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# Atopic dysfunction and risk of central nervous system tumours in children

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ABSTRACT

Risk factors for central nervous system (CNS) tumours in children remain largely unknown. Evidence of an inverse relationship between atopy and tumour development exists in adults but little is known about childhood tumours. This study aims to examine the risk of childhood CNS tumours given a history of eczema and asthma.

Cases of children diagnosed with CNS tumours ($n = 575$) and controls ($n = 6292$) from the UK Childhood Cancer Study (UKCCS) were analysed using conditional logistic regression comparing reported histories of allergic disease.

Asthma was statistically significantly and negatively associated with all CNS tumours (odds ratios, OR 0.75, confidence of interval, $CI_{95\%}$: 0.58–0.97), though this was not observed for eczema (OR 0.94, $CI_{95\%}$: 0.74–1.18). Individuals who had suffered both asthma and eczema showed the most significant reduction in risk (OR 0.48, $CI_{95\%}$: 0.28–0.81). Analysis by tumour subtype showed the strongest effect for the medulloblastoma/PNET group.

These results may have a biological explanation with raised immunosurveillance in atopic individuals protecting against the development of brain tumours. Alternative explanations might include bias, reverse causality or confounding.



## 1. Introduction

Central nervous system (CNS) tumours comprise approximately 20% of all childhood cancers in Europe[1], making them the second most common group of childhood malignancies after leukaemia. Pathology of childhood CNS tumours is distinct from those of adults[2]. Attempts to identify underlying environmental risk factors have largely been unsuccessful with only ionising radiation known to confer an increased risk[3]. Rare genetic disorders such as neurofibromatosis I, Turcot's syndrome and Gorlin's syndrome can also predispose children to CNS tumours, but have been observed in less than 5% of cases[4,5].

Atopy is allergic hypersensitivity stemming from the overproduction of IgE antibodies, typically associated with a Th2 response against common environmental allergens, resulting from an imbalance between the Th1 and the Th2 driven immune responses[6]. Atopy has a complex genetic component [7] and is also influenced by environmental exposures[8].

Atopic individuals are at increased risk of allergic diseases such as asthma, eczema and allergic rhinitis (hay fever), any or all of which can be indicators of atopic dysfunction. The

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prevalence of asthma [9], eczema and allergic rhinitis[10] has increased in developed countries in recent years, with the UK consistently found to have among the highest levels worldwide[9–11]. The reasons behind this relatively recent trend are not fully understood, though the hygiene hypothesis has some support[12]. This proposes that lower levels of microbial and viral exposure early in life are responsible for the increase in prevalence of allergic disease.

Possible links between atopy and cancer have been widely investigated [13]. Consistent negative associations have been observed with adult brain tumours[14–20]. Decreased risk of neuroblastoma in children has also been associated with atopy, although results did not attain significance[21]. However, there is a lack of published studies addressing the issue of atopy and the risk of childhood CNS tumours, the present study seeks to address this by utilising data from the UK Childhood Cancer Study (UKCCS).

## 2. Patients and methods

The UKCCS is a population-based case–control study set up with the aim of identifying risk factors for childhood cancer. Full details are described elsewhere[22]. Briefly, UK children diagnosed with cancer before 15 years of age were eligible for the study, which recruited subjects from 1991 to 1994 in Scotland and 1992–1996 in England and Wales. Following histopathological review CNS tumours were categorised into subgroups according to ICD-O morphology codes[22]; details are in Table 1.

Two controls were selected at random for each case from health authorities (England and Wales) or health boards (Scotland), individually matched by birth month/year and region. Non-participating controls were replaced until 2 controls were interviewed. A discussion of deprivation and participation in the study is provided by Law and colleagues[23].

Data were collected from personal interviews of mothers using the same *pro forma* for cases and controls. Mothers reported the history of their child's allergic disease as part of a questionnaire including medical history of the index child, maternal obstetric history, and social contact history.

The following definitions of allergic disease were used as explanatory variables:

(1) *Asthma*: The first version of the questionnaire (January 1992) included a single question on asthma 'Has (*name*) ever had asthma/wheezy bronchitis?' and no questions regarding eczema.The revised (January 1993) questionnaire incorporated a new section on allergic disease replacing the single asthma question. This included 'Has your child *ever* had asthma?' the response to this question in addition to the response to the single question in the first questionnaire provided the indicator variable for asthma in our analysis.

(2) *Wheezing:* The revised questionnaire also introduced detailed questions on wheezing: 'Has your child *ever* had wheezing or whistling in the chest at any time?' with further questions regarding the detail of wheezing if a positive answer was given. This question was asked alongside the asthma question discussed above. Responses were combined and categorised into three groups according to wheeze severity: none, mild/moderate and severe. Individuals were assigned a numerical score based on answers given to the additional questions if parents reported wheezing or whistling in the chest. Children reported by their mothers to have wheezed (yes/no) were given an initial score of 1, and scores were added as follows; the number of attacks suffered in the 12 months following wheeze onset (0 = 0, 1–3 = 1, 4+ = 2) and whether or not the individual had ever suffered limitation of speech or sleep disturbance (both no = 0, yes = 1). The final range of scores was therefore 0–5. Approximately, one-third of individuals reported to have wheezed had scores of 4 or 5 (485/1463 controls and 33/94 cases),

**Table 1 – Distribution of CNS tumour subgroups by age and sex**

| | Diagnosis age (years) | | Sex (⩾2 years only) | | % of tumours in study |
|---|---|---|---|---|---|
| | <2 | ⩾2 | Male (%) | Female (%) | |
| Controls | 1306 | 6292 | 3566 (56.7) | 2726 (43.3) | – |
| All CNS tumours | 108 | 575 | 287 (49.9) | 288 (50.1) | 100 |
| Glioma | 39 | 326 | 150 (46.0) | 176 (54.0) | 56.7 |
| Pilocytic astrocytoma[a] | 18 | 150 | 69 (46.0) | 81 (54.0) | 26.1 |
| Medulloblastoma/PNET[b] | 31 | 132 | 76 (57.6) | 56 (42.4) | 23.0 |
| Epyndymoma | 17 | 52 | 29 (55.8) | 23 (44.2) | 9.0 |
| Other CNS tumours | 21 | 65 | 32 (49.2) | 33 (50.8) | 11.3 |

*ICD-O morphology (M) codes for subgroups*

| | |
|---|---|
| Glioma | 9380-1, 9400-60, 9382, 9384, 9841 |
| Pilocytic astrocytoma | 9421/3 |
| Medulloblastoma/PNET | 9470-80 |
| Epyndymoma | 9383, 9390-4 |
| Other CNS tumours | Other morphology not listed above in topography C70–C72 (excluding germ cell tumours) |

Central nervous system tumours are represented in the topography codes C70–C72.
a Subgroup of glioma.
b Primitive neuroectodermal tumours.

these individuals comprise the 'severe wheeze' group, and individuals with scores of 1–3 make up the 'mild/moderate' group.

(3) *Eczema:* 'Has your child *ever* had eczema?' the yes/no response to this question was used as the explanatory indicator variable for eczema and was present in the revised questionnaire only.

(4) *Early onset flexural rash*: A separate group of questions concerning history and severity of any persistent rash were also included. A variable describing the presence of early onset flexural rash was defined as an additional explanatory variable. This was based on published criteria[24] shown to be a good indicator of atopic eczema [25]; using answers given in the questionnaire indicating the presence of itchy rash with a history of flexural involvement and onset before 2 years of age.

Both mothers and fathers were interviewed about their own medical history (including asthma), employment history, residential history and social habits. Parental history of asthma was also used as an indicator variable, defined as either parent reporting developing asthma before 14 years of age. If data were unavailable for either parent, the value was recorded as missing.

For a subset of the children, data were available from primary care (general practice (GP)) records from 3 UKCCS regions. Data describing whether the child's medical notes contained a GP diagnosis of asthma, were available for 169 cases (29.2%) and 1543 controls (24.5%). These data were not therefore subject to parental recall bias.

Linear regression analyses were carried out to investigate any potential confounding effect of deprivation. This was defined using Townsend deprivation score (5 categories)[26] derived from the residential address at the time of diagnosis (cases) or the date on which the matched control child reached the same age as the case at tumour diagnosis (pseudo-diagnosis).

Estimates of odds ratios (OR) and 95% confidence intervals (CI) were obtained using logistic regression. Although cases were individually matched with controls, unconditional logistic regression is generally used in UKCCS studies to maximise power by utilising all available controls[27,28]. Here, however, conditional logistic regression was used to eliminate any potential effect of age differentiated recall bias. Individuals were stratified according to 1 year age categories, sex and region. Analyses were adjusted for Townsend deprivation category. Analyses were carried out for all CNS tumours and by the diagnostic groups glioma, pilocytic astrocytoma and PNET. Numbers were insufficient to analyse ependymoma and 'other CNS tumours' separately. A separate analysis of tumours more typically observed in adults, such as non-pilocytic astrocytomas and other gliomas was carried out to facilitate comparison with the existing literature regarding atopy and adult glioma. These were defined as tumours with ICD-O M codes 9380–9390, 9400–9420, 9423–9460, 9474–9480 with an associated CNS topography code (C70-72).

Children diagnosed with a tumour under the age of 2 and their matched controls were excluded to minimise potential bias arising from children diagnosed with CNS tumours early in life having less opportunity to be diagnosed with asthma or eczema.

## 3. Results

There were 683 CNS cases and 7598 controls available. The participation rate was 82% for cases and 64% for controls. Children under the age of 2 years at diagnosis or diagnosis of their matched case were excluded ($n = 108$ cases, 1306 controls). Demographic information on cases and controls is given in Table 1.

Of the remaining 575 cases, 90 (15.7%) completed the January 1992 questionnaire, as did 474 (7.5%) of the 6292 controls before the revised January 1993 version was introduced. Consequently, information regarding eczema, rash and wheezing was not asked of these individuals (see Table 2).

The smaller proportion of controls completing the initial questionnaire is explained by the average interval from (pseudo)diagnosis to interview being 6 months for cases and 14 months for controls.

Control parents (17.3%) reported that their child ever having asthma, and 25.1% reporting ever wheezing or having whistling in the chest. Eczema was reported by 23.5% of control parents, 18.0% reported their child ever suffering from an itchy rash, and 10.4% early onset flexural rash. There was no evidence to suggest differential reporting of asthma between control parents completing the original and revised questionnaires (16.3% versus 17.7%, $t$-test, $p = 0.44$).

A strong positive association was present between the reported presence of asthma and eczema within a child ($\chi^2$ test, $p < 0.001$), supporting a common atopic background of the disease. Linear regression analyses showed that children from more deprived areas were more likely to suffer from asthma ($p = 0.022$) and wheeze ($p < 0.001$), but less likely to suffer from eczema ($p < 0.001$) and itchy rash ($p < 0.001$).

Reporting of asthma increased with the age of the index child in both male and female controls. Overall prevalence amongst males was 20.1% compared to 14.4% in females.

The proportion of controls reporting ever having eczema and itchy rash declined with the age of the index child (linear regression; $\beta = -0.008$ $p < 0.001$, $\beta = -0.005$ $p < 0.001$) suggesting a bias in reporting by the age of the child. To adjust for this potential bias, the analyses were stratified by age categories.

The odds ratio of diagnosis of a CNS tumour was significantly reduced in individuals reported to have ever had asthma (OR 0.75, $CI_{95\%}$: 0.58–0.97). Moderate and severe wheeze were both associated with reduced odds ratios; this reached significance for moderate wheeze (OR 0.72, $CI_{95\%}$: 0.55–0.97), but not severe wheeze (OR 0.77, $CI_{95\%}$: 0.53–1.13).

However, no significant inverse association was found between CNS tumours and eczema (OR 0.94, $CI_{95\%}$: 0.74–1.18), or having early onset flexural rash (OR 0.95, $CI_{95\%}$: 0.68–1.34).

Reporting of both asthma and eczema showed a very strong negative association with CNS tumours (OR 0.48, $CI_{95\%}$: 0.29–0.81).

Odds ratios for the risk of CNS tumours in relation to allergic disorders tended to be more strongly reduced in females than males, however none of the interaction terms were significant.

**Table 2 – Relation of parental reported allergic disease to the risk of CNS tumours**

| Exposure | Controls | | All CNS tumours | | | Glioma | | | PNET/medulloblastoma | | | Pilocytic astrocytoma[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | OR | *n* | % | OR | *n* | % | OR | *n* | % | |
| *Asthma* | | | | | | | | | | | | | | |
| Yes | 1089 | 17.3 | 80 | 13.9 | 0.75 (0.58–0.97)* | 52 | 16.0 | 0.90 (0.66–1.23) | 11 | 8.3 | 0.43 (0.23–0.81)** | 24 | 16.0 | 0.96 (0.61–1.51) |
| No | 5084 | 80.8 | 486 | 84.5 | 1.00 | 269 | 82.5 | 1.00 | 119 | 90.2 | 1.00 | 124 | 82.7 | 1.00 |
| Unknown | 119 | 1.9 | 9 | 1.6 | | 5 | 1.5 | | 2 | 1.5 | | 2 | 1.3 | |
| Not asked | 0 | | 0 | | | 0 | | | 0 | | | 0 | | |
| *Wheezing* | | | | | | | | | | | | | | |
| Severe | 485 | 8.3 | 33 | 6.8 | 0.77 (0.53–1.13) | 16 | 5.8 | 0.71 (0.42–1.2) | 7 | 6.3 | 0.68 (0.31–1.50) | 9 | 7.3 | 0.91 (0.45–1.84) |
| Moderate | 978 | 16.8 | 61 | 12.6 | 0.72 (0.55–0.97)* | 39 | 14.2 | 0.86 (0.61–1.23) | 13 | 11.6 | 0.65 (0.35–1.14) | 13 | 10.5 | 0.63 (0.35–1.13) |
| None | 4179 | 71.8 | 371 | 76.5 | 1.00 | 207 | 75.5 | 1.00 | 86 | 76.8 | 1.00 | 95 | 76.6 | 1.00 |
| Unknown | 176 | 3.0 | 20 | 4.1 | | 12 | 4.4 | | 6 | 5.4 | | 7 | 5.6 | |
| Not asked | 474 | | 90 | | | 52 | | | 20 | | | 26 | | |
| *Eczema* | | | | | | | | | | | | | | |
| Yes | 1368 | 23.5 | 105 | 21.6 | 0.94 (0.74–1.18) | 55 | 20.1 | 0.89 (0.65–1.21) | 26 | 23.2 | 0.95 (0.60–1.50) | 25 | 20.2 | 0.90 (0.57–1.42) |
| No | 4378 | 75.2 | 375 | 77.3 | 1.00 | 215 | 78.5 | 1.00 | 86 | 76.8 | 1.00 | 97 | 78.2 | 1.00 |
| Unknown | 72 | 1.2 | 5 | 1.0 | | 4 | 1.5 | | 0 | 0.0 | | 2 | 1.6 | |
| Not asked | 474 | | 90 | | | 52 | | | 20 | | | 26 | | |
| *Early onset flexural rash* | | | | | | | | | | | | | | |
| Yes | 604 | 10.4 | 42 | 8.7 | 0.95 (0.68–1.34) | 27 | 9.9 | 1.17 (0.77–1.79) | 10 | 8.9 | 0.96 (0.49–1.88) | 14 | 11.3 | 1.35 (0.75–2.42) |
| No | 5160 | 88.7 | 435 | 89.7 | 1.00 | 243 | 88.7 | 1.00 | 99 | 88.4 | 1.00 | 109 | 87.9 | 1.00 |
| Unknown | 56 | 1.0 | 8 | 1.6 | | 4 | 1.5 | | 3 | 2.7 | | 1 | 0.8 | |
| Not asked | 474 | | 90 | | | 52 | | | 20 | | | 26 | | |
| *Either asthma or eczema* | | | | | | | | | | | | | | |
| Yes | 2045 | 34.7 | 163 | 32.9 | 0.92 (0.75–1.13) | 94 | 33.3 | 0.98 (0.75–1.27) | 34 | 30.1 | 0.76 (0.50–1.16) | 46 | 35.4 | 1.09 (0.75–1.59) |
| No | 3705 | 62.9 | 325 | 65.5 | 1.00 | 183 | 64.9 | 1.00 | 78 | 69.0 | 1.00 | 81 | 62.3 | 1.00 |
| Unknown | 136 | 2.3 | 8 | 1.6 | | 5 | 1.8 | | 1 | 0.9 | | 3 | 2.3 | |
| Not asked | 474 | | 90 | | | 52 | | | 20 | | | 26 | | |
| *Both asthma and eczema* | | | | | | | | | | | | | | |
| Yes | 397 | 6.8 | 16 | 3.3 | 0.48 (0.28–0.81)** | 1.0 | 3.6 | 0.55 (0.28–1.06) | 2 | 1.8 | 0.27 (0.06–1.12)* | 2 | 1.6 | 0.25 (0.06–1.03)* |
| No | 5246 | 90.1 | 456 | 93.8 | 1.00 | 255 | 93.1 | 1.00 | 108 | 96.4 | 1.00 | 118 | 95.2 | 1.00 |
| Unknown | 180 | 3.1 | 14 | 2.9 | | 9 | 3.3 | | 2 | 1.8 | | 4 | 3.2 | |
| Not asked | 474 | | 90 | | | 52 | | | 20 | | | 26 | | |

Conditional logistic regression, stratified by age (1 year categories), sex and region. All analyses adjusted for Townsend deprivation category (quintiles).

a Subgroup of glioma.

* $p < 0.05$.

** $p < 0.01$.

6.9% of cases and 7.5% of controls reported one or both parents being diagnosed with asthma in childhood. There was no evidence to suggest that a parental history of asthma is associated with CNS tumours. (OR 0.93, $CI_{95\%}$: 0.64–1.37). The risk of brain tumours between allergic (i.e. those with reported asthma or eczema) subjects with a history of parental asthma compared to those without was slightly reduced (OR 0.60, $CI_{95\%}$: 0.30–1.19). However, the subgroups were relatively small.

Asthma data based on extracted GP notes were not significantly associated with CNS tumours (OR 1.20, $CI_{95\%}$: 0.74–1.94). Interestingly, when looking at parental reported asthma, the same cases and controls provide a reduced odds ratio (OR 0.77, $CI_{95\%}$: 0.49–1.21). This may indicate bias in the dataset.

Although there was no statistically significant heterogeneity in allergy risk between diagnostic subgroups, primitive neuroectodermal tumours showed substantially stronger negative associations with asthma, wheezing, and atopy than astrocytic tumours.

'Adult' type tumours made up 176 of 575 cases (30.6%). The odds ratio of developing an 'Adult' type tumour was non-significantly reduced in individuals reported to have suffered from asthma (OR 0.86, $CI_{95\%}$: 0.56–1.31), severe wheeze (OR 0.55, $CI_{95\%}$: 0.25–1.20), eczema (OR 0.89, $CI_{95\%}$: 0.58–1.35), and both asthma and eczema (OR 0.80, $CI_{95\%}$: 0.38–1.68). Marginally increased odds ratios were observed for moderate wheeze (OR 1.07, $CI_{95\%}$: 0.69–1.67) and early onset flexural rash (OR 1.05, $CI_{95\%}$: 0.58–1.91).

Conditional matched analyses were repeated using only controls individually matched to CNS cases ($n = 1143$), and similar results were observed.

## 4. Discussion

The results from our study find that the risk of developing a CNS tumour of any type is significantly reduced in children reported to have suffered from asthma or both asthma and eczema. The associations are strongly driven by findings for the PNET subgroup of tumours, despite the small numbers. To our knowledge, this is the first report of inverse associations between CNS tumours and allergies in children. Similar findings have been reported for adult onset brain tumours[14–20,29]; although in adults the most common types are high grade astrocytoma/glioblastoma and meningioma, which are rare in children. Tumour histologies typically observed in adults such as non-pilocytic astrocytomas and other gliomas within the UKCCS also displayed reduced odds ratios associated with allergies providing no evidence for heterogeneity of risk.

Various forms of wheeze in children may be reported as asthma[30] and this contributes to uncertainty in the data. The presence of allergy-associated disease is not a wholly accurate indicator of atopic dysfunction[31], and the difficulty of separating atopic and non-atopic skin disease may account for the lack of any observed association between eczema/early onset flexural rash and CNS tumours. A standard definition for atopic forms of both asthma and eczema would greatly improve future studies. The lack of a dose–response effect for the wheeze severity variable is a potential concern; however, wheeze severity may not necessarily be a good indicator of atopic asthma[30].

Reporting of asthma increased with the age of the index child at diagnosis in both males and females as would be expected. Asthma is known to have a gender specific prevalence[32]; males are more likely to exhibit symptoms up to 15 years of age, but females display a higher prevalence of asthma into adulthood. Our data are consistent with this observed male excess. Direct comparison of asthma prevalence data are not straightforward due to the use of different definitions. However, data from our study are similar to the results of other studies that have attempted to estimate the prevalence of asthma in the UK[11,33].

The decline with age in the proportion of controls for whom eczema is reported is potentially explained by less accurate reporting from mothers of older children where the recall time from event to report is longer. Two observations though lend validity to the data: there was no discernable gender difference in the distribution of eczema and rash, consistent with the literature[32], and the reported prevalence is comparable with other studies[33,34].

The interval between the date of (pseudo)diagnosis and interview was slightly longer for controls than cases and questions about asthma and eczema were phrased as 'ever' having disease. This phrasing may have led to higher prevalence rates of reported allergic conditions amongst controls if they had developed over these additional months. As reduced risks were only seen for asthma and not eczema and both questions were phrased in this way it is unlikely to fully explain the findings.

Our results are compatible with the published literature on adult brain tumours; a negative association between allergic disease and primary brain tumours in adults has been consistently identified by case control studies based on self-reported allergy history[14–18,20,29]. Wiemels [29] showed that the levels of food and respiratory allergen specific IgE are lower in glioma patients than controls, though reverse causality cannot be excluded. However, a cohort study by Schwartzbaum and colleagues[35] failed to find a significant association between primary brain tumours and allergic disease based on data from the Swedish twin registry, but included only 79 glioma and 67 meningioma cases with poor detail of allergic disease. A later study by Schwartzbaum and colleagues[36] reported an inverse relationship between polymorphisms in known asthma-related genes and glioblastoma multiforme. Menegaux and colleagues[21] also reported a non-significant inverse association between neuroblastoma and allergic disorders, although any similarities in aetiology are unclear.

In all case–control studies where parental questionnaires are used to collect information about risk factors, recall bias is a potential concern. Asthma and eczema are persistent conditions representing a significant impact on lifestyle and therefore are potentially more likely to be reported accurately.

Results based on GP records were inconsistent with those based on parental reporting for the same cases and controls. However, GP extracts were only available for a relatively small subset of individuals (29.2% of cases and 24.5% of controls). Alternatively, inconsistency may be due to pre-clinical tumour symptoms increasing parental inclination to attend general practice and make a GP diagnosis of asthma more likely.

Another UKCCS study also found inconsistent results between parental reporting of allergies and primary care data in leukaemia patients[28]. However, data based on one time GP diagnosis are not likely to be significantly better than parental recall at identifying atopic asthma due to the sometimes transient nature of asthma symptoms.

The UKCCS is subject to participation bias[23]; participating controls lived in more affluent areas, and displayed a lower deprivation index than first choice controls and their matched cases. Preliminary analysis indicated that deprivation is strongly associated with reporting of asthma, wheezing, eczema and rash. Deprivation is potentially a proxy for several factors that may influence CNS tumour risk or the prevalence of allergic disease; therefore models were adjusted for deprivation. However, it is possible that some confounding influence may remain. This is especially true of the wheezing severity variable where environmental tobacco smoke is likely to be a potential confounder.

Numerous studies have cited the immune surveillance hypothesis[37,38] as a possible cause of the observed negative association between brain tumours and allergic disease. This hypothesis proposes that the immune system plays an important role in tumour prevention, by eliminating abnormal cells before they undergo malignant transformation. It is perceived that a hypersensitive immune system, as observed in atopic individuals may be better equipped to purge nascent tumour cells[17]. Although the brain is commonly held to be immune privileged, immune cells have been shown to protect against tumours beyond the blood–brain barrier[39], though the response differs from other sites in the body. However, tumour immunology is poorly understood, especially in the brain, and no empirical evidence exists to suggest that atopic individuals have a more effective response against brain tumours.

Reverse causality is also a potential explanation for the observed results. Brain tumours are known to have a significant systemic effect on the immune system in adults[40,41]. Both these studies measured an increase in IL-10 production and a down-regulation of IL-12 production in brain tumour patients and similar immunological shifts towards a Th2 response have been shown to occur in response to helminth infection [42]. It is well established that helminth infection has a protective effect against allergy[43,44] and can also result in the attenuation of asthma[45] and brain tumours may suppress allergy by a similar mechanism, though further investigation is required.

It is possible that there is a confounding third factor that influences the risk of both atopy and CNS tumours. Recent epidemiological studies have implied that childhood CNS tumours may have an infectious aetiology [46–48]. These studies have suggested that children who are exposed to high levels of infection are at greater risk of CNS tumours. Atopy has a significant environmental component; and is thought to be associated with lack of exposure to infection in early childhood[49]. High levels of infectious exposure early in life may increase the risk of CNS tumours, whilst reducing that of atopy, thus explaining the observed association.

In conclusion, the study demonstrates a possible protective effect of asthma for childhood brain tumours, either alone or also in the presence of eczema. Although, in common with all case–control interview studies recall bias, reverse causality or confounding may have influenced the findings, the results are sufficiently strong to merit further investigation. New targeted, purpose-designed studies that explore the role of atopy in aetiology of childhood brain tumours are warranted.

## Conflict of interest statement

None declared.

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## REFERENCES


1. Peris-Bonet R et al. Childhood central nervous system tumours–incidence and survival in Europe (1978–1997): report from Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;**42**(13):2064–80.
2. McKinney PA. Central nervous system tumours in children: epidemiology and risk factors. *Bioelectromagnetics* 2005;**Suppl 7**:S60–8.
3. Linet MS, Wacholder S, Zahm SH. Interpreting epidemiologic research: lessons from studies of childhood cancer. *Pediatrics* 2003;**112**(1 Pt 2):218–32.
4. Bondy ML et al. Genetic epidemiology of childhood brain tumors. *Genet Epidemiol* 1991;**8**(4):253–67.
5. Little J. *Epidemiology of childhood cancer*. Lyon: International Agency for Research on Cancer; 1999 [IARC Scientific Publications, No. 149; 1999].
6. Romagnani S. The Th1/Th2 paradigm and allergic disorders. *Allergy* 1998;**53**(46 Suppl):12–5.
7. MacLean JA, Eidelman FJ. The genetics of atopy and atopic eczema. *Arch Dermatol* 2001;**137**(11):1474–6.
8. Barnes KC. Gene–environment and gene–gene interaction studies in the molecular genetic analysis of asthma and atopy. *Clin Exp Allergy* 1999;**29**(Suppl. 4):47–51.
9. Braman SS. The global burden of asthma. *Chest* 2006; **130**(1 Suppl):4S–12S.
10. Asher MI et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**(9537):733–43.
11. Asher MI, Weiland SK. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steering Committee. *Clin Exp Allergy* 1998;**28**(Suppl. 5):52–66 [discussion 90-1].
12. Romagnani S. The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? *Immunology* 2004;**112**(3):352–63.
13. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy* 2005;**60**(9):1098–111.
14. Schoemaker MJ et al. History of allergies and risk of glioma in adults. *Int J Cancer* 2006;**119**(9):2165–72.
15. Schoemaker MJ et al. History of allergic disease and risk of meningioma. *Am J Epidemiol* 2007;**165**(5):477–85.
16. Brenner AV et al. History of allergies and autoimmune diseases and risk of brain tumors in adults. *Int J Cancer* 2002;**99**(2):252–9.
17. Wiemels JL et al. History of allergies among adults with glioma and controls. *Int J Cancer* 2002;**98**(4):609–15.
18. Schlehofer B et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. *Int J Cancer* 1999;**82**(2):155–60.
19. Hochberg F et al. Nonoccupational risk indicators of glioblastoma in adults. *J Neurooncol* 1990;**8**(1):55–60.
20. Wigertz A et al. Allergic conditions and brain tumor risk. *Am J Epidemiol* 2007, in press, doi:10.1093/aje/kwm203.
21. Menegaux F et al. Day care, childhood infections, and risk of neuroblastoma. *Am J Epidemiol* 2004;**159**(9):843–51.
22. UK Childhood Cancer Study Investigators. The United Kingdom Childhood Cancer Study: objectives, materials and methods. *Br J Cancer* 2000;**82**(5):1073–102.
23. Law GR, Smith AG, Roman E. The importance of full participation: lessons from a national case–control study. *Br J Cancer* 2002;**86**(3):350–5.
24. Williams HC et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;**131**(3):383–96.
25. Fleming S et al. An application of the United Kingdom Working Party diagnostic criteria for atopic dermatitis in Scottish infants. *J Invest Dermatol* 2001;**117**(6):1526–30.
26. Townsend P, Phillimore P, Beattie A, editors. Health and deprivation: inequality and the north. London: Croom Helm Ltd; 1987. p. 221. ISBN 0-7099-4352-0.
27. Fear NT, Simpson J, Roman E. Childhood cancer and social contact: the role of paternal occupation (United Kingdom). *Cancer Causes Control* 2005;**16**(9):1091–7.
28. Hughes AM et al. Allergy and risk of childhood leukaemia: results from the UKCCS. *Int J Cancer* 2007;**121**(4): 819–24.
29. Wiemels JL et al. Reduced immunoglobulin E and allergy among adults with glioma compared with controls. *Cancer Res* 2004;**64**(22):8468–73.
30. Silverman M, Wilson N. Asthma—time for a change of name? *Arch Dis Child* 1997;**77**(1):62–4 [discussion 64-5].
31. Wang H, Diepgen TL. Atopic dermatitis and cancer risk. *Br J Dermatol* 2006;**154**(2):205–10.
32. Osman M et al. Gender-specific presentations for asthma, allergic rhinitis and eczema in primary care. *Prim Care Respir J* 2007;**16**(1):28–35.
33. Anderson HR et al. Trends in prevalence of symptoms of asthma, hay fever, and eczema in 12–14 year olds in the British Isles, 1995–2002: questionnaire survey. *Bmj* 2004;**328**(7447):1052–3.
34. Gupta R et al. Time trends in allergic disorders in the UK. *Thorax* 2007;**62**(1):91–6.
35. Schwartzbaum J et al. Cohort studies of association between self-reported allergic conditions, immune-related diagnoses and glioma and meningioma risk. *Int J Cancer* 2003;**106**(3):423–8.
36. Schwartzbaum J et al. Polymorphisms associated with asthma are inversely related to glioblastoma multiforme. *Cancer Res* 2005;**65**(14):6459–65.
37. Burnet M. Cancer; a biological approach. I. The processes of control. *Br Med J* 1957;**1**(5022):779–86.
38. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity* 2004;**21**(2):137–48.
39. Prins RM et al. NK and CD4 cells collaborate to protect against melanoma tumor formation in the brain. *J Immunol* 2006;**177**(12):8448–55.
40. Kumar R et al. Th1/Th2 cytokine imbalance in meningioma, anaplastic astrocytoma and glioblastoma multiforme patients. *Oncol Rep* 2006;**15**(6):1513–6.
41. Zou JP et al. Human glioma-induced immunosuppression involves soluble factor(s) that alters monocyte cytokine profile and surface markers. *J Immunol* 1999;**162**(8): 4882–92.
42. Carvalho EM, Bastos LS, Araujo MI. Worms and allergy. *Parasite Immunol* 2006;**28**(10):525–34.
43. Cooper PJ et al. Risk factors for atopy among school children in a rural area of Latin America. *Clin Exp Allergy* 2004;**34**(6):845–52.
44. Araujo MI et al. Inverse association between skin response to aeroallergens and *Schistosoma mansoni* infection. *Int Arch Allergy Immunol* 2000;**123**(2):145–8.
45. Medeiros Jr M et al. *Schistosoma mansoni* infection is associated with a reduced course of asthma. *J Allergy Clin Immunol* 2003;**111**(5):947–51.

46. Altieri A et al. Association between number of siblings and nervous system tumors suggests an infectious etiology. *Neurology* 2006;**67**(11):1979–83.
47. Shaw AK, Li P, Infante-Rivard C. Early infection and risk of childhood brain tumors (Canada). *Cancer Causes Control* 2006;**17**(10):1267–74.
48. Nyari TA et al. Childhood solid tumours in relation to population mixing around the time of birth. *Br J Cancer* 2003;**88**(9):1370–4.
49. Strachan DP. Family size, infection and atopy: the first decade of the 'hygiene hypothesis'. *Thorax* 2000;**55**(Suppl. 1): S2–S10.