (1.0%)	8,873 (1.1%)
Chinese or Other Group	3,473 (1.0%)	9,430 (1.2%)
Unknown	5,980 (1.7%)	28,099 (3.5%)
Missing	7,822 (2.3%)	92,761 (11.5%)
IMD quintile		
1 (least deprived)	91,507 (26.4%)	202,657 (25.2%)
2	82,035 (23.6%)	185,407 (23.1%)
3	73,086 (21.1%)	73,086 (21.1%)
4	57,544 (16.6%)	139,601 (17.4%)
5 (Most deprived)	42,856 (12.3%)	107,542 (13.4%)
Smoking status		
Non-smoker	180,176 (51.9%)	433,644 (53.9%)
Former smoker	114,570 (33.0%)	238,005 (29.6%)
Smoker	52,282 (15.1%)	132,650 (16.5%)
Alcohol status		
Non-drinker	111,151 (32.0%)	264,180 (32.8%)
Former drinker	15,793 (4.6%)	33,370 (4.1%)
Current drinker	184,974 (53.3%)	421,983 (52.5%)
Excess drinker	4,567 (1.3%)	11,964 (1.5%)
Unknown	30,543 (8.8%)	72,802 (9.1%)
BMI		
Mean (SD)	26.7 (±4.9)	26.8 (±5.2)
Median (SD)	26.7 (±5.0)	26.8 (±5.2)
Male (Mean (SD))	27.0 (±4.2)	27.2 (±4.5)
Female (Mean (SD))	26.5 (±5.4)	26.5 (±5.5)
Underweight (BMI<18.5) (n, %)	5,460 (1.6%)	15,034 (1.9%)
Overweight (BMI 25-30) (n, %)	135,448 (39.0%)	299,873 (37.3%)
Obese (BMI>30) (n, %)	73,341 (21.1%)	179,018 (22.3%)
Death		
Mean age (SD)	80.5 (±11.8)	82.6 (±10.2)
Death aged 75 years or older	74,601 (21.5%)	112,783 (14.0%)
Premature death (death below 75 years)	26,395 (7.6%)	26,986 (3.4%)

Number of long-term conditions		
Mean (SD)	12.4 (±6.7)	9.2 (±5.8)
Multimorbidity		
>1 conditions	346,786 (99.9%)	801,261 (99.6%)
>2 conditions	340,015 (97.8%)	747,644 (92.9%)
>3 conditions	328,767 (94.7%)	683,094 (84.9%)
>4 conditions	313,666 (90.4%)	614,290 (76.4%)
>5 conditions	295,731 (85.2%)	546,484 (67.9%)
>6 conditions	275,600 (79.4%)	481,561 (59.9%)

*Matched with cancer patients on age (±2), sex and general practice.

er in cancer survivors compared to the matched controls (92.3% vs 80.2%). Cancer survivors were more likely to be former smokers (33% vs 29.6%). Premature death (defined as death before the age of 75) was almost double in cancer survivors compared to controls (7.6% vs 3.4%). Cancer onset was the highest in the 60-75 age group (38.56%). The average number of comorbidities in cancer survivors was 12.4, compared to 9.2 in non-cancer patients (from the set of 204 conditions).

Prevalence of comorbidity in cancer survivors (all sites combined)

Compared to matched controls, cancer survivors had higher prevalence comorbidity in 22 out of 29 LTCs (**Table 2**). The comorbidities in order of prevalence were: hypertension (56.2%), painful conditions (39.8%), osteoarthritis (38.0%), depression (31.8%), constipation (31.4%), dermatitis (30.5%), hearing loss (24.4%), coronary heart disease (22.9%), anxiety and phobia (22.4%), chronic kidney disease (CKD) (21.4%), anaemia (19.8%), atrial fibrillation (18.7%), asthma (18.1%), obesity (16.1%) and Type 2 diabetes (15.2%), chronic obstructive pulmonary disease (COPD) (13.1%), osteoporosis (12.8%), heart failure (12.6%), cerebrovascular disease (11.4%), irritable bowel syndrome (10.3%), peptic ulcer disease (9.2%), dementia (8.9%), non-diabetic peripheral neuropathies (6.0%), alcohol problems (6.0%), liver disease (3.6%), epilepsy (3.3%), psychosis/bipolar disorder (1.8%) and chronic fatigue (1.40%).

Although cancer survivors had higher prevalence of most conditions, however, the prevalence of some conditions was not substantially different between cancer survivors and matched controls, e.g., depression. The comorbidities that were more prevalent in cancer survivors (all cancers combined) compared to controls were: constipation (+7.4%), hypertension (+7.0%), anaemia (+5.9%), CKD (+5.2%), painful conditions (+5%), atrial fibrillation (+5%), osteoarthritis (+4.5%), coronary heart disease (+4.0%), hearing loss (+3.9%), osteoporosis (+3.6%), COPD (+3.3%), heart failure (+2.8%), peptic ulcer disease (+2.3%), cerebrovascular disease (+2.1%), non-diabetic peripheral neuropathies (+1.4%) and type 2 diabetes (+1.1%).

Prevalence of comorbidity by cancer site

The prevalence of 29 comorbidities across 28 cancer groups and their matched controls is shown in **Figure 2**. Hypertension is the most prevalent condition in cancer survivors, regardless of cancer site. This is followed by painful conditions, constipation, depression, and osteoarthritis. Although dermatitis was common across all cancer sites, the prevalence is similar to that of non-cancer controls. Here, we notice patterns of comorbidity vary with cancer site. Alcohol related disease is higher in liver cancer survivors, anaemia is the highest in stomach, multiple myeloma and oesophageal cancer survivors, anxiety and phobia is most prevalent in cervical cancer survivors, constipation is higher in gastro-intestinal cancers and cancers of nearby organs, COPD is the highest in lung cancer, coronary heart disease is the highest in bladder cancer, depression is the highest in cervical cancer, epilepsy is highest in brain cancer, painful conditions are the highest in myeloma, mesothelioma and lung cancer survivors, type 2 diabetes is the highest in liver and pancreatic cancer survivors.

The fifteen most common comorbidities were chosen for further analysis using regression modelling to compare prevalence between cancer survivors and controls. Adjustment for

Table 2. Prevalence of long-term conditions in cancer survivors compared to matched controls

Long-term condition (in order of prevalence in cancer survivors)	Cancer survivors (n)	Cancer survivor (%)	Non-cancer controls* (n)	Non-cancer controls* (%)	Difference between survivors and controls (%)
Hypertension	194,967	56.2%	395,867	49.2%	7.0%
Painful conditions	137,988	39.8%	279,644	34.8%	5.0%
Osteoarthritis	131898	38.0%	269145	33.5%	4.5%
Depression	110,327	31.8%	267,283	33.2%	-1.4%
Constipation	109,110	31.4%	192,889	24.0%	7.4%
Dermatitis	105,991	30.5%	252,455	31.4%	-0.9%
Hearing loss	84,646	24.4%	165,219	20.5%	3.9%
Coronary artery disease	79,628	22.9%	152,002	18.9%	4.0%
Anxiety and phobia	77,713	22.4%	183,744	22.8%	-0.4%
Chronic kidney disease	74,370	21.4%	130,375	16.2%	5.2%
Anaemia	68,723	19.8%	111,752	13.9%	5.9%
Atrial fibrillation	64,979	18.7%	109,925	13.7%	5.0%
Asthma	62,969	18.1%	148,652	18.5%	-0.4%
Obesity	55,878	16.1%	123,614	15.4%	0.7%
Type 2 Diabetes	52,725	15.2%	113,087	14.1%	1.1%
Chronic obstructive pulmonary disease (COPD)	45472	13.1%	78847	9.8%	3.3%
Osteoporosis	44,539	12.8%	73,797	9.2%	3.6%
Heart failure	43,553	12.6%	78,586	9.8%	2.8%
Cerebrovascular disease	39,564	11.4%	75,028	9.3%	2.1%
Irritable bowel syndrome	35,736	10.3%	86,498	10.8%	-0.5%
Peptic ulcer disease	31,833	9.2%	55,207	6.9%	2.3%
Dementia	31,015	8.9%	65,780	8.2%	0.7%
Non-diabetic peripheral neuropathies	20,649	6.0%	36,819	4.6%	1.4%
Alcohol problems	20,983	6.0%	48,148	6.0%	0.0%
Liver disease	12,519	3.6%	23,627	2.9%	0.7%
Epilepsy	11,381	3.3%	23,022	2.9%	0.4%
Bipolar disorder	6,342	1.8%	16,517	2.1%	-0.3%
Chronic fatigue	4,867	1.4%	12,707	1.6%	-0.2%

*Matched with cancer patients on age (±2), sex and general practice.

shared risk factors had little effect on odds ratios, thus we only report the adjusted odds ratios and 95% CI for each comorbidity (**Table 3**). Cancer survivors (all sites combined) had higher odds of anaemia, constipation, chronic kidney disease, atrial fibrillation and CKD compared to non-cancer controls. Breast cancer survivors had higher odds of anxiety, constipation and depression. Prostate cancer survivors had higher odds of hypertension, coronary artery diseases and atrial fibrillation. For bladder cancer survivors, we found higher odds of chronic kidney disease, hypertension, and coronary artery disease. Amongst lung cancer patients, there was higher odds of painful conditions, anaemia, and constipation.

In **Figure 3**, we reported the risk of the fifteen comorbidities in 28 cancer sites compared to controls. We found strong evidence ($P<0.05$) of higher odds of the following conditions: constipation (25 of 28 cancers), anaemia (23 of 28 cancers), painful conditions (19 of 28 cancers), hypertension (18 of 28 cancers), Type 2 diabetes and obesity (15 of 28 cancers), coronary heart disease (14 of 28 cancers), atrial fibrillations (14 of 28 cancers), CKD (14 of 28 cancers), hearing loss (12 of 28 cancers), osteoarthritis (11 of 28 cancers), anxiety (6 of 28 cancers), depression & asthma (5 of 28 cancers). Odds of dermatitis was only slightly increased in two cancers, namely in non-Hodgkin lymphoma and skin cancer (**Figure 3**). The number of

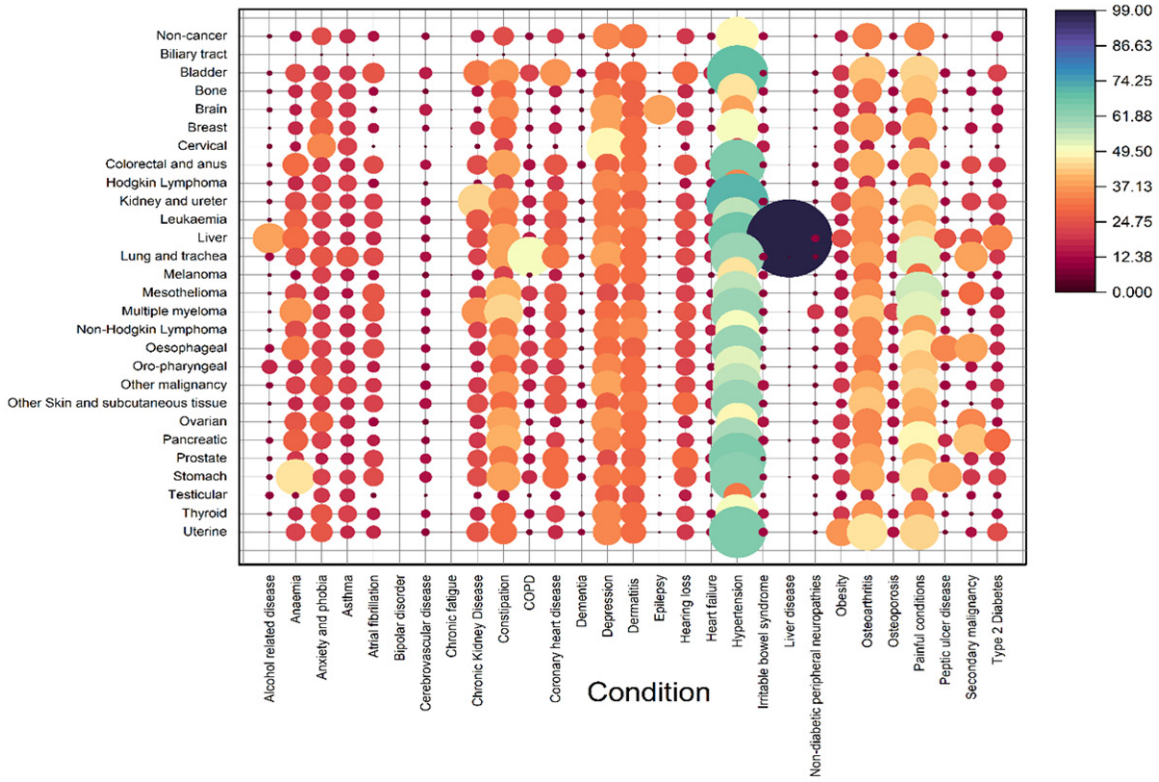


Figure 2. Prevalence of comorbidity in cancer survivors by cancer site.

Table 3. Adjusted odds of long-term conditions in cancer survivors compared to matched controls

Long-term conditions	All cancer sites (AOR, 95% CI)	Breast cancer (AOR, 95% CI)	Prostate cancer (AOR, 95% CI)	Colorectal cancer (AOR, 95% CI)	Bladder cancer (AOR, 95% CI)	Lung cancer (AOR, 95% CI)
Anaemia	1.42 (1.40-1.43)	1.19 (1.17-1.22)	1.37 (1.33-1.41)	2.43 (2.36-2.50)	1.70 (1.64-1.77)	1.69 (1.60-1.78)
Anxiety & phobia	0.94 (0.93-0.95)	1.24 (1.22-1.26)	0.59 (0.57-0.61)	0.79 (0.76-0.81)	0.77 (0.74-0.80)	1.04 (0.99-1.10)
Asthma	0.95 (0.94-0.96)	1.01 (0.98-1.03)	0.79 (0.77-0.82)	0.90 (0.87-0.93)	0.95 (0.91-0.99)	1.39 (1.32-1.46)
Atrial fibrillation	1.27 (1.26-1.29)	0.84 (0.82-0.86)	1.55 (1.51-1.59)	1.58 (1.54-1.63)	1.84 (1.77-1.91)	1.68 (1.59-1.78)
Chronic kidney disease	1.30 (1.29-1.31)	0.98 (0.96-1.00)	1.36 (1.32-1.39)	1.49 (1.45-1.54)	2.19 (2.11-2.27)	1.31 (1.23-1.38)
Constipation	1.32 (1.31-1.33)	1.22 (1.19-1.24)	1.37 (1.34-1.40)	1.72 (1.67-1.76)	1.55 (1.50-1.60)	1.73 (1.65-1.82)
Coronary artery disease	1.13 (1.12-1.14)	0.68 (0.67-0.70)	1.60 (1.56-1.64)	1.30 (1.26-1.34)	1.89 (1.83-1.96)	1.52 (1.45-1.60)
Depression	0.90 (0.89-0.91)	1.21 (1.19-1.24)	0.59 (0.58-0.61)	0.76 (0.74-0.78)	0.72 (0.69-0.75)	1.00 (0.96-1.05)
Dermatitis	0.95 (0.94-0.96)	0.96 (0.95-0.98)	0.85 (0.82-0.87)	0.89 (0.86-0.91)	0.91 (0.87-0.94)	0.95 (0.90-1.00)
Hearing loss	1.17 (1.16-1.18)	0.87 (0.86-0.89)	1.55 (1.52-1.59)	1.26 (1.23-1.30)	1.47 (1.41-1.52)	1.08 (1.03-1.15)
Hypertension	1.24 (1.23-1.25)	0.96 (0.95-0.98)	1.77 (1.73-1.82)	1.65 (1.60-1.69)	2.11 (2.04-2.19)	1.59 (1.51-1.67)
Obesity	1.06 (1.05-1.08)	1.17 (1.14-1.20)	1.00 (0.97-1.04)	1.12 (1.08-1.16)	1.33 (1.27-1.39)	1.16 (1.08-1.24)
Osteoarthritis	1.09 (1.08-1.10)	1.13 (1.11-1.15)	1.11 (1.08-1.14)	1.10 (1.08-1.13)	1.26 (1.22-1.30)	1.17 (1.11-1.23)
Painful condition	1.14 (1.13-1.15)	1.17 (1.15-1.20)	1.09 (1.06-1.12)	1.24 (1.21-1.27)	1.24 (1.20-1.28)	1.76 (1.68-1.85)
Type 2 diabetes	1.09 (1.08-1.11)	0.86 (0.84-0.88)	1.33 (1.29-1.37)	1.40 (1.35-1.45)	1.55 (1.49-1.62)	1.37 (1.29-1.46)

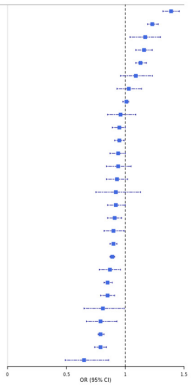
patients for mesothelioma was below 500, thus findings from this cancer should be interpreted cautiously.

Comparison of comorbidity before and after cancer diagnosis

In **Table 4**, we present the prevalence of comorbidity in cancer survivors before and after cancer diagnosis for all cancer sites combined. We also present this for the five most common cancers separately. We see that there was an increase in prevalence of all fifteen comorbidities after cancer diagnosis, with the highest increases in anaemia (+23.6%), constipation (+20.9%), dermatitis (+14.9%), asthma (+14.4%) and depression (+13.1%). For breast cancer patients, the comorbidities with the highest

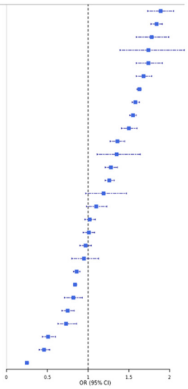
Asthma

Cancer site	Odds	95% LCI	95% UCI
Lung and trachea	1.39	1.32	1.46
Cervical	1.23	1.19	1.28
Hodgkin Lymphoma	1.17	1.04	1.3
Thyroid	1.16	1.09	1.23
Other cancers	1.13	1.09	1.18
Bone	1.09	0.96	1.23
Brain CNS and intracranial	1.03	0.93	1.14
Breast	1.01	0.98	1.03
Stomach	0.96	0.85	1.09
Non-Hodgkin Lymphoma	0.95	0.89	1
Bladder	0.95	0.91	0.99
Kidney and ureter	0.94	0.87	1
Secondary malignancy	0.94	0.84	1.05
Testicular	0.93	0.84	1.02
Biliary tract	0.92	0.75	1.13
Ovarian	0.92	0.85	1
Leukaemia	0.91	0.85	0.97
Multiple myeloma	0.9	0.82	0.99
Colorectal and anus	0.9	0.87	0.93
Other Skin & subcutaneous tissue	0.89	0.87	0.91
Oesophageal	0.87	0.78	0.96
Melanoma	0.85	0.82	0.89
Oro-pharyngeal	0.85	0.79	0.91
Liver	0.81	0.65	0.99
Pancreatic	0.79	0.67	0.93
Prostate	0.79	0.77	0.82
Uterine	0.79	0.74	0.84
Mesothelioma	0.65	0.49	0.86



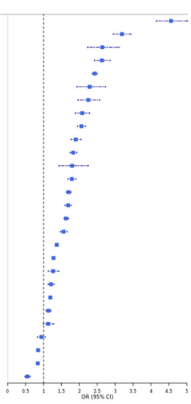
Atrial fibrillation

Cancer site	Odds	95% LCI	95% UCI
Multiple myeloma	1.89	1.73	2.05
Bladder	1.84	1.77	1.91
Stomach	1.78	1.59	1.99
Mesothelioma	1.74	1.39	2.18
Oesophageal	1.74	1.59	1.91
Lung and trachea	1.68	1.59	1.78
Other Skin and subcutaneous tissue	1.63	1.6	1.65
Colorectal and anus	1.58	1.54	1.63
Prostate	1.55	1.51	1.59
Leukaemia	1.5	1.41	1.6
Kidney and ureter	1.36	1.27	1.45
Biliary tract	1.35	1.11	1.64
Non-Hodgkin Lymphoma	1.28	1.21	1.36
Other cancers	1.26	1.21	1.32
Liver	1.19	0.97	1.47
Secondary malignancy	1.1	0.98	1.23
Thyroid	1.02	0.96	1.09
Uterine	1.01	0.94	1.08
Oro-pharyngeal	0.97	0.9	1.04
Pancreatic	0.95	0.8	1.13
Melanoma	0.86	0.82	0.9
Breast	0.84	0.82	0.86
Hodgkin Lymphoma	0.82	0.71	0.93
Ovarian	0.75	0.68	0.83
Bone	0.73	0.63	0.86
Brain CNS and intracranial	0.51	0.44	0.6
Testicular	0.46	0.4	0.53
Cervical	0.25	0.23	0.27



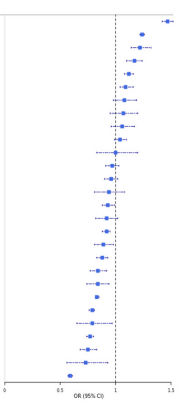
Anaemia

Cancer site	Odds	95% LCI	95% UCI
Stomach	4.56	4.15	5.02
Multiple myeloma	3.19	2.95	3.44
Biliary tract	2.64	2.23	3.12
Oesophageal	2.63	2.42	2.86
Colorectal and anus	2.43	2.36	2.5
Liver	2.29	1.93	2.73
Pancreatic	2.25	1.96	2.57
Secondary malignancy	2.08	1.89	2.29
Leukaemia	2.06	1.95	2.18
Ovarian	1.9	1.77	2.05
Non-Hodgkin Lymphoma	1.83	1.74	1.93
Mesothelioma	1.8	1.43	2.25
Kidney and ureter	1.79	1.68	1.91
Bladder	1.7	1.64	1.77
Lung and trachea	1.69	1.6	1.78
Other cancers	1.63	1.57	1.7
Uterine	1.56	1.47	1.66
Prostate	1.37	1.33	1.41
Other Skin and subcutaneous tissue	1.28	1.25	1.3
Hodgkin Lymphoma	1.27	1.13	1.43
Oro-pharyngeal	1.21	1.13	1.3
Breast	1.19	1.17	1.22
Thyroid	1.14	1.07	1.21
Bone	1.13	0.99	1.29
Brain CNS and intracranial	0.94	0.83	1.05
Cervical	0.85	0.81	0.89
Melanoma	0.84	0.8	0.88
Testicular	0.55	0.48	0.63



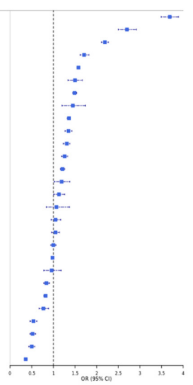
Anxiety and phobia

Cancer site	Odds	95% LCI	95% UCI
Cervical	1.47	1.42	1.52
Breast	1.24	1.22	1.26
Ovarian	1.22	1.14	1.32
Uterine	1.17	1.1	1.24
Other cancers	1.12	1.08	1.16
Thyroid	1.09	1.04	1.16
Brain CNS and intracranial	1.08	0.98	1.19
Bone	1.07	0.95	1.2
Secondary malignancy	1.06	0.96	1.17
Lung and trachea	1.04	0.99	1.1
Biliary tract	1	0.83	1.2
Kidney and ureter	0.97	0.91	1.03
Oro-pharyngeal	0.96	0.9	1.02
Pancreatic	0.94	0.81	1.08
Leukaemia	0.93	0.88	0.99
Hodgkin Lymphoma	0.92	0.82	1.02
Melanoma	0.92	0.88	0.95
Oesophageal	0.89	0.81	0.98
Non-Hodgkin Lymphoma	0.88	0.83	0.93
Multiple myeloma	0.84	0.77	0.92
Stomach	0.84	0.74	0.94
Other Skin and subcutaneous tissue	0.83	0.82	0.85
Colorectal and anus	0.79	0.76	0.81
Liver	0.79	0.65	0.97
Bladder	0.77	0.74	0.8
Testicular	0.75	0.68	0.83
Mesothelioma	0.73	0.56	0.93
Prostate	0.59	0.57	0.61



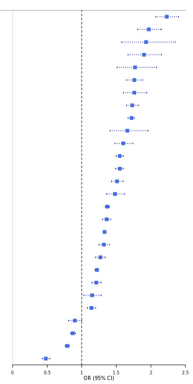
Chronic kidney disease

Cancer site	Odds	95% LCI	95% UCI
Kidney and ureter	3.69	3.49	3.89
Multiple myeloma	2.7	2.5	2.92
Bladder	2.19	2.11	2.27
Leukaemia	1.71	1.62	1.82
Other Skin and subcutaneous tissue	1.58	1.55	1.6
Stomach	1.5	1.34	1.67
Colorectal and anus	1.49	1.45	1.54
Liver	1.45	1.2	1.74
Prostate	1.36	1.32	1.39
Uterine	1.35	1.27	1.43
Lung and trachea	1.31	1.23	1.38
Non-Hodgkin Lymphoma	1.26	1.19	1.33
Other cancers	1.21	1.16	1.26
Pancreatic	1.19	1.02	1.38
Secondary malignancy	1.13	1.01	1.26
Mesothelioma	1.07	0.84	1.37
Oesophageal	1.05	0.95	1.17
Ovarian	1.05	0.96	1.14
Thyroid	1	0.94	1.06
Breast	0.98	0.96	1
Biliary tract	0.96	0.78	1.18
Oro-pharyngeal	0.84	0.78	0.91
Melanoma	0.82	0.78	0.85
Bone	0.77	0.67	0.89
Hodgkin Lymphoma	0.54	0.46	0.62
Testicular	0.52	0.46	0.59
Brain CNS and intracranial	0.5	0.43	0.57
Cervical	0.36	0.34	0.39



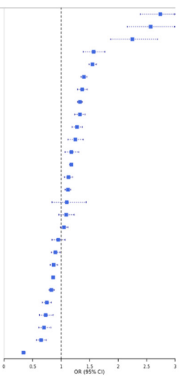
Constipation

Cancer site	Odds	95% LCI	95% UCI
Multiple myeloma	2.23	2.07	2.4
Secondary malignancy	1.97	1.81	2.15
Mesothelioma	1.93	1.58	2.35
Pancreatic	1.9	1.67	2.15
Biliary tract	1.77	1.51	2.08
Ovarian	1.76	1.65	1.88
Stomach	1.76	1.6	1.94
Lung and trachea	1.73	1.65	1.82
Colorectal and anus	1.72	1.67	1.76
Liver	1.66	1.41	1.96
Oesophageal	1.6	1.48	1.74
Bladder	1.55	1.5	1.6
Other cancers	1.55	1.49	1.6
Kidney and ureter	1.51	1.43	1.6
Brain CNS and intracranial	1.48	1.36	1.62
Prostate	1.37	1.34	1.4
Non-Hodgkin Lymphoma	1.36	1.3	1.42
Other Skin and subcutaneous tissue	1.33	1.31	1.34
Leukaemia	1.32	1.25	1.4
Uterine	1.27	1.2	1.34
Breast	1.22	1.19	1.24
Oro-pharyngeal	1.21	1.15	1.28
Bone	1.15	1.03	1.28
Thyroid	1.14	1.08	1.2
Hodgkin Lymphoma	0.9	0.81	1
Melanoma	0.87	0.84	0.91
Cervical	0.79	0.76	0.82
Testicular	0.48	0.43	0.54



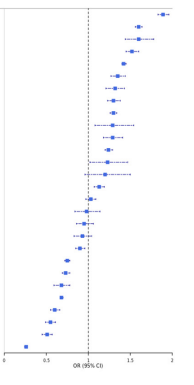
COPD

Cancer site	Odds	95% LCI	95% UCI
Pancreatic	2.74	2.39	3.15
Liver	2.57	2.16	3.07
Biliary tract	2.25	1.87	2.69
Stomach	1.57	1.39	1.77
Bladder	1.55	1.49	1.62
Colorectal and anus	1.4	1.35	1.45
Lung and trachea	1.37	1.29	1.46
Prostate	1.33	1.29	1.37
Kidney and ureter	1.33	1.24	1.42
Leukaemia	1.28	1.19	1.37
Oesophageal	1.25	1.12	1.39
Myeloma	1.18	1.07	1.31
Other Skin & subcutaneous tissue	1.18	1.15	1.2
Uterine	1.13	1.06	1.2
Other malignancy	1.12	1.07	1.17
Mesothelioma	1.1	0.84	1.44
Secondary malignancy and metastasis	1.09	0.96	1.23
Non-Hodgkin Lymphoma	1.05	0.99	1.12
Brain other CNS and intracranial	0.95	0.84	1.07
Oro-pharyngeal	0.9	0.83	0.98
Thyroid	0.87	0.81	0.94
Breast	0.86	0.84	0.88
Melanoma	0.83	0.79	0.88
Ovarian	0.75	0.67	0.83
Bone and articular cartilage	0.73	0.62	0.86
Hodgkin Lymphoma	0.7	0.61	0.82
Testicular	0.65	0.57	0.74
Cervical	0.34	0.32	0.37



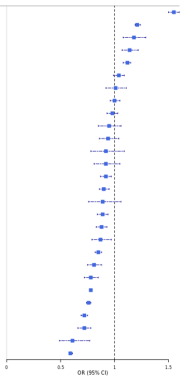
Coronary heart disease

Cancer site	Odds	95% LCI	95% UCI
Bladder	1.89	1.83	1.96
Prostate	1.6	1.56	1.64
Stomach	1.6	1.44	1.78
Lung and trachea	1.52	1.45	1.6
Other Skin and subcutaneous tissue	1.42	1.4	1.45
Kidney and ureter	1.35	1.27	1.44
Multiple myeloma	1.32	1.21	1.43
Leukaemia	1.3	1.23	1.38
Colorectal and anus	1.3	1.26	1.34
Biliary tract	1.29	1.08	1.54
Oesophageal	1.29	1.18	1.41
Other cancers	1.24	1.2	1.29
Liver	1.23	1.02	1.47
Mesothelioma	1.2	0.96	1.5
Non-Hodgkin Lymphoma	1.13	1.07	1.19
Thyroid	1.03	0.97	1.09
Pancreatic	0.98	0.84	1.14
Secondary malignancy	0.95	0.86	1.06
Hodgkin Lymphoma	0.93	0.83	1.04
Oro-pharyngeal	0.9	0.85	0.96
Melanoma	0.75	0.72	0.78
Uterine	0.73	0.69	0.78
Bone	0.68	0.59	0.78
Breast	0.68	0.67	0.7
Ovarian	0.6	0.55	0.66
Testicular	0.55	0.49	0.61
Brain CNS and intracranial	0.51	0.45	0.57
Cervical	0.26	0.24	0.27



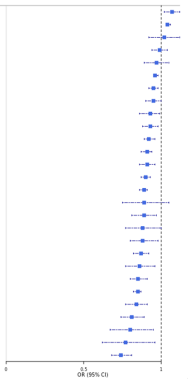
Depression

Cancer site	Odds	95% LCI	95% UCI
Cervical	1.55	1.5	1.6
Breast	1.21	1.19	1.24
Brain CNS and intracranial	1.18	1.08	1.29
Ovarian	1.14	1.07	1.22
Other cancers	1.12	1.08	1.15
Thyroid	1.04	0.99	1.09
Hodgkin Lymphoma	1.01	0.92	1.11
Lung and trachea	1	0.96	1.05
Uterine	0.98	0.93	1.03
Bone	0.95	0.85	1.06
Secondary malignancy	0.94	0.86	1.04
Liver	0.92	0.78	1.09
Pancreatic	0.92	0.81	1.05
Oro-pharyngeal	0.92	0.87	0.97
Non-Hodgkin Lymphoma	0.9	0.86	0.95
Biliary tract	0.89	0.76	1.06
Kidney and ureter	0.89	0.84	0.94
Leukaemia	0.88	0.83	0.93
Stomach	0.87	0.79	0.97
Melanoma	0.85	0.82	0.88
Multiple myeloma	0.81	0.75	0.88
Oesophageal	0.78	0.72	0.85
Other Skin and subcutaneous tissue	0.78	0.77	0.79
Colorectal and anus	0.76	0.74	0.78
Bladder	0.72	0.69	0.75
Testicular	0.72	0.66	0.78
Mesothelioma	0.61	0.49	0.77
Prostate	0.59	0.58	0.61



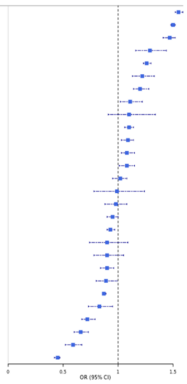
Dermatitis

Cancer site	Odds	95% LCI	95% UCI
Non-Hodgkin Lymphoma	1.07	1.02	1.12
Other Skin and subcutaneous tissue	1.04	1.03	1.06
Hodgkin Lymphoma	1.02	0.92	1.12
Leukaemia	0.99	0.94	1.04
Multiple myeloma	0.97	0.89	1.05
Breast	0.96	0.95	0.98
Cervical	0.95	0.92	0.98
Lung and trachea	0.95	0.9	1
Ovarian	0.93	0.86	0.99
Thyroid	0.93	0.88	0.98
Other cancers	0.92	0.89	0.96
Bladder	0.91	0.87	0.94
Uterine	0.91	0.86	0.96
Melanoma	0.9	0.87	0.93
Colorectal and anus	0.89	0.86	0.91
Liver	0.89	0.75	1.05
Secondary malignancy	0.89	0.81	0.97
Pancreatic	0.88	0.77	1
Stomach	0.88	0.8	0.98
Oro-pharyngeal	0.87	0.82	0.92
Bone	0.86	0.77	0.96
Kidney and ureter	0.85	0.8	0.91
Prostate	0.85	0.82	0.87
Oesophageal	0.84	0.77	0.91
Brain CNS and intracranial	0.81	0.74	0.89
Biliary tract	0.8	0.67	0.95
Mesothelioma	0.77	0.62	0.96
Testicular	0.74	0.68	0.81



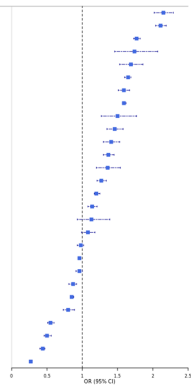
Hearing loss

Cancer site	Odds	95% LCI	95% UCI
Prostate	1.55	1.52	1.59
Other Skin and subcutaneous tissue	1.5	1.48	1.52
Bladder	1.47	1.41	1.52
Stomach	1.29	1.16	1.44
Colorectal and anus	1.26	1.23	1.3
Multiple myeloma	1.22	1.13	1.33
Leukaemia	1.2	1.14	1.28
Oesophageal	1.11	1.02	1.22
Liver	1.1	0.91	1.34
Other cancers	1.1	1.06	1.14
Non-Hodgkin Lymphoma	1.09	1.03	1.14
Lung and trachea	1.08	1.03	1.15
Oro-pharyngeal	1.08	1.01	1.15
Kidney and ureter	1.02	0.95	1.08
Mesothelioma	0.99	0.78	1.24
Secondary malignancy	0.98	0.88	1.08
Thyroid	0.95	0.9	1
Melanoma	0.93	0.9	0.97
Biliary tract	0.9	0.74	1.09
Pancreatic	0.9	0.78	1.05
Uterine	0.9	0.84	0.96
Brain CNS and intracranial	0.89	0.8	0.99
Breast	0.87	0.86	0.89
Bone	0.83	0.73	0.95
Ovarian	0.72	0.67	0.79
Testicular	0.66	0.6	0.73
Hodgkin Lymphoma	0.59	0.52	0.67
Cervical	0.45	0.42	0.47



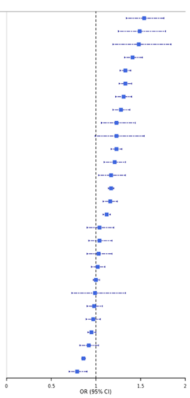
Hypertension

Cancer site	Odds	95% LCI	95% UCI
Kidney and ureter	2.15	2.02	2.29
Bladder	2.11	2.04	2.19
Prostate	1.77	1.73	1.82
Liver	1.74	1.46	2.07
Stomach	1.69	1.53	1.86
Colorectal and anus	1.65	1.6	1.69
Lung and trachea	1.59	1.51	1.67
Other Skin and subcutaneous tissue	1.59	1.57	1.62
Biliary tract	1.5	1.27	1.77
Multiple myeloma	1.46	1.35	1.58
Oesophageal	1.41	1.3	1.53
Uterine	1.37	1.3	1.45
Pancreatic	1.36	1.2	1.54
Leukaemia	1.27	1.21	1.34
Other cancers	1.2	1.17	1.25
Oro-pharyngeal	1.14	1.08	1.21
Mesothelioma	1.13	0.93	1.39
Secondary malignancy	1.08	0.99	1.18
Non-Hodgkin Lymphoma	0.98	0.93	1.02
Breast	0.96	0.95	0.98
Thyroid	0.96	0.91	1
Ovarian	0.87	0.81	0.92
Melanoma	0.85	0.83	0.88
Bone	0.8	0.73	0.89
Brain CNS and intracranial	0.55	0.51	0.6
Hodgkin Lymphoma	0.5	0.46	0.56
Testicular	0.44	0.4	0.47
Cervical	0.27	0.25	0.28



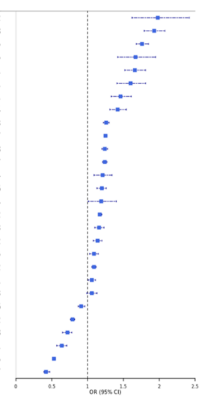
Obesity

Cancer site	Odds	95% LCI	95% UCI
Stomach	1.54	1.34	1.76
Pancreatic	1.49	1.25	1.78
Biliary tract	1.48	1.19	1.84
Uterine	1.41	1.32	1.52
Bladder	1.33	1.27	1.39
Cervical	1.33	1.26	1.4
Thyroid	1.31	1.22	1.4
Kidney and ureter	1.28	1.19	1.38
Bone	1.23	1.06	1.44
Liver	1.23	0.99	1.54
Other cancers	1.23	1.17	1.29
Ovarian	1.21	1.09	1.33
Brain CNS & intracranial	1.17	1.03	1.33
Breast	1.17	1.14	1.2
Lung and trachea	1.16	1.08	1.24
Colorectal and anus	1.12	1.08	1.16
Hodgkin Lymphoma	1.04	0.9	1.2
Oesophageal	1.04	0.92	1.18
Secondary malignancy	1.03	0.9	1.18
Non-Hodgkin Lymphoma	1.02	0.95	1.1
Prostate	1	0.97	1.04
Mesothelioma	0.99	0.73	1.33
Oro-pharyngeal	0.98	0.9	1.07
Leukaemia	0.97	0.89	1.05
Melanoma	0.95	0.91	1
Multiple myeloma	0.92	0.82	1.03
Other Skin & subcutaneous tissue	0.86	0.84	0.88
Testicular	0.79	0.7	0.9



Painful condition

Cancer site	Odds	95% LCI	95% UCI
Mesothelioma	1.98	1.62	2.42
Multiple myeloma	1.93	1.79	2.08
Lung and trachea	1.76	1.68	1.85
Biliary tract	1.67	1.42	1.95
Secondary malignancy	1.66	1.52	1.81
Pancreatic	1.6	1.41	1.81
Stomach	1.46	1.33	1.61
Oesophageal	1.42	1.31	1.54
Other cancers	1.26	1.22	1.3
Other Skin and subcutaneous tissue	1.25	1.23	1.27
Bladder	1.24	1.2	1.28
Colorectal and anus	1.24	1.21	1.27
Bone	1.21	1.09	1.34
Oro-pharyngeal	1.2	1.13	1.26
Liver	1.19	1.01	1.4
Breast	1.17	1.15	1.2
Kidney and ureter	1.16	1.1	1.23
Uterine	1.14	1.08	1.2
Leukaemia	1.09	1.03	1.15
Prostate	1.09	1.06	1.12
Non-Hodgkin Lymphoma	1.06	1.01	1.11
Ovarian	1.06	0.99	1.13
Thyroid	0.91	0.87	0.96
Melanoma	0.79	0.76	0.82
Brain CNS and intracranial	0.72	0.65	0.78
Hodgkin Lymphoma	0.64	0.57	0.71
Cervical	0.53	0.51	0.55
Testicular	0.42	0.39	0.47



Type 2 diabetes

Cancer site	Odds	95% LCI	95% UCI
Pancreatic	2.74	2.39	3.15
Liver	2.57	2.16	3.07
Biliary tract	2.25	1.87	2.69
Stomach	1.57	1.39	1.77
Bladder	1.55	1.49	1.62
Colorectal and anus	1.4	1.35	1.45
Lung and trachea	1.37	1.29	1.46
Prostate	1.33	1.29	1.37
Kidney and ureter	1.33	1.24	1.42
Leukaemia	1.28	1.19	1.37
Oesophageal	1.25	1.12	1.39
Myeloma	1.18	1.07	1.31
Other Skin & subcutaneous tissue	1.18	1.15	1.2
Uterine	1.13	1.06	1.2
Other malignancy	1.12	1.07	1.17
Mesothelioma	1.1	0.84	1.44
Secondary malignancy and metastasis	1.09	0.96	1.23
Non-Hodgkin Lymphoma	1.05	0.99	1.12
Brain other CNS and intracranial	0.95	0.84	1.07
Oro-pharyngeal	0.9	0.83	0.98
Thyroid	0.87	0.81	0.94
Breast	0.86	0.84	0.88
Melanoma	0.83	0.79	0.88
Ovarian	0.75	0.67	0.83
Bone and articular cartilage	0.73	0.62	0.86
Hodgkin Lymphoma	0.7	0.61	0.82
Testicular	0.65	0.57	0.74
Cervical	0.34	0.32	0.37

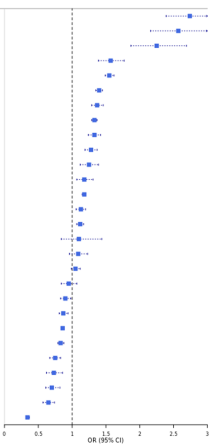


Figure 3. Prevalence of 15 most common comorbidities in cancer survivors compared to their age, sex and GP practice matched controls, further adjusted for BMI, ethnicity, and smoking status. OR, Odds ratio (adjusted). Dotted line represents OR=1, line of no difference.

Table 4. Comparison of prevalence of comorbidity before and after cancer diagnosis (all sites combined in order of difference in prevalence)

Comorbidity	Prevalence before cancer (%)	Prevalence after cancer (%)	Absolute difference (%)
Constipation	49.3	59.6	10.3
Anaemia	43.3	53.5	10.2
Painful conditions	54.3	61.3	7.0
Dermatitis	45	51.7	6.7
Depression	47.5	53.7	6.2
Asthma	38.2	43.7	5.5
Anxiety and phobia	42.3	47.4	5.1
Hearing loss	46	50.3	4.3
Chronic kidney disease	50	53.5	3.5
COPD	42.7	44.9	2.2
Obesity	39.9	42	2.1
Atrial fibrillation	49.6	50.9	1.3
Type 2 Diabetes	39.8	41	1.2
Hypertension	68.9	69.8	0.9
Coronary artery disease	49.6	49.7	0.1

increase in incidence were anaemia, constipation, and painful conditions. For prostate cancer patients, it was anaemia, depression, and constipation. For colorectal cancer patients, the largest increase before and after cancer diagnosis was found for painful conditions, anxiety/phobia, and constipation. For bladder cancer patients, the largest increase in before and after cancer diagnosis was found in asthma, anaemia, and constipation. For lung cancer patients, largest increase in before and after cancer was found in anaemia, constipation, and painful conditions. For all five malignancies, a notably higher prevalence in anaemia and constipation was observed after cancer diagnosis.

Discussion

In this comprehensive study of the prevalence of multimorbidity in cancer survivors compared to age, sex, and general practice matched controls, we found that cancer survivors had higher prevalence of 22 of 29 comorbidities. Of all the comorbidities, anaemia, constipation, chronic kidney disease, atrial fibrillation and COPD were the five that had notably greater odds in cancer survivors compared to the controls. The comorbidities with the highest difference in prevalence proportion between survivors and controls were constipation, hypertension, anaemia, CKD and painful conditions. The pattern of comorbidity varied by cancer sites with some interesting observations. Survivors of blood and gastro-intestinal cancers had an increased risk for many of the 29 conditions. We observed a statistically significant increase in odds of constipation in 25 of 28 cancers and anaemia in 23 of 28 cancers. Constipation was particularly high in myeloma, secondary malignancy, and pancreatic cancer survivors. We observed almost four times greater odds of anaemia in survivors of stomach cancer and 2.5 times or higher in myeloma and biliary tract survivors. Similarly, odds of type 2 diabetes were increased by 200% or more and obesity was increased by almost 150% in pancreatic, liver, and biliary tract cancer survivors. Coronary heart disease had the highest odds in bladder, prostate, and stomach cancer survivors. Depression and anxiety had the highest odds in cancers of females, e.g., cervical, breast, and ovarian cancers. Myeloma survivors had increased odds of every comorbidity except anxiety, depression, and dermatitis. When comparing the prevalence of comorbidities before and after cancer diagnosis, we found higher prevalence of anaemia, constipation, and painful conditions in survivors of all cancer sites combined and in the five most common cancers (**Table 5**).

Our finding that cancer survivors have significantly higher odds of reporting most comorbid diseases is consistent with similar studies [6, 35-37]. Hypertension, painful conditions, and depression were found to be the most prevalent conditions in cancer survivors by other studies [5, 10, 38]. Our study found that myeloma and bladder cancer survivors had the highest odds of almost all comorbidities whereas a similar previous study found this to be true for lung cancer survivors [5]. This could be because our study excluded patients who died within two years of diagnosis - which would have excluded many lung cancer patients. However, results from a large study conducted in New Zealand concur with our findings [10].

Table 5. Comparison of prevalence of comorbidity by cancer site (five most common cancers)

Comorbidity	Breast cancer		Prostate cancer		Colorectal cancer		Bladder cancer		Lung cancer	
	Prevalence before cancer	Prevalence after cancer	Prevalence before cancer	Prevalence after cancer	Prevalence before cancer	Prevalence after cancer	Prevalence before cancer	Prevalence after cancer	Prevalence before cancer	Prevalence after cancer
Anaemia	33.7	47.9	44.1	60.7	62.0	63.7	48.2	59.3	46.4	63.3
% Difference	14.2		16.6		1.7		11.1		16.9	
Anxiety and phobia	42.8	48.2	39.6	48.4	39.7	48.4	44.3	50.0	48.1	56.7
% Difference	5.4		8.8		8.7		5.7		8.6	
Asthma	36.6	41.4	40.8	45.5	43.9	43.9	41.4	52.9	49.7	59.7
% Difference	4.8		4.7		4.3		11.5		10	
Atrial fibrillation			44.6	51.4	50.4	53.3	53.6	55.9	51.9	57.5
% Difference	1.3		6.8		2.9		2.3		5.6	
Chronic kidney disease	42.7	47.0	47.9	54.8	49.5	55.4	58.8	64.6	49.0	52.4
% Difference	4.3		6.9		5.9		5.8		3.4	
Constipation	43.2	56.6	52.7	67.4	56.2	67.6	54.8	64.4	56.4	71.7
% Difference	13.4		14.7		11.4		9.6		15.3	
COPD	33.2	37.4	38.8	44.9	40.0	45.8	51.2	57.3	82.4	82.5
% Difference	4.2		6.1		5.8		6.1		0.1	
Coronary artery disease	40.6	42.1	47.8	55.6	49.2	51.4	58.3	59.7	55.7	57.4
% Difference	1.5		7.8		2.2		1.4		1.7	
Depression	49.2	55.3	42.9	55.3	44.8	52.0	48.8	55.0	54.8	61.7
% Difference	6.1		12.4		7.2		6.2		6.9	
Dermatitis	43.0	50.2	46.0	55.4	45.2	52.4	46.3	53.5	46.1	52.1
% Difference	7.2		9.4		7.2		7.2		6.0	
Hearing loss	39.4	44.4	51.0	58.4	46.2	52.6	49.9	54.7	43.5	49.0
% Difference	5		7.4		6.4		4.8		5.5	
Hypertension	63.7	65.1	71.5	77.2	72.5	75.4	77.5	78.5	70.5	70.9
% Difference	1.4		5.7		2.9		1.0		0.4	
Obesity	37.9	41.7	38.5	47.1	43.8	48.7	48.9	55.0	37.6	43.0
% Difference	3.8		8.6		4.9		6.1		5.4	
Painful conditions	51.5	61.6	53.5	66.9	54.9	67.7	57.8	65.4	65.5	76.0
% Difference	10.1		13.4		12.8		7.6		10.5	
Type 2 diabetes	36.2	39.2	36.6	46.2	44.7	45.6	45.9	49.1	42.7	45.3
% Difference	3.0		9.6		0.9		3.2		2.6	

Our finding that there are substantial differences in association between multimorbidity and cancer groups is consistent with other large similar studies [5, 10, 23]. Constipation as an important comorbidity in cancer survivors was highlighted previously [39], however there were not many studies reporting constipation in cancer survivors. This is because constipation is not uniformly assessed as part of any of the comorbidity scales and therefore is not recorded in many database-based studies of cancer survivors. Increased odds of constipation across 25 of 28 cancer sites is a unique finding of this study. The reasons behind the high prevalence of constipation in cancer survivors may be multifaceted - organic, functional or drug induced. It can be related to the cancer-site, e.g., gastro-intestinal (G) obstruction, pelvic tumour mass in GI and gynaecological cancers. It can be drug induced as opioids, pain killer medications and chemotherapy treatments induce constipation [39]. This may be further exacerbated by a low-fibre diet, low fluid intake, sedation, confinement to bed and low physical activity in cancer survivors [40]. The higher odds of anaemia in cancer patients have been reported previously [41-43], although ours is the only study to examine it across so many cancers. Higher odds of anaemia in blood and gastrointestinal cancers was also reported in a systematic review of anaemia in cancer patients [41]. There are several explanations which may contribute to higher odds of anaemia in cancer survivors including: cancer cells infiltrating the bone marrow and directly suppressing hemopoiesis. Cancer cells can also release cytokines that lead to iron sequestration and consequent reduced erythrocyte production. There may also be chronic blood loss from tumour sites. Erythrocytes and haemoglobin can be destroyed by cytotoxic chemotherapy. Additionally, there are a variety of ways that erythrocyte production may be hampered, including dietary deficits, bone marrow failure, and a muted erythropoietin response to tissue hypoxia [43, 44].

Higher prevalence of type 2 diabetes and obesity in pancreatic, liver, and biliary tract cancer is consistent with their risk profiles and other similar studies [25, 45]. Statistically higher odds of obesity and type 2 diabetes were found in 15 out of 28 cancers. These associations emphasise the need to combat obesity and type 2 diabetes. Our study found higher odds of depression compared to controls in only 5 out of 28 cancers, however there was a 13% increase in prevalence of depression after cancer diagnosis. In our study, elevated levels of depression were found in cancer related to female such as cervical, breast and ovarian cancer survivors, a finding reported in previous studies [46-49]. This may be hormone and treatment related, e.g., tamoxifen can increase the likelihood of depression [50]. However, two studies from the 1990s found no difference in depression between male and female cancers [51, 52]. Awareness and diagnosis of depression and a reduction in the potential stigma associated with mental health conditions may have improved considerably since then [53].

A major strength of this study is the size and breadth of the linked data sources that allowed us to analyse associations between multimorbidity in cancer survivors in granular detail. The significance of this is demonstrated by the variability observed in the association of cancer site and comorbidities, showing how important variations can be masked when comorbidities or cancers are grouped together. This study had the data and statistical power available to analyse 29 conditions in 28 cancers, specifically focusing on fifteen of the most common conditions. We used a consistent methodology across a wide range of cancers and outcomes and found results consistent with the existing literature, giving confidence that the observed patterns of multimorbidity represent real phenomena rather than methodological artefacts or chance. The benefits of employing CPRD GOLD data connected to secondary care data sources, notably for cancer have been shown by numerous validation studies [54-56]. Our results are generalisable to the UK and similar settings as CPRD GOLD data have been shown to be representative of the general UK population on key demographics [27].

Our study does have some limitations. We were unable to link to cancer registry data, however a previous study [55] has found little difference in the date of diagnosis of cancer between CPRD and cancer registry data. We were unable to access primary care prescribing data which would have helped to elucidate the potential causes of some of the associations seen. All the controls included in this study had at least

one of the 204 conditions, however, this could be construed as a strength as it means we are likely to have under-estimated the effect of comorbidity in cancer survivors compared to the controls. Furthermore, the list of 204 conditions was so comprehensive that it is likely that most of the adult population will have at least one of these conditions in their lifetime. Some individuals had missing BMI and smoking data, our complete-case analysis was predicated on the assumption that, relationships between cancer and morbidity do not differ between included and excluded participants [57]. However, even after exclusion of these patients the study is sufficiently powered due to its very large sample size.

This study did not have access to data on cancer treatments; thus, it was not possible to study associations between treatments and comorbidities. The contribution of cancer treatment to subsequent morbidity is very significant [58]. Given that cancer treatment changed dramatically in the last decade; it is important for future studies to account for the different treatment modalities (e.g., the novel immunotherapies which have different side effects).

Another useful research area would be developing a standard approach for measuring multimorbidity in cancer patients. A range of metrics of multimorbidity are utilised in the scientific literature to explore the association between comorbidity and cancer outcomes, but no consensus has been established on a gold standard measure of multimorbidity designed for cancer patients. Charlson's comorbidity index (CCI) is the most widely used comorbidity index to measure comorbidity. There are a few drawbacks to utilising CCI for cancer survivors. Since it does not account for some of the most common conditions that are related to cancer survivors, such as chronic pain, chronic fatigue, depression, anaemia, and constipation, the impacts of these comorbidities on cancer survivors cannot be determined by this index. CCI was created by including conditions that were associated to lower survival rates in the general population (57); these conditions might not have equal weighting for cancer survivors. Therefore, creating a multimorbidity index that is primarily designed for cancer survivors might be helpful for future research.

The effect of multimorbidity on primary and secondary care use by cancer patients and the associated costs are substantial [59-61]. This study highlights the comorbidities that are most common in cancer survivors and how these comorbidities vary by cancer site. These findings can be used to support integrated management of comorbidities customised to individual cancers through anticipatory care. These comorbidities can also be embedded in cancer care reviews in the UK, which have been reported to lack patient-centredness [62]. It also paves the way for further research into influence of comorbidity on each cancer site - including patient's quality of life, treatment, mortality, healthcare resource use and healthcare budgeting, which will help to enhance planning of healthcare systems and tailoring treatments hence improving cancer survivorship care.

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Disclosure of conflict of interest

None.

Abbreviations

AOR, Adjusted Odds Ratio; BMI, Body Mass Index; CI, Confidence Interval; CCI, Charlson Comorbidity Index; CKD, Chronic Kidney Disease; CMS, Cambridge Multimorbidity Score; COPD, Chronic Obstructive Pulmonary Disease; CPRD, Clinical Practice Research Datalink; CS, Cancer survivor; HES, Hospital Episode Statistics; LTC, Long term condition; ONS, Office of National Statistics; IMD, Index of Multiple Deprivation; NCI, National Cancer Institute; NCSI, National Cancer Survivorship Initiative; NCSS, National Coalition for Cancer Survivorship; OR, Odds ratio; PPI, Patient public

involvement; QOF, Quality of outcomes framework (QOF is a voluntary annual reward and incentive programme for GP practices in England, Wales and Northern Ireland to encourage them to record common long-term conditions from a set of 34 long-term conditions).

Address correspondence to: Tahania A Ahmad, Wolfson Institute of Population Health, Queen Mary University of London, Yvonne Carter Building, No. 58, Turner Street, London E1 2AB, The United Kingdom. ORCID: 0000-0003-3117-4428; E-mail: t.a.ahmad@qmul.ac.uk

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Supplementary File

The 204 conditions CPRD provided data on:

1. ADHD and hyperkinetic disorders
2. Adrenal insufficiency and Addison's disease
3. Alcohol dependence and related disease
4. Allergic and chronic rhinitis
5. Alopecia areata and scarring alopecia
6. Ankylosing spondylitis
7. Anaemia
8. Anxiety and phobia
9. Aortic aneurysm
10. Aplastic anaemias
11. Asbestosis
12. Asthma
13. Atrial fibrillation and flutter
14. Autism and Asperger's syndrome
15. Autoimmune liver disease
16. Barrett's oesophagus
17. Bipolar affective disorder and mania
18. Blistering autoimmune skin conditions
19. Bronchiectasis
20. Cardiac conduction defects
21. Cardiomyopathy other
22. Cerebral Palsy
23. Cerebrovascular disease
24. Cervical carcinoma in situ
25. Cholelithiasis
26. Chronic fatigue
27. Chronic Kidney Disease
28. Chronic sinusitis
29. Chronic ulcer of the skin
30. Chronic viral hepatitis
31. Coeliac disease
32. Collapsed vertebra
33. Congenital cardiac disease

34. Constipation
35. COPD
36. Coronary heart disease
37. Crohn's disease
38. Cystic Fibrosis
39. Cystic renal disease
40. Dementia
41. Depression
42. Dermatitis (atopic/contact/other/unspecified)
43. Diabetic eye disease
44. Diabetic neurological complications
45. Disorders of autonomic nervous system
46. Diverticular disease of intestine
47. Down's syndrome
48. Dysmenorrhoea
49. Eating disorders
50. End stage renal disease
51. Endometriosis
52. Enteropathic arthropathy
53. Enthesopathies & synovial disorders
54. Epilepsy
55. Erectile dysfunction
56. Female genital prolapse
57. Female infertility
58. Fibromyalgia
59. Folate deficiency, with and without anaemia
60. Fracture of hip
61. Gastritis and duodenitis
62. Gastrointestinal angiodysplasia
63. Gastro-oesophageal reflux disease
64. Giant Cell arteritis
65. Glaucoma
66. Glomerulonephritis and other nephritides
67. Gout
68. Hearing loss
69. Heart failure
70. Heart valve disease non-rheumatic

71. Hidradenitis suppurativa
72. HIV
73. Hodgkin Lymphoma
74. Hyperparathyroidism
75. Hyperplasia of prostate
76. Hyperprolactinaemia and prolactinoma
77. Hypertension
78. Hypertrophic Cardiomyopathy
79. Hypertrophy of nasal turbinates
80. Hypopituitarism
81. Hyposplenism
82. Immunodeficiencies
83. Infection of bones and joints
84. Intervertebral disc disorders
85. Intracerebral haemorrhage
86. Intracranial hypertension
87. Iron deficiency with and without anaemia
88. Irritable bowel syndrome
89. Juvenile arthritis
90. Learning disability
91. Leukaemia
92. Lichen planus
93. Liver failure and transplant
94. Liver fibrosis, sclerosis and cirrhosis
95. Lupus erythematosus (local and systemic)
96. Macular degeneration
97. Male infertility
98. Meniere disease
99. Menorrhagia and polymenorrhoea
100. Migraine
101. Motor neuron disease
102. Multiple myeloma and malignant plasma cell neoplasms
103. Multiple sclerosis
104. Myasthenia gravis
105. Myelodysplastic syndromes
106. Nasal polyp
107. Neuromuscular dysfunction of bladder

108. Non-acute cystitis
109. Non-alcoholic fatty liver disease and steatohepatitis
110. Non-diabetic peripheral neuropathies (excluding cranial nerves and carpal tunnel syndrome)
111. Non-Hodgkin Lymphoma
112. Non-malignant tumour of brain, central nervous system and pituitary
113. Obesity
114. Obsessive-compulsive disorder
115. Obstructive and reflux uropathy
116. Oesophagitis and oesophageal ulcer
117. Osteoarthritis (excl spine)
118. Osteoporosis
119. Other haemolytic anaemias
120. Other interstitial pulmonary diseases with fibrosis
121. Other psychoactive substance misuse
122. Painful conditions
123. Pancreatitis
124. Parkinson's disease
125. Peptic ulcer disease
126. Peripheral arterial disease
127. Peripheral venous and lymphatic disease
128. Personality disorder
129. Polycystic ovarian syndrome
130. Polycythaemia vera
131. Polymyalgia Rheumatica
132. Portal hypertension and oesophageal varices
133. Post-traumatic stress and stress-related disorders
134. Primary malignancy biliary tract
135. Primary malignancy bladder
136. Primary malignancy bone and articular cartilage
137. Primary malignancy brain, other CNS and intracranial
138. Primary malignancy breast
139. Primary malignancy cervical
140. Primary malignancy colorectal and anus
141. Primary malignancy kidney and ureter
142. Primary malignancy liver
143. Primary malignancy lung and trachea
144. Primary malignancy malignant melanoma

145. Primary malignancy mesothelioma
146. Primary malignancy oesophageal
147. Primary malignancy ovarian
148. Primary malignancy pancreatic
149. Primary malignancy prostate
150. Primary malignancy stomach
151. Primary malignancy testicular
152. Primary malignancy thyroid
153. Primary malignancy uterine
154. Primary Malignancy Oro-pharyngeal
155. Primary Malignancy-Other
156. Primary Malignancy-Other Skin and subcutaneous tissue
157. Psoriasis
158. Psoriatic arthropathy
159. Ptosis of eyelid
160. Pulmonary hypertension
161. Respiratory failure
162. Retinal detachments and breaks
163. Retinal vascular occlusions
164. Rheumatic valve
165. Rheumatoid Arthritis
166. Rosacea
167. Sarcoidosis
168. SARS-CoV-2
169. Schizophrenia and non-organic psychosis
170. Scoliosis
171. Seborrheic dermatitis
172. Secondary malignancy and metastasis
173. Secondary polycythaemia
174. Sick sinus syndrome
175. Sickle-cell anaemia
176. Sjogren's disease
177. Sleep apnoea
178. Somatoform and dissociative disorders
179. Spina bifida
180. Spinal stenosis
181. Spondylolisthesis

182. Spondylosis
183. Subarachnoid haemorrhage
184. Subdural haematoma
185. Supraventricular tachycardia
186. Systemic sclerosis
187. Thalassaemia
188. Thrombocytopenia - primary, secondary and other
189. Thrombophilia
190. Thyroid disease
191. Tinnitus
192. Trigeminal neuralgia
193. Tuberculosis
194. Type 1 Diabetes
195. Type 2 Diabetes
196. Ulcerative colitis
197. Unspecified or Rare Diabetes
198. Urinary Incontinence
199. Urolithiasis
200. Urticaria
201. Venous thromboembolism
202. Visual impairment and blindness
203. Vitamin B12 deficiency, with and without anaemia
204. Vitiligo