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Utilization of primary care before a childhood cancer diagnosis: Do socioeconomic factors matter? A nationwide population-based matched cohort study

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Abstract

Objectives: Early diagnosis of childhood cancer is critical. Nevertheless, little is known about the potential role of inequality. This study aims to describe the use of primary care two years before a childhood cancer diagnosis and to investigate whether socioeconomic factors influence the use of consultations and diagnostic procedures in primary care.

Design: A national population-based matched cohort study.

Setting and participants: This study uses observational data from four Danish nationwide registers. All children aged 0-15 diagnosed with cancer during 2008-2015 were included (N = 1,386). Each case was matched on gender and age with 10 references (N = 13,860).

Primary and secondary outcome measures: The primary outcome was additional rates for consultations and for diagnostic procedures for children with cancer according to parental socioeconomic factors. Furthermore, we estimated the association between socioeconomic factors and likelihood of frequent use of consultations, and the likelihood of receiving a diagnostic procedure within three months of diagnosis.

Results: Children with cancer had 2.43 (95% CI: 2.08:2.78) additional consultations two years before the diagnosis. Children with cancer from families with high income had 1.46 (95% CI: 1.23:1.69) additional consultations three months before diagnosis, whereas children from families with low income had 1.85 (95% CI: 1.60:2.11) additional consultations. The highest likelihood of frequent use of consultations was observed among children from low-income families (OR: 1.94, 95% CI: 1.24:3.03). A higher likelihood of receiving a diagnostic procedure was seen for children from families with mid-educational level (OR: 1.46, 95% CI: 1.09:1.95).

Conclusion: We found a socioeconomic gradient in the use of general practice before a childhood cancer diagnosis. This suggests that social inequalities exist in the pattern of healthcare utilization and the handling of these patients in general practice.

Article summary

- This large nationwide study is based on high-quality data from four nationwide registers.
- The risk of selection bias and information bias was limited.
- Matching was used to reduce potential confounding effects of age and gender.
- Multiple socioeconomic variables were examined in the analysis to ensure high validity of findings.
- A limitation was the lack of information on the reasons for requesting consultations and tests.

Introduction

Childhood cancer is the second most common cause of death among children in developed countries and is only outnumbered by accidents [1]. Denmark has one of the highest incidence rates of childhood cancer among high-income countries, with an annual incidence rate around 14 cases per 100,000 children below age 15 years [2, 3].

Diagnosis of childhood cancer is a challenging task in general practice as children with early-stage cancer often present with non-specific and vague symptoms that mimic common conditions such as viral infection [4, 5]. A Danish study showed that excess healthcare use, which can be seen as a proxy for symptoms of childhood cancer, occurs several months before the diagnosis is established [6]. The time leading up to the cancer diagnosis is often full of worries for the involved families. Moreover, delayed diagnosis can cause longstanding effects, such as distress in the family and poor quality of life, and may negatively affect the curability and survival [5, 7].

Several studies have documented inequalities in the healthcare use between patients with low and high socioeconomic position (SEP) [8-11]. Despite free access to general practice in Denmark, the utilization of preventive child health examinations is lower in the deprived part of the population [8]. Additionally, a growing body of research shows that parental socioeconomic factors influence childhood cancer survival, even in countries with free access to high-quality healthcare [12-15].

One question that arises in this context is whether socioeconomic differences influence the utilization of primary care for childhood cancer and (if positive) to what extent. Knowledge about inequality in early diagnosis of childhood cancer is essential to ensure an optimal diagnostic route, regardless of the patient's socioeconomic position.

The aim of this study is to describe the use of primary care two years before a diagnosis of childhood cancer and to investigate whether socioeconomic factors modify the use of consultations and the diagnostic procedures performed in primary care.

Method

We conducted a national population-based matched cohort study using data from four nationwide Danish registers: I) the Danish Civil Registration System, which holds basic demographic information on all Danish citizens, II) the Danish Cancer Register (DCR), which holds information on all cancer diagnoses in Denmark, III) the Danish National Health Insurance Service Register (NHSR), which holds information on all contacts to and services provided by general practice based on remuneration coding [16], and IV) Statistics Denmark, which is the central authority on Danish statistics and holds socioeconomic and demographic information on all citizens [17]. The civil registration number, a unique 10-digit personal identification number assigned to every Danish citizen at birth or immigration, was used to link data at the individual level.

Setting

The Danish healthcare system is tax-financed and offers equal and universal access to healthcare for all citizens. All Danish residents have direct and free access to general practitioners (GPs), and more than 98% of all citizens are registered with a specific general practice [18]. GPs act as gatekeepers to the rest of the healthcare system; they carry out initial diagnostic investigations including referrals to specialists. Specialist and hospital care is free of charge. Except for emergencies and ear-nose-throat and eye specialists, all citizens must first contact their general practice to get a referral.

Study population

All children aged 0-15 years diagnosed with an incident cancer according to the Danish version of the International Classification of Diseases (ICD-10) (C00-D48) in the period of 1 January 2008 to 31 December 2015 were identified in the DCR. All childhood cancers were divided into five diagnostic subgroups in accordance with the ICD-10 codes: leukaemia (C91-95), lymphoma (C81-85, C96), CNS tumour (C70-72, C75.1-3, D32-33, D35.2-4, D42-43, D44.3-5), bone tumour (C40-41) and other solid tumours (remaining ICD-10 cancer codes).

For each childhood cancer patient, ten random references were sampled and matched on date of birth and gender. Index date was the date of diagnosis for the matched cancer patient. The references had to be alive and resident in Denmark at the index date (i.e. date of diagnosis) and two years before the index date.

Socioeconomic factors

We used information on SEP from the calendar year before the index date in order to minimise the impact from the child's disease on the socioeconomic indicators. SEP indicators were categorised as described in

the following. Parental cohabitation status was divided into living with a partner (married/cohabitating) or living alone (divorced, widowed or never married). Household labour market affiliation was divided into employed, unemployed (unemployed, old age pension or early retirement pension, disability pension or welfare payments) and mixed (one parent employed, the other unemployed). Educational level was classified according to UNESCO's International Standard Classification of Education into three groups (low educational level: ≤10 years, medium educational level: >10 and ≤15 years, and high educational level: >15 years) and was based on the highest obtained educational level of the mother. In cases with no mother in the household, the highest obtained educational level of the father was used. Income was measured as equalised disposable household income (salaries, wages, all types of supplementary benefits and pensions) and comprised all income after taxation for the entire household adjusted for number of persons in the household [19]. Income was categorised into three groups: low (1st quartile), medium (2nd and 3rd quartile) and high (4th quartile). Number of children in the household was dichotomised as the presence of siblings (yes/no).

Primary healthcare services

The main outcomes were rates of consultations and diagnostic procedures performed in general practice; these data were obtained from the NHSR. Consultations included face-to-face consultations, home visits, telephone and email consultations during daytime. Planned vaccinations and preventive child health examinations were not included.

Diagnostic procedures included urine tests (stick, microscopy of urine and urine culture), blood tests (C-reactive protein (CRP), differential blood count, blood glucose, haemoglobin and blood samples, pulmonary function tests, electrocardiography (ECG) and tests for streptococcal throat infection.

Statistical analyses

We calculated the quarterly difference between rates for consultations and diagnostic procedures performed for children who were later diagnosed with cancer and reference children stratified for each socioeconomic factor. In the following, this incidence rate difference (IRD) will be referred to as 'additional rates'.

We calculated the absolute difference in 'additional rates' compared to the reference group for consultations and diagnostic procedures. We used generalised linear models with identity link for the

Poisson family. For both additional rates and absolute differences, we applied cluster robust variance estimation to account for repeated measurements for the subjects.

Logistic regression was used to estimate the association between socioeconomic variables and the likelihood of frequent use of consultations, frequent use was defined as having at least four consultations in the three months before diagnosis based on the fourth quartile. Two models were used. First, a basic model adjusted for cancer type, age and gender for each of the socioeconomic variables. Second, a model adjusted for cancer type, age, gender and all included socioeconomic variables. Similar models were used to estimate the association between SEP and the probability of receiving at least one diagnostic procedure during the last three months before diagnosis.

A p-value of 0.05 or less was considered statistically significant. Analyses were performed using Stata/IC version 15.0.

Ethics

The study was approved by the Danish Data Protection Agency (j.no. 2009-41-3471). According to Danish law, approval by the National Committee on Health Research Ethics was not required as no biomedical intervention was performed, and no biological material was collected [20].

Results

Characteristics of the study population

In all, 1,386 eligible children with cancer and 13,860 matched references were identified (Figure 1) and characteristics are shown in Table 1. The proportion of children consulting general practice within three months before diagnosis (i.e. index date) was 75% among cases and 38% among references. Diagnostic procedures were performed in primary care within three months before diagnosis for 29% of cases and 7% of references.

Consultation rates before diagnosis

The consultation rates for cases and references are shown in Table 2. Compared to references, a minor statistically significant increase in consultations was seen among children with cancer from 16-18 months before the diagnosis. A progressive increase was observed from 10-12 months before the diagnosis, especially during the last three months (incidence rate difference (IRD): 1.67 (95% CI: 1.55:1.80)) ($p < 0.001$) (Table 2).

Children from families with high educational level (IRD: 1.61 (95% CI: 1.43:1.80)) or high income (IRD: 1.46 (95% CI: 1.23:1.69)) had lowest additional consultation rates in the last three months before diagnosis, whereas children from families with low educational level (IRD: 1.83 (95% CI: 1.52:2.15)) or low income (IRD: 1.85 (95% CI: 1.60:2.11)) had more (Supplementary Table 1). No differences in additional consultation rates were observed for parental cohabitation status, having siblings or household labour market affiliation (Figure 2 and Supplementary Table 1).

Likelihood of frequent use of consultations

Of the children with cancer, 29% were frequent users of consultations three months before diagnosis. The proportion was modified by income; the highest likelihood of frequent use of consultations was observed among children from low-income families (odds ratio (OR): 1.94 (95% CI: 1.24:3.03)) (Table 3).

A sub-analysis revealed that this association was more pronounced for children with leukaemia (OR: 2.23, 95%: 0.95:5.26)) (Supplementary Table 2) and for children from medium-level educated families (OR: 1.91 (95% CI 1.09:3.33)) compared to children from high-level educated families. This association was not found for children with CNS or other solid tumours (Supplementary Table 2).

Diagnostic procedures

The rates of diagnostic procedures and additional rates are shown in Table 2. Children with cancer on average had 1.7 (95% CI: 1.55:1.87) diagnostic procedures performed during the two years before the diagnosis compared to 0.95 (95% CI: 0.92:0.98) among the references. A progressive increase in the rates of diagnostic procedures was observed in the 4-6 months before the diagnosis (Table 2).

During the three months before the diagnosis, 29% of children with cancer had at least one diagnostic procedure performed in primary care. We found a statistically significant higher likelihood of receiving a diagnostic procedure among children from families with medium-level education (OR: 1.46 (95% CI: 1.09:1.95)). We found no statistically significant associations between other socioeconomic variables and the likelihood of receiving one or more diagnostic procedures (Table 4).

Discussion

Principal findings

Children with cancer generally had more consultations and clinical investigations in general practice than the references. A progressive increase was seen in the 10-12 months before diagnosis, which was anticipated. However, the likelihood of receiving extra consultations and diagnostic procedures was modified by parental socioeconomic position.

Children with cancer from families with high-level education and high-level income had fewest additional consultations in the last three months before diagnosis. Children with cancer from households with low- and medium-level income were thus more likely to be frequent users of consultations in the three months before the diagnosis compared to high-income families. This trend was more pronounced for children with leukaemia than for children with other cancer types. The likelihood of receiving at least one diagnostic procedure during the last three months before diagnosis was higher for children from households with medium-level education compared to high- or low-level education.

Comparison with existing literature

The observed overall increase in the rates of both consultations and diagnostic procedures is in line with previous findings [6, 21, 22]. Previous studies have also documented an association between socioeconomic factors and a prolonged diagnostic interval in childhood cancer [23-26]. A prolonged interval might occur if the GP does not suspect cancer, or if the GP interprets the symptoms as something else, does not communicate or interact optimally with the child and the parents or postpones referral for

specialist investigation. Our findings indicate that some or several of these factors may be at play in parents with low education.

The GP's intuition plays an important role in the suspicion of serious disease [27-30]. A study from the UK reported that the GP-parent relationship had significant impact on the process of obtaining a paediatric leukaemia diagnosis [30]. For example, the GP's concerns and actions were partly shaped by how anxious s/he estimated the parents to be. The GP's initial perception of a parent as being a 'worrier' or too sensitive could influence the way the parents' concerns are dealt with; 'worriers' are generally taken less seriously. However, the importance of listening to the parents was highlighted by the GPs in one of the studies although many parents reported that the GP did not seem to take their worries seriously [30]. We were able to demonstrate that children from families with lower SEP tended to see the GP more often before diagnosis. This indicates that some of these mechanisms are seen in children of parents with low income and low education. In addition, children of parents with low income might have other diseases, which may also delay the suspicion of cancer in general practice.

The communication during a consultation is a complex matter, which is influenced by numerous factors. An international review showed that patients with low SEP communicate less actively when consulting a GP and receive less information from the GP than patients with high SEP [31]. This may partly explain why we observed differences in the utilization of primary care services before a cancer diagnosis. A Danish study has shown that higher SEP of the parents, such as high education, is associated with better survival of children with cancer [32]. One possible explanation raised by our study is that these children may have a delayed diagnosis.

Identifying the few children with malignant cancer disease is a major challenge in general practice, and it often includes wait-and-see strategies and very low positive predictive values for even serious symptoms of disease [33]. The use of 'safety-netting' as a strategy to manage diagnostic uncertainty is increasingly recognised as important in adult cancer diagnostics and may be even more pertinent in children [34]. This may be particularly relevant if the child comes from a family with limited socioeconomic resources.

Strengths and limitations of the study

This nationwide population-based matched cohort study was based on data from several Danish national registers. Danish registers are known to be very complete and valid [35-37]. A major strength was the low risk of selection bias and information bias concerning classification of diagnosis, socioeconomic factors and

healthcare use. Despite the low incidence of cancer in children, we obtained sufficient data to ensure high statistical precision. This allowed us to detect small, yet clinically relevant, differences between the groups.

Our broad categorisations of, for example, income and education might have caused loss of detailed information. As these categorisations were defined *a priori*, some groups could have been defined too broadly and caused loss of information or introduced residual confounding. Still, we based the definitions on international standard classifications [38].

A limitation of this study was the lack of information on the reasons for the requested consultations and performed tests. This potential bias was reduced by our use of a large dataset and the matching of cases. Potential confounding effects of age and gender were reduced by matching included cases with references. However, we cannot exclude that residual confounding by other factors (e.g. comorbidity) could have influenced our results. As the study concerned children only, this might be of limited less importance.

Our study has the advantage of using multiple socioeconomic variables in the analysis. There is consensus that SEP is a complex and multifaceted aspect, which should not be considered in isolation when exploring socioeconomic inequalities in health [39-41].

The generalisability of our results has certain limitations. Measuring SEP is a complex matter, and our findings may not apply to countries with different socioeconomic conditions or organisation of primary care. Yet, this challenge is seen in any study of socioeconomics and healthcare.

Conclusion and implications

This nationwide population-based cohort study shows that children who are later diagnosed with cancer tend to use primary care more often in the months before the diagnosis. The study also shows that children of parents with low income have more contacts with the GP than children of parents with high income. Despite the direct and free access to GPs and primary care, some social inequalities are seen in the healthcare utilization and handling of these patients in general practice. These variations are likely to affect the child's diagnostic pathway, treatment and prognosis. Our findings thus call for future research.

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Competing interests statement

All authors declare to have no competing interests.

Author contributions

All authors contributed in the development of the study protocol and design. CFA produced the first draft of the manuscript. JA and PV contributed to the interpretation of data and critical revision of the manuscript. All authors contributed with proofreading of the manuscript.

Data sharing statement

The datasets analysed in the current study are stored in a secured research database and may be available upon presentation of formal approval.

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Abbreviations

CI: Confidence interval

CNS: Central nervous system

DCR: Danish Cancer Register

ECG: Electrocardiography

GP: General practitioner

ICD-10: International Classification of Diseases, 10th edition

IRD: Incidence rate difference

NHSR: Danish National Health Insurance Service Register

OR: Odds ratio

SEP: Socioeconomic position

UNESCO: United Nations' Educational Scientific and Cultural Organization

References

1 Kaatsch P. Epidemiology of childhood cancer, *Cancer Treat Rev* 2010;36:277-85 doi:10.1016/j.ctrv.2010.02.003.

2 Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries, *Cancer* 2008;112:461-72 doi:10.1002/cncr.23205.

3 van der Horst M, Winther JF, Olsen JH. Cancer incidence in the age range 0-34 years: Historical and actual status in Denmark, *International Journal of Cancer* 2006;118:2816-26 doi:10.1002/ijc.21566.

4 Ahrensberg JM, Hansen RP, Olesen F, et al. Presenting symptoms of children with cancer: a primary-care population-based study, *British Journal of General Practice (journal of the Royal College of General Practitioners)* 2012;62:e458-465 doi:10.3399/bjgp12X652319.

5 Dixon-Woods M, Findlay M, Young B, et al. Parents' accounts of obtaining a diagnosis of childhood cancer, *The Lancet* 2001;357:670-4 doi:10.1016/S0140-6736(00)04130-1.

6 Ahrensberg JM, Fenger-Grøn M, Vedsted P. Use of primary care during the year before childhood cancer diagnosis: a nationwide population-based matched comparative study, *PloS One* 2013;8:e59098 doi:10.1371/journal.pone.0059098.

7 Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review, *Br J Cancer* 2015;112 Suppl 1:S92 doi:10.1038/bjc.2015.48.

8 Søndergaard G, Biering-Sørensen S, Ishøy Michelsen S, et al. Non-participation in preventive child health examinations at the general practitioner in Denmark: A register-based study, *Scand J Prim Health Care* 2008;26:5-11 doi:10.1080/02813430801940877.

9 Hoebel J, Rattay P, Prütz F, et al. Socioeconomic Status and Use of Outpatient Medical Care: The Case of Germany, *PloS One* 2016;11:e0155982 doi:10.1371/journal.pone.0155982.

10 Finnvold JE. Access to specialized health care for asthmatic children in Norway: The significance of parents? educational background and social network, *Soc Sci Med* 2006;63:1316-27 doi:10.1016/j.socscimed.2006.03.045.

11 Stirbu I, Kunst A, Mielck A, et al. Inequalities in utilisation of general practitioner and specialist services in 9 European countries, *BMC Health Services Research* 2011;11:288- doi:10.1186/1472-6963-11-288.

12 Mogensen H, Modig K, Tettamanti G, et al. Socioeconomic differences in cancer survival among Swedish children, *Br J Cancer* 2016;114:118 doi:10.1038/bjc.2015.449.

13 Adam M, Rueegg CS, Schmidlin K, et al. Socioeconomic disparities in childhood cancer survival in Switzerland : Socioeconomic disparities in cancer survival, *International Journal of Cancer* 2016;138:2856-66 doi:10.1002/ijc.30029.

14 Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study, *International Journal of Cancer* 2012;130:1870-8 doi:10.1002/ijc.26186.

15 Erdmann F, Winther JF, Dalton SO, et al. Survival from childhood hematological malignancies in Denmark: Is survival related to family characteristics? Family traits and hematological malignancies survival, *Pediatric Blood & Cancer* 2016;63:1096-104 doi:10.1002/pbc.25950.

16 Sahl Andersen J, De Fine Olivarius N, Krasnik A. The Danish National Health Service Register, *Scand J Public Health* 2011;39:34-7 doi:10.1177/1403494810394718.

17 Statistics Denmark 2017; Available at: http://www.dst.dk/en. Accessed 08/12, 2017.

18 Pedersen KM, Andersen JS, Sondergaard J. General practice and primary health care in Denmark, *J Am Board Fam Med* 2012;25(Suppl 1):S34–8.

19 OECD. What are equivalence scales? Available at: www.oecd.org/eco/growth/OECD-Note-EquivalenceScales.pdf. Accessed 01/25, 2018.

20 National Committee on Health Research Ethics. Act on research ethics review of health research projects. 2017; Available at: http://www.nvk.dk/english. Accessed 08/13, 2017.

21 Dommett RM, Redaniel MT, Stevens MCG, et al. Features of childhood cancer in primary care: a population-based nested case-control study, *Br J Cancer* 2012;106:982 doi:10.1038/bjc.2011.600.

22 Ansell P, Johnston T, Simpson J, et al. Brain tumor signs and symptoms: analysis of primary health care records from the UKCCS, *Pediatrics* 2010;125:112-9 doi:10.1542/peds.2009-0254 [doi] [published Online First: Jan].

23 Ahrensberg JM, Olesen F, Hansen RP, et al. Childhood cancer and factors related to prolonged diagnostic intervals: a Danish population-based study, *Br J Cancer* 2013;108:1280 doi:10.1038/bjc.2013.88.

24 Abdelkhalek E, Sherief L, Kamal N, et al. Factors associated with delayed cancer diagnosis in Egyptian children, *Clinical Medicine Insights Pediatrics* 2014;8:39.

25 Fajardo Gutiérrez A, Sandoval Mex AM, Mejía Aranguré JM, et al. Clinical and social factors that affect the time to diagnosis of Mexican children with cancer, *Med Pediatr Oncol* 2002;39:25-31 doi:10.1002/mpo.10100.

26 Dang-Tan T, Trottier H, Mery LS, et al. Delays in diagnosis and treatment among children and adolescents with cancer in Canada, *Pediatric Blood & Cancer* 2008;51:468-74 doi:10.1002/pbc.21600.

27 Hjertholm P, Moth G, Ingeman ML, et al. Predictive values of GPs' suspicion of serious disease: a population-based follow-up study, *British Journal of General Practice (journal of the Royal College of General Practitioners)* 2014;64:e346.

28 Scheel BI, Ingebrigtsen SG, Thorsen T, et al. Cancer suspicion in general practice: the role of symptoms and patient characteristics, and their association with subsequent cancer, *British Journal of General Practice (journal of the Royal College of General Practitioners)* 2013;63:e627.

29 Ingeman ML, Christensen MB, Bro F, et al. The Danish cancer pathway for patients with serious non-specific symptoms and signs of cancer-a cross-sectional study of patient characteristics and cancer probability, *BMC Cancer* 2015;15:421 doi:10.1186/s12885-015-1424-5.

30 Clarke RT, Jones CH, Mitchell CD, et al. 'Shouting from the roof tops': a qualitative study of how children with leukaemia are diagnosed in primary care, *BMJ Open* 2014;4:e004640 doi:10.1136/bmjopen-2013-004640.

31 Willems S, De Maesschalck S, Deveugele M, et al. Socio-economic status of the patient and doctor–patient communication: does it make a difference? *Patient Education and Counseling* 2005;56:139-46.

32 Simony SB, Lund LW, Erdmann F, et al. Effect of socioeconomic position on survival after childhood cancer in Denmark, *Acta Oncol* 2016;55:742-50 doi:10.3109/0284186X.2016.1144933.

33 Dommett RM, Redaniel MT, Stevens MC, et al. Features of childhood cancer in primary care: a population-based nested case-control study, *Br J Cancer* 2012;106:982-7 doi:10.1038/bjc.2011.600 [doi] [published Online First: Feb 28].

34 Nicholson BD, Mant D, Bankhead C. Can safety-netting improve cancer detection in patients with vague symptoms? *BMJ* 2016;355 [published Online First: 11/09].

35 Frank L. Epidemiology. When an entire country is a cohort, *Science* 2000;287:2398-9 doi:10.1126/science.287.5462.2398.

36 SSI. Validation of The Danish Cancer Registry and selected Clinical Cancer Databases - English Abstract. 2012; Available at: http://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygedomme-laegemidler-og-behandlinger/cancerregisteret. Accessed 08/16, 2017.

37 Thygesen LC, Daasnes C, Thaulow I, et al. Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving, *Scand J Public Health* 2011;39:12-6 doi:10.1177/1403494811399956.

38 UNESCO. International Standard Classification of Education. 2011; Available at: http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf. Accessed 01/24, 2018.

39 Shavers VL. Measurement of socioeconomic status in health disparities research, *J Natl Med Assoc* 2007;99:1013.

40 Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic Status in Health Research: One size does not fit all, *JAMA* 2005;294:2879-88 doi:10.1001/jama.294.22.2879.

41 Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research, *Br Med Bull* 2007;81-82:21-37 doi:10.1093/bmb/ldm001.

Tables

Table 1. Characteristics of the childhood cancer cohort and the gender- and age-matched reference cohort

	Cases		References	
	n	%	n	%
	1386	100.0	13860	100.0
Sex				
Girls	650	46.9	6500	46.9
Boys	736	53.1	7360	53.1
Age at diagnosis (index date)				
10-15 years	411	29.7	4110	29.7
5-9 years	360	26.0	3600	26.0
1-4 years	475	34.3	4750	34.3
0 years	140	10.1	1400	10.1
Type of cancer				
Leukaemia	347	25.0	-	-
Lymphoma	170	12.3	-	-
CNS tumour	367	26.5	-	-
Bone tumour	59	4.3	-	-
Other solid tumour	443	32.0	-	-
Siblings				
Yes	1044	75.3	10.329	74.5
No	276	19.9	2.870	20.7
Missing	66	4.8	661	4.8
Parental cohabitation status				
Living with a partner	915	66.0	8.972	64.7
Living alone	393	28.4	4.136	29.8
Missing	78	5.6	752	5.4
Educational level				
High (> 15 years)	547	39.5	5.587	40.3
Medium (>10-15 years)	531	38.3	5.267	38.0
Low (< 10 years)	211	15.2	2.091	15.1
Missing	97	7.0	915	6.6
Labour market affiliation				
Employed	987	71.2	9.876	71.3
Mixed	191	13.8	1.991	14.4
Unemployed	130	9.4	1.241	9.0
Missing	78	5.6	752	5.4
Household income				
High	330	23.8	3.294	23.8
Medium	655	47.3	6.601	47.6
Low	334	24.1	3.297	23.8
Missing	67	4.8	668	4.8

Table 2. Rates of consultations and performed diagnostic procedures among cases and references

Months before diagnosis	Rates of consultations (95%CI)		Additional rates (95% CI)	Rates of diagnostic procedures (95%CI)		Additional rates (95% CI)
	Cases (n= 1386)	References (n=13860)		Cases (n= 1386)	References (n=13860)	
1-3 months	2.43 (2.30:2.55)	0.75 (0.73:0.76)	**1.67 (1.55:1.80)**	0.72 (0.64:0.81)	0.12 (0.11:0.13)	**0.60 (0.52:0.69)**
4-6 months	1.02 (0.94:1.10)	0.82 (0.80:0.85)	**0.20 (0.12: 0.28)**	0.18 (0.14:0.23)	0.13 (0.12:0.14)	**0.05 (0.01:0.11)**
7-9 months	0.99 (0.91:1.08)	0.82 (0.80:0.84)	**0.18 (0.09:0.27)**	0.13 (0.11:0.17)	0.12 (0.11:0.13)	0.02 (-0.01:0.05)
10-12 months	0.95 (0.87:1.03)	0.83 (0.81:085)	**0.12 (0.04:0.20)**	0.13 (0.10:0.16)	0.12 (0.12:0.13)	0.01 (-0.02:0.04)
13-15 months	0.90 (0.82:0.98)	0.80 (0.78:0.83)	**0.10 (0.02:0.18)**	0.17 (0.13:0.21)	0.12 (0.53:0.13)	**0.05 (0.01:0.08)**
16-18 months	0.88 (0.80:0.95)	0.76 (0.74:0.79)	**0.11 (0.33: 0.19)**	0.13 (0.10:0.16)	0.11 (0.10:0.12)	0.02 (-0.01:0.05)
19- 21 months	0.85 (0.77:0.92)	0.79 (0.77:0.82)	0.05 (-0.03:0.13)	0.15 (0.11:0.18)	0.11 (0.10:0.12)	0.04 (-0.00:0.07)
22-24 months	0.79 (0.72:0.85)	0.79 (0.77:0.82)	0.00 (-0.08:0.07)	0.09 (0.07:0.11)	0.11 (0.11:0.13)	- 0.03 (-0.06:0.00)
Total (1-24 months)	8.82	6.38	**2.43 (2.08:2.78)**	1.71 (1.55:1.87)	0.95 (0.92:0.98)	**0.76 (0.64:0.88)**

Additional rates are the difference between consultation rates of cases and references.

Statistically significant additional rates are presented in bold type.

Table 3. Likelihood (OR) of frequent GP attendance in the last three months before diagnosis

	Basic model [a] OR (95% CI)	Adjusted model [b] OR (95% CI)
Parental cohabitation status		
Living with a partner	1.00	1.00
Living alone	0.90 (0.68:1.18)	0.86 (0.63:1.16)
Siblings		
No	1.00	1.00
Yes	1.23 (0.91:1.69)	1.19 (0.86:166)
Labour market affiliation		
Employed	1.00	1.00
Mixed	1.19 (0.84:1.67)	0.99 (0.68:1.47)
Unemployed	1.36 (0.92:2.02)	1.21 (0.73:1.99)
Educational level		
High	1.00	1.00
Medium	**1.35 (1.02:1.77)**	1.16 (0.87:1.55)
Low	1.25 (0.88:1.79)	0.98 (0.65: 1.47)
Income		
High	1.00	1.00
Medium	**1.76 (1.28:2.43)**	**1.70 (1.22:2.37)**
Low	**1.98 (1.38:2.85)**	**1.94 (1.24:3.03)**

[a]Adjusted for cancer subtype, age and gender

[b]Adjusted for cancer subtype, age, gender and all socioeconomic variables

Statistically significant estimates are presented in bold type.

Table 4. Likelihood (OR) of receiving a diagnostic procedure during the last three months before a childhood cancer diagnosis

	Basic model [a] OR (95% CI)	Adjusted model [b] OR (95% CI)
Parental cohabitation status		
Living with a partner	1.00	1.00
Living alone	0.88 (0.67:1.16)	0.88 (0.66:1.19)
Siblings		
No	1.00	1.00
Yes	1.12 (0.81:1.54)	1.06 (0.76:1.48)
Labour market affiliation		
Employed	1.00	1.00
Mixed	0.95 (0.66:1.35)	0.86 (0.57:1.28)
Unemployed	0.89 (0.59:1.37)	0.83 (0.49:1.42)
Educational level		
High	1.00	1.00
Medium	**1.42 (1.07:1.87)**	**1.46 (1.09:1.95)**
Low	1.14 (0.79:1.65)	1.26 (0.83:1.91)
Income		
High	1.00	1.00
Medium	1.12 (0.83:1.51)	1.03 (0.75:1.41)
Low	1.02 (0.71:1.44)	0.98 (0.63:1.54)

[a] **Adjusted for cancer subtype, age and gender**

[b] **Adjusted for cancer subtype, age, gender and all socioeconomic variables**

Statistically significant estimates are presented in bold type.

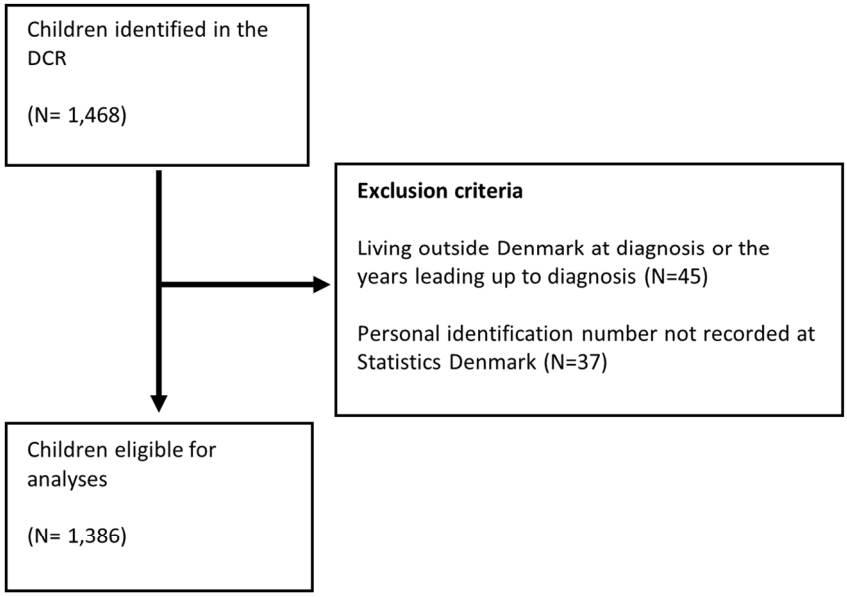

Figure 1. Sampling of children with cancer

122x82mm (300 x 300 DPI)

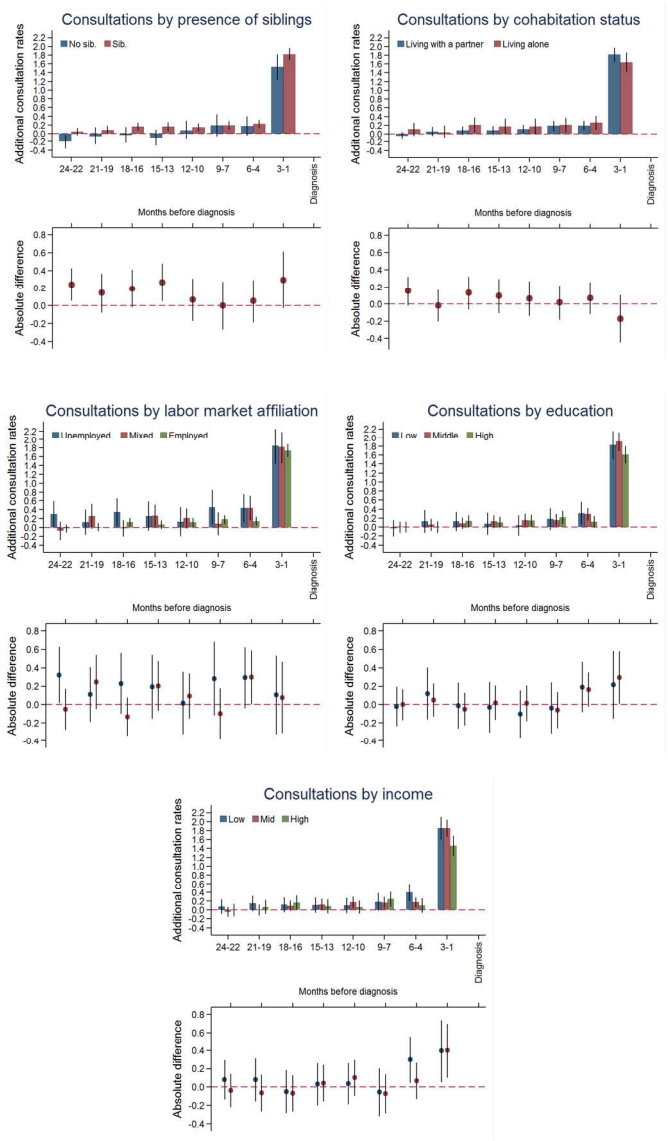

Figure 2. Consultation rates in general practice by socioeconomic factors.Upper part: Additional consultation rates in three-month intervals for children with cancer and references two years before diagnosis, with 95% confidence intervals. Lower part: Absolute difference in additional consultation rates, with 95% confidence intervals.

190x338mm (300 x 300 DPI)

Supplementary **Table 1a. Additional consultation rates and absolute difference in general practice in the 1-12 months before diagnosis by household socioeconomic factors and three-month intervals**

	1-3 months		4-6 months		7-9 months		10-12 months	
	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference
All	1.67 (1.55:1.88)	-	0.20 (0.12:0.28)	-	0.18 (0.09:0.27)	-	0.12 (0.04: 0.20)	-
Parental cohabitation status								
Living with a partner	1.81 (1.61:2.01)	Ref	0.19 (0.08:0.29)	Ref	0.19 (0.07:0.29)	Ref	0.11 (0.01:0.21)	Ref
Living alone	1.64 (1.42:1.87)	-0.17 (-0.45:0.10)	0.26 (0.01:0.41)	0.07 (-0.12:0.26)	0.20 (0.04:0.37)	0.01 (-0.18:0.22)	0.17 (-0.00:0.35)	0.06 (-0.14:0.27)
Siblings								
No	1.53 (1.2 4:1.81)	Ref	0.17 (-0.05:0.39)	Ref	0.19 (-0.06:0.44)	Ref	0.08 (-0.14:0.29)	Ref
Yes	1.89 (1.68:1.96)	0.29 (-0.02:0.61)	0.23 (0.13:0.32)	0.05 (-0.19:0.29)	0.19 (0.09:0.28)	0.00 (-0.27:0.27)	0.14 (0.05:0.24)	0.06 (-0.17:0.31)
Labour market affiliation								
Employed	1.74 (0.60:1.89)	Ref	0.14 (0.05:0.23)	Ref	0.18 (0.08:0.28)	Ref	0.12 (0.02:0.21)	Ref
Mixed	1.82 (1.46:2.18)	0,08 (-0.31:0.47)	0.44 (0.16:0.71)	0.30 (- 0.01:0.60)	0.08 (-0.18:0.24)	- 0.10 (-0.38:0.18)	0.21 (-0.02:0.43)	0.09 (-0.15:0.34)
Unemployed	1.85 (1.45:2.25)	0.11 (-0.32:0.53)	0.43 (0.12:0.75)	0.29 (-0.04:0.62)	0.46 (0.07:0.85)	0.28 (-0.11:0.68)	0.13 (-0.19:0.46)	0.01 (-0.32:0.35)
Educational level								
High	1.61 (1.43:1.80)	Ref	0.12 (-0.01:0.24)	Ref	0.21 (0.07:0.36)	Ref	0.14 (0.01:0.27)	Ref
Medium	1.91 (1.70:2.12)	**0.30 (0.04:0.57)**	0.29 (0.15:0.42)	0.17 (-0.02:0.35)	0.15 (0.02: 0.29)	-0.06 (-0.25:0.14)	0.16 (0.01:0.27)	0.02 (-0.18:0.20)
Low	1.83 (1.52:2.15)	0.22 (-0.15:0.58)	0.31 (0.06:0.56)	0.19 (-0.08:0.47)	0.18 (-0.06:0.41)	-0.03 (-0.31-0.24)	0.04 (-0.18:0.26)	-0.10 (-0.36:0.15)
Income								
High	1.46 (1.23:1.69)	Ref	0.10 (-0.06:0.26)	Ref	0.24 (0.07:0.41)	Ref	0.07 (-0.08:0.21)	Ref
Medium	1.86 (1.67:2.05)	**0.40 (0.10:0.70)**	0.17 (0.05:0.28)	0.07 (-0.13:0.26)	0.16 (0.36:0.29)	-0.08 (-0.29:0.14)	0.17 (0.04:0.30)	0.10 (-0.09:0.29)
Low	1.85 (1.60:2.11)	**0.39 (0.05:0.74)**	0.40 (0.19:0.60)	**0.30 (0.04:0.55)**	0.18 (-0.01:0.38)	-0.06 (-0.32:0.20)	0.10 (-0.07:0.28)	0.03 (-0.19:0.26)

Additional consultation rates defined as the difference between the cancer cohort and the reference cohort.
Absolute difference in additional consultation rates compared to the reference group.

Statistically significant absolute differences are shown in bold type.

Supplementary **Table 1b. Additional consultation rates and absolute difference in general practice in the 13-24 months before diagnosis by household socioeconomic factors and three-month intervals**

	13-15 months		16-18 months		19-21 months		22-24 months	
	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference
All	0.10 (0.02:0.18)	-	0.11 (0.03:0.19)	-	0.05 (-0.03:0.13)		-0.00 (-0.08:0.07)	-
Parental cohabitation status								
Living with a partner	0.08 (-0.02:0.18)	Ref	0.08 (-0.01:0.17)	Ref	0.06 (-0.05:0.16)	Ref	-0.06 (-0.14:0.04)	Ref
Living alone	0.18 (0.00:0.35)	0.09 (-0.11:0.29)	0.21 (0.04:0.38)	0.13 (-0.06:0.32)	0.04 (-0.01:0.19)	-0.02 (-0.02:0.16)	0.11 (-0.04:0.25)	0.15 (-0.02:0.32)
Siblings								
No	-0.10 (-0.29:0.09)	Ref	-0.04 (-0.21:-0.00)	Ref	-0.06 (-0.26:0.14)	Ref	-0.19 (-0.36:0.03)	Ref
Yes	0.16 (0.07:0.26)	0.26 (-0.05:0.48)	0.16 (0.07:0.25)	0.20 (-0.01:0.41)	0.09 (-0.01:0.18)	0.14 (-0.08:0.37)	0.04 (-0.04:0.14)	0.24 (-0.06:0.43)
Labour market affiliation								
Employed	0.06 (-0.03:0.16)	Ref	0.11 (0.02:0.21)	Ref	0.01 (-0.09:0.10)	Ref	-0.02 (-0.11:0.06)	Ref
Mixed	0.26 (0.01:0.52)	0.20 (-0.07:0.47)	-0.02 (-0.20:0.17)	-0.13 (-0.34:0.07)	0.25 (-0.03:0.53)	0.24 (-0.05:0.54)	-0.07 (-0.28:0.13)	-0.05 (-0.27:0.17)
Unemployed	0.25 (-0.08:0.59)	0.19 (-0.15:0.54)	0.34 (0.03:0.66)	0.23 (-0.10:0.56)	0.12 (-0.17:0.40)	0.11 (-0.19:0.41)	0.30 (0.01:0.59)	0.32 (0.02:0.63)
Educational level								
High	0.10 (-0.02:0.23)	Ref	0.14 (0.01:0.26)	Ref	0.01 (-0.12:0.37)	Ref	0.00 (-0.12:0.11)	Ref
Medium	0.12 (-0.01:0.26)	0.02 (-0.17:0.20)	0.09 (-0.04:0.21)	-0.05 (-0.23:0.13)	0.05 (-0.08:0.18)	0.04 (-0.13:0.23)	0.00 (-0.12:0.12)	0.00 (-0.16:0.20)
Low	0.07 (-0.17:0.32)	-0.03 (-0.30:0.24)	0.12 (-0.09:0.34)	-0.02 (-0.26:0.23)	0.12 (-0.13:0.38)	0.11 (-0.16:0.40)	-0.02 (-0.21:0.16)	-0.02 (-0.24-0.20)
Income								
High	0.08 (-0.08:0.23)	Ref	0.16 (0.00:0.33)	Ref	0.07 (-0.09:0.23)	Ref	0.00 (-0.15:0.14)	Ref
Medium	0.12 (-0.00:0.25)	0.04 (-0.16:0.24)	0.09 (-0.02:0.21)	-0.07 (-0.27:0.13)	0.00 (-0.12:0.12	-0.07 (-0.27:0.13)	-0.04 (-0.15:0.06)	-0.04 (-0.22:0.14)
Low	0.11 (-0.06:0.28)	0.02 (-0.20:0.26)	0.11 (-0.05:0.28)	-0.05 (-0.28:0.18)	0.14 (-0.03:0.32)	0.08 (-0.16:9.21	0.07 (-0.09:0.24)	0.08 (-0.14:0.29)

Additional consultation rates are defined as the difference between the cancer cohort and the reference cohort.
Absolute difference in additional consultation rates compared to the reference group.

Statistically significant absolute differences are shown in bold type.

Supplementary Table 2. Likelihood (OR) of frequent GP attendance (four or more consultations) among children with specific cancer types			
	Leukaemia (n=347)	**CNS** (n=367)	**Other solid tumors** (n= 443)
Parental cohabitation status			
Living with a partner	1.00	1.00	1.00
Living alone	0.84 (0.47:1.49)	0.90 (0.50:1.61)	0.99 (0.53:1.86)
Siblings			
No	1.00	1.00	1.00
Yes	1.43 (0.47:1.49)	1.12 (0,59:2.12)	1.10 (0.57:2.12)
Labour market affiliation			
Employed	1.00	1.00	1.00
Mixed	0.81 (0.39:1.63)	0.89 (0.40:2.01)	1.68 (0.79:3.52)
Unemployed	1.05 (0.41:2.72)	1.21 (0.50:2.94)	0.78 (0.24:2.51)
Educational level			
High	1.00	1.00	1.00
Medium	**1.91 (1.09:3.33)**	1.12 (0.64: 1.96)	0.74 (0.41:1.32)
Low	1.20 (0.53:2.69)	1.13 (0.51:2.49)	0.67 (0.28:1.61)
Income			
High	1.00	1.00	1.00
Medium	1.65 (0.90:3.04)	1.56 (0.80:3.0)	1.94 (0.97:3.88)
Low	2.23 (0.95:5.26)	1.41 (0.57:3.45)	1.68 (0.68:4.25)

The model is adjusted for age and gender.

Statistically significant estimates are shown in bold type.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4, 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, 5
Bias	9	Describe any efforts to address potential sources of bias	4, 5
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5, 6
		(*b*) Describe any methods used to examine subgroups and interactions	x
		(*c*) Explain how missing data were addressed	x
		(*d*) If applicable, explain how loss to follow-up was addressed	x
		(*e*) Describe any sensitivity analyses	x
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 and figure 1
		(b) Give reasons for non-participation at each stage	x
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7, 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8 Supp. Table 1 and 2, Table 2, 3 and 4
		(*b*) Report category boundaries when continuous variables were categorized	x
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	x
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7 Supp. Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8, 9, 10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Utilization of primary care before a childhood cancer diagnosis: Do socioeconomic factors matter? A Danish nationwide population-based matched cohort study

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Utilization of primary care before a childhood cancer diagnosis: Do socioeconomic factors matter? A Danish nationwide population-based matched cohort study

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Number of figures: 2

Number of references: 46

Abstract

Objectives: Early diagnosis of childhood cancer is critical. Nevertheless, little is known about the potential role of inequality. This study aims to describe the use of primary care two years before a childhood cancer diagnosis and to investigate whether socioeconomic factors influence the use of consultations and diagnostic tests in primary care.

Design: A national population-based matched cohort study.

Setting and participants: This study uses observational data from four Danish nationwide registers. All children aged 0-15 diagnosed with cancer during 2008-2015 were included (N = 1,386). Each case was matched on gender and age with 10 references (N = 13,860).

Primary and secondary outcome measures: The primary outcome was additional rates for consultations and for invoiced diagnostic tests for children with cancer according to parental socioeconomic factors. Furthermore, we estimated the association between socioeconomic factors and frequent use of consultations, defined as at least four consultations, and the odds of receiving a diagnostic test within three months of diagnosis.

Results: Children with cancer from families with high income had 1.46 (95% CI: 1.23:1.69) additional consultations three months before diagnosis, whereas children from families with low income had 1.85 (95% CI: 1.60:2.11) additional consultations. The highest odds of frequent use of consultations was observed among children from low-income families (OR: 1.94, 95% CI: 1.24:3.03). A higher odds of receiving an invoiced diagnostic test was seen for children from families with mid-educational level (OR: 1.46, 95% CI: 1.09:1.95).

Conclusion: We found a socioeconomic gradient in the use of general practice before a childhood cancer diagnosis. This suggests that social inequalities exist in the pattern of healthcare utilization in general practice.

Article summary

- This large nationwide study is based on high-quality data from four nationwide registers.
- The risk of selection bias and information bias was limited.
- Matching was used to reduce potential confounding effects of age and gender.
- Multiple socioeconomic variables were examined in the analysis to ensure high validity of findings.
- A limitation was the lack of information on the reasons for requesting consultations and tests.

Introduction

Childhood cancer is the second most common cause of death among children in developed countries and is only outnumbered by accidents [1]. Denmark has one of the highest incidence rates of childhood cancer among high-income countries, with an annual incidence rate around 14 cases per 100,000 children below age 15 years [2,3].

Diagnosis of childhood cancer is a challenging task in general practice as children with early-stage cancer often present with non-specific and vague symptoms that mimic common conditions such as viral infection [4,5]. A Danish study showed that excess healthcare use, which can be seen as a proxy for symptoms of childhood cancer, occurs several months before the diagnosis is established [6]. The time leading up to the cancer diagnosis is often full of worries for the involved families. Moreover, delayed diagnosis can cause longstanding effects, such as distress in the family and poor quality of life, and may negatively affect the curability and survival [5,7].

Several studies have documented inequalities in the healthcare use between patients with low and high socioeconomic position (SEP) [8-11]. Children from families with lower SEP are more frequent in contact with the health care system. They more often suffer from chronic diseases, are more likely to acquire infectious diseases and have increased risk of injuries [12-14]. However, the utilization of preventive child health examinations is lower in the deprived part of the population [8]. Additionally, a growing body of research shows that parental socioeconomic factors influence childhood cancer survival, even in countries with free access to high-quality healthcare [15-18].

One question that arises in this context is whether socioeconomic differences influence the utilization of primary care for childhood cancer and (if positive) to what extent. Knowledge about inequality in early diagnosis of childhood cancer is essential to ensure an optimal diagnostic route, regardless of the patient's socioeconomic position.

The aim of this study is to describe the use of primary care two years before a diagnosis of childhood cancer and to investigate whether socioeconomic factors modify the use of consultations and the diagnostic tests performed in primary care.

Method

We conducted a national population-based matched cohort study using data from four nationwide Danish registers: I) the Danish Civil Registration System, which holds basic demographic information on all Danish citizens, II) the Danish Cancer Register (DCR), which holds information on all cancer diagnoses in Denmark, III) the Danish National Health Insurance Service Register (NHSR), which holds information on all contacts to and services provided by general practice based on remuneration coding [19], and IV) Statistics Denmark, which is the central authority on Danish statistics and holds socioeconomic and demographic information on all citizens [20]. The civil registration number, a unique 10-digit personal identification number assigned to every Danish citizen at birth or immigration, was used to link data at the individual level.

Setting

The Danish healthcare system is tax-financed and offers equal and universal access to healthcare for all citizens. All Danish residents have direct and free access to general practitioners (GPs), and more than 98% of all citizens are registered with a specific general practice [21]. GPs act as gatekeepers to the rest of the healthcare system; they carry out initial diagnostic investigations including referrals to specialists. Specialist and hospital care is free of charge. Except for emergencies and ear-nose-throat and eye specialists, all citizens must first contact their general practice to get a referral.

Study population

All children aged 0-15 years diagnosed with an incident cancer according to the Danish version of the International Classification of Diseases (ICD-10) (C00-D48) in the period of 1 January 2008 to 31 December 2015 were identified in the DCR. All childhood cancers were divided into five diagnostic subgroups in accordance with the ICD-10 codes: leukaemia (C91-95), lymphoma (C81-85, C96), CNS tumour (C70-72, C75.1-3, D32-33, D35.2-4, D42-43, D44.3-5), bone tumour (C40-41) and other solid tumours (remaining ICD-10 cancer codes).

For each childhood cancer patient, ten random references were sampled and matched on date of birth and gender. Index date was the date of diagnosis for the matched cancer patient. The references had to be alive, without a history of cancer, and resident in Denmark at the index date (i.e. date of diagnosis) and two years before the index date.

The date of diagnosis in the DCR is based on the international hierarchy, that uses the dates of histological confirmation, admission to hospital and date of death. The histology date always takes precedence over any other date obtained [22] .

Socioeconomic factors

We used information on SEP from the calendar year before the index date in order to minimise the impact from the child's disease on the socioeconomic indicators. SEP indicators were categorised as described in the following. Parental cohabitation status was divided into living with a partner (married/cohabitating) or living alone (divorced, widowed or never married). Household labour market affiliation was divided into employed, unemployed (unemployed, old age pension or early retirement pension, disability pension or welfare payments) and mixed (one parent employed, the other unemployed). Educational level was classified according to UNESCO's International Standard Classification of Education into three groups (low educational level: ≤10 years, medium educational level: >10 and ≤15 years, and high educational level: >15 years) and was based on the highest obtained educational level of the mother. In cases with no mother in the household, the highest obtained educational level of the father was used. Income was measured as equalised disposable household income (salaries, wages, all types of supplementary benefits and pensions) and comprised all income after taxation for the entire household adjusted for number of persons in the household [23]. Income was categorised into three groups: low (1st quartile), medium (2nd and 3rd quartile) and high (4th quartile). Number of children in the household was dichotomised as the presence of siblings (yes/no).

Primary healthcare services

The main outcomes were rates of consultations and invoiced diagnostic tests per patient performed in general practice; these data were obtained from the NHSR. Consultations included face-to-face consultations, home visits, telephone and email consultations during daytime. Planned vaccinations and preventive child health examinations were not included.

Invoiced diagnostic tests included urine tests (stick, microscopy of urine and urine culture), blood tests (C-reactive protein (CRP), differential blood count, blood glucose and haemoglobin), pulmonary function tests, electrocardiography (ECG) and tests for streptococcal throat infection.

Statistical analyses

We calculated the quarterly difference between rates for consultations and invoiced diagnostic tests performed for children who were later diagnosed with cancer and reference children stratified for each socioeconomic factor. In the following, this incidence rate difference (IRD) will be referred to as 'additional rates'.

We calculated the absolute difference in 'additional rates' compared to the reference group for consultations and invoiced diagnostic tests. We used generalised linear models with identity link for the Poisson family. For both additional rates and absolute differences, we applied cluster robust variance estimation to account for repeated measurements for the subjects.

Logistic regression was used to estimate the association between socioeconomic variables and the odds of frequent use of consultations, frequent use was defined as having at least four consultations in the three months before diagnosis based on the fourth quartile. Two models were used. First, a basic model adjusted for cancer type, age and gender for each of the socioeconomic variables. Second, a model adjusted for cancer type, age, gender and all included socioeconomic variables. Similar models were used to estimate the association between SEP and the probability of receiving at least one invoiced diagnostic test during the last three months before diagnosis.

A p-value of 0.05 or less was considered statistically significant. Analyses were performed using Stata/IC version 15.0.

Ethics

The study was approved by the Danish Data Protection Agency (j.no. 2009-41-3471). According to Danish law, approval by the National Committee on Health Research Ethics was not required as no biomedical intervention was performed, and no biological material was collected [24].

Patient and public involvement

Patients or public were not involved in this study.

Results

Characteristics of the study population

In all, 1,386 eligible children with cancer and 13,860 matched references were identified (Figure 1) and characteristics are shown in Table 1. The proportion of children consulting general practice within three months before diagnosis (i.e. index date) was 75.3 % among cases and 37.7% among references. Invoiced diagnostic tests were performed in primary care within three months before diagnosis for 29.4 % of cases and 6.9 % of references (Table 1).

Consultation rates before diagnosis

The consultation rates for cases and references are shown in Table 2. Compared to references, a minor statistically significant increase in consultations was seen among children with cancer from 16-18 months before the diagnosis. A progressive increase was observed from 10-12 months before the diagnosis, especially during the last three months (incidence rate difference (IRD): 1.67 (95% CI: 1.55:1.80)) ($p < 0.001$) (Table 2).

Children from families with high educational level (IRD: 1.61 (95% CI: 1.43:1.80)) or high income (IRD: 1.46 (95% CI: 1.23:1.69)) had lowest additional consultation rates in the last three months before diagnosis, whereas children from families with low educational level (IRD: 1.83 (95% CI: 1.52:2.15)) or low income (IRD: 1.85 (95% CI: 1.60:2.11)) had more (Supplementary Table 1). No differences in additional consultation rates were observed for parental cohabitation status, having siblings or household labour market affiliation (Figure 2 and Supplementary Table 1).

Odds of frequent use of consultations

Of the children with cancer, 29% were frequent users of consultations three months before diagnosis. The proportion was modified by income; the highest odds of frequent use of consultations was observed among children from low-income families (odds ratio (OR): 1.94 (95% CI: 1.24:3.03)) (Table 3).

A sub-analysis revealed that this association was more pronounced for children with leukaemia (OR: 2.23, 95%: 0.95:5.26)) (Supplementary Table 2) and for children from medium-level educated families (OR: 1.91 (95% CI 1.09:3.33)) compared to children from high-level educated families. This association was not found for children with CNS or other solid tumours (Supplementary Table 2).

Invoiced diagnostic tests

The rates of invoiced diagnostic tests and additional rates are shown in Table 2. Children with cancer on average had 1.71 (95% CI: 1.55:1.87) invoiced diagnostic tests performed during the two years before the diagnosis compared to 0.95 (95% CI: 0.92:0.98) among the references. A progressive increase in the rates of diagnostic tests was observed in the 4-6 months before the diagnosis (Table 2).

During the three months before the diagnosis, 29.4 % of children with cancer had at least one invoiced diagnostic test performed in primary care (Table 1). We found a statistically significant higher odds of receiving a diagnostic test among children from families with medium-level education (OR: 1.46 (95% CI: 1.09:1.95)). We found no statistically significant associations between other socioeconomic variables and the odds of receiving one or more invoiced diagnostic tests (Table 4).

Discussion

Principal findings

Children with cancer generally had more consultations and clinical investigations in general practice than the references. A progressive increase was seen in the 10-12 months before diagnosis, which was anticipated. However, the probability of receiving more consultations and diagnostic tests was modified by parental socioeconomic position.

Children with cancer from families with high-level education and high-level income had fewest additional consultations in the last three months before diagnosis. Children with cancer from households with low- and medium-level income were thus more likely to be frequent users of consultations in the three months before the diagnosis compared to high-income families. This trend was more pronounced for children with leukaemia than for children with other cancer types. The odds of receiving at least one invoiced diagnostic test during the last three months before diagnosis was higher for children from households with medium-level education compared to high- or low-level education.

Comparison with existing literature

The observed overall increase in the rates of both consultations and diagnostic tests is in line with previous findings [6,25,26]. Previous studies have documented an association between socioeconomic factors and a prolonged diagnostic interval in childhood cancer [27-30]. A prolonged interval might occur if the GP does not suspect cancer, or if the GP interprets the symptoms as something else, does not communicate or interact optimally with the child and the parents or postpones referral for specialist investigation. Our

findings could indicate that some or several of these factors may be at play in parents with low education.

The GP's intuition plays an important role in the suspicion of serious disease [31-34]. A study from the UK reported that the GP-parent relationship had significant impact on the process of obtaining a paediatric leukaemia diagnosis [34]. For example, the GP's concerns and actions were partly shaped by how anxious s/he estimated the parents to be. The GP's initial perception of a parent as being a 'worrier' or too sensitive could influence the way the parents' concerns are dealt with; 'worriers' are generally taken less seriously. However, the importance of listening to the parents was highlighted by the GPs in one of the studies although many parents reported that the GP did not seem to take their worries seriously [34]. We were able to demonstrate that children from families with lower SEP tended to see the GP more often before diagnosis. This indicates that some of these mechanisms are seen in children of parents with low income and low education. In addition, children of parents with low income might have other diseases, which may also delay the suspicion of cancer in general practice.

The communication during a consultation is a complex matter, which is influenced by numerous factors. An international review showed that patients with low SEP communicate less actively when consulting a GP and receive less information from the GP than patients with high SEP [35]. This may partly explain why we observed differences in the utilization of primary care services before a cancer diagnosis. A Danish study has shown that higher SEP of the parents, such as high education, is associated with better survival of children with cancer [36]. One possible explanation raised by our study is that these children may have a delayed diagnosis.

Identifying the few children with malignant cancer disease is a major challenge in general practice, and it often includes wait-and-see strategies and very low positive predictive values for even serious symptoms of disease [37]. The use of 'safety-netting' as a strategy to manage diagnostic uncertainty is increasingly recognised as important in adult cancer diagnostics and may be even more pertinent in children [38]. The term 'safety-netting' was introduced to general practice by Roger Neighbour who considered it a core component of the consultation. He defined safety-netting as encompassing three questions GPs might ask themselves when they make a working diagnosis; If I'm right what do I expect to happen? How will I know if I'm wrong? What would I do then? The aim is to ensure patients are monitored until their symptoms are explained[39]. This may be particularly relevant if the child comes from a family with limited socioeconomic resources.

Strengths and limitations of the study

This nationwide population-based matched cohort study was based on data from several Danish national registers. Danish registers are known to be very complete and valid [40-42]. A major strength was the low risk of selection bias and information bias concerning classification of diagnosis, socioeconomic factors and healthcare use. Despite the low incidence of cancer in children, we obtained sufficient data to ensure high statistical precision. This allowed us to detect small, yet clinically relevant, differences between the groups.

Our broad categorisations of, for example, income and education might have caused loss of detailed information. As these categorisations were defined *a priori*, some groups could have been defined too broadly and caused loss of information or introduced residual confounding. Still, we based the definitions on international standard classifications [43].

A limitation of this study was the lack of information on the reasons for the requested consultations and performed tests. Potential confounding effects of age and gender were reduced by matching included cases with references. However, we cannot exclude that residual confounding by other factors (e.g. comorbidity) could have influenced our results. Another limitation to consider is that the date of diagnosis recorded by DCR might vary from the date of the clinical diagnosis. In some cases, the cancer may have been diagnosed clinically prior to the histopathological confirmation. However, we do not expect a systematic variation in registration according to SEP and the effect on number of consultations and diagnostic tests, if any, is therefore likely to be small.

Our study has the advantage of using multiple socioeconomic variables in the analysis. There is consensus that SEP is a complex and multifaceted aspect, which should not be considered in isolation when exploring socioeconomic inequalities in health [44-46].

The generalisability of our results has certain limitations. Measuring SEP is a complex matter, and our findings may not apply to countries with different socioeconomic conditions or organisation of primary care. Yet, this challenge is seen in any study of socioeconomics and healthcare.

Conclusion and implications

This nationwide population-based cohort study shows that children who are later diagnosed with cancer tend to use primary care more often in the months before the diagnosis. We were able to demonstrate that children from families with lower SEP tended to see the GP more often before cancer diagnosis.

This study shows that despite the direct and free access to GPs and primary care, some social inequalities are seen in the healthcare utilization and handling of these patients in general practice. These variations are likely to affect the child's diagnostic pathway, treatment and prognosis. Our findings thus call for future research.

Author contributions

JA, PV and CFA conceptualised and designed the study. CFA collected and analysed the data. JA, PV and CFA all contributed to the interpretation of the data. CFA drafted the article. PV and JA critically revised the article multiple times. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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Competing interests statement

All authors declare to have no competing interests.

Data sharing statement

The datasets analysed in the current study are stored in a secured research database and may be available upon presentation of formal approval.

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Abbreviations

CI: Confidence interval

CNS: Central nervous system

DCR: Danish Cancer Register

ECG: Electrocardiography

GP: General practitioner

ICD-10: International Classification of Diseases, 10th edition

IRD: Incidence rate difference

NHSR: Danish National Health Insurance Service Register

OR: Odds ratio

SEP: Socioeconomic position

UNESCO: United Nations' Educational Scientific and Cultural Organization

References

1. Kaatsch P. Epidemiology of childhood cancer. *Cancer Treat Rev*. 2010;36(4):277-285. doi: 10.1016/j.ctrv.2010.02.003.

2. Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. *Cancer*. 2008;112(3):461-472. doi: 10.1002/cncr.23205.

3. van der Horst M, Winther JF, Olsen JH. Cancer incidence in the age range 0-34 years: Historical and actual status in denmark. *International Journal of Cancer*. 2006;118(11):2816-2826. doi: 10.1002/ijc.21566.

4. Ahrensberg JM, Hansen RP, Olesen F, Schrøder H, Vedsted P. Presenting symptoms of children with cancer: A primary-care population-based study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2012;62(600):e458-465. doi: 10.3399/bjgp12X652319.

5. Dixon-Woods M, Findlay M, Young B, Cox H, Heney D. Parents' accounts of obtaining a diagnosis of childhood cancer. *The Lancet*. 2001;357(9257):670-674. doi: 10.1016/S0140-6736(00)04130-1.

6. Ahrensberg JM, Fenger-Grøn M, Vedsted P. Use of primary care during the year before childhood cancer diagnosis: A nationwide population-based matched comparative study. *PloS one*. 2013;8(3):e59098. doi: 10.1371/journal.pone.0059098.

7. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? systematic review. *Br J Cancer*. 2015;112 Suppl 1:S92. doi: 10.1038/bjc.2015.48.

8. Søndergaard G, Biering-Sørensen S, Ishøy Michelsen S, Schnor O, Nybo Andersen A. Non-participation in preventive child health examinations at the general practitioner in denmark: A register-based study. *Scand J Prim Health Care*. 2008;26(1):5-11. doi: 10.1080/02813430801940877.

9. Hoebel J, Rattay P, Prütz F, Rommel A, Lampert T. Socioeconomic status and use of outpatient medical care: The case of germany. *PloS one*. 2016;11(5):e0155982. doi: 10.1371/journal.pone.0155982.

10. Finnvold JE. Access to specialized health care for asthmatic children in norway: The significance of parents? educational background and social network. *Soc Sci Med*. 2006;63(5):1316-1327. doi: 10.1016/j.socscimed.2006.03.045.

11. Stirbu I, Kunst A, Mielck A, Mackenbach J. Inequalities in utilisation of general practitioner and specialist services in 9 european countries. *BMC Health Services Research*. 2011;11(1):288-288. doi: 10.1186/1472-6963-11-288.

12. Birken CS, Macarthur C. Socioeconomic status and injury risk in children. *Paediatrics & child health*. 2004;9(5):323.

13. Lous J, Friis K, Vinding AL, Fonager K. Social marginalization reduces use of ENT physicians in primary care. *Int J Pediatr Otorhinolaryngol*. 2011;76(3):370-373. doi: 10.1016/j.ijporl.2011.12.011.

14. NT, CS, HCS, HTS. Socioeconomic factors and risk of hospitalization with infectious diseases in 0- to 2-year-old danish children. *Eur J Epidemiol*. 2005;20(5):467-474. doi: 10.1007/s10654-005-0719-2.

15. Mogensen H, Modig K, Tettamanti G, Talbäck M, Feychting M. Socioeconomic differences in cancer survival among swedish children. *Br J Cancer*. 2016;114(1):118. doi: 10.1038/bjc.2015.449.

16. Adam M, Rueegg CS, Schmidlin K, et al. Socioeconomic disparities in childhood cancer survival in switzerland : Socioeconomic disparities in cancer survival. *International Journal of Cancer*. 2016;138(12):2856-2866. doi: 10.1002/ijc.30029.

17. Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. *International Journal of Cancer*. 2012;130(8):1870-1878. doi: 10.1002/ijc.26186.

18. Erdmann F, Winther JF, Dalton SO, et al. Survival from childhood hematological malignancies in denmark: Is survival related to family characteristics? : Family traits and hematological malignancies survival. *Pediatric Blood & Cancer*. 2016;63(6):1096-1104. doi: 10.1002/pbc.25950.

19. Sahl Andersen J, De Fine Olivarius N, Krasnik A. The danish national health service register. *Scand J Public Health*. 2011;39(7_suppl):34-37. doi: 10.1177/1403494810394718.

20. Statistics Denmark. http://www.dst.dk/en. Updated 2017. Accessed 08/12, 2017.

21. Pedersen KM, Andersen JS, Sondergaard J. General practice and primary health care in denmark. *J Am Board Fam Med*. 2012;25(Suppl 1):S34–8.

22. Sundhedsstyrelsen. *Det moderniserede cancerregister : Metode og kvalitet.* Sundhedsstyrelsen; 2009.

23. OECD. What are equivalence scales? www.oecd.org/eco/growth/OECD-Note-EquivalenceScales.pdf. Accessed 01/25, 2018.

24. The National Committee on Health Research Ethics. Act on research ethics review of health research projects. http://www.nvk.dk/english. Updated 2017. Accessed 08/13, 2017.

25. Dommett RM, Redaniel MT, Stevens MCG, Hamilton W, Martin RM. Features of childhood cancer in primary care: A population-based nested case-control study. *Br J Cancer*. 2012;106(5):982. doi: 10.1038/bjc.2011.600.

26. Ansell P, Johnston T, Simpson J, Crouch S, Roman E, Picton S. Brain tumor signs and symptoms: Analysis of primary health care records from the UKCCS. *Pediatrics*. 2010;125(1):112-119. doi: 10.1542/peds.2009-0254 [doi].

27. Ahrensberg JM, Olesen F, Hansen RP, Schrøder H, Vedsted P. Childhood cancer and factors related to prolonged diagnostic intervals: A danish population-based study. *Br J Cancer*. 2013;108(6):1280. doi: 10.1038/bjc.2013.88.

28. Abdelkhalek E, Sherief L, Kamal N, Soliman R. Factors associated with delayed cancer diagnosis in egyptian children. *Clinical medicine insights.Pediatrics*. 2014;8:39.

29. Fajardo Gutiérrez A, Sandoval Mex AM, Mejía Aranguré JM, Rendón?Macías ME, MartínezGarcía MdC. Clinical and social factors that affect the time to diagnosis of mexican children with cancer. *Med Pediatr Oncol*. 2002;39(1):25-31. doi: 10.1002/mpo.10100.

30. Dang-Tan T, Trottier H, Mery LS, et al. Delays in diagnosis and treatment among children and adolescents with cancer in canada. *Pediatric blood & cancer*. 2008;51(4):468-474. doi: 10.1002/pbc.21600.

31. Hjertholm P, Moth G, Ingeman ML, Vedsted P. Predictive values of GPs' suspicion of serious disease: A population-based follow-up study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2014;64(623):e346.

32. Scheel BI, Ingebrigtsen SG, Thorsen T, Holtedahl K. Cancer suspicion in general practice: The role of symptoms and patient characteristics, and their association with subsequent cancer. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2013;63(614):e627.

33. Ingeman ML, Christensen MB, Bro F, Knudsen ST, Vedsted P. The danish cancer pathway for patients with serious non-specific symptoms and signs of cancer-a cross-sectional study of patient characteristics and cancer probability. *BMC Cancer*. 2015;15(1):421. doi: 10.1186/s12885-015-1424-5.

34. Clarke RT, Jones CH, Mitchell CD, Thompson MJ. 'Shouting from the roof tops': A qualitative study of how children with leukaemia are diagnosed in primary care. *BMJ open*. 2014;4(2):e004640. doi: 10.1136/bmjopen-2013-004640.

35. Willems S, De Maesschalck S, Deveugele M, Derese A, De Maeseneer J. Socio-economic status of the patient and doctor–patient communication: Does it make a difference? *Patient Education and Counseling*. 2005;56(2):139-146. doi: https://doi.org/10.1016/j.pec.2004.02.011.

36. Simony SB, Lund LW, Erdmann F, et al. Effect of socioeconomic position on survival after childhood cancer in denmark. *Acta Oncol*. 2016;55(6):742-750. doi: 10.3109/0284186X.2016.1144933.

37. Dommett RM, Redaniel MT, Stevens MC, Hamilton W, Martin RM. Features of childhood cancer in primary care: A population-based nested case-control study. *Br J Cancer*. 2012;106(5):982-987. doi: 10.1038/bjc.2011.600 [doi].

38. Nicholson BD, Mant D, Bankhead C. Can safety-netting improve cancer detection in patients with vague symptoms? *BMJ*. 2016;355. http://www.bmj.com/content/355/bmj.i5515.abstract.

39. Neighbour R. *The inner consultation.* 2nd edition ed. Oxford: Radcliffe Publishing; 2004.

40. Frank L. Epidemiology. when an entire country is a cohort. *Science (New York, N.Y.)*. 2000;287(5462):2398-2399. doi: 10.1126/science.287.5462.2398.

41. Statens Serum Institut. Validation of the danish cancer registry and selected clinical cancer databases - english abstract . http://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-

sundhedsregistre/sygedomme-laegemidler-og-behandlinger/cancerregisteret. Updated 2012. Accessed 08/16, 2017.

42. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39(7_suppl):12-16. doi: 10.1177/1403494811399956.

43. Unesco. International standard classification of education. http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf. Updated 2011. Accessed 01/24, 2018.

44. Shavers VL. Measurement of socioeconomic status in health disparities research. *J Natl Med Assoc*. 2007;99(9):1013.

45. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic status in health research: One size does not fit all. *JAMA*. 2005;294(22):2879-2888. doi: 10.1001/jama.294.22.2879.

46. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull*. 2007;81-82(1):21-37. doi: 10.1093/bmb/ldm001.

Tables

Table 1. Characteristics of the childhood cancer cohort and the gender- and age-matched reference cohort

	Cases		References	
	n	%	n	%
	1386	100.0	13860	100.0
Sex				
Girls	650	46.9	6500	46.9
Boys	736	53.1	7360	53.1
Age at diagnosis (index date)				
10-15 years	411	29.7	4110	29.7
5-9 years	360	26.0	3600	26.0
1-4 years	475	34.3	4750	34.3
0 years	140	10.1	1400	10.1
Type of cancer				
Leukaemia	347	25.0	-	-
Lymphoma	170	12.3	-	-
CNS tumour	367	26.5	-	-
Bone tumour	59	4.3	-	-
Other solid tumour	443	32.0	-	-
Siblings				
Yes	1044	75.3	10.329	74.5
No	276	19.9	2.870	20.7
Missing	66	4.8	661	4.8
Parental cohabitation status				
Living with a partner	915	66.0	8.972	64.7
Living alone	393	28.4	4.136	29.8
Missing	78	5.6	752	5.4
Educational level				
High (> 15 years)	547	39.5	5.587	40.3
Medium (>10-15 years)	531	38.3	5.267	38.0
Low (< 10 years)	211	15.2	2.091	15.1
Missing	97	7.0	915	6.6
Labour market affiliation				
Employed	987	71.2	9.876	71.3
Mixed	191	13.8	1.991	14.4
Unemployed	130	9.4	1.241	9.0
Missing	78	5.6	752	5.4
Household income				
High	330	23.8	3.294	23.8
Medium	655	47.3	6.601	47.6
Low	334	24.1	3.297	23.8
Missing	67	4.8	668	4.8
GP consultation within three months before diagnosis/ index date	1044	75.3	5220	37.7
Diagnostic test performed within three months before diagnosis/ index date	407	29.4	960	6.9

Table 2. Rates of consultations and invoiced diagnostic tests among cases and references

Months before diagnosis	Rates of consultations (95%CI)		Additional rates (95% CI)	Rates of diagnostic tests (95%CI)		Additional rates (95% CI)
	Cases (n= 1386)	**References** (n=13860)		**Cases** (n= 1386)	**References** (n=13860)	
1-3 months	2.43 (2.30:2.55)	0.75 (0.73:0.76)	**1.67 (1.55:1.80)**	0.72 (0.64:0.81)	0.12 (0.11:0.13)	**0.60 (0.52:0.69)**
4-6 months	1.02 (0.94:1.10)	0.82 (0.80:0.85)	**0.20 (0.12: 0.28)**	0.18 (0.14:0.23)	0.13 (0.12:0.14)	**0.05 (0.01:0.11)**
7-9 months	0.99 (0.91:1.08)	0.82 (0.80:0.84)	**0.18 (0.09:0.27)**	0.13 (0.11:0.17)	0.12 (0.11:0.13)	0.02 (-0.01:0.05)
10-12 months	0.95 (0.87:1.03)	0.83 (0.81:085)	**0.12 (0.04:0.20)**	0.13 (0.10:0.16)	0.12 (0.12:0.13)	0.01 (-0.02:0.04)
13-15 months	0.90 (0.82:0.98)	0.80 (0.78:0.83)	**0.10 (0.02:0.18)**	0.17 (0.13:0.21)	0.12 (0.53:0.13)	**0.05 (0.01:0.08)**
16-18 months	0.88 (0.80:0.95)	0.76 (0.74:0.79)	**0.11 (0.33: 0.19)**	0.13 (0.10:0.16)	0.11 (0.10:0.12)	0.02 (-0.01:0.05)
19- 21 months	0.85 (0.77:0.92)	0.79 (0.77:0.82)	0.05 (-0.03:0.13)	0.15 (0.11:0.18)	0.11 (0.10:0.12)	0.04 (-0.00:0.07)
22-24 months	0.79 (0.72:0.85)	0.79 (0.77:0.82)	0.00 (-0.08:0.07)	0.09 (0.07:0.11)	0.11 (0.11:0.13)	- 0.03 (-0.06:0.00)
Total (1-24 months)	8.82	6.38	**2.43 (2.08:2.78)**	1.71 (1.55:1.87)	0.95 (0.92:0.98)	**0.76 (0.64:0.88)**

Additional rates are the difference between consultation rates of cases and references.

Statistically significant additional rates are presented in bold type.

Table 3. Odds (OR) of frequent GP attendance in the last three months before diagnosis

	Basic model [a] OR (95% CI)	Adjusted model [b] OR (95% CI)
Parental cohabitation status		
Living with a partner	1.00	1.00
Living alone	0.90 (0.68:1.18)	0.86 (0.63:1.16)
Siblings		
No	1.00	1.00
Yes	1.23 (0.91:1.69)	1.19 (0.86:166)
Labour market affiliation		
Employed	1.00	1.00
Mixed	1.19 (0.84:1.67)	0.99 (0.68:1.47)
Unemployed	1.36 (0.92:2.02)	1.21 (0.73:1.99)
Educational level		
High	1.00	1.00
Medium	**1.35 (1.02:1.77)**	1.16 (0.87:1.55)
Low	1.25 (0.88:1.79)	0.98 (0.65: 1.47)
Income		
High	1.00	1.00
Medium	**1.76 (1.28:2.43)**	**1.70 (1.22:2.37)**
Low	**1.98 (1.38:2.85)**	**1.94 (1.24:3.03)**

[a]Adjusted for cancer subtype, age and gender
[b]Adjusted for cancer subtype, age, gender and all socioeconomic variables

Statistically significant estimates are presented in bold type.

Table 4. Odds (OR) of receiving an invoiced diagnostic test during the last three months before a childhood cancer diagnosis

	Basic model [a] OR (95% CI)	Adjusted model [b] OR (95% CI)
Parental cohabitation status		
Living with a partner	1.00	1.00
Living alone	0.88 (0.67:1.16)	0.88 (0.66:1.19)
Siblings		
No	1.00	1.00
Yes	1.12 (0.81:1.54)	1.06 (0.76:1.48)
Labour market affiliation		
Employed	1.00	1.00
Mixed	0.95 (0.66:1.35)	0.86 (0.57:1.28)
Unemployed	0.89 (0.59:1.37)	0.83 (0.49:1.42)
Educational level		
High	1.00	1.00
Medium	**1.42 (1.07:1.87)**	**1.46 (1.09:1.95)**
Low	1.14 (0.79:1.65)	1.26 (0.83:1.91)
Income		
High	1.00	1.00
Medium	1.12 (0.83:1.51)	1.03 (0.75:1.41)
Low	1.02 (0.71:1.44)	0.98 (0.63:1.54)

[a] **Adjusted for cancer subtype, age and gender**

[b] **Adjusted for cancer subtype, age, gender and all socioeconomic variables**

Statistically significant estimates are presented in bold type.

Figure legends

Figure 1: Flowchart of children eligible for inclusion in the study.

Figure 2: Consultation rates in general practice by socioeconomic factors.

Upper part: Additional consultation rates, in three-month intervals, for children with cancer and references two years before diagnosis/index date with 95% confidence intervals.

Lower part: The absolute difference in additional consultation rates with 95% confidence intervals.

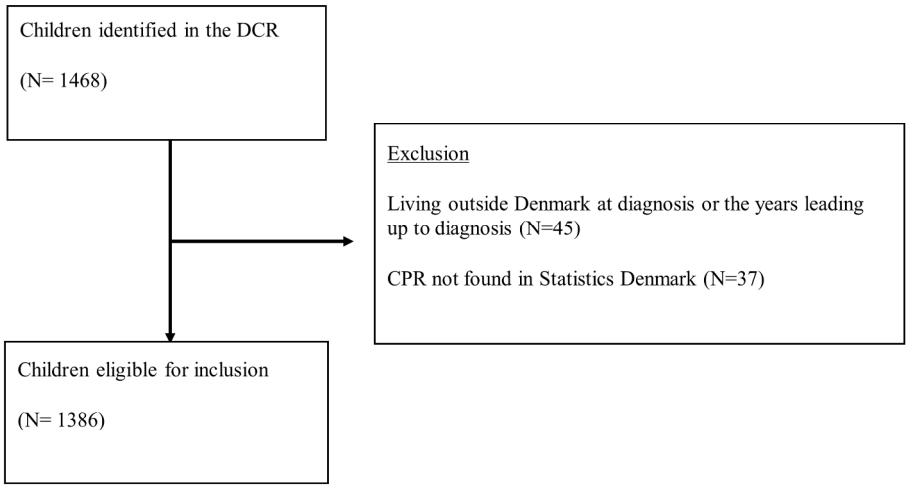

Figure 1: Flowchart of children eligible for inclusion in the study.

203x124mm (300 x 300 DPI)

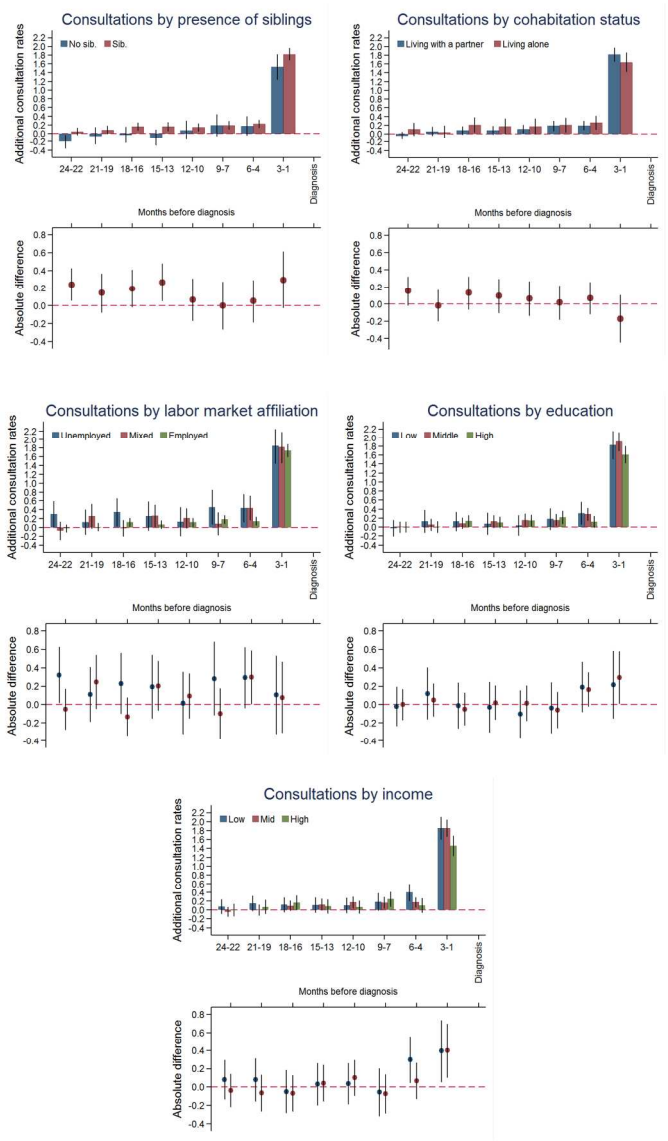

Figure 2. Consultation rates in general practice by socioeconomic factors.Upper part: Additional consultation rates in three-month intervals for children with cancer and references two years before diagnosis, with 95% confidence intervals. Lower part: Absolute difference in additional consultation rates, with 95% confidence intervals.

190x338mm (300 x 300 DPI)

***Supplementary* Table 1a. Additional consultation rates and absolute difference in general practice in the 1-12 months before diagnosis by household socioeconomic factors and three-month intervals**

	1-3 months		4-6 months		7-9 months		10-12 months	
	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference
All	1.67 (1.55:1.88)	-	0.20 (0.12:0.28)	-	0.18 (0.09:0.27)	-	0.12 (0.04: 0.20)	-
Parental cohabitation status								
Living with a partner	1.81 (1.61:2.01)	Ref	0.19 (0.08:0.29)	Ref	0.19 (0.07:0.29)	Ref	0.11 (0.01:0.21)	Ref
Living alone	1.64 (1.42:1.87)	-0.17 (-0.45:0.10)	0.26 (0.01:0.41)	0.07 (-0.12:0.26)	0.20 (0.04:0.37)	0.01 (-0.18:0.22)	0.17 (-0.00:0.35)	0.06 (-0.14:0.27)
Siblings								
No	1.53 (1.2 4:1.81)	Ref	0.17 (-0.05:0.39)	Ref	0.19 (-0.06:0.44)	Ref	0.08 (-0.14:0.29)	Ref
Yes	1.89 (1.68:1.96)	0.29 (-0.02:0.61)	0.23 (0.13:0.32)	0.05 (-0.19:0.29)	0.19 (0.09:0.28)	0.00 (-0.27:0.27)	0.14 (0.05:0.24)	0.06 (-0.17:0.31)
Labour market affiliation								
Employed	1.74 (0.60:1.89)	Ref	0.14 (0.05:0.23)	Ref	0.18 (0.08:0.28)	Ref	0.12 (0.02:0.21)	Ref
Mixed	1.82 (1.46:2.18)	0,08 (-0.31:0.47)	0.44 (0.16:0.71)	0.30 (- 0.01:0.60)	0.08 (-0.18:0.24)	- 0.10 (-0.38:0.18)	0.21 (-0.02:0.43)	0.09 (-0.15:0.34)
Unemployed	1.85 (1.45:2.25)	0.11 (-0.32:0.53)	0.43 (0.12:0.75)	0.29 (-0.04:0.62)	0.46 (0.07:0.85)	0.28 (-0.11:0.68)	0.13 (-0.19:0.46)	0.01 (-0.32:0.35)
Educational level								
High	1.61 (1.43:1.80)	Ref	0.12 (-0.01:0.24)	Ref	0.21 (0.07:0.36)	Ref	0.14 (0.01:0.27)	Ref
Medium	1.91 (1.70:2.12)	**0.30 (0.04:0.57)**	0.29 (0.15:0.42)	0.17 (-0.02:0.35)	0.15 (0.02: 0.29)	-0.06 (-0.25:0.14)	0.16 (0.01:0.27)	0.02 (-0.18:0.20)
Low	1.83 (1.52:2.15)	0.22 (-0.15:0.58)	0.31 (0.06:0.56)	0.19 (-0.08:0.47)	0.18 (-0.06:0.41)	-0.03 (-0.31-0.24)	0.04 (-0.18:0.26)	-0.10 (-0.36:0.15)
Income								
High	1.46 (1.23:1.69)	Ref	0.10 (-0.06:0.26)	Ref	0.24 (0.07:0.41)	Ref	0.07 (-0.08:0.21)	Ref
Medium	1.86 (1.67:2.05)	**0.40 (0.10:0.70)**	0.17 (0.05:0.28)	0.07 (-0.13:0.26)	0.16 (0.36:0.29)	-0.08 (-0.29:0.14)	0.17 (0.04:0.30)	0.10 (-0.09:0.29)
Low	1.85 (1.60:2.11)	**0.39 (0.05:0.74)**	0.40 (0.19:0.60)	**0.30 (0.04:0.55)**	0.18 (-0.01:0.38)	-0.06 (-0.32:0.20)	0.10 (-0.07:0.28)	0.03 (-0.19:0.26)

Additional consultation rates defined as the difference between the cancer cohort and the reference cohort.
Absolute difference in additional consultation rates compared to the reference group.

Statistically significant absolute differences are shown in bold type.

***Supplementary* Table 1b. Additional consultation rates and absolute difference in general practice in the 13-24 months before diagnosis by household socioeconomic factors and three-month intervals**

	13-15 months		16-18 months		19-21 months		22-24 months	
	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference
All	0.10 (0.02:0.18)	-	0.11 (0.03:0.19)	-	0.05 (-0.03:0.13)		-0.00 (-0.08:0.07)	-
Parental cohabitation status								
Living with a partner	0.08 (-0.02:0.18)	Ref	0.08 (-0.01:0.17)	Ref	0.06 (-0.05:0.16)	Ref	-0.06 (-0.14:0.04)	Ref
Living alone	0.18 (0.00:0.35)	0.09 (-0.11:0.29)	0.21 (0.04:0.38)	0.13 (-0.06:0.32)	0.04 (-0.01:0.19)	-0.02 (-0.02:0.16)	0.11 (-0.04:0.25)	0.15 (-0.02:0.32)
Siblings								
No	-0.10 (-0.29:0.09)	Ref	-0.04 (-0.21:-0.00)	Ref	-0.06 (-0.26:0.14)	Ref	-0.19 (-0.36:0.03)	Ref
Yes	0.16 (0.07:0.26)	0.26 (-0.05:0.48)	0.16 (0.07:0.25)	0.20 (-0.01:0.41)	0.09 (-0.01:0.18)	0.14 (-0.08:0.37)	0.04 (-0.04:0.14)	0.24 (-0.06:0.43)
Labour market affiliation								
Employed	0.06 (-0.03:0.16)	Ref	0.11 (0.02:0.21)	Ref	0.01 (-0.09:0.10)	Ref	-0.02 (-0.11:0.06)	Ref
Mixed	0.26 (0.01:0.52)	0.20 (-0.07:0.47)	-0.02 (-0.20:0.17)	-0.13 (-0.34:0.07)	0.25 (-0.03:0.53)	0.24 (-0.05:0.54)	-0.07 (-0.28:0.13)	-0.05 (-0.27:0.17)
Unemployed	0.25 (-0.08:0.59)	0.19 (-0.15:0.54)	0.34 (0.03:0.66)	0.23 (-0.10:0.56)	0.12 (-0.17:0.40)	0.11 (-0.19:0.41)	0.30 (0.01:0.59)	0.32 (0.02:0.63)
Educational level								
High	0.10 (-0.02:0.23)	Ref	0.14 (0.01:0.26)	Ref	0.01 (-0.12:0.37)	Ref	0.00 (-0.12:0.11)	Ref
Medium	0.12 (-0.01:0.26)	0.02 (-0.17:0.20)	0.09 (-0.04:0.21)	-0.05 (-0.23:0.13)	0.05 (-0.08:0.18)	0.04 (-0.13:0.23)	0.00 (-0.12:0.12)	0.00 (-0.16:0.20)
Low	0.07 (-0.17:0.32)	-0.03 (-0.30:0.24)	0.12 (-0.09:0.34)	-0.02 (-0.26:0.23)	0.12 (-0.13:0.38)	0.11 (-0.16:0.40)	-0.02 (-0.21:0.16)	-0.02 (-0.24-0.20)
Income								
High	0.08 (-0.08:0.23)	Ref	0.16 (0.00:0.33)	Ref	0.07 (-0.09:0.23)	Ref	0.00 (-0.15:0.14)	Ref
Medium	0.12 (-0.00:0.25)	0.04 (-0.16:0.24)	0.09 (-0.02:0.21)	-0.07 (-0.27:0.13)	0.00 (-0.12:0.12	-0.07 (-0.27:0.13)	-0.04 (-0.15:0.06)	-0.04 (-0.22:0.14)
Low	0.11 (-0.06:0.28)	0.02 (-0.20:0.26)	0.11 (-0.05:0.28)	-0.05 (-0.28:0.18)	0.14 (-0.03:0.32)	0.08 (-0.16:9.21	0.07 (-0.09:0.24)	0.08 (-0.14:0.29)

Additional consultation rates are defined as the difference between the cancer cohort and the reference cohort.
Absolute difference in additional consultation rates compared to the reference group.

Statistically significant absolute differences are shown in bold type.

***Supplementary* Table 2. Likelihood (OR) of frequent GP attendance (four or more consultations) among children with specific cancer types**

	Leukaemia (n=347)	**CNS** (n=367)	**Other solid tumors** (n= 443)
Parental cohabitation status			
Living with a partner	1.00	1.00	1.00
Living alone	0.84 (0.47:1.49)	0.90 (0.50:1.61)	0.99 (0.53:1.86)
Siblings			
No	1.00	1.00	1.00
Yes	1.43 (0.47:1.49)	1.12 (0,59:2.12)	1.10 (0.57:2.12)
Labour market affiliation			
Employed	1.00	1.00	1.00
Mixed	0.81 (0.39:1.63)	0.89 (0.40:2.01)	1.68 (0.79:3.52)
Unemployed	1.05 (0.41:2.72)	1.21 (0.50:2.94)	0.78 (0.24:2.51)
Educational level			
High	1.00	1.00	1.00
Medium	**1.91 (1.09:3.33)**	1.12 (0.64: 1.96)	0.74 (0.41:1.32)
Low	1.20 (0.53:2.69)	1.13 (0.51:2.49)	0.67 (0.28:1.61)
Income			
High	1.00	1.00	1.00
Medium	1.65 (0.90:3.04)	1.56 (0.80:3.0)	1.94 (0.97:3.88)
Low	2.23 (0.95:5.26)	1.41 (0.57:3.45)	1.68 (0.68:4.25)

The model is adjusted for age and gender.

Statistically significant estimates are shown in bold type.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4, 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, 5
Bias	9	Describe any efforts to address potential sources of bias	4, 5
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5, 6
		(*b*) Describe any methods used to examine subgroups and interactions	x
		(*c*) Explain how missing data were addressed	x
		(*d*) If applicable, explain how loss to follow-up was addressed	x
		(*e*) Describe any sensitivity analyses	x
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 and figure 1
		(b) Give reasons for non-participation at each stage	x
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7, 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8 Supp. Table 1 and 2, Table 2, 3 and 4
		(*b*) Report category boundaries when continuous variables were categorized	x
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	x
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7 Supp. Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8, 9, 10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Utilization of primary care before a childhood cancer diagnosis: Do socioeconomic factors matter? A Danish nationwide population-based matched cohort study

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Utilization of primary care before a childhood cancer diagnosis: Do socioeconomic factors matter? A Danish nationwide population-based matched cohort study

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Abstract

Objectives: Early diagnosis of childhood cancer is critical. Nevertheless, little is known about the potential role of inequality. This study aims to describe the use of primary care two years before a childhood cancer diagnosis and to investigate whether socioeconomic factors influence the use of consultations and diagnostic tests in primary care.

Design: A national population-based matched cohort study.

Setting and participants: This study uses observational data from four Danish nationwide registers. All children aged 0-15 diagnosed with cancer during 2008-2015 were included (N = 1,386). Each case was matched on gender and age with 10 references (N = 13,860).

Primary and secondary outcome measures: The primary outcome was additional rates for consultations and for invoiced diagnostic tests for children with cancer according to parental socioeconomic factors. Furthermore, we estimated the association between socioeconomic factors and frequent use of consultations, defined as at least four consultations, and the odds of receiving a diagnostic test within three months of diagnosis.

Results: Children with cancer from families with high income had 1.46 (95% CI: 1.23:1.69) additional consultations three months before diagnosis, whereas children from families with low income had 1.85 (95% CI: 1.60:2.11) additional consultations. The highest odds of frequent use of consultations was observed among children from low-income families (OR: 1.94, 95% CI: 1.24:3.03). A higher odds of receiving an invoiced diagnostic test was seen for children from families with mid-educational level (OR: 1.46, 95% CI: 1.09:1.95).

Conclusion: We found a socioeconomic gradient in the use of general practice before a childhood cancer diagnosis. This suggests that social inequalities exist in the pattern of healthcare utilization in general practice.

Article summary

- This large nationwide study is based on high-quality data from four nationwide registers.
- The risk of selection bias and information bias was limited.
- Matching was used to reduce potential confounding effects of age and gender.
- Multiple socioeconomic variables were examined in the analysis to ensure high validity of findings.
- A limitation was the lack of information on the reasons for requesting consultations and tests.

Introduction

Childhood cancer is the second most common cause of death among children in developed countries and is only outnumbered by accidents [1]. Denmark has one of the highest incidence rates of childhood cancer among high-income countries, with an annual incidence rate around 14 cases per 100,000 children below age 15 years [2,3].

Diagnosis of childhood cancer is a challenging task in general practice as children with early-stage cancer often present with non-specific and vague symptoms that mimic common conditions such as viral infection [4,5]. A Danish study showed that excess healthcare use, which can be seen as a proxy for symptoms of childhood cancer, occurs several months before the diagnosis is established [6]. The time leading up to the cancer diagnosis is often full of worries for the involved families. Moreover, delayed diagnosis can cause longstanding effects, such as distress in the family and poor quality of life, and may negatively affect the curability and survival [5,7].

Several studies have documented inequalities in the healthcare use between patients with low and high socioeconomic position (SEP) [8-11]. Children from families with lower SEP are more frequent in contact with the health care system. They more often suffer from chronic diseases, are more likely to acquire infectious diseases and have increased risk of injuries [12-14]. However, the utilization of preventive child health examinations is lower in the deprived part of the population [8]. Additionally, a growing body of research shows that parental socioeconomic factors influence childhood cancer survival, even in countries with free access to high-quality healthcare [15-18].

One question that arises in this context is whether socioeconomic differences influence the utilization of primary care for childhood cancer and (if positive) to what extent. Knowledge about inequality in early diagnosis of childhood cancer is essential to ensure an optimal diagnostic route, regardless of the patient's socioeconomic position.

The aim of this study is to describe the use of primary care two years before a diagnosis of childhood cancer and to investigate whether socioeconomic factors modify the use of consultations and the diagnostic tests performed in primary care.

Method

We conducted a national population-based matched cohort study using data from four nationwide Danish registers: I) the Danish Civil Registration System, which holds basic demographic information on all Danish citizens, II) the Danish Cancer Register (DCR), which holds information on all cancer diagnoses in Denmark, III) the Danish National Health Insurance Service Register (NHSR), which holds information on all contacts to and services provided by general practice based on remuneration coding [19], and IV) Statistics Denmark, which is the central authority on Danish statistics and holds socioeconomic and demographic information on all citizens [20]. The civil registration number, a unique 10-digit personal identification number assigned to every Danish citizen at birth or immigration, was used to link data at the individual level.

Setting

The Danish healthcare system is tax-financed and offers equal and universal access to healthcare for all citizens. All Danish residents have direct and free access to general practitioners (GPs), and more than 98% of all citizens are registered with a specific general practice [21]. GPs act as gatekeepers to the rest of the healthcare system; they carry out initial diagnostic investigations including referrals to specialists. Specialist and hospital care is free of charge. Except for emergencies and ear-nose-throat and eye specialists, all citizens must first contact their general practice to get a referral.

Study population

All children aged 0-15 years diagnosed with an incident cancer according to the Danish version of the International Classification of Diseases (ICD-10) (C00-D48) in the period of 1 January 2008 to 31 December 2015 were identified in the DCR. All childhood cancers were divided into five diagnostic subgroups in accordance with the ICD-10 codes: leukaemia (C91-95), lymphoma (C81-85, C96), CNS tumour (C70-72, C75.1-3, D32-33, D35.2-4, D42-43, D44.3-5), bone tumour (C40-41) and other solid tumours (remaining ICD-10 cancer codes).

For each childhood cancer patient, ten random references were sampled and matched on date of birth and gender. Index date was the date of diagnosis for the matched cancer patient. The references had to be alive, without a history of cancer, and resident in Denmark at the index date (i.e. date of diagnosis) and two years before the index date.

The date of diagnosis in the DCR is based on the international hierarchy, that uses the dates of histological confirmation, admission to hospital and date of death. The histology date always takes precedence over any other date obtained [22] .

Socioeconomic factors

We used information on SEP from the calendar year before the index date in order to minimise the impact from the child's disease on the socioeconomic indicators. SEP indicators were categorised as described in the following. Parental cohabitation status was divided into living with a partner (married/cohabitating) or living alone (divorced, widowed or never married). Household labour market affiliation was divided into employed, unemployed (unemployed, old age pension or early retirement pension, disability pension or welfare payments) and mixed (one parent employed, the other unemployed). Educational level was classified according to UNESCO's International Standard Classification of Education into three groups (low educational level: ≤10 years, medium educational level: >10 and ≤15 years, and high educational level: >15 years) and was based on the highest obtained educational level of the mother. In cases with no mother in the household, the highest obtained educational level of the father was used. Income was measured as equalised disposable household income (salaries, wages, all types of supplementary benefits and pensions) and comprised all income after taxation for the entire household adjusted for number of persons in the household [23]. Income was categorised into three groups: low (1st quartile), medium (2nd and 3rd quartile) and high (4th quartile). Number of children in the household was dichotomised as the presence of siblings (yes/no).

Primary healthcare services

The main outcomes were rates of consultations and invoiced diagnostic tests per patient performed in general practice; these data were obtained from the NHSR. Consultations included face-to-face consultations, home visits, telephone and email consultations during daytime. Planned vaccinations and preventive child health examinations were not included.

Invoiced diagnostic tests included urine tests (stick, microscopy of urine and urine culture), blood tests (C-reactive protein (CRP), differential blood count, blood glucose and haemoglobin), pulmonary function tests, electrocardiography (ECG) and tests for streptococcal throat infection.

Statistical analyses

We calculated the quarterly difference between rates for consultations and invoiced diagnostic tests performed for children who were later diagnosed with cancer and reference children stratified for each socioeconomic factor. In the following, this incidence rate difference (IRD) will be referred to as 'additional rates'.

We calculated the absolute difference in 'additional rates' compared to the reference group for consultations and invoiced diagnostic tests. We used generalised linear models with identity link for the Poisson family. For both additional rates and absolute differences, we applied cluster robust variance estimation to account for repeated measurements for the subjects.

Logistic regression was used to estimate the association between socioeconomic variables and the odds of frequent use of consultations, frequent use was defined as having at least four consultations in the three months before diagnosis based on the fourth quartile. Two models were used. First, a basic model adjusted for cancer type, age and gender for each of the socioeconomic variables. Second, a model adjusted for cancer type, age, gender and all included socioeconomic variables. Similar models were used to estimate the association between SEP and the probability of receiving at least one invoiced diagnostic test during the last three months before diagnosis.

A p-value of 0.05 or less was considered statistically significant. Analyses were performed using Stata/IC version 15.0.

Ethics

The study was approved by the Danish Data Protection Agency (j.no. 2009-41-3471). According to Danish law, approval by the National Committee on Health Research Ethics was not required as no biomedical intervention was performed, and no biological material was collected [24].

Patient and public involvement

Patients or public were not involved in this study.

Results

Characteristics of the study population

In all, 1,386 eligible children with cancer and 13,860 matched references were identified (Figure 1) and characteristics are shown in Table 1. The proportion of children consulting general practice within three months before diagnosis (i.e. index date) was 75.3 % among cases and 37.7% among references. Invoiced diagnostic tests were performed in primary care within three months before diagnosis for 29.4 % of cases and 6.9 % of references (Table 1).

Consultation rates before diagnosis

The consultation rates for cases and references are shown in Table 2. Compared to references, a minor statistically significant increase in consultations was seen among children with cancer from 16-18 months before the diagnosis. A progressive increase was observed from 10-12 months before the diagnosis, especially during the last three months (incidence rate difference (IRD): 1.67 (95% CI: 1.55:1.80)) ($p < 0.001$) (Table 2).

Children from families with high educational level (IRD: 1.61 (95% CI: 1.43:1.80)) or high income (IRD: 1.46 (95% CI: 1.23:1.69)) had lowest additional consultation rates in the last three months before diagnosis, whereas children from families with low educational level (IRD: 1.83 (95% CI: 1.52:2.15)) or low income (IRD: 1.85 (95% CI: 1.60:2.11)) had more (Supplementary Table 1). No differences in additional consultation rates were observed for parental cohabitation status, having siblings or household labour market affiliation (Figure 2 and Supplementary Table 1).

Odds of frequent use of consultations

Of the children with cancer, 29% were frequent users of consultations three months before diagnosis. The proportion was modified by income; the highest odds of frequent use of consultations was observed among children from low-income families (odds ratio (OR): 1.94 (95% CI: 1.24:3.03)) (Table 3).

A sub-analysis revealed that this association was more pronounced for children with leukaemia (OR: 2.23, 95%: 0.95:5.26)) (Supplementary Table 2) and for children from medium-level educated families (OR: 1.91 (95% CI 1.09:3.33)) compared to children from high-level educated families. This association was not found for children with CNS or other solid tumours (Supplementary Table 2).

Invoiced diagnostic tests

The rates of invoiced diagnostic tests and additional rates are shown in Table 2. Children with cancer on average had 1.71 (95% CI: 1.55:1.87) invoiced diagnostic tests performed during the two years before the diagnosis compared to 0.95 (95% CI: 0.92:0.98) among the references. A progressive increase in the rates of diagnostic tests was observed in the 4-6 months before the diagnosis (Table 2).

During the three months before the diagnosis, 29.4 % of children with cancer had at least one invoiced diagnostic test performed in primary care (Table 1). We found a statistically significant higher odds of receiving a diagnostic test among children from families with medium-level education (OR: 1.46 (95% CI: 1.09:1.95)). We found no statistically significant associations between other socioeconomic variables and the odds of receiving one or more invoiced diagnostic tests (Table 4).

Discussion

Principal findings

Children with cancer generally had more consultations and clinical investigations in general practice than the references. A progressive increase was seen in the 10-12 months before diagnosis, which was anticipated. However, the probability of receiving more consultations and diagnostic tests was modified by parental socioeconomic position.

Children with cancer from families with high-level education and high-level income had fewest additional consultations in the last three months before diagnosis. Children with cancer from households with low- and medium-level income were thus more likely to be frequent users of consultations in the three months before the diagnosis compared to high-income families. This trend was more pronounced for children with leukaemia than for children with other cancer types. The odds of receiving at least one invoiced diagnostic test during the last three months before diagnosis was higher for children from households with medium-level education compared to high- or low-level education.

Comparison with existing literature

The observed overall increase in the rates of both consultations and diagnostic tests is in line with previous findings [6,25,26]. Previous studies have documented an association between socioeconomic factors and a prolonged diagnostic interval in childhood cancer [27-30]. A prolonged interval might occur if the GP does not suspect cancer, or if the GP interprets the symptoms as something else, does not communicate or interact optimally with the child and the parents or postpones referral for specialist investigation. Our

findings could indicate that some or several of these factors may be at play in parents with low education.

The GP's intuition plays an important role in the suspicion of serious disease [31-34]. A study from the UK reported that the GP-parent relationship had significant impact on the process of obtaining a paediatric leukaemia diagnosis [34]. For example, the GP's concerns and actions were partly shaped by how anxious s/he estimated the parents to be. The GP's initial perception of a parent as being a 'worrier' or too sensitive could influence the way the parents' concerns are dealt with; 'worriers' are generally taken less seriously. However, the importance of listening to the parents was highlighted by the GPs in one of the studies although many parents reported that the GP did not seem to take their worries seriously [34]. We were able to demonstrate that children from families with lower SEP tended to see the GP more often before diagnosis. This indicates that some of these mechanisms are seen in children of parents with low income and low education. In addition, children of parents with low income might have other diseases, which may also delay the suspicion of cancer in general practice.

The communication during a consultation is a complex matter, which is influenced by numerous factors. An international review showed that patients with low SEP communicate less actively when consulting a GP and receive less information from the GP than patients with high SEP [35]. This may partly explain why we observed differences in the utilization of primary care services before a cancer diagnosis. A Danish study has shown that higher SEP of the parents, such as high education, is associated with better survival of children with cancer [36]. One possible explanation raised by our study is that these children may have a delayed diagnosis.

Identifying the few children with malignant cancer disease is a major challenge in general practice, and it often includes wait-and-see strategies and very low positive predictive values for even serious symptoms of disease [37]. The use of 'safety-netting' as a strategy to manage diagnostic uncertainty is increasingly recognised as important in adult cancer diagnostics and may be even more pertinent in children [38]. The term 'safety-netting' was introduced to general practice by Roger Neighbour who considered it a core component of the consultation. He defined safety-netting as encompassing three questions GPs might ask themselves when they make a working diagnosis; If I'm right what do I expect to happen? How will I know if I'm wrong? What would I do then? The aim is to ensure patients are monitored until their symptoms are explained[39]. This may be particularly relevant if the child comes from a family with limited socioeconomic resources.

Strengths and limitations of the study

This nationwide population-based matched cohort study was based on data from several Danish national registers. Danish registers are known to be very complete and valid [40-42]. A major strength was the low risk of selection bias and information bias concerning classification of diagnosis, socioeconomic factors and healthcare use. Despite the low incidence of cancer in children, we obtained sufficient data to ensure high statistical precision. This allowed us to detect small, yet clinically relevant, differences between the groups.

Our broad categorisations of, for example, income and education might have caused loss of detailed information. As these categorisations were defined *a priori*, some groups could have been defined too broadly and caused loss of information or introduced residual confounding. Still, we based the definitions on international standard classifications [43].

A limitation of this study was the lack of information on the reasons for the requested consultations and performed tests. Potential confounding effects of age and gender were reduced by matching included cases with references. However, we cannot exclude residual confounding by other factors. For example, comorbidity or geographic factors such as distance to GP or nearest hospital, could have influenced our results. It could be argued that geographic factors may influence the use of GP services, as there is a shortage of GPs in the more remote parts of Denmark. This might affect the accessibility and waiting time in the remote parts of Denmark, where a higher proportion of the population have lower SEP. This could potentially influence GP attendance and underestimates the effect of socioeconomic factors on utilization of primary care. Another limitation to consider is that the date of diagnosis recorded by DCR might vary from the date of the clinical diagnosis. In some cases, the cancer may have been diagnosed clinically prior to the histopathological confirmation. However, we do not expect a systematic variation in registration according to SEP and the effect on number of consultations and diagnostic tests, if any, is therefore likely to be small.

Our study has the advantage of using multiple socioeconomic variables in the analysis. There is consensus that SEP is a complex and multifaceted aspect, which should not be considered in isolation when exploring socioeconomic inequalities in health [44-46].

The generalisability of our results has certain limitations. Measuring SEP is a complex matter, and our findings may not apply to countries with different socioeconomic conditions or organisation of primary care. Yet, this challenge is seen in any study of socioeconomics and healthcare.

Conclusion and implications

This nationwide population-based cohort study shows that children who are later diagnosed with cancer tend to use primary care more often in the months before the diagnosis. We were able to demonstrate that children from families with lower SEP tended to see the GP more often before cancer diagnosis.
This study shows that despite the direct and free access to GPs and primary care, some social inequalities are seen in the healthcare utilization and handling of these patients in general practice. These variations are likely to affect the child's diagnostic pathway, treatment and prognosis. Our findings thus call for future research.

Author contributions

JA, PV and CFA conceptualised and designed the study. CFA collected and analysed the data. JA, PV and CFA all contributed to the interpretation of the data. CFA drafted the article. PV and JA critically revised the article multiple times. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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Competing interests statement

All authors declare to have no competing interests.

Data sharing statement

The datasets analysed in the current study are stored in a secured research database and may be available upon presentation of formal approval.

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Abbreviations

CI: Confidence interval

CNS: Central nervous system

DCR: Danish Cancer Register

ECG: Electrocardiography

GP: General practitioner

ICD-10: International Classification of Diseases, 10th edition

IRD: Incidence rate difference

NHSR: Danish National Health Insurance Service Register

OR: Odds ratio

SEP: Socioeconomic position

UNESCO: United Nations' Educational Scientific and Cultural Organization

References

1. Kaatsch P. Epidemiology of childhood cancer. *Cancer Treat Rev*. 2010;36(4):277-285. doi: 10.1016/j.ctrv.2010.02.003.

2. Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. *Cancer*. 2008;112(3):461-472. doi: 10.1002/cncr.23205.

3. van der Horst M, Winther JF, Olsen JH. Cancer incidence in the age range 0-34 years: Historical and actual status in denmark. *International Journal of Cancer*. 2006;118(11):2816-2826. doi: 10.1002/ijc.21566.

4. Ahrensberg JM, Hansen RP, Olesen F, Schrøder H, Vedsted P. Presenting symptoms of children with cancer: A primary-care population-based study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2012;62(600):e458-465. doi: 10.3399/bjgp12X652319.

5. Dixon-Woods M, Findlay M, Young B, Cox H, Heney D. Parents' accounts of obtaining a diagnosis of childhood cancer. *The Lancet*. 2001;357(9257):670-674. doi: 10.1016/S0140-6736(00)04130-1.

6. Ahrensberg JM, Fenger-Grøn M, Vedsted P. Use of primary care during the year before childhood cancer diagnosis: A nationwide population-based matched comparative study. *PloS one*. 2013;8(3):e59098. doi: 10.1371/journal.pone.0059098.

7. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? systematic review. *Br J Cancer*. 2015;112 Suppl 1:S92. doi: 10.1038/bjc.2015.48.

8. Søndergaard G, Biering-Sørensen S, Ishøy Michelsen S, Schnor O, Nybo Andersen A. Non-participation in preventive child health examinations at the general practitioner in denmark: A register-based study. *Scand J Prim Health Care*. 2008;26(1):5-11. doi: 10.1080/02813430801940877.

9. Hoebel J, Rattay P, Prütz F, Rommel A, Lampert T. Socioeconomic status and use of outpatient medical care: The case of germany. *PloS one*. 2016;11(5):e0155982. doi: 10.1371/journal.pone.0155982.

10. Finnvold JE. Access to specialized health care for asthmatic children in norway: The significance of parents? educational background and social network. *Soc Sci Med*. 2006;63(5):1316-1327. doi: 10.1016/j.socscimed.2006.03.045.

11. Stirbu I, Kunst A, Mielck A, Mackenbach J. Inequalities in utilisation of general practitioner and specialist services in 9 european countries. *BMC Health Services Research*. 2011;11(1):288-288. doi: 10.1186/1472-6963-11-288.

12. Birken CS, Macarthur C. Socioeconomic status and injury risk in children. *Paediatrics & child health*. 2004;9(5):323.

13. Lous J, Friis K, Vinding AL, Fonager K. Social marginalization reduces use of ENT physicians in primary care. *Int J Pediatr Otorhinolaryngol*. 2011;76(3):370-373. doi: 10.1016/j.ijporl.2011.12.011.

14. NT, CS, HCS, HTS. Socioeconomic factors and risk of hospitalization with infectious diseases in 0- to 2-year-old danish children. *Eur J Epidemiol*. 2005;20(5):467-474. doi: 10.1007/s10654-005-0719-2.

15. Mogensen H, Modig K, Tettamanti G, Talbäck M, Feychting M. Socioeconomic differences in cancer survival among swedish children. *Br J Cancer*. 2016;114(1):118. doi: 10.1038/bjc.2015.449.

16. Adam M, Rueegg CS, Schmidlin K, et al. Socioeconomic disparities in childhood cancer survival in switzerland : Socioeconomic disparities in cancer survival. *International Journal of Cancer*. 2016;138(12):2856-2866. doi: 10.1002/ijc.30029.

17. Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. *International Journal of Cancer*. 2012;130(8):1870-1878. doi: 10.1002/ijc.26186.

18. Erdmann F, Winther JF, Dalton SO, et al. Survival from childhood hematological malignancies in denmark: Is survival related to family characteristics? : Family traits and hematological malignancies survival. *Pediatric Blood & Cancer*. 2016;63(6):1096-1104. doi: 10.1002/pbc.25950.

19. Sahl Andersen J, De Fine Olivarius N, Krasnik A. The danish national health service register. *Scand J Public Health*. 2011;39(7_suppl):34-37. doi: 10.1177/1403494810394718.

20. Statistics Denmark. http://www.dst.dk/en. Updated 2017. Accessed 08/12, 2017.

21. Pedersen KM, Andersen JS, Sondergaard J. General practice and primary health care in denmark. *J Am Board Fam Med*. 2012;25(Suppl 1):S34–8.

22. Sundhedsstyrelsen. *Det moderniserede cancerregister : Metode og kvalitet.* Sundhedsstyrelsen; 2009.

23. OECD. What are equivalence scales? www.oecd.org/eco/growth/OECD-Note-EquivalenceScales.pdf. Accessed 01/25, 2018.

24. The National Committee on Health Research Ethics. Act on research ethics review of health research projects. http://www.nvk.dk/english. Updated 2017. Accessed 08/13, 2017.

25. Dommett RM, Redaniel MT, Stevens MCG, Hamilton W, Martin RM. Features of childhood cancer in primary care: A population-based nested case-control study. *Br J Cancer*. 2012;106(5):982. doi: 10.1038/bjc.2011.600.

26. Ansell P, Johnston T, Simpson J, Crouch S, Roman E, Picton S. Brain tumor signs and symptoms: Analysis of primary health care records from the UKCCS. *Pediatrics*. 2010;125(1):112-119. doi: 10.1542/peds.2009-0254 [doi].

27. Ahrensberg JM, Olesen F, Hansen RP, Schrøder H, Vedsted P. Childhood cancer and factors related to prolonged diagnostic intervals: A danish population-based study. *Br J Cancer*. 2013;108(6):1280. doi: 10.1038/bjc.2013.88.

28. Abdelkhalek E, Sherief L, Kamal N, Soliman R. Factors associated with delayed cancer diagnosis in egyptian children. *Clinical medicine insights.Pediatrics*. 2014;8:39.

29. Fajardo Gutiérrez A, Sandoval Mex AM, Mejía Aranguré JM, Rendón?Macías ME, MartínezGarcía MdC. Clinical and social factors that affect the time to diagnosis of mexican children with cancer. *Med Pediatr Oncol*. 2002;39(1):25-31. doi: 10.1002/mpo.10100.

30. Dang-Tan T, Trottier H, Mery LS, et al. Delays in diagnosis and treatment among children and adolescents with cancer in canada. *Pediatric blood & cancer*. 2008;51(4):468-474. doi: 10.1002/pbc.21600.

31. Hjertholm P, Moth G, Ingeman ML, Vedsted P. Predictive values of GPs' suspicion of serious disease: A population-based follow-up study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2014;64(623):e346.

32. Scheel BI, Ingebrigtsen SG, Thorsen T, Holtedahl K. Cancer suspicion in general practice: The role of symptoms and patient characteristics, and their association with subsequent cancer. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2013;63(614):e627.

33. Ingeman ML, Christensen MB, Bro F, Knudsen ST, Vedsted P. The danish cancer pathway for patients with serious non-specific symptoms and signs of cancer-a cross-sectional study of patient characteristics and cancer probability. *BMC Cancer*. 2015;15(1):421. doi: 10.1186/s12885-015-1424-5.

34. Clarke RT, Jones CH, Mitchell CD, Thompson MJ. 'Shouting from the roof tops': A qualitative study of how children with leukaemia are diagnosed in primary care. *BMJ open*. 2014;4(2):e004640. doi: 10.1136/bmjopen-2013-004640.

35. Willems S, De Maesschalck S, Deveugele M, Derese A, De Maeseneer J. Socio-economic status of the patient and doctor–patient communication: Does it make a difference? *Patient Education and Counseling*. 2005;56(2):139-146. doi: https://doi.org/10.1016/j.pec.2004.02.011.

36. Simony SB, Lund LW, Erdmann F, et al. Effect of socioeconomic position on survival after childhood cancer in denmark. *Acta Oncol*. 2016;55(6):742-750. doi: 10.3109/0284186X.2016.1144933.

37. Dommett RM, Redaniel MT, Stevens MC, Hamilton W, Martin RM. Features of childhood cancer in primary care: A population-based nested case-control study. *Br J Cancer*. 2012;106(5):982-987. doi: 10.1038/bjc.2011.600 [doi].

38. Nicholson BD, Mant D, Bankhead C. Can safety-netting improve cancer detection in patients with vague symptoms? *BMJ*. 2016;355. http://www.bmj.com/content/355/bmj.i5515.abstract.

39. Neighbour R. *The inner consultation.* 2nd edition ed. Oxford: Radcliffe Publishing; 2004.

40. Frank L. Epidemiology. when an entire country is a cohort. *Science (New York, N.Y.)*. 2000;287(5462):2398-2399. doi: 10.1126/science.287.5462.2398.

41. Statens Serum Institut. Validation of the danish cancer registry and selected clinical cancer databases - english abstract . http://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-

sundhedsregistre/sygedomme-laegemidler-og-behandlinger/cancerregisteret. Updated 2012. Accessed 08/16, 2017.

42. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39(7_suppl):12-16. doi: 10.1177/1403494811399956.

43. Unesco. International standard classification of education. http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf. Updated 2011. Accessed 01/24, 2018.

44. Shavers VL. Measurement of socioeconomic status in health disparities research. *J Natl Med Assoc*. 2007;99(9):1013.

45. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic status in health research: One size does not fit all. *JAMA*. 2005;294(22):2879-2888. doi: 10.1001/jama.294.22.2879.

46. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull*. 2007;81-82(1):21-37. doi: 10.1093/bmb/ldm001.

Tables

Table 1. Characteristics of the childhood cancer cohort and the gender- and age-matched reference cohort

	Cases		References	
	n	%	n	%
	1386	100.0	13860	100.0
Sex				
Girls	650	46.9	6500	46.9
Boys	736	53.1	7360	53.1
Age at diagnosis (index date)				
10-15 years	411	29.7	4110	29.7
5-9 years	360	26.0	3600	26.0
1-4 years	475	34.3	4750	34.3
0 years	140	10.1	1400	10.1
Type of cancer				
Leukaemia	347	25.0	-	-
Lymphoma	170	12.3	-	-
CNS tumour	367	26.5	-	-
Bone tumour	59	4.3	-	-
Other solid tumour	443	32.0	-	-
Siblings				
Yes	1044	75.3	10.329	74.5
No	276	19.9	2.870	20.7
Missing	66	4.8	661	4.8
Parental cohabitation status				
Living with a partner	915	66.0	8.972	64.7
Living alone	393	28.4	4.136	29.8
Missing	78	5.6	752	5.4
Educational level				
High (> 15 years)	547	39.5	5.587	40.3
Medium (>10-15 years)	531	38.3	5.267	38.0
Low (< 10 years)	211	15.2	2.091	15.1
Missing	97	7.0	915	6.6
Labour market affiliation				
Employed	987	71.2	9.876	71.3
Mixed	191	13.8	1.991	14.4
Unemployed	130	9.4	1.241	9.0
Missing	78	5.6	752	5.4
Household income				
High	330	23.8	3.294	23.8
Medium	655	47.3	6.601	47.6
Low	334	24.1	3.297	23.8
Missing	67	4.8	668	4.8
GP consultation within three months before diagnosis/ index date	1044	75.3	5220	37.7
Diagnostic test performed within three months before diagnosis/ index date	407	29.4	960	6.9

Table 2. Rates of consultations and invoiced diagnostic tests among cases and references

Months before diagnosis	Rates of consultations (95%CI)		Additional rates (95% CI)	Rates of diagnostic tests (95%CI)		Additional rates (95% CI)
	Cases (n= 1386)	**References** (n=13860)		**Cases** (n= 1386)	**References** (n=13860)	
1-3 months	2.43 (2.30:2.55)	0.75 (0.73:0.76)	**1.67 (1.55:1.80)**	0.72 (0.64:0.81)	0.12 (0.11:0.13)	**0.60 (0.52:0.69)**
4-6 months	1.02 (0.94:1.10)	0.82 (0.80:0.85)	**0.20 (0.12: 0.28)**	0.18 (0.14:0.23)	0.13 (0.12:0.14)	**0.05 (0.01:0.11)**
7-9 months	0.99 (0.91:1.08)	0.82 (0.80:0.84)	**0.18 (0.09:0.27)**	0.13 (0.11:0.17)	0.12 (0.11:0.13)	0.02 (-0.01:0.05)
10-12 months	0.95 (0.87:1.03)	0.83 (0.81:085)	**0.12 (0.04:0.20)**	0.13 (0.10:0.16)	0.12 (0.12:0.13)	0.01 (-0.02:0.04)
13-15 months	0.90 (0.82:0.98)	0.80 (0.78:0.83)	**0.10 (0.02:0.18)**	0.17 (0.13:0.21)	0.12 (0.53:0.13)	**0.05 (0.01:0.08)**
16-18 months	0.88 (0.80:0.95)	0.76 (0.74:0.79)	**0.11 (0.33: 0.19)**	0.13 (0.10:0.16)	0.11 (0.10:0.12)	0.02 (-0.01:0.05)
19- 21 months	0.85 (0.77:0.92)	0.79 (0.77:0.82)	0.05 (-0.03:0.13)	0.15 (0.11:0.18)	0.11 (0.10:0.12)	0.04 (-0.00:0.07)
22-24 months	0.79 (0.72:0.85)	0.79 (0.77:0.82)	0.00 (-0.08:0.07)	0.09 (0.07:0.11)	0.11 (0.11:0.13)	- 0.03 (-0.06:0.00)
Total (1-24 months)	8.82	6.38	**2.43 (2.08:2.78)**	1.71 (1.55:1.87)	0.95 (0.92:0.98)	**0.76 (0.64:0.88)**

Additional rates are the difference between consultation rates of cases and references.

Statistically significant additional rates are presented in bold type.

Table 3. Odds (OR) of frequent GP attendance in the last three months before diagnosis

	Basic model [a] OR (95% CI)	Adjusted model [b] OR (95% CI)
Parental cohabitation status		
Living with a partner	1.00	1.00
Living alone	0.90 (0.68:1.18)	0.86 (0.63:1.16)
Siblings		
No	1.00	1.00
Yes	1.23 (0.91:1.69)	1.19 (0.86:166)
Labour market affiliation		
Employed	1.00	1.00
Mixed	1.19 (0.84:1.67)	0.99 (0.68:1.47)
Unemployed	1.36 (0.92:2.02)	1.21 (0.73:1.99)
Educational level		
High	1.00	1.00
Medium	**1.35 (1.02:1.77)**	1.16 (0.87:1.55)
Low	1.25 (0.88:1.79)	0.98 (0.65: 1.47)
Income		
High	1.00	1.00
Medium	**1.76 (1.28:2.43)**	**1.70 (1.22:2.37)**
Low	**1.98 (1.38:2.85)**	**1.94 (1.24:3.03)**

[a]Adjusted for cancer subtype, age and gender
[b]Adjusted for cancer subtype, age, gender and all socioeconomic variables

Statistically significant estimates are presented in bold type.

Table 4. Odds (OR) of receiving an invoiced diagnostic test during the last three months before a childhood cancer diagnosis

	Basic model [a] OR (95% CI)	Adjusted model [b] OR (95% CI)
Parental cohabitation status		
Living with a partner	1.00	1.00
Living alone	0.88 (0.67:1.16)	0.88 (0.66:1.19)
Siblings		
No	1.00	1.00
Yes	1.12 (0.81:1.54)	1.06 (0.76:1.48)
Labour market affiliation		
Employed	1.00	1.00
Mixed	0.95 (0.66:1.35)	0.86 (0.57:1.28)
Unemployed	0.89 (0.59:1.37)	0.83 (0.49:1.42)
Educational level		
High	1.00	1.00
Medium	**1.42 (1.07:1.87)**	**1.46 (1.09:1.95)**
Low	1.14 (0.79:1.65)	1.26 (0.83:1.91)
Income		
High	1.00	1.00
Medium	1.12 (0.83:1.51)	1.03 (0.75:1.41)
Low	1.02 (0.71:1.44)	0.98 (0.63:1.54)

[a] **Adjusted for cancer subtype, age and gender**

[b] **Adjusted for cancer subtype, age, gender and all socioeconomic variables**

Statistically significant estimates are presented in bold type.

Figure legends

Figure 1: Flowchart of children eligible for inclusion in the study.

Figure 2: Consultation rates in general practice by socioeconomic factors.

Upper part: Additional consultation rates, in three-month intervals, for children with cancer and references two years before diagnosis/index date with 95% confidence intervals.

Lower part: The absolute difference in additional consultation rates with 95% confidence intervals.

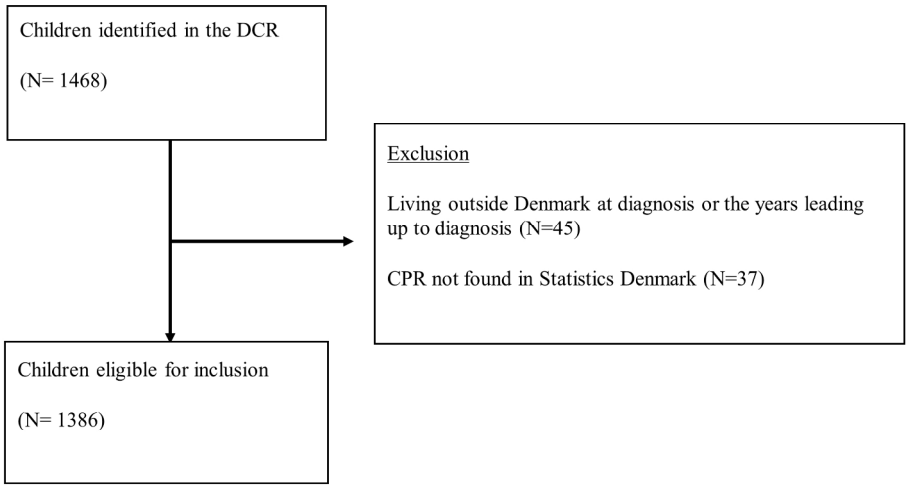

Figure 1: Flowchart of children eligible for inclusion in the study.

203x124mm (300 x 300 DPI)

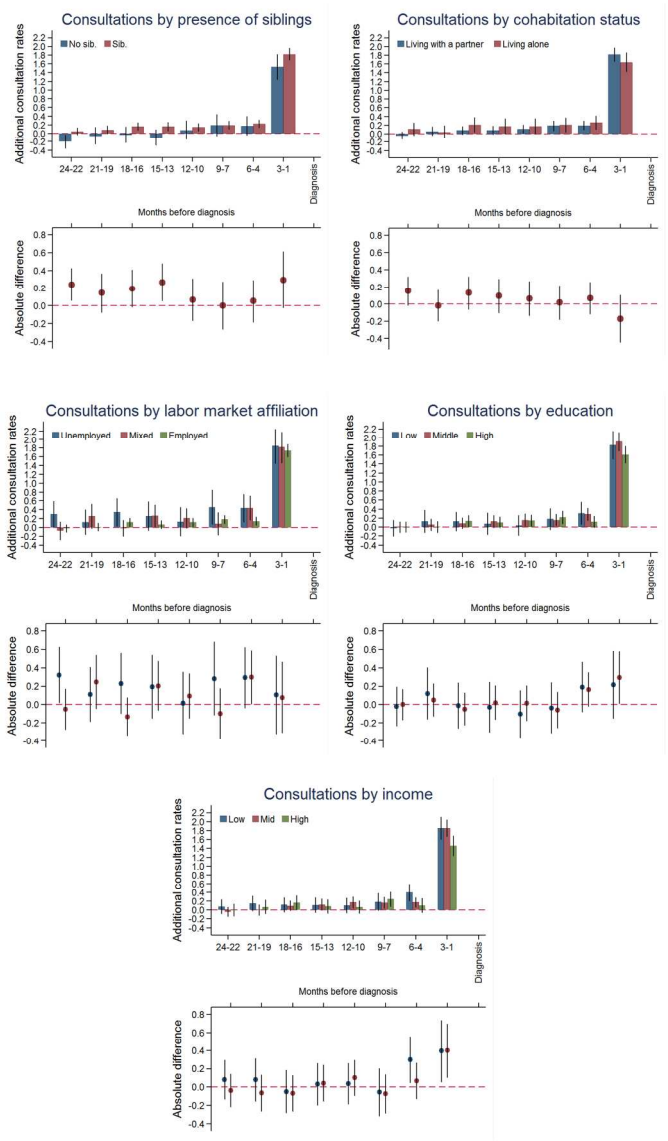

Figure 2. Consultation rates in general practice by socioeconomic factors.Upper part: Additional consultation rates in three-month intervals for children with cancer and references two years before diagnosis, with 95% confidence intervals. Lower part: Absolute difference in additional consultation rates, with 95% confidence intervals.

190x338mm (300 x 300 DPI)

***Supplementary* Table 1a. Additional consultation rates and absolute difference in general practice in the 1-12 months before diagnosis by household socioeconomic factors and three-month intervals**

	1-3 months		4-6 months		7-9 months		10-12 months	
	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference
All	1.67 (1.55:1.88)	-	0.20 (0.12:0.28)	-	0.18 (0.09:0.27)	-	0.12 (0.04: 0.20)	-
Parental cohabitation status								
Living with a partner	1.81 (1.61:2.01)	Ref	0.19 (0.08:0.29)	Ref	0.19 (0.07:0.29)	Ref	0.11 (0.01:0.21)	Ref
Living alone	1.64 (1.42:1.87)	-0.17 (-0.45:0.10)	0.26 (0.01:0.41)	0.07 (-0.12:0.26)	0.20 (0.04:0.37)	0.01 (-0.18:0.22)	0.17 (-0.00:0.35)	0.06 (-0.14:0.27)
Siblings								
No	1.53 (1.2 4:1.81)	Ref	0.17 (-0.05:0.39)	Ref	0.19 (-0.06:0.44)	Ref	0.08 (-0.14:0.29)	Ref
Yes	1.89 (1.68:1.96)	0.29 (-0.02:0.61)	0.23 (0.13:0.32)	0.05 (-0.19:0.29)	0.19 (0.09:0.28)	0.00 (-0.27:0.27)	0.14 (0.05:0.24)	0.06 (-0.17:0.31)
Labour market affiliation								
Employed	1.74 (0.60:1.89)	Ref	0.14 (0.05:0.23)	Ref	0.18 (0.08:0.28)	Ref	0.12 (0.02:0.21)	Ref
Mixed	1.82 (1.46:2.18)	0,08 (-0.31:0.47)	0.44 (0.16:0.71)	0.30 (- 0.01:0.60)	0.08 (-0.18:0.24)	- 0.10 (-0.38:0.18)	0.21 (-0.02:0.43)	0.09 (-0.15:0.34)
Unemployed	1.85 (1.45:2.25)	0.11 (-0.32:0.53)	0.43 (0.12:0.75)	0.29 (-0.04:0.62)	0.46 (0.07:0.85)	0.28 (-0.11:0.68)	0.13 (-0.19:0.46)	0.01 (-0.32:0.35)
Educational level								
High	1.61 (1.43:1.80)	Ref	0.12 (-0.01:0.24)	Ref	0.21 (0.07:0.36)	Ref	0.14 (0.01:0.27)	Ref
Medium	1.91 (1.70:2.12)	**0.30 (0.04:0.57)**	0.29 (0.15:0.42)	0.17 (-0.02:0.35)	0.15 (0.02: 0.29)	-0.06 (-0.25:0.14)	0.16 (0.01:0.27)	0.02 (-0.18:0.20)
Low	1.83 (1.52:2.15)	0.22 (-0.15:0.58)	0.31 (0.06:0.56)	0.19 (-0.08:0.47)	0.18 (-0.06:0.41)	-0.03 (-0.31-0.24)	0.04 (-0.18:0.26)	-0.10 (-0.36:0.15)
Income								
High	1.46 (1.23:1.69)	Ref	0.10 (-0.06:0.26)	Ref	0.24 (0.07:0.41)	Ref	0.07 (-0.08:0.21)	Ref
Medium	1.86 (1.67:2.05)	**0.40 (0.10:0.70)**	0.17 (0.05:0.28)	0.07 (-0.13:0.26)	0.16 (0.36:0.29)	-0.08 (-0.29:0.14)	0.17 (0.04:0.30)	0.10 (-0.09:0.29)
Low	1.85 (1.60:2.11)	**0.39 (0.05:0.74)**	0.40 (0.19:0.60)	**0.30 (0.04:0.55)**	0.18 (-0.01:0.38)	-0.06 (-0.32:0.20)	0.10 (-0.07:0.28)	0.03 (-0.19:0.26)

Additional consultation rates defined as the difference between the cancer cohort and the reference cohort.
Absolute difference in additional consultation rates compared to the reference group.

Statistically significant absolute differences are shown in bold type.

***Supplementary* Table 1b. Additional consultation rates and absolute difference in general practice in the 13-24 months before diagnosis by household socioeconomic factors and three-month intervals**

	13-15 months		16-18 months		19-21 months		22-24 months	
	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference	Additional consultation rates	Absolute difference
All	0.10 (0.02:0.18)	-	0.11 (0.03:0.19)	-	0.05 (-0.03:0.13)		-0.00 (-0.08:0.07)	-
Parental cohabitation status								
Living with a partner	0.08 (-0.02:0.18)	Ref	0.08 (-0.01:0.17)	Ref	0.06 (-0.05:0.16)	Ref	-0.06 (-0.14:0.04)	Ref
Living alone	0.18 (0.00:0.35)	0.09 (-0.11:0.29)	0.21 (0.04:0.38)	0.13 (-0.06:0.32)	0.04 (-0.01:0.19)	-0.02 (-0.02:0.16)	0.11 (-0.04:0.25)	0.15 (-0.02:0.32)
Siblings								
No	-0.10 (-0.29:0.09)	Ref	-0.04 (-0.21:-0.00)	Ref	-0.06 (-0.26:0.14)	Ref	-0.19 (-0.36:0.03)	Ref
Yes	0.16 (0.07:0.26)	0.26 (-0.05:0.48)	0.16 (0.07:0.25)	0.20 (-0.01:0.41)	0.09 (-0.01:0.18)	0.14 (-0.08:0.37)	0.04 (-0.04:0.14)	0.24 (-0.06:0.43)
Labour market affiliation								
Employed	0.06 (-0.03:0.16)	Ref	0.11 (0.02:0.21)	Ref	0.01 (-0.09:0.10)	Ref	-0.02 (-0.11:0.06)	Ref
Mixed	0.26 (0.01:0.52)	0.20 (-0.07:0.47)	-0.02 (-0.20:0.17)	-0.13 (-0.34:0.07)	0.25 (-0.03:0.53)	0.24 (-0.05:0.54)	-0.07 (-0.28:0.13)	-0.05 (-0.27:0.17)
Unemployed	0.25 (-0.08:0.59)	0.19 (-0.15:0.54)	0.34 (0.03:0.66)	0.23 (-0.10:0.56)	0.12 (-0.17:0.40)	0.11 (-0.19:0.41)	0.30 (0.01:0.59)	0.32 (0.02:0.63)
Educational level								
High	0.10 (-0.02:0.23)	Ref	0.14 (0.01:0.26)	Ref	0.01 (-0.12:0.37)	Ref	0.00 (-0.12:0.11)	Ref
Medium	0.12 (-0.01:0.26)	0.02 (-0.17:0.20)	0.09 (-0.04:0.21)	-0.05 (-0.23:0.13)	0.05 (-0.08:0.18)	0.04 (-0.13:0.23)	0.00 (-0.12:0.12)	0.00 (-0.16:0.20)
Low	0.07 (-0.17:0.32)	-0.03 (-0.30:0.24)	0.12 (-0.09:0.34)	-0.02 (-0.26:0.23)	0.12 (-0.13:0.38)	0.11 (-0.16:0.40)	-0.02 (-0.21:0.16)	-0.02 (-0.24-0.20)
Income								
High	0.08 (-0.08:0.23)	Ref	0.16 (0.00:0.33)	Ref	0.07 (-0.09:0.23)	Ref	0.00 (-0.15:0.14)	Ref
Medium	0.12 (-0.00:0.25)	0.04 (-0.16:0.24)	0.09 (-0.02:0.21)	-0.07 (-0.27:0.13)	0.00 (-0.12:0.12	-0.07 (-0.27:0.13)	-0.04 (-0.15:0.06)	-0.04 (-0.22:0.14)
Low	0.11 (-0.06:0.28)	0.02 (-0.20:0.26)	0.11 (-0.05:0.28)	-0.05 (-0.28:0.18)	0.14 (-0.03:0.32)	0.08 (-0.16:9.21	0.07 (-0.09:0.24)	0.08 (-0.14:0.29)

Additional consultation rates are defined as the difference between the cancer cohort and the reference cohort.
Absolute difference in additional consultation rates compared to the reference group.

Statistically significant absolute differences are shown in bold type.

***Supplementary* Table 2. Likelihood (OR) of frequent GP attendance (four or more consultations) among children with specific cancer types**

	Leukaemia (n=347)	**CNS** (n=367)	**Other solid tumors** (n= 443)
Parental cohabitation status			
Living with a partner	1.00	1.00	1.00
Living alone	0.84 (0.47:1.49)	0.90 (0.50:1.61)	0.99 (0.53:1.86)
Siblings			
No	1.00	1.00	1.00
Yes	1.43 (0.47:1.49)	1.12 (0,59:2.12)	1.10 (0.57:2.12)
Labour market affiliation			
Employed	1.00	1.00	1.00
Mixed	0.81 (0.39:1.63)	0.89 (0.40:2.01)	1.68 (0.79:3.52)
Unemployed	1.05 (0.41:2.72)	1.21 (0.50:2.94)	0.78 (0.24:2.51)
Educational level			
High	1.00	1.00	1.00
Medium	**1.91 (1.09:3.33)**	1.12 (0.64: 1.96)	0.74 (0.41:1.32)
Low	1.20 (0.53:2.69)	1.13 (0.51:2.49)	0.67 (0.28:1.61)
Income			
High	1.00	1.00	1.00
Medium	1.65 (0.90:3.04)	1.56 (0.80:3.0)	1.94 (0.97:3.88)
Low	2.23 (0.95:5.26)	1.41 (0.57:3.45)	1.68 (0.68:4.25)

The model is adjusted for age and gender.

Statistically significant estimates are shown in bold type.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4, 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, 5
Bias	9	Describe any efforts to address potential sources of bias	4, 5
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5, 6
		(*b*) Describe any methods used to examine subgroups and interactions	x
		(*c*) Explain how missing data were addressed	x
		(*d*) If applicable, explain how loss to follow-up was addressed	x
		(*e*) Describe any sensitivity analyses	x
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 and figure 1
		(b) Give reasons for non-participation at each stage	x
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7, 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8 Supp. Table 1 and 2, Table 2, 3 and 4
		(*b*) Report category boundaries when continuous variables were categorized	x
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	x
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7 Supp. Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8, 9, 10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.