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Incident cardiovascular events and imaging phenotypes in UK Biobank participants with past cancer

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ABSTRACT

Objectives To evaluate incident cardiovascular outcomes and imaging phenotypes in UK Biobank participants with previous cancer.

Methods Cancer and cardiovascular disease (CVD) diagnoses were ascertained using health record linkage. Participants with cancer history (breast, lung, prostate, colorectal, uterus, haematological) were propensity matched on vascular risk factors to non-cancer controls. Competing risk regression was used to calculate subdistribution HRs (SHRs) for associations of cancer history with incident CVD (ischaemic heart disease (IHD), non-ischaemic cardiomyopathy (NICM), heart failure (HF), atrial fibrillation/flutter, stroke, pericarditis, venous thromboembolism (VTE)) and mortality outcomes (any CVD, IHD, HF/NICM, stroke, hypertensive disease) over 11.8±1.7 years of prospective follow-up. Linear regression was used to assess associations of cancer history with left ventricular (LV) and left atrial metrics.

Results We studied 18 714 participants (67% women, age: 62 (IQR: 57–66) years, 97% white ethnicities) with cancer history, including 1354 individuals with cardiovascular magnetic resonance. Participants with cancer had high burden of vascular risk factors and prevalent CVDs. Haematological cancer was associated with increased risk of all incident CVDs considered (SHRs: 1.92–3.56), larger chamber volumes, lower ejection fractions, and poorer LV strain. Breast cancer was associated with increased risk of selected CVDs (NICM, HF, pericarditis and VTE; SHRs: 1.34–2.03), HF/NICM death, hypertensive disease death, lower LV ejection fraction, and lower LV global function index. Lung cancer was associated with increased risk of pericarditis, HF, and CVD death. Prostate cancer was linked to increased VTE risk.

Conclusions Cancer history is linked to increased risk of incident CVDs and adverse cardiac remodelling independent of shared vascular risk factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Few studies have reported associations of past cancer with incident cardiovascular outcomes in large population-based cohorts, and none have included cardiovascular imaging.

WHAT THIS STUDY ADDS

⇒ We studied 18 714 UK Biobank participants with history of six common cancers and an equal number of non-cancer comparators propensity matched on vascular risk factors. Our results demonstrate association of cancer history with increased risk of a wide range of incident cardiovascular disease and mortality outcomes over 12 years of prospective follow-up. In participants with cardiovascular magnetic resonance (n=1354), cancer history was linked to adverse cardiac remodelling. The greatest range and magnitude of risk was observed in those with past breast and haematological cancers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ People with past cancer have heightened cardiovascular risk, which appears independent of vascular risk factors and persists several years after initial cancer diagnosis. This study highlights the specific cardiovascular care needs of patients with cancer and supports consideration of cancer-specific exposures in cardiovascular risk stratification.

INTRODUCTION

Patients with cancer history represent a growing cohort at heightened cardiovascular risk, attributed to shared vascular risk factors, cardiotoxicities of cancer therapies, and biological processes related to the cancer itself.[1 2] There is differential propensity to cardiovascular disease (CVD) across cancer sites, reflecting variation in these risk exposures.[3 4]

Existing work indicates highest risk of cardiovascular complications to be in the first year after cancer diagnosis.[5] Few researchers have examined longer term cancer-specific cardiovascular risk in population samples. Such analyses are important for informing cardiovascular risk stratification, surveillance, and treatment of patients with past cancer.

Cardiovascular imaging has a key role in detecting subclinical cardiotoxicity. However, associations of cancer with cardiovascular remodelling in population cohorts have not been previously reported.

We evaluated cardiovascular health in 18 714 UK Biobank participants with previous cancer, characterising disease and risk factor burden, incident disease and mortality outcomes, and cardiovascular remodelling patterns.

METHODS

Setting and study population

The UK Biobank includes over 500 000 participants aged 40–69 years, characterised in detail at baseline recruitment (2006–2010).[6] Incident health events are prospectively tracked through extensive health record linkages (Hospital Episode Statistics (HES), cancer register, death register). The UK Biobank Imaging Study, which includes cardiovascular magnetic resonance (CMR), is underway and aims to scan 100 000 of the original participants.

Ascertainment of cancer history

Cancer history was ascertained from cancer registry and HES records (online supplemental table 1). We created six categories (lung, breast, prostate, haematological, uterus, colorectal) to capture the most common cancer sites.[7] The primary cancer site was defined from the first code for cancer in any of the linked databases.

Ascertainment of incident cardiovascular outcomes

We defined incident CVD (ischaemic heart disease (IHD), stroke, atrial fibrillation (AF)/flutter, heart failure (HF), non-ischaemic cardiomyopathies (NICM), venous thromboembolism (VTE; deep vein thrombosis (DVT), pulmonary embolus (PE)), pericarditis) and mortality outcomes (IHD, stroke, hypertensive diseases, HF or NICMs) using HES and death registration records (online supplemental table 2).

CMR acquisition and analysis

CMR scans were performed according to predefined protocols and analysed using automated pipelines.[8–10] These are research scans without any clinical indication. The following metrics were included: left ventricular (LV) end-diastolic volume (LVEDV), LV ejection fraction (LVEF), LV global function index (LVGFI), LV global longitudinal strain (GLS), left atrial (LA) maximum volume (LAV) and LA ejection fraction (LAEF).

Statistical analysis

Statistical analysis was performed using R studio V.4.1.0 (https://www.R-project.org/) and Stata V.17.[11] Baseline characteristics are presented as number (percentage) for categorical variables, mean (SD) for normally distributed continuous variables and median (IQR) for non-normally distributed continuous variables. A propensity matched non-cancer comparator cohort was created with a priori selection of covariates (online supplemental figure 1, tables 3 and 4). Comparators were participants without record of cancer at baseline. Each cancer exposed participant was matched to one non-exposed participant using nearest neighbour propensity score matching on 20 predefined baseline covariates. Pairs were discarded if no matching participant had logit propensity score within 0.2 SDs of the case.[12] Balance of covariates was assessed in the unmatched and matched samples using the standardised mean difference between exposed and non-exposed groups (online supplemental figure 2). Missing data values were imputed using single centre imputation from the multiple chained equation algorithm.

Competing risks regression was used to calculate subdistribution HRs (SHR) and 95% CIs for the association of cancer history at baseline with incident disease and mortality outcomes. Participants with the outcome of interest at baseline were excluded from analyses for that outcome (but included in analyses of other outcomes). Incident events were first occurrence of the outcome after baseline. Prevalent events were conditions present at baseline. The censor date was 26 March 2021, providing mean prospective follow-up of 11.8±1.7 years. We performed sensitivity analyses using cause-specific Cox regression, limiting to cases with complete data (no imputation), and to cancers diagnosed within 5 years prior to baseline. Given possible heterogeneities within the haematological cancer category, we examined associations with incident outcomes within its subcategories (lymphoma, leukaemia, myeloma). We tested for interaction of cancer exposure with time by defining time from cancer diagnosis to baseline for cases and assigning the same time to their matched controls.

Linear regression was used to estimate association of cancer exposure with each CMR metric, reporting standardised beta coefficients, 95% CIs, and p values. For this analysis, cancer status was ascertained at imaging (any cancer diagnosis had been established prior to imaging). The samples all matched well on overall propensity score; individual covariates that were less well matched were included as covariates in final models, as per Nguyen *et al* (online supplemental figure 3).[13] We repeated the analysis excluding individuals with CVD at time of imaging. A two-sided significance level of 0.05 was used for all comparisons.

RESULTS

Baseline characteristics

We analysed 18 714 participants with past cancer (online supplemental figure 4). Smoking was most common in those with lung (82.9%), colorectal (54.4%) and prostate (53.0%) cancer (table 1). Diabetes was most common in lung (9.9%), uterine (9.5%), and colorectal (8.8%) cancer. The highest rates of hypertension were in prostate (45.6%), colorectal (39.5%), and uterine (38.4%) cancer. Individuals with uterine cancer had the highest average body mass index. Among those with cancer, 17.6% had pre-existing CVD (table 2).

Incident events

Almost one-third of participants with cancer developed one of the incident CVDs (table 2). The highest rates of incident CVD were in participants with lung (49.5%), haematological (48.4%), and prostate (40.6%) cancer. Incident IHD, AF/flutter and HF were the top three incident CVDs across all cancers. Over the study period, 18.8% of participants with cancer died compared with 8.5% of controls. In those with cancer, 8.2% (287/3514) of deaths were primary cardiovascular deaths.

Breast cancer

Among participants with breast cancer, 22.3% (2130/9531) developed one of the incident CVDs considered and 15.3% (1454/9531) died. The most common incident CVDs were IHD (5.9%), AF/flutter (5.8%), HF (3.5%), VTE (3.2%) and stroke (2.2%). NICMs occurred in 0.9% and pericarditis in 0.8% of participants with breast cancer. A total of 5.1% (74/1454) of all deaths were primary cardiovascular deaths. The most common causes of CVD death were stroke and IHD.

Compared with matched non-cancer controls, those with past breast cancer had over twofold greater risk of incident pericarditis (SHR 2.03 (1.36, 3.00); p=0.0004), 80% greater risk of incident NICM (SHR 1.80 (1.27, 2.56), p=0.0008), and 45% greater risk of incident VTE (SHR 1.45 (1.21, 1.73); $p=6.61\times10^{-5}$) (table 3,

Table 1 Baseline participant characteristics

	Cases	Controls	Breast	Lung	Prostate	Colorectal	Uterus	Haem
N	18714	18714	9531*	313	3291	2412	937	2230
Age	62 (57–66)	62 (57–66)	61 (56–65)	62 (58–66)	65 (62–67)	63 (59–66)	63 (59–66)	60 (53–65)
Men	6095 (32.6)	6095 (32.6)	0 (0)	170 (54.3)	3291 (100)	1383 (57.3)	0 (0)	1251 (56.1)
Women	12619 (67.4)	12619 (67.4)	9531 (100)	143 (45.7)	0 (0)	1029 (42.7)	937 (100)	979 (43.9)
White ethnicity	18002 (96.7)	18025 (96.7)	9201 (96.9)	301 (96.2)	3143 (96.1)	2324 (96.6)	910 (97.5)	2146 (96.7)
BAME	617 (3.3)	611 (3.3)	299 (3.2)	12 (3.8)	129 (3.9)	81 (3.4)	23 (2.5)	73 (3.3)
Townsend score	−2.3 (−3.7 to 0.3)	−2.3 (−3.7 to 0.3)	−2.3 (−3.7 to 0.2)	−0.7 (−3.3 to 2.5)	−2.4 (−3.8 to −0.1)	−2.2 (−3.7 to 0.4)	−2.2 (−3.6 to 0.0)	−2.2 (−3.6 to 0.5)
Degree or professional qualification	8329 (45.5)	8300 (45.4)	4259 (45.5)	96 (32.1)	1513 (47.1)	1022 (43.3)	382 (42.0)	1057 (48.5)
SBP (mm Hg)	140.2±19.2	140.1±19.1	138.5±19.4	137.7±19.3	145.0±17.8	142.6±19.2	141.2±18.7	137.5±18.9
DBP (mm Hg)	82.0±10.1	82.0±10.0	81.4±9.9	81.5±11.2	84.0±9.9	82.6±10.1	82.1±9.6	81.1±10.6
HR (bpm)	70.5 (63.5–78.5)	70(63-78)	71.5(65-79)	75 (67–83.5)	67.5 (60.5–75.5)	69.5 (62.5–77.5)	71(64-78)	70.5(63-80)
BMI (kg/m^2)	26.8 (24.2–30.0)	26.7 (24.1–29.9)	26.4 (23.7–29.7)	26.7 (24.3–30.1)	27.4 (25.1–30.0)	27.2 (24.7–30.2)	28.4 (24.7–33.7)	26.8 (24.2–30.0)
Physical activity (METS/week)	1695 (754–3426)	1742 (782–3471)	1695 (777–3336)	1175 (375–2799)	1874 (817–3848)	1626 (704–3412)	1624 (710–3506)	1578 (693–3279)
Ever smoked	8909 (48.0)	9141 (49.2)	4225 (44.6)	257 (82.9)	1725 (53.0)	1304 (54.4)	342 (36.8)	1056 (47.6)
HbA1c (mmol/mol)	36 (33.5–38.7)	35.9 (33.4–38.5)	36 (33.7–38.5)	37 (34.1–39.7)	36 (33.4–38.6)	36 (33.4–39.1)	36.4 (34.1–39.2)	35.5 (32.8–38.4)
Random glucose (mmol/L)	5.0 (4.7–5.4)	5.0 (4.6–5.4)	5.0 (4.7–5.4)	4.9 (4.6–5.4)	5.0 (4.7–5.5)	5.1 (4.7–5.5)	5.0 (4.7–5.5)	5.0 (4.6–5.4)
Total cholesterol (mmol/L)	5.8±1.2	5.8±1.2	6.0±1.2	5.6±1.3	5.4±1.1	5.6±1.2	5.9±1.2	5.6±1.2
HDL (mmol/L)	1.4 (1.2–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.8)	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.4 (1.1–1.7)	1.5 (1.3–1.7)	1.3 (1.1–1.6)
LDL (mmol/L)	3.5 (2.9–4.2)	3.6 (2.9–4.2)	3.6 (3.0–4.3)	3.4 (2.8–4.1)	3.4 (2.8–4.0)	3.4 (2.8–4.1)	3.6 (3.0–4.3)	3.5 (2.9–4.1)
Triglyceride level (mmol/L)	1.6 (1.1–2.2)	1.5 (1.1–2.2)	1.5 (1.1–2.1)	1.7 (1.2–2.3)	1.7 (1.2–2.4	1.7 (1.2–2.4)	1.6 (1.2–2.2)	1.6 (1.1–2.4)
Diabetes	1222 (6.5)	1238 (6.6)	463 (4.9)	31 (9.9)	264 (8.0)	211 (8.8)	89 (9.5)	164 (7.4)
Hypertension	6421 (34.3)	6443 (34.4)	2761 (29.0)	108 (34.5)	1499 (45.6)	953 (39.5)	360 (38.4)	740 (33.2)
High cholesterol	5659 (30.2)	5627 (30.1)	2272 (23.8)	115 (36.7)	1431 (43.5)	882 (36.6)	304 (32.4)	655 (29.4)

Count variables are shown as N (%). Continuous variables are shown as mean±SD or median (IQR) if skewed.
*39 males excluded
BAME, black, Asian and minority ethnic; BMI, body mass index; DBP, diastolic blood pressure; Haem, haematological; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; MET, metabolic equivalent; SBP, systolic blood pressure.

Table 2 Prevalent and incident cardiovascular diseases and mortality

	Cases	Controls	Breast	Lung	Prostate	Colorectal	Uterus	Haem
N (total)	18 714	18 714	9531	313	3291	2412	937	2230
Prevalent CVDs (N, %)	3289 (17.6)	2856 (15.3)	1119 (11.7)	116 (37.1)	805 (24.5)	554 (23.0)	121 (12.9)	574 (25.7)
IHD	1238 (6.6)	1286 (6.9)	348 (3.7)	45 (14.4)	375 (11.4)	222 (9.2)	45 (4.8)	203 (9.1)
NICM	52 (0.3)	33 (0.2)	21 (0.2)	1 (0.3)	11 (0.3)	7 (0.3)	2 (0.2)	10 (0.4)
HF	152 (0.8)	97 (0.5)	44 (0.5)	7 (2.2)	38 (1.2)	21 (0.9)	4 (0.4)	38 (1.7)
AF/flutter	431 (2.3)	394 (2.1)	111 (1.2)	23 (7.3)	138 (4.2)	71 (2.9)	14 (1.5)	74 (3.3)
Stroke	426 (2.3)	448 (2.4)	160 (1.7)	18 (5.8)	100 (3.0)	63 (2.6)	15 (1.6)	70 (3.1)
Pericarditis	35 (0.2)	22 (0.1)	17 (0.2)	1 (0.3)	7 (0.2)	4 (0.2)	0	6 (0.3)
VTE (DVT/PE)	955 (5.1)	576 (3.1)	418 (4.4)	21 (6.7)	136 (4.1)	166 (6.9)	41 (4.4)	173 (7.8)
Incident CVDs (N, %) (rate per 1000 person-years)	5753 (30.7) (21.5)	4594 (24.5) (16.3)	2130 (22.3) (14.7)	155 (49.5) (32.3)	1335 (40.6) (27.6)	803 (33.3) (22.8)	250 (26.7) (15.9)	1080 (48.4) (30.7)
IHD	1584 (8.5) (7.8)	1425 (7.6) (7.0)	560 (5.9) (5.5)	40 (12.8) (19.4)	385 (11.7) (12.3)	245 (10.2) (20.8)	68 (7.3) (6.9)	286 (12.8) (14.1)
NICM	225 (1.2) (1.0)	134 (0.7) (0.6)	90 (0.9) (0.8)	2 (0.6) (0.7)	38 (1.2) (1.1)	31 (1.3) (1.2)	7 (0.7) (0.6)	57 (2.6) (2.5)
HF	950 (5.1) (4.3)	705 (3.8) (3.2)	337 (3.5) (3.2)	32 (10.2) (12.5)	205 (6.2) (5.8)	107 (4.4) (4.2)	42 (4.5) (3.9)	227 (10.2) (10.0)
AF/flutter	1539 (8.2) (7.2)	1317 (7.0) (6.1)	555 (5.8) (5.4)	38 (12.1) (15.4)	382 (11.6) (11.6)	236 (9.8) (9.7)	69 (7.4) (6.3)	259 (11.6) (11.8)
Stroke	590 (3.2) (2.7)	477 (2.5) (2.2)	211 (2.2) (2.0)	16 (5.1) (6.6)	148 (4.5) (4.4)	83 (3.4) (3.3)	30 (3.2) (2.8)	102 (4.6) (4.6)
Pericarditis	188 (1.0) (0.8)	94 (0.5) (0.4)	75 (0.8) (0.7)	12 (3.8) (4.8)	28 (0.9) (0.8)	19 (0.8) (0.7)	7 (0.7) (0.6)	47 (2.1) (2.0)
VTE (DVT/PE)	677 (3.6) (3.4)	442 (2.4) (2.1)	302 (3.2) (2.9)	15 (4.8) (5.8)	149 (4.5) (4.3)	82 (3.4) (3.4)	27 (2.9) (2.7)	102 (4.6) (4.7)
Mortality outcomes (N, %) (rate per 1000 person-years)	3514 (18.8) (17.0)	1582 (8.5) (7.2)	1454 (15.3) (13.5)	160 (51.1) (59.0)	683 (20.8) (18.9)	499 (20.7) (19.1)	113 (12.1) (10.4)	605 (27.1) (25.7)
Any CVD	287 (1.5) (1.4)	265 (1.4) (1.2)	74 (0.8) (0.7)	17 (5.4) (6.3)	83 (2.5) (2.3)	54 (2.2) (2.1)	12 (1.3) (1.1)	47 (2.1) (2.0)
IHD	154 (0.8) (0.7)	160 (0.9) (0.7)	24 (0.3) (0.2)	14 (4.5) (5.2)	53 (1.6) (1.5)	34 (1.4) (1.3)	3 (0.3) (0.3)	26 (1.2) (1.1)
HF/NICM	37 (0.2) (0.2)	17 (0.1) (0.1)	17 (0.2) (0.2)	0	7 (0.2) (0.2)	5 (0.2) (0.2)	3 (0.3) (0.3)	5 (0.2) (0.2)
Stroke	65 (0.3) (0.3)	60 (0.3) (0.3)	21 (0.2) (0.2)	2 (0.6) (0.7)	16 (0.5) (0.4)	11 (0.5) (0.4)	5 (0.5) (0.5)	10 (0.4) (0.4)
Hypertensive diseases	21 (0.1) (0.1)	9 (0.1) (0.04)	8 (0.1) (0.1)	0	5 (0.2) (0.1)	3 (0.1) (0.1)	2 (0.2) (0.2)	3 (0.1) (0.1)

Figures are numbers of participant with each condition/outcome. Percentages are shown in brackets with denominator taken as the total number of participants in each category ('total' row). Prevalent CVDs were present at baseline recruitment. Incident CVDs represent first occurrence of the condition after baseline.
AF, atrial fibrillation; CVD, cardiovascular disease; DVT, deep vein thrombosis; Haem, haematological; HF, heart failure; IHD, ischaemic heart disease; NICM, non-ischaemic cardiomyopathies; PE, pulmonary embolism; VTE, venous thromboembolism.

figure 1). Breast cancer history was associated with 8.5-fold greater risk of death from HF or NICM (SHR 8.50 (1.95, 36.97); p=0.004) and eightfold greater risk of death from hypertensive diseases (SHR 8.00 (1.00, 64.07); p=0.05).

Lung cancer

Among the cancer sites considered, participants with a history of lung cancer (n=313) had the highest rates of incident CVD (49.4%), all-cause death (51.1%), and CVD death (5.4%). The most common incident CVDs were IHD (12.8%), AF/flutter (12.1%) and HF (10.2%). Among participants with lung cancer who died, 10.1% (17/160) died of a primary cardiovascular cause.

Lung cancer was associated with over 12-fold greater risk of incident pericarditis (SHR 12.18 (1.57, 94.63); p=0.017), 88% greater risk of incident HF (SHR 1.88 (1.07, 3.29); p=0.029), and almost 2.5-fold greater risk of CVD death (SHR 2.46 (1.00, 5.99); p=0.05). The risk of IHD death was increased in lung cancer patients, although with wide CIs (SHR 1.99 (0.79, 5.05); p=0.14).

Prostate cancer

Among 3291 participants with prostate cancer, 40.6% developed incident CVD and 20.8% died. Primary cardiovascular deaths contributed 12.2% (83/683) of all deaths. The most common incident CVDs were IHD (11.7%), AF/flutter (11.6%), and HF (6.2%). Incident stroke and VTE each occurred in 4.5%, NICMs in 1.2% and pericarditis in 0.9%.

Compared with matched non-cancer controls, participants with prostate cancer had increased risk of incident VTE (SHR 1.70 (1.30, 2.23); p=0.0001) and all-cause death (HR 1.65 (1.46, 1.86); $p=2.40\times10^{-16}$). Associations with all other outcomes were statistically non-significant.

Colorectal cancer

One-third (803/2412) of participants with colorectal cancer developed incident CVD, 20.7% died and 2.2% died of primary cardiovascular causes (10.8% of all deaths: 54/499). The most

Table 3 Associations of cancer patients with incident cardiovascular events compared with propensity matched non-cancer controls

	Breast	Lung	Prostate	Colorectal	Uterus	Haematological
Incident disease						
IHD	1.05 (0.93, 1.19)	1.03 (0.68, 1.57)	0.92 (0.79, 1.07)	1.14 (0.94, 1.38)	1.03 (0.74, 1.42)	**1.92 (1.57, 2.34)**
	0.428	0.899	0.297	0.181	0.868	2.02×10^{-10}
NICM	**1.80 (1.27, 2.56)**	–	1.16 (0.73, 1.86)	1.25 (0.73, 2.14)	3.49 (0.72, 16.78)	**2.51 (1.54, 4.10)**
	0.0008	–	0.543	0.416	0.121	0.002
Heart failure	**1.34 (1.14, 1.57)**	**1.92 (1.07, 3.46)**	1.04 (0.85, 1.26)	**0.77 (0.60, 0.99)**	1.38 (0.86, 2.18)	**3.56 (2.69, 4.66)**
	0.0004	0.029	0.72	0.044	0.181	1.19×10^{-19}
AF/flutter	1.11 (0.98, 1.25)	1.39 (0.84, 2.32)	1.00 (0.86, 1.15)	**1.26 (1.04, 1.52)**	1.00 (0.71, 1.42)	**1.97 (1.60, 3.22)**
	0.114	0.206	0.969	0.02	0.996	4.43×10^{-6}
Stroke	1.13 (0.91, 1.38)	1.23 (0.58, 2.61)	1.17 (0.92. 1.49)	1.12 (0.82, 1.52)	1.15 (0.68, 1.95)	**2.27 (1.60, 2.44)**
	0.259	0.575	0.194	0.48	0.59	2.62×10^{-10}
Pericarditis	**2.03 (1.36, 3.00)**	**12.18 (1.57, 94.63)**	1.16 (0.68, 2.01)	1.36 (0.68, 2.72)	3.49 (0.73, 16.95)	**2.94 (1.67, 5.21)**
	0.0004	0.017	0.585	0.385	0.119	0.0002
VTE	**1.45 (1.21, 1.73)**	1.14 (0.53, 2.46)	**1.70 (1.30, 2.23)**	1.21 (0.87, 1.67)	1.70 (0.91, 3.19)	**2.69 (1.86, 3.94)**
	6.61×10^{-5}	0.736	0.0001	0.2639	0.095	2.47×10^{-7}
Mortality outcomes						
All-cause	**2.48 (2.25, 2.72)**	**5.00 (3.63, 6.89)**	**1.65 (1.46, 1.86)**	**2.08 (1.79, 2.41)**	**2.41 (1.73, 3.32)**	**4.14 (3.49, 4.90)**
	3.65×10^{-80}	7.25×10^{-21}	2.40×10^{-16}	1.30×10^{-21}	3.06×10^{-7}	3.10×10^{-59}
Any CVD	0.97 (0.70, 1.34)	2.46 (1.00, 5.99)	0.87 (0.65, 1.17)	1.20 (0.80, 1.79)	1.20 (0.56, 2.59)	1.48 (0.94, 2.32)
	0.871	0.05	0.371	0.374	0.64	0.087
IHD	0.63 (0.38, 1.05)	1.99 (0.79, 5.05)	0.87 (0.60, 1.26)	1.06 (0.65, 1.72)	–	1.73 (0.91, 3.29)
	0.079	0.14	0.461	0.820	–	0.090
Heart failure or NICM	**8.50 (1.95, 36.97)**	–	0.78 (0.29, 2.10)	5.00 (0.58, 42.95)	–	1.01 (0.29, 3.49)
	0.004	–	0.615	0.142	–	0.991
Stroke	0.88 (0.49, 1.57)	–	0.94 (0.47, 1.86)	1.22 (0.51, 2.94)	5.00 (0.58, 42.95)	1.12 (0.45, 2.77)
	0.656	–	0.853	0.652	0.142	0.806
Hypertensive diseases	**8.00 (1.00, 64.07)**	–	1.25 (0.34, 4.66)	–	–	–
	0.050	–	0.741	–	–	–

Results are subdistribution HR (95% CI) and p value associated with cancer exposure (vs no cancer). Blank cells indicate that no analysis was performed due to small number of outcomes (<5) in that category. Comparators are matched on age, sex, ethnicity, deprivation, education, blood pressure, heart rate, body mass index, glycated haemoglobin, random glucose, total cholesterol, high density lipoprotein, low density lipoprotein, triglyceride level, physical activity, smoking, diabetes, hypertension and high cholesterol. The bold cells represent statistically significant associations.
AF, atrial fibrillation; CVD, cardiovascular disease; IHD, ischaemic heart disease; NICM, non-ischaemic cardiomyopathies; VTE, venous thromboembolism.

common incident CVDs were IHD (10.2%), AF/flutter (9.8%), and HF (4.4%).

Participants with colorectal cancer had 26% greater risk of incident AF/flutter (SHR 1.26 (1.04, 1.52); p=0.02) compared with matched non-cancer controls. Colorectal cancer was associated with higher risk of HF/NICM death, but with wide CIs (SHR 5.00 (0.58, 42.95); p=0.14). Aside from all-cause death, there was no statistically significant difference in risk of any other outcome.

Uterine cancer

Among the 937 participants with uterine cancer, 26.7% developed incident CVD and 12.1% died. Primary cardiovascular deaths contributed 10.6% (12/113) of all deaths. The most common incident CVDs were AF/flutter (7.4%), IHD (7.3%) and HF (4.5%). Incident stroke occurred in 3.2%, VTE in 2.9% and NICMs and pericarditis were each observed in 0.7% of individuals.

Compared with matched non-cancer controls, uterine cancer patients had increased (statistically non-significant) risk of incident NICM (SHR 3.49 (0.72, 16.78); p=0.12), pericarditis (SHR 3.49 (0.73, 16.95); p=0.12) and stroke death (SHR 5.00 (0.58, 42.95); p=0.14).

Haematological cancer

Among 2230 participants with past haematological cancer, 48.4% (n=1080) developed incident CVD and 27.1% died. A total of 7.8% (47/605) of all deaths were attributed to a primary cardiovascular cause. The most common CVDs were IHD (12.8%), AF/flutter (11.6%), and HF (10.2%). Incident stroke and VTE each occurred in 4.6%, NICMs in 2.6% and pericarditis in 2.1% of haematological cancer patients.

Participants with past haematological cancer had significantly greater risk of all incident CVDs (table 3, figure 1). The risk of incident HF was increased by over 3.5-fold (SHR 3.56 (2.69, 4.66); $p=1.19\times10^{-19}$), pericarditis by almost threefold (SHR 2.94 (1.67, 5.21); p=0.0002)], and there was over 2.5-fold greater risk of both incident VTE (SHR 2.69 (1.86, 3.94); $p=2.47\times10^{-7}$] and NICM (SHR 2.51 (1.54, 4.10); p=0.002). There was almost twofold increased risk of incident AF/flutter (SHR 1.97 (1.60, 2.44); $p=2.62\times10^{-10}$) and IHD (SHR 1.92 (1.57, 2.34); $p=2.02\times10^{-10}$). Associations with CVD mortality outcomes were statistically non-significant; however, participants with a history of haematological cancer appeared at higher risk of CVD (SHR 1.48 (0.94, 2.32); p=0.087) and IHD (SHR 1.73 (0.91, 3.29); p=0.090) death.

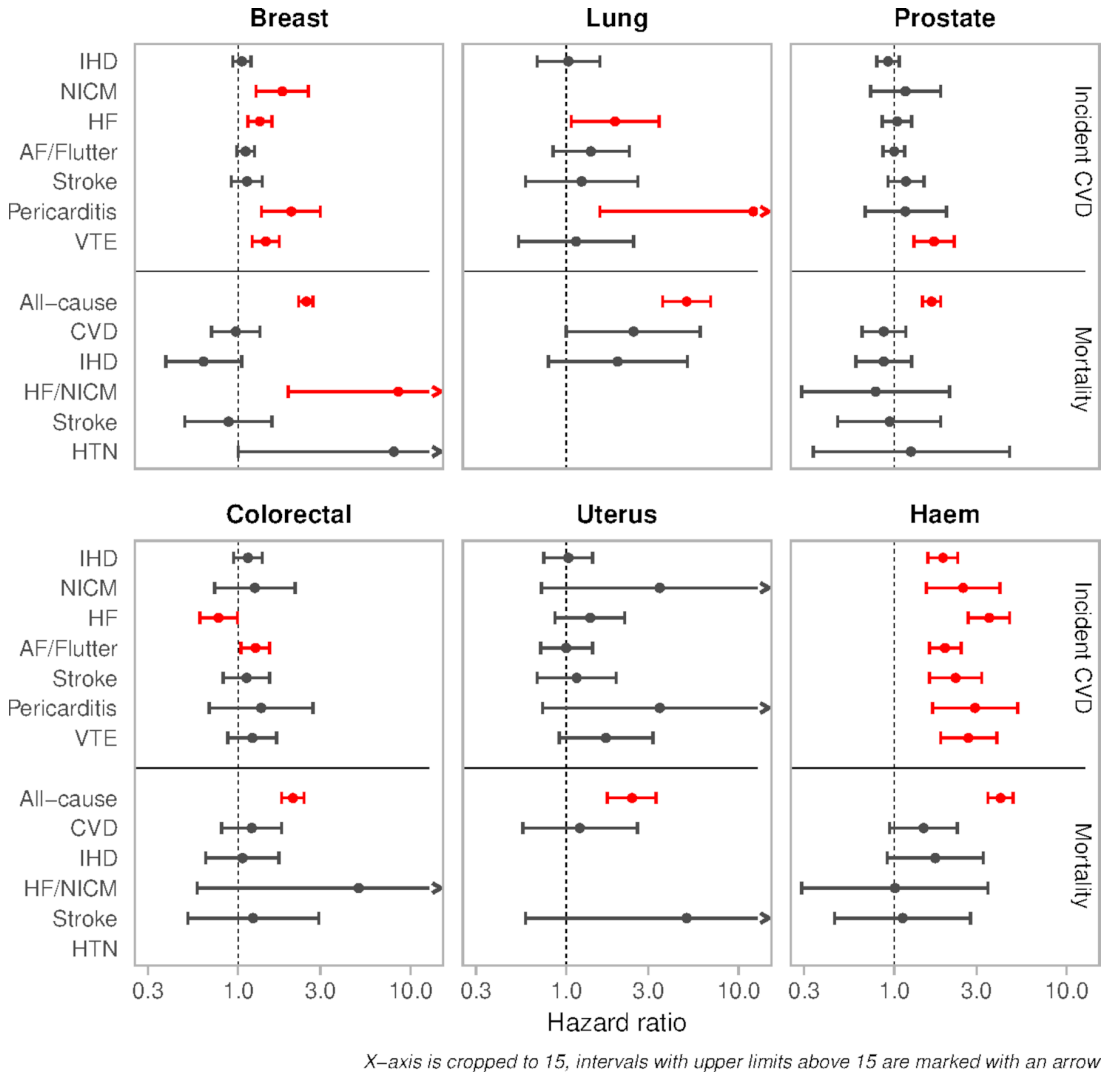

Figure 1 Associations of cancer exposure with incident cardiovascular disease and mortality outcomes. Results are association of cancer exposure with incident outcomes presented as subdistribution HRs and 95% CIs from competing risk regression, except for all-cause death where we report HR from Cox hazard proportional regression. HRs and 95% CIs are presented on a $\log_{10}$ scale. The comparators are propensity matched non-cancer controls. The dots represent the point estimate, and the intervals are the CIs. The greyed-out intervals indicate statistically non-significant associations. AF, atrial fibrillation; CVD, cardiovascular disease; NICM, non-ischaemic cardiomyopathies; Haem, haematological; HF, heart failure; HTN, hypertension; IHD, ischaemic heart disease.

Associations with incident events were broadly similar across myeloma, leukaemia, and lymphomas (online supplemental tables 5 and 6).

Sensitivity analyses

In analyses limiting to cases with complete data, associations remained similar across all outcomes (online supplemental tables 7 and 8). The results were consistent in cause-specific Cox regression models (online supplemental table 9) and when restricting to participants diagnosed with cancer within 5 years of baseline (online supplemental tables 10 and 11). The interaction of cancer exposure with time from diagnosis was non-significant for all models, except for the association of lung cancer with incident stroke, where risk was higher in the earlier years after cancer incidence.

Associations with CMR metrics

We investigated associations of past cancer with cardiovascular phenotypes in 1354 participants who had CMR data available (online supplemental table 12). Compared with matched non-cancer controls, participants with past haematological cancer had larger LVEDV, poorer LV function by both LVEF and LV GLS, larger LAV, and lower LAEF (table 4, figure 2). Breast cancer was associated with significantly poorer LV function by LVEF and LVGFI. These relationships were similar in individuals without CVD at imaging (online supplemental table 13).

DISCUSSION

Summary of findings

In this large population-based study, covering an average of 12 years prospective follow-up, past cancer was linked to increased risk of a wide range of incident cardiovascular outcomes and adverse remodelling, independent of shared vascular risk factors. Previous haematological cancer was linked to increased incidence of all CVDs considered, poorer LV function (by LVEF and GLS), larger LV and LA size, and poorer LA function (lower LAEF). Past breast cancer was linked to increased incidence of NICM, HF, pericarditis, VTE, HF/NICM mortality,

Table 4 Association of cancer with CMR metrics

	Breast	Lung	Prostate	Colorectal*	Uterus*	Haem*
LVM (g)	0.07 (−0.05, 0.18)	−0.41 (−1.27, 0.46)	−0.01 (−0.14, 0.12)	−0.23 (−0.78, 0.32)	0.14 (−0.23, 0.51)	0.11 (−0.11, 0.33)
	0.27	0.33	0.84	0.40	0.45	0.33
LVEDV (mL)	0.10 (−0.01, 0.22)	−0.56 (−1.48, 0.35)	0.05 (−0.08, 0.18)	−0.32 (−0.85, 0.22)	−0.01 (−0.37, 0.35)	0.22 (−0.00, 0.44)
	0.07	0.21	0.44	0.24	0.94	0.05
LVEF (%)	**−0.18 (−0.30, −0.06)**	0.62 (−0.26, 1.50)	0.02 (−0.10, 0.15)	−0.12 (−0.60, 0.36)	0.03 (−0.34, 0.41)	**−0.28 (−0.49, −0.06)**
	0.003	0.15	0.73	0.61	0.87	0.01
LVGFI (%)	**−0.14 (−0.26, −0.02)**	0.25 (−0.68, 1.18)	0.05 (−0.07, 0.18)	−0.13 (−0.59, 0.34)	−0.06 (−0.45, 0.33)	−0.18 (−0.39, 0.04)
	0.02	0.56	0.41	0.58	0.76	0.10
LV GLS (%)	−0.02 (−0.13, 0.10)	−0.87 (−1.71, −0.04)	−0.03 (−0.17, 0.11)	0.38 (−0.26, 1.02)	0.33 (−0.14, 0.80)	**0.25 (0.03, 0.47)**
	0.78	0.05	0.65	0.24	0.17	0.02
LAV max (mL)	0.08 (−0.04, 0.20)	−0.82 (−1.69, 0.05)	0.02 (−0.11, 0.16)	−0.35 (−0.76, 0.05)	−0.01 (−0.39, 0.37)	**0.30 (0.06, 0.53)**
	0.18	0.06	0.75	0.09	0.96	0.01
LAEF (%)	−0.12 (−0.24, 0.00)	0.42 (−0.11, 0.94)	−0.02 (−0.15, 0.11)	0.15 (−0.24, 0.54)	−0.07 (−0.41, 0.27)	**−0.33 (−0.56, −0.11)**
	0.06	0.11	0.74	0.45	0.68	0.004

The results are standardised beta-coefficients and 95% CIs, thus representing SD change in CMR metrics with change in cancer exposure status from non-cancer to cancer; for SD of each metric, please refer to online supplemental table 5. The bold and yellow shaded cells represent statistically significant associations.
*Doubly robust model.
GLS, LV global longitudinal strain; LA, left atrium; LAEF, LA ejection fraction; LAV, LA maximum volume; LV, left ventricle; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVGFI, LV global function index; LVM, LV mass.

hypertensive disease death, and poorer LV function (by LVEF and LVGFI). Lung cancer was associated with increased risk of incident HF, pericarditis and CVD death. Colorectal cancer was associated with increased risk of incident AF/flutter. Prostate cancer was linked to increased VTE risk.

Comparison with previous work

The most common incident CVDs in our cancer-exposed cohort were IHD, AF/flutter, and HF. This distribution reflects both the risk factor profile of individuals with cancer and general population trends.[14] Consistent with previous reports, we found high burden of vascular risk factors in participants with cancer.[15 16] The observed CVD patterns are similar to studies from China and the USA.[15 17] In our cancer cohort, 8.2% of deaths were attributed to primary cardiovascular causes. Similarly, an analysis of the UK Clinical Primary Records Datalink identified CVD as the primary cause of death in 9.7% of men and 7.7% of women with cancer.[18]

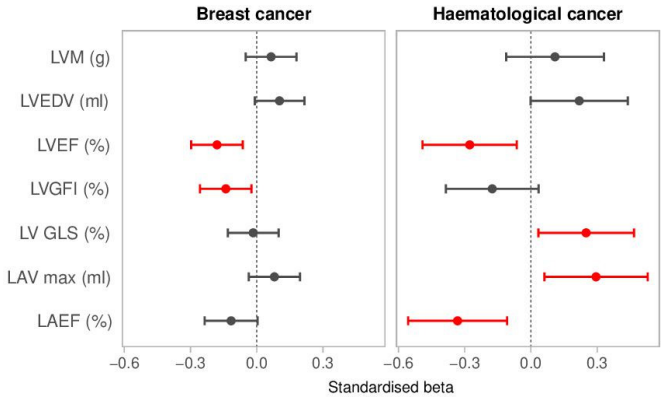

Figure 2 Association of breast and haematological cancer exposure with CMR metrics. Results are standardised beta-coefficients and 95% CIs, thus representing SD change in CMR metrics with change in cancer exposure status from non-cancer to cancer. CMR, cardiovascular magnetic resonance; GLS, LV global longitudinal strain; LA, left atrium; LAEF, LA ejection fraction; LAV, LA maximum volume; LV, left ventricle; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVGFI, LV global function index; LVM, LV mass.

Our work extends previous reports by isolating cardiovascular risk associated with cancer independent of shared risk factors. A recent study from the UK used linked primary care and hospitalisation records to examine risk of incident disease-specific CVDs in patients with cancer independent of vascular risk factors.[3] Our findings validate these observations in an independent cohort and provide new insights by considering disease associations alongside CMR remodelling.

Participants with previous haematological cancer had significantly increased risk of all incident CVDs. They also had increased size and poorer function of both the LA and LV. Haematological cancer patients are exposed to many cardiotoxic cancer therapies such as tyrosine kinase inhibitors,[19] cyclophosphamide,[20] anthracyclines,[21] and mediastinal radiotherapy.[22] The observed pattern of LV remodelling associated with haematological cancer may reflect subclinical cardiotoxicity, indicating a dilated LV with lower ejection fraction and poorer longitudinal function, and is consistent with our finding of increased risk of incident NICM and HF. The atrial remodelling patterns of a dilated and poorly functioning LA may reflect haemodynamic consequences of increased LV filling pressures that accompanies HF. There may also be direct effects on the atria via radiotherapy or other treatments. Regardless of underlying mechanism, atrial remodelling is both precipitated by and predisposes to AF, which we found to be significantly associated with haematological cancer history. We also found increased risk of stroke associated with past haematological cancer, which is likely driven by both ischaemic and haemorrhagic mechanisms, with the latter precipitated by coagulopathies related to the primary cancer and greater use of anticoagulants in these patients.

Increased risk of VTE was observed in participants with haematological, breast, and prostate cancer. Many factors promote a prothrombotic state in the setting of cancer, such as the systemic biological processes of the cancer itself, tumour compression effects, chemotherapy, and long-term indwelling venous catheters. Previous studies have documented augmented risk of VTE in patients with cancer.[23] In our study, the magnitude

of increased VTE risk was highest among participants with past haematological cancer.

Radiation-induced heart disease has a range of possible manifestations.[24] Mediastinal radiotherapy has been linked to initiation and progression of atherosclerosis. Patients with lymphomas are often exposed to mediastinal radiotherapy, which may be a driver of the increased risk of IHD in participants with previous haematological cancer in our cohort. Our findings are consistent with a previous study by van Nimwegen *et al*,[25] who also report increased risk of IHD in Hodgkin lymphoma survivors and attribute this, in part, to radiotherapy exposure.

Participants with previous lung, breast or haematological cancer had increased risk of pericardial disease, with lung cancer patients having a markedly increased risk (over 12-fold). This may reflect metastatic disease presentations. Pericardial disease may also be an adverse consequence of mediastinal radiotherapy,[24] which is common in all three cancers.

Participants with breast cancer had increased risk of incident HF, incident NICMs and death from HF or NICM. Furthermore, breast cancer history was associated with poorer LV function by LVGFI and LVEF. These observations likely reflect cardiotoxicity linked to breast cancer therapies.[21 26] An interesting observation in our results was a markedly increased risk of death due to hypertensive disease (eightfold increase) in participants with previous breast cancer, which may reflect suboptimal control of hypertension in this cohort.

Participants with uterine cancer had the highest average body mass index of all cancers, high rates of hypertension and diabetes and increased risk of stroke death. The clustering of cardiometabolic factors has been previously reported in uterine cancer.[27 28] In our analysis, uterine cancer was linked to increased stroke mortality but with very wide CIs.

Clinical implications

Patients with cancer have a constellation of demographic and clinical risk factors that place them at higher cardiovascular risk. Our findings underscore the importance of controlling modifiable risk factors for all patients during and after their cancer treatment, as well as specific areas of risk where surveillance and/or preventive strategies should be focused. Importantly, we demonstrate that past cancer confers an increased risk of cardiovascular events, independent of traditional vascular risk factors and that this risk may extend several years beyond the initial cancer diagnosis. Thus, our results support consideration of cancer-specific exposures in cardiovascular risk stratification and lower thresholds for treatment of modifiable risk factors in this patient group. We demonstrate particular vulnerability of individuals with past breast and haematological cancer, who appeared at greatest risk, both with regards risk of incident clinical disease and adverse cardiac remodelling.

We found significant associations between breast and haematological cancer history and selected CMR metrics, even in the absence of prevalent CVD. The most consistent associations were observed with LVEF. We also demonstrate potential value of LVGFI, GLS, and LAEF as emerging novel imaging biomarkers of subclinical disease.

Limitations

Ascertainment of incident outcomes from health records may be subject to miscoding. We may be underpowered to detect associations in cancers with small sample sizes (eg, lung and uterine). Our dataset does not permit characterisation by cancer histology or stage. Information about specific cancer therapies was not available, and we cannot make inferences about treatment-specific effects. We are unable to consider ethnic disparities as our sample comprises a predominantly white cohort; future studies in more diverse cohorts are needed.

CONCLUSIONS

Individuals with past cancer have heightened cardiovascular risk, which appears independent of vascular risk factors and persists several years after initial cancer diagnosis. The pattern of CVDs varies by cancer site, likely reflecting specific characteristics of the cancer and its therapies. CMR measures of LV and LA structure and function provide preclinical indicators of cardiovascular health in this context.

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Competing interests SEP provides consultancy to Cardiovascular Imaging Inc, Calgary, Alberta, Canada. The remaining authors have nothing to disclose.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study complies with the Declaration of Helsinki; the work was covered by the ethical approval for UK Biobank studies from the NHS National Research Ethics Service on 17 June 2011 (Ref 11/NW/0382) and extended on 18 June 2021 (Ref 21/NW/0157) with written informed consent obtained from all participants. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. This research was conducted using the UK Biobank resource under access application 2964. UK Biobank will make the data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: http://www.ukbiobank.ac.uk/register-apply.

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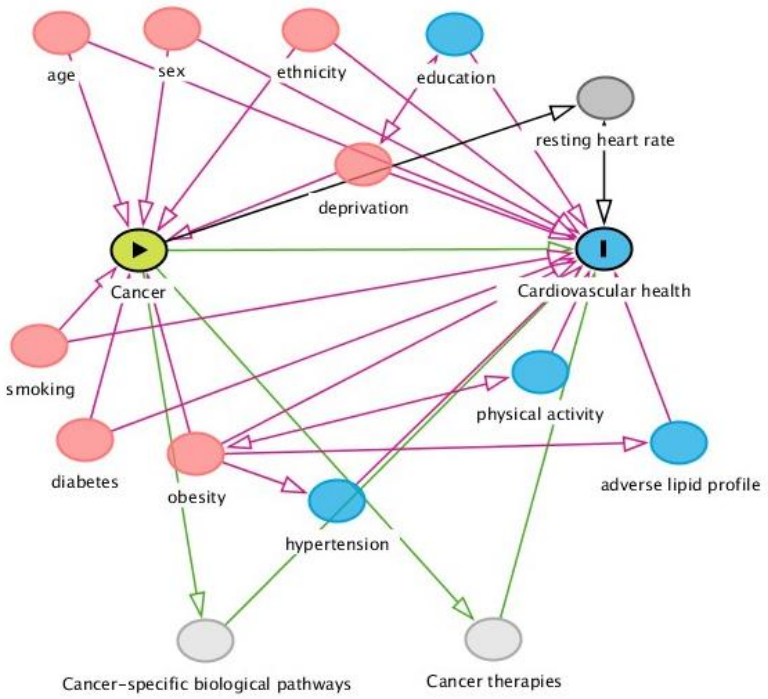
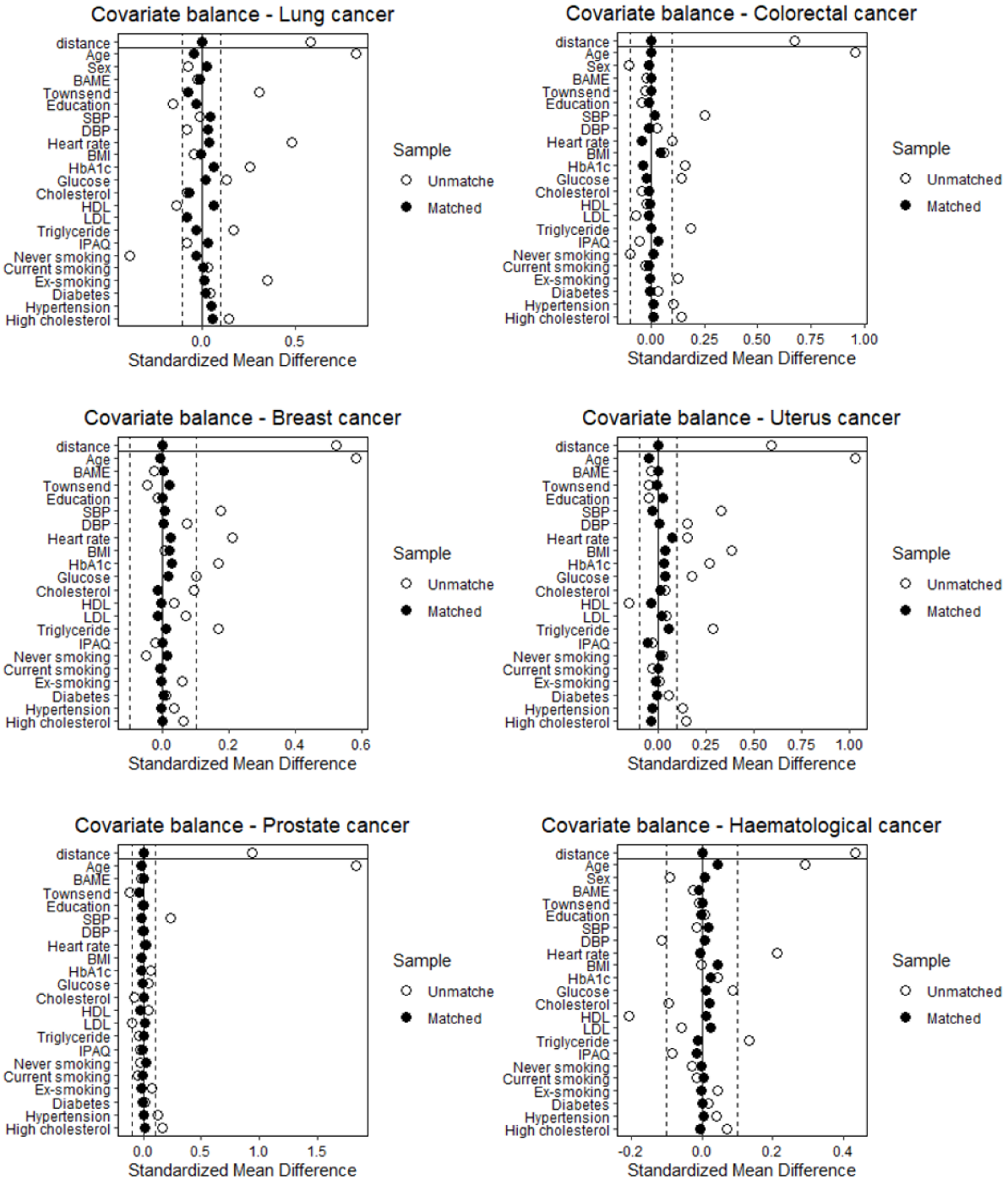
Supplementary Figure 1. Postulated causal pathways and potential and true confounders of the relationship between cancer and cardiovascular health



Supplementary Figure 1 footnote. Figure created using the dagitty package: Johannes Textor, Benito van der Zander, Mark K. Gilthorpe, Maciej Liskiewicz, George T.H. Ellison. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *International Journal of Epidemiology* 45(6):1887-1894, 2016.

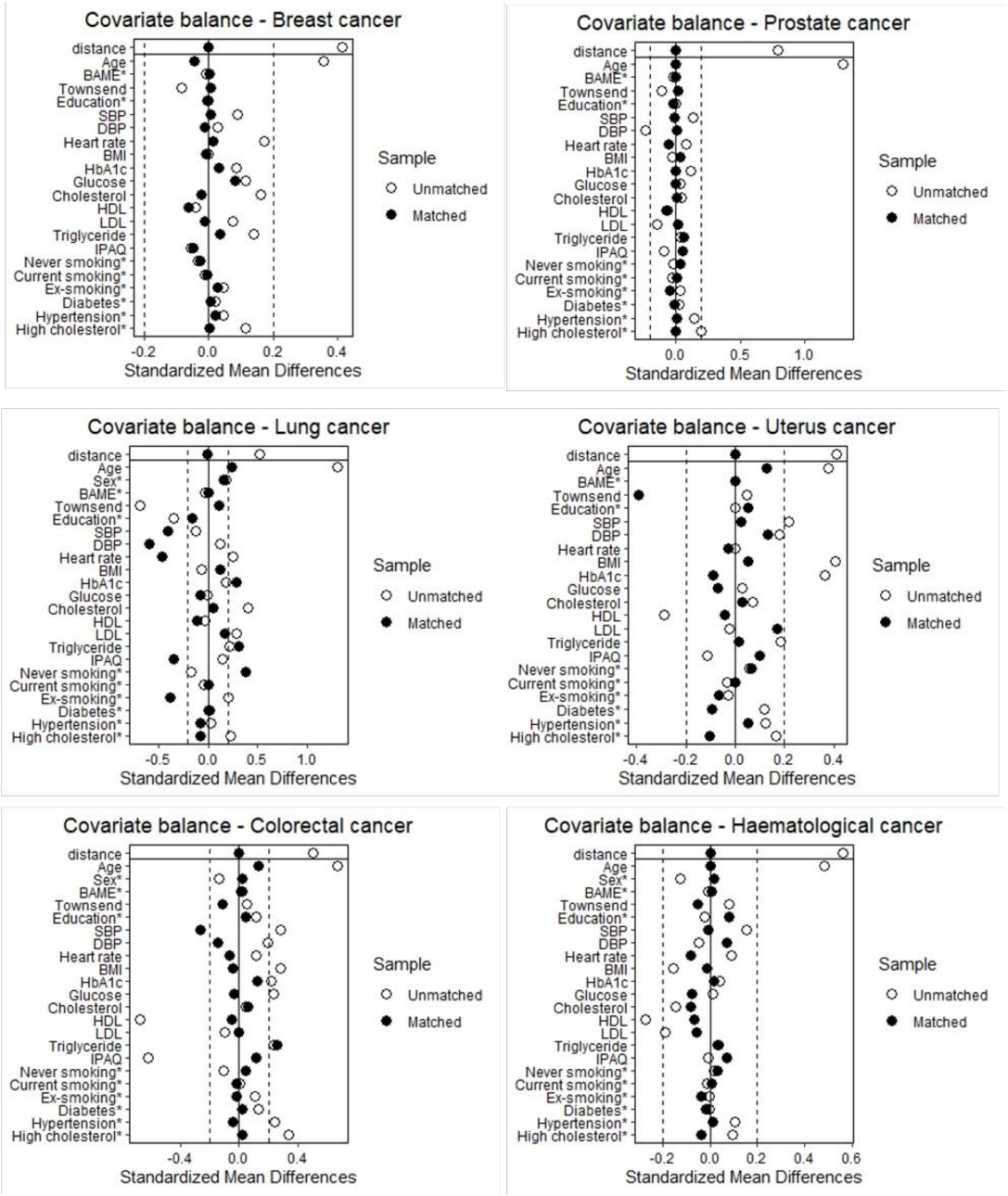
Supplementary Figure 2. Balance plots for propensity score matching in the baseline set



Supplementary Figure 2 footnote. Vertical dashed lines show threshold of 0.1 standardised mean difference. There was good balance of overall propensity score and individual covariates for all cancer categories in the baseline set. BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated

haemoglobin, HDL: high density lipoprotein, IPAQ: international physical activity questionnaire; LDL: low density lipoprotein; METS: metabolic equivalent; SBP: systolic blood pressure.

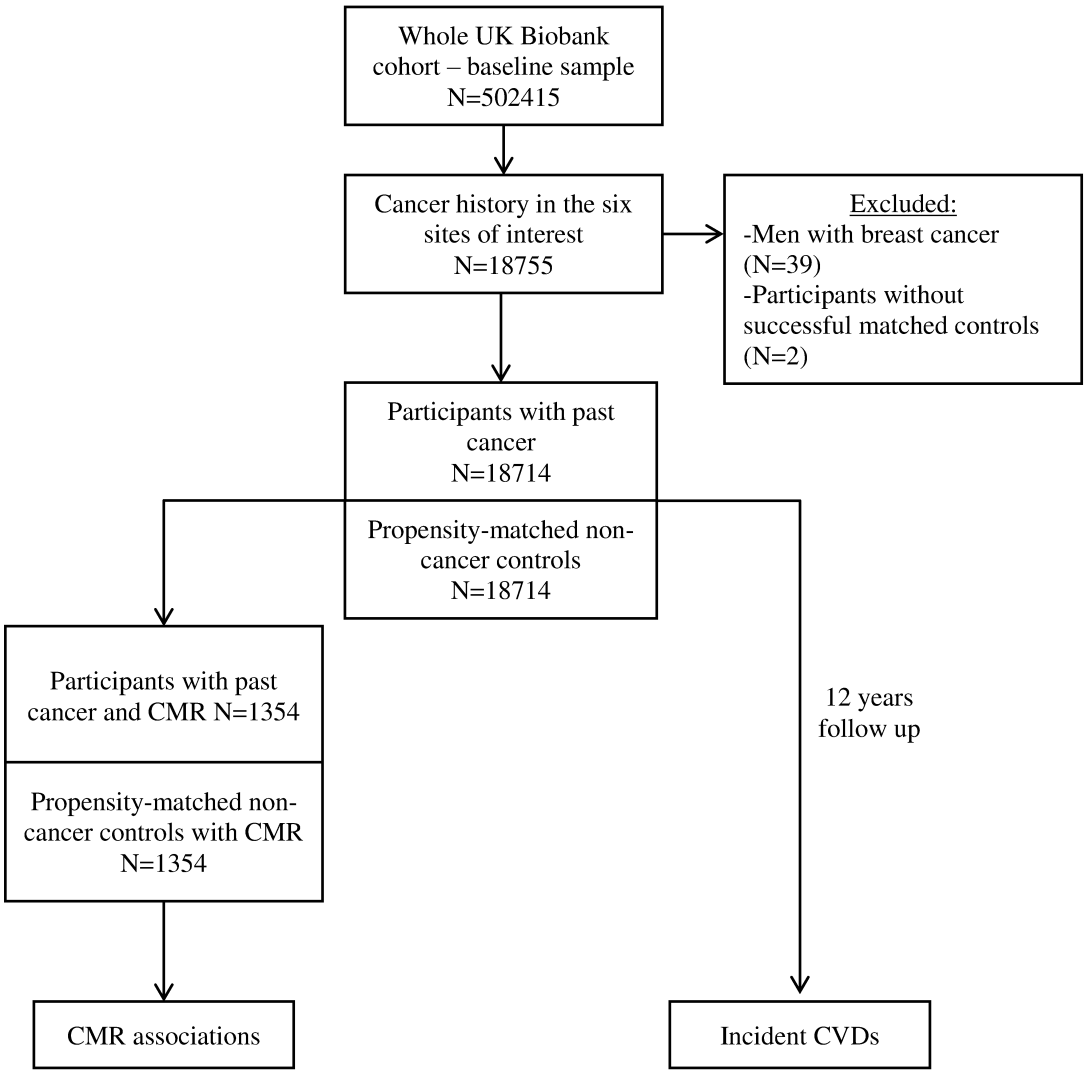
Supplementary Figure 3. Balance plots for propensity score matching in the imaging set



Supplementary Figure 3 footnote. Vertical dashed lines show threshold of 0.1 standardised mean difference. Dotted lines show caliper threshold of 0.2 standard deviations. We excluded 5 men with breast cancer. In the lung cancer category, age, sex, smoking, education, SBP, DBP, TG, IPAQ, heart rate and hba1c all have SMD >0.2. Townsend, BMI, HDL, LDL, hypertension and high cholesterol>0.1. For prostate cancer, 1 pair outside caliper was discarded. For colorectal cancer, 1 pair outside caliper discarded and age, ethnicity, Townsend, Education, SBP, DBP, hba1c,IPAQ, smoking

all had SMD >0.1. For uterine cancer, 1 pair was unmatched and Townsend score SMD>0.2, whilst age, qualifications,DBP,LDL,IPAQ, smoking, diabetes, hypertension, high cholesterol all had SMD >0.1. For haematological cancer, Education had SMD>0.1. In conclusion, covariate balance is good for breast and prostate cancer. Overall propensity is balanced for the outcomes, but some individual covariates lack balance (SMD>0.1) and thus we used a doubly robust approach by including these as covariates in the final models as per Nguyen et al. (Nguyen TL, Collins GS, Spence J, Daurès JP, Devereaux PJ, Landais P, Le Manach Y. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol. 2017 Apr 28;17(1):78. doi: 10.1186/s12874-017-0338-0.). BMI: body mass index; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin, HDL: high density lipoprotein, IPAQ: international physical activity questionnaire; LDL: low density lipoprotein; METS: metabolic equivalent; SBP: systolic blood pressure.

Supplementary Figure 4. Flow of participants included in study



Supplementary Figure 4 footnote. CVD: cardiovascular disease.

Supplementary Table 1. ICD-9 and ICD-10 codes used for ascertainment of cancer status

Cancer site	ICD9/10 code	Description
Breast	1740	Malignant neoplasm of female breast - nipple and areola
	1743	Malignant neoplasm of female breast - lower-inner quadrant
	1744	Malignant neoplasm of female breast - upper-outer quadrant
	1745	Malignant neoplasm of female breast - lower-outer quadrant
	1748	Malignant neoplasm of female breast - other site
	1749	Malignant neoplasm of female breast - unspecified site
	1740	Malignant neoplasm of female breast - nipple and areola
	1743	Malignant neoplasm of female breast - lower-inner quadrant
	C50.0	Nipple and areola
	C50.1	Central portion of breast
	C50.2	Upper-inner quadrant of breast
	C50.3	Lower-inner quadrant of breast
	C50.4	Upper-outer quadrant of breast
	C50.5	Lower-outer quadrant of breast
	C50.6	Axillary tail of breast
	C50.8	Overlapping lesion of breast
	C50.9	Breast, unspecified
Lung	1623	Malignant neoplasm of upper lobe, bronchus or lung
	1629	Malignant neoplasm of bronchus and lung, unspecified
	C34.0	Main bronchus
	C34.1	Upper lobe, bronchus, or lung
	C34.2	Middle lobe, bronchus, or lung
	C34.3	Lower lobe, bronchus, or lung
	C34.8	Overlapping lesion of bronchus and lung
	C34.9	Bronchus or lung, unspecified
Prostate	1859	Malignant neoplasm of prostate
	C61	Malignant neoplasm of prostate
Colorectal	1530	Malignant neoplasm of colon, hepatic flexure
	1532	Malignant neoplasm of descending colon
	1533	Malignant neoplasm of sigmoid colon
	1534	Malignant neoplasm of caecum
	1536	Malignant neoplasm of ascending colon
	1537	Malignant neoplasm of colon, splenic flexure
	1539	Malignant neoplasm of colon, unspecified
	C18.0	Caecum
	C18.1	Appendix
	C18.2	Ascending colon
	C18.3	Hepatic flexure
	C18.4	Transverse colon
	C18.5	Splenic flexure
	C18.6	Descending colon
	C18.7	Sigmoid colon
	C18.8	Overlapping lesion of colon
	C18.9	Colon, unspecified
	C19	Malignant neoplasm of rectosigmoid junction
	C20	Malignant neoplasm of rectum
Uterus	1820	Malignant neoplasm of corpus uteri, except isthmus
	C54.0	Isthmus uteri
	C54.1	Endometrium
	C54.2	Myometrium
	C54.3	Fundus uteri
	C54.8	Overlapping lesion of corpus uteri
	C54.9	Corpus uteri, unspecified
	C55	Malignant neoplasm of uterus, part unspecified
Haematological	2001	Lymphosarcoma
	2015	Hodgkin's disease, nodular sclerosis
	2016	Hodgkin's disease, mixed cellularity

Cancer site	ICD9/10 code	Description
	2017	Hodgkin's disease, lymphocytic depletion
	2019	Hodgkin's disease, unspecified
	2020	Nodular lymphoma
	2024	Leukaemic reticuloendotheliosis
	2028	Other lymphomas
	2029	Other malig. neoplasm of lymphoid and histiocytic tissue
	2040	Acute lymphoid leukaemia
	2050	Acute myeloid leukaemia
	2051	Chronic myeloid leukaemia
	2059	Unspecified myeloid leukaemia
	C81.0	Lymphocytic predominance
	C81.1	Nodular sclerosis
	C81.2	Mixed cellularity
	C81.3	Lymphocytic depletion
	C81.4	Lymphocyte-rich classical Hodgkin lymphoma
	C81.7	Other Hodgkin's disease
	C81.9	Hodgkin's disease, unspecified
	C82.0	Small cleaved cell, follicular
	C82.1	Mixed small cleaved and large cell, follicular
	C82.2	Large cell, follicular
	C82.3	Follicular lymphoma grade IIIa
	C82.4	Follicular lymphoma grade IIIb
	C82.5	Diffuse follicle centre lymphoma
	C82.6	Cutaneous follicle centre lymphoma
	C82.7	Other types of follicular non-Hodgkin's lymphoma
	C82.9	Follicular non-Hodgkin's lymphoma, unspecified
	C83.0	Small cell (diffuse)
	C83.1	Small cleaved cell (diffuse)
	C83.2	Mixed small and large cell (diffuse)
	C83.3	Large cell (diffuse)
	C83.4	Immunoblastic (diffuse)
	C83.5	Lymphoblastic (diffuse)
	C83.6	Undifferentiated (diffuse)
	C83.7	Burkitt's tumour
	C83.8	Other types of diffuse non-Hodgkin's lymphoma
	C83.9	Diffuse non-Hodgkin's lymphoma, unspecified
	C84.0	Mycosis fungoides
	C84.1	Sezary's diease
	C84.3	Lymphoepithelioid lymphoma
	C84.4	Peripheral T-cell lymphoma
	C84.5	Other and unspecified T-cell lymphomas
	C84.6	Anaplastic large cell lymphoma, ALK-positive
	C84.7	Anaplastic large cell lymphoma, ALK-negative
	C84.8	Cutaneous T-cell lymphoma, unspecified
	C84.9	Mature T/NK-cell lymphoma, unspecified
	C85.0	Lymphosarcoma
	C85.1	B-cell lymphoma, unspecified
	C85.2	Mediastinal (thymic) large B-cell lymphoma
	C85.7	Other specified types of non-Hodgkin's lymphoma
	C85.9	Non-Hodgkin's lymphoma, unspecified type
	C86.0	Extranodal NK/T-cell lymphoma, nasal type
	C86.2	Enteropathy-type (intestinal) T-cell lymphoma
	C86.3	Subcutaneous panniculitis-like T-cell lymphoma
	C86.4	Blastic NK-cell lymphoma
	C86.5	Angioimmunoblastic T-cell lymphoma
	C86.6	Primary cutaneous CD30-positive T-cell proliferations
	C88.0	Waldenstrom's macroglobulinaemia
	C88.2	Gamma heavy chain disease
	C88.3	Immunoproliferative small intestinal disease

Cancer site	ICD9/10 code	Description
	C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
	C88.7	Other malignant immunoproliferative diseases
	C88.9	Malignant immunoproliferative disease, unspecified
	C90.0	Multiple myeloma
	C90.1	Plasma cell leukaemia
	C90.2	Plasmacytoma, extramedullary
	C90.3	Solitary plasmacytoma
	C91.0	Acute lymphoblastic leukaemia
	C91.1	Chronic lymphocytic leukaemia
	C91.2	Subacute lymphocytic leukaemia
	C91.3	Prolymphocytic leukaemia
	C91.4	Hairy-cell leukaemia
	C91.5	Adult T-cell leukaemia
	C91.6	Prolymphocytic leukaemia of T-cell type
	C91.7	Other lymphoid leukaemia
	C91.8	Mature B-cell leukaemia Burkitt-type
	C92.0	Acute myeloid leukaemia
	C92.1	Chronic myeloid leukaemia
	C92.2	Subacute myeloid leukaemia
	C92.3	Myeloid sarcoma
	C92.4	Acute promyelocytic leukaemia
	C92.5	Acute myelomonocytic leukaemia
	C92.6	Acute myeloid leukaemia with 11q23-abnormality
	C92.7	Other myeloid leukaemia
	C92.8	Acute myeloid leukaemia with multilineage dysplasia
	C93.0	Acute monocytic leukaemia
	C93.1	Chronic monocytic leukaemia
	C93.3	Juvenile myelomonocytic leukaemia
	C93.9	Monocytic leukaemia, unspecified
	C94.0	Acute erythraemia and erythroleukaemia
	C94.2	Acute megakaryoblastic leukaemia
	C94.4	Acute panmyelosis
	C94.5	Acute myelofibrosis
	C94.6	Myelodysplastic and myeloproliferative disease, not elsewhere classified
	C94.7	Other specified leukaemias
	C95.0	Acute leukaemia of unspecified cell type
	C95.1	Chronic leukaemia of unspecified cell type
	C95.9	Leukaemia, unspecified
	C96.1	Malignant histiocytosis
	C96.2	Malignant mast cell tumour
	C96.3	True histiocytic lymphoma
	C96.4	Sarcoma of dendritic cells (accessory cells)
	C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis
	C96.6	Unifocal Langerhans-cell histiocytosis
	C96.7	Other specified malignant neoplasms of lymphoid, haematopoietic and related tissue
	C96.8	Histiocytic sarcoma
	C96.9	Malignant neoplasms of lymphoid, haematopoietic and related tissue, unspecified

Supplementary Table 1 footnote. ICD: international classification of disease

Supplementary Table 2. Ascertainment of CVD outcomes, ICD and UK Biobank field codes

Source	ICD code/UKB filed	Description
Ischaemic heart disease (IHD)		
ICD9	4139	Angina pectoris
	4140	Coronary atherosclerosis
	4141	Aneurysm of heart
	4148	Other specified forms of chronic ischaemic heart disease
	4149	Chronic ischaemic heart disease, unspecified
	4119	Other acute and subacute forms of ischaemic heart disease
Self-report	20002	Angina
ICD10	I20	Angina pectoris
	I24	Other acute ischaemic heart diseases
	I25	Chronic ischaemic heart disease
First occurrences	131296	Angina pectoris
	131304	Other acute ischaemic heart diseases
	131306	Chronic ischaemic heart disease
Diagnosed by doctor	3627	Age angina diagnosed
	6150: 2	Angina
Ischaemic heart disease (Myocardial infarction)		
ICD9	4109	Acute myocardial infarction
	4129	Old myocardial infarction
Self-report	20002	Heart attack/myocardial infarction
ICD9	410	Acute myocardial infarction
	411	Other acute and subacute forms of ischaemic heart disease
	412	Old myocardial infarction
ICD10	I21	Acute myocardial infarction
	I22	Subsequent myocardial infarction
	I23	Certain current complications following acute myocardial infarction
First occurrences	131298	Acute myocardial infarction
	131300	Subsequent myocardial infarction
	131302	Certain current complications following acute myocardial infarction
Diagnosed by doctor	3894	Age heart attack diagnosed
	6150: 1	Heart attack
Algorithm	42000	Date of myocardial infarction
Non-ischaemic cardiomyopathies		
ICD9	4254	Other primary cardiomyopathies
Self-report	20002	Cardiomyopathy
	20002	Hypertrophic cardiomyopathy (HCM / HOCM)
ICD10	I42	Cardiomyopathy
	I43	Cardiomyopathy in diseases classified elsewhere
	I11	Hypertensive heart disease
	I13	Hypertensive heart and renal disease
First occurrences	131338	Cardiomyopathy
	131340	Cardiomyopathy in diseases classified elsewhere
	131288	Hypertensive heart disease
	131292	Hypertensive heart and renal disease
Heart failure (unspecified aetiology)		
ICD9	4280	Congestive heart failure
	4281	Left heart failure
Self-report	20002	Heart failure/pulmonary oedema
ICD10	I50.0	Congestive heart failure
	I50.1	Left ventricular failure
	I50.9	Heart failure, unspecified
First occurrences	131354	Heart failure
Cardiac arrhythmia (Atrial fibrillation)		
Self-report	20002	Atrial fibrillation
ICD9	4273	Atrial fibrillation and flutter
ICD10	I48.0	Paroxysmal atrial fibrillation
	I48.1	Persistent atrial fibrillation

Source	ICD code/UKB filed	Description
	I48.2	Chronic atrial fibrillation
	I48.9	Atrial fibrillation and atrial flutter, unspecified
Stroke		
Self-report	20002	Stroke
	20002	Ischaemic stroke
	20002	Brain haemorrhage
ICD9	431	Intracerebral haemorrhage
	4349	Occlusion of cerebral arteries, unspecified
ICD10	I64	Stroke, not specified as haemorrhage or infarction
	I63	Cerebral infarction
	I61	Intracerebral haemorrhage
	I62	Other nontraumatic intracranial haemorrhage
First occurrences	131368	Date I64 first reported (stroke, not specified as haemorrhage or infarction)
	131366	Cerebral infarction
	131362	Intracerebral haemorrhage
	131364	other nontraumatic intracranial haemorrhage
Diagnosed by doctor	4056	Age stroke diagnosed
	6150: 3	Stroke
Algorithm	42006	Date of stroke
	42008	Date of ischaemic stroke
	42010	Date of intracerebral haemorrhage
Pericarditis		
ICD10	I30.0	Acute nonspecific idiopathic pericarditis
	I30.1	Infective pericarditis
	I30.8	Other forms of acute pericarditis
	I30.9	Acute pericarditis, unspecified
	I31.0	Chronic adhesive pericarditis
	I31.1	Chronic constrictive pericarditis
	I31.2	Haemopericardium, not elsewhere classified
	I31.3	Pericardial effusion (noninflammatory)
	I31.8	Other specified diseases of pericardium
	I31.9	Disease of pericardium, unspecified
	I32.0	Pericarditis in bacterial diseases classified elsewhere
	I32.1	Pericarditis in other infectious and parasitic diseases classified elsewhere1
	I32.8	Pericarditis in other diseases classified elsewhere
Venous thromboembolism (DVT/PE)		
ICD9	4151	Pulmonary embolism
	4538	Embolism and thrombosis of other specified veins
ICD10	I26.0	Pulmonary embolism with mention of acute cor pulmonale
	I26.9	Pulmonary embolism without mention of acute cor pulmonale
	I801	Phlebitis and thrombophlebitis of femoral vein
	I802	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
	I803	Phlebitis and thrombophlebitis of lower extremities, unspecified
	I82.8	Embolism and thrombosis of other specified veins
	I82.9	Embolism and thrombosis of unspecified vein
Self report	20002	pulmonary embolism +/- DVT
	20002	deep venous thrombosis (DVT)
Hypertensive disease (for death certificate, main/underlying cause of death)		
ICD10	I10	Essential (primary) hypertension
	I11.0	Hypertensive heart disease with (congestive) heart failure
	I11.9	Hypertensive heart disease without (congestive) heart failure
	I12.0	Hypertensive renal disease with renal failure
	I12.9	Hypertensive renal disease without renal failure
	I13.0	Hypertensive heart and renal disease with (congestive) heart failure
	I13.1	Hypertensive heart and renal disease with renal failure
	I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
	I13.9	Hypertensive heart and renal disease, unspecified

Source	ICD code/UKB filed	Description
	I15.0	Renovascular hypertension
	I15.1	Hypertension secondary to other renal disorders
	I15.2	Hypertension secondary to endocrine disorders
	I15.8	Other secondary hypertension
ICD9	4010	Essential hypertension, specified as malignant
	4011	Essential hypertension, specified as benign
	4019	Essential hypertension, not specified as malignant or benign
	4039	Hypertensive renal disease, not specified as malignant or benign

Supplementary Table 2 footnote. CVD: cardiovascular disease; DVT: deep vein thrombosis; ICD: international classification of disease; PE: pulmonary embolism.

Supplementary Table 3. Covariates included in the propensity score models

	Notes and UK Biobank data field	Baseline set	Imaging set
Socio-demographics			
Age (years)	21003	Instance 0	Instance 2
Sex	31		
Ethnicity	21000		
Townsend score	189		
Education	6138	Instance 0	Instance 2
Physical measurements			
Systolic blood pressure (mmHg)	Average of automated readings if available (4080), otherwise refer to manual reading (93)	Instance 0	Instance 2
Diastolic blood pressure (mmHg)	Average of automated readings if available (4079), otherwise refer to manual reading (94)	Instance 0	Instance 2
Heart rate (bpm)	Average of automated readings (102) if available, otherwise refer to manual reading (95) – reject heart rates below 40bpm	Instance 0	Instance 2
Body mass index (kg/m^2)	Calculate from height (50) and weight (21002 - or 3160 if not available).	Instance 0	Instance 2
Laboratory tests			
HbA1c (mmol/mol)	30750	Instance 0	Instance 0
Random glucose (mmol/L)	30740	Instance 0	Instance 0
Total cholesterol (mmol/L)	30690	Instance 0	Instance 0
HDL (mmol/L)	30760	Instance 0	Instance 0
LDL direct (mmol/L)	30780	Instance 0	Instance 0
Triglyceride level (mmol/L)	30870	Instance 0	Instance 0
Vascular risk factors			
Physical activity (METS/week)	As per IPAQ		
Smoking status	20116	Instance 0	Instance 2
Diabetes	As per Table 4	ICD codes until instance 0	ICD codes until instance 2
Hypertension	As per Table 4	ICD codes until instance 0	ICD codes until instance 2
High cholesterol	As per Table 4	ICD codes until instance 0	ICD codes until instance 2

Supplementary Table 3 footnote. Instance 0 indicates baseline visit, instance 2 indicates imaging visit. HbA1c: glycated haemoglobin, HDL: high density lipoprotein, IPAQ: international physical activity questionnaire; LDL: low density lipoprotein; METS: metabolic equivalent.

Supplementary Table 4. ICD and UK Biobank field codes used to define clinical diagnosis of prevalent diabetes, hypertension, and high cholesterol

Diabetes		
Self-report	20002	Diabetes
	20002	Type 1 diabetes
	20002	Type 2 diabetes
Medications	6177, 6153: 3	Insulin
ICD9	250	Diabetes mellitus
ICD10	E10	Type 1 diabetes mellitus
	E11	Type 2 diabetes mellitus
	E13	Other specified diabetes mellitus
	E14	Unspecified diabetes mellitus
	G590	Diabetic mononeuropathy
	G632	Diabetic polyneuropathy
	H280	Diabetic cataract
	H360	Diabetic retinopathy
	M142	Diabetic arthropathy
	N083	Glomerular disorders in diabetes mellitus
	O240	Diabetes mellitus in pregnancy: Pre-existing type 1 diabetes mellitus
	O241	Diabetes mellitus in pregnancy: Pre-existing type 2 diabetes mellitus
	O243	Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, unspecified
	O244	Diabetes mellitus arising in pregnancy
	O249	Diabetes mellitus in pregnancy, unspecified
	Y423	Insulin and oral hypoglycaemic [antidiabetic] drugs
First occurrences	130706	Date E10 first reported (insulin-dependent diabetes mellitus)
	130708	Date E11 first reported (non-insulin-dependent diabetes mellitus)
	130712	Date E13 first reported (other specified diabetes mellitus)
	130714	Date E14 first reported (unspecified diabetes mellitus)
Diagnosed by doctor	2443	Diabetes diagnosed by doctor
	2976	Age diabetes diagnosed by doctor
High cholesterol		
Self-report	20002	High cholesterol
Medications	6177, 6153: 1	Cholesterol lowering medication
ICD9	272	Disorders of lipoid metabolism
ICD10	E780	Pure hypercholesterolaemia
	E782	Mixed hyperlipidaemia
	E783	Hyperchylomicronaemia
	E784	Other hyperlipidaemia
	E785	Hyperlipidaemia, unspecified
First occurrences	130814	Date E78 first reported (disorders of lipoprotein metabolism and other lipidaemias)
Hypertension		
Self-report	20002	Essential hypertension
	20002	Hypertension
Medications	6177, 6153: 2	Blood pressure medication
First occurrences	131286	Date I10 first reported (essential (primary) hypertension)
Diagnosed by doctor	2966	Age high blood pressure diagnosed
	6150: 4	High blood pressure
ICD10	I10	Essential (primary) hypertension
	I11.0	Hypertensive heart disease with (congestive) heart failure
	I11.9	Hypertensive heart disease without (congestive) heart failure
	I12.0	Hypertensive renal disease with renal failure
	I12.9	Hypertensive renal disease without renal failure
	I13.0	Hypertensive heart and renal disease with (congestive) heart

		failure
	I13.1	Hypertensive heart and renal disease with renal failure
	I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
	I13.9	Hypertensive heart and renal disease, unspecified
	I15.0	Renovascular hypertension
	I15.1	Hypertension secondary to other renal disorders
	I15.2	Hypertension secondary to endocrine disorders
	I15.8	Other secondary hypertension
ICD9	4010	Essential hypertension, specified as malignant
	4011	Essential hypertension, specified as benign
	4019	Essential hypertension, not specified as malignant or benign
	4039	Hypertensive renal disease, not specified as malignant or benign

Supplementary Table 4. ICD: international classification of disease

Supplementary Table 5. Number of incident events in the composite haematological cancer category and in subtypes of myeloma, lymphoma, and leukaemia.

	All haem	Myeloma	Lymphoma	Leukaemia
Incident CVDs (N, %)	2032	198	1495	525
IHD	286	27	193	65
NICM	57	2	41	14
HF	227	21	157	47
AF/flutter	259	25	167	66
Stroke	102	11	59	30
Pericarditis	47	3	32	12
VTE (DVT/PE)	102	11	27	63
Mortality outcomes (N, %)	496	109	351	140
Any CVD	47	8	26	12
IHD	26	4	15	7
HF/NICM	5	1	4	0
Stroke	10	1	6	2
Hypertensive diseases	3	1	1	1

Supplementary Table 5 footnote. AF: atrial fibrillation; CVD: cardiovascular disease; IHD: ischaemic heart disease; NICM: non-ischaemic cardiomyopathies; VTE: venous thromboembolism

Supplementary Table 6. Associations with events for those with any haematological cancer and in subtypes of myeloma, lymphoma, and leukaemia- compared to controls

	All haem	Myeloma	Lymphoma	Leukaemia
Incident disease				
IHD	1.96 (1.58-2.43)	1.61 (0.87-2.97)	1.95 (1.52-2.51)	1.97 (1.31-3.00)
	6.0e-10	0.132	1.2e-7	0.001
NICM	2.53 (1.53-4.16)	2.01 (0.18-22.31)	2.29 (1.31-4.01)	3.56 (1.15-10.91)
	0.0003	0.570	0.004	0.03
Heart failure	3.48 (2.61-4.62)	4.44 (1.65-11.97)	3.29 (2.39-4.53)	4.44 (2.29-8.58)
	1.0e-17	0.003	3.1e-13	9.0e-6
AF/flutter	2.00 (1.60-2.50)	1.73 (0.90-3.35)	1.67 (1.30-2.16)	4.10 (2.46-6.82)
	9.4e-10	0.102	0.0001	6.0e-8
Stroke	2.45 (1.68-3.58)	1.39 (0.55-3.53)	1.99 (1.27-3.10)	3.90 (1.80-8.33)
	3.7e-6	0.488	0.002	0.0005
Pericarditis	2.95 (1.64-5.32)	3.02 (0.31-29.24)	2.66 (1.38-5.21)	6.11 (1.36-27.39)
	0.0003	0.341	0.003	0.02
VTE	2.69 (1.80-4.00)	2.83 (0.89-9.07)	2.92 (1.77-4.76)	2.23 (1.13-4.35)
	1.2e-6	0.079	0.00003	0.02
Mortality outcomes				
All-cause	3.78 (3.17-4.52)	7.74 (4.82-12.44)	3.78 (3.06-4.66)	3.67 (2.64-5.05)
	7.5e-49	2.9e-17	8.0e-35	7.8e-15
Any CVD	1.26 (0.79-2.01)	8.10 (1.00-65.85)	1.00 (0.58-1.73)	2.46 (0.91-6.62)
	0.329	0.05	0.99	0.07
IHD	1.58 (0.80-3.09)	4.01 (0.44-36.35)	1.25 (0.58-2.67)	3.53 (0.73-16.95)
	0.186	0.217	0.57	0.12
Heart failure or NICM	0.81 (0.22-3.01)	-	0.80 (0.21-3.00)	-
	0.749	-	0.74	-
Stroke	1.01 (0.40-2.54)	-	1.00 (0.32-3.11)	-
	0.988	-	0.999	-
Hypertensive diseases	-	-	-	-
	-	–	-	-

Supplementary Table 6 footnote. AF: atrial fibrillation; CVD: cardiovascular disease; IHD: ischaemic heart disease; NICM: non-ischaemic cardiomyopathies; VTE: venous thromboembolism

Supplementary Table 7. Incident events observed by cancer site (including all prevalent cancers, without covariate imputation – only those with complete data)

Complete cases	Breast	Lung	Prostate	Colorectal	Uterus	Haem	Total
Incident disease							
IHD	307	21	241	142	32	188	931
NIC	42	1	19	22	2	28	114
HF	156	14	121	71	17	138	517
AF/flutter	272	18	245	141	36	157	869
Stroke	101	8	90	44	11	62	316
Pericarditis	45	7	16	16	3	28	115
VTE	148	7	89	47	14	62	367
Mortality outcomes							
All-cause	693	82	419	290	46	339	1869
CVD (any)	10	5	31	20	3	17	86
IHD	6	0	5	4	3	2	20
HF/NIC	11	1	12	2	0	9	35
Stroke	2	0	3	2	1	1	9
Hypertensive diseases	33	7	53	27	6	32	158

Supplementary Table 7 footnote. AF: atrial fibrillation; CVD: cardiovascular disease; DVT: deep vein thrombosis; HF: heart failure; IHD: ischaemic heart disease; NICM: non-ischaemic cardiomyopathies; PE: pulmonary embolism.

Supplementary Table 8. Associations of cancer with incident events amongst all prevalent cancers with complete data (no imputation)

	Breast	Lung	Prostate	Colorectal	Uterus	Haem
Incident disease						
IHD	1.13 (0.96, 1.34)	1.42 (0.70, 2.89)	1.01 (0.84, 1.22)	1.08 (0.85, 1.38)	0.90 (0.54, 1.51)	1.88 (1.48, 2.41)
	0.141	0.326	0.926	0.51	0.705	3.22×10^{-7}
NICM	1.75 (1.06, 2.92)	–	0.90 (0.49, 1.68)	2.20 (1.07, 4.57)	–	3.53 (1.60, 7.77)
	0.028	–	0.754	0.033	–	0.002
HF	1.31 (1.03, 1.67)	2.05 (0.76, 5.58)	0.94 (0.74, 1.21)	1.21 (0.85, 1.70)	1.62 (0.73, 3.60)	2.18 (1.62, 2.94)
	0.028	0.159	0.653	0.285	0.244	2.75×10^{-7}
AF/flutter	1.11 (0.93, 1.31)	1.32 (0.62, 2.86)	0.91 (0.76, 1.09)	1.34 (1.04, 1.70)	1.26 (0.78, 2.05)	1.79 (1.38, 2.29)
	0.986	0.466	0.343	0.023	0.346	9.00×10^{-6}
Stroke	1.00 (0.76, 1.31)	1.15 (0.44, 3.00)	0.83 (0.63, 1.11)	0.79 (0.52, 1.19)	0.92 (0.40, 2.12)	2.89 (1.77, 4.76)
	0.986	0.783	0.206	0.248	0.844	2.67×10^{-5}
Pericarditis	1.84 (1.12, 3.03)	2.36 (0.61, 9.30)	0.80 (0.41, 1.55)	2.69 (1.04, 6.89)	–	3.13 (1.48, 6.69)
	0.017	0.215	0.508	0.04	–	0.003
VTE (DVT/PE)	1.62 (1.23, 2.1)	1.51 (0.41, 5.47)	1.20 (0.89, 1.62)	1.02 (0.67, 1.55)	1.07 (0.53, 2.18)	2.34 (1.49, 3.71)
	0.0005	0.537	0.243	0.927	0.841	0.0002
Mortality outcomes						
All-cause	2.35 (2.01, 2.90)	6.40 (0.79, 10.80)	1.65 (1.41, 1.92)	2.31 (1.88, 2.83)	2.18 (1.31, 3.62)	3.77 (3.01, 4.70)
	5.80×10^{-36}	3.65×10^{-12}	1.66×10^{-10}	8.28×10^{-16}	0.003	1.43×10^{-31}
Any CVD	0.90 (0.56, 1.43)	1.75 (0.50, 6.11)	0.91 (0.63, 1.34)	1.28 (0.73, 2.25)	2.01 (0.50, 8.08)	1.60 (0.92, 2.80)
	0.638	0.378	0.636	0.392	0.321	0.092
IHD	0.63 (0.28, 1.38)	2.51 (0.48, 13.2)	0.72 (0.45, 1.15)	1.67 (0.81, 3.39)	–	1.00 (0.51, 1.97)
	0.245	0.278	0.166	0.168	–	0.997
HF/NIC	2.01 (0.50, 8.00)	–	1.67 (0.40, 6.96)	–	–	–
	0.323	–	0.484	–	–	–
Stroke	0.84 (0.38, 1.90)	–	1.92 (0.662, 4.35)	–	–	9.03 (1.14, 71.52)
	0.686	–	0.258	–	–	0.037
Hypertensive diseases	–	–	–	–	–	–
	–	–	–	–	–	–

Supplementary Table 8 footnote. Results are sub-distribution hazard ratio (95% confidence interval) and p-value associated with cancer exposure (vs no cancer). Comparators are matched on age, sex, ethnicity, deprivation, education, blood pressure, heart rate, body mass index, glycated haemoglobin, random glucose, total cholesterol, high density lipoprotein, low density lipoprotein, triglyceride level, physical activity, smoking, diabetes, hypertension, and high cholesterol. AF: atrial fibrillation; CVD: cardiovascular disease; IHD: ischaemic heart disease; NICM: non-ischaemic cardiomyopathies; VTE: venous thromboembolism. AF: atrial fibrillation; CVD: cardiovascular disease; DVT: deep vein thrombosis; HF: heart failure; IHD: ischaemic heart disease; NIC: non-ischaemic cardiomyopathies; PE: pulmonary embolism.

Supplementary Table 9. Associations of cancer with incident cardiovascular events compared to matched controls (cause specific hazard ratios)

	Breast	Lung	Prostate	Colorectal	Uterus	Haematological
Incident disease						
IHD	1.12 (0.99, 1.26)	1.43 (0.95, 2.18)	0.97 (0.84, 1.13)	**1.23 (1.02, 1.49)**	1.06 (0.77, 1.48)	**2.14 (1.75, 2.61)**
	0.085	0.089	0.712	**0.032**	0.697	1.40×10^{-13}
NICM	**1.92 (1.36, 2.72)**	–	1.22 (0.76, 1.97)	1.36 (0.79, 2.34)	3.63 (0.76, 17.64)	**2.89 (1.77, 4.71)**
	0.0002	–	0.399	0.257	0.107	0.00002
Heart failure	**1.42 (1.21, 1.68)**	**2.59 (1.45, 4.66)**	1.11 (0.90, 1.34)	0.84 (0.66, 1.08)	1.42 (0.90, 2.27)	**4.01 (3.03, 5.26)**
	0.00002	0.001	0.343	0.187	0.138	3.10×10^{-23}
AF/flutter	**1.17 (1.04, 1.32)**	**1.88 (1.14, 3.13)**	1.06 (0.91, 1.22)	**1.36 (1.13, 1.65)**	1.03 (0.73, 1.46)	**2.20 (1.79, 2.72)**
	0.011	**0.014**	0.451	0.002	0.846	1.4×10^{-13}
Stroke	1.20 (0.97, 1.46)	1.72 (0.83, 3.60)	1.25 (0.98, 1.57)	1.21 (0.89, 1.67)	1.20 (0.71, 2.01)	**2.53 (1.80, 3.60)**
	0.087	0.150	0.078	0.219	0.498	1.6×10^{-7}
Pericarditis	**2.14 (1.45, 3.19)**	**16.78 (2.16, 131.63)**	1.23 (0.71, 2.14)	1.48 (0.74, 2.94)	3.63 (0.75, 17.46)	**3.35 (1.90, 5.99)**
	0.0002	0.007	0.454	0.270	0.109	0.00003
VTE	**1.52 (1.27, 1.82)**	1.54 (0.73, 3.25)	**1.79 (1.36, 2.32)**	1.30 (0.94, 1.80)	1.75 (0.94, 3.29)	**3.03 (2.08, 4.39)**
	4.60×10^{-6}	0.263	0.00003	0.114	0.076	7.9×10^{-9}
Mortality outcomes						
All-cause	**2.48 (2.25, 2.72)**	**5.00 (3.63, 6.89)**	**1.65 (1.46, 1.86)**	**2.08 (1.79, 2.41)**	**2.41 (1.73, 3.32)**	**4.14 (3.49, 4.90)**
	3.65×10^{-80}	7.25×10^{-21}	2.40×10^{-16}	1.30×10^{-21}	3.06×10^{-7}	3.10×10^{-59}
Any CVD	1.04 (0.76, 1.43)	**3.49 (1.43, 8.50)**	0.93 (0.69, 1.26)	1.31 (0.88, 1.95)	1.26 (0.59, 2.69)	**1.70 (1.08, 2.66)**
	0.809	**0.006**	0.646	0.181	0.553	**0.022**
IHD	0.68 (0.40, 1.13)	**2.94 (1.16, 7.39)**	0.93 (0.64, 1.35)	1.16 (0.71, 1.88)	–	**1.99 (1.04, 3.78)**
	0.131	**0.02**	0.693	0.551	–	0.036
Heart failure or NICM	**9.12 (2.10, 39.65)**	–	0.83 (0.31, 2.23)	5.42 (0.64, 45.50)	–	1.17 (0.34, 4.10)
	0.003	–	0.708	0.121	–	0.797
Stroke	0.93 (0.52, 1.68)	–	1.00 (0.51, 1.99)	1.35 (0.56, 3.25)	5.00 (0.58, 42.95)	1.28 (0.52, 3.22)
	0.816	–	0.995	0.498	0.142	0.587
Hypertensive diseases	**8.58 (1.07, 68.72)**	–	1.34 (0.36, 5.00)	–	**–**	–
	0.043	**–**	0.668	–	**–**	–

Supplementary Table 9 footnote. Results are cause specific hazard ratio (95% confidence interval) and p-value associated with cancer history (vs no cancer). Comparators are matched on age, sex, ethnicity, deprivation, education, blood pressure, heart rate, body mass index, glycated haemoglobin, random glucose, total cholesterol, high density lipoprotein, low density lipoprotein, triglyceride level, physical activity, smoking, diabetes, hypertension, and high cholesterol. AF: atrial fibrillation; CVD: cardiovascular disease; IHD: ischaemic heart disease; NICM: non-ischaemic cardiomyopathies; VTE: venous thromboembolism.

Supplementary Table 10. Incident events observed by cancer site (including cancers within preceding 5 years)

within 5 years	Breast	Lung	Prostate	Colorectal	Uterus	Haem	Total
Incident disease							
IHD	197	17	273	136	29	99	751
NIC	33	0	22	15	4	21	95
HF	120	15	133	55	15	85	423
AF/flutter	178	22	261	120	25	120	726
Stroke	69	14	105	36	11	37	272
Pericarditis	27	6	20	10	3	17	83
VTE (DVT/PE)	129	14	108	43	10	47	351
Mortality outcomes							
All-cause	594	124	502	321	56	309	1906
CVD (any)	30	9	58	25	7	20	149
IHD	15	7	38	19	2	14	95
HF/NIC	4	0	6	2	2	0	14
Stroke	7	1	10	3	2	6	29
Hypertensive diseases	2	0	4	2	2	0	10

Supplementary Table 10 footnote. AF: atrial fibrillation; CVD: cardiovascular disease; DVT: deep vein thrombosis; HF: heart failure; IHD: ischaemic heart disease; NIC: non-ischaemic cardiomyopathies; PE: pulmonary embolism.

Supplementary Table 11. Associations of cancer with incident events amongst all prevalent cancers for cases diagnoses in the preceding 5 years

	Breast	Lung	Prostate	Colorectal	Uterus	Haem
Incident disease						
IHD	1.15 (0.93, 1.40)	0.93 (0.45, 1.92)	0.94 (0.79, 1.13)	1.12 (0.86, 1.45)	0.76 (0.47, 1.21)	1.16 (0.85, 1.57)
	0.195	0.843	0.518	0.399	0.245	0.347
NICM	1.84 (1.03, 3.29)	–	0.70 (0.41, 1.22)	1.07 (0.52, 2.25)	4.01 (0.44, 36.23)	2.64 (1.16, 5.99)
	0.038	–	0.213	0.847	0.215	0.02
HF	1.52 (1.14, 2.01)	1.57 (0.66, 3.71)	0.94 (0.79, 1.19)	0.79 (0.55, 1.11)	0.75 (0.39, 1.43)	2.12 (1.48, 3.06)
	0.004	0.302	0.592	0.17	0.378	5.35×10^{-5}
AF/flutter	0.98 (0.79, 1.21)	1.65 (0.84, 3.25)	0.94 (0.79, 1.12)	1.02 (0.79, 1.32)	0.76 (0.44, 1.27)	1.68 (1.25, 2.27)
	0.859	0.153	0.485	0.864	0.29	0.001
Stroke	0.90 (0.65, 1.26)	1.57 (0.66, 3.71)	1.06 (0.80, 1.40)	1.06 (0.66, 1.72)	0.79 (0.35, 1.75)	1.92 (1.11, 3.35)
	0.567	0.307	0.67	0.79	0.56	0.021
Pericarditis	3.03 (1.42, 6.42)	6.05 (0.73, 50.91)	1.54 (1.13, 2.10)	0.59 (0.27, 1.30)	–	2.44 (1.00, 5.87)
	0.004	0.096	0.006	0.186	–	0.049
VTE (DVT/PE)	1.90 (1.40, 2.53)	2.89 (1.08, 7.69)	1.54 (1.13, 2.10)	1.19 (0.75, 1.86)	0.71 (0.34, 1.51)	2.14 (1.28, 3.53)
	2.14×10^{-5}	0.034	0.006	0.47	0.375	0.004
Mortality outcomes						
All-cause	3.40 (2.89, 4.01)	6.12 (4.1, 9.14)	1.69 (1.47, 1.95)	3.20 (2.58, 3.96)	1.55 (1.03, 2.34)	4.48 (3.50, 5.72)
	1.56×10^{-48}	6.69×10^{-19}	2.14×10^{-13}	1.13×10^{-26}	0.037	3.55×10^{-33}
Any CVD	0.97 (0.58, 1.60)	1.12 (0.42, 2.97)	1.12 (0.76, 1.63)	1.26 (0.70, 2.27)	1.19 (0.4, 3.53)	1.43 (0.73, 2.77)
	0.898	0.824	0.56	0.449	0.761	0.298
IHD	1.00 (0.49, 2.03)	1.39 (0.43, 4.48)	1.16 (0.73, 1.86)	1.27 (0.64, 2.51)	–	1.39 (0.62, 3.16)
	0.997	0.578	0.541	0.491	–	0.424
HF/NIC	–	–	2.01 (0.50, 8.00)	–	–	–
	–	–	0.326	–	–	–
Stroke	0.70 (0.27, 1.84)	–	0.83 (0.36, 1.92)	–	–	3.00 (0.61, 14.88)
	0.472	–	0.83	–	–	0.179
Hypertensive diseases	–	–	–	–	–	–
	–	–	–	–	–	–

Supplementary Table 11 footnote. Results are sub-distribution hazard ratio (95% confidence interval) and p-value associated with cancer exposure (vs propensity-matched non-cancer controls). AF: atrial fibrillation; CVD: cardiovascular disease; DVT: deep vein thrombosis; HF: heart failure; IHD: ischaemic heart disease; NIC: non-ischaemic cardiomyopathies; PE: pulmonary embolism.

Supplementary Table 12. Characteristics of the imaging subset

	Cases	Controls	Breast	Lung	Prostate	Colorectal	Uterus	Haem
N	1354	1354	586	13	473	47	76	159
Age	68 [62-72]	68 [62-72]	66 [59-70]	68 [64-69]	70 [66-73]	67 [62-71]	66 [59-70]	67 [62-72]
Men	603 (44.5)	609 (45.0)	0 (0)	4 (30.8)	473 (100)	29 (61.7)	0 (0)	61.0 (97)
Women	751 (55.5)	745 (55.0)	586 (100)	9 (69.2)	0 (0)	18 (38.3)	76 (100)	62 (39.0)
White ethnicity	1329 (98.2)	1333 (98.6)	576 (98.3)	13 (100)	466 (98.5)	45 (95.7)	74 (97.4)	155 (98.1)
BAME	24 (1.8)	19 (1.4)	10 (1.7)	0 (0)	7 (1.5)	2 (4.3)	2 (2.6)	3 (1.9)
Townsend score	-2.8 [-4.0, -0.9]	-2.8 [-4.0, -0.7]	-2.8 [-3.9, -0.9]	-3.3 [-4.3, -2.7]	-3.0 [-4.1, -1.5]	-2.5 [-4.0, -0.8]	-2.6 [-3.6, -0.9]	-2.5 [-3.8, 0.0]
Degree or professional qualification	882 (65.3)	879 (65.0)	377 (64.4)	4 (30.8)	316 (67.0)	36 (76.6)	49 (64.5)	100 (63.3)
SBP (mmHg)	138.9 ±17.9	139.2 ±18.8	135.3 ± 18.3	133.9 ± 13.1	142.7 ±16.1	142.2 ±18.8	137.8 ± 19.8	140.1 ±18.0
DBP (mmHg)	77.9 ±9.5	77.8 ± 9.8	77.1 ±9.4	79.9 ±7.5	78.4 ±9.3	80.2 ±9.1	78.6 ±9.5	78.2 ±10.4
HR (bpm)	70 [62.5-79.5]	71 [63-79.5]	72.5 [65-81.5]	73.5 [62-86]	67 [60-76]	69.8 [61-81]	70.5 [64.5-78]	69.5 [62-79]
BMI (kg/m^2)	26.0 [23.4 – 29.0]	25.9 [23.5-28.6]	25.2 [22.7-28.6]	26.7 [23.1-29.3]	26.5 [24.5-28.9]	27.1 [24.4- 31.8]	27.7 [24.2- 31.3]	25.5 [22.9- 28.6]
Physical activity (METS/week)	2026 [1006-3566]	1939 [938-3492]	2179 [1009-3546]	1701 [1026-3572]	1983 [1045-3594]	1194 [718-2549]	1662 [974-3512]	2039 [1055 – 4086]
Ever Smoking	508 (38.3)	532 (40.0)	210 (36.6)	7 (53.9)	195 (42.1)	22 (46.8)	19 (25.3)	55 (35.3)
HbA1c (mmol/mol)	35.1 [32.8- 37.4]	35.2 [32.5- 37.5]	35 [32.7- 37.1]	34.2 [33.1-37.7]	35.4 [33.1-37.5]	35 [32.4- 38.3]	36.0 [33.5- 38.7]	34.8 [32.5-37.2]
Random glucose (mmol/L)	4.9 [4.6- 5.3]	4.9 [4.6- 5.3]	4.9 [4.6- 5.3]	5.0 [4.1- 5.6]	4.9 [4.6- 5.3]	5.0 [4.7- 5.5]	4.9 [4.5- 5.2]	4.9 [4.5- 5.2]

	Cases	Controls	Breast	Lung	Prostate	Colorectal	Uterus	Haem
Total cholesterol (mmol/L)	5.7 ±1.2	5.7 ±1.1	5.9 ±1.2	6.1 ±1.1	5.4 ±1.1	5.5 ±1.4	5.8 ±1.1	5.4 ±1.1
HDL (mmol/L)	1.4 [1.2- 1.7]	1.4 [1.2- 1.7]	1.6 [1.3- 1.8]	1.5 [1.2- 1.6]	1.2 [1.1- 1.5]	1.3 [1.0- 1.5]	1.4 [1.3- 1.8]	1.3 [1.1- 1.6]
LDL direct (mmol/L)	3.5 [3.0- 4.1]	3.5 [2.9- 4.1]	3.6 [3.0- 4.2]	3.7 [3.2- 4.4]	3.4 [2.9- 4.0]	3.4 [2.8- 4.0]	3.4 [3.0- 4.1]	3.4 [2.9-4.0]
Triglyceride level (mmol/L)	1.5 [1.1- 2.1]	1.5 [1.0- 2.1]	1.4 [1.0- 1.9]	1.4 [1.4- 2.4]	1.7 [1.2- 2.4]	1.6 [1.3- 2.2]	1.5 [0.9- 1.9]	1.5 [1.0- 2.2]
Diabetes	109 (8.1)	121 (8.9)	34 (5.8)	1 (7.7)	47 (9.9)	8 (17.0)	11 (14.5)	8 (5.0)
Hypertension	505 (37.3)	485 (35.8)	160 (27.3)	4 (30.8)	230 (48.6)	24 (51.1)	26 (34.2)	61 (38.4)
High cholesterol	618 (45.6)	631 (46.6)	206 (35.2)	7 (53.9)	280 (59.2)	30 (63.8)	30 (39.5)	65 (40.9)
LVM (g)	-	-	70.9 ± 12.8	80.4 ± 17.8	99.7 ± 17.4	92.4 ± 21.3	75.3 ± 18.0	91.1 ± 25.7
LVEDV (ml)	-	-	128.6 ± 22.1	131.7 ± 34.1	163.2 ± 32.1	150.0 ± 33.5	133.4 ±27.5	155.4 ± 42.2
LVEF (%)	-	-	60.5 ± 6.2	62.2 ± 3.3	57.8 ± 6.6	59.3 ± 4.5	61.8 ± 5.1	57.3 ± 6.7
LVGFI (%)	-	-	0.50 ± 0.07	0.49 ± 0.05	0.45 ± 0.07	0.46 ± 0.06	0.50 ± 0.06	0.45 ± 0.07
LV GLS (%)	-	-	-19.1 ± 3.0	-19.5 ± 2.2	-17.7 ± 2.6	-17.7 ± 2.5	-19.4 ± 2.4	-17.4 ± 2.7
LAV max (ml)	-	-	66.9 ± 19.4	62.8 ± 26.0	77.3 ± 29.7	72.3 ± 22.5	71.4 ± 22.7	77.4 ± 29.6
LAEF (%)	-	-	61.6 ± 9.1	62.5 ±14.3	59.1 ± 10.6	61.2 ± 8.5	61.4 ± 7.5	58.3 ± 10.8

Supplementary Table 12 footnote. Continuous variables are shown as mean ±standard deviation, or median [IQR] if skewed. Count variables are shown as N (%). BAME: Black, Asian, and Minority ethnic; HbA1c: glycated haemoglobin, HDL: high density lipoprotein, LDL: low density lipoproteinDBP: diastolic blood pressure; METS: metabolic equivalent of task; SBP: systolic blood pressure. LA: left atrium; LV: left ventricle; LA ejection fraction (LAEF); LA maximum volume (LAV); LV end-diastolic volume (LVEDV); LV mass (LVM); LV ejection fraction (LVEF); LV global function index (LVGFI); LV global longitudinal strain (GLS).

Supplementary Table 13. Association of cancer with CMR metrics in participants without cardiovascular disease at time of imaging

	Breast	Lung	Prostate	Colorectal†	Uterus†	Haem†
LVM (g)	0.05 (-0.08, 0.18)	-0.55 (-1.52, 0.41)	-0.12 (-0.29, 0.06)	-0.69 (-1.36, -0.02)	0.16 (-0.22, 0.54)	0.08 (-0.20, 0.37)
	0.44	0.22	0.19	0.04	0.40	0.56
LVEDV (ml)	0.07 (-0.05, 0.19)	-0.69 (-1.96, 0.58)	-0.07 (-0.23, 0.10)	-0.88 (-1.60, -0.15)	0.14 (-0.25, 0.53)	0.19 (-0.10, 0.47)
	0.26	0.24	0.42	0.02	0.47	0.20
LVEF (%)	-0.17 (-0.30, -0.04)	0.24 (-1.07, 1.55)	0.12 (-0.04, 0.29)	0.33 (-0.62, 1.29)	0.15 (-0.23, 0.53)	-0.26 (-0.52, -0.00)
	0.01	0.68	0.14	0.47	0.42	0.05
LVGFI (%)	-0.14 (-0.27, -0.01)	-0.08 (-1.72, 1.56)	0.13 (-0.04, 0.3)	0.22 (-0.74, 1.18)	0.16 (-0.24, 0.56)	-0.17 (-0.42, 0.08)
	0.04	0.91	0.13	0.64	0.42	0.19
LV GLS (%)	-0.02 (-0.15, 0.10)	-0.43 (-1.72, 0.86)	0.03 (-0.14, 0.21)	-0.11 (-1.11, 0.89)	-0.00 (-0.37, 0.37)	0.19 (-0.09, 0.47)
	0.74	0.45	0.71	0.82	0.99	0.18
LAV max (ml)	0.09 (-0.04, 0.21)	-1.10 (-2.28, 0.08)	-0.03 (-0.21, 0.15)	-0.92 (-1.80, 0.05)	0.21 (-0.13, 0.55)	0.21 (-0.07, 0.48)
	0.18	0.06	0.74	0.04	0.23	0.13
LAEF (%)	-0.15 (-0.27, -0.02)	0.59 (0.03, 1.15)	-0.01 (-0.18, 0.16)	0.54 (-0.12, 1.21)	-0.07 (-0.38, 0.24)	-0.324(-0.60, -0.05)
	0.03	0.04	0.90	0.10	0.66	0.02

Supplementary Table 13 footnote. The results are standardised beta-coefficients and 95% confidence intervals, thus representing standard deviation change in CMR metrics with change in cancer exposure status from non-cancer to cancer; for standard deviation of each metric please refer to Supplementary Table 5. The bold and yellow shaded cells represent statistically significant associations. LA: left atrium; LV: left ventricle; LV end-diastolic volume (LVEDV), LV mass (LVM), LVM: LVEDV, LV stroke volume (LVSV), LV ejection fraction (LVEF), LV global function index (LVGFI), LV global longitudinal strain (GLS), LA maximum volume (LAV), LA ejection fraction (LAEF).