# Cohort Selection *in Utero* Against Male Twins and Childhood Cancers: A Population-Based Register Study

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## ABSTRACT

**Background:** Cancer ranks as the second leading cause of death among children aged 1 to 14 years in the US. Previous research finds that strong cohort selection *in utero* against males precedes a reduction in live-born males considered frail. We examine whether such cohort selection *in utero* may similarly affect the frequency of childhood cancers among male live births.

**Methods:** We examined 1,368 childhood cancers among males born in Sweden over 144 months, from January 1990 to December 2001, and followed to age 15 in the Swedish Cancer Registry. We retrieved the count of male twins by birth month from the Swedish Birth Registry. We applied autoregressive, integrated, moving average (ARIMA) time-series methods to identify and control for temporal patterns monthly childhood cancers and to evaluate robustness of results.

**Results:** Fewer childhood cancers occur among monthly male birth cohorts with elevated selection *in utero* (i.e., a low count of live-born male twins). This association appears in the concurrent month (coef=.04, 95% CI = 0.001-0.079) as well as in the following month in which most births from the twin's conception cohort are "scheduled" to be born (coef=.055, 95% CI =0.017-0.094).

**Conclusions:** Elevated cohort selection *in utero* may reduce the number of frail male gestations that would otherwise have survived to birth and received a cancer diagnosis during childhood.

**Impact:** This novel result warrants further investigation of prenatal exposures, including those at the population level, that may induce cohort selection *in utero* for some cancer types but not others.

## INTRODUCTION

Childhood cancer remains a major contributor to the burden of disease in the United States and elsewhere despite the fact that treatment advances since the 1970s have substantially improved five-year survival rates.[1] Cancer ranks as the second leading cause of death among children aged 1 to 14 years in the US.[2] Survivors of childhood cancer, moreover, show an elevated risk of morbidity[3] including not only chronic somatic illness and hospitalizations,[4] but also lower self-reported mental health and wellbeing.[5] In addition, both male[6] and female[7,8] childhood cancer survivors show reduced reproductive success in adulthood. A better understanding of its natural history, therefore, remains high on the research agenda for the health sciences.

Much of the etiology of childhood cancers remains unknown.[9] Increasing research, however, indicates that genetic and epigenetic alterations during particular windows of prenatal development may play a role.[10] For example, research on acute lymphocytic leukemia—the most prevalent childhood cancer—indicates a prenatal origin.[11,12] This work, in conjunction with research on broader ambient, time-varying exposures *in utero* (e.g., air pollution), indicates that studies on relevant factors during gestation may help to trace additional causes of childhood cancer.[13]

One prenatal phenomenon examined in the epidemiology of childhood diseases, but not previously applied to cancers, involves cohort selection *in utero*.[14,15] Cohort selection *in utero* refers to the spontaneous termination, without live birth, of thirty to seventy percent of human gestations.[16,17] The gestations terminated do not represent a random sample of their conception cohort. Among terminations that clinicians detect, a disproportionate fraction involve fetuses exhibiting chromosomal anomalies and/or

congenital defects.[18] In addition, the terminated fraction of abnormal fetuses in conception cohorts varies across place and over time.[14,19,20]

Previous research finds that birth cohorts exhibiting signals of unexpectedly great selection *in utero* also show a reduced risk of birth defects among live-born males.[21,22] The authors reasoned that, consistent with strong evolutionary theory, worsening environmental threats to maternal resources or infant health would induce greater selection *in utero* against fetuses. The researchers focused on males because, given that they die in infancy more frequently than do females despite receiving relatively more maternal investment, any prenatal mechanism(s) conserved by natural selection *in utero* would favor termination of frail males unlikely to thrive if born.[23–26] Evolutionary theory, therefore, predicts that natural selection would conserve any mutation that terminated gestations of male fetuses with birth defects during stressful times. Findings from California using almost half a million births support the hypothesis in that monthly birth cohorts with unexpectedly strong signals of selection *in utero* show a reduced risk of defects among live-born males.[21,22]

In this paper we explore the possibility that childhood cancers diagnosed through age <15 years among monthly birth cohorts will vary with indicators of selection *in utero*. We conduct our test using data from Sweden which maintains the world's highest quality and most complete cancer and birth registries.[27] Consistent with theory and previous work, we focus our exploration on the outcome of childhood cancers among on males.

We, as with prior work, use as the exposure of cohort selection the frequency of live-born male twins.[28–30] Mothers of male twins historically show low reproductive fitness because male twins exhibit the highest rate of infant mortality and the lowest

lifetime reproductive success, relative to female twins and singleton males and females.[31,32] Consistent with the aforementioned theory that spontaneous abortion of fetuses with low potential reproductive fitness increases when the environment becomes threatening, the frequency of twins among live male births falls following population stressors (e.g., economic downturns, mass shootings).[33] Based on theory and these empirical studies, the frequency of live-born male twins falls with increased selection *in utero* for the entire conception cohort.[34] We, therefore, explore whether a reduction in the count of live-born male twins corresponds with a reduction in childhood cancers among males. Beyond contributing to the basic literature concerned with selection *in utero*, this exploration could, depending on the outcome, add to, or subtract from, the impetus to pursue more intrusive research into the fetal origins of childhood cancer.

## MATERIALS AND METHODS

### Data and Variables

We acquired information on childhood cancers from the Swedish Cancer registry.[23] All newly diagnosed cancers in Sweden must be reported to this Register, by clinicians, pathologists or cytologists. We defined childhood cancers as those diagnosed before age 15 among males born in 1990 (earliest available cohort for which the corresponding number of male twins could be linked) through 2001 (most recent cohort reaching age 15 at the time of our test). To assist with comparing cancers over time, the register harmonizes all International Classification of Diseases (ICD) for cancer across waves with the ICD-7 code. We retrieved the count, by sex, of the following cancer diagnoses: leukemia, brain and spinal cord tumors, neuroblastoma, Wilms tumor, lymphoma (including both Hodgkin and non-Hodgkin), and bone cancer (including

osteosarcoma and Ewing sarcoma). Table 1 provides the ICD-7 codes used to retrieve these childhood cancers as well as corresponding ICD-10 codes (for reference).

We obtained monthly counts of male live-born twins from the Swedish Medical Birth Registry.[35] Together, the cancer and birth registry data allowed us to create time series characterized by 144 monthly birth cohorts (i.e., January 1990 to December 2001). The time series ends with the December 2001 birth cohort to allow for complete follow-up of cancer diagnosis to <15 years, as 2016 represents the last year in which data from the Sweden's Cancer Registry were retrieved.

Analysis

Childhood cancers may exhibit patterns over time such as trend, seasonality, or the tendency for high or low monthly values to persist into subsequent months.[1] A trend, for instance, could arise simply from increasing size of the birth cohorts at risk over time. These patterns, collectively referred to as autocorrelation, violate the assumption of correlational tests because the expected value of childhood cancers in any month is not the mean of all months. To address this autocorrelation issue, we used several steps recommended in the time-series literature to estimate the association between the frequency of male twins and childhood cancers.[36]

1. We regressed male childhood cancers in monthly birth cohorts on those in *female* birth cohorts. This step removes from male cohorts any temporal variation, including autocorrelation and the effect of data recording artifacts, shared with female cohorts.

2. We used Box-Jenkins[37] methods to identify and model autocorrelation in the residuals of the regression that are unique to males.
3. We used Box-Jenkins methods to identify and model autocorrelation, if any, in the count of male twins born in each month. The residuals of this model gauge the difference between the observed and expected values of male twin births. These residuals become the independent variable of our test.
4. We specified and estimated a Box-Jenkins transfer function formed by adding the residuals of the model estimated in step 3 to predictors in the model estimated in step 2. Given that over half of male twins are born preterm,[38] we specified the residuals not only in the same month as the incidence of childhood cancers in male birth cohorts (i.e., month t), but also in the two previous months (i.e., months t-1 and t-2). This specification acknowledges that most male twins delivered in month t "belong" to a conception cohort "scheduled" to be born one or two months later. Our test equation, therefore, was as follows:

$$MC_t = c + \omega_1 FC_t + \omega_2 MT_t + \omega_3 MT_{t-1} + \omega_4 MT_{t-2} + (1-\theta B^q)/(1-\phi B^p)a_t$$

$MC_t$ is the count of childhood cancers among males born in month t.

c is a constant.

$\omega_1$ through $\omega_4$ are effect parameters.

$FC_t$ is the count of childhood cancers among *females* born in month t.

$MT_t$ through $MT_{t-2}$ are residual counts (derived in step 3 above) of male twins born in months t, t-1, and t-2.

$\theta$ is a moving average parameter.

$\phi$ is an autoregressive parameter.

B is the "backshift operator," or value of a for month t-q or at month t-p.

$a_t$ is the residual of the model at year t.

If male conception cohorts signaling relatively great selection *in utero* yielded fewer than expected live births of males eventually diagnosed with childhood cancers, $\omega_1$ and $\omega_2$ will appear detectably greater than 0. We set the criterion for detection at twice the standard error.

**RESULTS**

We observed 2,485 childhood cancers over the test period, of which 1,368 occurred among males (Table 2). Leukemia and neuroblastomas account for 38.4% and 36.9% (respectively) of the total cancers examined (Table 3). The mean monthly count of childhood cancers among male birth cohorts is 9.5 (Standard Error [SE] = 0.31). These cancers appear more frequently among males than among females (female monthly mean = 7.7; SE= 0.24). Figure 1A shows the count of childhood cancers among males born over 144 months (i.e., Jan 1990 to Dec 2001) and followed to age 15 years.

Steps 1 and 2, predicting male childhood cancers from those among females and from autocorrelation produced the following coefficients:

$$MC_t = 7.565 + 0.228FC_t + 1/(1-0.210B^7)\, a_t$$

The positive FC coefficient (i.e., 0.228, SE=0.104, p<.05) measures the association between male and female childhood cancers. The autoregressive parameter (i.e., -0.210 at t+7) indicates that about 20% of high or low values of male childhood cancers "echo" 7 months later.

Over the 144 months, 17,294 of all births were male twins (monthly mean = 120.10). The best-fitting Box-Jenkins model, estimated in Step 3, for the count of male twins, was as follows:

$$MT_t = 121.625 + 1/(1\text{-}0.343B^{12})\, a_t$$

The autoregressive parameter at t-12 (0.343, SE=0.080, p<.05) months gauges the known seasonality in fertility in general and in twinning in particular.[39,40] Figure 2 shows the fitted (i.e., expected) and observed values of this variable over the test period. The differences between these values (i.e., expected – observed) measure the degree to which selection *in utero* varied over conception cohorts.

Table 2 shows the results of Step 4 in which we estimated our test equation. The coefficients for the residualized count of male twins suggests a positive association between selection *in utero* (i.e., a decreased count of live-born male twins) and childhood cancers among monthly male birth cohorts. This association appears in the synchronous month (coef=.04, 95% CI = 0.001-0.079) as well as in the month after (coef=.055, 95% CI =0.017-0.094)) male twins increase unexpectedly (i.e., childhood cancers among birth cohort in month t and male twin counts in month t-1).

We conducted outlier adjustment routines to determine whether extreme values in male childhood cancers distorted our estimation of standard errors for the male twin

coefficients. Results from the outlier-adjusted model produced essentially the same inference as in the original test (Supplementary Table 1), although the confidence interval for the coefficient of the synchronous month moved further from the null.

To give the reader a sense of the magnitude of our findings, we estimated the number of male childhood cancer cases associated with a standard deviation increase in selection *in utero* against males, as gauged by a reduction in the count of live-born male twins. The monthly standard deviation in the count of male twins is 15.96. Multiplication of the coefficients discovered in Table 2 by this standard deviation (i.e., 0.04 at no lag and 0.055 at lag 1 month) indicates 1.52 fewer than expected live-born males ultimately diagnosed with childhood cancer. Application of this reduction to the mean equates to a 7.96% reduction in childhood cancers among males statistically attributable to a one standard deviation increase in cohort selection *in utero* against males.

## DISCUSSION

Epidemiologic evidence suggests that selection pressure against frail fetuses leads to fewer birth defects among live-born males.[22] We explored whether the monthly count of male twins, an indicator of selection *in utero,* similarly predicts the likelihood of childhood cancers among monthly male birth cohorts in Sweden. Our results suggest a positive association such that low counts of male twins in a month correspond with fewer than expected childhood cancers among males <15 years of age that were born in that same month and one month later. Findings support the inference that selection *in utero* may reduce the number of frail male gestations that would otherwise have survived to birth and received a cancer diagnosis during childhood.

Strengths of our approach include that the association we found cannot arise from seasonality or from any "third variable" that exhibits autocorrelation because we removed such autocorrelation from male childhood cancers. Adjustment for childhood cancers among females, moreover, minimizes the threat of confounding by variables which affect the likelihood of childhood cancer in both males and females. In addition, the Swedish Registry provides complete case ascertainment through to <15 years of age for all birth cohorts in our test period, which lends external validity to the population base of Sweden. The fact that the Registry data permit alignment by monthly birth cohort, moreover, should encourage examinations of prenatal causes of cohort variation in childhood cancer incidence.

Our findings align with previous research on cohort variation in selection *in utero* against other conditions that impose severe morbidity (e.g., birth defects).[21,22,39] However, the mechanism, or set of mechanisms, by which relatively frail fetuses may "signal" their hardiness to the mother remains unknown. Data limitations precluded examination of the relation between other candidate measures of cohort selection and male childhood cancers. Cohort values of human chorionic gonadotropin, for instance, may serve as one biomarker that signals offspring quality, albeit with some error.[40–42] To the extent that other registries routinely collect such biomarker and/or "omics" information on pregnancies, linkage of this information to birth cohorts and cancer registries may identify other candidates which signal unusually high or low strength of selection *in utero*.

Given the rarity of childhood cancers among males in any particular birth month, we (owing to statistical considerations) combined several types of childhood cancers. These cancers, however, show distinct etiology and may have different prenatal

antecedents.[2] We, therefore, do not know if our results generalize equivalently to each cancer type. Societies larger than Sweden may show larger monthly frequency of the more common cancers (e.g., leukemia, brain and other nervous system tumors). Studies of these larger populations, such as in the US following ambient shocks (e.g., terrorist attacks of 9/11, the Great Recession), may permit identification of which childhood cancer type appears particularly responsive to temporal variation in cohort selection. We also did not include some embryonal tumors (e.g., hepatoblastoma) in the aggregate-level analysis owing to the inability to separate from earlier ICD versions these distinct diagnoses from broader disease categories.

Other limitations include that we did not have access to individual-level data, thereby precluding an analysis of demographic or biological factors that affect risk of twinning and/or childhood cancers. For instance, whereas the incidence of dizygotic twinning (owing to increased use of *in vitro* fertilization [IVF] technologies) likely increased over the study period, our aggregate-level data could not assess the potential role of changing twin composition over time on childhood cancers.[43] Our time-series methods rigorously control for any potential pattern (e.g., trend) in childhood cancers induced by compositional changes over time in zygosity of twins. We, nevertheless, recommend additional work using individual-level data to more carefully examine the extent to which changes over time in dizygotic twinning affect child health.

Researchers attribute the etiology of childhood cancers to inherited and acquired gene mutations, as well as to environmental factors that cause mutations (e.g., radiation).[44,45] Some children inherit mutations from a parent, thus increasing their risk of certain types of cancer.[44,45] However, most childhood cancers reportedly stem from acquired mutations that may occur in gestation.[44,45] Common embryonal tumors,

established in fetal tissue, include neuroblastomas and Wilm's tumors.[46] Although causes of many childhood cancer remain unknown, epidemiologic studies report that childhood cancers correspond with risk factors such as birth weight, parental age, consumption of substances including alcohol and/or tobacco, and congenital anomalies.[47] Many, but not all, studies of maternal pregnancy histories also find that children born to mothers with a prior 2nd or 3rd trimester spontaneous abortion show an increased risk of childhood cancer diagnosis.[48–50] Additionally, studies find an increased incidence of childhood cancers among males as opposed to females at every age of childhood and adolescence.[51] This sex difference warrants further investigation into whether variation in cohort selection *in utero* may correspond with a change in the sex ratio of childhood cancers.

Known population indicators of cohort selection *in utero* almost exclusively assume more selection in males than in females.[14] This circumstance reflects the facts that more male than female fetal deaths occur among recorded losses and that males disproportionately fall on the left tail of the frailty distribution.[52,53] Theory and recent empirical evidence, however, asserts that female fetuses may experience strong cohort selection – especially in the first trimester.[54] Owing to the lack of a validated cohort measure of selection *in utero* among females, our work is limited in that we could not explore the potential relation between selection and childhood cancers among females.

We did not set out to identify specific antecedents of cohort selection against frail males because previous work in Sweden and elsewhere already reports these findings. Time-series analyses report seasonality in indicators of selection *in utero*; our discovery of seasonality in male twins converges with this prior work.[29,55,56] In addition, temperature extremes[57], mass shootings[33], terrorist attacks[19,20], and economic

downturns[56] (among other stressors) precede an increase in male fetal death and/or reductions in births of males considered to fall at the left tail of the fetal frailty distribution. To the extent that childhood cancers among males may also fall disproportionately in this category, these ambient stressors may also precede fewer than expected childhood cancers among male birth cohorts. Examination of such population-level antecedents of childhood cancers would serve as a logical next step for research in this area. Antecedents of interest could include those that are seasonally patterned (e.g., temperature) or sudden ambient shocks (e.g., November 2015 Paris terrorist attacks) that demonstrably stress populations.

At the population level, factors during the prenatal period that affect the risk of loss may not only adversely affect fetal development but also select against a subset of pregnancies at the left tail of the frailty distribution. Live births that ultimately are diagnosed with cancer before age 15 may disproportionately occupy this left tail. This work, if replicated, coheres with the "reproductive suppression"[39,58] argument of the conservation of maternal mechanisms that spontaneously abort gestations unlikely to thrive if born. Scholars from a range of disciplines contend that, over much of human history, the subset of childhood cancers arising from chromosomal translocations, mutations in oncogenes and/or mutations in tumor suppressor genes during fetal development would have undergone strong selection *in utero*.[11,12,59] This selection would have occurred because, prior to 1970, childhood cancers resulted in death before reproductive age and therefore incurred a high fitness cost. Whereas modern advances in treatment dramatically improved childhood cancer survival, our findings indicate that—at least in the modern era in Sweden—a fraction of these cases continue to undergo selection *in utero*.

Additional research examining a more complete set of childhood cancers at other age ranges may further bolster the "reproductive suppression" argument. For instance, the majority of several cancer types are diagnosed before age 5 years. Examination of these early childhood cancers would permit inclusion of more recent birth cohort years owing to the shorter follow-up time necessary to identify complete cases. We recommend replication of our results using earlier ages and a more complete set of cancer types (e.g., retinoblastoma, hepatoblastoma, rhabdomyosarcoma). Such work would benefit from use of larger national datasets than those we used for our study.

Intuition suggests that our work has more implications for the basic understanding of childhood cancers than for clinical practice. We suspect, however, that whatever motivates the search for clinical applications of prenatal screening could also lead to a similar search for applications of knowing the depth of selection in conception cohorts. In addition, the observation that these cancers show substantial temporal variation across birth cohorts (Figure 1A) indicates that exploration of their temporal antecedents merits further inquiry. Such work might examine not only exposures presumed to increase genetic mutations and the risk of childhood cancers, but also population-level factors that may induce cohort selection among particular subtypes of cancer.

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## Tables

**Table 1.** List of International Classification of Diseases (ICD), 7th Revision codes used to identify childhood cancer diagnoses with current ICD 10 Codes for reference.

| ICD 7 Code | ICD 10 Code | Cancer Site Description |
|---|---|---|
| 196 | C40-41 | Bone (osteosarcomas and Ewing sarcomas) |
| 193 | C70-72 | Brain, central nervous system (neuroblastomas) |
| 201 | C81 | Hodgkin lymphoma |
| 200,202 | C82-86, C965 | Non-Hodgkin lymphoma |
| 180 | C64 | Kidney (Wilms tumor) |
| 204-7 | C91-95 | Leukemia |

**Table 2.** Count of Childhood Cancers by Sex and Age of Diagnosis among live births in Sweden born from 1990 to 2001 and followed to age 15 years.

| Age of Diagnosis | Male | Female |
|---|---|---|
| Birth to <1 year | 61 | 67 |
| 1 to <5 years | 510 | 453 |
| 5 to <15 years | 801 | 593 |

**Table 3.** Count of Childhood Cancers by Site among live births in Sweden, 1990 to 2001, and followed to age <15 years.

| **Cancer Site** | **N** |
|---|---|
| Bone (osteosarcomas and Ewing sarcomas) | 116 |
| Brain, central nervous system (neuroblastomas) | 916 |
| Hodgkin lymphoma | 78 |
| Non-Hodgkin lymphoma | 247 |
| Kidney (Wilms tumor) | 174 |
| Leukemia | 954 |

**Table 4.** Estimated parameters for test equation predicting monthly counts of childhood cancers among males born in Sweden from January 1990 to Dec 2001. (95% CI in parentheses).

| Parameter | Point Estimate | 95% CI |
|---|---|---|
| Constant | 7.501 | (5.700-9.298)** |
| Male twin residuals at t | 0.040 | (0.001-0.079)* |
| at t-1 | 0.055 | (0.017-0.094)* |
| at t-2 | 0.001 | (- 0.038-0.040) |
| Female childhood cancers at t | 0.226 | (0.009-0.443)* |
| Autoregression at t-7 | 0.225 | (0.051-0.398)* |

*p<.05, **p<.0

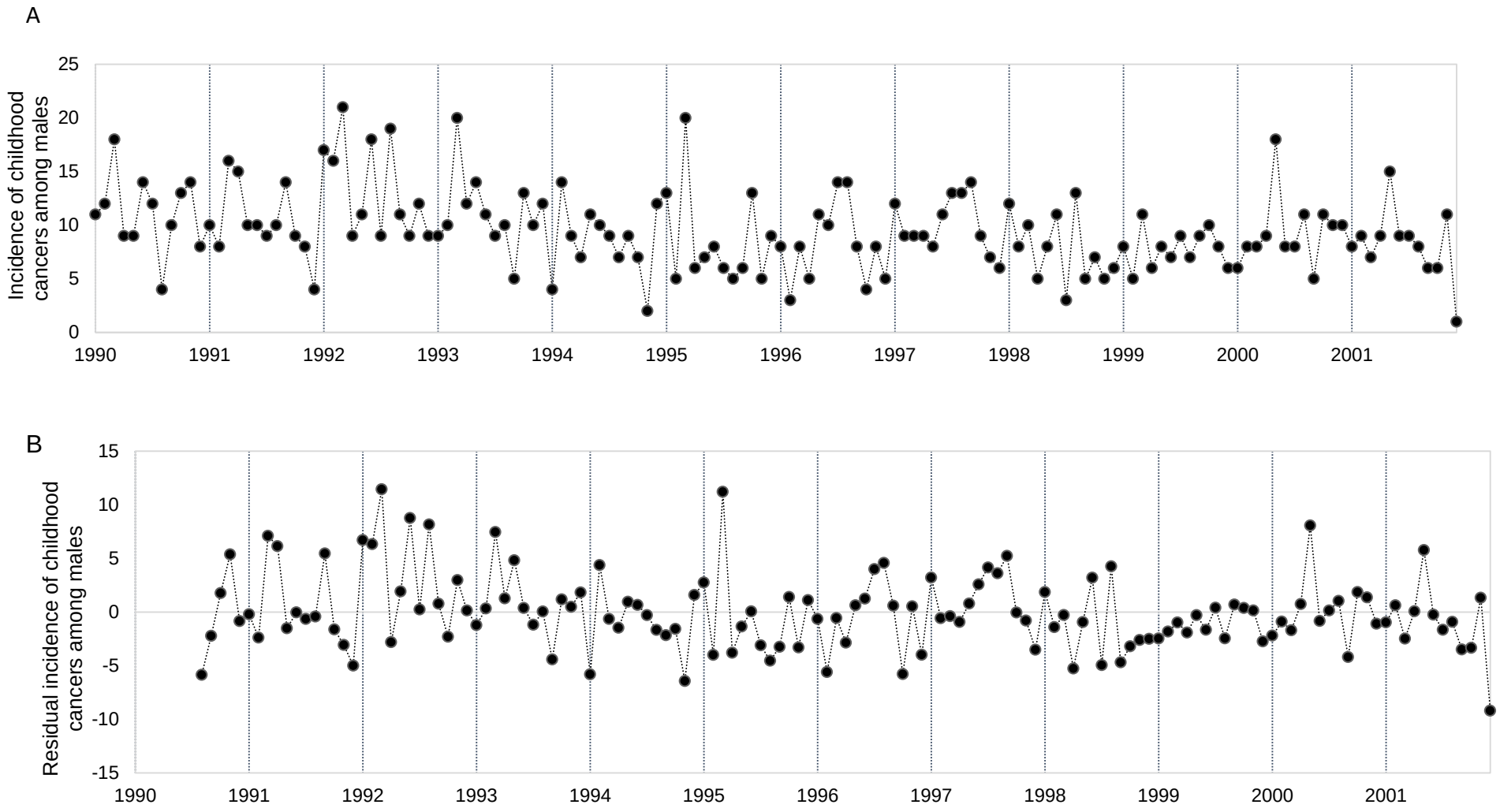
**Figure 1.** Male incidence of childhood cancer over 144 months in Sweden. Panel A plots the observed incidence; Panel B plots the residual incidence after removal of autocorrelation (first seven months lost to time-series modelling). Januaries demarcated with vertical lines.

[Figure uploaded in another file]

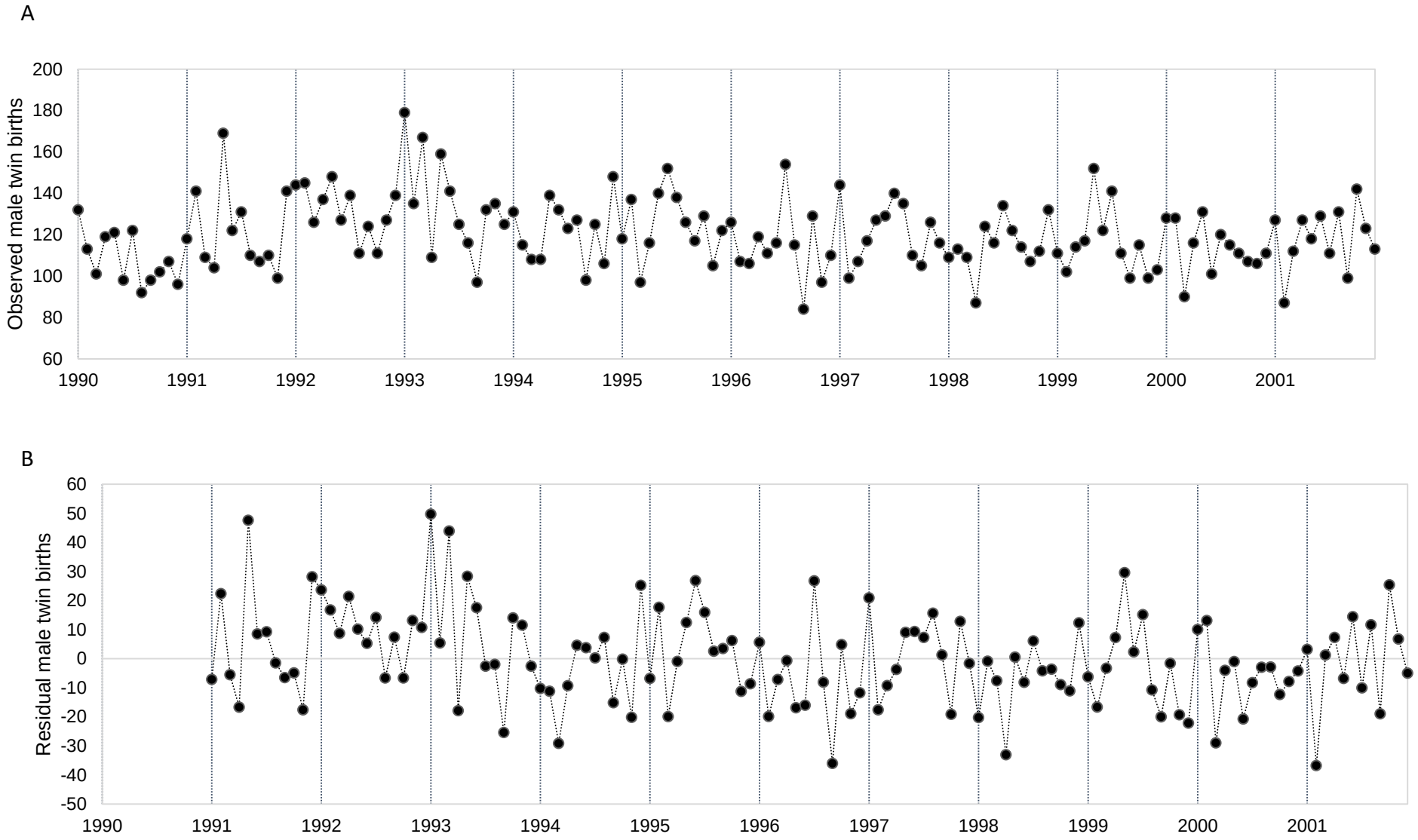
**Figure 2.** Frequency of male twins over 144 months in Sweden. Panel A plots the observed count; Panel B plots the residual count after removal of autocorrelation (first 12 months lost to time-series modelling). Januaries demarcated with vertical lines.

[Figure uploaded in another file]

# Figure 1



# Figure 2



Cancer Epidemiology, Biomarkers & Prevention

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