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Antenatal maternal bereavement and childhood cancer in the offspring: a population-based cohort study in 6 million children

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BACKGROUND: Prenatal stress may increase the susceptibility to childhood cancer by affecting immune responses and hormonal balance. We examined whether antenatal stress following maternal bereavement increased the risk of childhood cancer.

METHODS: All children born in Denmark from 1968 to 2007 ($N = 2\,743\,560$) and in Sweden from 1973 to 2006 ($N = 3\,400\,212$) were included in this study. We compared cancer risks in children born to women who lost a first-degree relative (a child, spouse, a parent, or a sibling) the year before pregnancy or during pregnancy with cancer risks in children of women who did not experience such bereavement.

RESULTS: A total of 9795 childhood cancer cases were observed during follow-up of 68 360 707 person years. Children born to women who lost a child or a spouse, but not those who lost other relatives, had an average 30% increased risk of any cancer (hazard ratio (HR) 1.30, 95% confidence interval (CI) 0.96–1.77). The HRs were the highest for non-Hodgkin disease (512 cases in total, HR 3.40, 95% CI 1.51–7.65), hepatic cancer (125 cases in total, HR 5.51, 95% CI 1.34–22.64), and testicular cancer (86 cases in total, HR 8.52, 95% CI 2.03–37.73).

CONCLUSION: Our data suggest that severe antenatal stress following maternal bereavement, especially due to loss of a child or a spouse, is associated with an increased risk of certain childhood cancers in the offspring, such as hepatic cancer and non-Hodgkin disease, but not with childhood cancer in general.

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Childhood cancer is the second leading cause of death in children in high-income countries (Parkin *et al*, 2002; Kaatsch, 2010). Almost half of the childhood cancers are diagnosed before 5 years of age (Kaatsch, 2010), highlighting the importance of identifying early-life risk factors (Kimmel, 2005; Anderson, 2006). Only a few risk factors have, however, been established, such as radiation for leukaemia (Giles *et al*, 1956; Bross and Natarajan, 1972) and cryptorchidism for testicular cancer (Garner *et al*, 2005), whereas associations between most other factors and childhood cancer risk remain inconclusive (Garner *et al*, 2005; Eden, 2010). We need to know more about the aetiology of childhood cancer to plan effective prevention strategies (Parkin *et al*, 2002; Kaatsch, 2010).

The fetal programming concept proposes that environmental factors operating during the peri-conceptional and fetal periods affect the propensity to diseases in adulthood (Gluckman and Hanson, 2006; Harris and Seckl, 2011). Maternal stress during pregnancy may cause excessive production of glucocorticoids and other hormones, which readily passes the placenta (Benediktsson *et al*, 1997; Gitau *et al*, 1998). These hormones may have immediate effects on fetal development and long-term effects on health (Kapoor *et al*, 2006; Davis *et al*, 2011; Harris and Seckl, 2011). Prenatal stress has been related to several diseases related to brain function and chronic degenerative diseases (Davis *et al*, 2011; Harris and Seckl, 2011). Experimental research has suggested that its effects on endocrine or immune function may also increase the susceptibility to cancer (Reiche *et al*, 2004; Ekbom, 2006). It remains, however, unknown whether antenatal stress can lead to childhood cancer in humans (Bermejo *et al*, 2007).

Bereavement by the death of a child or a husband is classified as one of the most stressful events a woman can experience (Skodol and Shrout, 1989; American Psychiatric Association, 1994; Stroebe *et al*, 2001). Thus, we examined whether maternal stress following bereavement before and during pregnancy increased childhood cancer risk in the offspring. We used a large population-based cohort, based on combined national data from two Nordic countries. We hypothesised that prenatal stress increased the risks of certain cancers, especially those related to the immune and endocrine functions, such as leukaemia or testicular cancer (Reiche *et al*, 2004; Ekbom, 2006). We further examined whether the death of a child or a spouse was associated with a higher cancer risk in offspring than the death of other relatives (Skodol and Shrout, 1989).

MATERIALS AND METHODS

This population-based cohort study used data from national registers in Denmark and Sweden, and data collection has been

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described in detail previously (Li *et al*, 2010). In short, all live-born children and new residents in Denmark and Sweden are assigned a unique civil personal registration number, which is used in the national registration system that includes detailed information on birth, death, and immigration. All children born in Denmark from 1968 to 2007 ($N = 2\,743\,560$) and in Sweden from 1973 to 2006 ($N = 3\,400\,212$) were included and linked to their next of kin (mother, father, siblings, mother's siblings, and mother's parents) by using the personal number. The exposure for this study is defined as maternal bereavement by the death of a child, a spouse/partner, a parent or a sibling. The exposure time window started from 12 months before the estimated date of conception to the date of child birth, as bereavement before conception may have a long-term detrimental effect on mothers (McEwen, 1998; Gluckman *et al*, 2008; Harris and Seckl, 2011). Follow-up started at birth and ended at the date of a cancer diagnosis, death, emigration, 14 completed years of age (i.e., before the 15th birthday), or end of follow-up (31 December 2006 in Sweden, and 31 December 2007 in Denmark), whichever came first.

Cancer diagnosis

The Danish Cancer Registry includes data on all cancer cases in Denmark diagnosed since 1943. Quality of the Danish Cancer Registry is secured by manual coding and validation of data, which provides a high degree of completeness (Gjerstorff, 2011). From 1943 to 1977 the Registry used the modified seventh revision of the International Classification of Disease (ICD-7), and from 1978 and onwards ICD-10 was used for cancer diagnosis (Gjerstorff, 2011). The Swedish Cancer Registry was established in 1958 and contains individual data on all newly diagnosed malignant tumours within Sweden. Tumours are reported to the Swedish Cancer Registry separately by both the diagnosing clinician and the responsible pathologist or cytologist. Nearly 100% of all diagnosed cancers are reported, with histological verification of 97% of the tumours. Cancer cases are classified using a 4-digit diagnostic code according to the ICD-7. In addition, a pathological anatomic diagnosis (PAD) is used to define the histological classification of cancers (http://www.socialstyrelsen.se/register/halsodataregister/cancerregistret/inenglish).

The main outcomes of interest were all incident cancers (ICD-7 codes 104-205, ICD-10 codes C00-97) and several main childhood cancers that have been proposed to have prenatal origin (Reiche *et al*, 2004; Ekbom, 2006). Specific cancers of interest included leukaemia (ICD-7 204, ICD-10 C91-95), Hodgkin's lymphoma (ICD-7 201, ICD-10 C81), non-Hodgkin's lymphoma (ICD-7 200,202, ICD-10 C82-83), hepatic tumours (ICD-7 155, ICD-10 C22), testicular cancer (ICD-7 178, ICD-10 C62), Wilms' tumour (ICD-7 180 and PAD 886, ICD-10 C64.9), retinoblastoma of the eye (ICD-7 192 and PAD 436, ICD-10 C69.2), and central nervous system tumours (ICD-7 193, ICD-10 C70-71).

Statistical analysis

Hazards ratios with 95% confidence limits were estimated using Cox regression models with the PHREG procedure in SAS. Proportional hazard assumption was verified by Kaplan–Meier curves, using PROC LIFETEST procedure. The analyses were stratified by sex of the child, cause of death, type of bereavement, and timing of exposure, which are expected to have a role in the association (Skodol and Shrout, 1989; American Psychiatric Association, 1994; Stroebe *et al*, 2001). For potential confounders, we included maternal characteristics (Parkin *et al*, 2002; Kaatsch, 2010) (maternal age ($\leqslant$26, 27–30, $\geqslant$31 years), parity (1, 2, $\geqslant$3), education level (low ($\leqslant$9 years), middle (10–14 years), and high ($\geqslant$15 years)) (available for Swedish data at 1990, 1995, 2000, and 2005, available data for Danish data for 1980–2007), smoking during pregnancy (yes, no) (available 1983–2006 in Sweden and 1991–2007 in Denmark)). We also controlled for child's sex (male, female), birth characteristics (Tower and Spector, 2007; Von Behren *et al*, 2011), including birth weight ($<$2500 g, 2500–3249 g, 3250–3999 g, $\geqslant$4000 g), gestational age ($<$37 weeks, $\geqslant$37 weeks), and Apgar score at 5 min (0–6, 7–10). All data handling and statistical analyses were performed with the SAS version 9.2 statistical software package (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Population characteristics

The baseline characteristics of the study population (6 143 772 children) are shown in Table 1 according to exposure status. Children born to mothers over 30 years of age, mothers with at least three births, mothers with low education, and mothers

Table 1 Baseline characteristics of the study population[a]

	Exposed cohort ($N = 139\,520$)		Unexposed cohort ($N = 6\,004\,252$)	
Variables	***n* (%)**	**Person years**	***n* (%)**	**Person years**
Sex				
Boys	71 425 (51)	799 073	3 083 078 (51)	34 268 383
Girls	68 095 (49)	765 933	2 921 153 (49)	32 527 249
Apgar score at 5 min[b]				
1–6	1461 (1)	13 472	50 987 (1)	461 113
7–10	128 391 (93)	1 428 407	4 820 664 (92)	51 419 896
Unknown	7765 (6)	97 654	1 1132 600 (8)	4 818 647
Gestational age[b]				
$<$37 Weeks	8749 (6)	91 522	293 656 (6)	2 948 407
$\geqslant$37 Weeks	126 326(92)	1 419 911	4 759 095 (90)	51 288 333
Unknown	2542 (2)	28 100	214 060 (4)	2 462 916
Birth weight[b]				
$<$2500 g	7154(5)	74 466	230 571 (4)	2 322 122
2500–3250 g	34 950 (25)	398 063	1 291 867 (25)	14 111 440
3251–3999 g	68 880 (51)	776 834	2 631 003 (50)	28 358 674
$\geqslant$4000 g	24 830 (18)	271 772	890 216 (17)	9 351 608
Unknown	1803 (1)	18 398	223 155 (4)	2 555 812
Maternal age				
$\leqslant$26	39 044(28)	480 211	2 363 722 (39)	28 680 957
27–30	39 074 (28)	450 164	1 741 535 (29)	19 220 683
$\geqslant$31	61 401 (44)	634 616	1 887 791 (31)	18 770 340
Parity[b]				
1	44 965 (33)	499 224	2 201 940 (42)	23 598 539
2	51 789 (38)	579 917	1 859 081 (35)	19 997 833
$\geqslant$3	39 389 (29)	445 209	992 345 (19)	10 642 374
Unknown	1474 (1)	15 184	213 445 (1)	2 460 910
Maternal education[c]				
Low, $\leqslant$9 years	65 916 (47)	800 766	2 245 073 (38)	26 945 063
Middle, 10–14 years	38 258 (28)	400 919	1 425 480 (24)	14 445 228
High, $\geqslant$15 years	29 062 (21)	290 018	1 018 674 (17)	9 496 784
Unknown	6284 (5)	73 301	1 315 025 (22)	15 908 625
Maternal smoking during pregnancy[d]				
Yes	22 884 (19)	252 803	675 522 (15)	7 316 062
No	64 821 (54)	626 318	2 618 413 (59)	23 706 869
Unknown	51 815 (28)	685 884	2 710 317 (26)	35 772 770

[a]Value is *n* (%). Study population includes all children born in Denmark in 1968–2007, born in Sweden in 1973–2006. [b]Data available period: 1978–2007 in Denmark, 1973–2006 in Sweden. [c]Data available period: 1980–2007 in Denmark, 1973–2006 in Sweden. [d]Data available period: 1991–2007 in Denmark, 1983–2006 in Sweden.

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who smoked during pregnancy were slightly overrepresented in the exposed cohort.

Overall cancer risk

Table 2 presents the associations between maternal bereavement and overall childhood cancer risk in offspring. A total of 9795 children were diagnosed with cancer, of which 249 were in the exposed group. Overall, exposed children had a similar risk of cancer (hazard ratio (HR) 1.04, 95% confidence interval (CI) 0.91–1.18), compared with unexposed children. Children born to mothers who lost an earlier born child or a spouse had a 30% elevated risk of cancer (HR 1.30, 95% CI 0.96–1.77), although the association was not statistically significant. Maternal bereavement by death of other relatives was not associated with an increased risk (HR 0.99, 95% CI 0.85–1.14). Bereavement due to unexpected death of a relative was associated with a similar HR related to bereavement due to other death. We did not observe any significant difference in HRs during the three periods within the exposure time window (12–7 months before conception, 6–0 months before conception, and pregnancy).

Stratification on sex of the child yielded similar findings (data not shown).

The risk of specific childhood cancers

Table 3 shows results for the specific childhood cancers. For most cancers, the numbers of cases were small, and differences in risk estimates between exposed and unexposed were not statistically significant. The highest risks were observed in children born to mothers who lost an earlier born child or a spouse for non-Hodgkin disease (HR 3.40, 95% CI 1.51–7.65), hepatic cancer (HR 5.51, 95% CI 1.34–22.64), and testicular cancer (HR 8.52, 95% CI 2.03–37.73).

DISCUSSION

This large population-based cohort study revealed increased risks in children born to mothers who experienced a death of a child or spouse during pregnancy or 1 year before pregnancy for some specific childhood cancers, including non-Hodgkin disease, hepatic cancer, and testicular cancer. These excess risks were not dependent on sex of the child, birth characteristics of child (birth weight, gestational age, and Apgar score at 5 min), and maternal factors (age, parity, education, and smoking during pregnancy).

Underlying biological mechanisms

The potential mechanisms between prenatal stress and childhood cancer remain largely unknown (Anderson *et al*, 2000; Reiche *et al*, 2004; Ekbom, 2006; Kaatsch, 2010). Excessive stress hormones (mostly glucocorticoids) in pregnant mothers could inhibit the function of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) that serves as the feto-placental 'barrier' to maternal hormones, which would lead to adverse effects on immune and neuroendocrine systems in the fetus (Kapoor *et al*, 2006; Davis *et al*, 2011; Harris and Seckl, 2011). Endocrine dysregulation following stress could influence fetal development and potentially programme cancer risk by neuroendocrine–immune interactions (Anderson *et al*, 2000; Reiche *et al*, 2004; Ekbom, 2006). The effects of excessive glucocorticoids on HPA axis and immune system could lead to compromised immune responses against cancer cell growth, and promote the initiation and progression of some types of cancer (Anderson *et al*, 2000; Reiche *et al*, 2004; Ekbom, 2006). It has also been suggested that such hormones, acting as growth factors, can affect stem cells, introduce malignant transformation, and increase the rate of genetic mutations (Anderson *et al*, 2000; Reiche *et al*, 2004; Ekbom, 2006).

Overall cancer risk in offspring and antenatal maternal bereavement

We observed that prenatal stress exposure following maternal bereavement by the death of any first relative was not associated with an overall increased risk of childhood cancer. This was not unexpected because specific cancers have different aetiologies and it is unlikely that all cancers are affected by stress-induced changes (Anderson *et al*, 2000; Reiche *et al*, 2004; Ekbom, 2006). An earlier study indicated that parental death during pregnancy has been associated with an increased risk of several childhood cancers in the offspring (Bermejo *et al*, 2007), but these findings were based on fewer cases and the comparison group was the general population of children. We observed that the increased cancer risk in offspring was mainly restricted to maternal bereavement by the death of a child/spouse, which is consistent with our prior hypothesis regarding severity of stress (Skodol and Shrout, 1989). The relative risks in relation to different periods within the exposure time window were similar, possibly due to the variances in the sensitive timing windows for different individual cancers (Anderson *et al*, 2000; Reiche *et al*, 2004).

Other prenatal factors, such as birth weight or birth order, have been shown to be associated with childhood cancer (Tower and Spector, 2007; Von Behren *et al*, 2011). Various possible biological

Table 2 HRs for childhood cancer according to exposure (bereavement) status

Bereavement	Cancer cases (rate, 1/1000)	Crude HR	Adjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]
All exposed	249 (1.8)	1.12	1.04 (0.91–1.18)	1.04 (0.91–1.18)
Type of the deceased relative				
Child/spouse	48 (2.2)	1.29	1.30 (0.96–1.75)	1.30 (0.96–1.77)
Other relatives	201 (1.7)	1.09	0.99 (0.86–1.15)	0.99 (0.85–1.14)
Cause of death				
Unexpected death	30 (1.9)	1.16	1.14 (0.79–1.64)	1.16 (0.81–1.67)
Other death	219 (1.8)	1.12	1.03 (0.89–1.18)	1.02 (0.89–1.18)
Timing of death				
12–7 Months before conception	78 (2.0)	1.20	1.10 (0.87–1.39)	1.11 (0.87–1.40)
6–0 Months before conception	81 (1.8)	1.15	1.05 (0.83–1.32)	1.06 (0.84–1.33)
Pregnancy	90 (1.6)	1.04	0.98 (0.80–1.22)	0.96 (0.77–1.19)
Unexposed	9546 (1.6)	1.0 (ref)	1.0 (ref)	1.0 (ref)

Abbreviations: CI = confidence interval; HR = hazard ratio. [a]Adjusted for country, sex, maternal factors at child birth (age, education, smoking during pregnancy). [b]Adjusted for country, sex, maternal factors at child birth (age, parity, education, and smoking during pregnancy), birth characteristics (low birth weight, Apgar score at 5 min, gestational age), restricted to period when birth characteristics were available (1978–2007 in Denmark, 1973–2006 in Sweden).

Table 3 HRs for specific childhood cancers according to type of deceased relatives

Cancer	Type of deceased relatives	Cancer cases (rate, 1/1000)	Crude HR	Adjusted HR[a] (95% CI)	Adjusted HR[b] (95% CI)
Leukaemia	Child or spouse	13 (0.6)	1.21	1.20 (0.68–2.11)	1.25 (0.71–2.20)
	Other relatives	70 (0.6)	1.29	1.18 (0.92–1.51)	1.18 (0.92–1.51)
	Unexposed	2780 (0.5)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Hodgkin's disease	Child or spouse	1 (<0.1)	1.83	—	—
	Other relatives	2 (<0.1)	0.76	0.62 (0.15–2.53)	0.64 (0.15–2.53)
	Unexposed	136 (<0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Hodgkin disease	Child or spouse	6 (0.3)	3.14	3.20 (1.43–7.16)[c]	3.40 (1.51–7.65)[c]
	Other relatives	10 (0.1)	1.04	0.89 (0.48–1.67)	0.90 (0.48–1.69)
	Unexposed	496 (0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
CNS tumours	Child or spouse	8 (0.4)	0.72	0.70 (0.33–1.46)	0.69 (0.33–1.46)
	Other relatives	57 (0.5)	1.02	0.93 (0.71–1.22)	0.93 (0.71–1.22)
	Unexposed	2898 (0.5)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Retinoblastoma	Child or spouse	0	—	—	—
	Other relatives	8 (0.1)	1.09	1.12 (0.53–2.38)	1.12 (0.53–2.37)
	Unexposed	339 (0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Wilms' tumour	Child or spouse	4 (0.2)	1.79	1.95 (0.73–5.22)	1.98 (0.74–5.32)
	Other relatives	9 (0.1)	0.78	0.68 (0.34–1.36)	0.68 (0.35–1.37)
	Unexposed	598 (0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Hepatic cancer	Child or spouse	3 (0.1)	4.50	4.77 (1.18–19.33)[c]	5.51 (1.34–22.64)[c]
	Other relatives	2 (<0.1)	0.86	0.82 (0.20–3.34)	0.84 (0.21–3.39)
	Unexposed	120 (<0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Bone cancer	Child or spouse	1 (<0.1)	0.77	0.91 (0.13–6.46)	0.93 (0.13–6.63)
	Other relatives	9 (0.1)	1.43	1.35 (0.67–2.74)	1.34 (0.66–2.71)
	Unexposed	327 (0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Testicular cancer	Child or spouse	2 (0.1)	6.57	7.64 (1.87–31.26)[c]	8.52 (2.03–37.73)[c]
	Other relatives	1 (<0.1)	0.63	0.67 (0.09–4.86)	0.68 (0.09–4.90)
	Unexposed	83 (<0.1)	1.0 (ref)	1.0 (ref)	1.0 (ref)

Abbreviations: CI = confidence interval; CNS = central nervous system; HR = hazard ratio. [a]Adjusted for country, sex, maternal factors at child birth (age, education, smoking during pregnancy). [b]Adjusted for country, sex, maternal factors at child birth (age, parity, education, and smoking during pregnancy), birth characteristics (low birth weight, Apgar score at 5 min, gestational age), restricted to period when birth characteristics were available (1978–2007 in Denmark, 1973–2006 in Sweden). [c]$P<0.05$.

mechanisms have been proposed, including the involvement of insulin growth factors or maternal oestrogen (Milne *et al*, 2007; Tower and Spector, 2007; Von Behren *et al*, 2011), which have also been related to prenatal stress (Wadhwa, 2005). As the estimates did not change when we adjusted for these factors, the association between maternal stress exposure and childhood cancer risk in offspring may operate via other pathways (Petridou *et al*, 1990; Greaves, 2002; Law, 2008).

Risk of specific childhood cancers in offspring and antenatal maternal bereavement

The associations between prenatal stress following maternal bereavement and risk of some main childhood cancers are noteworthy. So far, studies on fetal origins of childhood cancer have mostly focused on the associations between leukaemia and certain environmental exposures (Linet *et al*, 2003; Little, 2009). We observed an increased risk of leukaemia (albeit not statistical significant) and non-Hodgkin's lymphoma as also shown in another study (Bermejo *et al*, 2007). Our findings also support a role of prenatal stress for testicular cancer (Bermejo *et al*, 2007), consistent with observations on cryptorchidism (Schottenfeld *et al*, 1980), indicating a role of intrauterine hormonal disturbances (Garner *et al*, 2005). Although low birth weight (Reynolds *et al*, 2004), maternal age, and smoking during pregnancy have been proposed to be associated with hepatoblastoma (McLaughlin *et al*, 2006), the associations are weak and the aetiology of hepatoblastoma remains unclear. Stress hormones, acting as growth factors, might have a role in the pathways (Ekbom, 2006).

Strengths and limitations

The strengths of our study include the longitudinal design, large sample size, almost complete follow-up, and detailed data on covariates (Frank, 2000). To evaluate the hypothesis of an association between prenatal stress exposure and offspring risk of childhood cancer is difficult due to the rarity of childhood cancer and difficulties in measuring stress exposure. Much of the heterogeneity of previous results might be due to small sample sizes and lack of control for potential confounding by both child and maternal factors. The population-based cohort design based on high-quality data met the above challenges. The design also eliminates the impact of selection and recall bias, which are common problems in case–control studies. The registry system in the Nordic countries provides both a complete case ascertainment and accurate linkage with other data, which allow complete follow-up with least impact of misclassification error (Frank, 2000; Gjerstorff, 2011).

One limitation is that we lack information on risk factors after birth. We cannot rule out the role of other factors related to bereavement, such as breast feeding and other environmental exposures in later life. Although our cohort is very large, the small numbers of specific cancer cases limited the study power investigating the associations between bereavement and risks of many specific cancer types. Thus, both positive and negative findings should be read with caution as indicated by the wide CIs for the estimates. Another limitation of the study is that we only included exposure to stress due to loss of a close relative, not stress from other sources. Stress could arise from many other situations, such as the death of a close friend, or a serious illness of a next to kin, which may have a similar effect, which will be misclassified as non-exposed in this study. This misclassification is likely non-differential and would thus have drawn the risk estimates towards unity.

CONCLUSIONS

Severe antenatal stress exposure due to maternal loss of the closest family member, a child or a spouse, was associated with an

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increased risk of certain childhood cancers in offspring, but not with the childhood cancer in general. Hormonal disturbance may be involved in the observed associations (Reiche *et al*, 2004; Ekbom, 2006), but our findings may be due to chance and need to be replicated in an independent data source.

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Conflict of interest

The authors declare no conflict of interest.

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