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SOCIOECONOMIC FACTORS AND CHILDHOOD CANCER: SURVIVAL AND LONG-TERM CONSEQUENCES

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Socioeconomic factors and childhood cancer: Survival and long-term consequences

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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Till alla som kämpar, man behöver inte kämpa ensam.

POPULAR SCIENCE SUMMARY

Childhood cancer is rare, occurring in around 400-450 children and teenagers every year in Sweden. In the last decades, the diagnosis and treatment of children with cancer has greatly improved and many more children survive the disease today – most recently, 85% of the children diagnosed in Sweden survive at least five years. This has led to an increasing population of adult childhood cancer survivors. Despite these improvements, childhood cancer is the most common disease-related cause of death in Swedish children aged 1-14 years old.

In studies from other countries, social inequalities in survival from childhood cancer have been seen – studies suggest that the survival from childhood cancer is lower in children from disadvantaged socioeconomic backgrounds. We do not know if such differences exist in Sweden where healthcare is open for all residents and free of charge for children. In research contexts, a child's socioeconomic background is often defined by the education or income level of their parents, or other factors such as employment. In Study I-III in this thesis, different socioeconomic and familial factors were assessed in relation to survival after a childhood cancer diagnosis.

Childhood cancer survivors may face various health effects from their disease and/or the treatment that continue into adulthood. We have limited knowledge about how survivors are coping with regard to socioeconomic consequences, such as attaining upper secondary education, which is important for future work-life opportunities. This gap in knowledge was addressed in Study IV in this thesis.

Investigating socioeconomic factors among parents of children with cancer, as well as among childhood cancer survivors, can be challenging. There is a risk that, for example, parents to very sick children, or survivors who have a lot of health problems, do not participate in studies investigating these issues. Moreover, since childhood cancer is rare, it is problematic to investigate small subgroups. These issues make it challenging to draw robust conclusions. Sweden and the Nordic countries have a unique system with several population and health data registers that cover all residents and can be linked together by the personal identity number. These sources of information were used in this thesis to overcome methodological difficulties in previous studies.

The first three studies in the thesis focused on social factors and the potential association with survival from childhood cancer. Study I included children with cancer in Sweden and we observed that children to parents with a lower level of education had worse survival from childhood cancer, while no differences were observed for household income. The differences by parental education were seen already within the first year after diagnosis. These findings led us to investigate potential socioeconomic differences in deaths occurring within three months after the cancer diagnosis (referred to as early mortality), in children diagnosed with cancer in Sweden and Denmark (Study III). We observed that children from disadvantaged backgrounds were at increased risk of early mortality. In Study II we investigated another

aspect of social family circumstances, number of siblings and birth order, in relation to survival from childhood leukaemia in Sweden. It had previously been suggested that children with siblings had lower survival after childhood leukaemia, but this was not seen in our study.

In Study IV, we looked at attainment of upper secondary education in young adult survivors of childhood cancer in Sweden, Denmark, and Finland, in comparison to individuals from the general population and to the survivors' siblings. We observed that delays in education were more common among survivors compared to their peers, but, by the age of 25 years, many survivors had caught up. However, we identified some groups that were less likely to have attained upper secondary education by age 25 years; survivors diagnosed with central nervous system tumours, survivors diagnosed with acute lymphoid leukaemia in the 1970s and 1980s (a period in which this group of patients were treated with cranial radiotherapy), and survivors in need of more contact with healthcare, either at the time period around their cancer treatment, but also later in life.

In summary, we have observed social inequalities in survival from childhood cancer in the Nordic countries, despite universal healthcare access. We saw social differences in survival already shortly after diagnosis and these findings need further attention. We have also shown that although survivors of childhood cancer may experience delays in their education, many catch up. However, there are vulnerable risk groups that need further support. The included studies show the potential and importance of Nordic collaborations in research of rare diseases and give an example of how valuable Nordic population and health data registers are for research in this field.

POPULÄR VETENSKAPLIG SAMMANFATTNING

Socioekonomiska faktorer och barncancer: Överlevnad och långsiktiga konsekvenser

Barncancer är ovanligt och drabbar omkring 400-450 barn och tonåringar i Sverige varje år. Under de senaste decennierna har diagnostiken och behandlingen av barncancer förbättrats avsevärt och många fler barn överlever sjukdomen idag. Femårsöverlevnaden för barn diagnostiserade med cancer i Sverige de senaste åren är 85%. Trots dessa framgångar är barncancer den vanligaste sjukdomsrelaterade dödsorsaken bland svenska barn i åldern 1-14 år.

I studier från andra länder har man sett sociala ojämlikheter i överlevanden efter barncancer – studier har observerat att överlevnaden i barncancer är sämre bland barn från lägre socialgrupper. Vi ville undersöka om sådana skillnader finns i Sverige där sjukvården är öppen för alla invånare och utan kostnad för barn. I forskningssammanhang definierar man ofta ett barns sociala bakgrund efter föräldrarnas utbildnings eller inkomstnivå, eller utifrån andra faktorer såsom föräldrarnas sysselsättning. I Studie I-III i den här avhandlingen studerades olika socioekonomiska- och familjefaktorer i relation till överlevnad efter en barncancerdiagnos.

Barncanceröverlevare kan drabbas av olika negativa hälsoeffekter av sin sjukdom och/eller behandling, effekter som kan påverka överlevarna även i vuxen ålder. Vi har begränsad kunskap kring socioekonomiska konsekvenser av att ha haft cancer som barn, såsom hur det går att uppnå gymnasiekompetens, en utbildningsnivå som är viktig för det framtida arbetslivet. Denna kunskapslucka adresserades i Studie IV i denna avhandling.

Att undersöka socioekonomiska faktorer hos föräldrar till barn med cancer, samt bland barncanceröverlevare, kan vara svårt. Det finns, till exempel, en risk att föräldrar till väldigt sjuka barn, eller barncanceröverlevare med många hälsoproblem, inte deltar i studier som undersöker dessa samband. Vidare är barncancer ovanligt och det kan vara problematiskt att undersöka små subgrupper separat. De här aspekterna kan göra det svårt att dra säkra slutsatser. Sverige och övriga nordiska länder har ett unikt system med flera populations- och hälsodataregister som inkluderar alla invånare och som kan länkas ihop via personnummer. Denna information användes i den här avhandlingen för att hantera de metodologiska svårigheter som funnits i tidigare studier.

De första tre studierna fokuserar på sociala faktorer och deras möjliga association med överlevnad i barncancer. Studie I inkluderar barn med cancer i Sverige och vi observerade att barn till föräldrar med lägre utbildning hade sämre överlevnad i barncancer, samtidigt sågs inga skillnader när vi jämförde barn från hushåll med olika inkomst. Skillnaderna i överlevnad mellan barn med föräldrar med olika utbildning sågs redan det första året efter diagnos. De här resultaten gjorde att vi fortsatte med att undersöka potentiella socioekonomiska skillnader i dödsfall som skedde inom tre månader efter diagnosen (hädanefter kallad tidig mortalitet), bland barn som diagnostiserats med cancer i Sverige och

Danmark (Studie III). Vi såg att barn från lägre socialgrupper hade en ökad risk för tidig mortalitet efter barncancer. I Studie II undersökte vi en annan aspekt av sociala familjeförhållanden, antalet syskon och födelseordning, i relation till överlevnad i barnleukemi. Tidigare studier hade funnit att barn med syskon hade lägre överlevnad efter barnleukemi, men det såg vi inte i vår studie.

I Studie IV studerade vi om barncanceröverlevare genomgår gymnasieutbildning i samma utsträckning som individer från totalbefolkningen och sina syskon. Vi undersökte detta i Sverige, Danmark och Finland. Vi såg att förseningar under utbildningen var vanligare bland barncanceröverlevarana än bland jämförelsegrupperna, men vid 25 års ålder hade många barncanceröverlevare kommit ifatt. Dock identifierade vi vissa riskgrupper som inte hade uppnått gymnasieutbildning vid 25 års ålder i samma utsträckning; barncanceröverlevare som hade diagnostiserats med en tumör i det centrala nervsystemet, barncanceröverlevare som diagnostiserats med akut lymfatisk leukemi under 1970- och 1980-talet (en period när denna patientgrupp behandlades med kranial strålbehandling), och barncanceröverlevare som hade haft mer kontakt med hälso-och sjukvården, dels i samband med cancerbehandlingen, och dels senare i livet.

Sammanfattningsvis har vi i studierna i denna avhandling observerat sociala ojämlikheter i överlevnaden efter en barncancerdiagnos, i de nordiska länderna där sjukvården är allmän för alla invånare. Vi såg sociala skillnader i överlevnad redan tidigt efter diagnos och dessa resultat kräver ytterligare uppmärksamhet. Vi har också visat att även om barncanceröverlevare oftare upplever förseningar under sin utbildning, så kommer många ifatt. Dock finns det utsatta grupper som behöver ytterligare support. De inkluderade studierna visar potentialen och vikten av nordiska samarbeten i forskning som rör ovanliga sjukdomar, samt visar hur värdefulla nordiska population- och hälsodataregister är inom detta forskningsfält.

ABSTRACT

Childhood cancer is rare and survival rates have increased substantially over the past 60 years as a result of better diagnostics and treatments. Despite this, childhood cancer is the most common disease-related cause of death among children aged 1-14 years in Sweden. Moreover, there are indications that the progress in survival has not been gained by all groups equally and socioeconomic differences in childhood cancer survival have been observed across the world. However, if such differences are seen within Sweden, a country with universal healthcare that is free of charge for children, has not previously been investigated. The increased survival rates have also resulted in a growing population of adult childhood cancer survivors. Survivors may face various late health effects but less is known about the socioeconomic consequences of having had cancer as a child.

To address these issues, the overall aims of this thesis were to determine if and how survival from childhood cancer varies by socioeconomic factors and to investigate long-term socioeconomic consequences, in particular educational attainment, in young adult survivors of childhood cancer. The research questions were addressed in four studies that utilized information in the Nordic population and health data registers.

Study I-III investigated socioeconomic and familial factors in relation to survival from childhood cancer. **Study I** was a cohort study including children diagnosed with cancer in Sweden from 1991 to 2010. In this study we observed socioeconomic differences in overall survival – children of parents with a lower level of education had worse survival from childhood cancer, while no differences were observed for household income. The differences by parental education were seen already in the first year after diagnosis. These findings, together with the publication of a seminal study from the US, led us to investigate potential socioeconomic differences in early mortality from childhood cancer. In **Study III**, we included children diagnosed with cancer in Sweden and Denmark during 1991-2014 and assessed the association between parental socioeconomic factors and early mortality (defined as deaths occurring within 90 days after cancer diagnosis). We observed that children from disadvantaged backgrounds were at increased risk of early mortality, with parental education and maternal income showing the most pronounced associations. Associations with later mortality (defined as deaths occurring 1 to 5 years after cancer diagnosis), were attenuated or close to unity in this study. In **Study II** we investigated another aspect of social family circumstances, number of siblings and birth order, in relation to survival from acute lymphoid leukaemia (ALL) and acute myeloid leukaemia (AML) in children diagnosed 1991-2015 in Sweden. In this study we found no evidence supporting a previously suggested hypothesis of lower survival after leukaemia among children with siblings, but we rather observed the opposite. We also included clinical information for children diagnosed with ALL and saw that the superior survival among children with siblings was seen mainly within children with low-risk profiles.

In **Study IV**, we compared attainment of upper secondary education in young adult survivors of childhood cancer, matched population comparisons, and the survivors' siblings in Sweden,

Denmark and Finland. We observed that delays in attaining this education level were more common among survivors of all cancer types compared to their peers. However, by the age of 25 years, many survivors had caught up with regard to upper secondary education. Particular risk groups were survivors diagnosed with central nervous system (CNS) tumours, and survivors diagnosed with ALL in the early time period. We also saw that survivors who had spent more time in hospital around the time of diagnosis or had hospital contacts, in particular for psychiatric diseases, in the age range 20-24 years were at increased risk of not having attained upper secondary education by age 25 years.

In conclusion, we have observed social inequalities in survival from childhood cancer in the Nordic countries with universal healthcare access. The differences were seen already early in the disease course, and these findings need further attention. We have also shown that although survivors of childhood cancer may experience delays in their education, many catch up. However, there are vulnerable risk groups that need further support. The results in this thesis are based on information from nationwide, population and health data registers, which minimized the risk of bias from non-participation, loss to follow-up, and self-reports. Moreover, the included studies highlight the potential and importance of Nordic collaborations in research of rare diseases.

Key words: Child; Child, Preschool; Infant; Adolescent; Neoplasms; Leukaemia; Central Nervous System Neoplasms; Lymphoma; Mortality; Educational Status; Income; Siblings; Birth Order; Cancer Survivors, Population Registers; Sweden; Denmark; Finland

LIST OF SCIENTIFIC PAPERS

I. **Mogensen H**, Modig K, Tettamanti G, Talback M, Feychting M. Socioeconomic differences in cancer survival among Swedish children. British Journal of Cancer. 2016; 114:118-24

II. **Mogensen H**, Modig K, Talbäck M, Erdmann F, Heyman M, Feychting M, Tettamanti G. Number of siblings and survival from childhood leukaemia: a national register-based cohort study from Sweden. British Journal of Cancer. 2021; 125:112-8

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IV. **Mogensen H**, Tettamanti G, Frederiksen LE, Talbäck M, Härkonen J, Modig K, Pedersen C, Krøyer A, Hirvonen E, Kyrönlahti A, Heyman M, Holmqvist AS, Hasle H, Madanat-Harjuoja L, Malila N, Winther JF, Erdmann F, Feychting M. Educational attainment in survivors of childhood cancer in Denmark, Finland, and Sweden— A register-based cohort study from the SALiCCS research program. *Manuscript*

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*Included as an Appendix in the Thesis
** Frederiksen LE and Mogensen H have contributed equally to this work and share second authorship

CONTENTS

LIST OF ABBREVIATIONS

ALL	Acute Lymphoid Leukaemia
AML	Acute Myeloid Leukaemia
CI	Confidence Interval
CNS	Central Nervous System
DAG	Directed Acyclic Graph
GDPR	General Data Protection Regulation
HeH	High Hyperdiploidy
HR	Hazard Ratio
ICCC	International Classification of Childhood Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
ISCED	International Standard Classification of Education
NOPHO	Nordic Society of Pediatric Hematology and Oncology
OR	Odds Ratio
RERI	Relative Excess Risk due to the Interaction
RR	Risk Ratio
SALiCCS	Socioeconomic consequences in Adult Life after Childhood Cancer in Scandinavia
SEER	Surveillance Epidemiology and End Results
SES	Socioeconomic Status
WHO	World Health Organization

1 INTRODUCTION

Getting cancer as a child is rare but despite this, cancer contributes to a substantial burden of mortality in children after the first year of life. The aetiology of childhood cancer is not yet well understood and therefore we have very limited possibilities for prevention. However, survival rates in childhood cancer have increased substantially over the past 60 years and adult childhood cancer survivors constitute an increasing population.

Despite the improvements in survival, there are indications that not all groups have benefitted equally and socioeconomic differences in childhood cancer survival have been observed across the world. At the outset of this thesis work, little was known about potential socioeconomic differences in childhood cancer survival in Sweden, a country with universal healthcare that is free of charge for children. There was also little knowledge about the mechanisms behind potential socioeconomic differences in childhood cancer survival. By investigating the time pattern of potential survival differences, as well as several different socioeconomic factors, one could get closer to understanding potential mechanisms.

The growing population of survivors of childhood cancer means that there is urgent need for research into later life consequences of childhood cancer. Survivors may face various late health effects, but less is known about the socioeconomic consequences of having had cancer as a child. For example, a childhood cancer diagnosis may have implications for educational attainment in early adulthood, an important step for future work-life opportunities.

There are methodological challenges when conducting research on socioeconomic factors since non-participation and self-reporting in studies may influence the results. The Nordic population and health data registers constitute a unique source of information that provides an opportunity to answer these questions in studies with high validity. These registers include information on the total population, which implies that we can identify all children with cancer and appropriate comparison groups, without bias from selection into the studies. Individual socioeconomic information is available on an annual basis, which means that we can retrieve information for everyone at the time point of interest - in contrast to studies that are limited by the use of area-based measures or information from a specific time point. The rarity of childhood cancer also requires cross-national collaborations, which is possible in the Nordic context because of the similar healthcare systems, traditions of collaborations in the treatment of childhood cancer, and similar national population and health data registers.

The work in this thesis utilises this unique source of register-based information in the Nordic countries and examines the association between socioeconomic factors and childhood cancer survival, as well as the long-term socioeconomic consequences, in particular regarding education, for the survivors. The first two studies include Swedish data while the third study is a collaboration with the Danish Cancer Society including Swedish and Danish data. The fourth study is part of the SALiCCS (Socioeconomic consequences in Adult Life after Childhood Cancer in Scandinavia) research programme, a cohort study including childhood cancer survivors, population comparisons and siblings from Sweden, Denmark, and Finland.

2 BACKGROUND

2.1 CHILDHOOD CANCER

Every year, around 400-450 children and teenagers in Sweden are diagnosed with cancer (1), and despite much improved survival rates, childhood cancer makes up the most common disease-related cause of death in Swedish children aged 1-14 years (2, 3). Tumours also causes deaths in children within the first year of life, but also other causes of deaths contribute in this age group (2, 3). Childhood cancer is also the leading cause of disease-related mortality in the age group 1-14 years in other western European countries (4).

Childhood cancer includes several different cancer types that vary widely with regard to incidence, symptoms, treatment, and prognosis. In Sweden, as well as in most other regions in the world, the most common types of cancers occurring before age 15 years are leukaemia and central nervous system (CNS) tumours, followed by lymphoma (5, 6). Leukaemia makes up 30% of all cases among children diagnosed <15 years old (6), and the two most common subtypes are acute lymphoid leukaemia (ALL) and acute myeloid leukaemia (AML). ALL is much more common than AML and has a peak in the age group 2-4 year olds (6, 7). Childhood CNS tumours include several subtypes, such as ependymomas, astrocytomas and other gliomas, and embryonal tumours with the most common being medulloblastomas, with different incidence depending on age group (8). Lymphomas comprise around 12% of the cancers diagnosed in children <15 years old (5, 6), while it is the most common tumour type among older teenagers (15-19 years old) (5).

2.1.1 Incidence

Cancers occurring in children and adolescents are rare. In the last 10 years, the annual incidence in Sweden has ranged from 17.5-21.2 per 100 000 persons aged 0-19 years old (1). The World Health Organization (WHO) has reported annual incidence rates of 5-20 per 100 000 among children, and 9-30 per 100 000 among adolescents (9). As indicated by the wide range, comparisons of incidence between countries and time periods are challenging because of the differences in quality and availability of data. An initiative from the International Agency for Research on Cancer and the International Association of Cancer Registries has gathered comparable data from cancer registers worldwide (5). Comparisons of this kind are important since it has been suggested that the incidence of childhood cancer has increased over time, although better diagnostics and reporting might be, at least, a partial explanation for such changes (9-13). The most recently published data on childhood cancer incidence worldwide, to my knowledge, includes information from 153 registers and confirms the diverse incidence patterns of cancer subtypes in different geographical regions, as well as the increase in incidence over time (5).

2.1.2 Survival

Since the 1950's, survival after childhood cancer has increased remarkably in Europe, including Sweden (6, 9, 14, 15); from survival figures of less than 30% (6, 9, 16) to a five-

year survival proportion of more than 80% among children diagnosed until 2007 in most parts of Europe (14). Reports of children diagnosed more recently in Sweden indicate even further improvements (7, 17-19). However, there are also indications from the U.S. and Europe, that the positive developments in survival for several subtypes of childhood cancer have been slowing down or even plateauing (6, 9, 13).

Survival differs greatly between childhood cancer types; whereas 88% of children diagnosed with ALL in the period 2005-2007 in Europe survived 5 years, the corresponding figure for all CNS tumours combined was 58% (14). As previously described for estimates of incidence, overarching studies comparing survival across the world are challenging because of differences in reporting between countries and time periods. However, the CONCORD programme is an initiative to collect survival data from cancer registers across the world (17, 20, 21), and CONCORD-3 includes information for children with ALL, brain tumours and lymphomas, for the years 2000-2014 (17). There are enormous differences in survival of childhood cancer across the world and differences between countries are suggested to be even larger than for adult cancers (17, 22)

2.1.2.1 Treatment

The improved survival rates in the past decades have been attributed to better diagnostics, treatment protocols and collaborations (6, 9, 13, 14, 22). Treatment of childhood cancer varies greatly between subtypes and may include surgery, radiotherapy, chemotherapy, stem cell transplantation and immunotherapy (23). The aim of modern treatments is increased survival, but also reduced toxicity and late effects. Further developments of the risk-stratification and risk-adapted therapy of treatment have contributed to improvements (16). For example: tumours can be genetically characterized to improve subgrouping and adaption of treatment (16); in AML, residual disease is measured after the first induction courses and is a strong prognostic factor, which guides further therapy (24); for some diagnoses (e.g. CNS tumours, sarcoma, neuroblastoma, and Hodgkin lymphoma), the use of proton beam therapy instead of ordinary photon radiotherapy seems to be beneficial in reducing toxicity and late effects (25). Collaborative efforts, such as the cooperation within the Nordic Society of Pediatric Hematology and Oncology (NOPHO), are driving these improvements. NOPHO has registered all children with acute lymphoblastic leukaemia (ALL) in Sweden, Denmark, Finland, Norway and Iceland since 1981, and developed common treatment protocols that have been applied since 1992 (26). This has led to improvements in ALL therapy, for example reduced CNS-irradiation which is of importance for survivors and their risk of late effects (26). NOPHO has also developed common treatment protocols for children with AML since the 1980s (27).

Healthcare in Sweden, as well as in the other Nordic countries, is mainly financed by taxes and includes universal access for all citizens (28). For children, healthcare is free of charge and the first contact is often through the general practitioner (28). Treatment of children with cancer in Sweden is handled by six paediatric oncology centres in the country.

2.1.2.2 Early mortality

There is a group of children with cancer that die very early after their cancer diagnosis, likely before having had any benefits of the provided treatment. This group is rather small and has seldom been the focus of population-based studies (29-32). In the U.S., 1.5% of the children diagnosed with cancer from 1992 to 2011, died within one month after their cancer diagnosis (29), a number that is rather similar to other population-based estimates from Germany and Italy (30, 31). This figure from the U.S., was calculated from the Surveillance Epidemiology and End Results (SEER) registers and was higher compared to estimates of early death from clinical trials, likely because children dying this early might not be included in trials (29). This highlights the need for using population-based information when studying this group.

2.1.3 Risk and prognostic factors

Despite rather extensive research, only a few risk factors for childhood cancer have been established (8, 10, 33, 34). Some genetic syndromes are associated with an increased cancer risk; e.g., children with Down's syndrome have a considerably increased risk of leukaemia (10), while neurofibromatosis and tuberous sclerosis increase the risk of brain tumours (8). For environmental factors, exposure to ionizing radiation (for example from nuclear accidents or therapeutic radiation given for a prior cancer) is the only recognized causal factor (8, 10, 33). The incidence of different childhood cancer types varies by age (6), and the prognosis varies largely by cancer type and age at diagnosis (14). Prognosis also varies a lot within cancer types; for example, in CNS tumours by histological type (8) and in ALL by immunophenotype and genotype (26).

2.1.3.1 Hypotheses regarding the risk of childhood leukaemia

Differences in incidence of childhood leukaemia have been observed between geographical regions, and it has been suggested that the incidence is higher in populations with higher socioeconomic status (SES) (9, 35). Even though it is unclear if this is a true difference in incidence or a difference in the likelihood of diagnosis and reporting, it has led to discussions regarding aetiology (9, 10). Two theories are often discussed; Greaves' "Delayed-infection hypothesis" and Kinlen's "Population mixing hypothesis", in which infections, or immune response to infections, are involved in the aetiology (36, 37). Greaves' hypothesis, which primarily focuses on B-precursor ALL, suggests that the development of leukaemia requires at least two "hits", where the first occurs prenatally and is rather common (36, 37). A necessary but not sufficient cause, using Rothman's terminology (38). Greaves suggests that the second hit is an unusual response to infections – infections that the child has not been exposed to before in early life (36, 37). The epidemiological basis for this hypothesis is that children who develop leukaemia seem to have had less infections in their first year of life, even if studies of this association are not conclusive (36, 37, 39). In addition, day-care attendance in the first year of life seems to be protective for the risk of leukaemia (36, 37, 39). Kinlen's hypothesis addresses the geographical clustering of childhood leukaemia that has been observed through time. According to this hypothesis, the reason for the clustering is

that populations have been mixed and children have been exposed to common, but for them new, infections that in rare cases lead to leukaemia (36, 40).

2.2 SOCIOECONOMIC FACTORS AND SURVIVAL FROM CHILDHOOD CANCER

There are indications that the improvements in childhood cancer survival have not been gained by all groups equally. A very recent report from the WHO Europe highlighted that there are social inequalities in survival of children with cancer, both between and within countries (22). An association between lower SES and higher mortality in childhood cancer has been seen clearly in low- and middle-income countries (41), but also seems to be present in high income countries (41, 42). A systematic review by Gupta et al. of studies published in 2012 and earlier, included 26 studies from high income countries and indicated that lower SES was associated with poorer survival (41). In this review, indicators of income did not show an association with survival, although seldom investigated, while parental education and having health insurance had an impact (41). Together with colleagues, I conducted an updated review of studies published December 2012 to June 2018 regarding social factors and survival from childhood cancer in high income countries (42), see Appendix. We included 24 studies (out of 333 identified in a literature search in PubMed) and concluded that even though findings differ, there is a pattern of worse survival from childhood cancer in children from families of lower SES (42). We did not find clear differences between SES indicators or cancer types in the association of SES and survival, in the published studies, although such differences are expected. However, the comparisons between studies were limited by the diverse setup of the individual studies (42).

2.2.1 Measuring socioeconomic factors

There are various social factors or indicators of SES that have been used as exposures in previous studies investigating socioeconomic inequalities in childhood cancer (42). Instead of seeing them as proxies of the same underlying characteristics, they might be associated with survival from childhood cancer through different pathways (43-46). As an example, while income reflects material resources, education captures knowledge (45). Number of siblings can also be seen as an indirect measure of the family's social circumstances and has previously been examined in relation to survival from childhood cancer in a few studies (47-51). A methodological suggestion has been to include several measurements of SES in the same study, discuss potential mechanisms linking each included SES factor to the outcome of interest, and that the role of SES indicators that are not included should be acknowledged (43).

In studies of childhood cancer, social factors related to the parents, or the family, are of relevance. It is important that the social factors are measured before the child's cancer diagnosis to ensure temporality, since the diagnosis might have an effect on the family's resources (52). In some studies, area-based measures of SES are used instead of individual measures. This could be when individual measures of SES are not available, or if the

hypothesis concerns how the neighbourhood in itself affect health (46), for example through the structure of healthcare. However, as other authors have also acknowledged (46, 53, 54), using area-based measures as proxies for individual measures, can lead to ecological fallacy, if the combined area-based measure is not correct for that individual (e.g. highly educated parents living in a neighbourhood where the majority of people have low education). This is an example of non-differential exposure misclassification, which leads to diluted effect estimates, and thus may hide an actual association.

2.2.2 Mechanisms

Socioeconomic factors may influence childhood cancer across the continuum from incidence and survival to long-term survivorship, through different mechanisms (22, 44). A review article of potential mechanisms linking SES to cancer survival, mainly among adults, has described mechanisms related to diagnosis (e.g. cancer stage at diagnosis), treatment (e.g. choice of treatment), or factors related to the patient (e.g. co-morbidities) (55). As discussed also by other authors, some of these pathways are not likely to be relevant for childhood cancers and not in the Nordic setting with universal healthcare, while other pathways might be of importance (44, 48, 56). In our review article regarding social inequalities in survival from childhood cancer in high income countries (42), we discuss potential underlying mechanisms, and they are also outlined below.

2.2.2.1 Type of disease

As earlier described, there are hypotheses and some epidemiological studies suggesting a link between SES and the risk of certain subtypes of childhood cancer, such as B-precursor ALL (35-37). Since the prognosis differs between subtypes, a potential association between SES and survival might be explained by this mediation if it is not accounted for.

2.2.2.2 Disease severity at diagnosis and time to diagnosis

Among adults, stage at diagnosis is an established mediator of the association between SES and cancer survival; individuals with lower SES tend to have a more advanced stage at diagnosis (55). Among children, staging of cancer is not as straightforward and stage criteria differ between subtypes (22, 57). Some non-stage prognostic factors such as white blood cell count in ALL (58), are sometimes used as indicators of stage at diagnosis (53, 59).

One could hypothesize that children from families of lower SES seek care later or have greater difficulties in navigating the healthcare system and therefore get diagnosed later, which might influence survival negatively. Danish studies have seen an increase in the use of primary care six months or even longer before the child's cancer diagnosis (60, 61), and children of families with lower income had more additional contacts (60). However, it is not clear that a longer time to diagnosis is related to prognostic factors or poorer survival in childhood cancer. In fact, the opposite has been observed; better survival among children with a longer delay in diagnosis (62). This probably relates to the fact that more aggressive tumours are detected faster because they give more clinical symptoms (62).

This highlights the complexity in investigating and drawing conclusions from stage and time to diagnosis as a mediating step in the association between SES and survival in childhood cancer.

2.2.2.3 Treatment phase

The Nordic countries collaborate and common standardized treatment protocols for children with leukaemia have been used since the 1980s and 1990s (26, 27). In this setting, one would not expect that differences in given treatment contributes to potential survival differences by SES groups. However, a very recent study from Denmark, including 173 children with ALL, indicated that lower drug doses during maintenance therapy were prescribed to children of parents with lower education (63). A Swiss study observed an association between SES and survival especially for children with CNS tumours and speculated that this could be explained by a less common use of standardized treatment protocols (64).

Maybe the most discussed mechanism linking SES to childhood cancer survival is parent/child adherence to treatment (see for example (47, 65, 66)), although this has seldom been directly investigated. Treatment adherence is important because a lower adherence is associated with a higher risk of relapse, shown among children with ALL (67, 68). Treatment for ALL spans over a long time period, up to 2.5 years after diagnosis, where most of the time the oral treatment is given at home (66, 69). A British study found that differences in survival from ALL between social groups began at the time point when therapy moved from inpatient care to home, i.e., when the parental responsibility increased (66). Moreover, when treatment adherence has been examined more directly, lower SES was associated with worse adherence in two studies from the U.S. and France (67, 70), while a recent study from Denmark observed no association between familial social background and adherence to ALL maintenance treatment (63). More parental obligations and difficulties with treatment adherence and follow-up care has also been discussed in a few studies that have observed lower cancer survival in children with siblings, compared to children without siblings (47, 48).

2.2.2.4 Timing of survival differences

Identifying the timing when potential SES differences in survival occur can give some insight into mechanisms. The results by Lightfoot et al. (66) of survival differences starting 6-9 months after diagnosis, support the hypothesis of differences in treatment adherence. Yet, Green et al. (29) observed higher mortality after a cancer diagnosis already within the first month in children living in disadvantaged areas, which suggests mechanisms earlier in the disease course. By studying different social factors one can also get closer to potential underlying mechanisms. Potential differences by parental education may represent difficulties with navigating the healthcare system, both before and after the cancer diagnosis. Differences by parental country of birth may also indicate such differences, especially in relation to language barriers. Although we are limited in the level of details regarding specific

underlying mechanisms when we use register data, we instead have the possibility of detecting overall patterns that are not affected by bias from selective participation.

2.3 SURVIVORS

The improved survival rates in the last decades have led to an increasing population of childhood cancer survivors. Several estimates of the number of survivors have been reported. In 2005, Olsen and colleagues (71) estimated that 0.1% of inhabitants in the Nordic countries were childhood cancer survivors. Estimates from the SEER program in the U.S. reported 388,500 survivors in 2011 (72). The Swedish Childhood Cancer foundation reports a prevalence of 11,000 survivors of childhood cancer in Sweden in 2020 (18). It has been suggested that 20-27% of the survivors are aged above 40 years (13, 73).

2.3.1 Somatic and psychiatric late effects

Survivors may face somatic late effects following their cancer diagnosis and treatment, that can continue throughout adult life (74, 75). Somatic late effects that have been reported are, among others, an increased rate of overall inpatient care (74), higher risks for a second primary cancer (71), endocrine disorders (76), gastrointestinal and liver disease (77), and neurological disorders (78, 79). Survivors have also been shown to be at increased risk of psychiatric hospital care compared to siblings and matched individuals from the general population, although the absolute difference in risk was small (80).

Late effects differ by cancer type and given treatment. It has been estimated that a large proportion of survivors have neurocognitive dysfunctions (72), and survivors of CNS tumours and survivors that have been treated with cranial radiotherapy are at a particular risk for cognitive decline because of the tumour itself, potential surgical complications, and radiotherapy (81). Young children have a fast developing brain and are particularly sensitive to radiation (81).

2.4 SOCIOECONOMIC CONSEQUENCES IN SURVIVORS OF CHILDHOOD CANCER

While somatic late effects among survivors of childhood cancer have been rather well documented, an increasing body of evidence is now investigating socioeconomic consequences of having had a diagnosis of cancer in childhood. We have conducted a systematic review on this topic (82), with the aim to summarize the evidence regarding educational achievements, work-life, income, and use of social security in childhood cancer survivors, and to identify risk groups. The review included 52 articles published between 2000 and 2017. We observed that survivors of childhood cancer may face adverse socioeconomic consequences, including problems when attaining an education, getting a lower income, and receiving social security benefits to a larger extent than comparison groups (82). Young age at diagnosis, cranial radiotherapy, and diagnosis with a CNS tumour were identified as risk factors. However, we also noted the diversity in included studies, which complicated the comparisons. Moreover, there were several severe methodological

limitations in studies within this topic, related to self-reporting of social outcomes and loss-to follow-up, which may bias the results (82).

2.4.1 Educational attainment

Having had cancer as a child may affect the survivor's educational trajectories through several pathways. For example, cognitive impairment from the disease or the toxicity of the treatment may affect the learning ability and school results, both early after diagnosis and later on in adult life. The missed time in school during the treatment phase, or later due to complications, may leave the child behind. Later health problems due to late effects may lead to both missed time in education and a decreased ability to benefit from teaching.

In our review of socioeconomic outcomes in childhood cancer survivors, we observed that survivors had higher risk of some educational problems during the school period, such as lower marks and need of special education (82). Inconclusive results were found with regard to whether survivors were more likely to repeat a grade. The results regarding highest attained education level suggested that survivors attained a lower level of education, although there were also studies in the opposite direction (82). Similarly, a very recent review including guidelines for surveillance of education in survivors, concluded that survivors were at risk of lower educational achievement, but the level of evidence was graded to be "very low" (83). This is noteworthy since there are rather many studies on this topic, including another review (84) and two meta-analyses (85, 86), although they include overlapping studies to some extent. The conclusions from these reviews are that survivors of CNS tumours and survivors treated with CNS-directed therapy have poorer educational achievements than their comparisons, but results for other survivors are unconvincing (82, 84-86). The group of non-CNS and non-CNS treated survivors is, however, diverse and their educational achievements may differ. Some types of childhood cancers are very rare and small studies may not be able to conduct subgroup analyses or may not be able to detect potential differences due to lack of statistical power. Moreover, as mentioned also in earlier reviews, there are methodological limitations in previous studies, mainly related to the risk of bias from non-participation, self-reporting and follow-up. Four out of 11 studies in the meta-analysis by Gummersall et al. were population-based (85). Saatchi et al. reported that six out of 26 included studies were population studies, and that the mean response rate was 70% (86). Molcho et al. considered two out of the 14 included studies as good quality (84).

There have been a few studies from the Nordic countries investigating different educational achievements in childhood cancer survivors (87-94). Three of the studies have looked at several levels of education among all childhood cancers and grouped them at least by CNS and non-CNS tumours (87, 90, 94). They came to similar conclusions as the previously reported reviews: survivors of CNS tumours or those treated with CNS-therapy have lower educational achievements, but this does not seem to be the case for survivors of other cancer types (87, 90, 94). Four studies have looked at school performance at the end of 9th grade among survivors of leukaemia (91), brain tumours (89, 93), and lymphoma or Wilms tumour (92). Survivors of brain tumours and non-Hodgkin lymphoma had poorer grades at this stage

(89, 92, 93), while such difference was not seen for survivors of Hodgkin lymphoma or Wilms tumour (92). Survivors of leukaemia treated with cranial radiation, or females diagnosed before age 7 years had lower grades (91).

2.4.1.1 Delays in education

A broad range of outcomes regarding educational difficulties and achievements in survivors have been investigated, both during the school period and in young adult life. It has been suggested that childhood cancer survivors may experience delays in their educational pathways, but they catch up with time, which has been supported by a Swiss study (95). However, the authors of this questionnaire-based study also concluded that survivors of CNS tumour and survivors who experience relapse, do not catch up (95). The distinction between a delay in education or a permanent difference is an important question that needs further attention.

2.4.1.2 Risk and effect modifying factors

In our review, we observed that survivors diagnosed at young age seemed to be a vulnerable group for lower educational achievements (82). There were also some indications that sex modified the association, with some studies showing female survivors to be more negatively affected with regard to education (82).

Somatic and psychiatric disease burden during or after cancer treatment, as well as late effects among survivors, may also affect educational attainment, which has not been thoroughly investigated. A study among 820 survivors in Germany, that were diagnosed in adolescence, suggested that survivors with visual or hearing late effects had a lower probability of obtaining a high school degree, while neuropsychological late effect were associated with not obtaining a university degree (96). This study also reported a potential association between length of treatment and university degree, although the article contains insufficient information to judge the relevance of this finding (96). Research from the Childhood Cancer Survivor Study (CCSS) showed that physical performance limitations and cancer-related pain were associated with lower high school completion in survivors of rhabdomyosarcoma (97). Results from the British Childhood Cancer Survivor Study showed that epilepsy or repeated seizures affected educational attainment negatively in analyses combining survivors of all cancer types (98). Also among survivors of CNS tumours, seizures, but also paralysis, stroke or hearing impairment, have been shown to influence neurocognitive functioning negatively, which is correlated with educational performance (99, 100).

Parental education has a strong impact on the child's educational attainment in the general population (101) and this is also seen in childhood cancer survivors; survivors with parents having a lower education level have more educational difficulties (89, 94, 95, 102, 103). However, effect modification by parental education has seldom been taken into consideration when studying educational attainment of childhood cancer survivors. One can hypothesize that parents with a higher education level may have more means to compensate and help their

child to keep up with their peers despite the cancer diagnosis. This hypothesis is in line with the social theory of "Compensatory advantage" (104). In that case, one would see a stronger association between survivorship and educational attainment in children of parents having low education. Two earlier studies have to some extent approached this question. One has reported that survivors of ALL had lower educational attainment than their peers, even if one parent had a high education level (105). However, the authors did not examine this association only in children who had parents of lower education level. Koch et al performed an interaction analysis with parental education and concluded that this risk factor had similar impact on educational attainment in survivors as in controls, although with some deviation for survivors of CNS tumours (94).

2.5 RESEARCH GAPS

Social inequalities in childhood cancer survival and socioeconomic consequences in young adult survivors have been acknowledged and highlighted in the literature and in a recent WHO report (22).

There is a growing body of evidence suggesting that parental SES is associated with childhood cancer survival, but the literature regarding specific factors of importance, such as which cancer types, crucial time points and mechanisms, is limited. There is a need for high quality studies investigating the association between specific social factors and survival from different types of childhood cancer, considering different time-points and taking clinical factors into account when needed, to better understand potential pathways. The Nordic countries with universal healthcare provide a context in which pathways relating to direct financial obstacles to healthcare access are not likely to be of importance, which gives the opportunity to investigate other potential mechanisms.

As the population of childhood survivors is growing, there is an increasing need to investigate socioeconomic consequences, such as educational attainment. However, several previous studies on this topic had methodological limitations, including the use of surveys. Other studies have combined analyses of heterogenous groups of childhood cancer survivors because of the rarity of subtypes. Moreover, comprehensive analyses of how somatic and psychiatric disease burden affects educational attainment in survivors of different types of cancer are lacking, as are appropriate analyses of effect modification by parental education.

Investigating socioeconomic factors, both as determinants and outcomes, imposes a challenge since they might also influence participation in studies (106, 107). Moreover, severity of the disease or late complications might influence participation among parents, or survivors of childhood cancer. The Nordic health and population registers that include all citizens, give a unique opportunity to conduct studies on both the role of socioeconomic factors in survival of childhood cancer and socioeconomic consequences among young adult survivors, limiting the risk of selection and information bias.

3 RESEARCH AIMS

The overall aims of this thesis were to determine if and how survival from childhood cancer varies by socioeconomic factors, and to investigate long-term socioeconomic consequences, in particular educational attainment, in young adult survivors of childhood cancer.

The four included studies had the specific aims to:

- Determine if parental education and household income, measured at the time of the child's diagnosis, are associated with survival from childhood cancer, overall and by main cancer types, in Sweden (Study I).
- Investigate if a larger number of siblings in the household at the time of the child's cancer diagnosis and birth order, are associated with poorer survival from childhood ALL and AML in Sweden, and to assess if potential associations are explained or modified by clinical characteristics (Study II).
- Investigate if children from disadvantaged social backgrounds are at increased risk of early mortality (death within three months after diagnosis) in childhood cancer in Sweden and Denmark, and to assess if potential associations differ from associations with later mortality (Study III).
- Study whether having had a cancer diagnosis as a child affects attainment of upper secondary education in Sweden, Denmark, and Finland, and to identify vulnerable subgroups (Study IV).

4 MATERIALS AND METHODS

All four studies in this thesis are register-based cohort studies. Study I and II are national studies, including Swedish register data for children with cancer. Study III is conducted together with the Danish Cancer Society and includes register-based information from Sweden and Denmark for children with cancer. Study IV is a part of the SALiCCS research programme (https://www.cancer.dk/saliccs/the-saliccs-research-program/), which is a collaboration between Karolinska Institutet, the Danish Cancer Society and the Finnish Cancer Registry that has formed a three-country wide register-based cohort of childhood cancer survivors, matched population comparisons, and siblings to the survivors (108).

4.1 DATA SOURCES

All the Nordic countries have population and health data registers including all residents (28). The setup and key variables included are similar, even though coverage periods, definitions and specific variables may differ (28). All residents in the Nordic countries also have a personal identity number that is included in the population and health data registers which allows linkage between them (28, 109). These features make it possible to conduct both national and cross-national Nordic register-based studies. Registers used in this thesis are outlined below, with focus on the Swedish registers, while also referring to the corresponding Danish and Finnish registers used in Study III and IV.

4.1.1 Total population registers and cause of death registers

The Swedish Total Population Register was established in 1968 and includes all individuals with a personal identity number in Sweden (110). The registers of the total population in Denmark and Finland were established in 1968 and 1971, respectively (28). The registers contain information on vital status, migrations, country of birth, and civil status (28). The Swedish Total Population Register is used to create the Multi-generation Register where all individuals that were born 1932 and later who were registered in Sweden at any time since 1961 are included, with links to biological and adoptive parents (110, 111). With the Multi-generation register biological siblings can be identified, while the Total Population Register can be used to identify family members that are registered at the same address and are related through marriage, common children or parenthood (including biological/adoptive/foster parents and other guardians) (110, 112).

More detailed information about the cause of death can be obtained from the Swedish National Cause of Death register, established in 1952 and held by the National Board of Health and Welfare. Similar registers are found in Denmark and Finland, established in 1970 and 1969 respectively. These registers include, in addition to the date of death, codes according to the International Classification of Diseases (ICD) of the underlying cause of death as well as the contributing causes of death (28).

4.1.2 National health data registers

The Swedish nationwide health data registers are held by the National Board of Health and Welfare and reporting to them is mandatory. In this thesis, the National Cancer Register (described in detail below), the National Medical Birth Register and the National Patient Register have been used. Similar national registers are found in Denmark and Finland.

The medical birth registers, established in 1973 (Sweden and Denmark) and 1987 (Finland), include characteristics of the mother and the child during pregnancy and at birth (28). For example, the birth registers have been one source to define cancer-predisposing syndromes in this thesis. The patient registers include information on admission and discharge dates as well as ICD-codes for diagnoses (28). The time periods for nationwide inclusion of in- and outpatient contacts for somatic and psychiatric diseases varies between the three countries, with all registers being more inclusive in later years (28). In Sweden, the part of the National Patient Register that covers inpatient care became nationwide in 1987 (113), while contacts with specialized outpatient care has been covered since 2001.

4.1.2.1 Cancer registers

The Swedish National Cancer Register was established in 1958. Newly diagnosed tumours should be reported to the register by the clinics, and the basis for the diagnosis can be clinical, morphological and other laboratory examinations, or autopsy (114). The completeness has been reported to be very high and a validation study of year 1998 reported an underreporting in total of 3.7%, which increased with age at diagnosis (114). However, children and teenagers where not reported separately in the validation study. In Study II where we included children with ALL and AML from both the Swedish National Cancer Register and the quality register for childhood cancer, we observed that 3% of the included children were not registered in the National Cancer Register.

The Danish and the Finnish national cancer registers were founded in 1942 and 1952, respectively, and have a similar structure as the Swedish. However, in contrast to the Swedish cancer register, the Danish and Finish cancer registers get information on cancer diagnosis also from death certificates (115). Moreover, since 2004, the Danish cancer register also includes cases from the Danish National Patient Register, the National Register for Pathology and the National Cause of Death Register (115). From 2004, the Danish cancer register also records the exact reported date of diagnosis, before this the information regarding date of diagnosis was registered on the level of month (115).

4.1.3 National registers with socioeconomic information

In Sweden, national registers including socioeconomic information are held by Statistics Sweden. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) is the register that was the most used in the projects in this thesis. LISA contains information regarding education, income, and employment for individuals aged 16 years and older (116). The information is available yearly since 1990, and each annual

register update refers to the situation of December 31, or the combined yearly information until this time point (116). The information in LISA is retrieved from several sources, among others the Education Register (116). The Education register includes information on highest attained education level retrieved from several sources, including questionnaires for newly arrived immigrants (that don't have a degree in Swedish registers), and can be used to retrieve information annually, also for the years prior to 1990 (117). Otherwise, socioeconomic information on Swedish inhabitants is available from the population and housing censuses that were conducted every five years between 1960 and 1990. However, the information collected differ between the years (118).

Socioeconomic information in Denmark and Finland is also available from nationwide registers managed by the Statistical Institutes. Examples of Danish registers used in this thesis are the Education registers, The Income Statistics Register, The Integrated Database for Labour Market Research and Danish Civil Registration System (119-122). In Finland, information on education was available from Statistics Finland on a yearly basis from 1987 (123).

4.1.4 Quality register

The Swedish Childhood Cancer Register is a quality register to which clinics from the six national childhood cancer centres report (124, 125). Information has been reported since the beginning of the 1980s for some cancer types and includes clinical characteristics and treatment information. In contrast to the Swedish National Cancer Register, inclusion in the quality register of childhood cancer is voluntary, however, a high coverage of around 90% has been suggested (124, 125). The register consists of diagnosis specific parts and in this thesis the ALL (Study II and III) and AML (Study II) registers have been used.

4.2 STUDY BASE

4.2.1 Studies of survival

In **Study I**, we included all children diagnosed with their first cancer between 1991 and 2010 at the ages 1-14 years, identified from the Swedish National Cancer Register, who could be linked to at least one parent in the household. The children were followed for maximum 10 years from cancer diagnosis until death, final emigration (within the follow-up period), or December 31, 2011, whichever occurred first.

In **Study II**, we had a similar setup as in Study I but focused on children with ALL or AML, without Down syndrome. In addition to identifying children from the National Cancer Register, we also included children registered only in the Swedish Childhood Cancer Register if they were registered as living in Sweden at the time of diagnosis. Because of some discrepancies between the registers, we used the earliest date of diagnosis reported in any of the two registers but excluded 18 children where the date differed by more than 30 days. We had more updated data available, compared to Study I, and could include children diagnosed between January 1, 1991, and June 30, 2015. The children were followed for a maximum of

10 years from cancer diagnosis until death, emigration, or end of follow-up December 31, 2015 (the follow-up period was thus also extended compared to Study I).

Study III focused on a rare outcome, early mortality, defined as death within three months after cancer diagnosis. Therefore, the Swedish and the Danish national cancer registers were the base of our population in this study. We included children diagnosed with cancer aged 0-19 years during 1991-2014 that could be linked to at least one biological parent. Children with the cancer pre-disposing syndromes Down syndrome, neurofibromatosis, and tuberous sclerosis were excluded from the study. We excluded the few individuals who were not registered in the country at time of diagnosis (0.4%) and those who emigrated within the first year after diagnosis (0.2%). This was done to ensure that we could follow the children for mortality during the first three months after diagnosis, which was the period in which we evaluated the main outcome. In Study III, we also evaluated associations with later mortality (death within one to five years after diagnosis) in comparison to our main analyses of early mortality. To do this, we created a sub-population that were diagnosed during 1991-2010 and had no emigrations within five years after diagnosis. The part of this subpopulation that had survived at least one year after their cancer diagnosis, were followed up for mortality for up to four years, starting one year after diagnosis, during 1992-2015.

4.2.2 Studies of educational attainment

Study IV builds on the SALiCCS cohort and included survivors of childhood cancer, matched population comparisons, and siblings of the survivors, from Sweden, Denmark, and Finland. We have described the SALiCCS project in detail in a Cohort profile paper (108). The base cohort includes five-year survivors of childhood cancer that has been identified from the national cancer registers of Sweden, Denmark and Finland, together with population comparisons and siblings. The population comparisons were randomly selected from the population registers and matched (ratio 1:5) by sex, year of birth and country of residence (municipality in Sweden) at the time of the diagnosis of the matched survivor. Siblings constitute a second comparison group and include full and half biological and adopted siblings (in Finland only biological siblings are included). In the particular study included in this thesis, we included survivors diagnosed during 1971-2005 at the ages 0-14 years old, who were born 1960-1990, and were alive (and had not emigrated) at the end of the year they turned 25. These restrictions were made because the main outcome was assessed at age 25 during the years 1985-2015. For Finland the outcome data was only available until 2014 which also restricted the inclusion of survivors by one year. We included population comparisons and siblings to the survivors (with an age difference of $\leq$5 years) using the same criteria. The reference date of the population comparisons is set to the date of diagnosis for the corresponding survivor. For siblings, reference date is the date at which they were the same age as their corresponding survivor. In all three groups, we excluded children with Down syndrome, neurofibromatosis and tuberous sclerosis. In a sub-analysis we assessed educational attainment at age 30 and therefore restricted our population to those who could be followed until that age.

4.3 CLASSIFICATION OF CHILDHOOD CANCER

Childhood cancers are categorized according to the International Classification of Childhood Cancer (ICCC) that has been published in three versions (126-128). The third version that is currently in use, bases the categories on diagnostic codes from the International Classification of Diseases for Oncology, version 3 (ICD-O-3)(126). The Swedish National Cancer register has coded tumours according to the ICD-O-3 version since 2005 (129). The register also includes variables of the cancer diagnoses coded in earlier versions of the ICD. E.g. a tumour registered in 2007 is reported with a diagnostic code from the four different ICD-versions (ICD-O-3, ICD-O2/10, ICD-9, and ICD-7) that has been used by the register, together with corresponding morphology codes. This means that the categorization of childhood cancers according to ICCC-3 was straight forward for children diagnosed 2005 and later, but for patients diagnosed earlier additional work was required.

In **Study I**, we did not use the ICCC classification but instead categorized childhood cancers in groups according to ICD-7 since these codes were already available for the whole study population. We developed the categorization of tumours for **Study II-IV** (and other studies, see related publications) so the categories were based on ICCC. The updated categorization mimics the ICCC-3 groups as far as possible, and the ICD-version that was in use at the time of the diagnosis was used to classify each tumour. The re-categorization from older ICD-versions were conducted by me and colleagues, and was, in addition to the reference literature on ICCC (126, 127), also based on coding instructions from the Swedish Cancer Register (129). For the older ICD-versions (ICD-7 and 9) we also used the backtranslation done by the National Board of Health and Welfare for cases diagnosed 2005 an onwards as a reference. Discrepancies were solved by detailed assessment of individual cases. Table 1 shows how the grouping was done for lymphoid leukaemia and AML. In Denmark and Finland, the categorization into ICCC-categories was done by the respective cancer register.

Table 1. Definition of lymphoid leukaemia and acute myeloid leukaemia used in Study II-IV.

Year of diagnosis	Lymphoid leukaemia	Acute myeloid leukaemia
2005-2015	ICCC-3: Group Ia according to Steliarova-Foucher et al (2005), additionally ICD-O-3 morphology codes 9812-9818.	ICCC-3: Group Ib according to Steliarova-Foucher et al (2005), additionally ICD-O-3 morphology codes 9865, 9869, 9898, 9911.
1993-2004	ICCC-2: Group Ia according to Kramarova & Stiller (1996).	ICCC-2: Group Ib according to Kramarova & Stiller (1996), additionally ICD-O-2 morphology code 9984.
1987-1992	ICD-9: 204	ICD-9: 205.0, 205.1 (morphology 296), 206.0 (morphology 256), 207.0 (morphology 286), 207.2 (morphology 296)
1971-1986	ICD-7: 204	ICD-7: 205.0, 206.0 (morphology 256), 207.2 (morphology 286), 207.3 (morphology 296)

ICCC: International classification of childhood cancer; ICD: International classification of diseases; ICD-O: International classification of diseases for oncology

4.4 OUTCOME, EXPOSURE AND COVARIATE DEFINITION

4.4.1 Outcomes

In **Study I-III**, the outcome was mortality from any cause. In Study I and II, we assess the time to death from the cancer diagnosis, while in Study III, the main outcome was binary and defined as death within three months (0-90 days) after cancer diagnosis, or not. In Study III, we also compared the associations for early mortality with associations for later mortality. In those analyses we defined the outcome 'later mortality' as death within one to five years (366-1825 days) after cancer diagnosis (binary).

We obtained the dates of cancer diagnosis from the national cancer registers in Study I and III. In Sweden, the date of diagnosis is defined as the date of the first examination/test underlying the diagnosis (129), and in Denmark it is defined as the "*admission date for the first contact during which the diagnosis was confirmed*" (130).

In Study II, where children with cancer are included from both the Swedish National Cancer Register and the Swedish Childhood Cancer Register, we defined the date of diagnosis as the earliest date recorded in either of the two registers.

In **Study IV** the outcome was binary and defined as attainment of upper secondary education at age 25 or not. This outcome was chosen because attaining this level of education is important for future work-life and career possibilities. The outcome was defined according to International Standard Classification of Education (ISCED) (131), as attainment of ISCED level 3. The choice of the standardized classification system was particularly important since the information on education level is collected from registers held by statistical institutes in three different countries. In Study IV, we also assessed potential delay in educational attainment. We defined the outcome 'attainment of upper secondary education without delay' as having attained this education level by age 19 in Sweden and Finland, and by age 20 in Denmark. It was necessary to use different ages to define delay because the pattern of education in the three countries has been different, depending on somewhat diverse education system and traditions (132). The different patterns in attainment of upper secondary education at ages 19-25 years are visualized in the supplementary material of Study IV, and when comparing to official statistics, the population comparison group reflect very well the education level of young adults in the three countries (133-135).

4.4.2 Exposures

In **Study I-III** we investigated social and familial factors in relation to survival from childhood cancer. In Study I and II, the factors investigated relate to the household the child lived in at time of cancer diagnosis, rather than the biological parents only. The household was defined on December 31, the year preceding the diagnosis, because of the structure of the register. Children diagnosed in their first year of life were excluded from Study I and II, partly because we could not accurately link all of them to their household. In **Study I**, we investigated highest attained education level (by the mother in the household if available,

otherwise father) and household disposable income obtained from the LISA register in the year before the child's cancer diagnosis. Parental education was categorized in three categories (compulsory or less, upper-secondary and postsecondary education), and income was categorized in quartiles based on the annual distribution of household disposable income in the study population. In **Study II**, we investigated the number of siblings and birth order in relation to survival. The number of siblings was based on the number of children living in the household (hence, not restricted to biological siblings). We also looked separately at only the number of siblings younger than the index child since younger children may require more attention from the parents. Birth order was defined from the Multi-generation register by counting live-births of the biological mother occurring before the birth month of the index child.

Similar to Study I, we included parental education and income, as well as parental employment, cohabitation, and country of birth in **Study III**. However, in this study, the parental information was based on biological parents, irrespectively of where the child lived. Parental education was also categorized here into three levels and income in quartiles. However, the income variables in this study referred to the personal disposable income of each parent and the quartiles were constructed based on the sex- and calendar year specific income distribution of the entire population in Denmark and Sweden, respectively, to better reflect the income level in relation to the society. Parental employment, cohabitation status, and country of birth were binary variables. We chose the categories Nordic and non-Nordic country of birth as we believe it captures more vulnerable groups than only Swedish/non-Swedish (or Danish/non-Danish). It was also a trade off with statistical power that did not allow us to have more specific categories.

In **Study IV**, survivors of childhood cancer are compared to two comparison groups (matched population comparisons and siblings) with regard to educational attainment, and the exposure is defined as being a survivor of childhood cancer.

4.4.3 Other covariates

In all four studies, we have adjusted for sex, age at diagnosis and time period of diagnosis, which are important prognostic factors in childhood cancer. In Study II and IV, we have adjusted for country of diagnosis since diagnostic procedures, as well as the definition and/or the registration of socioeconomic factors, may vary between countries. We have also conducted country-specific analyses in Study II and IV to assess if the examined associations differ between the countries.

We have conducted stratified analyses by cancer type in all four studies. As prognosis and treatment differ widely between cancer types, it is likely that also the associations examined in this thesis do. Although analyses of all cancer types combined may be of value for showing an overall pattern and increase awareness (of potential associations for a more general audience), the cancer type specific analyses are important to investigate specific mechanisms and identify risk groups.

In Study IV we conducted several stratified analyses because we hypothesized that sex, age, and time periods of diagnosis, as well as parental education, may modify the associations between cancer survivorship and educational attainment. We also stratified the survivors based on somatic and psychiatric hospital contacts between age 20 and 24 years, and by time spent in hospital during and after diagnosis. These variables were based on information from the national patient registers. For the hospital contacts between age 20 and 24 years, we identified if the survivor had any contacts for specified somatic conditions or any psychiatric diseases. We used somatic diseases that have previously been defined as related to late effects (74), for example excluding codes related to pregnancy. We differentiated between somatic hospital contacts that had cancer as the main diagnosis, and other somatic diseases. We have also used this grouping in other SALiCCS studies when we stratified for somatic diseases (80, 136). We chose the age of 20-24 years as the time period for assessing these contacts because we didn't want to include contacts in the years closest to the cancer diagnosis when the treatment could be ongoing, as the burden of the cancer treatment period was assessed in a separate variable. Time spent in hospital during and after cancer diagnosis was based on the number of days spent in hospital in the five years following the cancer diagnosis, with the intention to capture length of treatment and occurrence of complications. We dichotomized the variable into 'short' and 'long' by the median value in each group of cancer type, country, and calendar period, to have a value that was relative to other survivors diagnosed with similar diagnoses and in similar years.

4.5 STATISTICAL ANALYSES

4.5.1 Cox regression

In **Study I and II** we used a time-to-event analysis to compare survival time between children in different exposure categories. In both studies, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with Cox proportion hazards models, using time since diagnosis as the underlying time scale. In Study I, in addition to the main adjusted model, we also included time-varying coefficients to assess if the effect of parental education on survival during the first year differed from the effect on survival 1-10 years after diagnosis.

4.5.2 Logistic regression

In **Study III and IV**, we studied binary outcomes and used logistic regression models to estimate odds ratios (ORs) and 95% CIs comparing the likelihood of the outcome in strata of parental social factors (Study III) and between survivors and comparison groups (Study IV).

In Study III, we used logistic regression instead of a time-to-event analysis because of the uncertainty in defining the date of diagnosis. This uncertainty comes both from the disease as such, childhood cancer has no clear onset, and from the way date of diagnosis have been registered in the cancer registers. There might be differences in practices of how to set the date of diagnosis between time periods and regions. Moreover, before 2004 we only had

information on the month of diagnosis from Denmark. Logistic regression models are less sensitive to this uncertainty.

In Study IV, we used unconditional logistic regression models, crude and adjusted for the matching factors, to compare survivors to population comparisons. When survivors were compared to their siblings, we used conditional logistic regression models to make the comparisons within the set of siblings. Both crude and adjusted analyses were conducted, and the adjustment factors were sex and reference year since these factors can vary within a sibling set.

Study III and IV are cohort studies where we estimate ORs. In Study III, the outcome (early mortality) is rare, and the ORs are close to the risk ratios. However, in Study IV, the outcome (not having attained upper secondary education by age 25) is common and the OR is an overestimation of the risk ratio (137). As an additional analysis I estimated the risk ratio in this study using log-binomial regression. See Section 6.4.3.2 in the Methodological considerations, for a further discussion of this issue.

4.5.3 Other statistical methods used

In Study I, survival curves obtained with the Kaplan-Meier estimator was used to describe overall survival in children of parents with different educational levels. In this study, we also estimated the correlation between parental education and household income using Spearman's rank correlation and tested the proportional hazards assumption of the Cox regression model using Schoenfeld residuals.

In Study II and III, we assessed the association between number of siblings (Study II), parental social factors (Study III), and clinical characteristics among children with ALL, by comparing observed values in each stratum with expected values, using Pearson's Chi-squared test. In Study II, we also estimated the association between number of siblings and birth order, and survival in ALL, by strata of clinical characteristics. The interaction was assessed by comparing the strata specific HRs using the method suggested by Altman & Bland (138).

In Study IV, we assessed the likelihood of not having attained upper secondary education by age 25 comparing survivors to population comparisons, also in strata of parental education level. In addition, we constructed and included exposure variables of the four possible combinations of cancer survivorship and parental education in one model where the outcome was educational attainment, and assessed the interaction on the additive scale by calculating the relative excess risk due to the interaction (RERI). The RERI, also referred to as the interaction contrast ratio, is a measure of biological interaction presented by Rothman (139, 140). It estimates the additional joint effect of two exposures, in this case, estimates the effect of being a survivor and have parents with a low level of education in combination, the effect that is additional to the two individual factors. It is calculated as:

$RERI = RR_{11} – RR_{10} – RR_{01} +1$ (139, 140)

And in this scenario defined as:

$$RERI = OR_{Surv\_Parents\ having\ low\ educ} - OR_{Surv\_Parents\ having\ high\ educ} - OR_{PopComp\_Parents\ having\ low\ educ} - 1$$

The confidence intervals were derived from the covariance matrix from the model (139), and as seen in the formula, RERI=0 indicates the absence of interaction.

Table 2. Summary of methodological aspects in the four included cohort studies.

Study	Population	Follow-up	Exposure	Outcome	Covariates used for adjustment	Covariates used for stratified analyses	Statistical method
I	Children diagnosed with cancer during 1991-2010, aged 1-14 years old in Sweden (identified from the Swedish National Cancer Register), n=4723	Ten years after diagnosis 1991-2011	Parental education (from the mother in the household if available, otherwise father) Household disposable income	Overall mortality	Sex, age at diagnosis, year of diagnosis, health region, parental age, number of: siblings, parents born outside of Sweden, parents in household	Cancer type: Leukaemia (ALL), tumours of the nervous system (brain tumours), and lymphoma	Survival curves obtained with the Kaplan-Meier estimator Cox proportional hazard models, including time-varying coefficients in an additional analysis
II	Children diagnosed with ALL (n=1481) or AML (n=211) during 1991-mid 2015, aged 1-14 years old in Sweden (identified from the Swedish National Cancer Register and the Swedish Childhood Cancer Register).	Ten years after diagnosis 1991-2015	Number of siblings in the household Birth order	Overall mortality	Sex, age at diagnosis, year of diagnosis, parental education, age, and cohabitation	Cancer type: ALL and AML Age Clinical characteristics	Cox proportional hazard models Pearson's Chi-squared test HRs compared across strata with the method suggested by Altman & Bland 2003
III	Children diagnosed with cancer during 1991-2014, aged 0-19 years old in Sweden and Denmark (identified from the national cancer registers), n=13,926. Subpopulation: Children diagnosed with cancer during 1991-2010 (n=11,262), that had survived for at least one year after diagnosis, n= 10,339	Three months after diagnosis 1991-2015	Maternal and paternal education, disposable income, cohabitation status, employment, and country of birth.	Mortality (from any cause) within three months after diagnosis Mortality (from any cause) within one to five years after diagnosis	Sex, age at diagnosis, time period of diagnosis, country	Cancer type: ALL, AML, CNS tumours and non-CNS-solid tumours Country	Logistic regression Pearson's Chi-squared test
IV	Survivors of childhood cancer diagnosed during 1971-2005, aged 0-14 years old, born 1960-1990, and alive at the end of the year they turned 25, in Sweden, Denmark, and Finland (identified from the national cancer registers), n=7,629. Two comparison groups were included using the same criteria: matched population comparisons (n=35,411) and siblings (n=6,114).	At age 25 1985-2015 (Finland 1985, 1987-2014)	Childhood cancer survivorship (cancer diagnosis aged <15)	Not having attained upper secondary education by age 25 Attainment of upper secondary education without delay	Sex, age at diagnosis, time period of diagnosis, country	Cancer type: ALL, Other leukaemia, Lymphoma, CNS tumours, non-CNS solid tumours Sex, age and time period of diagnosis, country, time spent in hospital, somatic and psychiatric hospital contacts, parental education	Logistic regression; unconditional (survivors vs population comparisons), conditional (survivors vs siblings) (Log-Binomial regression) Relative Excess Risk due to interaction

4.6 ETHICAL AND LEGAL ASPECTS

The studies included in this thesis builds on sensitive, personal data since it includes individual information regarding health (141). Most of the data are obtained from national registers where all residents are included without giving informed consent. Such research can be conducted if the purpose is in public interest according to the General Data Protection Regulation (GDPR) (141), and if the benefits outweigh the harm according to the Swedish Law on Ethical Vetting (142). The benefits with these projects include the possibility to answer research questions of importance for health and equalities that would not be possible with other methods. Previous research has shown that participation in studies might be associated with socioeconomic status; when social factors are the main exposure or the outcome, such bias may preclude the possibility of obtaining valid results. When instead information from national registers is used, such bias is avoided. Regarding potential harm of the participants, the data used in this thesis are already collected for other purposes and these studies imply no extra burden for the included individuals. However, there is a potential harm from intrusion of personal integrity that needs to be limited.

In Sweden, ethical permission for research needs to be obtained from the Ethical Review Board, which has been done for all studies included in this thesis. After ethical approval, when an application for data is sent to Statistics Sweden and the National Board of Health and Welfare, they will do their own investigation regarding if the data can be handed out without risk of harm to the registered individuals. When the research group obtains the data, we have the same responsibilities for data protection and secrecy as the original data holders. The linkage between the registers is done with the personal identity number (109), but this number is replaced by a pseudonymized number by Statistics Sweden and the National Board of Health and Welfare (and corresponding authorities in Denmark and Finland), and the code key is kept only at the Statistics offices. It is important that no individual can be identified, since the information includes many variables, and only results on an aggregated level can be shown. Another way to minimize intrusion of personal integrity is to handle the data in a safe way. In these projects, the Swedish data are stored at Karolinska Institutet in a secure IT environment, with limited and controlled access. In the cross-national collaborations, the data from all included countries are stored at a secure server at Statistics Denmark, reached by remote access only by involved researchers. As an extra precaution, Statistics Denmark has replaced the pseudonymized identification number with yet another coded number, and this code key is kept only at Statistics Denmark.

Childhood cancer is a rare disease and international collaborations are crucial to reach enough statistical power to be able to conduct important subgroup analyses, which are not possible based on Swedish data alone (and even less so based on only Danish or Finnish data). Study III and IV are international collaborations including Sweden, Denmark and Finland. There are challenges with sharing data across borders. The SALiCCS study was initiated in 2016 and in 2018 the GDPR became law. The difficulties and challenges with epidemiological studies and Nordic collaborations after the implementation of GDPR have been described

previously (143, 144). The changes and different interpretations of regulations, and time-consuming procedures described (143, 144) are recognized also in the projects included in this thesis. Getting legal agreements into place was time-consuming, but we have been able to pool individual data from two (Study III) and three (Study IV) countries and store them at Statistics Denmark, which has created a unique possibility to conduct analyses also on rare subtypes of childhood cancer.

5 RESULTS

5.1 SOCIOECONOMIC FACTORS AND SURVIVAL FROM CHILDHOOD CANCER

5.1.1 Parental education, household income, and overall mortality

Study I included 4,723 children diagnosed with cancer at ages 1-14 during 1991-2010 in Sweden. In this population, 847 children (18%) died during the follow-up period of maximum 10 years after diagnosis. Among the included children, 32% had a diagnosis of leukaemia, 30% were diagnosed with nervous system tumours, 11% had a lymphoma diagnosis, and 28% other cancer diagnoses. Among all cancer types combined, the most common age group at diagnosis was 1-4 years, 40% of the children were diagnosed in this age range. This figure differed between children with leukaemia and nervous system tumours where 52% and 34% were diagnosed at ages 1-4 years, respectively. While 15% of the children had parents with compulsory or less education, 51% and 34% of the children had parents with upper secondary and postsecondary education, respectively.

Children of parents with a higher education level had better survival after childhood cancer, illustrated in the unadjusted survival curves in Figure 1 for children with leukaemia and nervous system tumours separately.

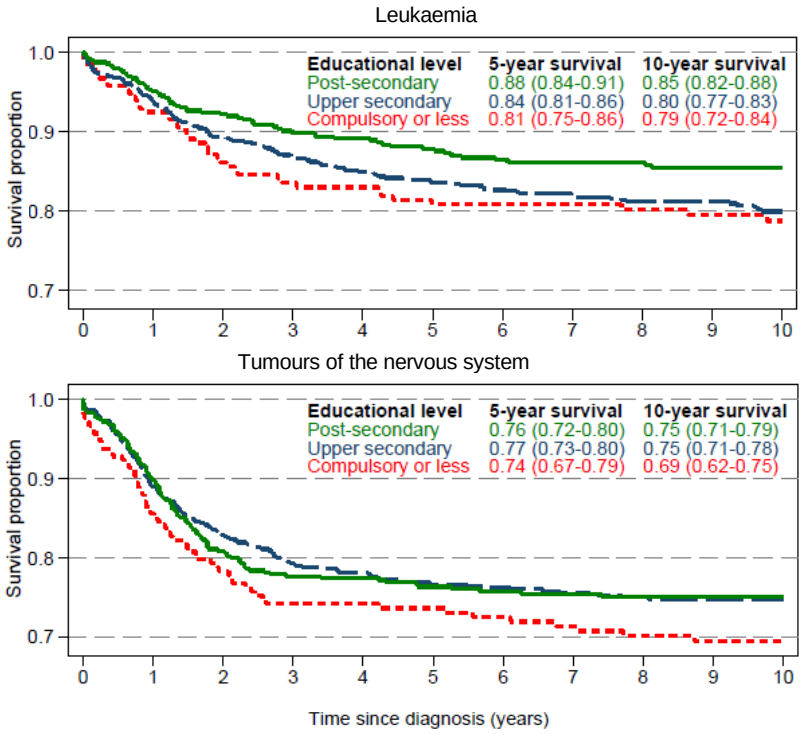

Figure 1. Survival after childhood leukaemia and tumours of the nervous system, obtained by the Kaplan-Meier estimator.
Figure adapted from Mogensen et al (2016) Br J Cancer.

The survival differences by parental education level were seen also when adjusting for sex, year of diagnosis, age at diagnosis, and region (Table 3). Associations in the same direction were seen for all cancer types, although most clearly among children with leukaemia (Table 3) and children with brain tumours ($HR_{Comp\ or\ less}$ 1.39 (95% CI 0.96–2.01); $HR_{Upper\ sec}$ 1.14 (0.86–1.51), compared to children with parents with postsecondary education level). There were no associations between household income and survival among all diagnoses combined, nor in any of the examined cancer types.

Table 3. Mortality after a childhood cancer diagnosis by parental education level and household income, in children diagnosed in Sweden aged 1-14 years old during 1991-2010, hazard ratios and 95% confidence intervals.

	Adjusted HR (95%CI)			
	All diagnoses combined	*Leukaemia*	*Lymphoma*	*Nervous system tumours*
Parental education level				
Compulsory or less	1.28 (1.03–1.59)	1.39 (0.93–2.08)	1.13 (0.46–2.77)	1.25 (0.90–1.73)
Upper secondary	1.17 (1.00–1.38)	1.28 (0.95–1.74)	1.35 (0.69–2.64)	0.99 (0.77–1.26)
Postsecondary	1	1	1	1
Household disposable income				
Q1 (lowest)	1.03 (0.85–1.26)	1.22 (0.83–1.78)	1.37 (0.62–3.02)	1.07 (0.79–1.43)
Q2	0.96 (0.79–1.18)	1.06 (0.72–1.56)	1.36 (0.63–2.94)	0.87 (0.64–1.19)
Q3	0.85 (0.69–1.04)	1.05 (0.72–1.53)	0.67 (0.28–1.56)	0.78 (0.57–1.07)
Q4 (highest)	1	1	1	1

Adjusted for sex, age at diagnosis, year of diagnosis, and region. Mutually adjusted for parental education level and household income.
ALL: Acute Lymphoid Leukaemia; CI: Confidence Interval; HR: Hazard Ratio
Summarizing results from Mogensen et al (2016) Br J Cancer.

When time-varying coefficients were used in the Cox regression model, we observed that the differences in survival between children with parents of different education levels were present already within the first year after diagnosis. The effects in the first year were compared to the effects in the following 9 years, and there were no statistically significant differences. However, there was an indication of differences in the pattern of survival from leukaemia compared to survival from nervous system tumours. Among children with leukaemia, the differences between having parents of compulsory or less education and postsecondary education continued after the first year ($HR_{1st\ year}$ 1.44 (0.76-2.73) and $HR_{>1year}$ 1.36 (0.82-2.26)), while for children with nervous system tumours, the differences were primarily seen in the first year after diagnosis ($HR_{1st\ year}$ 1.44 (0.90-2.30) and $HR_{>1year}$ 1.10 (0.71-1.71)).

5.1.2 Number of siblings, birth order, and overall mortality

Study II included 1,481 children with ALL and 211 children with AML diagnosed at ages 1-14 during 1991- mid 2015 in Sweden. In this population, 166 children (11%) with ALL and 74 children (35%) with AML died during the follow-up period of maximum 10 years after diagnosis. Twenty-three percent of the children with ALL had no siblings in the household, the corresponding proportion among children with AML were 18%.

There was a tendency of better survival from ALL in children with siblings compared to children without siblings (Table 4). Indications of an association in the same direction were also seen in children with AML but disappeared when adjusting for birth order ($HR_{1 \text{ vs } 0 \text{ sibs}}$ 0.97 (0.46–2.07); $HR_{\geq 2 \text{ vs } 0 \text{ sibs}}$ 0.88 (0.37–2.12), after adjustment). Moreover, for children with AML, the association tended to go in the opposite direction when only younger siblings were accounted for. Second born children had better survival from AML compared to firstborn children.

Table 4. Mortality after a diagnosis with childhood ALL or AML by number of siblings and birth order, in children diagnosed in Sweden aged 1-14 years old during 1991-mid 2015, hazard ratios 95% confidence intervals.

	Adjusted HR (95% CI)	
	ALL	*AML*
Nr of siblings in the household		
0	1	1
1	0.73 (0.49–1.10)	0.68 (0.36–1.29)
≥2	0.63 (0.40–1.00)	0.71 (0.34–1.48)
Nr of younger siblings		
0	1	1
1	0.84 (0.59–1.20)	1.81 (1.04–3.15)
≥2	0.57 (0.29–1.12)	1.17 (0.39–3.49)
Birth order		
First	1	1
Second	0.85 (0.59–1.23)	0.55 (0.31–0.99)
Third or later	0.85 (0.54–1.33)	0.67 (0.33–1.34)

Adjusted for sex, age at diagnosis, year of diagnosis. Models assessing siblings are additionally adjusted for parental education, parental age, and parental cohabitation. Models assessing birth order are additionally adjusted for maternal education and maternal age. Each indicator is included in separate models and indicators are not mutually adjusted.
ALL: Acute Lymphoid Leukaemia; AML: Acute Myeloid Leukaemia; CI: Confidence Interval; HR: Hazard Ratio
Summarizing results from Mogensen et al (2021) Br J Cancer.

The tendency of superior survival from ALL among children with siblings was primarily seen among children with low-risk profiles, i.e., B-cell precursor ALL, favourable genotype (high hyperdiploidy (HeH)*/ETV6-RUNX1*), white blood cell count of 50 or below, treated in low-risk protocols and without stem cell transplantation, although the estimates of the association were mostly not statistically significantly different.

5.1.3 Parental social factors and early mortality

Study III included 13,926 children diagnosed with cancer at ages 0-19 years during 1991-2014 in Sweden and Denmark. In this population, 355 children (2.5%) died within three months after diagnosis. Early mortality was more common among children diagnosed before turning 1 year, in earlier time periods, and among children diagnosed with AML or CNS tumours.

There was a pattern of higher early mortality among children with disadvantaged social backgrounds for most indicators under study, while weak or null associations were seen

between parental social factors and later mortality (Table 5). This pattern was observed in both Sweden and Denmark. Associations of parental education and maternal income with early mortality were most pronounced. The indicators of importance differed slightly between the cancer types, but also in the cancer type specific analyses most indicators pointed in the direction of a higher early mortality among children from disadvantaged backgrounds.

Table 5. Early and later mortality after a childhood cancer diagnosis by parental education level and income, in children diagnosed in Sweden and Denmark aged 0-19 years old during 1991-2014*, odds ratios and 95% confidence intervals.

	Adjusted OR (95%CI)			
	All diagnoses combined		*ALL*	*CNS tumours*
	Early mortality	**Later mortality**	**Early mortality**	**Early mortality**
Maternal education level				
Lower secondary or less	1.65 (1.22-2.23)	1.02 (0.85-1.23)	1.05 (0.48-2.27)	1.84 (1.10-3.09)
Upper secondary	1.10 (0.84-1.43)	1.04 (0.90-1.20)	1.00 (0.55-1.84)	0.98 (0.62-1.56)
Postsecondary	1	1	1	1
Paternal education level				
Lower secondary or less	1.35 (0.97-1.88)	1.09 (0.91-1.31)	1.01 (0.41-2.49)	1.79 (1.05-3.06)
Upper secondary	1.22 (0.92-1.61)	0.97 (0.83-1.13)	1.71 (0.86-3.38)	0.83 (0.51-1.36)
Postsecondary	1	1	1	1
Maternal income				
Q1 (lowest)	1.77 (1.25-2.49)	1.08 (0.86-1.36)	2.70 (1.19-6.13)	0.90 (0.44-1.86)
Q2	1.03 (0.74-1.44)	0.94 (0.78-1.13)	1.12 (0.47-2.67)	1.11 (0.64-1.93)
Q3	1.28 (0.99-1.65)	0.94 (0.81-1.09)	1.59 (0.84-3.01)	1.15 (0.74-1.79)
Q4 (highest)	1	1	1	1
Paternal income				
Q1 (lowest)	1.10 (0.77-1.58)	1.03 (0.83-1.28)	0.70 (0.27-1.86)	1.37 (0.73-2.56)
Q2	1.04 (0.77-1.42)	1.14 (0.96-1.36)	1.08 (0.55-2.10)	1.22 (0.71-2.10)
Q3	1.03 (0.79-1.34)	1.03 (0.89-1.20)	0.64 (0.33-1.25)	1.13 (0.71-1.80)
Q4 (highest)	1	1	1	1

Adjusted for sex, age at diagnosis, country, and time period of diagnosis. Each social factor is included in separate models and not mutually adjusted.
*Later mortality is assessed in children diagnosed up until 2010.
ALL: Acute Lymphoid Leukaemia; CI: Confidence Interval; OR: Odds Ratio
Summarizing results from Study III.

In Swedish children with ALL, the associations with early mortality were primarily seen for parental education and income as in the main analysis, although imprecise. There were no associations between parental education and clinical characteristics in this group. However, there was an association between maternal income and genotype, although with an unclear pattern. This association was partly explained by age at diagnosis.

5.2 EDUCATIONAL ATTAINMENT IN CHILDHOOD CANCER SURVIVORS

Study IV included 7,629 survivors of childhood cancer that had been diagnosed at ages 0-14 years during 1971-2005 in Sweden, Denmark, and Finland, and were alive at age 25 years. The study also included two comparison groups consisting of 35,411 matched population comparisons, and 6,114 siblings. In the study population, 47% of the survivors were diagnosed when they were aged 0-6 years, and this proportion differed between survivors of

ALL, lymphoma, CNS tumours, and non-CNS solid tumours where the corresponding proportions were 66%, 26%, 39% and 50%, respectively.

Among survivors of all cancer types combined, 80% had attained upper secondary education by age 25, which was compared to 84% in population comparisons and siblings. However, the proportions differed markedly by cancer type. Elevated ORs of not having attained upper secondary education by age 25 were primarily seen among survivors who were; diagnosed with a CNS tumours (OR 2.05 (95%CI 1.83-2.29)), diagnosed with ALL in the years 1971-1989 (OR 1.21 (95%CI 1.02-1.44)), hospitalized for a longer time around the cancer diagnosis (OR 1.61 (95%CI 1.48-1.76)), or had hospital contacts in early adulthood ($OR_{SomaticCancer}$1.33 (95%CI 1.17-1.51); $OR_{SomaticOther}$1.77 (95%CI 1.58-1.99); $OR_{Psychiatric}$4.00 (95%CI 3.26-4.90)), when compared to matched population comparisons (analyses adjusted for the matching factors country, sex, age and calendar period of diagnosis). On the other hand, survivors of leukaemia other than ALL, lymphoma and non-CNS solid tumours had attained upper secondary education by age 25 to the same extent as population comparisons, although also these survivors were more likely to experience delays in their education.

Being a cancer survivor decreased the likelihood of having attained upper secondary education by age 25, and so did having parents with a low education level. However, the disadvantage of being a cancer survivor in relation to educational attainment, was most pronounced among children to parents with higher education. In fact, survivors of leukaemia and non-CNS tumours whose parents had low education, had similar (or even higher) odds of attaining upper secondary education by age 25 years as population comparisons whose parents had low education. However, survivors of CNS tumours with parents having low education had a particularly increased risk of not having attained upper secondary education by age 25 years, compared to population comparisons with parents having higher education. However, the additive interactions (estimated by the RERI) were not statistically significant.

Highest attained education levels by age 19, 25 and 30 years were described among survivors, population comparisons and siblings that could be followed until age 30. By age 30, the proportion of survivors of ALL and CNS tumours that had attained tertiary education was lower than for population comparisons and siblings. In contrast, survivors of non-CNS solid tumours had attained tertiary education by age 30 to at least the same extent as population comparisons and siblings; the corresponding proportions were 36% among survivors and 35% among population comparisons and siblings.

6 DISCUSSION

6.1 SUMMARY OF MAIN FINDINGS

In **Study I**, we observed socioeconomic differences in overall survival from childhood cancer in Sweden – children of parents with a lower level of education had worse survival, while no differences were observed for household income. The differences by parental education were seen already in the first year after diagnosis. Based on these findings and the publication of a seminal study from the US (29), that reported socioeconomic differences in mortality within one month after diagnosis, we sought a Nordic collaboration to further investigate potential socioeconomic differences in early mortality from childhood cancer. In **Study III**, we saw that children from disadvantaged backgrounds were at increased risk of early mortality in Sweden and Denmark, with parental education and maternal income showing the most pronounced associations. We observed attenuated or null association with later mortality in this study (III). In **Study II** we investigated another aspect of social family circumstances, number of siblings and birth order, in relation to survival from ALL and AML in Sweden. In this study we found no evidence supporting a previously suggested hypothesis of lower survival in leukaemia among children with siblings, but we rather observed the opposite. In Study II we included clinical information for children diagnosed with ALL and saw that the superior survival among children with siblings was seen mainly within children with low-risk profiles.

In **Study IV** we investigated educational attainment in young adult survivors of childhood cancer, in comparison with matched population comparisons and siblings in Sweden, Denmark, and Finland. We observed that delays in the attainment of upper secondary education were more common among survivors of all cancer types compared to their peers. However, by the age of 25, many survivors had caught up to this educational level. Risk groups for not having attained upper secondary education by age 25 were survivors diagnosed with CNS tumours and survivors diagnosed with ALL in the 1970s and 1980s. Survivors who had spent more time in hospital around the time of diagnosis or had hospital contacts between age 20 and 24 years were also risk groups, in particular survivors with a history of psychiatric hospital contacts.

6.2 SOCIOECONOMIC FACTORS AND SURVIVAL FROM CHILDHOOD CANCER

Study I-III were, to my knowledge, the first studies examining socioeconomic and familial factors in relation to survival from childhood cancer in Sweden. The studies used a register-based design, which was important to ensure that all children with cancer were included and could be followed up, independent of socioeconomic and familial factors, severeness of disease, and survival.

In agreement with our results from Sweden, the systematic review conducted by Gupta et al (41), and our updated review (42) suggested social differences in childhood cancer survival also in high-income countries, with children from families of lower SES more often

experiencing worse survival. It should be noted, however, that Study I was included as one of the 24 studies in our review (42).

As suggested before, it is difficult to compare results of studies from different settings in terms of society and organization of healthcare. The Nordic countries have rather comparable settings (28), and three other studies assessing the association between parental education and income, and survival from childhood cancer, have been conducted in Nordic settings (47, 145, 146). The first of these studies, conducted in Norway, found better survival among children of mothers with higher education, while no difference in survival was found for income, in line with our study. In the Danish study, a suggestion of better overall cancer survival among children with higher parental education or higher maternal income was found, although not statistically significant (145). The results from Finland showed that children to parents of lower income had worse survival in childhood cancer (146). The Finnish study also indicated worse survival for children of parents of lower education, in particular in the latest time period (146)

Before Study I was conducted, it had been suggested that social differences in survival after childhood cancer, in particular ALL, were related to adherence to the long oral treatment mainly given outside of hospitals (66). This hypothesis was supported by results from a British study showing that survival curves of children with ALL of different social strata started to diverge when treatment moved from hospitals, around 6-9 months after diagnosis (66). However, the results from Study I, both for all diagnostic groups combined and for leukaemia, showed that the differences in survival started already within the first year after diagnosis. We looked further into the issue of timing of social differences in Study III, where we examined early mortality. To my knowledge there has only been one previous study investigating social differences in early mortality from childhood cancer in particular (29). This study was conducted within the SEER register in the U.S. and indicated that children living in disadvantaged areas had a higher risk of dying from haematological malignancies within one month after diagnosis, compared to children living in advantaged areas. Social differences were also indicated for CNS tumours (29). We also observed such differences in Sweden and Denmark, and in contrast to the American study we measured social factors on an individual level and in settings with universal healthcare, independent of insurance status. From our results, we could not clearly conclude if the risk of early deaths among children with disadvantaged social backgrounds were more pronounced for some diagnostic groups; the results differed between social factors, and early deaths in childhood cancer are rare which meant that the statistical power was limited. Although we cannot rule out that some associations in Study III might have been seen due to chance, the overall pattern of social inequalities in early mortality in childhood cancer in Sweden and Denmark is of importance. Social differences that occur this early in the disease course are unlikely to be explained by differences in treatment adherence, but must have other explanations.

In Study II, we examined the number of siblings in the household and birth order in relation to survival from ALL and AML and observed a better survival in ALL among children with

siblings. These associations have been previously investigated in a few studies. In contrast to our results, a Norwegian study showed worse survival from childhood cancer (all diagnoses combined) among children with siblings compared to children without (47). However, this study contained no analyses stratified by diagnostic groups. Furthermore, a Finnish study reported no association between the number of siblings and childhood cancer survival, but unfortunately did not report any effect estimates (146). Studies that have focused on haematological malignancies, or more specifically ALL, have reported diverse findings; children with siblings tended to have poorer (48, 49, 145), better (51), or similar (50) survival. Taken together, our findings of superior survival from ALL among children with siblings, were in contrast to some previous studies. However, previous studies were few, the studies on haematological malignancies were conducted only in three countries (Denmark, Germany, and Greece), and none of the studies provided conclusive results (including our Study II).

What are the potential underlying mechanisms for an association between number of siblings and survival? Number of siblings has sometimes been used as a measure of SES, but such use can be questioned since the correlation may differ between settings and the underlying pathways might be very different (46). However, it has been discussed that a large number of siblings by itself, and thereby more parental obligations, might be negative for treatment adherence (47, 48), which was not supported by our results. The number of older siblings is sometimes used as a proxy for infections early in life, which has been suggested to be associated with B-precursor ALL (Greave's hypothesis) (36, 37). Children with B-precursor ALL have a better prognosis than children with T-cell ALL (26). These associations might explain a potential association between number of siblings and survival if detailed information on cancer subtype is not considered in the analyses. See Figure 2 for a simple directed acyclic graph (DAG).

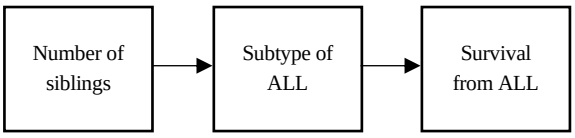

Figure 2. DAG of a potential pathway between number of siblings and survival from ALL, mediated by subtype.

To address this potential explanation, we conducted analyses stratified for clinical characteristics among children with ALL. In these analyses we also observed the pattern with a better survival among children with siblings, mainly among children with low-risk profiles. This means that a difference in risk of different subtypes of ALL does not explain the association between number of siblings in the household and survival.

In summary, Study I and III indicated that social inequalities in childhood cancer survival also exist in Sweden and Denmark. It is not likely that treatment adherence is the only explanation for these social differences, since they occur early in the disease course, and they seem to be present in children with diverse cancer diagnoses that are treated differently. For

example, one would expect that the social differences would be larger for diagnoses that were treated for a long period in the child's home, such as ALL, than for diagnoses that are mainly treated within hospitals, if parent/child treatment adherence was the main pathway, but such differences were not observed. Difficulties with treatment adherence has also been proposed as an underlying mechanism behind worse survival in children with a larger number of siblings, but this was not supported in Study II. The differences in early mortality observed in Study III indicated that there could be differences in the timeliness of diagnosis. Two previous studies from Denmark have shown that even months before diagnosis, children with cancer seek primary care more often than comparisons (60, 61). The additional use is larger in children from disadvantaged backgrounds (60). This may suggest that the time from first symptoms to a diagnosis is longer for children from disadvantaged backgrounds which may depend on the parents' ability to navigate and communicate within the healthcare system. Such diagnostic delay would result in a shorter recorded survival time in our study, however, if diagnostic delay has a negative impact on survival is not clear, and seem to differ between diagnoses (62). Nevertheless, a prolonged diagnostic procedure might be difficult for the whole family. Further studies investigating potential socioeconomic differences throughout the pathway of care more directly, are needed to shed light on these underlying mechanisms.

6.3 EDUCATIONAL ATTAINMENT IN CHILDHOOD CANCER SURVIVORS

In comparison to previous studies in this field, Study IV was a large study including childhood cancer survivors diagnosed during a period of more than 30 years, from three countries, which allowed us to look at specific analyses by diagnostic groups as well as several other important stratified analyses. The study further contributed to the research field because of the thorough methodology, including identifying survivors and two comparison groups from population registers, as well as assessing educational attainment from population registers.

We observed, in line with most other studies in this field (82, 84-86), that survivors of CNS tumours were particularly vulnerable with regard to educational attainment. This group has been highlighted as a risk group in guidelines for surveillance of education (83). We have also observed that survivors of CNS tumours were at higher risk of other adverse socioeconomic outcomes, such as health-related unemployment, in another study from the SALiCCS programme (136). Many of the hypothesized mechanisms of how childhood cancer may affect educational attainment are particularly valid for CNS tumour survivors; the location of the tumour as well as complications of surgery, and cranial irradiation all have negative impact on cognition (81).

Cranial irradiation has also been given to survivors of ALL in earlier treatment eras (69), and earlier studies have consistently shown that also survivors of ALL treated with cranial irradiation are at increased risk for negative educational outcomes (88, 91, 98, 147). We did not have information on treatment in Study IV but we believe that the result of a higher likelihood of not having attained upper secondary education by age 25 among survivors of ALL diagnosed 1971-1989 is explained by this, especially as we did not find a similar

association for the later time period. There have also been studies showing a negative impact from treatment with methotrexate on cognition or educational attainments (81, 147), although the effect has been smaller than for cranial irradiation.

Even though these associations have been shown before, it was important to confirm them in this study, which is population-based and not affected by potential bias from non-participation. In addition to previous literature, we also showed that survivors who had spent longer time in hospital at time of diagnosis and survivors who had a history of hospital contacts in early adulthood, were at increased risk of not having attained upper secondary education by age 25 years. Although we used an overall measure of somatic disease burden, compared to earlier studies of specific conditions (96-100), the results were in the same direction and showed a higher risk of educational difficulties among survivors with complications directly after diagnosis and/or late effects. In particular, survivors who had psychiatric hospital contacts in the age range 20-24 years were at increased risk of not having attained upper secondary education by age 25 years. This finding is important since we have also observed an increased relative risk of psychiatric disorders in childhood cancer survivors in SALiCCS (80). Despite the increased relative risks, this is a small group of survivors, but in light of their vulnerability, further analyses on educational trajectories would be of importance.

Another important finding from Study IV is that some survivors did as well as their peers with regard to attainment of upper secondary education by age 25, which we could show in stratified analyses, discussed below. However, in all diagnostic groups, we saw that survivors were more likely to experience delays in their educational achievements. This is in line with results from a Swiss study that also indicated that survivors may experience delays in their education, but survivors aged 27 and above had caught up with the general population (95). Exceptions from this were survivors of CNS tumours and survivors who had experienced a relapse (95). Moreover, in the meta-analysis by Saatci et al (86), the authors concluded that survivors without CNS involvement attained tertiary education to the same extent as comparisons, based on estimates from seven individual studies (87, 90, 95, 148-151). Although this was not our main outcome, we also looked at the proportion of survivors that had attained tertiary education at the age of 30. We observed a similar proportion of the survivors of non-CNS solid tumours that had attained tertiary education, compared to population comparisons and siblings. Moreover, for our main outcome, attainment of upper secondary education by age 25, we observed no disadvantage for survivors of ALL and non-CNS solid tumours who spent shorter time in hospital around the time of diagnosis and/or did not have hospital contacts in early adulthood, compared to population comparisons.

6.3.1 Support and surveillance

A recent systematic review including studies from 18 countries across the world, reported that there is limited evidence of how educational support is utilized among childhood cancer survivors and they identified very little research evaluating the effect of educational

interventions (152). As the authors acknowledged, the offered support differed widely between countries and settings.

Educational support should be offered to children with cancer in Sweden today according to the Swedish Education Act (153). This includes support during and after the treatment phase such as teaching in hospitals, home-based teaching, and special assistance when returning to school (153). Children treated for CNS tumours are known to be a vulnerable group, which was also observed in Study IV, and there is an early focus on these aspects from the rehabilitation- and psycho-social team. Children treated for cancer of different types meet these teams, and it is recommended that the neuropsychological assessment lay ground for the planning of support in school (154).

Devine et al have compiled international recommendations for surveillance of education among survivors of childhood cancer (83). These recommendations are rather overarching, similar to other standards for psychosocial care of children with cancer (155), since they are intended for survivors of heterogenous cancer types (83). The guidelines recommend surveillance of education in survivors, which should start at diagnosis and continue throughout long-term follow-up visits until young adulthood, and referral to specialists should be made if needed (83). In addition to survivors of CNS tumours and survivors treated with CNS-directed therapy, survivors with late effects were also highlighted as particular risk groups in the guidelines. The results from Study IV supports these conclusions, but also adds knowledge that can be used to develop more specific interventions. Our results showed that survivors who had spent more time in hospital around the time of diagnosis and survivors with hospital contacts in early adulthood were risk groups, particularly those who sought care for psychiatric conditions. This enhances a possibility to identify vulnerable survivors at different time points from diagnosis to young adulthood.

Survivors with parents having low education were also emphasized as a risk group of lower educational achievements in the recommendations for surveillance (83). This is in line with several previous studies showing poorer educational outcomes among survivors with parents having low education, compared to survivors with parents having a higher education level (89, 95, 102, 103). The results of Study IV shed further light on this association. We also observed that survivors whose parents had lower education level were at increased risk of not attaining upper secondary education by age 25, compared to survivors whose parents had a higher level of education. However, when the comparisons were made between survivors and population comparisons in strata of parental education, the disadvantage of having experienced cancer as a child was greater among individuals having parents with a higher education level. For example, among survivors of ALL whose parents had a lower education level, there were no difference in attainment of upper secondary education by age 25, compared to population comparisons whose parents had low education, although such a difference was observed among survivors whose parents had a higher education level. This might suggest that supportive measurements have benefitted the group of survivors with parents having a lower education level, but were not enough for survivors with parents having

a higher education level. However, it also suggests a large effect of support from home in educational achievements in the general population. This results in a more notable impact on educational achievements, from the experience of a childhood cancer diagnosis and its consequences, in young adults that have a higher likelihood of achieving higher education levels from the beginning.

6.4 METHODOLOGICAL CONSIDERATIONS

6.4.1 Register-based cohort studies vs other study designs

6.4.1.1 Strengths

The major strength of the papers in this thesis is the use of high-quality nationwide population-based administrative and health data registers. The advantages of this study design can be divided in two main parts.

Identification of the population

Identification of the population from registers ensured that of all children with cancer, regardless of severeness of disease or survival, were included. Population registers were also used to randomly select matched comparisons in Study IV, as well as to identify the siblings to the survivors. Children with cancer, population comparisons, and siblings, were included in the studies irrespective of social background or educational attainments. In this way ***selection bias*** (156) from non-participation was avoided. It has been demonstrated in several studies that socioeconomic factors or health status influence participation in research (106, 107, 157). As an example, a British study showed no association between SES and the risk of childhood leukaemia, but when they restricted their analyses to cases and controls that agreed to be interviewed, an association between low SES and higher risk of childhood leukaemia was seen (107). This illustrates an example of when controls with low SES were less likely to participate in the interview stage of the study. Another example can be seen in the meta-analysis of educational attainment by Saatci et al. where the mean response rate was 70%, and it often differed in the individual studies between the case and comparison groups (86).

Information on parental socioeconomic factors and educational attainment

With the use of population registers we could obtain information on parental socioeconomic factors before the cancer diagnosis, which is important to ensure temporality. Having a child with cancer may affect socioeconomic factors within the family (52, 158), and the access to national register based information before the cancer diagnosis meant that we could avoid bias from a form of ***reverse causation*** *(156).* Such bias could otherwise arise if the severeness of the child's disease affected familial socioeconomic factors. The Swedish, and Nordic, registers include individual measurements of socioeconomic factors, in contrast to area-based, which limits the risk of ***nondifferential misclassification*** *(156)* in these studies, where we are interested in the effect of the family's socioeconomic situation rather than the community's.

We also assessed educational attainment in young adulthood through population registers. One advantage with this was that the information was obtained in the same way for survivors, population comparisons, and siblings, avoiding ***differential misclassification*** (156) of the outcome. Follow-up and assessment of the outcome from registers also minimized the risk of ***selection bias*** (156) due to loss to follow-up. This source of bias may otherwise potentially have an impact on the results in either direction. On one hand, one can hypothesize that survivors that have a lot of educational difficulties are more interested in participating in studies on this subject. On the other hand, survivors with more late effects and health problems might be less likely to participate. These sources of bias are not likely to have affected our results since the population registers contain information on education for almost everyone.

6.4.1.2 Limitations

The use of register-based information in all four included studies also implied some limitations. With the information at hand, we are limited in what conclusions we can draw regarding underlying pathways. With regard to the survival studies, we observed survival differences according to social background early in the disease course and we can speculate if this could be related to the timing of diagnosis and difficulties navigating the healthcare system. However, we don't know if such difficulties were experienced or if there was a long period before the child got a diagnosis. Moreover, we have limited knowledge about which household children spend most time in, from the registers. We tried to minimize this problem in Study I and II by identifying the households where the children were registered, rather than the biological parents' households, but children to separated parents are only registered in one household even if they spend an equal amount of time in two. In Study I we saw that around 20% of the children were not registered in the same household as both their biological parents.

In Study IV we can also draw limited conclusions regarding underlying pathways for observed differences between survivors and comparison groups. For example, we do not know the reason for delaying an education. This could be due to health or cognitive problems, or missed time in school, but there are also other reasons such as taking a gap year for travelling or study abroad that may delay the completion of upper secondary education.

In all studies we have limited clinical information. The Swedish National Cancer Register does not record any information regarding treatment, whereas limited and incomplete treatment information can be found in the Finnish Cancer register (115). In Study II and III we used clinical information from the quality register for childhood cancer, which was a considerable strength, but the information was limited to Swedish children with ALL.

6.4.2 Choice of comparison groups

In Study I-III, our study population is children diagnosed with cancer and the comparisons between children of different social backgrounds are made within this group. The outcome in all three studies is mortality. If this study had been conducted in adults with cancer, it would

have been important to adjust for the generally higher mortality in the lower socioeconomic groups (e.g. by calculating relative survival (159, 160)). However, in Sweden and the other Nordic countries, mortality in the general population of children is very low, which means that it is not likely that the results in Study I-III are explained by a mortality pattern seen in children without cancer.

The population comparison group in Study IV was matched by sex, birth year and region of residence on a ratio of 1:5. All these variables were potential confounders since they may both be associated with the exposure (cancer survivorship) and may predict the outcome (educational attainment). The matching takes away the association between the matching factors and the exposure at the point of matching (161). However, it has been suggested that some adjustments for the matching factors should be done anyway, for example if censoring is potentially changing the covariate balance (161). As expected, the crude and adjusted effect estimates in Study IV were very similar.

We also included siblings as a second comparison group in Study IV. Siblings partially share genetic and social background and by having siblings as a comparison group, these shared factors are accounted for (162). To ensure that the familial situation was similar between the siblings, and that the outcome was measured in a similar time period (which is important since the educational pattern in the population have changed over time), we only included siblings with an age difference of maximum 5 years, and defined the reference date for the sibling as the time when the sibling was of the same age as the sibling survivor. Adding siblings as a second comparison group increased the validity of our findings, however, there are also some features to have in mind when interpreting these results. Having a sibling that is affected by cancer affects the whole family and may also affect the educational attainment of the sibling, in epidemiological terms called a "carryover effect" (163). Moreover, in the analysis phase, only information from siblings that are discordant for the outcome is taken into account, which decreases statistical power (162), as can be seen in our results where confidence intervals are wider for effect estimates based on the sibling comparison group.

6.4.3 Choice of statistical method

6.4.3.1 Binary outcomes vs time-to-event analysis

In Study III we defined a binary outcome (death within 90 days after cancer diagnosis) instead of using the exact survival time calculated from the records in the cancer registers and cause of death registers. The reason for this was that we believed it better reflected and fitted the uncertainty in the date of diagnosis. First, the disease itself has no clear date of onset (compared with, for example, the date of a myocardial infarction). Secondly, the date of diagnosis in the Swedish National Cancer Register is defined as the date of the first clinical, morphological or other laboratory examination/test underlying the diagnosis (129). However, there might be differences between regions and time periods in how the date of diagnosis is determined. We know from personal communication with clinicians that the date of the pathology examination is often used as the date of diagnosis, which may be later than the date

of the first health care visit leading up to the diagnosis. Moreover, in the Danish part of the data, there is a time period (before 2004) where we know that the recorded date may differ by up to two weeks compared to the clinical date, since it is recorded on monthly level rather than the actual day (115). These uncertainties have a greater impact when studying early mortality than when studying 5- or 10-year survival as in Study I and II. A time-to-event analyses would have been more sensitive to how date of diagnosis was defined. By defining deaths within the first three months, we believe we capture early mortality and the uncertainties explained, in fact, most of the early deaths (211/355) occurred in the first month after cancer diagnosis. This also explains why the results of the sensitivity analysis in Study III where we define early death as death within 30 days, are very similar to the main results.

6.4.3.2 Odds ratios vs risk ratios

In Study IV we used odds ratios to estimate the association between cancer survivorship and educational attainment. Since this was a cohort study where the outcome was relatively common, the OR overestimates the RR (137). To illustrate this, the adjusted ORs estimated by logistic regression (reported in Study IV) were compared with adjusted RRs estimated by log-binomial regression (Table 6).

Table 6. Difference between odds ratios and risk ratios. Likelihood of not having attained upper secondary education by the age of 25, odds ratios, risk ratios and 95% confidence intervals.

	Survivors	*Population comparisons*		
	$n_{\text{Have not attained}}$	$n_{\text{Have not attained}}$	**OR (95% C)**	**RR (95% C)**
Cancer type				
All diagnoses combined	1509 (20%)	5531 (16%)	1.32 (1.23-1.40)	1.24 (1.18-1.31)
ALL	305 (17%)	1232 (15%)	1.15 (1.00-1.33)	1.11 (1.00-1.24)
CNS- tumours	573 (28%)	1537 (16%)	2.05 (1.83-2.29)	1.73 (1.60-1.87)

Odds ratios are estimated with unconditional logistic regression.
Risk ratios are estimated with log-binomial regression.
All analyses are unmatched and adjusted for country, sex, age, calendar period of diagnosis.
ALL: Acute Lymphoid Leukaemia; CI: Confidence Interval; OR: Odds Ratio; RR: Risk Ratio

The difference between the ORs and RRs was most pronounced in the analyses of children with CNS tumours where the outcome, fail to achieve upper secondary education, was the most common. If one wants to estimate RR in a cohort study log-binomial regression has been suggested as a suitable method (137). However, it is acknowledged in the literature that models estimated with log-binomial regression often runs into problems with convergence (137), which we also experienced. We also wanted to conduct both matched and unmatched analyses which we did using conditional and unconditional logistic regression. These aspects, together with the use of logistic regression in previous literature, contributed to the final decision to report odds ratios in the manuscript, although they should not be interpreted as risk ratios.

6.4.4 Reporting and interpreting null findings or findings in contrast to the hypothesis

Reporting null findings is as important as reporting pronounced associations. In a meta-analysis regarding educational attainments in childhood cancer survivors by Gummersall et al., there were signs of publication bias, indicating that small studies where survivors had superior educational outcomes than comparisons had not been published (85). One of the most important findings from Study IV is that survivors of leukaemia other than ALL, lymphomas and non-CNS tumours, attain upper secondary education to a similar extent as population comparisons, which of course needs to be published. However, interpreting a null finding can be difficult. Sometimes, associations are incorrectly interpreted as null findings exclusively based on lack of statistical significance. An example can be found in Syse et al. (47) where the authors summarize that the lower survival among children to mothers with lower education is restricted to cancers that involve long-term treatment. Their summary is based on stratified analyses showing two essentially identical results but interpreted by the authors as different: an OR of 0.82 (95% CI 0.69-0.98) for chronic and of 0.81 (95%CI 0.64-1.03) for resolving disease, respectively. The importance of not focusing on statistical significance but instead look at the point estimate and the variability of the data through the confidence intervals, becomes apparent, which has also been thoroughly discussed by other epidemiologists (164-166).

Publication bias may also be an issue when the findings run in contrast to the hypothesis. In Study II, we hypothesized that a larger number of siblings may be negative for survival, but we observed an association rather in the opposite direction. Also, in Study IV, we observed a more pronounced association between cancer survivorship and educational attainment, in individuals with parents having a higher level of education. This finding was not in accordance with our hypothesis or the theory of "Compensatory advantage" (104), suggesting that the disadvantage of being a cancer survivor would be compensated by parents having higher education. It is of course of high importance to publish and show these results for the research field to move forward.

6.4.5 Generalizability

Generalizability, or external validity, first of all relies on internal validity. As pointed out throughout this thesis, the use of information from register has in several ways strengthened the internal validity of the four individual studies.

So, for the next step, are the findings in this thesis applicable to other settings? How socioeconomic factors affect access to healthcare, treatment, and in the end survival, probably depends a lot on the context. In Sweden we have universal access to healthcare and no economic barriers to childhood cancer treatment. Such barriers were suggested in the WHO Europe report (22) as one of the mechanisms underlying survival differences in childhood cancer. The findings of this thesis suggest that other underlying pathways are also of importance, and one could speculate that since we observe social inequalities in this setting, larger inequalities are expected in other settings.

Educational attainment among survivors also depends on the context and what kind of support is offered to survivors. However, the vulnerable groups of survivors that were identified in this thesis are probably also generalizable outside of the Nordic context.

Another question is if the findings of social inequalities in childhood cancer in Sweden have implications for other childhood diseases? Childhood cancer is a serious condition, treated according to protocols in six paediatric oncology centres. One could hypothesize that social inequalities are also present in other childhood diseases and conditions with less standardized treatments. Such differences have been indicated by other authors (see for example, 167, 168), however, such conclusions are outside the scope of this thesis.

7 CONCLUSIONS

The studies included in this thesis have assessed how socioeconomic and family factors affect survival in childhood cancer in Nordic countries with universal healthcare and examined educational attainment in young adult survivors of childhood cancer in this context. The use of information from Swedish and Nordic health and population registers increased the validity of our findings by minimizing the impact of non-participation and self-reporting, which in other studies have been problematic.

From the four included studies, I we have concluded that:

- Mortality in childhood cancer differed by parental socioeconomic factors, with higher mortality among disadvantaged children in two countries with universal healthcare. The social inequalities were seen already, and to some extent particularly, in early mortality, i.e. during the first few months after diagnosis (Study I & III).
- Having siblings in the household at the time of diagnosis was not associated with a decreased survival in childhood leukaemia, as suggested in some previous studies. Our results rather suggested the opposite and indicated a better survival in childhood ALL in children with siblings (Study II).
- Even though childhood cancer survivors were more likely to experience delays in their education, several groups had caught up with their peers by age 25, with regard to attainment of upper secondary education. In accordance with previous literature, we confirmed that vulnerable groups of survivors were those diagnosed with CNS tumours, or survivors diagnosed with ALL in the earlier time period, which is likely associated with irradiation to the CNS. We also identified survivors who had spent more time in hospital around the time of diagnosis and survivors with hospital contacts in early adulthood as risk groups. Moreover, we observed that parental education modified the association between having had cancer as a child and attaining upper secondary education; the most pronounced differences between survivors and comparisons were seen in children to parents with high education. Taken together, these results highlight the need for, and possible benefits with, surveillance and directed interventions (Study IV).

8 POINTS OF PERSPECTIVE

As pointed out in the recently published WHO report (22), inequalities in childhood cancer may arise across the continuum, from healthcare access before the diagnosis to survivorship after completed treatment. In the studies included in this thesis we have observed inequalities in survival from childhood cancer in Nordic countries with universal healthcare access. Our results indicated that the differences were apparent already early in the disease course, which highlights the need for research investigating the healthcare pathway to a childhood cancer diagnosis in different socioeconomic groups. Are there differences in the health seeking behaviour of the parents (i.e. patient's delay), or are there differences in the time between first contacts with healthcare and the cancer diagnosis (i.e. doctor's delay)? Do socioeconomic factors influence the management of early toxicity once the child has been diagnosed and treatment has started? Does the risk of relapse differ between children from different socioeconomic backgrounds? These questions remain to be answered.

There is also a need for studies directly investigating treatment adherence and potential difficulties with this, in the Nordic context. Furthermore, the findings in this thesis raise the question of potential social inequalities in children with serious conditions other than cancer. Moreover, studies including children with less severe diseases, and healthcare contacts for such diagnoses, would be of importance to increase the understanding of where and when potential social inequalities occur.

Childhood cancer survivors are a growing population, and so are older survivors. Improvements in treatment have led to decreased late effects for some diagnostic groups and continued improvements will benefit future survivors. However, we also have a part of the survivor population that was treated a long time ago and it is important that we acknowledge the somatic and socioeconomic late effects they may experience and identify vulnerable survivors. Moreover, it is of importance that we continue to follow-up survivors treated more recently with regard to late effects and socioeconomic consequences, since treatment for some diagnoses have intensified. However, it is also important that we communicate the message that for some groups of survivors we did not identify any disadvantage in achieving the level of upper secondary education; some of these groups might have benefitted from the societal support given to childhood cancer survivors. Future studies on educational trajectories including tertiary education are of importance, as well as studies including survivors that were diagnosed with cancer as older teenagers.

This thesis shows the strengths of using information from population and health data registers to study research questions for which other study designs would likely be affected by bias from non-participation, loss to follow-up, or self-reports. The studies also show the immense potential and importance of Nordic collaborations in research of rare diseases.

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APPENDIX

Mogensen H, Modig K, Tettamanti G, Erdmann F, Heyman M, Feychting M. Survival After Childhood Cancer-Social Inequalities in High-Income Countries. Frontiers in Oncology. 2018; 8:485

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Survival After Childhood Cancer–Social Inequalities in High-Income Countries

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Despite substantial improvements in survival from childhood cancer during the last decades, there are indications that survival rates for several cancer types are no longer improving. Moreover, evidence accumulates suggesting that socioeconomic and sociodemographic factors may have an impact on survival also in high-income countries. The aim of this review is to summarize the findings from studies on social factors and survival in childhood cancer. Several types of cancer and social factors are included in order to shed light on potential mechanisms and identify particularly affected groups. A literature search conducted in PubMed identified 333 articles published from December 2012 until June 2018, of which 24 fulfilled the inclusion criteria. The findings are diverse; some studies found no associations but several indicated a social gradient with higher mortality among children from families of lower socioeconomic status (SES). There were no clear suggestions of particularly vulnerable subgroups, but hematological malignancies were most commonly investigated. A wide range of social factors have been examined and seem to be of different importance and varying between studies. However, potential underlying mechanisms linking a specific social factor to childhood cancer survival was seldom described. This review provides some support for a relationship between lower parental SES and worse survival after childhood cancer, which is a finding that needs further attention. Studies investigating predefined hypotheses involving specific social factors within homogenous cancer types are lacking and would increase the understanding of mechanisms involved, and allow targeted interventions to reduce health inequalities.

Keywords: childhood neoplasms, leukemia, nervous system neoplasms, socioeconomic factors, survival, review

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INTRODUCTION

From low survival rates in the 1970's and earlier, overall 5 years survival from childhood cancer is now exceeding 80% in most of Europe (1, 2). Nonetheless, despite these advances a significant number of children with cancer fail to reach this milestone, with varying proportions according to cancer type (2). Moreover, reports from the US and Europe indicate that survival improvements for several childhood cancer types have leveled off during recent years (2, 3). At the same time, evidence

accumulates suggesting that socioeconomic and sociodemographic factors may be associated with survival even in high-income countries where children are presumed to have equal access to health care services, see for example (4–7). This does not only highlight a potential inequality that needs attention, but might imply a possibility of improving childhood cancer survival rates overall, by addressing this potential gap. However, even though several studies support an association between higher parental socioeconomic status (SES) and better survival, findings differ between countries, cancer types, and SES indicator studied. Some of the differences might be explained by inconsistent methodology between studies, but might also indicate different mechanisms in which parental SES affects survival. For example, differences in treatment and prognosis between cancer types are likely to influence.

Gupta et al. (8) conducted a systematic review evaluating the association between SES and childhood cancer survival, including studies published until 2012. This review indicated that in high income countries, parental income is not the driver of the association but instead other SES indicators such as education, having insurance, or place of residence seemed to be of importance (8). However, parental income was only assessed in few studies. Since 2012, there have been several studies examining the association between parental SES and survival from childhood cancer in high income countries, and these are the focus of the current review.

The objectives of this review are (i) to summarize the findings from studies on social factors and survival from childhood cancer in high-income countries, by cancer type, and (ii) to elucidate the role of different socioeconomic and sociodemographic factors (parental education, income, social status based on occupation, cohabitation, and marital status, place of residence, number of siblings, and birth order) on the association, in order to shed light on potential mechanisms and to identify particularly affected groups.

METHODS

A literature search was conducted in PubMed (the 15th of June 2018) and included articles published from December 2012 until mid-June 2018, this corresponds to the time period following the previous systematic review (8). The search included terms related to cancer, survival, children, and socioeconomic and sociodemographic factors (for details see **Supplementary Table 1**). Titles, abstracts and full-texts were screened for relevance by one of the authors (HM). *A priori* defined inclusion criteria were: non-ecological, original articles, conducted in high-income countries, that restricted analyses to childhood cancer of any type and assessed the association with at least one socioeconomic or sociodemographic factor in relation to overall survival, relative survival or event-free survival. Studies focusing on cancer types primarily affecting adults were excluded. Included individual measures of SES were parental education, parental income, parental occupation, parental cohabitation and marital status, place of residence, number of siblings and birth order. Also studies using area-based measures of SES were included. No restrictions on language were applied.

From all included studies information on setting, cancer diagnoses, study size and diagnostic period, source of identification of cancer cases, socioeconomic, and sociodemographic measurements of relevance, outcome of relevance, as well as main results of interest were extracted by one of the authors (HM). Also results of the association between specific social factors and survival, from each of the included studies, were extracted and included in tables by cancer type, most often in terms of hazard ratios (HR) and corresponding 95% confidence intervals (CI). Similar to the previous review in this field (8), no quantitative meta-analysis was considered due to the diversity of social factors included, but findings were summarized in a narrative synthesis.

RESULTS

Twenty-four of the 333 articles identified by the literature search met the inclusion criteria and were included in this review (**Table 1**). Exclusions were made based on titles (179 articles), abstracts (98 articles), and full-texts (32 articles), **Figure 1** shows the reasons for exclusion in a flow diagram. **Tables 2A**,**B** summarize the main results of the included studies.

All Diagnoses Combined

Combining all types of childhood cancer make the study population diverse but provides an overall pattern of potential inequalities. Four recent European register studies have looked at such associations. In Switzerland and Sweden, lower parental education was associated with higher mortality among children with cancer (5, 6), and a similar tendency was seen in Denmark (9). In Finland such an association was seen for the most recent years (7). An association between lower income and higher mortality was observed in Finland (7) and suggested in Denmark (9), but not found in Sweden (6). Furthermore, worse survival was observed for children with siblings, single parents, or poor living conditions (5, 9).

Hematological Malignancies

Hematological malignancies are the most common types of childhood cancer, and were also most frequently investigated regarding the association between SES and survival; 16 of the studies examined these diagnoses. In addition, one meta-analysis has been published (30), but due to its broader scope, the individual studies of relevance for this review will be discussed separately.

Various findings are reported regarding the association between parental SES and survival from hematological malignancies; while some studies found no association, others reported a gradient with lower survival among disadvantaged children, although the SES indicators of importance differed between studies. Overall, SES differences seemed to be less pronounced in hematological malignancies compared to childhood cancer overall. For leukemia and acute lymphoblastic leukemia (ALL), the associations with both parental education and income were inconclusive (5, 6, 12, 13). Disadvantaged

TABLE 1 | Description of included studies.

References	Setting	Included diagnoses	Study size and diagnostic period	Source of identification of cancer cases	Socioeconomic and sociodemographic measurements of relevance	Outcome of relevance
(9)	Denmark	All diagnoses combined; hematological malignancies– ALL, CNS tumors, non-CNS solid tumors	3,797 children, diagnosed <20 years old during 1990-2009	Danish cancer registry	Individual level: Maternal and paternal education, maternal income, parents' cohabitation status, and number of full siblings <19 years, based on registries	Overall survival
(5)	Switzerland	All diagnoses combined; leukemia-ALL, lymphoma, CNS tumors, bone and soft tissue tumors, embryonal tumors	1,602 children, diagnosed <16 years old during 1991– 2006	Swiss childhood cancer registry	Individual level: Maternal and paternal education, and living conditions (number of rooms per person, living space), based on census. Area-based: SES-index	5 year cumulative mortality
(6)	Sweden	All diagnoses combined; leukemia-ALL, tumors of the nervous system- brain tumors, lymphoma	4,723 children, diagnosed 1-14 years old during 1991–2010	Swedish cancer registry	Individual level: Parental education, and household income, based on registries	Overall survival, follow-up for maximum 10 years
(7)	Finland	All diagnoses combined; ALL and LBL, CNS tumors, all other malignant neoplasms	4,437 children diagnosed <20 years old during 1990–2009	Finnish cancer registry	Individual level: Combined parental income, highest parental education, maternal and paternal employment status, based on registers	Cause specific mortality (death from primary cancer) and childhood cancer specific survival, follow-up for maximum 5 years
(10)	Northern England	Leukemia; ALL, acute non-lymphocytic leukemia	1,007 children, diagnosed 0-14 years old during 1968-2010	Northern region young persons malignant disease registry	Individual level: Paternal occupational social class, based on birth certificate	Overall mortality
(11)	U.S	Hematologic malignancies, CNS tumors, solid tumors	36,337 children, diagnosed 0-19 years old during 1992–2011	SEER	Area-based: Poverty, education, unemployment, language isolation, foreign-born, and income, based on census	Death within one month of diagnosis
(12)	West Germany	ALL	647 children, diagnosed <15 years old during 1992–1994	German childhood cancer registry	Individual level: Maternal and paternal education, family income, and residential area, based on telephone interviews (response rate 82%)	Overall survival and event-free survival, follow-up for maximum 10 years
(13)	Greece	ALL, AML	994 children, diagnosed 0–14 years old during 1996–2010	Nationwide registry for childhood hematological malignancies	Individual level: Parental marital status, parental socioprofessional category, maternal education, number of children, place of living, and travel distance, based on questionnaires	Overall mortality
(14)	West Germany	ALL	647 children, diagnosed <15 years old during 1992–1994	The German childhood cancer registry	Individual level: Birth order, number of siblings, place of residence, based on questionnaires (response rate 82%)	Overall survival and event-free survival, follow-up for maximum 10 years
(15)	Canada	ALL	1,541 children diagnosed <18 years old during 1995–2011	Pediatric oncology group of ontario networked information system	Individual level: Rurality, distance from tertiary center Area-based: Neighborhood income, based on census	Event-free survival

(Continued)

TABLE 1 | Continued

References	Setting	Included diagnoses	Study size and diagnostic period	Source of identification of cancer cases	Socioeconomic and sociodemographic measurements of relevance	Outcome of relevance
(16)	California, U.S.	ALL	9,295 children diagnosed 0–19 years old during 1988–2011	California cancer registry	Area-based: Neighborhood SES, based on census	Overall survival
(17)	Texas & Florida, U.S.	ALL	4,719 children diagnosed 1–18 years old during 1995–2008	Florida cancer data system and the Texas cancer registry	Area-based: Neighborhood-level poverty rate, based on census	Overall survival
(18)	U.S.	ALL	8,516 children, diagnosed <19 years old during 1999–2009	Pediatric health information system	Area-based: ZIP-code based median household income, based on census	Inpatient mortality, death during the induction period. The children were followed from the first day of chemotherapy (in inpatient care) until maximum 60 days
(19)	U.S.	AML	3,651 children diagnosed 0–19 years old during 1973–2012	SEER	Area-based: SES factors and clusters constructed from 23 socioeconomic variables, based on census	Overall mortality
(20)	Denmark	Hematological malignancies; ALL, AML, non-Hodgkin lymphoma	1,819 children diagnosed <20 years old during 1973–2006	Danish cancer registry	Individual level: Birth order, number of full and half siblings, place of residence, based on registers	Overall survival, follow-up for maximum 10 years
(21)	Ontario, Canada	Lymphoma; Hodgkin lymphoma, non-Hodgkin lymphoma	692 children diagnosed 0–14 years old during 1985–2006	Pediatric oncology group of ontario networked information system database	Area-based: Neighborhood income and material deprivation, based on census	Overall survival and event-free survival
(22)	Denmark	CNS tumors; astrocytomas and other gliomas, embryonal CNS tumors	1,261 children diagnosed <20 years old during 1973–2006	Danish Cancer Registry	Individual level: Birth order, number of siblings, number of children living in the household, place of residence, parental cohabitation, maternal education, based on registries	Overall survival, follow-up for maximum 10 years
(23)	Texas, U.S.	Primary CNS solid tumors	2,421 children diagnosed <19 years during 1995 and 2009	Texas cancer registry	Individual level: Driving distance to cancer center Area-based: Block level SES index, based on census	Overall survival
(24)	Texas, U.S.	Non-CNS solid tumor	4,603 children diagnosed <19 years old during 1995-2009	Texas cancer registry	Individual level: Driving distance to cancer center Area-based: Block level SES index, based on census	Overall survival
(25)	Texas, U.S.	Melanoma	235 children diagnosed <19 years old during 1995–2009	Texas cancer registry	Individual level: Driving distance to cancer center Area-based: Block level SES index, based on census	Overall survival

(Continued)

TABLE 1 | Continued

References	Setting	Included diagnoses	Study size and diagnostic period	Source of identification of cancer cases	Socioeconomic and sociodemographic measurements of relevance	Outcome of relevance
(26)	Northern England	Renal tumors combined: Wilms tumors	209 patients (183 in SES analysis) diagnosed 0–24 years old during 1968–2012 Multivariate analyses are performed only among children diagnosed 0–14 years old with Wilms' tumor	Northern region young persons' malignant disease registry	Individual level: Paternal occupational social class based on birth certificate	Overall survival
(27)	U.S.	Well-differentiated thyroid cancer	9,585 children <22 years old from the register 1998–2012	National cancer database	Area-based: ZIP-code based median income and education, categorized by census data	Overall mortality
(28)	U.S.	Disseminated Langerhans cell histiocytosis	145 children diagnosed 0–19 years old during 2000–2009	SEER	Area-based: Crowding, educational attainment, poverty level, and rural/urban county, based on census	5 year relative survival
(29)	U.S.	Retinoblastoma	830 children 0–9 years old diagnosed 2000–2010	SEER	Area-based: County-level poverty, educational attainment, crowding, unemployment, immigration, language isolation, and SES-index, based on census	5 year relative survival

ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; CNS, Central nervous system; LBL, Lymphoblastic lymphoma; SEER, The Surveillance, Epidemiology, and End Results.

parental SES, based on occupation, was associated with worse leukemia and ALL survival (10, 13), while no pattern was detected when the association between parental employment and survival was assessed in Finland (7). However, two studies reported point estimates suggesting an opposite gradient between parental education and survival from leukemia (5) and ALL (13), but these results were imprecise and not consistent between maternal and paternal education (5). Based on area-level indicators of SES, worse ALL and AML survival among children from low SES areas was observed in the US (16, 17, 19), also when insurance status was controlled for (16), while no association with event-free survival in ALL was seen in Canada (15). For lymphoma, higher parental education was suggested to be associated with better survival (5, 6), while findings for area-based SES indicators are inconclusive (5, 21).

An association between a larger number of siblings or higher birth order, and poorer survival from subtypes of hematological malignancies was suggested by studies conducted in Denmark (9, 20), while those pattern were not seen in Germany or Greece (13, 14).

Two US studies have looked at mortality close to a diagnosis of a hematological malignancy (11) or ALL (18). While one study reported an increased risk of death within the first month for children from lower SES neighborhoods (11), the other found no association between area-based income and inpatient mortality during the first period of chemotherapy (18).

Tumors of the Nervous System

The association between parental SES and survival after tumors of the nervous system were examined in seven of the included studies. Three studies suggest lower mortality among children of higher educated parents (5–7), while others did not find similar associations (9, 22). Individually measured parental income was assessed in three of the studies and these did not detect any statistically significant associations (6, 7, 9). Studies on other individually measured SES indicators suggested lower mortality among children of cohabitating parents (9, 22), or better living conditions (5), while no association with the number of siblings or birth order was found (9, 22). In addition, results of area-based indicators pointed toward an association between lower SES and higher mortality; in Texas children with the lowest SES-index had a higher risk of advanced stage disease and worse overall survival, although these associations were diluted in adjusted analyses (23). Another study from the US reported an association between several markers of disadvantaged SES areas and a higher risk of early deaths in CNS tumors, in univariate analyses (11).

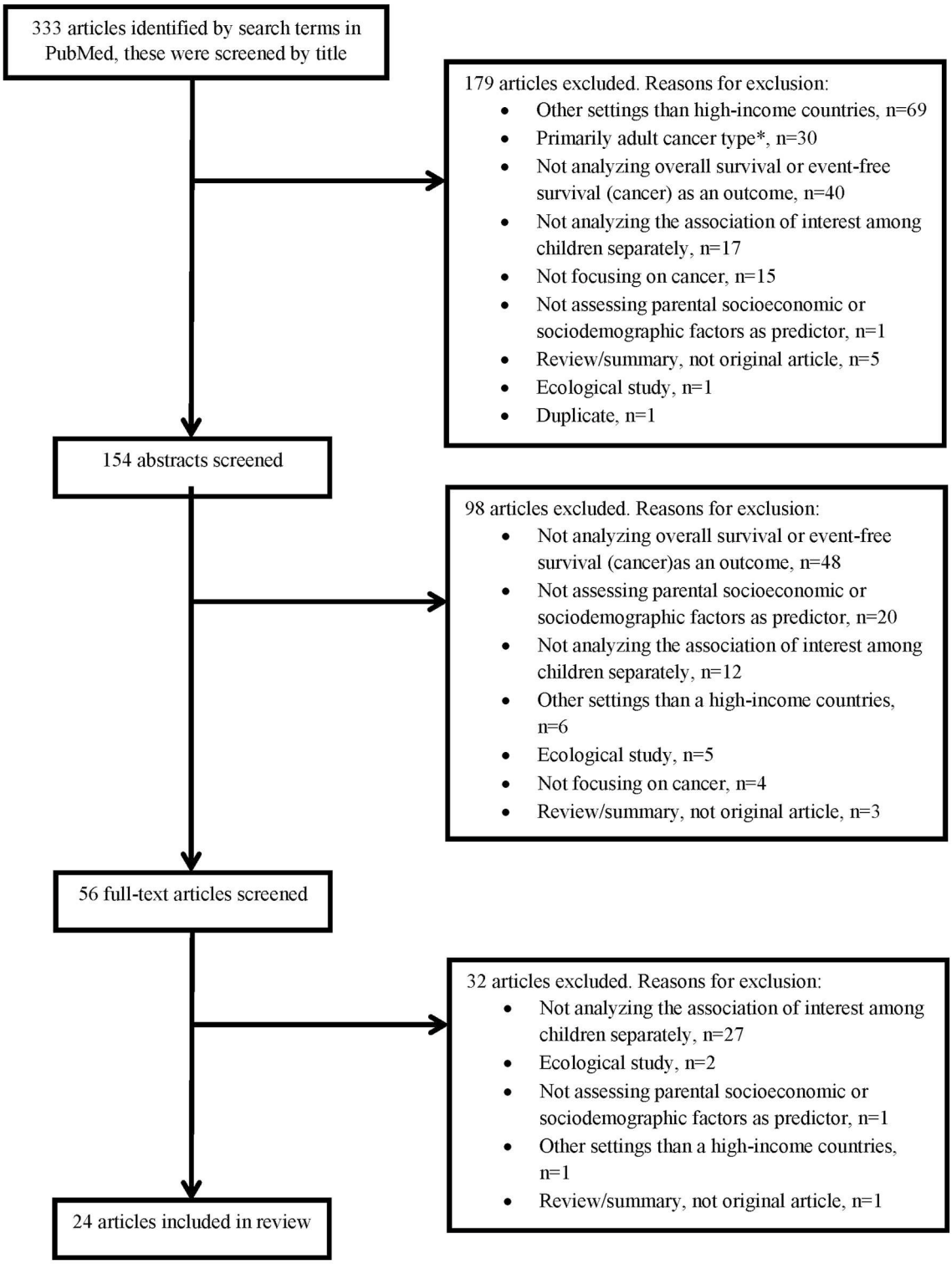

FIGURE 1 | Flow chart of title, abstract and full-text screening.

TABLE 2A | Main results of the included studies regarding the associations between socioeconomic factors and survival.

References	Education		Income		Employment/occupation		Area-based SES indicator	
		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)
ALL DIAGNOSES COMBINED								
(9)	**Maternal**		**Maternal, quartiles**					
	Basic	1 (ref)	1st (lowest)	1 (ref)				
	Vocational	0.93 (0.75–1.15)	2nd	1.01 (0.84–1.21)				
	Higher	0.88 (0.69–1.13)	3rd	0.92 (0.75–1.14)				
	Unknown	1.05 (0.74–1.49)	4th	0.84 (0.66–1.08)				
	Paternal							
	Basic	1 (ref)						
	Vocational	0.90 (0.74–1.10)						
	Higher	0.89 (0.70–1.13)						
	Unknown	1.05 (0.75–1.46)						
(5)	**Maternal**						**SES index, tertiles**	
	Compulsory	1 (ref)					Lower	1 (ref)
	Secondary	0.81 (0.65–1.02)					Medium	0.93 (0.71–1.20)
	Tertiary	0.67 (0.45–0.98)					Upper	0.95 (0.73–1.24)
	Paternal							
	Compulsory	1 (ref)						
	Secondary	0.85 (0.64–1.11)						
	Tertiary	0.72 (0.53–0.98)						
(6)	**Parental**		**Household, quartiles**					
	Postsecondary	1 (ref)	4th (highest)	1 (ref)				
	Upper secondary	1.17 (1.00–1.38)	3rd	0.85 (0.69–1.04)				
	Compulsory or less	1.28 (1.03–1.59)	2nd	0.96 (0.79–1.18)				
			1st	1.03 (0.85–1.26)				
(7)	**Parental**		**Combined parental, quartiles**		**Maternal employment status**			
	Primary or less	1 (ref)	1st (lowest)	1 (ref)	Employed	1 (ref)		
	Secondary	1.00 (0.79–1.27)	2nd	0.83 (0.63–1.09)	Unemployed	0.84 (0.64–1.09)		
	Post-secondary	0.84 (0.66–1.06)	3rd	0.76 (0.58–1.00)	Student	1.39 (0.98–1.98)		
			4th	0.68 (0.52–0.89)	Pensioner	0.91 (0.51–1.62)		
			Information missing	0.93 (0.61–1.41)	Other non-working	1.10 (0.90–1.35)		
			Structural missing	0.78 (0.53–1.15)	Information missing	1.61 (0.98–2.66)		
					Paternal employment status			
					Employed	1 (ref)		
					Unemployed	1.14 (0.89–1.47)		
					Student	1.31 (0.80–2.15)		
					Pensioner	1.00 (0.65–1.54)		
					Other non-working	1.41 (0.87–2.29)		
					Information missing	1.26 (0.91–1.75)		

(Continued)

TABLE 2A | Continued

References	Education		Income		Employment/occupation		Area-based SES indicator	
		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)
HEMATOLOGICAL CANCERS								
(9)	**Maternal**	**Maternal, quartiles**						
	Basic	1 (ref)	1st (lowest)	1 (ref)				
	Vocational	1.05 (0.71–1.56)	2nd	1.17 (0.85–1.60)				
	Higher	1.10 (0.70–1.73)	3rd	0.81 (0.55–1.20)				
	Unknown	1.00 (0.54–1.86)	4th	0.82 (0.53–1.28)				
	Paternal							
	Basic	1 (ref)						
	Vocational	1.14 (0.78–1.66)						
	Higher	0.95 (0.60–1.50)						
	Unknown	1.94 (1.07–3.49)						
(11)							**Education[b]**	
							Univariate	
							Advantaged	1 (ref)
							Disadvantaged	1.43 (1.12–1.83)
							Income[b]	
							Univariate	
							Advantaged	1 (ref)
							Disadvantaged	1.66 (1.30–2.12)
							Adjusted	
							Advantaged	1 (ref)
							Disadvantaged	1.51 (1.07–2.14)
LEUKEMIA								
(5)	**Maternal**						**SES index, tertiles**	
	Compulsory	1 (ref)					Lower	1 (ref)
	Secondary	1.06 (0.69–1.61)					Medium	0.90 (0.56–1.42)
	Tertiary	1.05 (0.58–1.91)					Upper	1.06 (0.66–1.71)
	Paternal							
	Compulsory	1 (ref)						
	Secondary	1.39 (0.81–2.38)						
	Tertiary	1.45 (0.82–2.58)						
(6)	**Parental**		**Household, quartiles**					
	Postsecondary	1 (ref)	4th (highest)	1 (ref)				
	Upper secondary	1.28 (0.95–1.74)	3rd	1.05 (0.72–1.53)				
	Compulsory or less	1.39 (0.93–2.08)	2nd	1.06 (0.72–1.56)				
			1st	1.22 (0.83–1.78)				
(10)					**Paternal social class based on occupation**			
					I/II (most advantaged)	1 (ref)		
					IIIN/M	1.66 (1.20–2.29)		
					IV/V	1.96 (1.35–2.86)		

(Continued)

TABLE 2A | Continued

References	Education		Income		Employment/occupation		Area-based SES indicator
		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)	HR[a] (95% CI)
ALL and LBL							
(7)	**Parental**		**Combined parental, quartiles**		**Maternal employment status**		
	Primary or less	1 (ref)	1st (lowest)	1 (ref)	Employed	1 (ref)	
	Secondary	1.12 (0.66–1.88)	2nd	0.91 (0.49–1.71)	Unemployed	0.66 (0.35–1.28)	
	Post-secondary	0.82 (0.48–1.40)	3rd	0.76 (0.40–1.44)	Student	2.02 (0.88–4.64)	
			4th	0.86 (0.47–1.57)	Pensioner	0.50 (0.07–3.58)	
			Information missing	0.60 (0.18–2.08)	Other non-working	1.24 (0.82–1.89)	
			Structural missing	1.08 (0.45–2.60)	Information missing	1.72 (0.54–5.50)	
					Paternal employment status		
					Employed	1 (ref)	
					Unemployed	1.43 (0.85–2.42)	
					Student	0.85 (0.21–3.46)	
					Pensioner	0.81 (0.26–2.59)	
					Other non-working	1.20 (0.38–3.80)	
					Information missing	1.13 (0.50–2.58)	
ALL							
(6)	**Parental**		**Household, quartiles**				
	Postsecondary	1 (ref)	4th (highest)	1 (ref)			
	Upper secondary	1.26 (0.86–1.87)	3rd	1.20 (0.74–1.94)			
	Compulsory or less	0.98 (0.55–1.74)	2nd	0.95 (0.57–1.59)			
			1st	1.24 (0.76–2.04)			
(10)					**Paternal social class based on occupation**		
					I/II (most advantaged)	1 (ref)	
					IIIN/M	1.68 (1.20–2.36)	
					IV/V	1.86 (1.24–2.77)	
(12)	**Maternal**		**Family**				
	No degree	1.07 (0.38–3.04)	<2,000 DM	1.21 (0.60–2.44)			
	Low degree	1 (ref)	2,000–4,000 DM	1 (ref)			
	Intermediate degree	0.69 (0.41–1.17)	4,000–6,000 DM	0.80 (0.47–1.38)			
	High degree	0.92 (0.52–1.62)	6,000–8,000 DM	1.27 (0.52–3.06)			
			>8,000 DM	1.11 (0.37–3.29)			
(13)	**Maternal**				**Parental socioprofessional category**		
	Four categories, per increase of one level	1.11 (0.90–1.37)			Three categories, per increase of one level	0.71 (0.54-0.94)	

(Continued)

TABLE 2A | Continued

References	Education		Income		Employment/occupation		Area-based SES indicator	
	HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)	
(15)							**Neighborhood median income, quintiles**	
							1st (lowest)	Ref
							2nd	0.93 (0.62–1.40)
							3rd	1.03 (0.69–1.54)
							4th	1.09 (0.74–1.62)
							5th	1.09 (0.72–1.64)
(16)							**Neighborhood SES, quintiles**	
							1st (lowest 20%)	1.39 (1.18–1.64)
							2nd	1.15 (0.97–1.35)
							3rd	1.13 (0.95–1.33)
							4th	1.17 (0.99–1.39)
							5th	1 (ref)
(17)							**Neighborhood-level poverty rate (% of households living in poverty)**	
							0-<5	1 (ref)
							5-<20	1.29 (1.03–1.61)
							20–100	1.80 (1.41–2.30)
(18)							**Median household income based on ZIP-code**	
							Univariate	
							For every $10,000/year increase	0.95 (0.84–1.07)
AML								
(10)					**Paternal social class based on occupation**			
					Unadjusted			
					I/II (most advantaged)	1 (ref)		
					IIIN/M	1.47 (0.57–3.80)		
					IV/V	2.05 (0.77–5.44)		
(13)	**Maternal**				**Parental socioprofessional category**			
	Four categories, per increase of one level	0.99 (0.65-1.52)			Three categories, per increase of one level	0.89 (0.49-1.62)		
(19)							**SES factors and clusters**	
							One unit increase in the average score of each factor	
							Factor 1 (economic and educational disadvantage)	1.07 (1.02–1.12)
							Factor 2 (immigration)	0.99 (0.94–1.04)

(Continued)

TABLE 2A | Continued

References	Education		Income		Employment/occupation	Area-based SES indicator	
		HR[a] (95% CI)		HR[a] (95% CI)	HR[a] (95% CI)		HR[a] (95% CI)
						Factor 3 (housing instability)	1.05 (1.00–1.10)
						Factor 4 (low rates of moving within the state)	0.98 (0.93–1.03)
						Clusters were formed based on factors and compared. Lowest AML mortality was seen in Cluster 1 which reflected low Factor 1, 2, & 3.	
LYMPHOMA							
(5)	**Maternal**					**SES index, tertiles**	
	Compulsory	1 (ref)				Lower	1 (ref)
	Secondary	0.71 (0.30–1.66)				Medium	1.09 (0.38–3.09)
	Tertiary	0.40 (0.05–3.19)				Upper	1.51 (0.55–4.16)
	Paternal						
	Compulsory	1 (ref)					
	Secondary	0.40 (0.16–1.02)					
	Tertiary	0.26 (0.08–0.85)					
(6)	**Parental**		**Household, quartiles**				
	Postsecondary	1 (ref)	4th (highest)	1 (ref)			
	Upper secondary	1.35 (0.69–2.64)	3rd	0.67 (0.28–1.56)			
	Compulsory or less	1.13 (0.46–2.77)	2nd	1.36 (0.63–2.94)			
			1st	1.37 (0.62–3.02)			
(21)						**Material deprivation, quintiles**	
						Hodgkin lymphoma	
						1st	0.63 (0.13–3.17)
						2nd	1.16 (0.38–3.52)
						3rd	1.41 (0.52–3.83)
						4th	0.99 (0.30–3.27)
						5th (least deprived)	1 (ref)
						Non-hodgkin lymphoma	
						1st	1.26 (0.49–3.24)
						2nd	1.45 (0.57–3.68)
						3rd	1.37 (0.57–3.29)
						4th	2.33 (1.03–5.30)
						5th (least deprived)	1 (ref)
CNS TUMORS/TUMORS OF THE NERVOUS SYSTEM							
(9)	**Maternal**		**Maternal, quartiles**				
	Basic	1 (ref)	1st (lowest)	1			
	Vocational	1.20 (0.79–1.82)	2nd	0.92 (0.66–1.28)			
	Higher	1.17 (0.73–1.89)	3rd	0.84 (0.58–1.22)			
	Unknown	1.42 (0.73–2.78)	4th	0.86 (0.55–1.34)			

(Continued)

TABLE 2A | Continued

References	Education		Income		Employment/occupation		Area-based SES indicator	
		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)
	Paternal							
	Basic	1 (ref)						
	Vocational	0.82 (0.58–1.17)						
	Higher	0.89 (0.58–1.36)						
	Unknown	0.73 (0.39–1.36)						
(5)	**Maternal**						**SES index, tertiles**	
	Compulsory	1 (ref)					Lower	1 (ref)
	Secondary	0.59 (0.39–0.90)					Medium	0.70 (0.43–1.15)
	Tertiary	0.52 (0.26–1.05)					Upper	0.71 (0.44–1.15)
	Paternal							
	Compulsory	1 (ref)						
	Secondary	0.62 (0.38–1.01)						
	Tertiary	0.48 (0.28–0.81)						
(6)	**Parental**		**Household, quartiles**					
	Postsecondary	1 (ref)	4th (highest)	1 (ref)				
	Upper secondary	0.99 (0.77–1.26)	3rd	0.78 (0.57–1.07)				
	Compulsory or less	1.25 (0.90–1.73)	2nd	0.87 (0.64–1.19)				
			1st	1.07 (0.79–1.43)				
(7)	**Parental**		**Combined parental, quartiles**		**Maternal employment status**			
	Primary or less	1 (ref)	1st (lowest)	1 (ref)	Employed	1 (ref)		
	Secondary	0.75 (0.48–1.17)	2nd	0.62 (0.35–1.07)	Unemployed	0.77 (0.45–1.32)		
	Post-secondary	0.69 (0.44–1.08)	3rd	0.92 (0.54–1.55)	Student	1.47 (0.81–2.67)		
			4th	0.69 (0.40–1.18)	Pensioner	0.97 (0.31–3.06)		
			Information missing	1.16 (0.51–2.63)	Other non-working	0.98 (0.67–1.43)		
			Structural missing	0.56 (0.25–1.28)	Information missing	1.70 (0.54–5.38)		
					Paternal employment status			
					Employed	1 (ref)		
					Unemployed	1.01 (0.61–1.67)		
					Student	1.34 (0.59–3.04)		
					Pensioner	1.10 (0.48–2.52)		
					Other non-working	2.11 (0.86–5.16)		
					Information missing	1.38 (0.70–2.72)		
(11)							**Education[b]**	
								Univariate
							Advantaged	1 (ref)
							Disadvantaged	1.30 (0.94–1.79)
							Income[b]	
								Univariate
							Advantaged	1 (ref)
							Disadvantaged	1.19 (0.87–1.65)
(22)	**Maternal**							
	Short	0.91 (0.68–1.23)						
	Medium	1.10 (0.87–1.39)						
	Higher	1 (ref)						

(Continued)

TABLE 2A | Continued

References	Education		Income		Employment/occupation		Area-based SES indicator	
		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)		HR[a] (95% CI)
(23)							**SES index, quartiles**	
							<25%	1.13 (0.90–1.43)
							25–50%	1.17 (0.93–1.48)
							51–75%	0.97 (0.77–1.22)
							>75%	1 (ref)
OTHER TUMORS								
(9)	**Maternal**		**Maternal, quartiles**					
	Basic	1 (ref)	1st (lowest)	1 (ref)				
	Vocational	0.79 (0.56–1.11)	2nd	0.88 (0.65–1.20)				
	Higher	0.66 (0.44–0.99)	3rd	1.11 (0.80–1.55)				
	Unknown	0.88 (0.48–1.63)	4th	0.81 (0.53–1.24)				
	Paternal							
	Basic	1 (ref)						
	Vocational	0.81 (0.59–1.11)						
	Higher	0.97 (0.65–1.43)						
	Unknown	0.87 (0.45–1.54)						
(11)							**Education[b]**	
							Univariate	
							Advantaged	1 (ref)
							Disadvantaged	1.05 (0.73-1.49)
							Income[b]	
							Univariate	
							Advantaged	1 (ref)
							Disadvantaged	1.20 (0.84-1.71)
(24)							**SES index, quartiles**	
							<25%	1.1 (0.9–1.3)
							25–50%	1.0 (0.8–1.2)
							50–75%	1.0 (0.8–1.2)
							>75%	1 (ref)
(25)							**SES index, quartiles**	
							<=25%	2.8 (0.8-9.6)
							26–50%	1.6 (0.4-6.3)
							51–75%	0.9 (0.3-3.6)
							>75%	1 (ref)
(26)					**Paternal social class based on occupation**			
					Renal tumors (age 0–24), univariate			
					I/II (most affluent)	1 (ref)		
					IIIN/M	1.18 (0.60–2.30)		
					IV/V	1.17 (0.53–2.62)		
					Wilms' tumor (age 0-14), multivariate			
					I/II (most affluent)	1 (ref)		
					IIIN/M	1.12 (0.48–2.59)		
					IV/V	1.47 (0.55–3.91)		

(Continued)

TABLE 2A | Continued

References	Education	Income	Employment/occupation	Area-based SES indicator
	HR[a] (95% CI)	HR[a] (95% CI)	HR[a] (95% CI)	HR[a] (95% CI)
(27)				**Median income and education, quartiles** No estimates reported. Overall survival curves show no statistical significant differences between the groups.
(28)				*5 year relative survival rates (%)* **Percent low educated[b]** <=16.6: 97.0 (78.0–99.6) >16.6: 87.8 (79.1–93.0) (*p*-value 0.156) **Percent below poverty level[b]** <=8.85: 94.3 (85.0–97.9) >8.85: 85.6 (73.7–92.3) (*p*-value 0.123)
(29)				*5 year relative survival rates (%)* **Poverty level[b]** Low: 98.8 High: 96.4 (*p*-value 0.054) **Education level[b]** High: 98.5 Low: 96.8 (*p*-value 0.154) **Socioeconomic index[b]** Low: 98.9 High (more disadvantages counties): 96.5 (*p*-value 0.070)

[a]*Adjusted results if not otherwise stated. RR instead of HR is presented in some studies.*

[b]*Several area-based indicators were reported in the study but only measures corresponding to education, income and SES index are included in this table*

ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; CI, Confidence interval; CNS, Central nervous system; HR, Hazard ratio; LBL, Lymphoblastic lymphoma; SEER, The Surveillance, Epidemiology, and End Results.

However, only poverty was included in the final adjusted model and the risk estimate was not reported (11).

Other Tumors

This section summarizes the findings for very diverse tumor types. Three studies investigated non-CNS solid tumors combined; a pattern of higher mortality among children of mothers with lower education was suggested (9), however, other indicators such as income and area-based SES-index did not show associations with mortality (9, 11, 24). Five of the studies were of small size or focused on cancer types with a very good survival which is reflected in the imprecise estimates and lack of statistical power (26–29). However, the point estimates in the majority of these studies were in the direction of lower survival among children of lower SES.

DISCUSSION

Findings of the 24 reviewed studies are diverse; some studies found no associations between socioeconomic or sociodemographic factors and survival while several indicated a social gradient with higher mortality among children from families of lower SES. When comparing the association within different cancer types, there is no clear suggestion of a particularly vulnerable subgroup, but hematological malignancies were most frequently investigated. Different indicators of SES appeared to be of importance in the studies which may indicate underlying mechanisms that vary between cancer types and health-care contexts, but can also be a result of diverse methodology, bias or random variation.

It has been acknowledged previously that different measurements of SES should not be understood as proxies for each other but instead they might have associations with

TABLE 2B | Main results of the included studies regarding the associations between sociodemographic factors and survival.

References	Siblings and birth order		Place of residence		Parental cohabitation/ marital status		Other individual based indicators	
	HR* (95% CI)		HR* (95% CI)		HR* (95% CI)		HR* (95% CI)	
ALL DIAGNOSES COMBINED								
(9)	**Number of full siblings <19 years**				**Cohabitation status**			
	0	1 (ref)			Alone	1 (ref)		
	1	1.12 (0.95–1.31)			Together	0.82 (0.69–0.99)		
	=>2	1.26 (1.03–1.53)						
(5)							**Rooms per person**	
							<1	1 (ref)
							1–1.25	0.76 (0.59–0.98)
							>1.25	0.80 (0.62–1.04)
							Living space, tertiles	
							Lower	1 (ref)
							Medium	0.78 (0.60–1.02)
							Upper	0.78 (0.60–1.03)
HEMATOLOGICAL CANCERS								
(9)	**Number of full siblings <19 years**				**Cohabitation status**			
	0	1 (ref)			Alone	1 (ref)		
	1	1.08 (0.81–1.44)			Together	0.92 (0.66–1.29)		
	=>2	1.18 (0.83–1.69)						
LEUKEMIA								
(5)							**Rooms per person**	
							<1	1 (ref)
							1–1.25	0.89 (0.55–1.43)
							>1.25	1.19 (0.76–1.87)
							Living space, tertiles	
							Lower	1 (ref)
							Medium	0.97 (0.59–1.58)
							Upper	1.01 (0.62–1.63)
ALL								
(12)			**Residential area**					
			Urban	1 (ref)				
			Mixed	1.16 (0.71-1.91)				
			Rural	0.88 (0.50–1.55)				
(13)	**Number of children**		**Place of living**		**Marital status**			
	Per increase of one child	0.99 (0.80–1.25)	Rural	1.08 (0.69–1.70)	Married	0.47 (0.27–0.83)		
			Semiurban	1.16 (0.74–1.81)	Other	1 (ref)		
			Urban	1 (ref)				
			Travel distance (km) to hospital					
			<50	1 (ref)				
			50–249	1.29 (0.80–2.10)				
			250+	1.24 (0.82–1.87)				

(Continued)

TABLE 2B | Continued

References	Siblings and birth order		Place of residence		Parental cohabitation/ marital status		Other individual based indicators
		HR* (95% CI)		HR* (95% CI)		HR* (95% CI)	HR* (95% CI)
(14)	**Birth order**		**Place of residence**				
	1st	1 (ref)	Urban	1 (ref)			
	2nd	0.64 (0.37–1.10)	Mixed	1.12 (0.69–1.84)			
	3rd and later	1.04 (0.55–1.95)	Rural	0.85 (0.49–1.49)			
	Number of siblings						
	0	1 (ref)					
	1	0.86 (0.48–1.52)					
	2	0.83 (0.42–1.67)					
	=>3	1.58 (0.73–3.44)					
(15)			**Distance from tertiary center**				
				Univariate			
			Short	1 (ref)			
			Long	1.05 (0.79–1.38)			
			Rurality				
			Rurality				
				Univariate			
			Urban	1 (ref)			
			Rural	1.15 (0.80–1.64)			
(20)	**Birth order**		**Place of residence**				
	1st	1 (ref)	Greater Copenhagen area	1 (ref)			
	2nd	1.05 (0.78–1.42)	Provincial cities	1.18 (0.88–1.59)			
	3rd	1.27 (0.85–1.89)	Rural areas	1.24 (0.81–1.91)			
	4th and later	1.62 (0.85–3.09)	Peripheral rural areas	1.15 (0.55–2.40)			
	Full siblings						
	0	1 (ref)					
	1	1.05 (0.76–1.46)					
	2	1.19 (0.80–1.77)					
	=>3	1.31 (0.83–2.08)					
	Full and half siblings						
	0	1 (ref)					
	1	1.05 (0.71–1.55)					
	2	1.28 (0.82–1.98)					
	=>3	1.25 (0.76–2.05)					
AML							
(13)	**Number of children**		**Place of living**		**Marital status**		
	Per increase of one child	1.07 (0.69–1.66)	Rural	1.08 (0.48–2.46)	Married	0.83 (0.23–2.94)	
			Semiurban	0.52 (0.22–1.24)	Other	1 (ref)	
			Urban	1 (ref)			
			Travel distance (km) to hospital				
			<50	1 (ref)			
			50–249	0.84 (0.34–2.07)			
			250+	1.06 (0.48–2.31)			

(Continued)

TABLE 2B | Continued

References	Siblings and birth order		Place of residence		Parental cohabitation/ marital status	Other individual based indicators	
		HR* (95% CI)		HR* (95% CI)	HR* (95% CI)		HR* (95% CI)
(20)	**Birth order**		**Place of residence**				
	1st	1 (ref)	Greater Copenhagen area	1 (ref)			
	2nd	1.62 (1.01–2.59)	Provincial cities:	0.87 (0.54–1.40)			
	3rd	2.22 (1.13–4.34)	Rural areas	0.83 (0.45–1.55)			
	4th and later	5.76 (2.01–16.51)	Peripheral rural areas	0.54 (0.18–1.63)			
	Full siblings						
	0	1 (ref)					
	1	1.11 (0.65–1.90)					
	2	1.09 (0.59–2.00)					
	=>3	2.27 (0.92–5.58)					
	Full and half siblings						
	0	1 (ref)					
	1	1.48 (0.79–2.75)					
	2	1.34 (0.67–2.67)					
	=>3	2.69 (1.11–6.52)					
LYMPHOMA							
(5)						**Rooms per person**	
						<1	1 (ref)
						1–1.25	0.88 (0.35–2.23)
						>1.25	0.35 (0.12–1.06)
						Living space, tertiles	
						Lower	1 (ref)
						Medium	0.61 (0.22–1.70)
						Upper	0.31 (0.08–1.11)
(20)	**Birth order**		**Place of residence**				
	1st	1 (ref)	Greater Copenhagen area	1 (ref)			
	2nd	0.97 (0.49–1.94)	Provincial cities	0.82 (0.41–1.63)			
	3rd	1.18 (0.41–3.40)	Rural areas	1.03 (0.38–2.78)			
	4th and later	1.00 (0.20–5.11)	Peripheral rural areas	1.09 (0.23–5.17)			
	Full siblings						
	0	1 (ref)					
	1	1.06 (0.44–2.59)					
	2	2.26 (0.88–5.79)					
	=>3	0.91 (0.26–3.20)					
	Full and half siblings						
	0	1 (ref)					
	1	2.51 (0.63–9.92)					
	2	5.25 (1.40–19.70)					
	=>3	3.87 (0.92–16.31)					

(Continued)

TABLE 2B | Continued

References	Siblings and birth order		Place of residence		Parental cohabitation/ marital status		Other individual based indicators	
	HR* (95% CI)		HR* (95% CI)		HR* (95% CI)		HR* (95% CI)	
CNS TUMORS/TUMORS OF THE NERVOUS SYSTEM								
(9)	**Number of full siblings <19 years**				**Cohabitation status**			
	0	1 (ref)			Alone	1		
	1	0.89 (0.67–1.18)			Together	0.70 (0.51–0.97)		
	=>2	1.03 (0.72–1.48)						
(5)							**Rooms per person**	
							<1	1 (ref)
							1–1.25	0.61 (0.39–0.97)
							>1.25	0.56 (0.34–0.92)
							Living space, tertiles	
							Lower	1 (ref)
							Medium	0.71 (0.43–1.17)
							Upper	0.61 (0.37–1.01)
(22)	**Birth order**		**Place of residence at diagnosis**		**Cohabitation status**			
	1st	1.0 (ref)	Greater Copenhagen area	1.0 (ref)	Living together	1 (ref)		
	2nd	0.97 (0.78–1.21)	Provincial cities	1.23 (0.98–1.56)	Living not together	1.07 (0.85–1.36)		
	3rd and later	1.00 (0.75–1.32)	Rural areas	1.38 (1.00–1.90)				
	Full siblings		Peripheral rural areas	1.17 (0.63–2.18)				
	0	1.0 (Ref)						
	1	1.12 (0.88–1.42)						
	2	0.98 (0.73–1.31)						
	=>3	0.87 (0.57–1.32)						
	Children living in the household							
	1	1.0 (Ref)						
	2	1.18 (0.91–1.52)						
	=>3	1.07 (0.79–1.44)						
(23)			**Driving distance to cancer center (miles)**					
			0–25	1 (ref)				
			26–50	0.97 (0.78–1.20)				
			>50	0.91 (0.76–1.11)				
OTHER TUMORS								
(9)	**Number of full siblings <19 years**				**Cohabitation status**			
	0	1 (ref)			Alone	1 (ref)		
	1	1.45 (1.11–1.89)			Together	0.80 (0.59–1.08)		
	=>2	1.29 (0.93–1.79)						

(Continued)

TABLE 2B | Continued

References	Siblings and birth order	Place of residence	Parental cohabitation/ marital status	Other individual based indicators
	HR* (95% CI)	HR* (95% CI)	HR* (95% CI)	HR* (95% CI)
(24)		**Driving distance to cancer center (miles)**		
		<25 1 (ref)		
		25–50 1.1 (1.0–1.3)		
		>50 1.1 (1.0–1.3)		
(25)		**Driving distance to cancer center (miles)**		
		Univariate		
		<25 1 (ref)		
		25–49 0.6 (0.2–1.9)		
		>=50 0.7 (0.2–2.0)		

*Adjusted results if not otherwise stated. RR instead of HR is presented in some studies.
ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; CI, Confidence interval; CNS, Central nervous system; HR, Hazard ratio.

health outcomes through different mechanisms (31). While income would indicate that economic resources of the family are of importance, education may reflect health literacy. However, our diverse findings do not clearly suggest a specific SES indicator of particular importance for childhood cancer survival. Parental education was more frequently investigated than income and also showed somewhat stronger associations; most often children of parents with lower education experienced higher mortality, however, there were also some findings pointing in the opposite direction but these were not statistically significant and not consistent. Only one study reported a statistically significant association between lower income and poorer survival (7), but point estimates in the other studies either pointed in the same direction, or were around the null value. These findings are very similar to the previous review by Gupta et al. (8).

Potential Mechanisms

The finding of poorer survival among children with lower parental SES requires further attention. Understanding the underlying mechanisms is the basis for any strategy to reduce health inequalities, but is a challenge since they likely differ between health-care setting and also childhood cancer types. Most studies focused on leukemia, and especially ALL, which does not necessarily reflect a particularly strong hypothesis connecting parental SES to survival from this cancer type, but might be the result of difficulties with statistical power in studies including more rare diagnoses. In fact, one of the studies found the strongest association for CNS tumors (5). A reason for this might be that, compared to leukemia, a low proportion of children with CNS tumors are treated within international standardized protocols in Switzerland (5). With less standardized protocols, there might be more room for influence from parents from higher SES, for example for referrals or second opinions, although this hypothesis has not yet been examined (5).

Another suggested mechanism is related to differences in how parents manage treatment adherence. The treatment of childhood cancer differs substantially between diagnoses, and the treatment strongly influences if the child will stay in hospital or at home. For example, treatment of ALL is long and a substantial part takes place at home where parents are usually responsible for the oral administration of drugs, see Lightfoot et al. (4) for a visualization. The results from the study by Lightfoot et al. demonstrated that SES differences in survival emerged during this period (4), which suggests that treatment adherence may be involved. This hypothesis is supported by other studies suggesting that higher SES, measured by different indicators, are associated with better treatment compliance (32–34), and compliance is of importance for treatment results in children with ALL (34, 35). In addition, when only inpatient mortality during induction chemotherapy was compared between children with ALL of different area-based income levels, no differences were observed (18). If parental responsibility for adherence to treatment was the main explanation of SES differences in survival, one would not expect any differences in mortality during inpatient treatment. With this reasoning one would also expect survival differences in ALL to be more pronounced compared to survival differences in AML, since AML is mainly treated within hospitals; however, included studies provide insufficient data to evaluate this hypothesis.

Not only have socioeconomic differences in childhood cancer survival been observed after a period of time, but also within the first month (11), and during the first year (6) after diagnosis. Possibly, early SES differences reflect differences in disease severity at diagnosis. Some of the studies have adjusted for this, but an association between SES and survival was still found (5, 10). When a potential association between SES and stage, or disease severity, at diagnosis has been assessed, some studies found no or very weak associations (10, 21, 23, 24, 26), while others indicated that children of lower SES may be more likely to have advanced disease (25, 27, 29).

Another potential explanation for socioeconomic survival differences might be related to differences in incidence of

subtypes of cancers with different prognosis. Few of the studies have taken detailed subtype into account. However, Erdmann et al. (12) conducted a sensitivity analysis including only B-lineage ALL which resulted in similar conclusions as for all immunophenotypes of ALL combined, and Adam et al. (5) adjusted for histopathological group in their analysis of CNS tumors, which did not change their results.

Methodology of Reviewed Studies

Several of the reviewed studies used register-based information which limits the risk of bias from non-participation and loss to follow-up. Most of the studies have identified their study population from cancer registers which also have been used by the International Agency for Research on Cancer for estimating cancer incidence (36, 37). Even if high registry coverage is even more important in incidence estimations, it is also important when assessing the association between social factors and survival. If the likelihood of being included in a study is associated with both SES and survival, biased results are obtained. However, such bias is not likely to have affected the conclusion of this review.

The source of information regarding social factors differed between studies, for example registers, birth certificates or questionnaires. One important aspect is, however, the temporality. Since a child's cancer diagnosis can affect some of the social factors, for example income, it is important that this information is collected before the diagnosis. All but one of the studies including individual measures of income assessed this before the child's cancer diagnosis. Income information in the study by Erdmann et al. (12) is based on interviews conducted within 2 years after a diagnosis, however, no association between family income and survival was found in this study. When area-based information is used, temporality is not that crucial since the child's diagnosis does not affect the income level in the neighborhood.

A general limitation with register-based studies is that they often are limited in terms of information on relevant confounders and mediators, such as severity of disease, treatment and adherence. As a result, several of the above discussed mechanisms are suggested but few are examined. Moreover, the choice of included SES indicators was seldom motivated in the reviewed studies.

Statistical power is weak in several of the studies, which reflects that the effect sizes are not very large, the overall prognosis is good and childhood cancer is rare. Different cancer types need to be considered separately due to diverse treatments and prognosis, however, this also decrease statistical power and studies on rare cancer types may not be able to detect potential socioeconomic differences. Of these reasons it is important to look at the direction and consistency of findings rather than only statistical significance. This is also important when interpreting the results of studies using area-based indicators of SES. As previously acknowledged, e.g., (10, 15), using area-based measures of SES as proxies for individual measurements can lead to ecological fallacy, a non-differential exposure misclassification which might dilute an association should one exist.

Time period of diagnosis differed greatly between studies. Studies focusing on recent periods have lower statistical power due to limited number of included children and increased survival rates. However, the association between parental SES and survival may have changed with calendar time; e.g., Njoku et al. (10) included children diagnosed 1968-2010 and showed a tendency of less SES differences during the latest years. However, focusing on more recent time periods, Tolkkinen et al. (7) found differences in survival according to parental education primarily in children diagnosed during 2000–2009, compared to in the 1990's.

Another time aspect is the differences in follow-up time between the included studies. While a few studies assessed mortality closely after the cancer diagnosis, most of the studies focused on mortality up to 5 or 10 years. Comparisons between these two types of studies should be done with caution since the mechanisms behind potential SES differences in mortality directly at time of diagnosis and several years after are probably very different.

Strengths and Limitations

This review was based on an extensive literature search and includes studies of several indicators of SES and their associations with survival from different types of childhood cancer. The search strategy and study selection are described in detail to ensure reproducibility. Moreover, descriptions of included studies and relevant results are shown in detail to visualize the diversity. Since the choice of SES indicators, definition of study population, and adjustment variables differed to such extent between studies a comparison of effect estimates is hampered (8).

Some limitations with this review need to be acknowledged. Only one data source (PubMed) was used to identify studies; potential articles searchable only in databases other than PubMed are therefore not included. However, in the field of childhood cancer epidemiology we find it unlikely that significant articles are not identified in PubMed. Another limitation is that no formal bias assessment was performed. However, the methodology of included studies are described in **Table 1** for transparency, and commented in the above section. In addition, we cannot rule out that some publication bias may be present, i.e., that studies showing no associations are less likely to be published. In such case, the conclusions from our review may be too strong regarding the association of low SES and worse childhood cancer survival.

CONCLUSION

This review has summarized the most recent publications on the association between parental SES and childhood cancer survival in high-income countries. Even though some of the reviewed studies found no differences in survival between children from diverse socioeconomic backgrounds, worse survival among children of lower SES were observed for several cancer types, contexts, and SES indicators. Studies that more carefully investigate specific underlying mechanisms for the socioeconomic differences in survival are lacking. Collaborative studies are needed to increase statistical power to enable

investigation of the association within homogenous cancer types which will increase the understanding of the mechanisms involved, and allow targeted interventions to reduce health inequalities.

AUTHOR CONTRIBUTIONS

HM, KM, FE, GT, MH, and MF contributed to the design of the study. HM screened titles, abstracts and full-texts. HM drafted the manuscript. HM, KM, FE, GT, MH, and MF reviewed the manuscript and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00485/full#supplementary-material

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