Parental Well-being in Pediatric Oncology in Sweden - Nationwide Evidence from the Swedish Registers

Liu, Yishan

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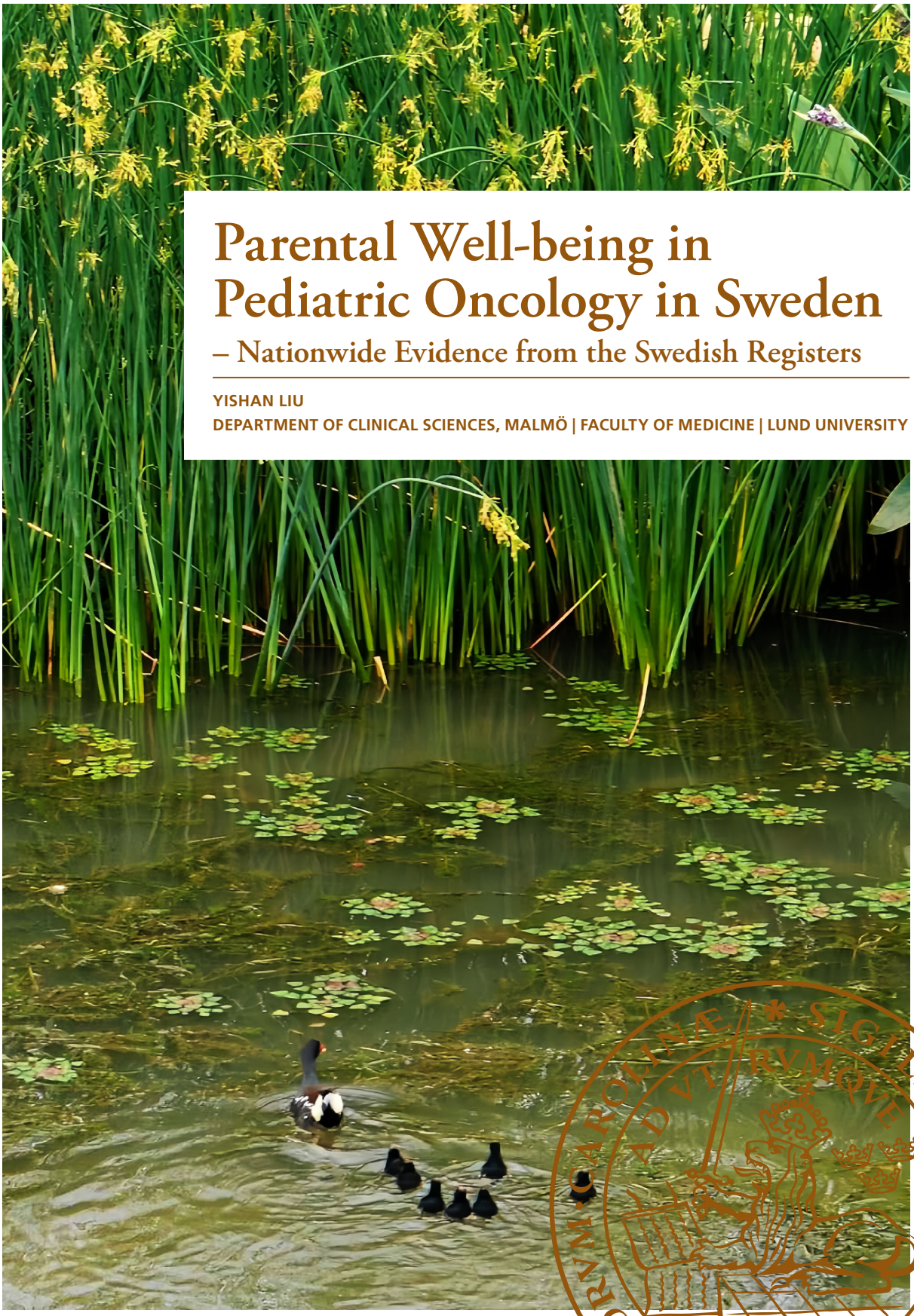

Parental Well-being in Pediatric Oncology in Sweden

– Nationwide Evidence from the Swedish Registers

YISHAN LIU
DEPARTMENT OF CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

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Yishan Liu
刘怡杉

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Abstract: Despite the average 5-year survival rate exceeding 85%, childhood cancer is still the most common cause of death among children in Sweden. A cancer diagnosis is profoundly traumatic not only for children themselves, but also for the entire family, particularly the primary caregivers, their parents. This project aimed to investigate the extent to which a childhood cancer diagnosis affected parental mental and somatic health, and, in turn, whether the compromised parental mental well-being influenced the child's subsequent cancer prognosis.

Using several Swedish nationwide registers, we identified all children aged 0–14 years diagnosed with cancer and linked them to their parents. For studies I, II, and IV, up to five parents of cancer-free children were randomly selected and matched to each parent of a child with cancer, conditional on their baseline characteristics. Information on parental outcomes was extracted from the National Patient Register and the Prescribed Drug Register, including hospital visits for mental health disorders, use of psychotropic medication, and the burden of somatic diseases. In study III, we compared the survival status of cancer-diagnosed children whose parents experienced mental illness after the child's diagnosis with those whose parents remained free of mental illness.

It was found that parents of children with cancer experienced intense stress and had sustained mental health challenges. Both mothers and fathers showed elevated risks of mental health disorders, but with distinct patterns. Mothers exhibited a continually worsening mental health condition over seven years, whereas fathers demonstrated a consistently elevated but stable risk. Psychotropic medication use also increased following the child's cancer diagnosis, rising steadily among mothers and increasing sharply during the first year among fathers. Beyond mental health, parents experienced a substantial somatic disease burden, and this impact was long-lasting, recurrent, and involved multiple organ systems. Furthermore, a strong association was observed between parental mental well-being and child cancer prognosis, with newly onset illness particularly worsening child survival.

Overall, the diagnosis of childhood cancer profoundly and persistently affects both mental and physical health of parents, with especially notable deterioration in mothers' long-term mental well-being. These findings highlight the unmet needs for supports and interventions to parents. Moreover, the strong association between parental mental illness and child survival outcomes underlines the importance of integrating family-centered interventions into standard pediatric cancer care.

Key words: Childhood cancer; Parental health; Prognosis; Swedish Registers; Pediatric cancer care

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Yishan Liu
刘怡杉

LUND
UNIVERSITY

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Faculty of Medicine
Department of Clinical Sciences, Malmö

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To my mormor

Table of Contents

Abstract

Background Despite the average 5-year survival rate exceeding 85%, childhood cancer is still the most common cause of death among children in Sweden. A cancer diagnosis is profoundly traumatic not only for children themselves, but also for the entire family, particularly the primary caregivers, their parents. This project aimed to investigate the extent to which a childhood cancer diagnosis affected parental mental and somatic health, and, in turn, whether the compromised parental mental well-being influenced the child's subsequent cancer prognosis.
Method Using several Swedish nationwide registers, we identified all children aged 0–14 years diagnosed with cancer and linked them to their parents. For studies I, II, and IV, up to five parents of cancer-free children were randomly selected and matched to each parent of a child with cancer, conditional on their baseline characteristics. Information on parental outcomes was extracted from the National Patient Register and the Prescribed Drug Register, including hospital visits for mental health disorders, use of psychotropic medication as coping strategies, and the burden of somatic diseases. In study III, we compared survival status of cancer-diagnosed children whose parents experienced mental illness after the child's diagnosis with those whose parents remained free of mental illness.
Results It was found that parents of children with cancer experienced intense stress and had sustained mental health challenges. Both mothers and fathers showed elevated risks of mental health disorders, but with distinct patterns. Mothers exhibited a continually worsening mental health condition over seven years, whereas fathers demonstrated a consistently elevated but stable risk. Psychotropic medication use also increased following the child's cancer diagnosis, rising steadily among mothers and increasing sharply during the first year among fathers. Beyond mental health, parents experienced a substantial somatic disease burden, and this impact was long-lasting, recurrent, and involved multiple organ systems. Furthermore, a strong association was observed between parental mental well-being and child cancer prognosis, with newly onset illness particularly worsening child survival.
Conclusion Overall, the diagnosis of childhood cancer profoundly and persistently affects both mental and physical health of parents, with especially notable deterioration in mothers' long-term mental well-being. These findings highlight the unmet needs for support and interventions to parents. Moreover, the strong association between parental mental illness and child survival outcomes underlines the importance of integrating family-centered interventions into standard pediatric cancer care.

Popular Scientific Summary

Childhood cancer, despite high survival rates with current advanced treatments, remained the deadliest disease-caused threat to children in Sweden. Its impact extends far beyond the children themselves. Parents often experience the diagnosis of their child's cancer as a profound shock, and this research shows how deeply it affects their long-term health.

By analyzing the data from multiple nationwide Swedish health registers, the study followed parents of children with cancer and compared them with parents of cancer-free children. The findings revealed a clear pattern: parents faced significantly higher risks of mental health problems and multi-systemic physical illness after their child's diagnosis. Mothers' mental health continued to worsen for seven years, while fathers showed a sharp rise in illnesses then stabilized. Use of psychotropic medications increased for both parents, reflecting the strain of coping with their child's illness. Physical health is also compromised, with parents developing a wide range of long-lasting and recurring medical conditions. The research further showed that when parents developed mental illness after the child's diagnosis, the child's own chance of survival decreased.

Overall, the research highlighted how deeply a child's cancer affects their parents and underscored the call for better, family-focused support within standard pediatric cancer care.

List of Papers

This thesis is based on the following four papers, referred to in the text by Roman numerals and included in full at the end of the thesis.

Paper I

Liu Y, Sundquist J, Sundquist K, Zheng D, Ji J. Mental health outcomes in parents of children with a cancer diagnosis in Sweden: A nationwide cohort study. *EClinicalMedicine.* 2022 Nov 17;55:101734.

Paper II

Liu Y, Jiang Z, Sundquist J, Sundquist K, Ji J. Long-Term Pattern of Psychotropic Medication Uses Among Swedish Parents of Children Diagnosed with Cancer. *J Natl Compr Canc Netw.* 2024 Nov;22(9):e247048.

Paper III

Liu Y, Sundquist J, Sundquist K, Ji J. Exploring the Influence of Parental Mental Illness on Childhood Cancer Mortality: A Nationwide Cohort Study in Sweden. *J Natl Compr Canc Netw.* 2025 Apr 30;23(6):241-247.

Paper IV

Liu Y, Jansåker F, Sundquist J, Sundquist K, Ji J. Somatic disease burden in parents of children with cancer - a nationwide cohort study in Sweden. *Prev Med.* 2025 Oct;199:108382.

List of Papers not included in the thesis

Paper I
Jiang Z, Pan M, **Liu Y**, Lundh T, Pineda D, Schenk L, Saber AT, Vogel U, Ljunggren S, Ricklund N, Engfeldt M, Krais AM, Broberg K; SafeChrom Project Team. Integrative analyses of circulating microRNA expression profile in hexavalent chromium exposed workers - A cross-sectional study within the SafeChrom project. J Hazard Mater. 2025 May 5;488:137367.

Paper II
Jiang Z, **Liu Y**, Lindh C, Pineda D, Carøe TK, Catalán J, Ebbehøj NE, Givelet L, Huusom AJ, Kines P, Krais AM, Aimonen K, Lundh T, Loeschner K, Rastkhani H, Tondel M, Saber AT, Vogel U, Broberg K; SafeChrom project team and SAM-Krom project team. Per- and polyfluoroalkyl substances exposure in hexavalent chromium exposed workers and the effects of exposure mixtures on oxidative stress and genomic instability. Environ Pollut. 2025 Dec 15;387:127255.

Abbreviations

ASR	Age-standardized rate
ATC	Anatomical therapeutic category
CCI	Charlson comorbidity index
CI	Confidence interval
CNS	Central nervous system
DDD	Defined daily dose
GEE	Generalized estimating equation
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	International classification of diseases
ITS	Interrupted time series
LISA	Longitudinal Integrated Database for Health Insurance and Labour Market Studies
NHL	Non-Hodgkin's lymphoma
NPR	National Patient Register
PDR	Prescribed Drug Register
QIC	Quasi-likelihood Criteria
RR	Rate ratio
SD	Standard deviation
SMD	Standardized mean difference
SNOMED	Systematized nomenclature of medicine

Introduction

Although cancer is relatively rare in childhood, it remains the leading cause of disease-related mortality among children in Sweden (1) and many other high-income countries (2-4). A childhood cancer diagnosis places a considerable emotional and practical strain on the entire family. With advances in diagnostics, clinical care, and treatment over recent decades, the 5-year survival rate for childhood cancer in Sweden now approximates 85% (5). However, surviving this life-threatening illness does not mark the end of challenges. Many survivors often experience long-term and late effects that can influence their physical health, psychosocial well-being, and overall quality of life. The survivorship experience often extends beyond the affected child (6), placing a range of medical, psychological, and societal concerns to their families as well (7).

Childhood Cancer

Epidemiology

Globally, an estimated 300,000 children aged 0−14 are diagnosed with cancer annually (8). In 2022, there were 211,080 new cases of childhood tumors and 78,441 deaths worldwide, as estimated by the Global Cancer Observatory (9). Incidence rates were slightly higher in boys than in girls, and higher in children aged 0–4 years than in those aged 5–9 or 10–14 years. Rates also varied considerably across regions (Figure 1) (10). As displayed in Figure 2, the most common childhood cancer type was leukemia, accounting for 36.79% of the total incident cases in 2022, followed by brain and central nervous system (CNS) tumors (14.62%), non-Hodgkin's lymphoma (NHL) (11.21%), with Hodgkin's lymphoma, kidney tumors, and others less frequently. The leading causes of death in childhood cancer were leukemia (39.66%), brain and CNS tumors (19.81%), followed by NHL and kidney tumors. Germ cell and gonadal tumors were more common in girls than in boys (10).

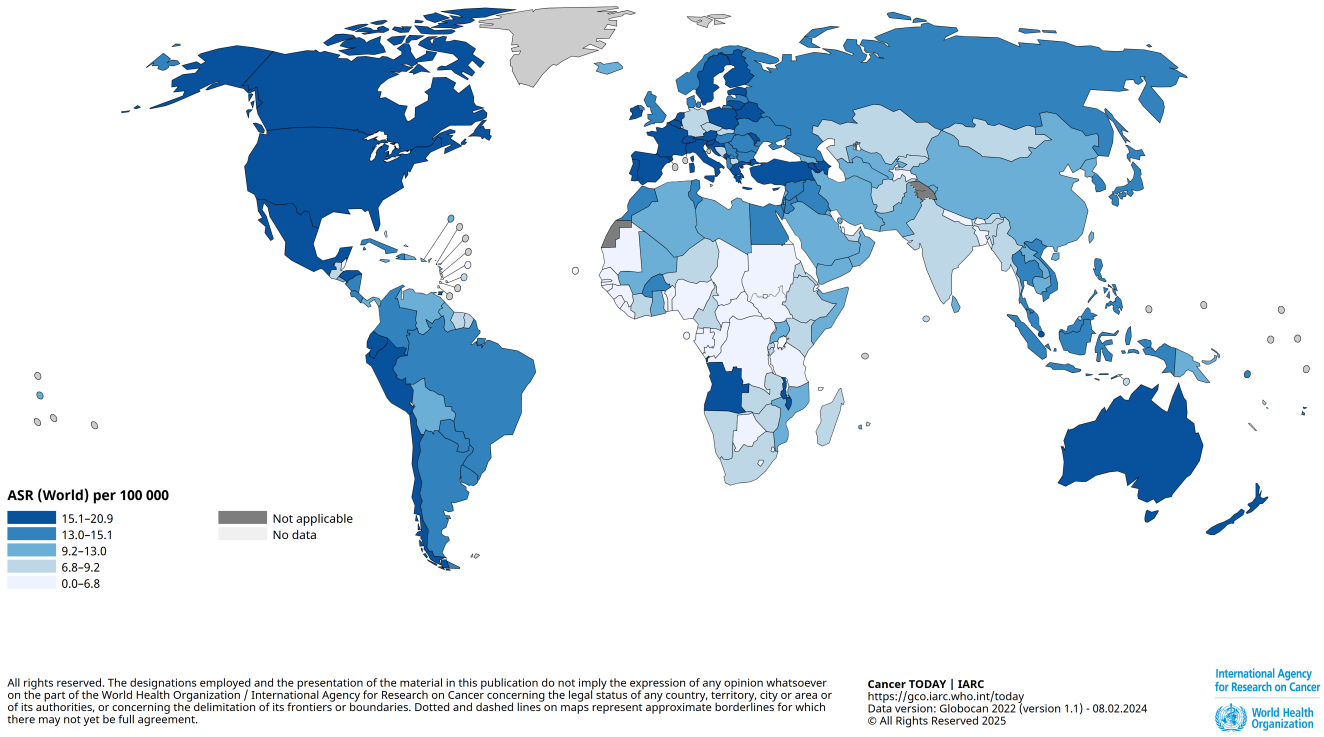


Figure 1. Global Age-standardized incidence rates of childhood cancer diagnosed at ages 0–14 years in 2022. Visualization generated by the author using the Global Cancer Observatory (Cancer Today, IARC/WHO) (11). *ASR: age-standardized rate (world) per 100,000 person-years.

In Sweden, fewer than 300 children aged 0−14 were diagnosed with cancer each year between 1987 and 2018 (12). In 2022, the age-standardized incidence rate (world standard) was 15.4 per 100,000 person-years, and the age-standardized mortality rate was 2.3 per 100,000 person-years. As shown in Figures 2 and 3, the three most common childhood cancer types in Swedish children were leukemia, brain and CNS tumors, and kidney tumors. Advances in pediatric oncology have transformed childhood cancer from a largely fatal disease into a survivable and often chronic condition. Despite these gains, childhood cancer remains the leading cause of disease-related death among children in Sweden. The leading causes of childhood cancer deaths were brain and CNS tumors and leukemia.

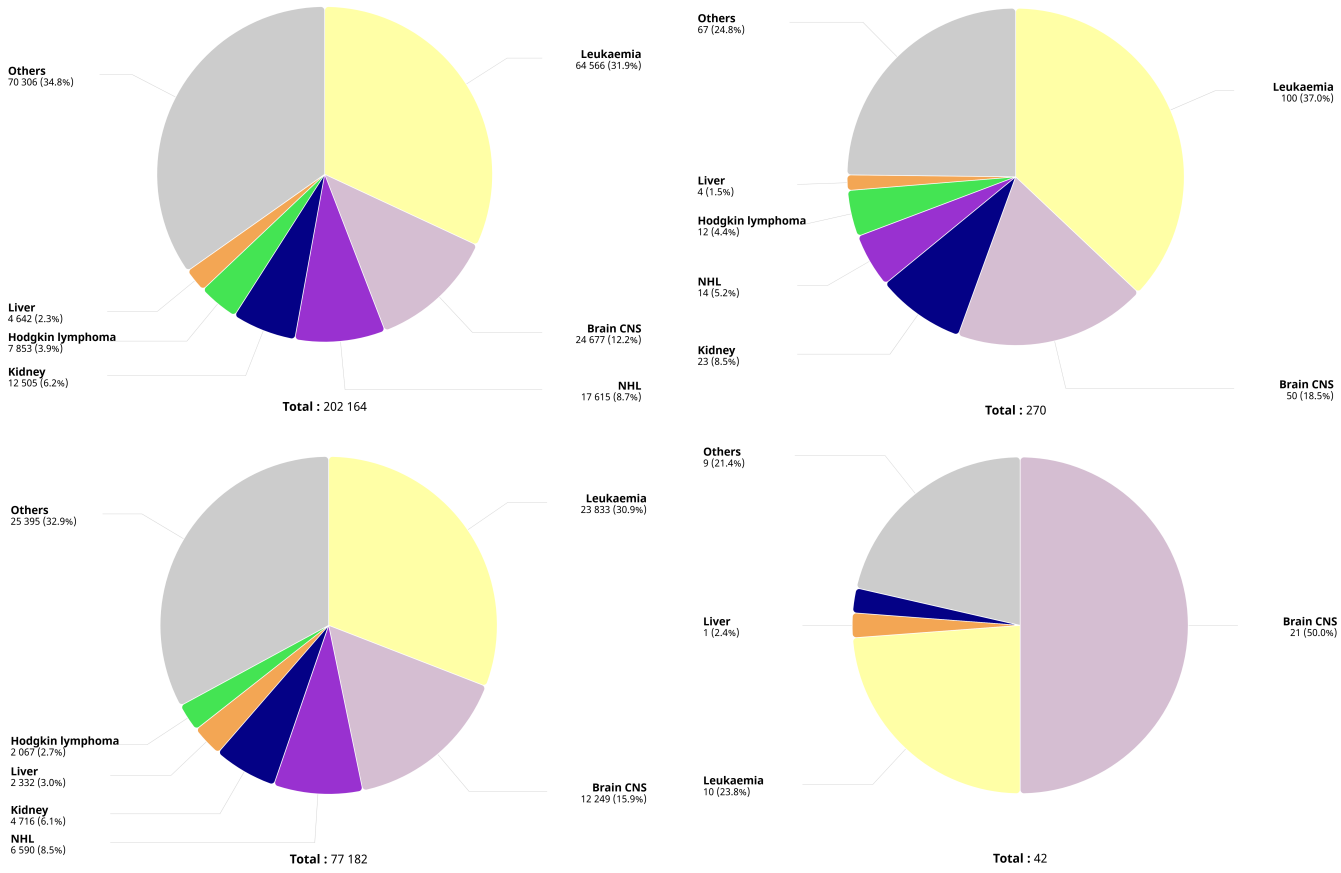
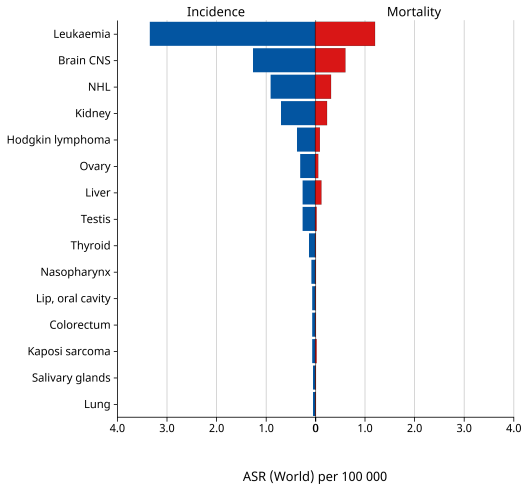


Figure 2. Distribution of childhood cancer types in 2022: a) incidence worldwide; b) incidence in Sweden; c) mortality worldwide; d) mortality in Sweden.



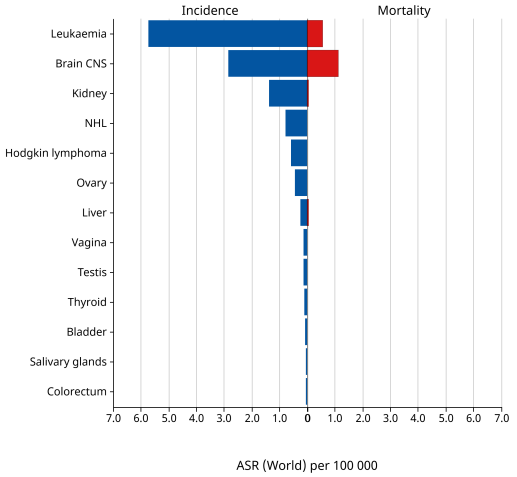


Figure 3. Age-standardized (world) incidence and mortality rates of childhood cancer types in 2022: a) worldwide; b) in Sweden. *ASR: age-standardized rate per 100,000 person-years.

Risk Factors

Childhood cancer is generally not caused by lifestyle or environmental exposures in the same way as the onset in adulthood is. In most cases, the exact cause remains obscure. However, certain risk factors have been identified in previous research.

Genetic and hereditary risk factors

One of the clearly established risk factors for childhood cancer is genetic predisposition, although it accounts for only a minority of all cancers in children (13). A recent genomic study estimates that adrenocortical carcinomas (≈50%), hypodiploid B-ALL (≈28%), as well as K27-wild-type high-grade gliomas, atypical teratoid/rhabdoid tumors, SHH-activated medulloblastomas, and retinoblastomas (≈15–25% each) (13) are predisposed by genetics. These predispositions often originate from germline pathogenic variants, some of which are inherited from a parent, while many arise newly during early embryonic development. Such variants disrupt genes involved in DNA repair, cell-cycle regulation, or tumor suppression pathways, leading to cancer predisposition syndromes that substantially elevate the likelihood of developing malignancies in childhood. For example, *Li-Fraumeni syndrome*, also called *the sarcoma, breast, leukemia, and adrenal gland cancer syndrome*, greatly increases risks of several types of childhood cancers due to germline pathogenic variants in the *TP53* tumor-suppressor gene (14). Familial retinoblastoma is another classic predisposition syndrome resulting from germline pathogenic variants in the *RB1* tumor-suppressor gene (15), while *Down syndrome* (trisomy 21) (16) is well known to confer a markedly increased risk of childhood leukemia (17). Moreover, germline alterations in genes such as *LZTR1*, *TSC2*, and *CHEK2* have been increasingly recognized as contributors to heightened susceptibility to specific pediatric malignancies (13).

Environmental exposures

Although evidence is inconsistent, certain environmental exposures have been suggested to be associated with higher risks of childhood cancer. During early childhood, exposures such as second-hand tobacco smoke (18), ultraviolet (UV) radiation (13), and ionizing radiation (19, 20) have been linked in some studies to increased cancer risk. Parental exposures may also play a role in cancers in offspring. In utero exposure to ionizing radiation (19), maternal infections (21, 22), maternal immune activation (23), maternal consumption of cured meats (24), certain medications, or lack of folate intake (25) may elevate risks of leukemia and brain or spinal cord tumors. Even before conception, parental tobacco use (26) and parental occupational exposure to pesticides (27) have been reported as possible contributors to increased risk of leukemia and brain tumors in offspring. Despite these observations, the environmental causes of childhood cancer remain difficult to identify, and most associations remain suggestive.

Challenges

Difficulties faced by children with cancer

Childhood cancers are rare and can differ from adult cancers in their growth, spread, and response to treatment. A diagnosis of cancer presents intense and often overwhelming challenges for children. Children with cancer frequently experience a wide range of adverse physical, psychological, and social health conditions.

Once diagnosed with cancer, children are thrust into a demanding medical world involving frequent hospital visits, invasive diagnostic procedures, and intense treatment schedules. Treatment regimens, such as chemotherapy, radiation therapy, surgery, or combinations, are typically aggressive for children. While these therapies are lifesaving, they may cause substantial side effects, including pain, nausea, vomiting, fatigue (28), mucositis (29), sleep disturbances (30), and heightened susceptibility to infections due to immunosuppression (31). Medical management during treatment is equally complex. In early treatment, children often undergo repeated needle insertions for blood tests and intravenous medications, which can trigger significant procedural anxiety and distress (32). The need for strict infection controls further limits social interaction and participation in activities. Cares include multiple health care transitions (33) and frequent hospitalizations (34), which disrupt daily routines, schooling, and peer relationships (35). Some children may require additional supportive care, such as nutritional assistance, management of treatment-induced symptoms, or interventions for acute organ toxicities (36). The severity of illness raises children's concern about prognosis, the future, and even mortality (37). With all these burdens, children's psychological well-being is often affected (38), and many experience posttraumatic stress symptoms (39).

Advances in diagnostics, clinical care, and treatment in pediatric oncology have raised the average five-year survival rate to approximately 85% in Sweden (5). Survivorship now emerges as a central focus in research. Many survivors often report lower health-related quality of life (HRQoL) (40, 41). Their long-term psycho-social functioning may be compromised as well (42). Persistent challenges include heightened anxiety and depression, decreased physical activity, social isolation, lower academic performance, and communication difficulties (43). Even years after treatment ends, childhood cancer continues to influence survivors' lives negatively (44, 45). Long-term and late effects may include cardiometabolic complications (46, 47), neurocognitive impairments (48), endocrine and growth disturbances (49), fertility concerns (50, 51), increased late mortality (52, 53), and inadequate health-care transitions in adulthood (54, 55). Survivors may also experience difficulties with concentration (56), stress resilience, and empathy (57). diminished self-concept (58), and disruptions in their pursuit of independence (59).

These late effects often hinder everyday functioning across social, educational, and work domains, contributing to persistent life-spanning concerns.

Strains on Parents

The onset of childhood cancer is typically sudden and profoundly disruptive, not only for the affected children but also for their entire family systems. The children's symptoms can be nerve-wracking, frightening, and destabilizing, especially when they occur during crucial developmental stages.

Parents, central in pediatric care, are often involved in making decisions on multiple treatment options (60), closely monitoring the child's symptoms (61), and managing frequent hospital visits and health care transitions (62). In addition to supporting their child through complex medical procedures and treatment-related events, parents need to be responsible for many other tasks, such as providing more intensive daily care (63), reorganizing family routines (64), managing and supporting the child's emotional needs (65), coping with disruptions to work and social life (66), and balancing the needs of other family members (63, 67). All these demands place a substantial and sustained burden on the parents (68-70).

Throughout the cancer trajectory, parents often bear the heaviest emotional burden. They commonly struggle with uncertainty from diagnosis and treatment to survivorship (71). Uncertainty on their child's prognosis, treatment response, and future development has been consistently associated with anxiety, depression (70, 72), post-traumatic stress symptoms (73), parenting stress, difficulties in productivity and relationships, and reduced HRQoL (71, 74, 75). The helplessness and emotional distress are often more intense as they confront the threat of their child's potential premature mortality and late effects of treatment (42, 76, 77).

Parents are at increased risk of developing mental health problems, with symptoms that may persist long after treatment (70, 78-81). In addition to psychological difficulties, caregiving demands, chronic stress, and lifestyle changes can contribute to somatic health problems (68, 82, 83). Parents may develop somatic health disorders, or their pre-existing conditions may be exacerbated (84, 85). Previous studies have reported that parents of children with cancer experienced fatigue, difficulty sleeping, digestive system disorders, genitourinary system diseases, as well as neoplasms (86).

In the meantime, parents and children influence each other through a dynamic feedback loop. A child's diagnosis, ongoing symptoms, treatment complications, and emotional distress can amplify parental stress and uncertainty. In turn, heightened parental distress is suggested to be associated with worse parent-reported child emotional, school, and psychosocial functioning, as well as lower HRQoL (87-90). Previous studies have established an association between parental mental illness and an increased risk of psychological and neurodevelopmental

problems in children (91-96), and even a higher likelihood of premature mortality from birth through early adulthood (97, 98). This interdependence may become particularly pronounced in the context of childhood cancer.

Furthermore, socioeconomic factors, such as limited support network (89), lower educational attainment (99), unstable employment (100-102), and financial strain (103), can adversely affect parental quality of life and diminish their ability to engage fully in caregiving (104, 105). Lower socioeconomic status may also restrict access to healthcare, limit health literacy, and reduce the capacity to maintain consistent treatment routines (106). These barriers may lead to longer diagnostic intervals (107). Delays in timely medical evaluation, diagnosis, and initiation of treatment can negatively affect the child's cancer prognosis (108).

Aims

The overall aim of this thesis was to explore the extent to which a childhood cancer diagnosis affected parental mental and somatic health, and, in turn, whether the potentially compromised parental mental well-being influenced the child's subsequent cancer prognosis.

The specific aims of each study were as follows:

Paper I: To explore the subsequent short- and long-term mental health outcomes among parents following their children's cancer diagnosis and examine potential differences in responses between mothers and fathers.

Paper II: To explore how a child's cancer diagnosis affects both short- and long-term psychotropic medication dosage in parents. Additionally, to assess the dynamics in the proportion of parents who use psychotropic medication.

Paper III: To examine whether parental mental illness following the child's cancer diagnosis is associated with an increased risk of childhood cancer mortality. Furthermore, to assess whether the association persists among parents with newly onset mental illness after the child's cancer diagnosis.

Paper IV: To investigate the long-term somatic health burden among parents of children with cancer.

Methods

Disclosure of ethical compliance

These four nationwide retrospective cohort studies were approved by the Ethical Review Board in Lund (number 2012/795 and later amendments). The studies were based on secondary data from nationwide Swedish health and population registers, obtained through the relevant Swedish authorities. Informed consent from individuals was not required. The data linkage among national registers was achieved by using pseudonymized serial numbers to protect integrity, which were assigned consistently by Swedish Statistics to all individuals registered in Sweden. To further ensure confidentiality and data protection, all data analyses were performed on secure servers at Lund University in Malmö, Sweden.

Use of generative AI tools

In this thesis, generative AI tools were used solely to improve language editing, including grammar and flow of the text. All academic and scientific content was produced independently by the author.

Study design

Data source

All studies included in this thesis were conducted using retrospective cohort designs based on Swedish national register data. The Swedish registers cover the entire population of Sweden. Details of the registers used in this thesis are displayed in Table 1.

Table 1. Summary of the data sources of the studies included in this thesis.

Data source	Period	Brief Description
Swedish National Cancer Register (NCR)	1958–2018	This is an incidence-based register containing data on diagnosed primary tumors (109). For each tumor, the date of diagnosis, type, location and morphology are recorded, with high coverage, accurate coding, and histopathological confirmed (about 99%) (110).
Multi-Generation Register(111)	1932–2018	It includes all individuals who have held a residence permit in Sweden since 1961 and who were born from 1932 onward (index persons). For each index person, the demographic information was covered, including year and month of birth, sex, and country of birth, as well as links to their biological parents.
National Cause of Death Register(112)	1961–2018	This register contains date, underlying cause of death on all deceased persons in Sweden. It has excellent coverage back many decades and is considered reliable.
Total Population Register (RTB)	1968–2018	This register contains information about the national registration of the population and its annual changes. The variables largely reflect the content of the population register of the Swedish Tax Agency (113).
Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA)	1990–2018	This is an annual, individual-level socioeconomic database (aged ≥16 years, since 2010 individuals aged ≥ 15 years) that includes education, employment, income, and social welfare variables (114).
National Patient Register (NPR)	Inpatient: 1964–2018 Outpatient: 2001–2018	This register records inpatient admissions nationwide since the 1960s and specialist outpatient care from 2001 onwards. The NPR contains ICD diagnoses, dates of contact and procedure codes, with good accuracy and low missingness (115).
Prescribed Drug Register (PDR)(116)	July 2005–2018	It contains data on all prescription drugs dispensed at Swedish pharmacies. It provides dates dispensed, drug ATC codes, defined daily doses, and the quantity prescribed.
CPF Primary Health Care Dataset	Varied from counties.	This dataset contains regional primary care data (for example, the VAL data warehouse in Stockholm (117)) including electronic health record diagnoses and visit data at the regional level. Coverage and establish date vary by region.

Study population

Using the Swedish Cancer Register (NCR) together with the Multi-Generation Register, we identified all children aged 0–14 years with a primary cancer diagnosis and linked them to their biological parents. The diagnosis periods were covered differently across papers, as detailed in Table 2. The study observation ended on December 31, 2018, when the most recent and complete data was available to us. In Paper III, children without available information on both biological parents or who died within the same month of diagnosis were excluded. In Papers I, II, and IV, up to five parents of cancer-free children were randomly selected and matched to each parent of a child with cancer. Matching was based on baseline demographic characteristics of both children and parents, including the child's age, child's sex, parents' age, parents' sex, and country of birth. In addition, Papers I and II included the registered municipality at the year of diagnosis as a matching condition, while Paper IV incorporated parental comorbidities at baseline to enhance comparability. The baseline was set as the same date as the child's cancer diagnosis date and applied to the matched comparisons. If more than one child within the same family was diagnosed with cancer, the earliest diagnosis date was used as the baseline for their parents.

Assessment of variables

The overview of exposure, outcome, and follow-up periods for four papers is summarized in Table 2.

Exposure definition

For Papers I, II, and IV, the exposure was defined as having a child diagnosed with primary cancer between 0 and 14 years of age.

In Paper III, the primary exposure was parental stress-related mental illness occurring after the child's cancer diagnosis. The secondary exposure definition was applied in a subpopulation restricted to children whose parents had no history of mental illness before the child's cancer diagnosis. The exposure was defined as the incidence of parental stress-related mental illness. Parental mental illness was identified using multiple data sources, if meeting either of the following criteria:
(1) clinical diagnosis: a primary clinical diagnosis of any mental or behavioral disorder recorded in the National Patient Register or regional primary health care datasets, classified by 10th revision of the International Classification of Diseases (ICD-10) codes F10–F19, F30–F39, and F40–F49; and/or
(2) psychotropic medication: dispensation of prescribed drugs categorized under the Anatomical Therapeutic Category (ATC) codes with prefixes of N05A, N05B (excluding N05BB), N05C (excluding N05CM), N06A, N06C, and N03AE.(118).

Additionally, parental mental illness was treated as a time-dependent exposure (illustrated in Figure 4), thus allowing children to transition from a period of non-exposure (from cancer diagnosis to parental mental illness onset) to a period of exposure (from parental mental illness onward for the remainder of follow-up). To meet the criteria for exposure, children had to survive until the onset of parental mental illness.

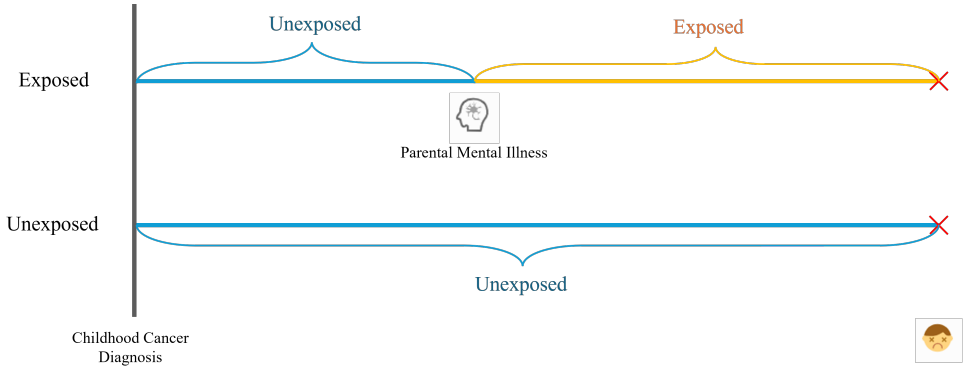


Figure 4. Illustration of time-dependent exposure in Paper III.
Parental mental illness was treated as a time-varying variable. The blue line represents the unexposed period (from the cancer diagnosis in a child to the onset of parental mental illness), whereas the yellow line represents the exposed period (from the onset of parental mental illness onwards). For some individuals in the exposed group, the unexposed period could be zero if parents experienced mental illness in the same month as the child's cancer diagnosis.

Outcome definition

In Paper I, the primary outcome was the number of hospital contacts, including inpatient admissions and outpatient visits, in which parents received a main diagnosis of any mental health disorder. Hospital contacts for mental health disorders were retrieved from the NPR using ICD-10 codes F00 to F99. The secondary outcomes focused on specific sub-groups of mental health disorders, including alcohol abuse (ICD-10 code: F10), drug abuse (ICD-10 code: F19), severe depressive disorder (ICD-10 codes: F32.2 and F32.3), recurrent depressive disorder (ICD-10 code: F33), and adjustment disorder (ICD-10 code: F43).

In Paper II, the primary outcome was the annual dosage of dispensed psychotropic medication among parents, which was obtained from the PDR. To allow comparisons across medications, dosage was standardized using defined daily doses (DDDs), and cumulative DDDs dispensed to each parent were summed per year. Psychotropic medications were identified using ATC code groups N05A, N05B (excluding N05BB), N05C, N06A, N06C (excluding N05CM), and N03AE. Secondary outcomes included two commonly used sub-groups(119, 120) of psychotropic medications: anxiolytics and hypnotics (N05BA, N05CD, and

N05CF), and antidepressants (N06A), as well as the annual proportion of parents using psychotropic medication.

In Paper III, the outcome was childhood all-cause mortality following a cancer diagnosis. Child mortality, including the date and cause of death, was obtained from the Cause of Death Register.

In Paper IV, the outcome was parental recurrent somatic health conditions, which were defined as repeated healthcare visits for diseases within the same categories during the follow-up period. Somatic disease diagnoses were identified using clinical records from both the NPR and the primary health care database. To distinguish recurrent events from continuous care episodes, such as multiple records due to healthcare transitions for the same disease, a minimum 30-day interval was applied. Fourteen major categories of somatic conditions were classified based on ICD codes, with detailed groupings provided in Table S1 of Paper IV.

Sociodemographic and clinical covariates

Information on children's and parental age, sex, and country of birth was obtained or derived from the Multi-Generation Register. The municipality of living at baseline was retrieved from RTB. Parental highest educational attainment (and for paper II, individual disposable income) was extracted from LISA. Parental comorbidities were assessed using the Charlson Comorbidity Index (CCI) (121), a weighted score calculated by identifying relevant comorbid conditions recorded in the NPR from its establishment till the baseline date.

Country of birth was dichotomized into Sweden and other countries. Based on geography and population, we grouped the municipalities of living into three places of residence: metropolitan areas, northern Sweden, and southern Sweden. Parental highest educational attainment was categorized by duration of schooling: <10, 10–12, or >12 years. In Paper II, we additionally include individual disposable income, categorized into quintiles based on the distribution of the total study population. In Papers I and II, CCI was treated as a continuous variable, while in Paper IV, it was categorized into no comorbidity (CCI = 0), low comorbidity (CCI = 1–2), and high comorbidity (CCI ≥ 3). Due to very small numbers in the high comorbidity group (n = 3 matched pairs), these individuals were excluded to ensure model stability.

To examine potential heterogeneity in the child's cancer characteristics, we reassembled the childhood cancer sites into three categories: hematological malignancies, tumors in the nervous system, and other cancer types. The child's age was grouped as 0–4 years, 5–9 years, and 10–14 years, corresponding to key developmental stages. Tumor malignancy status, in Papers III and IV, was determined using the Systematized Nomenclature of Medicine (SNOMED), a standardized clinical terminology for morphology (122). Children with SNOMED codes with 3, 6, or 9 as the fifth digit were classified as having malignant tumors (123).

Statistical Analysis

Comparability assessment

In Papers I, II, and IV, we calculated standardized mean differences for each baseline demographic characteristic to assess the comparability between parents of children with cancer and their comparisons (124, 125). The standardized difference with a value of less than 10% indicates the similarity of variables between the two groups. In Paper III, independent t-test and chi-square test were used to compare the characteristics between children with parental mental illness and those without.

Main Analytic Frameworks

The primary statistical analysis approaches used in Papers I-IV are summarized in Table 2.

Interrupted Time Series Framework (Papers I, II)

In Papers I and II, we employed an interrupted time series (ITS) analytic framework to evaluate the pattern of changes in parental outcomes upon the child's cancer diagnosis (126). In Paper I, the annual number of parental hospital contacts for mental health disorders was analyzed using a negative binomial regression model with a logarithm link function. In Paper II, the annual parental psychotropic medication dosage (unit: DDDs) was modeled using a generalized linear model within the same ITS structure. Both analyses were estimated via generalized estimating equations (GEEs) (127) with the same model shown in Equation (1), differing only in the parental outcome and specification in its distribution. In addition, we specified the working correlation structure as being first-order autoregressive (AR(1)). This choice assumed that annual outcomes from the same parent become less correlated as the time interval increases.

$$Parental\ outcome = \beta_0 + \beta_1 * time + \beta_2 * group + \beta_3 * group * time + \beta_4 * group * event + \beta_5 * time_{post} * group * event + X^T\eta \quad (1)$$

Equation (1) incorporates interactions among group, time, and the event. The parameters can be interpreted as follow: β_1 indicates the time trend in parental outcomes; β_2 indicates the baseline intercept difference between parents of children with cancer and their comparisons before the diagnostic event; β_3 indicates the potential trend difference before diagnosis between groups; β_4 indicates the level change (immediate effect) in the outcome among parents of cancer-affected children around the year of cancer diagnosis; β_5 indicates the

long-term change (sustained effect) in parents of children with cancer; X is the covariate vector and η are the effects of corresponding covariates.
A visual explanation of each coefficient in Equation (1) is provided as Figure 5.

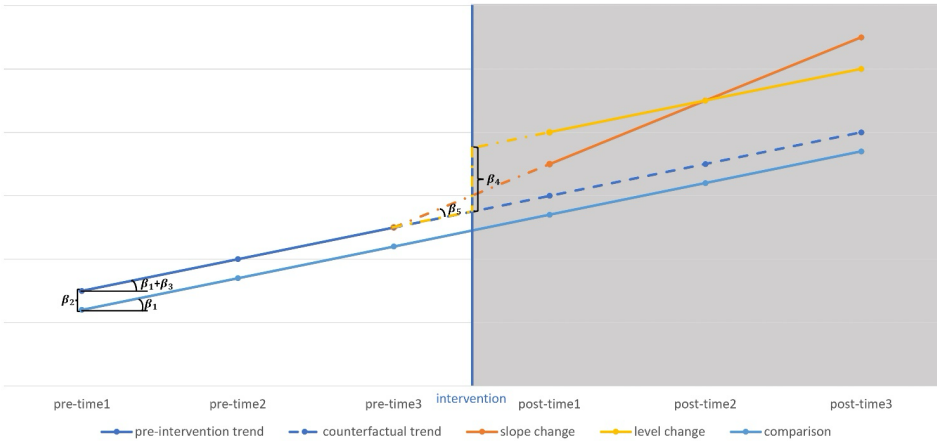


Figure 5. Explanation of Robust Interrupted Time Series Design Equation

To select the most appropriate model, robust models were initially fitted that included all parameters listed in Equation (1) (pre-diagnosis level and trend differences, as well as level and slope changes in the post-diagnosis segment). Quasi-likelihood Criteria (QIC) values were then compared to identify the optimal fitting model (128, 129).
The primary focus of the equation lies in estimating parameters β_4 and β_5. To be specific, we interpret these two parameters as (1) any abrupt change in parental outcomes in the year of their child's diagnosis (β_4), and (2) a gradual slope change in parental outcomes (β_5).
In Paper I, rate ratios (RRs) and 95% confidence intervals (CIs) were estimated. All parents were followed for clinical diagnoses of mental health disorders for up to 12 years, ranging from 5 years before until 7 years after the child's cancer diagnosis, death, or the end of the study period (Dec 31, 2018), whichever occurred first. In Paper II, average differences in annual psychotropic medication dosage and 95% CIs were estimated. All parents were followed for psychotropic medication dispensation for up to 8 years, from 4 years before to up to 4 years after their child's cancer diagnosis date, until death or the end of the study period (Dec 31, 2018), whichever came first. For both papers, parental demographic and clinical factors were adjusted in multivariate analyses, including parents' age, country of birth, place of residence, educational attainment, individual income (in Paper II), and CCI scores.

Cox proportional hazards regression (Papers III and IV)

In Paper III, to address potential immortal time bias, we used time-dependent Cox regression to calculate hazard ratios (HRs) and 95% CIs for mortality among children with cancer in relation to parental mental illness (130). Follow-up began at the date of cancer diagnosis, and continued until death, emigration, or the study's end date (Dec 31, 2018), whichever occurred first. Covariates were further adjusted in the multivariable regression model, encompassing the child's sex, age at diagnosis, birth country, registered place of residence at diagnosis, cancer site, and tumor malignancy status, as well as parental educational attainment, age at baseline, and history of mental illness before the child's cancer diagnosis.

In the sensitivity analysis of Paper IV, we examined the risk of incident somatic disease diagnoses among parents after their child's cancer diagnosis. For each disease category, a sub-cohort was constructed by excluding parents with a history of diagnosis in the corresponding disease category before the baseline. Cox proportional hazards models were used to estimate the association between having a child with cancer and the incidence of specific somatic disease diagnoses. The parents in each sub-cohort were followed up until the first relevant diagnosis, death, emigration, or end of observation, whichever occurred first. Models were adjusted for the same set of covariates as the recurrent event analyses, detailed in the next paragraph.

Recurrent time-to-event model (Paper IV)

We examined parental somatic disease burden using a marginal means/rates model within the recurrent event framework. Given that in this study, somatic diseases were grouped into broad diagnostic categories, each containing multiple heterogeneous conditions, and the dependence structure within each category is complex and unknown, we adopted a marginal modeling approach. The marginal structure model offers greater flexibility (131) and enables estimation of population-level effects without imposing strong assumptions about the dependence among recurrent events within individuals (132). This aligns with the objective of the study, which focuses on the overall somatic disease burden rather than on interpreting individual event trajectories. Time since the child's cancer diagnosis was used as the underlying time scale in all recurrent event models. Individuals were followed from study entry until emigration, death, or the end of the observation period (Dec 31, 2018), whichever came first, allowing for up to two years of follow-up after the latest child cancer diagnosis in 2016. Furthermore, parental educational attainment, country of birth, place of residence, and the history of corresponding diseases for each disease category, as well as the number of biological children were adjusted in the final model.

Additional Analysis

Attributable proportion (Paper II)

We estimated the attributable proportion (AP) of the change in dispensed psychotropic medication dosage among parents that could be attributable to their child's cancer diagnosis. The attributable proportion was calculated using Equation 2 (133, 134), where $\overline{D}_t^e$ denotes the predicted annual dosage of psychotropic medication for parents of children with cancer at time t, with t_0 indicating the year before diagnosis and t_1 the year after, and $\overline{D}_t^c$ denotes the predicted annual dosage for the comparison group.

$$AP = \frac{(\overline{D}_{t_1}^e - \overline{D}_{t_0}^e) - (\overline{D}_{t_1}^c - \overline{D}_{t_0}^c)}{\left(\overline{D}_{t_1}^e - \overline{D}_{t_0}^e\right)} \times 100\% \quad (2)$$

Stratification analysis

The overview of stratification analyses conducted in Papers I-IV is listed in Table 2. The stratification analyses by demographic and disease-related factors can further reveal potential heterogeneity in the associations examined. Stratification was performed by the child's age at diagnosis (0–4 years, 5–9 years, and 10–14 years) (in all Papers), corresponding to key developmental stages that may influence varieties in caregiving demands; the cancer types (in all papers) and tumor malignancy status (in Papers III and IV), as proxies for cancer severity and prognosis; parents' sex (in all papers), indicating potential sex-specific response to child's cancer diagnosis or influence on child; as well as parental educational attainment (in Paper II), number of affected parents (in Paper III), number of biological children at baseline, and calendar periods (in Paper IV).

Sensitivity analysis

In Paper II, changes observed in the population-level dosage of psychotropic medication dispensed to parents may reflect not only variations in individual medication dosage but also shifts in the proportion of parents using such medication. To isolate changes in dosage among users, we conducted a subgroup analysis restricted to parents with a history of psychotropic medication use in the 1 to 4 years prior to the cancer diagnosis and matched them to comparable parents without a cancer-diagnosed child. We then calculated differences in average dosage between the pre-diagnosis and post-diagnosis periods. In addition, to provide further insights into population-level dynamics, we analyzed changes in the proportion of parents using psychotropic medication within the ITS framework, following a binomial distribution.

In Paper III, to strengthen the robustness of the analyses and account for different temporal relationships between parental mental health and child mortality, we first conducted a subgroup analysis restricted to parents with mental illness predating the

child's cancer diagnosis. It was less likely for those parents to be influenced by the diagnosis or cancer characteristics. Additionally, we applied a landmark analysis (135, 136) with a fixed time point at two years after the child's diagnosis to capture both early and delayed onset of parental mental illness, representing a critical period for psychological adjustment and the establishment of coping mechanisms. Only children who remained under observation up to the landmark were included, which reduced immortal time bias while maintaining sufficient statistical power. The exposure status of children was determined according to whether their parents had a mental illness by the landmark.

For all analyses, a 2-tailed $P<.05$ was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc.).

Table 2. Overview of Time Frames, Key Variables and Statistical Analysis for Papers I-IV.

Paper	Diagnosis Period	Exposure	Outcome	Matching Conditions	Follow-up Period
I	1 Jan 2006 – 31 Dec 2016	Child's cancer diagnosis	Yearly counts of parental hospital visits for mental health disorders	Child's age and sex, along with parents' age, sex, country of birth, and the registered municipality	5 years before to 7 years after the diagnosis, censored at death, emigration, or the end of the study period (31 December 2018).
II	1 Jul 2009 – 31 Dec 2015	Child's cancer diagnosis	Annual dosage of psychotropic medication uses among parents; annual proportion of parents using psychotropic medication	Child's age and sex, along with parents' age, sex, country of birth, and the registered municipality	4 years before to 4 years after the diagnosis, censored at death, emigration, or the end of the study period (31 December 2018).
III	1 Jan 2005 – 31 Dec 2016	Parental mental illness	Child's mortality	–	Censored at death, emigration, or the end of the study period (31 December 2018).
IV	1 Jan 1987 – 31 Dec 2016	Child's cancer diagnosis	Parental somatic burden	Child's age, sex, and country of birth, along with parents' age, sex, and the comorbidity conditions	Censored at death, emigration, or the end of the observation period (31 December 2018).

Table 2. (continued)

Paper	Primary Analytic Framework	Adjustors	Stratifications
I	Interrupted time series (ITS) framework with generalized linear models	Parental age, country of birth, place of residence, educational attainment, and comorbidities at baseline	Parent's sex, the child's age at diagnosis, childhood cancer sites
II	Interrupted time series (ITS) framework with generalized linear models	Parental age, country of birth, place of residence, educational attainment, individual income, and comorbidities at baseline	Parent's sex, the child's age at diagnosis, childhood cancer sites, parental educational attainment
III	Survival analysis framework using time-dependent Cox regression	Child's sex, age at diagnosis, country of birth, place of residence, cancer sites, and tumor malignancy status, as well as parents' educational attainment, age and history of mental illness	Parent's sex, number of affected parents, the child's age at diagnosis, childhood cancer sites, tumor malignancy status
IV	Recurrent event framework using marginal means/rates model	Parents' educational attainment, country of birth, place of residence and history of corresponding diseases for each disease category, as well as the number of biological children	Parents' sex, the child's age at diagnosis, childhood cancer sites, tumor malignancy status, number of biological children at baseline, calendar periods

Results

Paper I

In total, we identified 2,852 mothers and 2,769 fathers of children diagnosed with cancer and matched them to 13,347 mothers and 12,939 fathers of cancer-free children. Baseline demographic characteristics were comparable between parents of children with cancer and their matched counterparts. Generally, both mothers and fathers exhibited increased rates of hospital contacts for mental health disorders over time, as shown in Figure 6.

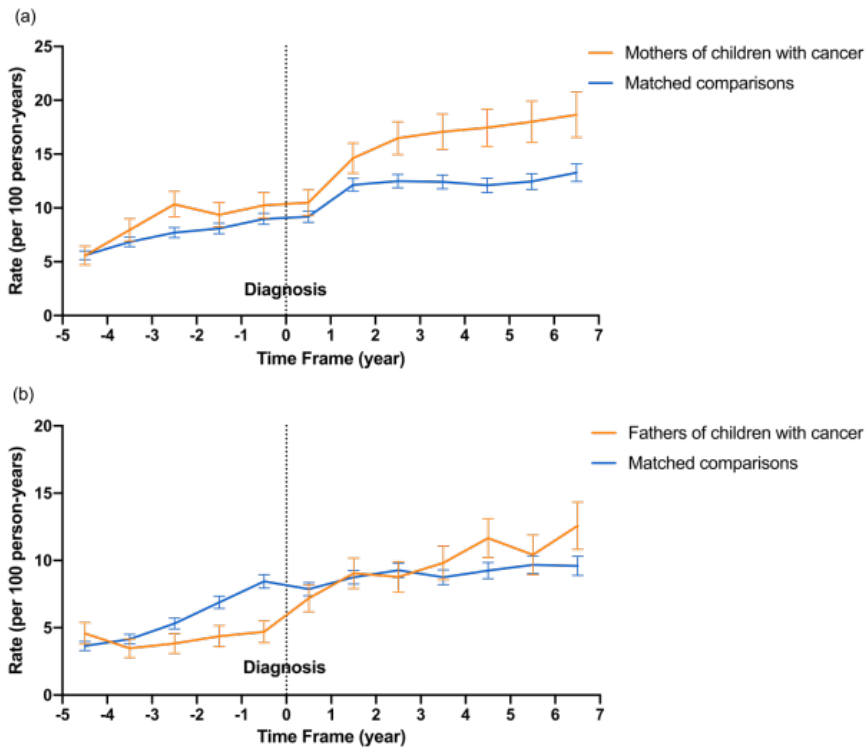


Figure 6. Rates of mental health-related hospital contacts among (a) mothers; (b) fathers before and after the diagnosis of childhood cancer (per 100 person-years).

Using the ITS analytic framework, we observed distinct patterns of hospital contacts for mental health disorders among fathers and mothers following a child's cancer diagnosis. Among fathers, a significant immediate deterioration in mental health was observed in the year of diagnosis. As shown in Figure 7, fathers of children with cancer had a 31% higher rate of hospital contacts for mental health disorders compared with matched fathers (rate ratio (RR): 1.31, 95% CI: 1.01–1.71). When examining specific disorders, significant associations were observed for severe depressive disorders (RR: 3.32, 95% CI: 1.06–10.39) and adjustment disorders (RR: 3.32, 95% CI: 1.06–10.39) (Figure 8).

In contrast, maternal mental health exhibited a sustained and progressively worsening pattern. As illustrated in Figure 7, compared with mothers of cancer-free children, mothers of children with cancer experienced a 17% higher rate of hospital contacts in the first year after diagnosis (RR: 1.17, 95% CI: 1.03–1.32) and, notably, increasing by approximately 3% per year thereafter and reaching a 36% higher rate by the seventh year of follow-up (RR: 1.36, 95% CI: 1.07–1.74). Nearly all subtypes of mental health disorders showed significant associations among mothers (Figure S3 in Paper I). Mothers faced substantially elevated risks of severe depressive disorders (first year: RR 2.15, 95% CI, 1.37–3.38; seventh year: RR 4.64, 95% CI, 1.88–11.41), recurrent depressive disorders (first year: RR 1.48, 95% CI, 1.18–1.85; seventh year: RR 2.18, 95%CI, 1.38–3.44), and adjustment disorders (first year: RR 1.56, 95% CI, 1.27–1.90; seventh year: RR 2.42, 95% CI, 1.62–3.62) (Figure 9). Conversely, they exhibited a lower risk of alcohol abuse in the first year (RR:0.56, 95% CI: 0.34–0.91) and the seventh year (RR: 0.31, 95%CI: 0.12–0.84) following the child's cancer diagnosis.

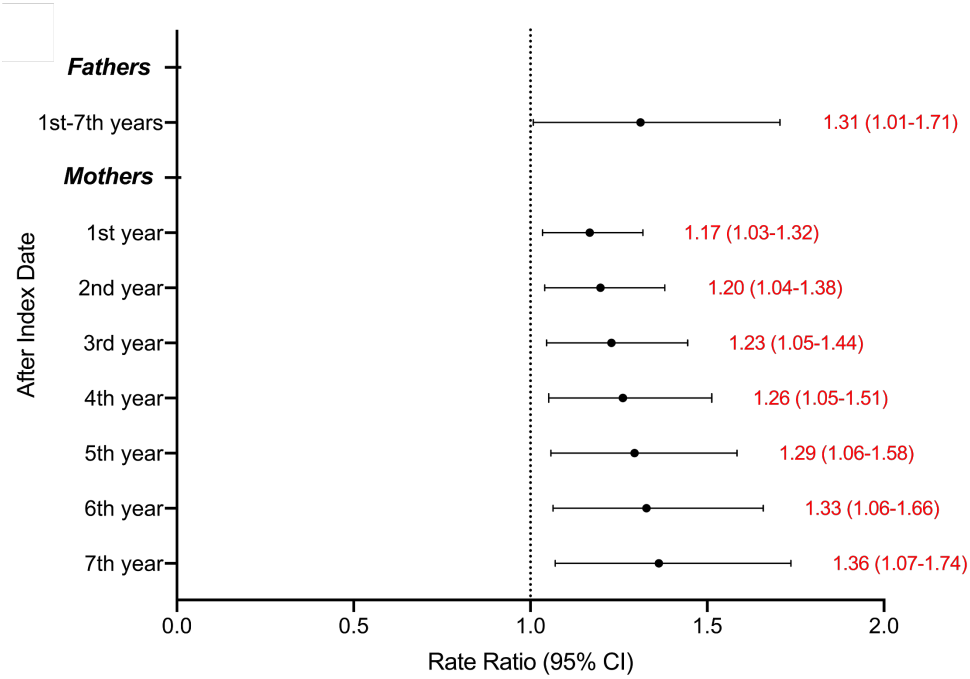


Figure 7. The rate ratio (95% CI) of hospital contacts for mental health disorders in parents of children with cancer.

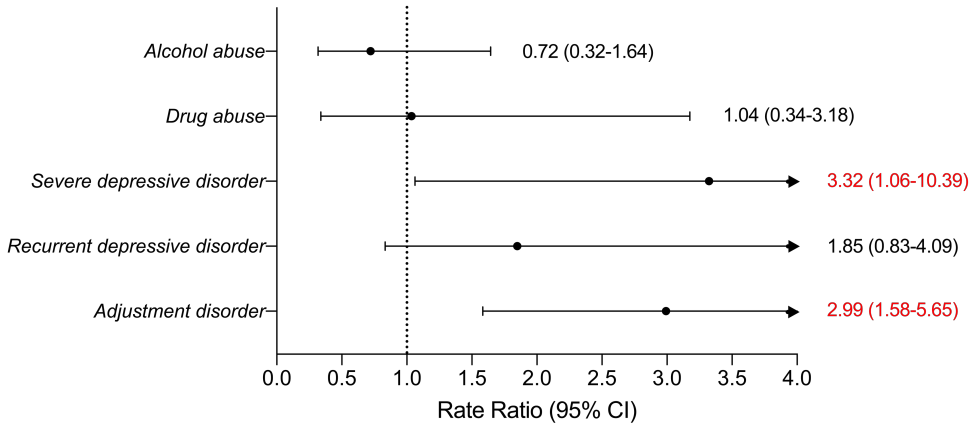


Figure 8. The rate ratio (95% CI) of hospital contacts for specific mental health disorder subtypes in fathers of children with cancer.

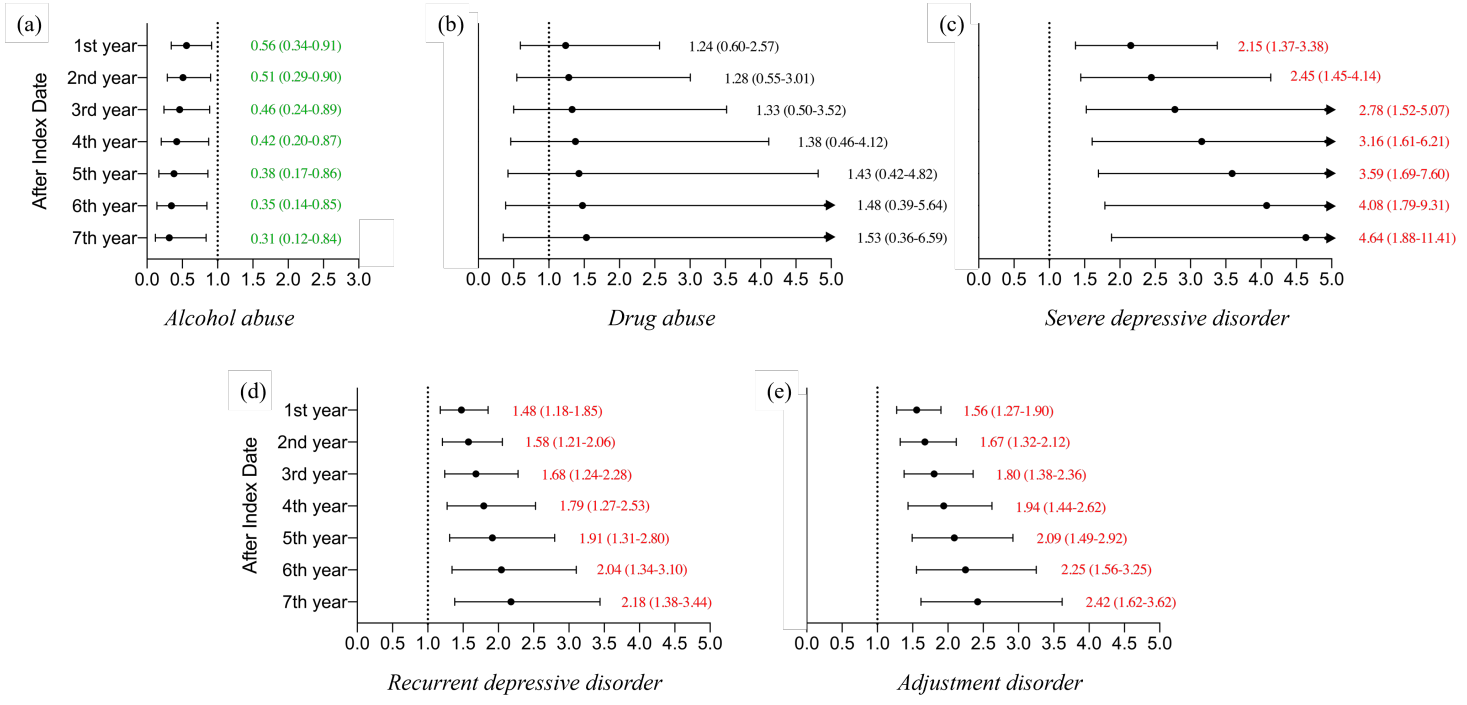


Figure 9. The rate ratio (95% CI) of hospital contacts for specific mental health disorder subtypes in mothers of children with cancer.

Paper II

A total of 1,715 mothers and 1,661 fathers of children with cancer were matched with 8,033 mothers and 7,775 fathers of cancer-free children, with comparable baseline demographics.

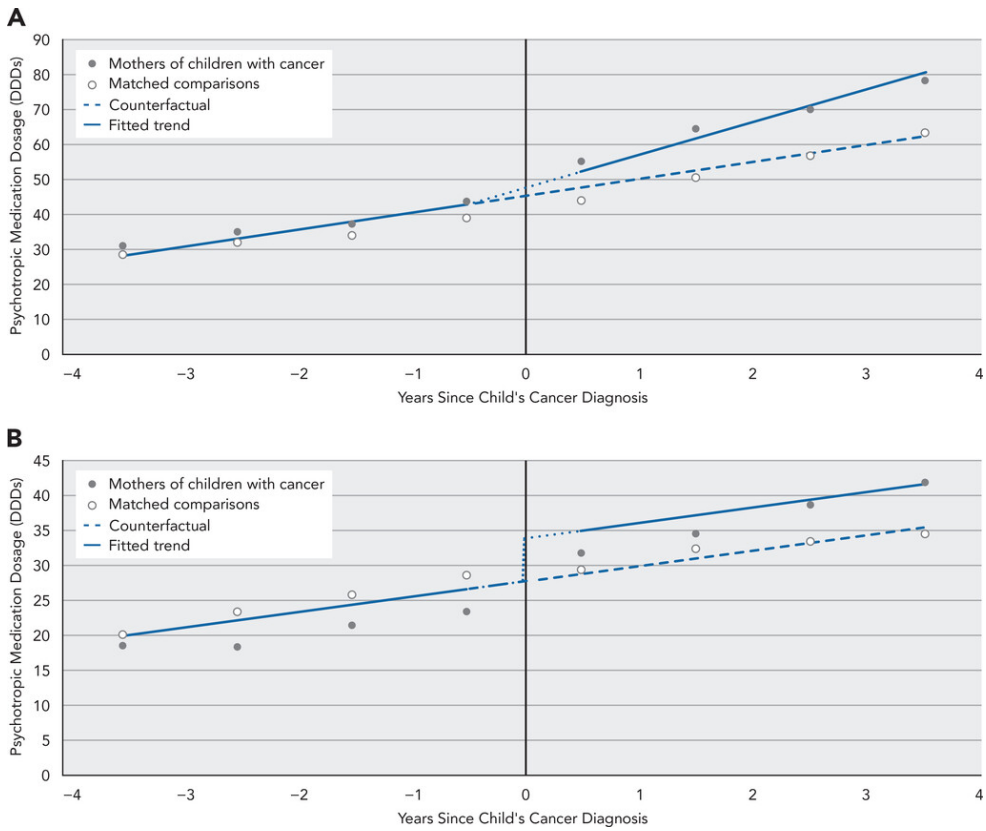
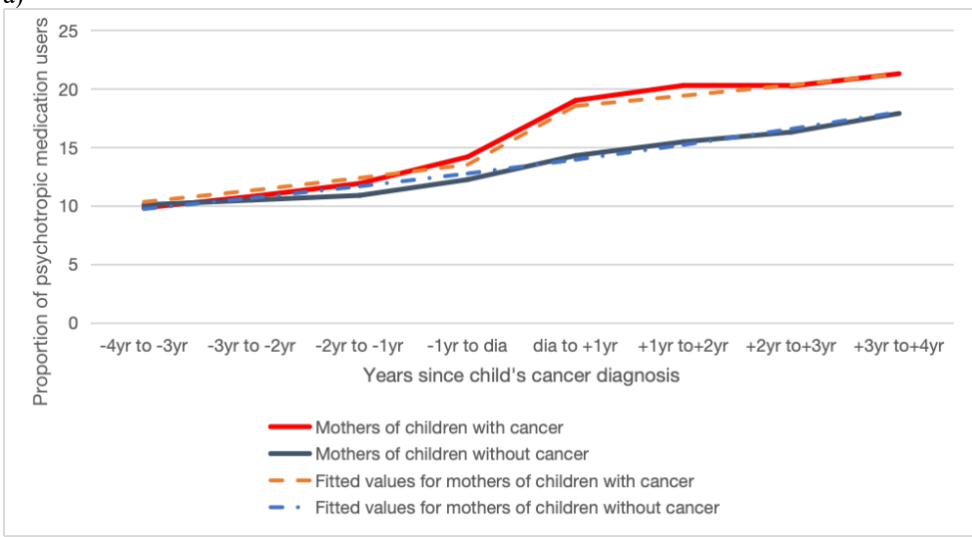


Figure 10. Annual average dosage of psychotropic medication dispensed to (A) mothers and (B) fathers.

During the study period, the annual average dosage of dispensed psychotropic medication steadily increased for all parents, as shown in Figure 10. Notably, mothers consistently received higher dosages than fathers. At baseline, 9.7% of mothers and 6.3% of fathers had been dispensed psychotropic medication, with the proportion increasing over time (Figure 11).

a)



b)

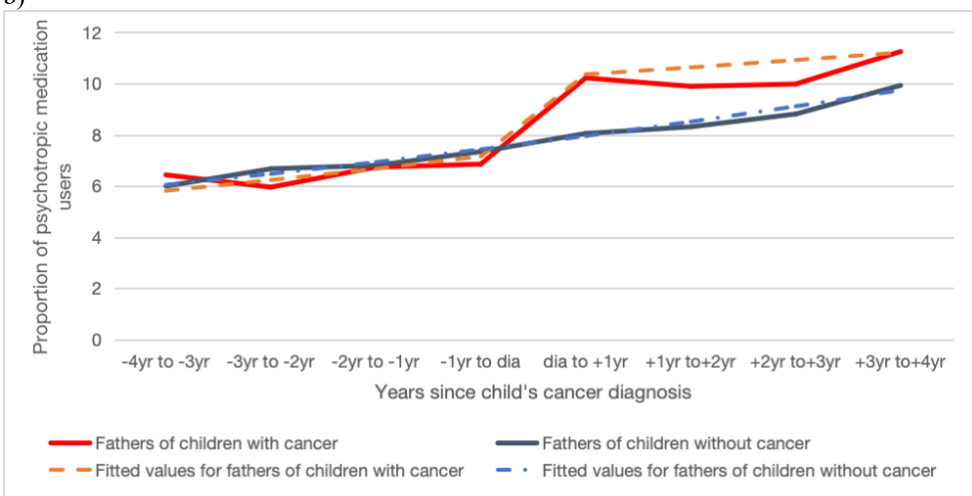


Figure 11. Proportion of psychotropic medication users among a) mothers, b) fathers. The dashed lines represent fitted lines created using robust ITS models.

Using a concise ITS framework, distinct post-diagnosis patterns emerged by parental sex. Among mothers of children with cancer, psychotropic medication use increased gradually over time, with an estimated annual increase of 4.90 DDDs (95% CI: 4.33–5.47) compared with their matched comparisons. In contrast, fathers experienced an abrupt increase in medication dosage with 5.76 DDDs (95% CI: 1.07–10.46) around the year of diagnosis. Furthermore, the proportion of parents using psychotropic medication also increased significantly in the subsequent year following the child's diagnosis. Although the proportion of maternal users declined significantly later, both mothers and fathers consistently exhibited higher

proportions of psychotropic medication use than their matched parents throughout follow-up.

For specific medications, mothers showed a slope change in antidepressant use, while significant level changes were identified in anxiolytics and hypnotics use. Among fathers, only anxiolytics and hypnotics showed a significant level increase following the child's cancer diagnosis.

Paper III

A total of 2,867 children diagnosed with cancer aged 0–14 years were included, who had at least one identifiable biologic parent in the national registers and survived beyond the month of diagnosis. Among these children, 1,801 were exposed to parental mental illness during follow-up, whereas 1,066 remained unexposed by the end of the study. The median follow-up was 89 months, comprising a median non-exposed period of 10 months from cancer diagnosis to the onset of parental mental illness, and the exposed period thereafter.

Children who experienced parental mental illness after their cancer diagnosis had a 47% higher risk of mortality (HR: 1.47, 95% CI: 1.18–1.84) compared with those whose parents did not have mental illness. As depicted in Figure 12, elevated risks of death were observed regardless of whether the affected parent was the mother or father and were even higher when both parents experienced mental illness (HR: 2.16, 95% CI: 1.58–2.97). Notably, when restricted to children whose parents had no history of mental illness, parental mental illness developing after the child's cancer diagnosis was associated with a 77% higher mortality risk (HR: 1.77, 95% CI: 1.33–2.36).

Stratification by the child's age at diagnosis and by cancer type revealed no substantial variation in risk. Stratification by malignancy status exhibited a higher but not significant risk among children with benign tumors (HR: 2.11, 95% CI: 0.93–4.79) and a slightly lower but significant risk among those with malignancies (HR: 1.45, 95% CI: 1.15–1.82). Moreover, the landmark analysis, which assessed parental mental health within a fixed 2-year period postdiagnosis, revealed an HR of 1.68 (95% CI: 1.15–2.44) for the association with child mortality, as shown in Figure 4 of Paper III.

Subgroup	Children with Parental Mental Illness	Children without Parental Mental Illness	Adjusted HR (95% CIs)
Overall	1801	1066	1.47(1.18-1.84)
Parents			
Father	903	1919	1.85(1.44-2.37)
Mother	1491	1372	1.35(1.08-1.70)
Number of Parents			
Single parent	1181	1044	1.31(1.03-1.67)
Both parents	593	1044	2.16(1.58-2.97)
Cancer Type			
Hematological Malignancies	758	457	1.26(0.85-1.88)
Nervous System Tumors	508	300	1.57(1.10-2.23)
Other Childhood Cancers	535	309	1.45(0.94-2.23)
Malignancy Status			
Benign	225	149	2.11(0.93-4.79)
Malignant	1576	917	1.45(1.15-1.82)
Parental Mental Illness Before Childhood Cancer			
With previous mental illness	936	225	1.13(0.82-1.58)
Without previous mental illness	865	841	1.77(1.33-2.36)

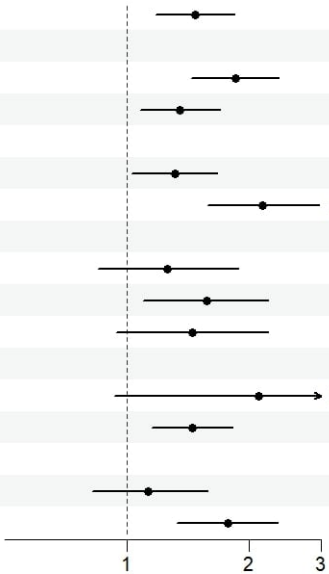


Figure 12. Hazard ratios (95% CI) for childhood cancer mortality associated with parental mental illness, overall and stratified by parental sex, number of affected parents, cancer type, tumor malignancy status, and parental mental illness history

Paper IV

A total of 7,098 mothers and 6,859 fathers of children with cancer were matched with 33,394 mothers and 31,780 fathers of cancer-free children, with comparable baseline demographics. Overall, parents of children with cancer exhibited higher rates and incidence of somatic health conditions than parents of cancer-free children across most disease categories.

Recurrent event analyses showed significantly higher rates among parents of children with cancer for several disease categories, as demonstrated in Table 3. In particular, they experienced a 9 % higher rate of neoplasm-related events (HR: 1.09, 95 % CI: 1.04–1.13), a 9 % higher rate of conditions related to blood and immune mechanisms (HR: 1.09, 95 % CI: 1.00–1.19), a 6 % higher rate of circulatory system diseases (HR: 1.06, 95 % CI: 1.03–1.10), and a 5 % higher rate of genital organ diseases (HR: 1.05, 95 % CI: 1.01–1.08). Findings from incidence models were largely consistent with the recurrent event analyses, particularly for circulatory system disease (HR: 1.05, 95%CI: 1.01–1.08), and genital organ diseases (HR: 1.06, 95 % CI: 1.02–1.10), as well as the non-significant associations observed for digestive, skin, musculoskeletal, and urinary diseases.

Stratified analyses revealed relatively consistent risk estimates for most disease categories across subgroups. However, notable heterogeneity was observed among fathers and mothers for neoplasms (HR: 1.15 vs. 1.04), eye and adnexa diseases (HR: 1.08 vs. 1.02), and circulatory system diseases (HR: 1.03 vs. 1.11). Elevated risks were also more pronounced among parents of children diagnosed with cancer at older ages (10–14 years), particularly for blood and immune diseases (HR: 1.28, 95 % CI: 1.09–1.51). Differences by cancer type were modest overall, but elevated risks for neoplasms, eye diseases, circulatory system diseases, and genital organ diseases were observed among parents of children with malignant tumors, whereas associations were weaker or inverse for benign tumors. Furthermore, parents with four or more children tended to show higher rates across several categories, including endocrine, nervous system, and circulatory diseases.

Table 3. Rates and Estimated Risks of Incident and Recurrent Somatic Health Conditions Among Biological Parents of Children Diagnosed with Cancer in Sweden (1987-2016) Compared to Parents of Children without Cancer.

Disease categories	Parents of children with cancer (N = 13,957)			Parents of children without cancer (N = 65,174)			Cox proportional hazards model (HR)		Marginal means/rates model (HR)	
	Overall rate #	Sub-cohort &		Overall rate #	Sub-cohort &		Unadjusted	Adjusted †	Unadjusted	Adjusted ††
		N	Incidence #		N	Incidence #				
1. Infectious and parasitic diseases	3.2	11,483	1.9	3.1	46,826	1.9	1.00 (0.96–1.03)	0.99 (0.96–1.03)	0.99 (0.96–1.03)	0.99 (0.96–1.02)
2. Neoplasms	5.4	12,573	1.8	4.8	54,942	1.7	1.03 (0.99–1.06)	1.02 (0.99–1.06)	1.10 (1.05–1.15) *	1.09 (1.04–1.13) *
3. Endocrine, nutritional, and metabolic diseases	8.0	13,186	1.3	7.6	59,472	1.3	1.02 (0.99–1.07)	1.03 (0.99–1.07)	1.00 (0.96–1.05)	0.99 (0.95–1.04)
4. Diseases of blood and immune mechanism	1.2	13,575	0.4	1.1	61,936	0.4	1.06 (0.99–1.13)	1.06 (0.99–1.14)	1.10 (0.99–1.21)	1.09 (1.00–1.19) *
5. Diseases of the nervous system	4.4	13,043	1.4	4.2	58,009	1.3	0.99 (0.96–1.03)	0.99 (0.96–1.03)	1.01 (0.96–1.06)	1.01 (0.96–1.07)
6. Diseases of the eye and adnexa	2.7	12,955	1.3	2.5	57,218	1.3	1.03 (0.99–1.08)	1.03 (0.99–1.07)	1.05 (1.00–1.10) *	1.04 (1.00–1.09)
7. Diseases of the ear and mastoid process	2.8	12,718	1.5	2.7	55,827	1.4	1.04 (1.00–1.08) *	1.n (1.00–1.08) *	1.02 (0.98–1.06)	1.02 (0.98–1.06)
8. Diseases of the circulatory system	10.1	13,038	2.1	9.2	58,107	2.0	1.04 (1.01–1.08) *	1.05 (1.01–1.08) *	1.06 (1.02–1.10) *	1.06 (1.03–1.10) *
9. Diseases of the respiratory system	9.0	9949	3.1	9.0	38,689	3.0	0.98 (0.95–1.02)	0.98 (0.95–1.01)	0.98 (0.95–1.01)	0.97 (0.94–1.00)
10. Diseases of the digestive system	5.7	11,300	2.1	5.5	45,180	2.0	1.02 (0.98–1.05)	1.02 (0.98–1.06)	1.01 (0.97–1.05)	1.01 (0.97–1.04)
11. Diseases of the skin and subcutaneous tissue	5.7	12,011	2.4	5.7	50,881	2.4	0.98 (0.95–1.01)	0.98 (0.95–1.01)	0.98 (0.94–1.01)	0.98 (0.94–1.01)
12. Diseases of the musculoskeletal system and connective tissue	18.2	10,899	4.3	17.9	43,732	4.2	1.00 (0.97–1.03)	1.00 (0.97–1.03)	0.99 (0.97–1.02)	1.00 (0.98–1.03)
13. Diseases of the urinary system	3.0	12,679	1.2	3.0	55,433	1.0	1.00 (0.96–1.05)	1.00 (0.96–1.04)	0.99 (0.94–1.04)	0.98 (0.94–1.03)
14. Diseases of the genital organs	4.6	11,744	1.8	4.3	48,523	1.7	1.07 (1.03–1.11) *	1.06 (1.02–1.10) *	1.05 (1.01–1.08) *	1.05 (1.01–1.08) *

Discussion

This thesis examined the health consequences of childhood cancer for parents across multiple dimensions, including mental health–related hospital visits, psychotropic medication use, somatic disease burden, and the implications of parental mental illness for child survival. Using nationwide Swedish register data to establish complete population cohorts and employing diverse analytic approaches, the four studies provide a comprehensive picture of how a child's cancer diagnosis affects parental health trajectories over time and how parental mental health, in turn, influences the child's prognosis.

Main findings

A consistent pattern was observed across the papers, highlighting a complex and bidirectional interplay between childhood cancer and parental health challenges. A child's diagnosis is a profound stressor, leading to sustained health challenges for parents, while parental mental health may also influence the child's cancer outcomes. Papers I and II demonstrated that parents experienced persistently higher rates of hospital contacts for mental health disorders and greater use of psychotropic medication following their child's diagnosis. The adverse impact appeared not only immediately around diagnosis but also constantly for years, particularly worsening among mothers. In turn, the impaired parental mental health may impair parenting capacity and contribute to a more stressful family environment, which could result in a compromised prognosis for children. Paper IV further extended the observed effect beyond parental mental health to their somatic conditions. It was shown that parents of children with cancer also experienced elevated rates of recurrent healthcare visits for a range of somatic health conditions across multiple disease categories. Overall, these findings suggest that the impact of childhood cancer on parents is multifaceted, encompassing both psychological and broader physiological consequences, potentially driven by cumulative effects of chronic stress, caregiving demands, and lifestyle changes, with potential implications for the child's survival.

Temporal patterns and heterogeneity in parental health

Trajectories of parental mental health

In line with previous studies showing adverse effects of child's cancer on parental mental health outcomes (62, 118, 120, 137), and consistent with a comprehensive review reporting that approximately 27% of parents continue to experience clinical levels of psychological distress up to 5 years after their child's cancer diagnosis (69), our findings revealed persistently increased rates of mental health-related hospital contacts and greater use of psychotropic medication among parents of children with cancer. Several factors may underlie these observations, encompassing the acute emotional shock triggered by the initial diagnosis, prolonged caregiving responsibilities, ongoing concerns about prognosis and potential late effects, and employment or financial strains (138).

Using interrupted time series frameworks in Papers I and II, distinct patterns were consistently observed for mothers and fathers across mental health–related hospital contacts and annual psychotropic medication dosage. Mothers exhibited a sustained deterioration in mental health over the long term, whereas fathers demonstrated an acute decline around the time of diagnosis, and the risk remained consistently stable over time. These patterns suggest that mothers may experience a progressively accumulating mental health burden, whereas fathers exhibit a more acute but comparatively stable response. However, when examining the proportion of psychotropic-medication users, the trajectories showed some notable differences. For both parents, the proportion of users increased significantly in the subsequent year following diagnosis, but among mothers, this was followed by a statistically significant decline in the post-diagnosis period. Despite this decline, both mothers and fathers consistently maintained a higher proportion than their matched parents. This pattern may indicate that the existing users among mothers may increase their dosage to manage the heightened levels of psychological distress. A cumulative cycle of caregiving burden (139), physical and emotional exhaustion, and exacerbated health problems in children may explain the ever-increasing risk among mothers.

Parental cumulative somatic disease burden

Paper IV demonstrated that the health impact of childhood cancer on parents extends beyond mental illness to include recurrent somatic diseases. The use of recurrent event models enabled us to capture the cumulative disease burden across repeated healthcare visits rather than only focusing on incident diagnoses. Importantly, the sensitivity analyses restricted to incident somatic diseases yielded similar patterns, further supporting the robustness of our primary findings.

The observed increased risks across multiple disease categories may be driven by multiple factors. For instance, the elevated neoplasm-related healthcare visits may reflect shared genetic susceptibility or enhanced medical surveillance, leading to higher detection rates and more frequent follow-up. Beyond the psychological toll, chronic stress may also adversely affect parental physical health through the stress-induced biological mechanisms (140). The systemic inflammation (141), endothelial dysfunction (142), immune dysregulation (143-145), hormone disruption (142, 146), and stress-related epigenetic modification (147) may contribute to increased risks of cardiovascular, immune, and reproductive disorders, as well as tumor development and progression. It is also important to note that other categories, such as musculoskeletal, respiratory, infectious, urinary, and nervous system diseases, showed non-significant group differences, suggesting that not all areas of parental somatic health are impacted.

Sex-specific differences were also observed, with fathers exhibiting a significantly increased risk for neoplasm-related events and eye and adnexa conditions, whereas mothers were adversely affected in endocrine, nutritional, metabolic, and circulatory disease categories.

Specific health outcomes

In relation to specific mental health disorders, parents of children with cancer had higher rates of hospital contacts for severe depressive disorder and adjustment disorder compared to their matched counterparts, consistent with a prior study(80). Additionally, an increased risk of recurrent depressive disorder was shown among mothers. Interestingly, both parents showed a lower risk of alcohol abuse, contrary to previous studies (148, 149). This may reflect differences in measurement, as earlier research often relied on screening tools rather than clinical diagnoses, and caregiving-related social isolation may reduce opportunities for alcohol consumption.

In general, anxiety and depression are two separate but often co-occurring conditions (150). Among post-diagnosis increased dosage of psychotropic medication among mothers of children with cancer, over 80% was attributed to the use of antidepressants. Interestingly, we observed a significant level increase in the dispensation of anxiolytics and hypnotics among mothers in response to their child's cancer diagnosis, rather than a slope impact pattern. One prior study also revealed a significant reduction only in anxiety over time among parents of children diagnosed with craniopharyngioma (151). For fathers of children with cancer, nearly half of the level shift was because of the use of antidepressants, while more than half was due to the use of anxiolytics and hypnotics. Anxiolytics and hypnotics are medications that induce calmness or sleep. The first year following a child's cancer diagnosis can be particularly stressful, which might lead to a surge in anxiety and disrupted sleep patterns, an acute response for both mothers and fathers. The

subsequent stable level shift in anxiolytics and hypnotics medication uptake might reflect the heightened state of anxiety that persisted. The antidepressant usage among fathers showed a non-significant level shift, while a continuous annual increase with statistical significance was found among mothers. This is consistent with the primary finding, reflecting the progressively depressive symptoms in mothers over time.

Sex-specific mechanisms

Despite the sex difference in the incidence and vulnerability of numerous psychiatric disorders (152) and somatic conditions, the sex-specific patterns observed in our studies likely reflect differences in parental roles (84, 101, 153, 154), coping strategies (155, 156), healthcare-seeking behavior (157), and societal expectations (84, 155). Mothers may often assume a greater share of caregiving and household work during a child's illness, which may result in prolonged emotional strain and cumulative physiological wear affecting metabolic and cardiovascular health. Moreover, the abrupt heightened use of antidepressants and anxiolytics among fathers may contribute to ophthalmic side effects such as dry eye (158), partially explaining their higher rates of eye and adnexa conditions.

Thus, the consistent sex-specific patterns observed in Papers I and II, together with the distinct differences in somatic health conditions, underscore that mothers and fathers may need different types of support in both clinical care and other supportive interventions.

Heterogeneity across subgroups

Given that individual personalities, socioeconomic status, past experiences, available support network, and overall health history may play a role in parental response to a child's cancer diagnosis, the effects can vary widely between parents (70, 159-161). Across all papers, we estimated population-level changes while also exploring the subgroup differences to identify vulnerable groups. Notably, the increases in annual psychotropic medication dosage associated with the child's cancer diagnosis were largest among parents with the lowest educational attainment for both mothers and fathers. This pattern is consistent with existing evidence showing that caregivers with fewer years of education face a significantly higher psychosocial risk (69, 162). Potential differences in coping style, reduced access to psychosocial and healthcare resources, and poorer health literacy (151, 163) may negatively appraise the child's health condition (164, 165), and these parents become more vulnerable to the impact of their child's cancer diagnosis. In paper IV, elevated risks were more evident among families with more children, suggesting parents in larger families likely have greater caregiving demands, heightened financial strain, and less time for self-care.

While the magnitude of associations was not fully consistent across papers, heterogeneity by child characteristics was consistently observed, such as age at diagnosis, cancer types, and malignancy status, suggesting that parental burden can be shaped by the developmental stage of the child and disease-related factors. These findings highlight the need for tailored support that accounts for both parental and child characteristics.

Parental mental illness and child prognosis

Implications of parental mental health for children's cancer outcomes

Our findings extend the impact of parental mental health on the child's prognosis that parental mental illness may increase mortality risk for children with cancer, suggesting that parental mental health is not only a health issue for parents themselves but may also have implications for the child's cancer outcomes. Several mechanisms may explain the association. Emerging evidence highlights the critical role of parental mental health on multiple aspects of a child's cancer trajectory, including emotional adjustment (72, 159, 166, 167), coping ability (65, 168), treatment adherence (169), long-term behavioral issues (170, 171), and overall quality of life (172-174). Parental mental illness can impair their capacity to provide consistently high-quality caregiving and to manage complex medical demands, which are essential for optimizing a child's prognosis. Additionally, parental psychological distress may influence the emotional environment of the child to adversely affect cancer outcomes by exacerbating the child's own stress response and potentially leading to an increased vulnerability of the immune system (175, 176).

Variation in associations

No significant association was observed either between prior parental mental illness and child mortality, or among parents with pre-existing illness who also experienced mental illness after the child's diagnosis. Despite the potential vulnerability to recurrence due to stressors, parents with prior mental health conditions may have developed coping strategies or support systems that mitigate the impact of their illness on caregiving quality. In contrast, parents who develop mental illness for the first time after their child's diagnosis may struggle to adjust effectively, which is associated with a higher risk of child mortality.

Stratified analyses provided further insights into the influence of various factors on the associations observed between parental mental illness and child mortality. Notably, child mortality risk was increased when both parents experienced mental

illness, indicating a potential cumulative adverse effect on caregiving capacity. The effects remained across various strata of child age at diagnosis and cancer types. Interestingly, the association appeared stronger among children with benign tumors than with malignant tumors, although the association for benign tumors did not reach statistical significance. The elevated risks underscore the need for awareness and monitoring in vulnerable groups.

Methodological considerations

Overall strength

A major strength of the studies included in this thesis lies in the use of Swedish nationwide, population-based registers with long follow-up, enabling us to explore relatively rare exposures with minimal selection bias and robust statistical power. The organized, systematic data collection, sourced from NPR, PDR, and primary health care datasets, facilitated access to objective measurements with clinical diagnosis and medication use, strengthening the reliability of our findings and minimizing the potential for response bias (177). In addition, the exact matching procedure in Papers I, II, and III, along with the model adjustments applied across all papers, reduced confounding and improved the validity of our findings. The combination of cohort designs, interrupted time series analyses, time-dependent survival models, and recurrent event models allowed us to examine different aspects of parental health and children's cancer while addressing specific methodological challenges.

ITS framework

In Papers I and II, the use of the ITS framework, a quasi-experimental design, strengthened causal inference by comparing within-parent changes before the child's cancer diagnosis with the forecasted counterfactual values afterward (128), considering both pre-diagnosis trends and preexisting differences from their matched comparisons (178). In Paper I, although the matching procedure ensured overall comparability, there was a slightly lower rate of hospital contacts in the pre-diagnosis period. In general, this type of imbalance is difficult to address with traditional methods, but ITS accounted for pre-diagnosis differences when estimating counterfactual values for parents of children with cancer and therefore yielded more reliable effect estimates.

A limitation of using generalized linear estimation within the ITS framework is the assumption of the separate linear trends in the pre- and post- diagnosis periods according to the relevant link functions (log link for negative binomial distribution,

identity link for continuous outcome, and logit link for binomial distribution). However, in Paper II, potential nonlinearity was recognized in the post-diagnosis period for population-level psychotropic medication use, particularly in the proportion of parental users. Although incorporating additional post-diagnosis segments could theoretically capture these complexities, identifying universal breakpoints is challenging. The timing of psychological deterioration, adaptation, or consilience varies considerably across parents, making it unrealistic to determine a generic breakpoint. Introducing arbitrary or population-level breakpoints could therefore lead to misspecification and bias. Alternatively, higher-order polynomial terms could model the non-linearity to some extent but would complicate the interpretation in the meantime. Thus, we selected this simpler approach to provide a straightforward and interpretable estimate of the average population-level effect.

Time-varying exposure and temporal association in Paper III

In paper III, time-dependent Cox regression was performed to address immortal time bias, which can occur when the exposure status is defined after cohort entry. Several sensitivity analyses were conducted to further enhance the robustness of the study and explore different temporal relationships between parental mental illness and child mortality. In particular, the landmark method was applied to mitigate bias associated with time-varying exposure. The consistent results across these analyses additionally support the validity of our primary findings.

When considering causal inference, it's essential to acknowledge the inherent limitations of observational data that the significant associations observed between parental mental illness and child mortality could be bidirectional. Parental mental illness may arise from the child's deteriorating health rather than serve as a contributing factor to child mortality. Prior evidence indicated that parents typically recognize their child's lack of a realistic chance for cure approximately 106 days before the child's death (179). This suggests a relatively short window in which the child's poor prognosis could influence parental mental health conditions. In contrast, our study found a median duration of 60 months from the onset of parental mental illness to child mortality, against reverse causation triggered by the recognition of the child's poor prognosis. Nonetheless, caution remains warranted when interpreting the directionality of the observed associations.

Measurement proxies and covariates

In Papers I and II, mental health-related hospital contacts and psychotropic medication use were used as objective indicators of parental mental health outcomes. Hospital contacts tend to capture more severe or acute conditions, whereas psychotropic medication use is more sensitive to detect subtle changes. However, increases in hospital contacts or medication dosage may not always reflect the

worsening parental mental health conditions. Repeated outpatient contacts may represent prolonged self-willed engagement in care as opposed to sustained mental health disorders and increases in medication use may stem from early dosage adjustments for mitigating adverse effects, particularly common among new users or existing users switching medications. In addition, some drugs have multiple indications, potentially introducing misclassification of mental health status. Conversely, these proxies may also underestimate parental outcomes as they capture only those who seek healthcare or receive prescriptions and miss those with undetected mental health needs.

Paper IV used broad ICD-10 chapters to define disease categories and detect overall patterns. However, broad categories may mask important variations in disease burden by obscuring within-category heterogeneities in biological mechanisms, severity, chronicity, and prognosis. The use of a 30-day interval to define recurrence is a common approach to avoid counting follow-up visits for the same episode as separate events, but it may not fit all conditions, as some diseases may recur earlier or later than 30 days, even within the same disease.

Across all four papers, some key variables, such as CCI, educational attainment, country of birth, place of residence, and child cancer characteristics, worked as proxies and were included to adjust for confounding and explore heterogeneity. The CCI served as an indicator of general parental health condition, but it captures only specific chronic diseases and may not reflect overall functional status. Educational attainment, country of birth, and place of residence served as proxies for socioeconomic status, health literacy, and healthcare access. We used child cancer malignancy status and cancer type to approximate cancer severity and prognosis, but they are not perfect proxies as they inevitably simplify the clinical complexity and heterogeneities in childhood cancer.

Furthermore, several important factors are not included in our studies, encompassing treatment-related variables, family structure dynamics, social supports, and employment changes. In addition, the reliance on administrative data means that lifestyle factors (such as smoking and physical activity), genetic predispositions, or biological stress markers were not available either. These unmeasured factors introduce potential residual confounding and may partly explain heterogeneity in associations.

Clinical and public health implications

In paper II, the adjusted attributable proportion of psychotropic medication use was 46.0% for mothers and 72.1% for fathers in the subsequent year following the child's cancer diagnosis. These substantial proportions underscore the necessity of

timely intervention and the potential benefits of early psychological support to alleviate parental mental health challenges.

Although the large size of the study population increases the likelihood of chance findings, particularly in Paper IV, where the modest associations were observed across multiple disease categories, this does not suggest the lack of clinical importance. Even small elevations in somatic or mental health burden among parents may accumulate over time and contribute to profound impairment in parenting.

In terms of generalizability, the consistent reporting standards and the equivalence of the healthcare settings in Sweden support the applicability of our findings to the present, even though data collection ended in 2018 due to the timing of the ethical approval and data availability. Notably, our findings reflect routine healthcare conditions, unaffected by the substantial disruptions of the Covid-19 pandemic in 2020 (180). However, the generalizability to other countries may be limited by distinct characteristics of Swedish healthcare and social welfare systems, which provide universal coverage and a relatively low financial burden for families (181, 182). In regions without comparable healthcare access for both parents and cancer-diagnosed children, the observed associations may not hold. Furthermore, variations in familial caregiving structures across societies may further restrict the generalization of our findings. These factors should be considered when extending our findings to broader populations.

Overall, the findings of this thesis have important implications for pediatric oncology care. They highlight the need to systematically assess and support parental health, not only at diagnosis but throughout the cancer trajectory and into survivorship. Early identification of parents at risk for persistent distress or mental illness may benefit both parental well-being and child outcomes. The coordination between the pediatric oncology department and primary health services, as well as addressing socioeconomic barriers, may help mitigate the long-term health consequences among parents with cancer-affected children and further benefit their children's cancer outcomes. With the timely diagnosis and advances in treatments, the relatively high survival rates of childhood cancer in Sweden resulted in a growing population of parents who are long-term co-survivors of childhood cancer. Developing prevention and intervention strategies tailored to vulnerable parents is essential not only to support family well-being but also to reduce the strain on healthcare resources.

Conclusions

Taken together, the four studies demonstrate that childhood cancer has a profound and enduring impact on parental mental and physical health and that parental mental illness may, in turn, influence child survival. These findings highlight the bidirectional associations between child and parental health and underscore the importance of integrating family-centered interventions into standard pediatric cancer care in practice.

Future Perspectives

Future studies could further investigate the mechanisms underlying the associations between a child's cancer diagnosis and subsequent parental health trajectories. The psychosocial factors, such as caregiving intensity, balance between work and family, more detailed family structures, social support, and coping strategies, should be taken into account to help clarify the pathways of the observed associations. By incorporating these factors, we could better understand the sex-specific patterns observed in our studies.

More detailed assessments of parental mental and somatic health trajectories are warranted following the child's cancer diagnosis. As discussed earlier, the somatic health outcomes examined in our study integrated heterogeneous diseases into one category. Future studies should apply more precise and clinically meaningful groupings for targeted interventions, considering the biological mechanisms, severity, chronicity, and prognosis of diseases. Additionally, the timing, continuity, and adherence to mental health interventions should be examined to evaluate whether early psychological support can mitigate long-term mental health deterioration, further informing the development of targeted interventions.

The observed association between parental mental illness and child mortality highlights the need to explore potential mediators within the family-centered mechanisms. Future studies should assess whether parental mental health affects treatment adherence, healthcare transitions, healthcare-seeking behaviors, and the child's psychosocial environment, and subsequently influences the child's prognosis. In addition, incorporating data on tumor severity, symptom duration, treatment intensity, and family dynamics may further clarify the associations.

Given the prolonged survivorship and its potential impact into adulthood, future studies should extend follow-up into the child's adulthood for both parents and children. The evaluation could include whether parental mental and somatic health outcomes persist, recover, or evolve over time, and whether early parental health deterioration have lasting impact on the child's long-term health, development, and quality of life beyond survival as we examined in our study.

These research directions may contribute to getting a more holistic understanding of pediatric oncology care and survivorship, supporting not only the child but also the entire family.

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