Clinical Oncology 35 (2023) e708–e719

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Geographical Variation in Underlying Social Deprivation, Cardiovascular and Other Comorbidities in Patients with Potentially Curable Cancers in England: Results from a National Registry Dataset Analysis

J.V. Waterhouse [*†1], C.A. Welch [‡§1], N.M.L. Battisti [*†], M.J. Sweeting [‡¶], L. Paley [§], P.C. Lambert [‡||], J. Deanfield [**], M. de Belder [††], M.D. Peake [‡‡§§], D. Adlam [§§¶¶2], A. Ring [*†2]

[*] *Breast Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust, SM2 5PT, London, United Kingdom*
[†] *Breast Cancer Research Division, The Institute of Cancer Research, London, United Kingdom*
[‡] *Biostatistics Research Group, Department of Health Sciences, University of Leicester, University Road, LE1 7RH, Leicester, United Kingdom*
[§] *National Disease Registration Service, NHS England, 10 South Colonnade, Canary Wharf, E14 4PU, London, United Kingdom*
[¶] *Statistical Innovation, Oncology Biometrics, Oncology R&D, AstraZeneca, Cambridge, United Kingdom*
[||] *Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[**] *Institute of Cardiovascular Sciences, University College London, 62 Huntley St London, WC1E 6DD, United Kingdom*
[††] *National Institute for Cardiovascular Outcomes Research, NHS Arden & Greater East Midlands Commissioning Support Unit, 2nd floor 1 St Martin's le Grand London, EC1A 4AS, United Kingdom*
[‡‡] *Department of Health Sciences, University of Leicester, University Rd, Leicester, LE1 7RH, United Kingdom*
[§§] *University Hospitals of Leicester NHS Trust, Leicester, United Kingdom*
[¶¶] *Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, United Kingdom*

Abstract

Aims: To describe the prevalence of cardiovascular disease (CVD), multiple comorbidities and social deprivation in patients with a potentially curable cancer in 20 English Cancer Alliances.

Materials and methods: This National Registry Dataset Analysis used national cancer registry data and CVD databases to describe rates of CVD, comorbidities and social deprivation in patients diagnosed with a potentially curable malignancy (stage I–III breast cancer, stage I–III colon cancer, stage I–III rectal cancer, stage I–III prostate cancer, stage I–IIIA non-small cell lung cancer, stage I–IV diffuse large B-cell lymphoma, stage I–IV Hodgkin lymphoma) between 2013 and 2018. Outcome measures included observation of CVD prevalence, other comorbidities (evaluated by the Charlson Comorbidity Index) and deprivation (using the Index of Multiple Deprivation) according to tumour site and allocation to Cancer Alliance. Patients were allocated to CVD prevalence tertiles (minimum: <33.3rd percentile; middle: 33.3rd to 66.6th percentile; maximum: >66.6th percentile).

Results: In total, 634 240 patients with a potentially curable malignancy were eligible. The total CVD prevalence for all cancer sites varied between 13.4% (CVD $n = 2058$; 95% confidence interval 12.8, 13.9) and 19.6% (CVD $n = 7818$; 95% confidence interval 19.2, 20.0) between Cancer Alliances. CVD prevalence showed regional variation both for male (16–26%) and female patients (8–16%) towards higher CVD prevalence in northern Cancer Alliances. Similar variation was observed for social deprivation, with the proportion of cancer patients being identified as most deprived varying between 3.3% and 32.2%, depending on Cancer Alliance. The variation between Cancer Alliance for total comorbidities was much smaller.

Author for correspondence: D. Adlam, Department of Cardiovascular Sciences, University of Leicester and Leicester National Institute of Health Research Biomedical Research Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. Tel: +44-116-204-4751.
E-mail address: da134@leicester.ac.uk (D. Adlam).

[1] These authors contributed equally to this work.
[2] These authors are joint senior authors.

https://doi.org/10.1016/j.clon.2023.08.009

Conclusion: Social deprivation, CVD and other comorbidities in patients with a potentially curable malignancy in England show significant regional variations, which may partly contribute to differences observed in treatments and outcomes.

Key words: Cancer alliance; cardiology; cardiovascular disease; epidemiology; health care disparities; medical oncology

Introduction

There is considerable regional variation in cancer treatment received by patients in England. For common cancers, including those treatable with curative intent, there are differences in rates of surgery, radiotherapy and chemotherapy [1–6]. There are also regional variations in outcomes [6–9]. As of 2019, the difference between the lowest and the highest index of 1-year cancer survival between Clinical Commissioning Groups in England was 4.8% for breast cancer, 12.7% for colorectal cancer and 17.5% for lung cancer [10]. Potential explanations for these care and outcome disparities in different regions include differing rates of concomitant comorbidities, such as cardiovascular disease (CVD) and social deprivation.

Cancer and CVD share common risk factors and underlying pathophysiological processes, and frequently co-exist. In a recent analysis we found that 16.2% of patients with a potentially curable malignancy in England have a concurrent or previous diagnosis of CVD [11]. Pre-existing CVD can increase the risk of treatment complications, ranging from increased surgical/anaesthetic risk of cardiotoxicities leading to ischaemic events, new arrythmias, left ventricular systolic dysfunction and heart failure [12–14]. Therefore, CVD may impact on cancer treatment decision-making. This may impact on cancer treatment tolerability and warrant omitting, delaying or adapting treatments with the potential to impact on long-term outcomes [15–17]. Apart from CVD, other comorbidities (such as diabetes, lung or liver disease) and social deprivation may also influence diagnosis, reduced cancer treatment rates and outcomes [18–20].

There are few published data on rates of comorbidities, CVD and social deprivation in cancer patients in England. These may vary considerably in different parts of the country and influence the observed regional disparities in treatment, cancer outcomes and service provision, such as specialist cardio-oncology services.

Materials and Methods

Linkage

The Virtual Cardio-Oncology Research Initiative (VICORI) programme was established to investigate the interplay between CVD and cancer [21]. This programme links the National Cancer Registration Dataset [22], Hospital Episode Statistics (HES) [23] and National Institute for Cardiovascular Outcomes Research (NICOR) [24] audit databases. The procedures for linkage are described in detail elsewhere [11].

Identification of Cohort

We extracted data from the National Cancer Registration Dataset to identify a cohort of patients from England with tumours potentially eligible for treatment with curative intent (stage I–III breast cancer, stage I–III colon/rectal cancer, stage I–III prostate cancer, stage I–IIIA non-small cell lung cancer [NSCLC], stage I–IV diffuse large B-cell lymphoma [DLBCL] and stage I–IV Hodgkin lymphoma) from 1 January 2013 to 31 December 2018 [11,21]. If patients had more than one tumour diagnosed at different sites, we included the first tumour diagnosed in the analysis. If patients had synchronous cancer diagnoses, we included only the tumour with the worst prognosis based on a comparison of tumour stage and grade, receptor status (for the breast cancer cohort) and Gleason group (for the prostate cancer cohort). We excluded patients with missing tumour stage, synchronous tumours diagnosed in the same site with similar prognostic features and those with synchronous tumours diagnosed in different sites. We included patients aged between 25 and 100 years at cancer diagnosis, resident in England and with complete and comparable data on vital status, gender and National Health Service (NHS) number (to allow linkage). Full inclusion/exclusion criteria are shown in Supplementary Table S1.

Comorbidity, Cardiovascular Disease and Social Deprivation Ascertainment

Patient-specific information was extracted on age at cancer diagnosis, gender (as socially constructed role and patient-perceived guided by the SAGER guidelines [25]), ethnicity (defined as being self-assigned at the time of initial documentation, using nationally agreed guidelines), cancer stage (classified using the tumour, nodes and metastases [TNM] scoring system) and grade. In addition, we extracted data on CVD and non-CVD comorbidities as well as social deprivation from the linked datasets. Individual comorbidities defined within the Charlson Comorbidity Index (CCI) [26] were identified using HES admitted patient care diagnoses recorded within 5 years before the cancer diagnosis and derived a CCI excluding CVD to avoid counting them in both the CVD exposure and CCI (see Supplementary Table S2). We identified hospitalised CVD comorbidities from diagnoses recorded in any diagnostic position in HES admitted patient care (inpatient) data or a record in one of the four NICOR audits [24] within 5 years before the cancer diagnosis, as this is typically a requirement for trial participation in oncology [27]. International Classification of Diseases (ICD)-10 CVD diagnoses codes were obtained from a previous VICORI study (see

Supplementary Table S3) [28] and divided into the following main phenotypes: cerebrovascular; stroke (cerebrovascular subgroup); congestive cardiac failure; ischaemic heart disease; acute myocardial infarction (ischaemic heart disease subgroup); peripheral artery disease; valvular heart disease [11] (see Supplementary Table S4). CVD prevalence was defined according to the presence of an inpatient hospitalisation CVD diagnosis code and/or NICOR CVD audit record.

The Index of Multiple Deprivation (IMD) is the official measure of deprivation in England [29]. An established methodological framework is followed to derive seven distinct domains of deprivation, which are weighted and then combined to calculate an IMD at the Lower-layer Super Output Area (government-defined geographical region). We extracted the income domain of the IMD according to the patient's postcode of residence for analysis, which was already divided into quintiles of deprivation (1–5 where quintile 1 represents the least deprived patients and quintile 5 represents the most deprived patients at the population [not cancer] level).

Classification of Cancer Alliances

We extracted the Cancer Alliance of the hospital where the patients were diagnosed with cancer according to the hospital postcode. In total there are 20 Cancer Alliances with an average population of about 2.9 million people, established by NHS England in 2015 following recommendations by the Independent Cancer Taskforce report to regionally coordinate and connect pivotal health institutions to improve health outcomes [9,30,31].

Statistical Analysis

To investigate the non-linear association between CVD prevalence and the Cancer Alliance we divided the 20 Cancer Alliances into three groups (tertiles, with about equal patient numbers in each group): the minimum group (<33.3rd percentile) consists of the Cancer Alliance with the lowest CVD prevalence, the maximum group (>66.6th percentile) of the Cancer Alliance with the highest CVD prevalence.

We describe cancer type, age, gender, ethnicity, deprivation, CCI, stage, grade and treatment modality by patients of each Cancer Alliance tertile.

To evaluate the burden of disease, we reported bar charts showing numbers of patients, number of patients with a CVD comorbidity and CVD prevalence in each Cancer Alliance. We showed regional variation by presenting maps of England and report CVD prevalence in each Cancer Alliance separately for each cancer type. To understand existing deprivation in each Cancer Alliance, we plotted the percentage of patients in the most deprived quintile of the income domain of the IMD (IMD = 5) and (separately) at least four comorbidities using CCI excluding CVD comorbidities (CCI $\geq$4) in each Cancer Alliance by cancer type.

Funnel plots were used to investigate variations in regional CVD rates by plotting standardised CVD ratios separately for each cancer type. We calculated standardised CVD ratios by dividing the observed number of patients with a CVD comorbidity in each Cancer Alliance by the predicted number of patients with a CVD comorbidity, obtained from a logistic regression model [32]. Standardised CVD ratios that fell outside the 99.8% confidence bands were flagged as outliers because the Cancer Alliance CVD prevalence is more extreme compared with the expected CVD prevalence from the logistic regression model. Logistic models progressively adjusted for main effects of age at diagnosis, gender (if appropriate for the cancer type), cancer stage, income domain of IMD and CCI (excluding CVD comorbidities; CCI in categories 0, 1, 2, 3, $\geq$4). If the Cancer Alliance moves from being an outlier to within the 99.8% confidence band after adjusting for confounders, the confounder explains some of the chance variation. Non-linear effects of age at diagnosis were modelled using a restricted cubic spline function with three knots, calculated separately for each cancer type.

All analyses were carried out in Stata MP version 16 and R version 4.0.2 [33,34].

Results

In total, 634 240 patients were included into the analysis; 226 516 had stage I–III breast cancer, 91 210 stage I–III colon cancer, 39 688 stage I–III rectal cancer, 175 639 stage I–III prostate cancer, 70 458 stage I–IIIA NSCLC, 23 426 stage I–IV DLBCL and 7303 stage I–IV Hodgkin lymphoma (see Supplementary Figure S1).

Table 1 shows the patient, disease, tumour and treatment characteristics with Cancer Alliance grouped into tertiles of CVD prevalence. Seven Cancer Alliances were allocated to the minimum tertile (n = 213 332) with the lowest CVD prevalence, five Cancer Alliances to the middle (n = 209 560), and 8 alliances to the maximum (n = 211 348) tertile with CVD prevalence ranging between 14.5% in the minimum and 18.6% in the maximum tertile.

Some cancer sites were found to have a higher representation in the maximum compared with the minimum tertile, such as NSCLC, where 14.1% of the upper tertile were NSCLC cases versus 9.5% of the lower tertile. For the breast and prostate cancer cohort, more patients were in the minimum as opposed to the maximum tertile (37% of the lower tertile versus 34.7% of the upper tertile were breast cancer cases; 28.4% of the lower tertile versus 25.1% of the upper tertile were prostate cancer cases). For DLBCL and Hodgkin lymphoma, the allocation to Cancer Alliance tertiles was more balanced.

Older age at cancer diagnosis was associated with higher representation within the maximum Cancer Alliance tertile. For groups aged 65 years or less, patients were more likely to be in the minimum as opposed to the maximum Cancer Alliance tertile, whereas the proportion of patients in any age group above age 65 years was higher within the maximum Cancer Alliance tertile (age at cancer diagnosis 76–85 years: 1.5% percentage point difference towards allocation in the maximum Cancer Alliance tertile versus

Table 1
Patient, disease, tumour and treatment characteristics overall and with Cancer Alliances grouped in tertiles of cardiovascular disease (CVD) prevalence

Cancer Alliance CVD prevalence tertile	Minimum	Middle	Maximum	All
Total	213,332	209,560	211,348	634,240
Number of Cancer Alliances	7	5	8	20
CVD prevalence, n (%; 95% CI)	30,844 (14.5; 14.3, 14.6)	32,585 (15.5; 15.4, 15.7)	39,405 (18.6; 18.5, 18.8)	102,834 (16.2; 16.1, 16.3)
Cancer site, n (% of the total; 95% CI)				
Breast	78,833 (37.0; 36.7, 37.2)	74,443 (35.5; 35.3, 35.7)	73,240 (34.7; 34.5, 34.9)	226,516 (35.7; 35.6, 35.8)
Colon	30,214 (14.2; 14.0, 14.3)	29,797 (14.2; 14.1, 14.4)	31,199 (14.8; 14.6, 14.9)	91,210 (14.4; 14.3, 14.5)
Rectal	12,956 (6.1; 6.0, 6.2)	12,885 (6.1; 6.0, 6.3)	13,847 (6.6; 6.4, 6.7)	39,688 (6.3; 6.2, 6.3)
Prostate	60,664 (28.4; 28.2, 28.6)	61,855 (29.5; 29.3, 29.7)	53,120 (25.1; 24.9, 25.3)	175,639 (27.7; 27.6, 27.8)
NSCLC	20,320 (9.5; 9.4, 9.6)	20,292 (9.7; 9.6, 9.8)	29,846 (14.1; 14.0, 14.3)	70,458 (11.1; 11.0, 11.2)
DLBCL	7817 (3.7; 3.6, 3.7)	7798 (3.7; 3.6, 3.8)	7811 (3.7; 3.6, 3.8)	23,426 (3.7; 3.6, 3.7)
Hodgkin lymphoma	2528 (1.2; 1.1, 1.2)	2490 (1.2; 1.1, 1.2)	2285 (1.1; 1.0, 1.1)	7303 (1.2; 1.1, 1.2)
Age at cancer diagnosis (years), n (% of total; 95% CI)				
25–34	2840 (1.3; 1.3, 1.4)	2714 (1.3; 1.2, 1.3)	2248 (1.1; 1.0, 1.1)	7802 (1.2; 1.2, 1.3)
35–44	8621 (4.0; 4.0, 4.1)	7834 (3.7; 3.7, 3.8)	6840 (3.2; 3.2, 3.3)	23,295 (3.7; 3.6, 3.7)
45–54	26,243 (12.3; 12.2, 12.4)	24,060 (11.5; 11.3, 11.6)	23,665 (11.2; 11.1, 11.3)	73,968 (11.7; 11.6, 11.7)
55–64	45,025 (21.1; 20.9, 21.3)	42,416 (20.2; 20.1, 20.4)	43,953 (20.8; 20.6, 21.0)	131,394 (20.7; 20.6, 20.8)
65–74	69,393 (32.5; 32.3, 32.7)	68,101 (32.5; 32.3, 32.7)	70,018 (33.1; 32.9, 33.3)	207,512 (32.7; 32.6, 32.8)
75–84	46,504 (21.8; 21.6, 22.0)	48,825 (23.3; 23.1, 23.5)	49,341 (23.3; 23.2, 23.5)	144,670 (22.8; 22.7, 22.9)
>85	14,706 (6.9; 6.8, 7.0)	15,610 (7.4; 7.3, 7.6)	15,283 (7.2; 7.1, 7.3)	45,599 (7.2; 7.1, 7.3)
Gender, n (% of total; 95% CI)				
Male	101,262 (47.5; 47.3, 47.7)	102,082 (48.7; 48.5, 48.9)	99,677 (47.2; 46.9, 47.4)	303,021 (47.8; 47.7, 47.9)
Female	112,070 (52.5; 52.3, 52.7)	107,478 (51.3; 51.1, 51.5)	111,671 (52.8; 52.6, 53.1)	331,219 (52.2; 52.1, 52.3)
Ethnicity, n (% of total; 95% CI)				
White	182,128 (85.4; 85.2, 85.5)	182,676 (87.2; 87.0, 87.3)	199,883 (94.6; 94.5, 94.7)	564,687 (89.0; 89.0, 89.1)
Mixed	1151 (0.5; 0.5, 0.6)	1068 (0.5; 0.5, 0.5)	475 (0.2; 0.2, 0.2)	2694 (0.4; 0.4, 0.4)
Asian	7139 (3.3; 3.3, 3.4)	6708 (3.2; 3.1, 3.3)	3076 (1.5; 1.4, 1.5)	16,923 (2.7; 2.6, 2.7)
Black	6431 (3.0; 2.9, 3.1)	5918 (2.8; 2.8, 2.9)	1230 (0.6; 0.5, 0.6)	13,579 (2.1; 2.1, 2.2)
Other	3426 (1.6; 1.6, 1.7)	2749 (1.3; 1.3, 1.4)	949 (0.4; 0.4, 0.5)	7124 (1.1; 1.1, 1.1)
Missing	13,057 (6.1; 6.0, 6.2)	10,441 (5.0; 4.9, 5.1)	5735 (2.7; 2.6, 2.8)	29,233 (4.6; 4.6, 4.7)
Income domain of the Index of Multiple Deprivation, n (% of total; 95% CI)				
1 – Least	57,878 (27.1; 26.9, 27.3)	44,453 (21.2; 21, 21.4)	38,542 (18.2; 18.1, 18.4)	140,873 (22.2; 22.1, 22.3)
2	52,368 (24.5; 24.4, 24.7)	49,513 (23.6; 23.4, 23.8)	43,030 (20.4; 20.2, 20.5)	144,911 (22.8; 22.7, 23.0)
3	45,246 (21.2; 21.0, 21.4)	46,360 (22.1; 21.9, 22.3)	40,017 (18.9; 18.8, 19.1)	131,623 (20.8; 20.7, 20.9)
4	36,685 (17.2; 17.0, 17.4)	38,788 (18.5; 18.3, 18.7)	38,758 (18.3; 18.2, 18.5)	114,231 (18.0; 17.9, 18.1)
5 – Most	21,155 (9.9; 9.8, 10.0)	30,446 (14.5; 14.4, 14.7)	51,001 (24.1; 23.9, 24.3)	102,602 (16.2; 16.1, 16.3)
Charlson Comorbidity Index[*,†], n (% of total; 95% CI)				
0	99,170 (46.5; 46.3, 46.7)	97,637 (46.6; 46.4, 46.8)	99,154 (46.9; 46.7, 47.1)	295,961 (46.7; 46.5, 46.8)
1	18,005 (8.4; 8.3, 8.6)	17,674 (8.4; 8.3, 8.6)	17,976 (8.5; 8.4, 8.6)	53,655 (8.5; 8.4, 8.5)
2	52,636 (24.7; 24.5, 24.9)	51,200 (24.4; 24.2, 24.6)	51,863 (24.5; 24.4, 24.7)	155,699 (24.5; 24.4, 24.7)
3	21,955 (10.3; 10.2, 10.4)	21,710 (10.4; 10.2, 10.5)	21,862 (10.3; 10.2, 10.5)	65,527 (10.3; 10.3, 10.4)
≥4	18,959 (8.9; 8.8, 9.0)	18,776 (9.0; 8.8, 9.1)	18,826 (8.9; 8.8, 9.0)	56,561 (8.9; 8.8, 9.0)
Missing[†]	2607 (1.2; 1.2, 1.3)	2563 (1.2; 1.2, 1.3)	1667 (0.8; 0.8, 0.8)	6837 (1.1; 1.1, 1.1)

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; NSCLC, non-small cell lung cancer.
[*] Five years before diagnosis excluding CVD.
[†] Missing if not linked to Hospital Episode Statistics.

age at cancer diagnosis 46–55 years: 1.1% percentage point difference towards the minimum Cancer Alliance tertile).

An adjusted proportional odds logistic regression model (with tertile as the outcome with three ordered categories) showed that social deprivation (least deprivation as reference versus most deprived: odds ratio 2.92, 95% confidence interval 2.88–2.97, $P < 0.001$) and NSCLC (breast cancer site as reference versus NSCLC: odds ratio 1.27, 95% confidence interval 1.24–1.30, $P < 0.001$) were associated with a higher risk of being in a Cancer Alliance tertile with a higher CVD prevalence (see Supplementary Table S5).

Types of CVD were analysed in the 102 604 patients with a diagnosis of CVD determined by HES (see Supplementary Table S6): ischaemic heart disease had the highest CVD prevalence percentage in the population (10.2%; 95% confidence interval 10.1–10.3), followed by congestive cardiac failure (3.4%; 95% confidence interval 3.3–3.4), peripheral arterial disease (3.3%; 95% confidence interval 3.3–3.3), cerebrovascular (3.2%; 95% confidence interval 3.2–3.3), valvular heart disease (2.8%; 95% confidence interval 2.8–2.8), acute myocardial infarction (1.6%; 95% confidence interval 1.6–1.7) and stroke (1.4%; 95% confidence interval 1.3–1.4).

Figure 1 shows the number of patients by Cancer Alliance with and without any CVD diagnosis code and the overall CVD prevalence by Cancer Alliance. This shows the variation in prevalence of CVD in cancer patients of between 13.4% (95% confidence interval 12.8–13.9) in South East London and 19.6% (95% confidence interval 19.1–20.0) in North East and Cumbria (Figure 1b; Supplementary Table S7). Given the different population sizes of the Cancer Alliances, Figure 1a illustrates the differences in absolute numbers of cancer patients with CVD according to Cancer Alliance.

There was geographical variation of CVD prevalence between Cancer Alliances in all male and female cancer patients with consistent findings of higher levels of CVD prevalence in the northern (male 26%; female 16%) compared with the central and southern Cancer Alliances (male 16%; female 8%) (Figure 2a, b). Similar regional variation between northern and central/southern Cancer Alliances was noted for the percentage of most deprived income domain of IMD quintile in male (2–35%) and female (2–35%) patients (Figure 3a, b).

CVD prevalence data (identified from HES and NICOR audits) for each Cancer Alliance reviewed for all cancer sites were also examined according to tumour sites with comparable patterns of CVD prevalence variation (following a south–north gradient towards higher CVD prevalence with centrifugal tendency from London) between different Cancer Alliances (see Supplementary Table S6a and S6b). For individual cancer types, the regional variation between Cancer Alliances was highest for NSCLC: difference of 9.7% in CVD prevalence (31.4%; 95% confidence interval 29.1–33.8 in the lowest Cancer Alliance and 41.1%; 95% confidence interval 39.9–42.4 in the highest). Absolute differences in CVD prevalence between Cancer Alliances for other tumour types were smaller: colon cancer 7.6% (range from 26.8% to 19.2%), prostate cancer cohort 8% (19.6%–11.6%) and lowest for breast cancer: 3.5% (9.5%–6.0%) (see Supplementary Figures S2a, S3a, S4a, S5a).

Similarly, for all cancer types, there was geographical variation of deprivation quintiles with higher prevalence of most socioeconomic deprived patients in Cancer Alliances in the north of England compared with the south of England (see Supplementary Figures S2b, S3b, S4b, S5b, S6b, S7b, S8b). To a lesser extent, this could be appreciated for DLBCL and Hodgkin lymphoma (see Supplementary Figures S4b and S5b).

Reviewing the distribution of patients with a higher CCI (cancer patients with four or more comorbidities, excluding CVD) throughout England (see Supplementary Figure S9), the variation between Cancer Alliances was less pronounced than for CVD prevalence and social deprivation (relative differences between the lowest and highest CCI percentage: 20% decrease for breast cancer, 25% for colon cancer, 20% for prostate cancer and 20% for NSCLC) and did not reflect the north/south divide seen for higher CVD prevalence.

After adjusting for age, TNM stage, deprivation and CCI for the different cancer types (Figure 4 funnel plots and Supplementary Table S8), the differences in standardised CVD ratio persisted for some Cancer Alliances for breast cancer, colon cancer, rectal cancer, prostate cancer and NSCLC. For both DLBCL and Hodgkin lymphoma, all Cancer Alliances were within the expected CVD prevalence range when adjusted.

Discussion

This analysis showed geographical variation of CVD prevalence for seven potentially curable malignancies in England ranging between 13.4% (95% confidence interval 12.8–13.9) and 19.6% (95% confidence interval 19.1–20.0) between all Cancer Alliances and highlighted areas of high concomitant CVD morbidity with a north–south decline. The highest regional variation was noted for NSCLC (9.7% percentage point difference of CVD prevalence between Cancer Alliances). It also demonstrated regional variation of socioeconomic deprivation in cancer patients, with the higher deprivation recorded for patients in the northern Cancer Alliances compared with southern Cancer Alliances (percentage in the deprived income domain of IMD quintile in the northern Cancer Alliances versus southern Cancer Alliances in male patients: 35%–2% versus in female patients: 35%–2%) (Figure 3a, b).

Prior studies have hypothesised that differences in demographics (including age, gender and ethnicity), cancer stage, deprivation, comorbidities, proximity to cancer centres and availability of specialised services may explain the observed regional variation of treatment rates and outcomes [2–5,35–39].

We recently showed that there is a significant burden of pre-existing CVD diagnoses in patients with a potentially curable cancer (16.2%; $n = 102\,834$) [11]. In this analysis we have now shown important geographical variation in CVD,

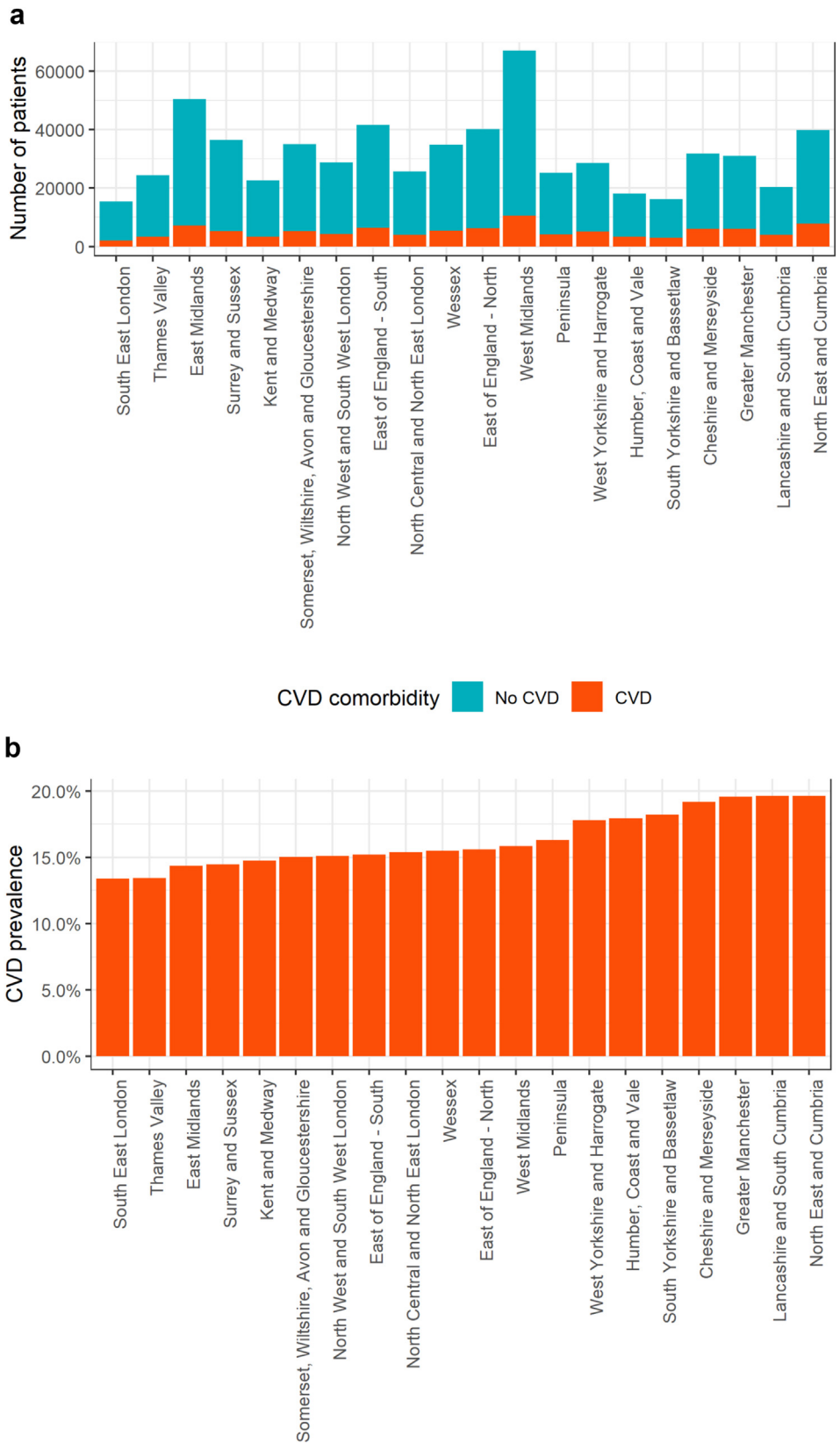

Fig 1. (a) Number of patients with any or no cardiovascular disease (CVD) diagnosis code and (b) prevalence of CVD for each Cancer Alliance. Both figures ordered by CVD prevalence, so Cancer Alliances are in the same order. CVD prevalence in cancer patients varied between Cancer Alliances. Given the different population sizes of the Cancer Alliances, a higher absolute number of cancer patients in a certain Cancer Alliance did not relate to a higher percentage of CVD prevalence.

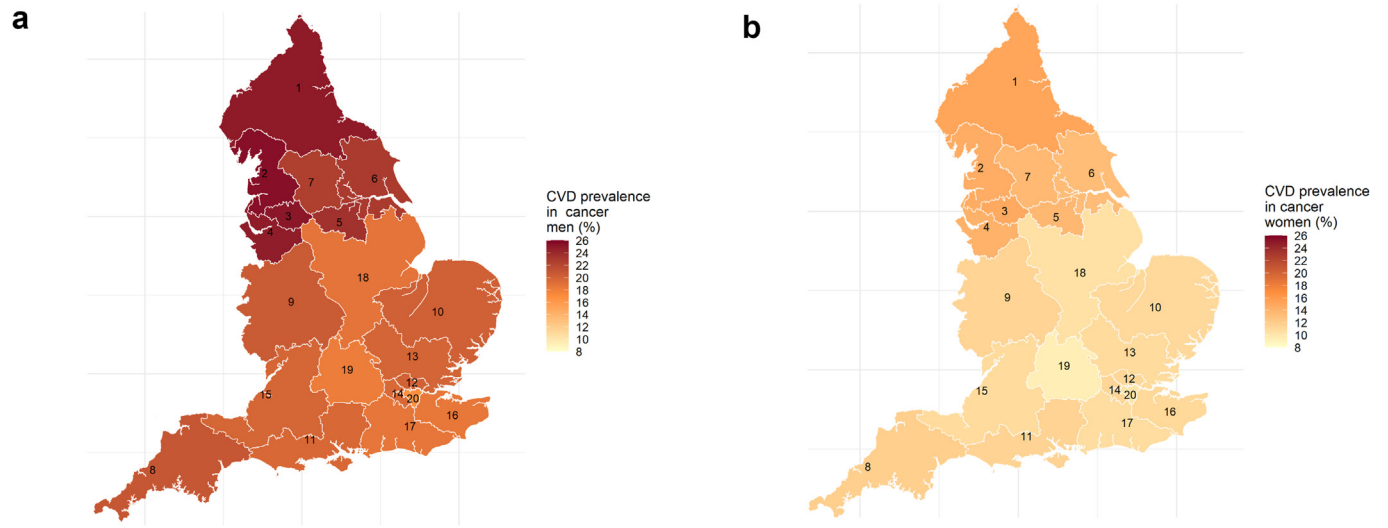

Fig 2. Prevalence of cardiovascular disease in (a) male (n = 303 021) and (b) female (n = 331 219) patients with cancer according to Cancer Alliance. Cardiovascular disease prevalence varied regionally between Cancer Alliances for all male and female cancer patients. 1, North East and Cumbria; 2, Lancashire and South Cumbria; 3, Greater Manchester; 4, Cheshire and Merseyside; 5, South Yorkshire and Bassetlaw; 6, Humber, Coast and Vale; 7, West Yorkshire and Harrogate; 8, Peninsula; 9, West Midlands; 10, East of England – North; 11, Wessex; 12, North Central and North East London; 13, East of England – South; 14, North West and South West London; 15, Somerset, Wiltshire, Avon and Gloucestershire; 16, Kent and Medway; 17, Surrey and Sussex; 18, East Midlands; 19, Thames Valley; 20, South East London.

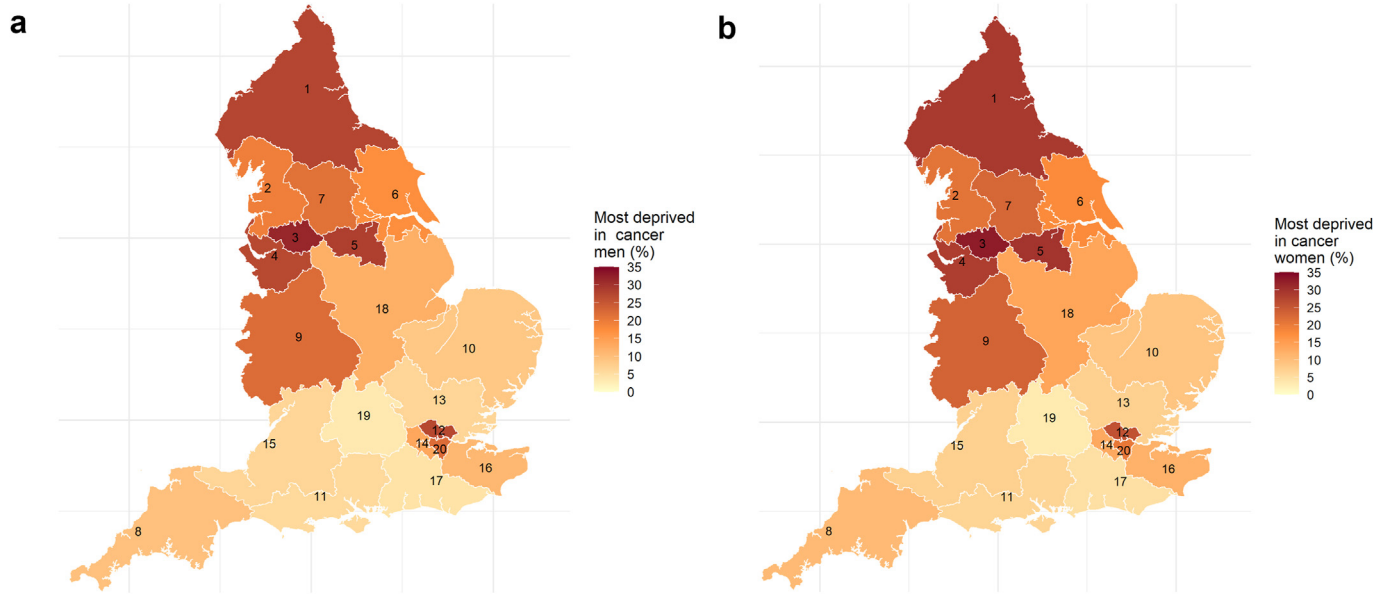

Fig 3. Percentage of the most deprived income domain of Index of Multiple Deprivation quintile in (a) male (n = 303 021) and (b) female (n = 331 219) patients with cancer according to Cancer Alliance. Social deprivation varied regionally between Cancer Alliances for all male and female cancer patients, mirroring the geographical pattern seen in Figure 2. 1, North East and Cumbria; 2, Lancashire and South Cumbria; 3, Greater Manchester; 4, Cheshire and Merseyside; 5, South Yorkshire and Bassetlaw; 6, Humber, Coast and Vale; 7, West Yorkshire and Harrogate; 8, Peninsula; 9, West Midlands; 10, East of England – North; 11, Wessex; 12, North Central and North East London; 13, East of England – South; 14, North West and South West London; 15, Somerset, Wiltshire, Avon and Gloucestershire; 16, Kent and Medway; 17, Surrey and Sussex; 18, East Midlands; 19, Thames Valley; 20, South East London.

other comorbidities and social deprivation in patients with potentially curable cancer. Such variation represents a plausible mechanism for at least some of the inequalities and treatment outcomes observed (including access to standard care and/or clinical trials, cancer recurrence and mortality rates).

This analysis has several strengths. Notably, the large sample and the use of registry data mean the findings will reflect the burden and variation of CVD in this patient population more accurately compared with its burden observed in more selective clinical trial-based analyses. Moreover, this analysis represented a novel approach to

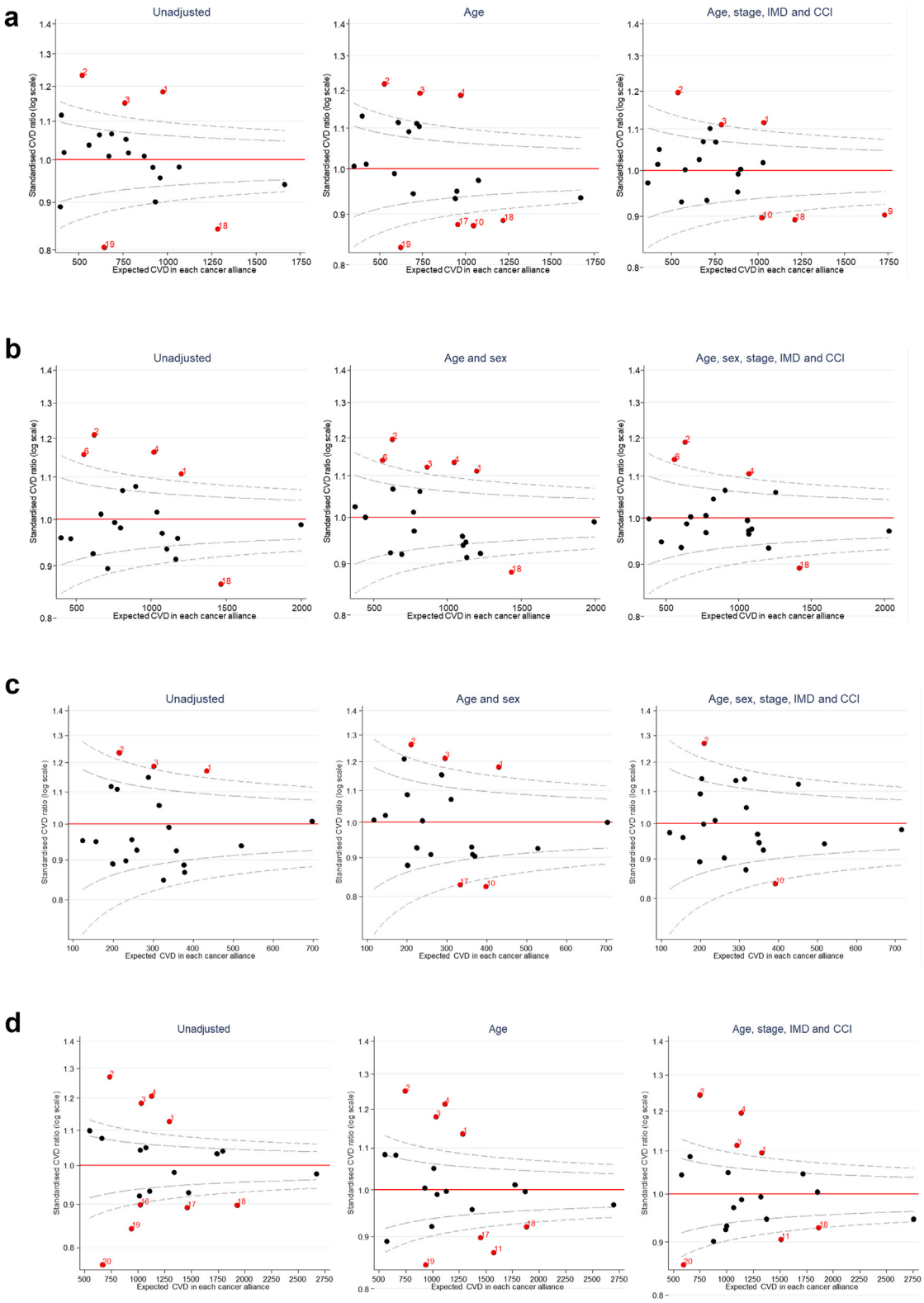

Fig 4. Standardised cardiovascular disease ratio for each Cancer Alliance by cancer type and adjusting for variables listed in the title of each graph. (a) Breast cancer; (b) colon cancer; (c) rectal cancer; (d) prostate cancer; (e) non-small cell lung cancer; (f) diffuse large B-cell lymphoma; (g) Hodgkin lymphoma. Differences in standardised cardiovascular disease ratio persisted for some Cancer Alliances for breast, colon, rectal, prostate and non-small cell lung cancer despite adjustment for age, tumour stage, deprivation and Charlson Comorbidity Index (5 years before diagnosis and excluding cardiovascular disease).

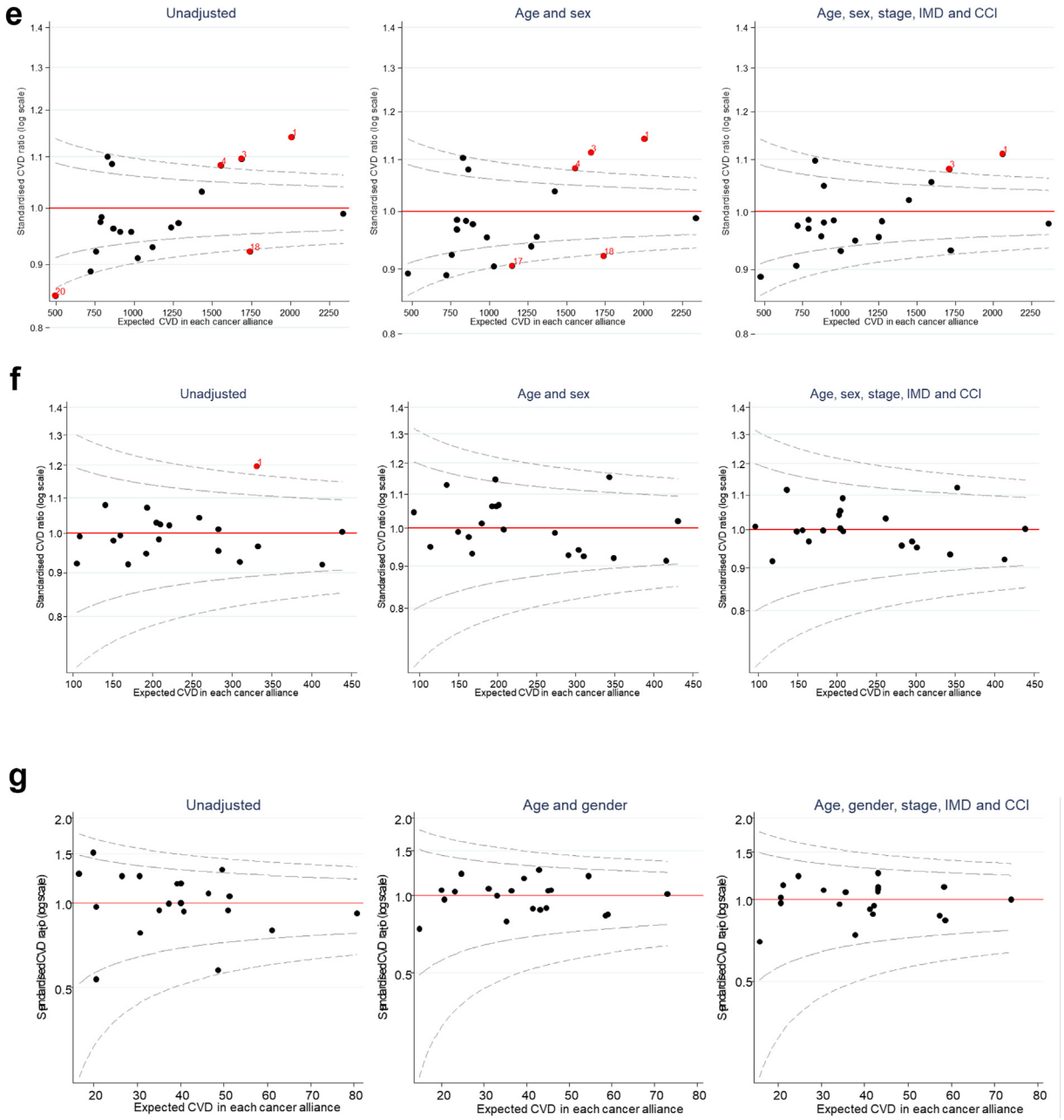

Fig 4. (*continued*).

gain insight on this specific outcome by combining data from large datasets.

There are also limitations: for example, this analysis does not account for the geographical variation of smoking prevalence in England, which may be a major driver of the high prevalence of CVD in patients with NSCLC. On the other hand, additional risk factors, such as levels of air pollution, physical activity, alcohol, obesity and diet may have influenced both cancer and CVD prevalence and are not accounted for in this study. Moreover, CVD cases recorded in primary care and following a cancer diagnosis have not been accounted for in this study, with possible underestimation of CVD prevalence.

As Cancer Alliances were identified using hospital postcodes, the tertile allocation may have been affected as some patients may have potentially been referred to hospitals across Cancer Alliance borders for specialist cardio-oncology or cancer care (although given the very limited availability of cardio-oncology services, this impact is probably limited).

The appropriate management and monitoring of CVD in cancer patients is key to cardiovascular risk stratification and the implementation of optimal prevention strategies in cancer patients [40]. This is a critical benefit of the implementation of cardio-oncology services. The European Association for Cardiology argues that access to specialist

cardio-oncology clinics should be regarded as a standard of care [41]. However, currently these centres are largely isolated in the North West and Central London Cancer Alliances [42]. These study findings support increased service provision with respect to specialist cardio-oncology services. Implementation of such services might be best started in areas of high CVD prevalence areas. Similarly, targeting socially deprived areas with public health and awareness campaigns may also have a positive impact on the risks of treatment delays and treatment uptake. Specific public health initiatives may include promoting a healthy lifestyle (e.g. smoking cessation, education on healthy diet, weight loss/physical exercise), establishment of modern healthcare facilities, disease prevention (e.g. early disease detection), increase in rehabilitation programmes and close collaboration with local communities and social sectors to improve access to optimal cancer care and outcomes [43].

A key direction for future research is whether lower rates of treatment and worse outcomes can be directly mapped onto those geographical regions with higher rates of CVD prevalence, comorbidities and social deprivation. However, the appropriate treatment for a given cancer would need to account for specific tumour subtypes, tumour stage and treatment modality being considered (surgery, radiotherapy or systemic therapy). Differences in cardio-oncological disease prevalence from different Cancer Alliances are not solely due to variations in age, TNM stage and comorbidities (Figure 4). Further research is warranted to investigate other potential causes for this geographical variation.

Conclusion

In conclusion, this study showed considerable geographical variation of CVD prevalence, other comorbidities and social deprivation in patients in England with curable cancers. These findings may at least partially explain different treatment patterns and outcomes in cancer patients in England and also provide some opportunities to address these inequalities.

Ethics

This study was reviewed and approved by the Virtual Cardio-Oncology Research Initiative Consortium Project Review Panel. The Virtual Cardio-Oncology Research Initiative research programme has received favourable ethical opinion from the North East – Newcastle & North Tyneside 2 Research Ethics Committee (REC reference 18/NE/0123). The study was performed in accordance with the Declaration of Helsinki. Consent for publication was not required because this manuscript does not contain any individual person's data.

Data

Data for this study are based on patient-level information collected by the NHS as part of the care and support of patients with cancers. The data are collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England. Data were requested through VICORI and the Office for Data Release. A VICORI guide (Version 2.0, 23 September 2021) to access raw data is available at https://vicori.le.ac.uk/accessing-the-data/.

Author contributions

DA is the guarantor of integrity of the entire study. CAW, NMLB, DA, MS, LP, PL, JD, MdB, MDP and AR were responsible for study concepts and design. JVW, CAW, NMLB, DA and AR carried out the literature research. JVW, CAW, NMLB, MS, LP, PL, JD, MdB, MDP, DA and AR carried out the experimental studies/data analysis. CAW, NMLB, MS and PL carried out the statistical analysis. JVW, CAW, DA and AR prepared the manuscript. JVW, CAW, NMLB, MS, LP, PL, JD, MdB, MDP, DA and AR edited the manuscript.

Conflicts of Interest

J.V. Waterhouse has received conference attendance fees from Pfizer. N. Battisti has received advisory board fees from Pfizer, Abbott and Sanofi, speaker fees from Pfizer, AbbVie, Roche, Sanofi and Novartis and travel grants from Exact Sciences Genomic Health, Lilly, Pfizer and Novartis. M. Sweeting is a full-time employee of AstraZeneca (with stock options). J. Deanfield received CME honoraria and/or consulting fees from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk and Bayer, research grants from the British Heart Foundation, Medical Research Council (UK), NIHR, Public Health England, MSD, Pfizer, Aegerion, Colgate, Roche, Cancer Research UK and Alzheimer's Research UK; he is also a member of SOUL and SELECT Study steering committees for Novo Nordisk. J. Deanfield and M. de Belder are on the executive steering committee for the DAPA MI trial, AstraZeneca. M. Peake received writing and speaker fees from MSD and AstraZeneca and chairs the IDMC for thoracic oncology trials in the Clinical Trials centre of University College London; he is also a board member of the British Thoracic Oncology Group and the UK Lung Cancer Coalition. D. Adlam reports financial support was provided by Cancer Research UK and the British Heart Foundation and administrative support by NIHR Leicester Biomedical Research Centre. D. Adlam has patents #EP3277337A1 and #PCT/GB2017/050 ,877 issued to the University of Leicester. D. Adlam has patent #UK2211616.4 pending to the University of Leicester. D. Adlam reports research funding and in-kind support from Astra Zeneca for unrelated research, has received educational funding from Abbott Vascular to support a clinical research fellow and conducted consultancy for General Electric to support general research funds. A. Ring has received advisory board and speaker fees from Roche, Novartis, Pfizer, MSD, Astrazeneca, Seagen, Gilead, Daiichi-Sankyo and Lilly, and support from Gilead and Lilly for conference attendances.

Acknowledgement

The work was supported by a joint research grant from the British Heart Foundation (grant number SP/16/5/32415) and Cancer Research UK (grant number C53325/A21134). The funders did not have any involvement in producing the manuscript. This project involves data that have been provided by or derived from patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England, formerly in Public Health England (PHE). Data have also been provided by the Healthcare Quality Improvement Partnership from the National Cardiac Audit Programme, part of the National Clinical Audit and Patient Outcomes Programme, which it commissions (for the period of analysis and the approved applications, but since June 2022 the Healthcare Quality Improvement Partnership no longer commissions the National Cardiac Audit Programme). Access to the data was facilitated by the PHE Office for Data Release. A. Ring and J.V Waterhouse acknowledge the support of the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. J.V. Waterhouse would like to acknowledge the support of the Cridlan Ross Smith Charitable Trust. D. Adlam acknowledges the support of the Leicester NIHR Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2023.08.009.

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