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Socio-economic patterning in early mortality of patients aged 0-49 years diagnosed with primary bone cancer in Great Britain, 1985-2008

Running title: Socio-economic patterning in early mortality of bone cancer patients

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ABBREVIATIONS

AIC	Akaike information criterion
CI	confidence interval
ICD-O-3	International Classification of Diseases for Oncology, third edition
NAEDI	National Awareness and Early Diagnosis Initiative
NCIN	National Cancer Registration and Analysis Service
NCRI	National Cancer Research Institute
OPCS	Office of Population Censuses and Surveys
OR	odds ratio
pph	persons per hectare
SAU	small area unit
TYA	Teenagers and young adults

ABSTRACT

Background: Studies have shown marked improvements in survival between 1981 and 2000 for Ewing sarcoma patients but not for osteosarcoma. This study aimed to explore socio-economic patterning in early mortality rates for both tumours.

Procedure: The study analysed all 2432 osteosarcoma and 1619 Ewing sarcoma cases, aged 0-49 years, diagnosed in Great Britain 1985-2008 and followed to 31/12/2009. Logistic regression models were used to calculate risk of dying within three months, six months, one year, three years and five years after diagnosis. Associations with Townsend deprivation score and its components were examined at small-area level. Urban/rural status was studied at larger regional level.

Results: For osteosarcoma, after age adjustment, mortality at three months, six months and one year was associated with higher area unemployment, OR = 1·05 (95% CI 1·00, 1·10), OR = 1·04 (95% CI 1·01, 1·08) and OR = 1·04 (95% CI 1·02, 1·06) respectively per 1% increase in unemployment. Mortality at six months was associated with greater household non-car ownership, OR = 1·02 (95% CI 1·00, 1·03). For Ewing sarcoma, there were no significant associations between mortality and overall Townsend score, nor its components for any time period. For both tumours increasing mortality was associated with less urban and more remote rural areas.

Conclusions: This study found that for osteosarcoma, early mortality was associated with residence at diagnosis in areas of higher unemployment, suggesting risk of early death may be socio-economically determined. For both tumours, distance from urban centres may lead to greater risk of early death.

1. Introduction

Initiatives by the National Cancer Research Institute (NCRI), the National Cancer Intelligence Network (now the National Cancer Registration and Analysis service) and the National Awareness and Early Diagnosis Initiative (NAEDI) have highlighted the need for early diagnosis of cancer to improve survival [1]. Studies have suggested that childhood bone cancer has a longer time to diagnosis compared to some other childhood cancers and that a longer time to diagnosis is associated with older age for bone cancer in children, teenagers and young adults (TYA) [2, 3]. The TYA age (13-24 years) group represents a unique challenge to the UK National Health Service as they often straddle paediatric and older adult services, experience variation in treatment protocols compared to younger children and have to cope with a cancer diagnosis during a key developmental part of their lives [4].

Previous studies have analysed incidence and survival from primary bone tumours using data from the northern part of England. In those analyses, over the twenty year period from 1981 to 2000 there were marked improvements in survival from Ewing sarcoma for children and for all patients aged less than 40 years at time of diagnosis, whereas no improvements were seen in survival from osteosarcoma [5, 6]. A previous national study of osteosarcoma and Ewing sarcoma survival data for those aged 0-39 years did not fully investigate geographical patterns in survival rates [7]. A study from Germany showed that delays in diagnosis of bone tumours may be greater for patients resident in rural areas [8]. Differences in survival between countries have also been demonstrated. A comparative survival analysis of Ewing sarcoma patients between the UK and Germany found that survival rates were lower for UK patients [9]. Furthermore, a recent study from the USA suggested that socioeconomic factors influence overall survival for osteosarcoma [10]. Taken together these previous findings suggest that there are geographically determined factors which are related to mortality and survival amongst patients diagnosed with bone tumours.

The aims of the present study were to determine if socio-economic patterning in early mortality rates for osteosarcoma and Ewing sarcoma were modulated by age, gender, area based measures of deprivation, and residence in urban or rural areas. This should provide better understanding of the possible reasons for longer time to diagnosis in the UK compared to other similar countries. It should also allow the reasons for lack of improvement in early mortality, especially for osteosarcoma, to be elucidated.

2. Methods

2.1. Study Subjects

The study population consisted of patients diagnosed with osteosarcoma or Ewing sarcoma in Great Britain between 1985 and 2008. Patients were followed to 31/12/2009 or date of death if earlier. The age range was limited to 0-49 years since there were very few Ewing sarcoma cases above this age and osteosarcoma over 50 years is most often associated with Paget's disease or is usually secondary to radiotherapy [11, 12].

The patient data were accessed from the ten former regional cancer registries that covered the whole of Great Britain. Patient data from the National Registry of Childhood Tumours [13] were also extracted and used to cross-check accuracy of data for those aged 0-14 years obtained from the regional registries. Analyses of these data showed similar results, and thus provided reassurance regarding data accuracy. The necessary regulatory and ethical approvals were obtained (UK National Research Ethics Service reference number 11/NE/0298).

2.2. Diagnostic groups

Cases were classified into diagnosis groups using the International Classification of Diseases for Oncology, third edition (ICD-O-3) [14]. The coding used information on both morphology and topography. Two specific diagnostic groups were specified a priori: (i) osteosarcoma (ICD-O-3 topography codes for sites classified as bones and joint: C400-C403, C408-C414, C418-C419 and associated morphology codes 9180/3, 9181/3, 9182/3, 9183/3, 9184/3, 9185/3, 9186/3, 9187/3, 9192/3, 9193/3, 9194/3, 9195/3) and (ii) Ewing sarcoma (ICD-O-3 topography codes for sites classified as bones and joint: C400-C403, C408-C414, C418-C419, C760-C768 and associated morphology codes 9260/3, 9261/3).

2.3. Outcome

The possibility that time to diagnosis could increase in older age groups suggested that survival time might not be a robust outcome measure and mortality, as defined by the number of deaths in specified time intervals, would be more appropriate. Survival was recorded in the dataset as time in days from date of diagnosis to date of death or 31/12/2009 if vital status was recorded as alive at that date. Extremely early death is unusual in bone sarcoma and therefore patients with survival time equal to 0 days were excluded from the analysis on the assumption that their true survival time was unknown. Mortality at each time point after diagnosis of three months, six months, one year, three years and five years was calculated where vital status was recorded as died and survival time was not greater than 91, 182, 365, 1096, or 1826 days respectively.

2.4. Boundary data

Widespread boundary changes impede analyses over a prolonged time span, particularly at the small area level. Geo-referenced bone cancer registration data were linked to 2001 census boundaries [15]. The census boundaries consisted of wards in England and Wales (0–49 population ranges from 297 to 29,300, median = 3,090) and postcode sectors in Scotland (0–49 population ranges from 23 to 15,916, median = 3,201). In England and Wales analyses were performed at the small area census ward level and in Scotland at the postcode sector level. The term small area unit (SAU) is used for convenience throughout this article.

There are no formal urban/rural classifications of wards/postal sectors or other small areas that cover the whole of Great Britain and therefore two ways of examining the urban/rural nature of areas were chosen. First, a scheme developed in 1991 by OPCS (Office of Population Censuses and Surveys) and updated by Champion and Norman was used. This grouped local authority areas into 13 area types

ranging from 'Inner London' to 'Remoter rural'. Secondly, a measure was created using 'persons per hectare' (pph) in the following way; a SAU with >33 pph was classified as 'Most urban', 26-33 pph 'Very urban', 13-26 pph 'Urban', 1-13 pph 'Rural' and <1 pph 'Most rural'.

2.5. Demographic data

Adjustment for deprivation was made using an area based, time-series of cross-sectional indicators. These were obtained from each of the censuses during the study period and geographically converted to be compatible with the 2001 SAUs [15]. The Townsend index is often used in similar geographical studies and comprises four components on unemployment, non-car ownership, non-home ownership and household overcrowding. To take account of any changes in deprivation for every SAU at the different time points, each Townsend component was expressed as a z-score relative to the GB average level over the study period. At each census time point, the z-scores were summed, equally weighted, to provide a set of deprivation scores in every SAU [16].

2.6. Statistical Analysis

Logistic regression models analysed the odds of dying within three months, six months, one year, three years and five years after diagnosis. Three year and five year follow up data were only available for patients diagnosed 1985-2006 and 1985-2004 respectively and therefore the analyses of these time periods were carried out on a subset of the patients analysed at the shorter time periods.

Associations with a time series of Townsend deprivation score and its components were examined at small-area level. The ecological (independent) variables were the census-derived small-area characteristics, which were allocated to the 2001 census geography using Norman's method [15].

A series of univariable and multivariable models were fitted separately for osteosarcoma and Ewing sarcoma and included the following independent variables: sex, age group at diagnosis (0-14, 15-19, 20-39 and 40-49 years), area based population density, Townsend score (as a composite). The four components of the Townsend score (percentage of overcrowded homes, percentage of households without a car, percentage of persons unemployed and percentage of homes that are not owner occupied) were included in separate models that did not include the composite score. Multivariable models comprised those variables which had shown a statistically significant relationship with mortality in a univariable model but only fitted if one of the variables was a deprivation variable i.e. Townsend composite score or a component. Model fit was assessed using the Akaike information criterion (AIC) with the final multivariable model selected as the one with the minimum AIC value. Interactions between age and the Townsend score and age and the individual Townsend components were considered for inclusion in the models. The likelihood ratio test was used to compare models with and without the interaction term. The effect of urban/rural area type on mortality was also examined using univariable logistic regression and then in multivariable models adjusting first for age and sex and then additionally but separately for Townsend score, area unemployment and non-car ownership in area of residence. Odds ratios (ORs) for the time periods from diagnosis are presented, together with 95% confidence intervals (CI). All analyses were carried out using STATA version 14.

3. Results

There were 2432 cases of osteosarcoma (58·2% male) and 1619 cases of Ewing sarcoma (60.0% male) included in the analysis after excluding those with survival equal to 0 days (1·3% of each cancer type). The demographic patient and area characteristics of the two groups are shown in Table 1 (the Townsend deprivation score ranged from –5·93 to 12·22 in 1971, -6·52 to 13·44 in 1981, -6·04 to 12·34 in 1991 and -7·32 to 7·89 in 2001). The number of diagnoses and deaths in the two groups are shown in Table 2. Cumulative mortality increased from 1.7% at three months after diagnosis to 45.4% at five years for osteosarcoma patients and similarly from 2.0% at three months to 49.4% at five years for Ewing sarcoma patients (Table 1). The percentage of patients in each age group who had died at each time point are shown in Figures 1a and 1b. For osteosarcoma patients there was little variation over time between the age groups for those aged <=39 years but considerably more variation in mortality between all age groups for Ewing sarcoma patients and notably as time elapsed.

3.1. Regression analysis: osteosarcoma

Independent effects of demographic characteristics and area deprivation on mortality are shown in Supplemental Table S1. Mortality was significantly higher in the older age groups (20-49 years) compared to the youngest group (0-14 years) at three months and in those aged 40-49 years at all time points except five years. The impact on mortality of being diagnosed aged 40-49 years decreased over time, OR = 10·2 (95% CI 3·45, 29·6) at three months and OR = 1·42 (95% CI 0·99, 2·05) at five years. There was no difference between males and females except at three and five years where mortality was lower for females, OR = 0·76 (95% CI 0·63, 0·91).

For the area deprivation variables, small but statistically significant increases in mortality were seen with increasing unemployment at three months, six months and one year after diagnosis, increased households without a car, at six months and one year and an increase in the overall Townsend score, at one year. As an example of the increase in mortality, the percentage of patients who died within three months of diagnosis increased by 5% for every one percent increase in unemployment (OR = 1·05; 95% CI 1·01, 1·10).

Multivariable logistic regression models were produced for the time points from diagnosis where at least one area deprivation variable had shown a significant association with mortality in the univariable analysis. The deprivation variable was adjusted for age group and sex and the models with the lowest AIC measure by time point are presented in Table 3 and again show a small but independent, significant effect of the deprivation variable after adjustment. The likelihood ratio tests showed no effect of including interaction terms of age and the Townsend score (P = 0·79) or age and Townsend components (P = 0·39, 0·93, 0·80, 0·95 respectively for unemployment, home ownership, overcrowding and non-car ownership).

In the models examined at six months the AIC measure for % unemployment and age group was little different to that for % households without a car and age group (0·3107 versus 0·3106). In this model the effect on mortality of living in an area with increased unemployment was very similar to that of increasing non-car ownership (OR 1·04 [95% CI 1·01, 1·08]; $P = 0·02$). However when both unemployment and non-car ownership were included in a model and adjusted for age group, neither variable remained statistically significant. A scatter plot (Supplemental Figure S1) showed that while there was a positive relationship between increasing unemployment and increasing non-car ownership in many areas, at the same time there were also many areas where non-car ownership was high but in contrast unemployment was low.

3.2. Regression analysis: Ewing sarcoma

Results for the univariable regression analysis for Ewing sarcoma patients are shown in Supplemental Table S2. Mortality was associated with age, being significantly higher for those aged 20-49 years at diagnosis compared to those aged 0-14 years. This effect was seen at all time points after diagnosis. The effect of age on mortality decreased with elapsed time for those aged 20-39 years but there was no trend for the older age group (40-49 years). For patients aged 15-19 years at diagnosis, mortality was also significantly higher than the youngest age group at one year, three years and five years after diagnosis. Mortality was not shown to be significantly related to any deprivation variable and therefore no multivariable model was considered.

3.3. Area type analysis

The effects of area type on mortality using the first urban/rural measure are shown in Figures 2a (osteosarcoma patients) and 2b (Ewing sarcoma patients). Inner London was used as the baseline comparison group in both analyses. Differences in mortality in the osteosarcoma group seemed to appear away from the major urban areas and into the more remote areas. This was less apparent for the Ewing sarcoma group.

Following these results, the effect of area type on mortality was examined further by adjusting for deprivation factors. Area type was firstly adjusted for age and sex to provide baseline measures and then additionally but separately for Townsend score, unemployment and non-car ownership.

These analyses were carried out for the early mortality periods of three months, six months and one year post diagnosis. There were no interactions between area type and Townsend score in any time period or in either group. In both the osteosarcoma and Ewing sarcoma groups, there appeared to be no additional impact for deprivation at 3 months (data not shown). At six months for the osteosarcoma group, adjusting for Townsend score increased the effect of a small number of areas on mortality but the effect was increased to a greater extent and for an increased number of areas when adjusted for non-car ownership (Supplemental Table S3). In contrast, for Ewing sarcoma patients, these adjustments showed no effect on mortality at six months. For the osteosarcoma group at one year, the effect of area type on mortality increased most extensively when adjusted for either Townsend score or non-car ownership but in general the effect was strengthened more with non-car

ownership (Supplemental Table S4). Adjusting for deprivation factors in the Ewing sarcoma group on mortality at one year appeared to only have an impact on mortality for three area types. These were "other metropolitan cities" when adjusted for Townsend score, OR = 2.56 (95% CI 1·04, 6·29), "remoter urban/rural" when adjusted for Townsend OR = 3·40 (95% CI 1·16, 9·91) and no-car OR = 2·95 (1·01, 8·62) and "small non-metropolitan cities" when adjusted for Townsend, OR = 3·64 (95% CI 1·23, 10·82), unemployment OR = 3·18 (95% CI 1·09, 9·25) and no-car OR = 3·23 (95% CI 1·09, 9·52). Scatter plots showed differences in the relationship between area unemployment and non-car ownership by area type (Supplemental Figure S2).

Using persons per hectare as a measure of urban/rural area type in the osteosarcoma group, showed no statistically significant differences in mortality for any period of follow-up between those areas with density classified as 'very urban', 'urban', 'rural' or 'very rural' compared to 'most urban' (data not shown). Using the same measure for the Ewing sarcoma patients, again there were no statistically significant differences compared to 'most urban' areas but there did appear to be a trend in the ORs showing increasing mortality in less urban and more rural areas for all periods except three months of follow-up (e.g. one year period, 'most urban' OR = 1, 'very urban' OR = 0·85, 'urban' OR = 1·09, 'rural' OR = 1·11, 'most rural' OR = 1·27).

4. Discussion

We have identified socio-economic patterning in early mortality rates for patients aged 0-49 years diagnosed with osteosarcoma in GB. Specifically the study found that for osteosarcoma, mortality at three months, six months and one year after diagnosis was significantly associated with residence in areas of higher unemployment. There were no significant associations with deprivation at three or five years post-diagnosis. There were also no overall significant associations between early mortality for patients diagnosed with Ewing sarcoma and socio-economic deprivation. However, there was some evidence for an effect of deprivation for certain types of area. Increased risk of early death for both osteosarcoma and Ewing sarcoma was linked with residence in less urban and more remote rural areas. There may also be a link with non-car ownership, though it appears that owning a car is not equally essential for access to services in all areas. However, the analyses were ecological and so the findings may not necessarily apply to individuals. The magnitudes of the effects of deprivation and urban or rural area type were much more pronounced for osteosarcoma than for Ewing sarcoma.

For both osteosarcoma and Ewing sarcoma mortality was significantly higher in older age groups (20-49 years) compared to children (0-14 years). The study period, 1985-2008, was mainly prior to the development of dedicated TYA centres in GB. Although specialist bone cancer centres (covering a much wider age range) were already well established, the availability of specialist treatment centres for children could have contributed to lower early mortality for this age group. There were little or no differences between males and females.

There has been little or no improvement in survival from osteosarcoma during the last twenty years [17]. Without major improvements in treatment strategies, delivery of the best available treatment is of vital importance. Key factors that impede optimal treatment include delays in diagnosis, compliance and access to care. All of these factors might be socio-economically determined. Evidence suggests that of all cancer types, the time from first symptom to diagnosis are longest for bone tumour patients of all ages, but especially for TYA [2, 18]. Some recent initiatives by the NCIN and the National Awareness & Early Diagnosis Initiative (NAEDI) have emphasised the importance for early cancer diagnosis to make improvements in patient outcomes [1].

Little research has focussed on delays in diagnosis in patients with bone tumours. However, socio-economic deprivation has been associated with worse survival for the more common cancers, including breast cancer and chronic myeloid leukaemia [19, 20]. The poorer outcomes associated with deprivation for breast cancer were attributed to both diagnostic delays as well as comorbidities. Findings from our present study suggested that residence in areas of greater deprivation (specifically areas with higher rates of unemployment) was associated with worse early mortality for osteosarcoma. Also, residence in less urban and more remote rural areas was associated with increased risk of early death for both osteosarcoma and Ewing sarcoma. One possible interpretation of these findings is that diagnostic delays (patient and/or professional) may be greater in more deprived areas. Other issues may also contribute including distance from a specialist treatment centre (http://www.clicsargent.org.uk/content/long-way-from-home-report). Another study from Germany found greater diagnostic delays in patients who were resident in rural areas [8].

A previous national UK study of osteosarcoma and Ewing sarcoma survival data did not fully investigate socio-economic patterning in survival rates [7]. Another comparative study found lower survival from Ewing sarcoma in UK patients compared with German patients [9]. This finding may be due to delays in referral or differences in treatment regimes. A few studies have examined the pre-diagnostic experiences amongst bone cancer patients. A retrospective interview study from a specialist centre in Birmingham found significant delays, which were attributed to 'professional' delays and not 'patient' delays [21]. However, another study of thirty patients with osteosarcoma around the knee from Malaysia found that delays in diagnosis was associated with both patient and professional delays [22].

A study of adherence to leukaemia maintenance therapy amongst children, adolescents and adults in south-eastern France found that low socio-economic status was associated with non-adherence to treatment [23]. A study from Brazil found that low educational level, but not low income, was associated with treatment compliance for chronic myeloid leukaemia [24]. A study from New York City found that housing needs amongst ethnic minorities was associated with lack of adherence to radiotherapy and chemotherapy [25]. However, access to health care in these three countries is markedly different from the UK, which has universal health insurance coverage. Nevertheless studies of common cancers suggest that access to care may be, at least partially, socio-economically determined, as postulated by the 'inverse care law'. For example, access may be determined by travel time to the treatment centre [26]. One study found that screening for oral cancer was inversely associated with lower uptake

amongst those most at risk [27]. Another study from the UK found that routes to diagnosis for sarcoma patients differ from other cancer [28]. However, access to care is unlikely to be socio-economically determined for children but for young people (ages 15-24 years) this is not the case as only around half are seen in regional specialist centres [29]. There is a need for studies of both compliance and access to care specifically for bone tumours in order to understand fully how these factors affect survival.

In conclusion, this novel study has used a population-based dataset with very high levels of case ascertainment and novel geo-coding of cases to allocate area-based levels of socioeconomic status. However, staging and treatment data were not available. The findings suggest that risk of early death may be socio-economically determined in patients diagnosed with osteosarcoma. There was limited evidence for an effect of deprivation for Ewing sarcoma, but this was confined to limited areas. However, for both osteosarcoma and Ewing sarcoma increasing mortality was associated with less urban and more remote rural areas, suggesting that distance from urban centres may lead to greater risk of early mortality. Further research is needed to fully explore the factors that may have led to this disparity. These include delays in diagnosis (patient or professional), compliance with treatment and access to care. The magnitudes of the disparities suggest that there is much more scope for improvement for osteosarcoma than for Ewing sarcoma.

Conflicts of Interest Statement

There are no conflicts of interest.

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Figure Legends

Figure 1a. Osteosarcoma cohort: Cumulative mortality at time after diagnosis by age group.
(3 year and 5 year follow up restricted to those diagnosed 1985-2006 and 1985-2004 respectively)

Figure 1b. Ewing Sarcoma cohort: Cumulative mortality at time after diagnosis by age group.
(3 year and 5 year follow up restricted to those diagnosed 1985-2006 and 1985-2004 respectively)

Figure 2a. Osteosarcoma: Effect of area on mortality (compared to Inner London)

Figure 2b. Ewing Sarcoma: Effect of area on mortality (compared to Inner London)

Supplemental Table Legends

Supplemental Table 1. Osteosarcoma: Effect of age, sex and area deprivation markers on mortality (univariable analysis) in each time period

Supplemental Table 2. Ewing Sarcoma: Effect of age, sex and area deprivation markers on mortality (univariable analysis) in each time period

Supplemental Table 3. Osteosarcoma: Effect of area (compared to Inner London) on mortality at 6 months post diagnosis, adjusted for age and sex and Townsend score, unemployment or non-car ownership (area sorted by OR when adjusted for age and sex).

Supplemental Table 4. Ewing sarcoma: Effect of area (compared to Inner London) on mortality at 1 year post diagnosis, adjusted for age and sex and Townsend score, unemployment or non-car ownership (area sorted by OR when adjusted for age and sex).

Supplemental Figure Legends

Supplemental Figure 1. Area unemployment and non-car ownership

Supplemental Figure 2. Area unemployment and non-car ownership by area type

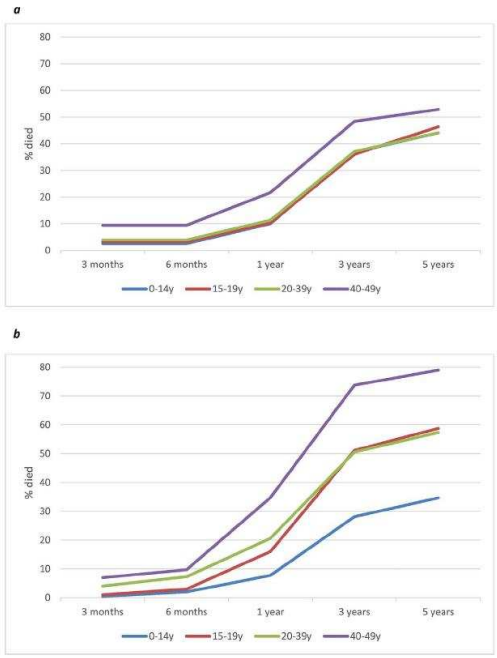

Fig. 1. a) Osteosarcoma cohort: Cumulative mortality at time after diagnosis by age group. (3 year and 5 year follow up restricted to those diagnosed 1985–2006 and 1985–2004 respectively). b) Ewing Sarcoma cohort: Cumulative mortality at time after diagnosis by age group. (3 year and 5 year follow up restricted to those diagnosed 1985–2006 and 1985–2004 respectively).

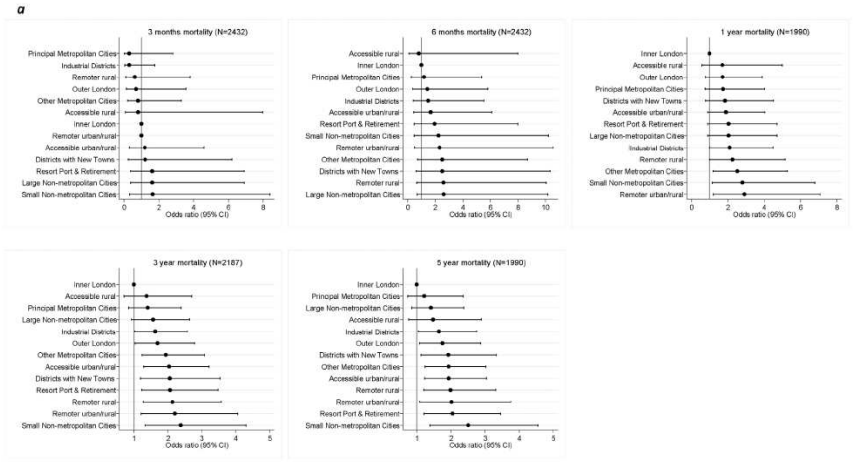

Fig. 2. a) Osteosarcoma: Effect of area on mortality (compared to Inner London). b) Ewing Sarcoma: Effect of area on mortality (compared to Inner London).

Table 1
Demographic patient and area of residence characteristics for patients diagnosed with Osteosarcoma or Ewing Sarcoma 1985–2008. Mortality in each group by period of diagnosis.

	Osteosarcoma N (%)	Ewing Sarcoma N (%)
Males	1416 (58.2)	972 (60.0)
Females	1016 (41.8)	647 (40.0)
Age 0–14 years	786 (32.2)	646 (39.9)
15–19	699 (28.7)	406 (25.1)
20–39	767 (31.5)	495 (30.5)
40–49	180 (7.4)	72 (4.5)
	Median (IQR) (Range)	Median (IQR) (Range)
Townsend score[a]	−1.18 (−3.01, 1.42) (−6.68, 12.34)	−1.17 (−3.15, 1.32) (−6.59, 10.85)
% Unemployment	4.78 (2.94, 7.63) (0.65, 42.7)	4.66 (2.81, 7.6) (0, 35.17)
% HH overcrowded	1.44 (0.88, 2.57) (0, 29.79)	1.45 (0.9, 2.61) (0, 19.74)
% HH without car	28.24 (18.56, 39.79) (3.50, 90.83)	27.62 (17.82, 39.6) (2.36, 84.37)
% HH property not owned	29.50 (20.16, 43.18) (3.24, 98.48)	29.25 (19.94, 42.15) (2.14, 93.69)
Population density (0–49 years)	15246 (5181, 29243) (16, 171820)	14186 (3433, 27502) (13, 159033)
Population density (All age)	22861 (7964, 42371) (25, 234751)	21202 (5236, 39267) (22, 204625)
Inner London	152 (6.3)	62 (3.8)
Outer London	214 (8.8)	127 (7.8)
Principal Metropolitan Cities	172 (7.0)	118 (7.3)
Other Metropolitan Cities	372 (15.3)	257 (15.9)
Large Non-metropolitan Cities	158 (6.5)	113 (6.9)
Small non-metropolitan Cities	93 (3.8)	51 (3.2)
Industrial Districts	340 (14.0)	236 (14.6)
Districts with New Towns	124 (5.1)	76 (4.7)
Resort Port and Retirement	158 (6.5)	78 (4.8)
Accessible Urban/Rural	337 (13.8)	233 (14.4)
Remoter Urban/Rural	90 (3.7)	74 (4.6)
Accessible Rural	62 (2.6)	47 (2.9)
Remoter Rural	160 (6.6)	147 (9.1)

[a] Increase in score = increase in deprivation.

Table 3
Osteosarcoma: Effect of area deprivation markers and age on mortality (multivariable analysis).

Time period	Variable	OR	(95% CI)	p value
≤3 months	% Unemployment	1.06	(1.01, 1.10)	0.02
	Males vs Females	1.20	(0.643, 2.24)	0.56
	Age 0–14 years	–		
	15–19	2.22	(0.752, 6.57)	0.14
	20–39	3.23	(1.17, 8.91)	0.02
	40–49	10.8	(3.67, 31.53)	< 0.001
≤6 months	% Household without car	1.02	(1.00, 1.03)	0.02
	Males vs Females	1.29	(0.840, 1.98)	0.24
	Age 0–14 years	–		
	15–19	1.25	(0.678, 2.33)	0.46
	20–39	1.51	(0.848, 2.69)	0.16
	40–49	4.23	(2.15, 8.28)	< 0.001
≤6 months	% Unemployment	1.04	(1.01, 1.08)	0.02
	Males vs Females	1.29	(0.843, 1.99)	0.23
	Age 0–14 years	–		
	15–19	1.25	(0.673, 2.32)	0.47
	20–39	1.55	(0.868, 2.76)	0.13
	40–49	4.23	(2.16, 8.29)	< 0.001
≤1 year	% Unemployment	1.04	(1.02, 1.06)	0.001
	Males vs Females	1.14	(0.883, 1.47)	0.31
	Age 0–14 years	–		
	15–19	1.02	(0.725, 1.43)	0.90
	20–39	1.12	(0.815, 1.56)	0.46
	40–49	2.57	(1.67, 3.94)	< 0.001