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Geographical and ecological analyses of childhood Wilms' tumours and soft-tissue sarcomas in North West England

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Abstract

The aim of this paper was to study the geographical distribution of Wilms' tumours (WT) and soft-tissue sarcomas (STS) for 0–14 year olds included in a population-based registry from North West England during 1976–2000. Standardised morbidity ratios (SMRs) were calculated. Relationships between incidence rates and small area (ward) population density, ethnic composition, deprivation index and urban–rural status were examined using Poisson regression. There was a non-linear relationship between WT incidence and population density ($P=0.008$), with a higher incidence associated with wards with low deprivation scores ($P=0.02$); and which included a greater proportion of whites ($P=0.01$). For STS, a higher incidence was associated with wards with low deprivation scores ($P=0.04$); and which were 'more rural/less urban' ($P=0.03$). These results are consistent with a role for localised environmental exposures, in combination with lifestyle factors, in the aetiology of WT. For STS, there is some evidence for the involvement of environmental and/or lifestyle factors.

Keywords: Aetiology; Children; Environment; Epidemiology; Lifestyle; Small-area analysis; Soft-tissue sarcoma; Wilms' tumour

1. Introduction

The Manchester Children's Tumour Registry (MCTR) collects incidence data on cancers in children, aged 0–14 years, from a defined geographical region of North West England. Ascertainment is estimated to be close to 100%, even during the early years of the registry [1,2]. Since the national cancer registration system was instituted in the United Kingdom (UK) in the early 1960s, cross-checking with this system has been carried out. Ascertainment of childhood cancers nationally is known to be very high [3].

Reporting practice to the Registry has been consistently good over the 49 years of the MCTR's existence. The registry retains histopathological material and diagnostic re-review is undertaken periodically. The MCTR, therefore, provides a unique data-set for the investigation of incidence patterns over a wide geographical area and time frame.

We have recently reported space-time clustering among cases of Wilms' tumour (WT) and soft-tissue sarcoma (STS) [4] included in the MCTR. The finding of space–time clustering points to the involvement of environmental factors in the aetiology of these particular groups of tumours even though, for both, genetic factors are also known to be involved [5,6]. Certain geographically varying exposures have been associated with a higher incidence of WT and STS. Pesticides have been linked to an increased risk of WT [7–9] and STS in children [10], whilst dioxin, chlorophenol and benzene

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have all been linked to an increased risk of STS in adults [11–14]. If these or other similar, geographically varying agents are involved in the aetiology of WT or STS (or both), then case exposure to the agents may be expected to vary according to the location of residence. Thus, the distributions of the cases may exhibit some systematic geographical variations. In order to explore further the role that geographically varying environmental factors may have in the aetiology of WT and STS, we have calculated standardised morbidity ratios (SMRs); performed tests for extra-Poisson variation to look for non-random geographical distributions [15–17] and tests for spatial autocorrelation to look for the proximity of areas of high (or low) incidence [18]; and examined the relationship between incidence rates and population density, measures of ethnic composition, measures of the level of deprivation and urban–rural status, all at the small area (census ward) level.

2. Patients and methods

The diagnostic groups included in this study comprise WT, STS and rhabdomyosarcoma (RMS) separately. All such cases, aged 0–14 years, diagnosed between 1 January 1976 and 31 December 2000, registered with the MCTR and resident in the counties of Lancashire and Greater Manchester were analysed.

The hierarchy of census small areas, for which population data are available, is as follows (largest to smallest): county (the childhood population ranged from 240 240 to 548 537); census district (the childhood population ranged from 8976 to 87 350); and census ward (the childhood population ranged from 117 to 4194). In this study, analyses were performed at the census district and census ward levels. During the study period, there were two national censuses. Two time periods (1976–1985; and 1986–2000) were considered for some analyses, because: (i) small-area census population data were only available from the 1981 and 1991 censuses [19,20]; and (ii) they provided sufficiently long time periods to allow adequate case numbers for analyses, but not so long for population shifts to dilute any area-specific effects. In addition, there were some boundary changes at the ward level, but not at the district level, between the 1981 and 1991 censuses. Populations were assumed to be constant within the time periods. No allowance for death and migration was made.

The reference address for all cases was the address at diagnosis. There were 24 districts in the study period, 519 wards in the 1981 census and 518 wards in the 1991 census. Cases were allocated to wards and districts [19,20].

Since no external standard rates were available, it was necessary to use MCTR data to generate standard rates for each diagnostic group (WT, STS and RMS). The iterative procedure, due originally to Mantel and Stark [21], but simplified by Breslow and Day [22] was used. Observed and expected numbers of cases were calculated by age–gender–area strata. These were then summated to obtain SMRs for each area.

Ward characteristics were derived from the small area statistics of the censuses [23,24]. These characteristics were population density, ethnic composition, level of deprivation and urban-rural status. The Townsend score for deprivation at the ward level (and not individual level) was calculated [25]. This is a combination of four census measures: unemployment, household access to a car, home ownership and household overcrowding. Wards were categorised as urban or rural using the Office for National Statistics (ONS) classification [26]. This is based on the predominant land use for the ward.

The Potthoff–Whittinghill test [15–17] was used to test for departures from the Poisson assumption at the district and ward levels, which would indicate a non-random distribution of cases. The Smans test [18] was used to test for spatial autocorrelation at the district and ward levels, which would indicate adjacency of areas with high (or low) rates.

Area-based analyses were carried out. Statistical analyses (ecological regressions) were performed using Poisson regression in Generalized Linear Interactive Modelling Package (GLIM) [27]. The number of cases observed in each ward was the dependent variable, and the log of the expected number of cases was used as the offset. The ecological (independent) variables were the stratified census-derived ward characteristics.

Continuous variables were cut into strata so that each stratum contained an (approximately) equal proportion of the childhood population. The following ward variables were cut into quintiles: population density, childhood population density, percentage white population, percentage Pakistani population, percentage Indian population (these were the three largest ethnic groups), the Townsend deprivation score and its components. As most wards were entirely urban, the urban-rural score formed three groups, comprising approximately 60, 20 and 20% of the childhood population, respectively.

A series of univariate analyses was carried out. For each quintile, the observed (O) and expected (E) numbers of cases were obtained and the ratio O/E was calculated. A relative risk (RR) was calculated, for each quintile, by comparing the ratio O/E with the lowest value of O/E. The quintile with the lowest value of O/E was assigned a RR of 1. Confidence intervals (CIs) were obtained using GLIM4 [27]. A test for linear trend (and a quadratic effect for certain analyses) was performed. Those variables found to have a statistically significant effect in the univariate models were then included in multivariate models. Statistical significance was taken as $P < 0.05$ throughout the analyses.

3. Results

The observed numbers of cases by age-group, time period, diagnostic group and gender are given in Table 1. The person-years at risk for the analyses are also presented.

3.1. Wilms' tumour (WT)

The Potthoff–Whittinghill test indicated weak evidence of a departure from the Poisson assumption at the district level ($P = 0.06$). The Smans test indicated no evidence for spatial autocorrelation. However, one district (Fig. 1a,b) had a significantly raised SMR for both 1976–1985 and 1986–2000 ('V', SMR = 371, 1976–1985 and SMR = 333, 1986–2000). Further analyses at the ward level showed evidence for a departure from Poisson variability for the first time period only ($P = 0.01$). This indicates that high rates are confined to very localised small areas for limited time periods.

Ecological analyses showed a number of interesting results at the ward level. There was a statistically significant non-linear relationship between the incidence of WT and population density quintile ($P = 0.008$ for quadratic effect), with the highest rates for both the least and most densely populated quintiles (Table 2). There were significant linear relationships between the incidence of WT and the percentage of whites in the ward (Table 2), the Townsend deprivation score (Table 3) and all four components of the Townsend deprivation score (Table 3). Higher rates were observed in wards containing greater percentages of whites (Table 2), and in less deprived, more affluent wards (Table 3).

The explanatory (ecological) variables, which were significant in the univariate analyses, were highly intercorrelated. For the period 1976–2000, bivariate analyses showed that, after allowing for population density, one component of the Townsend deprivation score, percentage of homes not owner-occupied, was significant

Table 1
Observed cases and person years at risk, by diagnostic group (Wilms' tumour (WT), soft tissue sarcoma (STS) and rhabdomyosarcoma (RMS)), time period, age–group and gender

	WT	STS	RMS	Person years at risk
1976–1985				
0–4 years	43	23	16	2402260
5–9 years	7	11	8	2667820
10–14 years	0	12	8	3235580
Male	26	23	17	4263330
Female	24	23	15	4042330
Total	50	46	32	8305660
1986–2000	WT	STS	RMS	Person years at risk
0–4 years	58	33	22	4087665
5–9 years	9	21	14	3874350
10–14 years	3	25	7	3587340
Male	35	39	21	5911845
Female	35	40	22	5637510
Total	70	79	43	11549355

Table 2
Wilms' tumours analyses (quintile 1 = lowest; quintile 5 = highest): RRs and 95% CIs

Quintile	Population density[a,b]	Childhood population density[a,c]	Percentage white[d,e]	Percentage Pakistani[d,f]	Percentage Indian[d,g]	Percentage rural[d,h]
1	RR = 2.19 (1.18–4.06)	RR = 2.38 (1.30–4.37)	RR = 1.12 (0.45–2.75)	RR = 3.11 (1.23–7.82)	RR = 1.31 (0.57–2.98)	RR = 1
2	RR = 1.44 (0.74–2.80)	RR = 1.18 (0.59–2.35)	RR = 1	RR = 2.99 (1.19–7.53)	RR = 1.48 (0.66–3.29)	
3	RR = 1.41 (0.73–2.73)	RR = 1.84 (0.98–3.45)	RR = 1.46 (0.63–3.43)	RR = 2.31 (0.89–6.02)	RR = 1.71 (0.78–3.74)	
4	RR = 1	RR = 1	RR = 2.17 (0.98–4.80)	RR = 1	RR = 1	RR = 1.09 (0.59–2.00)
5	RR = 2.11 (1.14–3.90)	RR = 1.80 (0.96-3.38)	RR = 2.20 (0.99-4.86)	RR = 2.27 (0.87-5.92)	RR = 1.47 (0.66-3.27)	RR = 1.24 (0.69-2.24)
Test for linear trend	$P = 0.61$	$P = 0.21$	$P = 0.01$	$P = 0.07$	$P = 0.90$	$P = 0.48$

RR, relative risk; 95% CI, 95% Confidence Interval.
[a] data available for wards: 1976–2000.
[b] Quintile boundaries: 1 (5–1245); 2 (1246–2158); 3 (2158–3176); 4 (3178–4356); 5 (4367–10420) persons per km^2.
[c] Quintile boundaries: 1 (1–251); 2 (253–434); 3 (437–653); 4 (653–887); 5 (894–3829) children per km^2.
[d] data only available for Wards: 1986–2000.
[e] Quintile boundaries: 1 (21.9–93.7); 2 (93.8–97.6); 3 (97.6–98.6); 4 (98.6–99.2); 5 (99.2–100) percentage of population.
[f] Quintile boundaries: 1 (0–0.05); 2 (0.05–0.1); 3 (0.1–0.4); 4 (0.4–1.9); 5 (2.0–50.4) percentage of population.
[g] Quintile boundaries: 1 (0–0.1); 2 (0.1–0.2); 3 (0.2–0.4); 4 (0.4–1.0); 5 (1.0–48.2) percentage of population.
[h] Quintile boundaries: 1 (all urban); 4 (3.0–6.9); 5 (7.0–100) percentage of 'rural' enumeration districts.

Table 3
Wilms' tumours analyses (quintile 1 = lowest, quintile 5 = highest, data available for wards: 1976–2000), RRs and 95% CIs

Quintile	Townsend score[a]	Unemployment[b]	Households without access to a car[c]	Tenancy[d]	Household overcrowding[e]
1	RR = 1.96 (1.08–3.56)	RR = 2.28 (1.23-4.24)	RR = 1.83 (1.02-3.29)	RR = 2.47 (1.35-4.54)	RR = 1.95 (1.08-3.53)
2	RR = 1.67 (0.91–3.09)	RR = 1.81 (0.96-3.44)	RR = 1.59 (0.87-2.89)	RR = 1.63 (0.85-3.13)	RR = 1.34 (0.71-2.52)
3	RR = 1.69 (0.92–3.10)	RR = 1.65 (0.86–3.15)	RR = 1.55 (0.85–2.82)	RR = 1.65 (0.87–3.15)	RR = 1.87 (1.04–3.38)
4	RR = 1.30 (0.69–2.47)	RR = 1.86 (0.99–3.49)	RR = 1.22 (0.65–2.29)	RR = 1.64 (0.86–3.12)	RR = 1
5	RR = 1	RR = 1	RR = 1	RR = 1	RR = 1.13 (0.59–2.16)
Test for linear trend	$P = 0.02$	$P = 0.02$	$P = 0.03$	$P = 0.006$	$P = 0.04$

RR, Relative Risk; 95% CIs, 95% Confidence Interval.

[a] Quintile boundaries: *1976–1985* 1 (−5.7 to −2.4); 2 (−2.3 to −0.7); 3 (−0.7 to 1.5); 4 (1.5 to 4.0); 5 (4.1 to 13.1); *1986–2000* 1 (−5.0 to −2.3); 2 (−2.3 to −0.7); 3 (−0.7 to 1.3); 4 (1.3 to 4.3); 5 (4.3 to 14.7).

[b] Quintile boundaries: *1976–1985* 1 (1.2 to 7.1); 2 (7.1 to 9.5); 3 (9.5 to 12.1); 4 (12.1 to 16.3); 5 (16.6 to 33.5) percent; *1986–2000* 1 (1.8 to 6.0); 2 (6.0 to 8.2); 3 (8.2 to 10.8); 4 (10.8 to 16.7); 5 (16.7 to 39.2) percent.

[c] Quintile boundaries: *1976–1985* 1 (9.0 to 30.7); 2 (30.7 to 40.8); 3 (41.0 to 49.3); 4 (49.4 to 58.8); 5 (58.9 to 86.0) percent; *1986–2000* 1 (4.6 to 25.0); 2 (25.1 to 34.1); 3 (34.2 to 42.2); 4 (42.3 to 51.9); 5 (51.9 to 81.4) percent.

[d] Quintile boundaries: *1976–1985* 1 (2.8 to 20.3); 2 (20.3 to 30.3); 3 (30.3 to 39.8); 4 (39.8 to 55.0); 5 (55.2 to 99.5) percent; *1986–2000* 1 (1.7 to 16.1); 2 (16.1 to 24.6); 3 (24.8 to 33.7); 4 (33.8 to 48.4); 5 (48.5 to 97.9) percent.

[e] Quintile boundaries: *1976–1985* 1 (0.2 to 1.9); 2 (1.9 to 2.8); 3 (2.8 to 3.8); 4 (3.8 to 5.1); 5 (5.1 to 21.8) percent; *1986–2000* 1 (0 to 1.0); 2 (1.0 to 1.5); 3 (1.5 to 2.1); 4 (2.1 to 2.9); 5 (3.0 to 21.0) percent.

($P = 0.02$). For the period 1986–2000, bivariate analyses showed that, after allowing for population density, the Townsend deprivation score was significant ($P = 0.04$), due specifically to the percentage of overcrowded households ($P = 0.03$) and percentage of homes not owner-occupied ($P = 0.04$).

3.2. Soft-tissue sarcomas (STS)

The Potthoff–Whittinghill test indicated no departure from the Poisson assumption at the district level ($P = 0.79$). However, there was a marginal, statistically significant evidence for spatial autocorrelation at the ward level ($P = 0.09$ for 1976–1985). This indicates a geographical proximity of wards with high or low rates. There were no raised SMRs for 1976–1985 (Fig. 1c). One district (Fig. 1d) had a significantly raised SMR for 1986–2000 ('T': SMR = 327). Further analyses at the ward level showed no departure from the Poisson distribution.

Ecological analyses showed that there was a significant difference in the incidence of STS between 'urban' and 'rural' wards (Table 4) and there was a significant linear relationship between the incidence of STS, the Townsend deprivation score and one component of the Townsend deprivation score—unemployment (Table 5). Higher rates were observed for the more 'rural' wards (Table 4) and in less deprived, more affluent wards, particularly those with lower unemployment (Table 5).

3.3. Rhabdomyosarcomas (RMS)

The Potthoff–Whittinghill test indicated no departure from the Poisson assumption at the district level. In addition, there was no significant evidence for spatial autocorrelation at the district level nor at the ward level. No districts had significantly high (or low) SMRs in either time period. Further analyses at the ward level again showed no departure from the Poisson distribution.

Ecological analyses showed no statistically significant relationships (data not shown).

4. Discussion

This is the first analysis to identify ecological relationships for WT and STS, which support the involvement of environmental or lifestyle factors in aetiology. The study has only been made possible by the availability of high quality and consistent population-based diagnostic and residential address data. Since ascertainment is close to 100%, there is no reason to suspect that there is any artefactual bias by area of diagnosis.

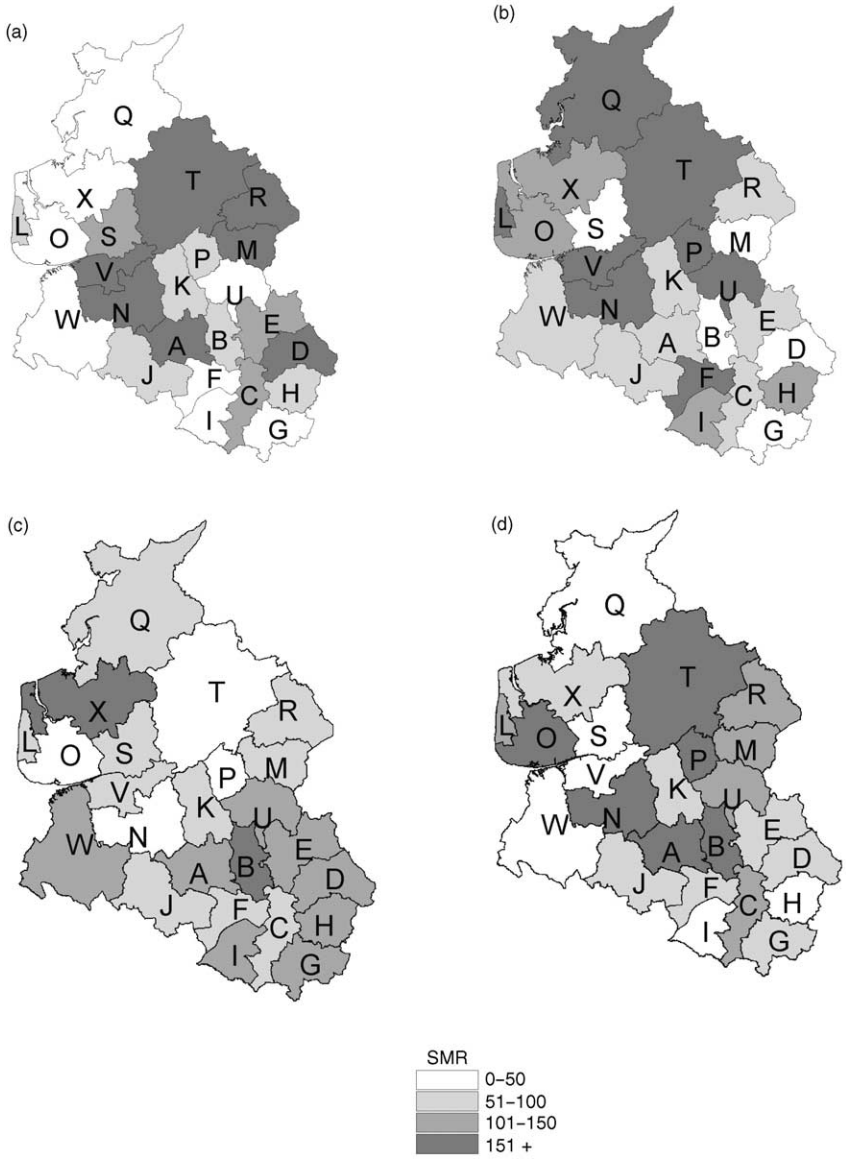

Fig. 1. Standardised morbidity ratios (SMRs) by census district for: (a) Wilms' tumours, 1976–1985; (b) Wilms' tumours, 1986–2000; (c) soft-tissue sarcomas, 1976–1985; (d) soft-tissue sarcomas, 1986–2000.

Several methodological points should be mentioned. First, SMRs were calculated using the indirect standardisation method of Breslow and Day [21], because no external rates were available. These estimates only allow comparison within the population and no attempt should be made to compare the point estimates with other studies [28]. Second, there is a tendency for those areas with few events to give extreme values owing to Poisson variation. Such areas are then given undue attention. To circumvent this problem, the SMRs may be 'adjusted' using the empirical Bayes method of Clayton and Kaldor [29]. However, due to small numbers, this approach added little to the analysis.

The ethnic composition of the ward is not related to individual characteristics and should only be regarded as an ecological measurement. Areal-level data have been assigned to individual cases. Caution should be exercised when making inferences from such grouped data concerning individual data. Specifically, such studies have limitations due to ecological bias. Multiple confounding factors may exist, which have the same pattern of geographical variation [30]. Finally, the analysis is based on residence at diagnosis. The residence at time of birth may be more relevant as regards putative aetiological exposures [4]. However, the use of residence at diagnosis (for which we have complete data) is unlikely to introduce much bias, since there is a close correlation between the distribution of the addresses at birth and the addresses at diagnosis for the levels of aggregation considered in the present study. For all MCTR cases, for which both birth and diagnosis addresses were available, 59% were less than 1 km apart and 91% were less than 10 km

Table 4
Soft tissue sarcomas analyses, (quintile 1 = lowest; quintile 5 = highest) RRs and 95% CIs

Quintile	Population density[a,b]	Childhood population density[a,c]	Percentage white[d,e]	Percentage Pakistani[d,f]	Percentage Indian[d,g]	Percentage rural[d,h]
1	RR = 1.76 (0.98–3.15)	RR = 1.60 (0.93–2.76)	RR = 1.02 (0.46–2.26)	RR = 2.14 (0.97–4.74)	RR = 1.31 (0.65–2.64)	RR = 1
2	RR = 1.58 (0.87–2.86)	RR = 1.20 (0.67–2.15)	RR = 1.66 (0.81-3.39)	RR = 1.89 (0.84–4.23)	RR = 1.07 (0.52–2.21)	
3	RR = 1.21 (0.65–2.26)	RR = 1.04 (0.57–1.89)	RR = 1	RR = 1	RR = 1.02 (0.48–2.13)	
4	RR = 1	RR = 1	RR = 1.33 (0.63–2.82)	RR = 2.35 (1.08–5.12)	RR = 1.28 (0.64–2.58)	RR = 1.77 (1.04–3.01)
5	RR = 1.45 (0.80–2.66)	RR = 1.12 (0.62–2.02)	RR = 1.59 (0.77–3.27)	RR = 1.44 (0.62–3.37)	RR = 1	RR = 1.72 (1.00–2.96)
Test for linear trend	$P = 0.18$	$P = 0.12$	$P = 0.44$	$P = 0.50$	$P = 0.66$	$P = 0.03$

RR, Relative Risk; 95% CIs, 95% Confidence Interval.
[a] Data available for wards:1976–2000;
[b] Quintile boundaries: 1 (5–1245); 2 (1246–2158); 3 (2158–3176); 4 (3178–4356); 5 (4367–10420) persons per km^2.
[c] Quintile boundaries: 1 (1–251); 2 (253–434); 3 (437–653); 4 (653–887); 5 (894–3829) children per km^2.
[d] Data only available for wards: 1986–2000
[e] Quintile boundaries: 1 (21.9–93.7); 2 (93.8–97.6); 3 (97.6–98.6); 4 (98.6–99.2); 5 (99.2–100) percentage of population.
[f] Quintile boundaries: 1 (0–0.05); 2 (0.05–0.1); 3 (0.1–0.4); 4 (0.4–1.9); 5 (2.0–50.4) percentage of population.
[g] Quintile boundaries: 1 (0–0.1); 2 (0.1–0.2); 3 (0.2–0.4); 4 (0.4–1.0); 5 (1.0–48.2) percentage of population.
[h] Quintile boundaries: 1 (all urban); 4 (3.0–6.9); 5 (7.0–100) percentage of 'rural' enumeration districts.

Table 5
Soft tissue sarcomas analyses (quintile 1 = lowest; quintile 5 = highest, data available for wards: 1976–2000), RRs and 95% CIs

Quintile	Townsend score[a]	Unemployment[b]	Households without access to a car[c]	Tenancy[d]	Household overcrowding[e]
1	RR = 1.88 (1.00–3.53)	RR = 2.01 (1.10–3.67)	RR = 1.55 (0.86–2.82)	RR = 1.65 (0.92–2.97)	RR = 1.57 (0.86–2.85)
2	RR = 2.33 (1.27–4.28)	RR = 2.05 (1.12–3.73)	RR = 1.88 (1.06–3.33)	RR = 1.53 (0.84–2.77)	RR = 1.81 (1.02–3.23)
3	RR = 1.51 (0.78–2.90)	RR = 1.48 (0.78–2.80)	RR = 1.37 (0.74–2.52)	RR = 1.63 (0.90–2.93)	RR = 1.26 (0.68–2.35)
4	RR = 1.86 (0.99–3.50)	RR = 1.46 (0.77–2.76)	RR = 1.30 (0.70–2.41)	RR = 1.24 (0.67–2.32)	RR = 1.48 (0.81–2.70)
5	RR = 1	RR = 1	RR = 1	RR = 1	RR = 1
Test for linear trend	$P = 0.04$	$P = 0.009$	$P = 0.06$	$P = 0.07$	$P = 0.10$

RR, Relative Risk; 95% CIs, 95% Confidence Interval.
[a] Quintile boundaries: *1976–1985* 1 (−5.7 to −2.4); 2 (−2.3 to −0.7); 3 (−0.7 to 1.5); 4 (1.5 to 4.0); 5 (4.1 to 13.1); *1986–2000* 1 (−5.0 to −2.3); 2 (−2.3 to −0.7); 3 (−0.7 to 1.3); 4 (1.3 to 4.3); 5 (4.3 to 14.7).
[b] Quintile boundaries: *1976–1985* 1 (1.2 to 7.1); 2 (7.1 to 9.5); 3 (9.5 to 12.1); 4 (12.1 to 16.3); 5 (16.6 to 33.5) percent; *1986–2000* 1 (1.8 to 6.0); 2 (6.0 to 8.2); 3 (8.2 to 10.8); 4 (10.8 to 16.7); 5 (16.7 to 39.2) percent.
[c] Quintile boundaries: *1976–1985* 1 (9.0 to 30.7); 2 (30.7 to 40.8); 3 (41.0 to 49.3); 4 (49.4 to 58.8); 5 (58.9 to 86.0) percent; *1986–2000* 1 (4.6 to 25.0); 2 (25.1 to 34.1); 3 (34.2 to 42.2); 4 (42.3 to 51.9); 5 (51.9 to 81.4) percent.
[d] Quintile boundaries: *1976–1985* 1 (2.8 to 20.3); 2 (20.3 to 30.3); 3 (30.3 to 39.8); 4 (39.8 to 55.0); 5 (55.2 to 99.5) percent; *1986–2000* 1 (1.7 to 16.1); 2 (16.1 to 24.6); 3 (24.8 to 33.7); 4 (33.8 to 48.4); 5 (48.5 to 97.9) percent.
[e] Quintile boundaries: *1976–1985* 1 (0.2 to 1.9); 2 (1.9 to 2.8); 3 (2.8 to 3.8); 4 (3.8 to 5.1); 5 (5.1 to 21.8) percent; *1986–2000* 1 (0 to 1.0); 2 (1.0 to 1.5); 3 (1.5 to 2.1); 4 (2.1 to 2.9); 5 (3.0 to 21.0) percent.

apart. Indeed, for the period 1976–2000, 68% of cases were diagnosed in the same ward as they were born and 82% of cases were diagnosed in the same ward as they were born or in a ward adjacent to the ward in which they were born.

The ecological analyses have shown an increased incidence of WT in less deprived wards and wards with a greater proportion of whites. Curiously, though, the highest incidence rates were found in both the least densely populated quintile and the most densely popu-

lated quintile. The geographical distribution points to a very high incidence of WT at very localised geographical points. These results support a potential role for both environmental and lifestyle factors in the aetiology of WT.

The non-linear relationship of WT incidence with population density is difficult to explain. The higher incidence with lower population density is consistent with the higher incidence of WT in less deprived wards and wards with a greater proportion of whites. The higher incidence with higher population density may point to an environmental factor that is present in both less densely and more densely populated areas or common lifestyle factors. The percentages of whites in wards in the lowest quintile ranged from 21.9 to 93.7%, and in the highest quintile from 99.2 to 100%. The percentages of Pakistanis in wards in the lowest quintile ranged from 0.0 to 0.05%, and in the highest quintile from 2.0 to 50.4%, with a highly skewed distribution. That is, even in the highest quintile, there were very few wards with large percentages of Pakistanis. Thus, the differences in incidence with ethnic composition of the ward should be interpreted as mainly reflecting some aspect of the socio economic make-up of the wards and should not be interpreted as being largely due to genetic factors. For example, there is a high correlation between the level of deprivation and ethnic composition of the wards; and there is a high correlation between greater population density and greater deprivation.

Even though the geographical distribution of RMS showed some heterogeneity, the ecological analyses found no significant relationships. For the STS, the ecological analyses provided evidence that the rates were higher in areas of less deprivation; and more rural/less urban areas. There is a correlation between the level of rurality and level of deprivation. Thus, these results support both environmental factors and lifestyle factors, but these are unlikely to be the same as those acting for WT.

It is of interest to note that both WT and STS exhibited space–time clustering, based on time and place of birth in recent analyses of data from the MCTR for the period 1954–1998 [4]. Addresses were classified as being located in more densely populated areas, or less densely populated areas. For WT, the space–time clustering was only present for space-time pairs involving at least one case from a less densely populated area. For STS, the space-time clustering was stronger for space-time pairs involving at least one case from a more densely populated area, than for space–time pairs involving at least one case from a less densely populated area.

In general, for WT, the geographical and ecological analyses are consistent with the reported pattern of space–time clustering. There is evidence for some localised aggregation or geographical clustering (extra-Poisson variation at the ward and district levels) for WT. The incidence of WT was greatest in less densely populated wards. The incidence in such wards is correlated with the incidence in wards with more whites, less Pakistanis and lower deprivation scores. However, there was an apparent inconsistency between the results, because higher incidence was also observed in the most densely populated wards. The space–time clustering analysis was based on the address at birth, whereas the present geographical study is based on the address at diagnosis. Nevertheless, there is a close correlation between the distributions of the addresses at birth and the addresses at diagnosis for the levels of geographical aggregation considered in the present study. Thus, there is supportive evidence for the role of two aetiological mechanisms. The first mechanism would involve a localised environmental exposure in the more affluent, less densely populated areas. The second mechanism would involve an environmental or lifestyle factor in more densely populated areas.

Comparing the two sets of results (space–time clustering and ecological analyses) for STS, there is some consistency between them. Space–time clustering was more marked in pairs involving at least one case from a more densely populated area than for pairs involving at least 1 case from a less densely populated area. The incidence of STS was greatest in less urban/more rural wards and in wards with lower deprivation scores. However, there was no direct relationship with the ward population density level. Even so, there is supportive evidence for the role of a localised environmental exposure that is present to a greater degree in the more affluent, more rural/less urban areas. The presence of this putative exposure may also be related to lifestyle factors.

Putative agents which may cause geographical variations in incidence include electrical power lines, traffic pollution, agrochemicals and factory emissions. Recent studies from Brazil [7], Norway [8] and the UK [9] have linked parental exposure to pesticides with increased risk of WT in the child. The evidence, from the present analysis of a small excess in the most densely populated quintile, may point to other chemical exposures common to both rural and inner city areas or two different agents. However, the association with level of deprivation may be indicative of a role for lifestyle factors. For STS, there is also a possible contribution from lifestyle factors, because of the association with the level of deprivation. Case–control studies in children have found statistically significant excesses of STS with home pesticide use [10], whilst case–control studies of adults have found statistically significant excesses of STS with dioxin exposure [11,12] and chlorophenol exposure [13].

In summary, we have found geographical heterogeneity in WT and STS. For WT, there was a higher incidence in less deprived wards and wards containing a higher proportion of whites. For STS, there was a higher incidence in less deprived wards and more rural/less urban wards. For both WT and STS, this evidence

would point to environmental factors as potential aetiological agents, or lifestyle factors. These are unlikely to be the same for WT as for STS. However, there is also a possibility that the results for both WT and STS may be chance findings and the associations need to be confirmed by other studies, using independent data. The results are based on ecological analyses and caution should be exercised when interpreting the results at the individual level. The results provide the basis for more targeted studies of aetiology.

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