CANCER EPIDEMIOLOGY

Poor academic performance in offspring of survivors with childhood or adolescent central nervous system tumor in Sweden

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Abstract
The number of children who were born after their parents were diagnosed with central nervous system (CNS) tumor is increasing, but it remains largely unknown regarding the academic performance of these children. We aimed to investigate whether children of survivors with childhood or adolescent CNS tumor were associated with poor academic performance. Children of survivors of CNS tumor were identified by combining the nationwide Swedish Cancer Register and the Multi-Generation Register, and those who have completed compulsory education in Sweden between 1989 and 2015 were included in our study. "Poor academic performance" was defined as a z-score of the academic performance below the 10th percentile. Conditional logistic regression and quantile regression were used to examine the association. A total of 655 children were born after their parental diagnosis of CNS tumor and they had 1.39 times higher risk of achieving poor academic performance as compared to the matched comparisons (95% CI = 1.10-1.76). The poor academic performance was even more pronounced in boys, among those with a paternal diagnosis of CNS tumor and those with a parental ependymoma. The observed association differed depending on preterm birth. In addition, the strength of the association declined with the increased quantiles of academic performance z-score. Our data suggest that parental CNS tumor affects the subsequent academic achievements among children born after the parental tumor.

KEYWORDS
academic performance, central nervous system tumor, epidemiology

1 INTRODUCTION

The development of medical therapies allows a greater number of patients with pediatric diseases, including patients with central nervous system (CNS) tumor, to survive until parenting age, leading to the increase in the number of children having a parent with physical illness.1 Available researches suggest that parental physical conditions might play a role in physical and psychological functioning for their children, and both of them might be related to academic performance in school.1–5

In the Nordic countries, CNS tumor ranks as the second most common cancer among the population below 20 years of age.6 Its...
incidence rate remains increasing but the mortality rate has been slightly decreased, which has led to a growing number of children born after their parents have been diagnosed with CNS tumor. The impact of parental CNS tumor on academic performance in their children might be more pronounced than other cancers, probably due to its neurocognitive late effects. The brain is developing continuously during childhood and adolescence and is more sensitive to various tumor treatments. It is well-recognized that parental cognitive function, educational and socioeconomic status play a crucial role in offering educational support. Furthermore, CNS tumor and its treatments were associated with a higher risk of subsequent reproductive impairment and adverse pregnancy outcomes, such as preterm birth, which were considered to be associated with long-term health issues as well as academic difficulties. It is thus plausible that parental diagnosis with CNS tumor in early life could affect their children’s academic performance. However, this topic remains under investigation.

In this nationwide cohort study, we aimed to investigate the association between parental diagnosis with CNS tumor in childhood or adolescence and the poor academic performance among their children and to explore whether histology- and age-specific parental CNS tumor will affect their children’s academic performance. In addition, we estimated how the association varied across the distribution of academic performance in quantile regression.

## 2 | METHODS

### 2.1 | Study population

All singleton live births in Sweden between 1973 and 1999 were identified by retrieving data from the Swedish Medical Birth Register, which was established in 1973. Linking to the Swedish Multi-Generation Register (including all offspring born after 1932 and their parents) and to the Swedish Cancer Registry (established in 1958) allowed us to identify their parental diagnosis of CNS tumor. The seventh version of the International Classification of Disease (ICD-7) code (193) was used to identify patients with CNS tumor from the Swedish Cancer Registry, which included the date at diagnosis and the histology of tumor. According to the 2016 World Health Organization Classification of Tumors of the Central Nervous System, we classified CNS tumor into seven categories: medulloblastoma, ependymoma, neurinoma, haemangioma, astrocytoma, meningioma and others (neuroblastoma, craniopharyngiomas, ependymoblastoma, pinealoma, ganglieneuroma and unknown types).

The study cohort included children whose mother or father had a previous diagnosis with CNS tumor below 20 years old and survived for more than 5 years. For each child in the study cohort, we randomly selected five children whose parents did not have CNS tumor to generate the comparison cohort. The comparison cohort was matched by the birth year, gender, maternal and paternal age at birth, as well as maternal and paternal highest education.

A unique individual national identification number was assigned to all the residents living in Sweden for more than 3 months. To ensure confidentiality, the national identification number was replaced by a series of numbers and was used to link the above national registers in our study.

### 2.2 | Assessment of covariates

Parental age at diagnosis with CNS tumor was retrieved from the Swedish Cancer Registry, modeled as childhood survivors (<14 years old) and adolescent survivors (15-19 years old). Parental age at childbirth was collected by linking the Swedish Medical Birth Register and the Swedish Multi-Generation Register. Parental highest education was collected from the Total Population Register, which was created in 1960. It was modeled as 1 to 9 years (compulsory high school or less), 10 to 11 years (practical high school or some theoretical high school) and 12+ years (theoretical high school and/or college and/or postgraduate study) in our study. Preterm birth was defined as a live birth occurring at less than 37 full weeks of gestation, which was obtained from the Swedish Medical Birth Register.

### 2.3 | Assessment of outcome

The outcome was academic performance measured by the final grade achieved after completing the compulsory years of education at age 16 years. The information was recorded in the Swedish Ninth Grade Register, which started in 1989 and was last updated in 2015. In Sweden, students from all regular schools receive the uniform school curriculum and evaluation criteria for academic performance. Two different grading systems were used during the study period, one with the mean score of academic performance ranging from 1 to 5 for children who achieved their final grade before 1998 (children born between 1973 and 1982) and the other ranging from 80 to 320 for those achieved from 1998 onwards (children born between 1982 and 1999). We thus calculated the year-standardized z-scores based on...
the original grades to ensure comparability between the two grading systems. In our study, we defined "poor academic performance" as a $z$-score of the academic performance below the 10th percentile in the logistic regression model. And, it was further modeled as continuous variables in the quantile regression model by modeling every tenth quantile from the 10th to the 90th.

### 2.4 Statistical analysis

A Chi-squared test was used to compare the distribution of the general characteristics between the study cohort and the matched comparisons. Conditional logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (95% CI) for the association between parental diagnosis with CNS tumor and poor academic performance in their children. The association was further stratified based on the child's gender (male and female), paternal or maternal survivors, and parental age at diagnosis (childhood tumor or adolescence tumor), type of tumor, parental highest education and the time interval between parental diagnosis and childbirth (<11, 11-20 and >20), and the analyses were done using conditional logistic regression by comparing with their matched comparisons. With consideration of preterm birth might act as a mediator for the observed association, we explored further whether the observed

| TABLE 1 | General characteristics among offspring of survivors with central nervous system tumor and matched comparisons |
|----------|-------------------------------------------------------------------------------------------------------------|
| Variables | Offspring of survivors | Matched comparisons |
|          | Number of individuals | Number of poor academic performance, n (%)a | Number of individuals | Number of poor academic performance, n (%)a | P-value |
| Overall  | 655                    | 91 (13.9) | 3275 | 327 (10.0) | .003 |
| Gender of offspring | | | | | |
| Female   | 304                    | 23 (7.6)  | 1520 | 123 (8.1)  | .758 |
| Male     | 351                    | 68 (19.4) | 1755 | 204 (11.6) | <.001 |
| Year of childbirth | | | | | |
| <1990    | 315                    | 49 (15.6) | 1575 | 162 (10.3) | .007 |
| ≥1990    | 340                    | 42 (12.4) | 1700 | 165 (9.7)  | .140 |
| Maternal age at birth | | | | | |
| <30      | 191                    | 44 (23.0) | 955  | 150 (15.7) | .014 |
| 30-34    | 227                    | 27 (11.9) | 1135 | 94 (8.3)   | .081 |
| ≥35      | 237                    | 20 (8.4)  | 1185 | 83 (7)     | .437 |
| Paternal age at birth | | | | | |
| <30      | 296                    | 48 (16.2) | 1480 | 164 (11.1) | .013 |
| 30-34    | 220                    | 30 (13.6) | 1100 | 99 (9.0)   | .035 |
| ≥35      | 139                    | 13 (9.4)  | 695  | 64 (9.2)   | .957 |
| Maternal highest education | | | | | |
| 1-9 years | 66                     | 27 (40.9) | 330  | 79 (23.9)  | .005 |
| 10-11 years | 372               | 56 (15.1) | 1860 | 193 (10.4) | .009 |
| 12+ years | 217                   | 8 (3.7)   | 1085 | 55 (5.1)   | .386 |
| Paternal highest education | | | | | |
| 1-9 years | 113                   | 25 (22.1) | 565  | 95 (16.8)  | .177 |
| 10-11 years | 325             | 54 (16.2) | 1625 | 168 (10.3) | .001 |
| 12+ years | 217                   | 12 (5.5)  | 1085 | 64 (5.9)   | .833 |
| Preterm birth | | | | | |
| Yes      | 44                     | 12 (27.3) | 157  | 16 (10.2)  | .004 |
| No       | 611                    | 79 (12.9) | 3118 | 311 (10.0) | .030 |
| Time interval between parental diagnosis and childbirth | | | | | |
| <11 years | 367                   | 63 (17.2) | 1835 | 210 (11.4) | .002 |
| 11-20 years | 189             | 21 (11.1) | 945  | 73 (7.7)   | .123 |
| >20 years | 99                     | 7 (7.1)   | 495  | 44 (8.9)   | .556 |

*a"Poor academic performance" was defined as $z$-score of academic performance below the 10th percentile in matched group."
association was affected by preterm birth through conditional logistic regression analysis and compared to the matched comparisons. We also calculated the remaining direct association between parental diagnosis and academic performance by multivariate logistic regression after taking into preterm birth and other factors used for the matching.

Quantile regression, which is a distribution-free method, was further used in our study due to the skewness of $z$ scores of academic performance. Rather than the limited estimation on only poor performance in the logistic regression model, this approach allowed us to examine if the association is stable across the entire distribution of $z$ scores (ie, to explore the possible different effects on the good or poor academic performance).

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

## RESULTS

As shown in Table 1, a total of 655 children were born after their parents were diagnosed with CNS tumor and had completed compulsory education in Sweden between 1989 and 2015. In addition, a total of 3275 controls were randomly selected conditional on the several variables listed in Table 1. The study cohort had a significantly higher proportion of children with poor academic performance as compared to the matched comparisons (13.9% vs 10.0%, $P$-value = .003).

### TABLE 2  Odd ratios for poor academic performance among offspring of survivors with central nervous system tumor compared to their matched comparisons

| Variables                                           | Number of offspring of survivors | Number of poor academic performance, n (%) | OR    | 95% CI     | $P$-value |
|-----------------------------------------------------|----------------------------------|--------------------------------------------|-------|------------|-----------|
| Overall                                             | 655                              | 91 (13.9)                                  | 1.39  | 1.10-1.76  | .005      |
| Gender of offspring                                  |                                  |                                            |       |            |           |
| Female                                              | 304                              | 23 (7.6)                                   | 0.94  | 0.60-1.46  | .767      |
| Male                                                | 351                              | 68 (19.4)                                  | 1.67  | 1.27-2.19  | <.001     |
| Parental diagnosis                                   |                                  |                                            |       |            |           |
| Maternal diagnosis                                  | 362                              | 46 (12.7)                                  | 1.23  | 0.89-1.70  | .208      |
| Paternal diagnosis                                  | 293                              | 45 (15.4)                                  | 1.61  | 1.15-2.25  | .006      |
| Parental age at diagnosis with CNS tumor            |                                  |                                            |       |            |           |
| Childhood                                           | 433                              | 58 (13.4)                                  | 1.34  | 1.01-1.79  | .0046     |
| Adolescence                                         | 222                              | 33 (14.9)                                  | 1.49  | 1.01-2.19  | .0046     |
| Time interval between parental diagnosis and childbirth |                                  |                                            |       |            |           |
| <11 years                                           | 367                              | 63 (17.2)                                  | 1.50  | 1.13-1.99  | .005      |
| 11-20 years                                         | 189                              | 21 (11.1)                                  | 1.44  | 0.89-2.34  | .142      |
| >20 years                                           | 99                               | 7 (7.1)                                    | 0.80  | 0.36-1.77  | .574      |
| Maternal highest education                          |                                  |                                            |       |            |           |
| 1-9 years                                           | 191                              | 44 (23.0)                                  | 1.71  | 1.10-2.65  | .016      |
| 10-11 years                                         | 227                              | 27 (11.9)                                  | 1.45  | 1.08-1.96  | .014      |
| 12+ years                                          | 237                              | 20 (8.4)                                   | 0.73  | 0.35-1.53  | .401      |
| Paternal highest education                          |                                  |                                            |       |            |           |
| 1-9 years                                           | 296                              | 48 (16.2)                                  | 1.32  | 0.85-2.05  | .222      |
| 10-11 years                                         | 220                              | 30 (13.6)                                  | 1.61  | 1.18-2.18  | .002      |
| 12+ years                                          | 139                              | 13 (9.4)                                   | 0.94  | 0.51-1.74  | .837      |
| Types of parental CNS tumor                         |                                  |                                            |       |            |           |
| Ependymoma                                          | 37                               | 7 (18.9)                                   | 2.92  | 1.15-7.41  | .024      |
| Neurinoma                                           | 61                               | 11 (18.0)                                  | 1.53  | 0.78-3.00  | .219      |
| Astrocytoma                                         | 364                              | 43 (11.8)                                  | 1.28  | 0.92-1.79  | .149      |
| Meningioma                                          | 28                               | 4 (14.3)                                   | 1.25  | 0.42-3.74  | .690      |
| Medulloblastoma                                      | 22                               | 4 (18.2)                                   | 1.18  | 0.40-3.50  | .770      |
| Hemangioma                                          | 13                               | 2 (15.4)                                   | 0.77  | 0.17-3.41  | .730      |
| Others                                              | 130                              | 20 (15.4)                                  | 1.54  | 0.93-2.54  | .092      |

Note: “Poor academic performance” was defined as $z$-score of academic performance below the 10th percentile in matched group. Abbreviations: CI, confidence intervals; CNS, central nervous system; OR, odd ratio.
In Table 2, we calculated the ORs for poor academic performance among children of survivors with CNS tumor, and we found that they experienced 1.39 times higher risk to achieve poor academic performance (95% CI = 1.10-1.76, P-value = .005). The association varied by gender, with an increased risk in boys but not in girls (ORmale = 1.67, 95% CI = 1.27-2.19; ORfemale = 0.94, 95% CI = 0.60-1.46). And, the positive association was slightly stronger with parental diagnosis in adolescence (ORchildhood = 1.34 vs ORadolescence = 1.49). Results from stratified analysis found that paternal diagnosis of CNS tumor was significantly associated with a poor academic performance in offspring, but not in children with a maternal diagnosis (ORpaternal = 1.61, 95% CI = 1.15-2.25; ORmaternal = 1.23, 95% CI = 0.89-1.70). In addition, the risk of achieving poor academic performance in the children was negatively associated with the time interval, with the strongest

**FIGURE 1** Path analysis among parental diagnosis with central nervous system tumor, preterm birth and poor academic performance

| Parental diagnosis with CNS tumor | Preterm birth | Direct association | Poor academic performance |
|----------------------------------|--------------|--------------------|---------------------------|
| **Total association**            | 1.39         | 1.10-1.76          |                           |
| Stratified by preterm birth      |              |                    |                           |
| Preterm birth                    | 2.22         | 2.02-4.86          |                           |
| No preterm birth                 | 1.31         | 1.02-1.67          |                           |
| **Direct association**           | 1.38         | 1.09-1.74          |                           |

**FIGURE 2** Coefficients at each decile for academic performance using quantile regression. *Gray area indicates 95% confidence intervals (CIs). A, Matched comparisons (Intercept); B, offspring of overall survivors; C, offspring of female survivors; D, offspring of male survivors
association (OR = 1.50) noted for children born within 10 years after parental diagnosis, followed by children born between 11 and 20 years postdiagnosis (OR = 1.44) and those born more than 20 years after diagnosis (OR = 0.80). The ORs differed from 1.71, 1.45 to 0.73 in children with the increasing level of the maternal highest education, and from 1.32, 1.61 to 0.94 in children with the increasing level of the paternal highest education. Regarding the specific histologic type, parental diagnosis of ependymoma (OR = 2.92) showed the strongest association with poor academic performance in children.

In Figure 1, we found that preterm birth strengthened the association (OR_{preterm} = 2.22, 95% CI = 2.02-4.86; OR_{full-term} = 1.31, 95% CI = 1.02-1.67). By including preterm birth in the multivariate logistic regression model, there was remaining direct association between parental CNS tumor and academic performance (OR = 1.38, 95% CI = 1.09-1.74).

Quantile regression showed that parental diagnosis with CNS tumor was associated with poor academic performance (Figure 2 and Table S1). The association was decreased with the increasing quantile of z-score. For example, at the 10th percentile of the z-score distribution, children of survivors were associated with a lower z-score of 0.259. The overall estimated coefficient increased to zero at the 60th percentile and then almost remained stable. A similar tendency was observed for the offspring of female survivors as well as for the offspring of male survivors, but paternal diagnosis strengthened the association across the board.

4 | DISCUSSION

In this nationwide population-based study, parental diagnosis with CNS tumor before the age of 20 years was associated with an increased risk of achieving poor academic performance in their children who were born after their diagnosis. The positive association was more pronounced in boys and in children with a paternal diagnosis of CNS tumor, and declined with the time interval between parental diagnosis and childbirth. However, higher parental education level was likely to weaken the observed positive association. In addition, the strength of the association varied by histological subtype of parental CNS tumor, with the strongest association noted for ependymoma. Preterm birth was suggested to be an important variable for the observed association. The association was noticeable only in the lower quantiles of z-score, suggesting that parental diagnosis was related to a higher risk of "poor" academic performance but not related to lower risk of "good" academic performance.

A Danish registered-based study found that children who experienced parental cancer in early adulthood achieved a slightly lower final grade and had a higher risk of achieving low educational attainment (relative risk ratio: 1.20; 95% CI 1.14-1.25). They observed that the highest risk to get lower socioeconomic attainment was found in children experiencing parental cancer under 4 years old; this indicates the persistence of the effect of parental cancer. The impact of parental cancer experience (children born before parental diagnosis) on children’s academic performance was largely represented through psychological functioning. However, children born after parental diagnosis of cancer might be affected by treatment-related late effects, physically and psychologically. But until now, the impact has not been investigated.

In this population-based study, we specifically explored the association of parental diagnosis of childhood or adolescent CNS tumor with children’s academic performance. We did find a significantly higher risk of having poor academic performance among children of these CNS tumor survivors as compared to the matched comparisons. It was reported that around 62% of survivors with childhood cancer had adverse late effects, which might lead to less caregiving and less support to their children; this may affect their children’s academic achievement. Interestingly, prior studies found that fathers’ involvement could strengthen the association between parents’ monitoring and school performance, and this association was stronger for boys, which was in agreement with our observation that the elevated risk to get poor academic performance was even more pronounced among boys compared to girls (1.67 in boys vs 0.94 in girls). In addition, we have previously observed a significantly higher risk of hospitalization among offspring of male survivors with childhood CNS tumor but not female childhood survivors, probably due to the greater complement of primordial follicles in younger females. Further analyses by the time interval between parental tumor diagnosis and subsequent childbirth indicated that the impact of parental CNS tumor or treatments on children’s academic performance might be diminished with time after treatments. It should be noted that the association might be histologic-specific, suggesting that further studies are highly needed to explore the underlying mechanisms.

Because of vulnerable brain and neuraxis in childhood and adolescence, survivors of CNS tumor in early life commonly experienced neurocognitive late effects caused by radiation therapy or chemotherapy. And it is well-known that neurocognitive impairments are strongly linked to poor intelligence quotient, poor academic performance and lower educational achievements. Parental educational level was always considered as an important factor for children’s academic achievements. Stratified analysis in our study showed that a higher level of parental education was prone to weaken the association, especially higher maternal education, suggesting educational involvement from parents might play a role in reducing the adverse effects of parental diagnosis with CNS tumor. However, it should be also noted that CNS tumor survivors who had a higher education might experience less aggressive medical treatment or their CNS tumor was less aggressive.

CNS tumor survivors were associated with an elevated risk of adverse reproductive outcomes, such as preterm birth, which was the leading global public health issue associated with the higher risk of long-term morbidity, including neurologic and developmental disabilities than infants born at term. Findings in this study also showed a considerably higher risk of poor academic performance among preterm-born children than children born at term, which suggests that more attention should be paid to the school performance of the study children who were born preterm. After including preterm birth as a
mediator in the multivariate logistic regression, there was a remaining direct association between poor academic performance and parental diagnosis with CNS tumor, indicating there are other unmeasured factors that could be involved in the observed association.

Furthermore, quantile regression found that the negative association between parental diagnosis and z-score of academic achievements declined with the increasing quantiles of z-score. This result was reasonable and supportive of the main finding in our study, suggesting that parental diagnosis tended to result in an increased risk of getting poor academic performance but did not make a difference in the likelihood of getting a good academic performance.

To the best of our knowledge, this is the first study to explore whether parental diagnosis with childhood or adolescent CNS tumor will affect children's academic performance. The nationwide register-based data on the identification of CNS tumor, the pedigree relationship and the uniform assessment of overall grades across the whole country ensured the accuracy of measurement of exposure and outcome. The national population allowed us to select matched comparisons conditional on several important confounding factors. A limitation was that Swedish Ninth Grade Register only includes the score of children who have completed compulsory education in the Swedish regular schools, and it is thus unknown whether children of CNS tumor survivors might have even worse academic performance if they did not complete the compulsory education. However, only 5.6% of children born between 1973 and 1999 did not have a record in the Swedish Ninth Grade Register, and there was no significant difference of the distribution between the study cohort and the comparison cohort (P-value = .146), thus suggesting that it might not affect the observed association. Lack of information about treatments of parental CNS tumor was another limitation, making it unavailable to examine the impact of different therapies.

In conclusion, children of survivors with CNS tumor below 20 years old were at higher risk of getting poor academic performance as compared to the controls, and the association was stronger among boys, children of male survivors, children of survivors with ependymoma and preterm-born children. However, higher parental education and a longer time interval between parental diagnosis and childbirth can weaken the association. Therefore, it is pivotal to provide recommendations for CNS tumor survivors who plan to have a childbirth. The authors appreciate the valuable comments on the text of the CPF's manuscript. The researchers were independent of the funding agencies.

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CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

DATA ACCESSIBILITY
Data cannot be shared publicly because of confidentiality under the current Swedish legislation. Registry data are available from the appropriate Swedish authorities (the Swedish National Board of Health and Welfare (https://www.socialstyrelsen.se/en) and Statistics Sweden (https://www.scb.se/en), for researchers who meet the criteria for access to confidential data.

ETHICS STATEMENT
The Ethics Committee at Lund University approved (February 6, 2013) this nationwide cohort study (Dnr 2012/795). The project database is located at the Center for Primary Health Care Research in Malmö, Sweden. Informed consent is not needed in Sweden for the register-based study.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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