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High parental occupational social contact and risk of childhood hematopoietic, brain and bone cancers

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ABSTRACT

Background: The etiology of childhood cancer is largely unknown, though some research suggests an infectious origin of hematopoietic, central nervous system (CNS) and bone cancers.

Methods: We examined parental occupational social contact as a proxy for exposure to infectious agents and risk of childhood cancer. This population-based case-control study utilized a linkage of four Danish data-registries, and included 3581 cases (< 17 years, diagnosed 1973–2012) and 358,100 age-matched controls. We examined the risks of leukemia, lymphoma, CNS and bone cancer related to high occupational social contact from (1) conception to birth and (2) birth to diagnosis.

Results: Acute lymphoblastic leukemia (ALL) and bone cancer were inversely associated with high maternal social contact from conception to birth (OR: 0.86, 95% CI: 0.67–1.10) and birth to diagnosis (OR: 0.54, 95% CI: 0.34–0.86). Children of fathers with high social contact from birth to diagnosis had an increased risk of bone cancers, particularly in rural areas (OR: 1.65, 95% CI: 1.03–2.63). Parental social contact was associated with increased risk of astrocytoma, with strongest associations found in first-born children (maternal: OR: 1.54, 95% CI: 1.02–2.32; paternal: OR: 1.82, 95% CI: 1.05–3.17).

Conclusion: Our results support the notion of a role of infections for some cancer types.

1. Introduction

Childhood cancer remains the second most common cause of death in children living in the United States and Europe, and little is known about the etiology of these diseases [1]. Studies have suggested that early exposure to infections are possible risk factors for childhood hematopoietic or brain cancers [2,3]. Few studies have examined occupational social contact as an indirect measure of infectious exposures in relation to childhood cancer risks, with research mainly focusing on paternal exposures [4–8].

In recent years, two infectious hypotheses have gained momentum to help explain childhood leukemia incidence. Greaves' 'delayed-infection' hypothesis suggests that individuals who have a relative paucity of exposures to infections early in life are more likely to develop cancer due to an abnormal immune response that fails to adapt to later challenges [3]. Alternatively, Kinlen's 'population-mixing' hypothesis suggests that the increased rates of hematopoietic cancers, and specifically acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), are due to exposure to a single, and yet unidentified, infectious agent [9].

Supporting Greaves' hypothesis, leukemia was inversely associated with exposure of infants and young children to environments that offered increased opportunities for infectious exposures, such as daycares, as well as higher parity and later birth order [10,11], suggesting that children who are diagnosed with leukemia tend to have fewer early childhood contacts with other children and infections, and thus experience less immune system stimulation [12]. Studies by Kinlen examined parental occupational social contact as a risk factor for childhood leukemia and found paternal social contact to be associated with risk of childhood leukemia in rural, but not urban, areas [6,7,13].

In most studies, high levels of occupational social contact was assigned to jobs that deal directly with young children or employment in the medical field [6–8]. Only two studies have been published that considered maternal occupational social contact, and both reported no

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difference in risk between high and low social contact jobs and hematopoietic cancers [5,14]. However, studies that examined childhood cancer risk by maternal job title, linked several maternal jobs known for high social contact (such as nurses, teachers and postal/communication workers) to increased risks of offspring hematopoietic, brain and bone cancers [15–17]. Although occupational social contact has not been studied in relation to other childhood cancer types, maternal employment in the medical and dental field was related to Wilms tumor and maternal employment as a hairdresser was associated with neuroblastoma [18,19].

We hypothesize that parents with high social contact jobs would likely expose their children to pathogenic agents in utero or during early life, resulting in ample opportunity to develop a strong immune response that decreases the risk for childhood hematopoietic, central nervous system (CNS) and bone cancers.

2. Materials and methods

Data for this population-based case-control study was obtained from a linked database we created that combined data from four different Danish registries: The Central Population Registry [20], the Danish Cancer Registry [21], the Supplementary Pension Fund [22] and the Danish Medical Birth Registry [23]. The Danish Cancer Registry was used to ascertain cases (< 17 years old) diagnosed 1973-2012. The Central Population Registry was used to ascertain 100 controls per case, all of whom were cancer-free at the time of diagnosis of the corresponding case. Controls with an equal probability of selection after matching by sex and year of birth were identified randomly from a population pool within the Central Population Registry in Denmark. More details on these registries can be found elsewhere [24]. Cases and controls had to have been born in Denmark to be eligible for the present study. Ethical approval for the current study was obtained from the University of California, Los Angeles institutional review board as well as from the Danish Data Protection Agency.

The Danish Supplementary Pension Fund is mandated for all wage earners 18–66 years of age who are working at least 9 h per week, and since 1978, for all wage earners 16–66 years of age. Occupations are categorized based on a five digit detailed version of the International Standard Industrial Classification of All Economic Activities [25,26]. Validation studies of this and other Danish registries have reported high accuracy and completeness and low rates of misclassification [21–23,27].

For the period 1973–2012, we identified 5190 cancer cases and 519,000 controls. We excluded anyone born outside of Denmark (N = 74) and those whose parents did not have any occupational history information recorded during relevant time periods (N = 27,658). Our analyses focused on cancers for which associations had been previously reported with occupational social contact, therefore cases were included if they were diagnosed with any hematopoietic, CNS or bone cancer [4,6,16,28]. In an exploratory analysis, we also examined the effects of parental social contact on some cancers for which a minimum of 125 total cases were available (retinoblastoma, specific brain cancer subtypes, neuroblastoma and Wilms tumor). Our final dataset consisted of 3581 hematopoietic, CNS and bone cancer cases and 358,100 birth-year matched controls.

To distinguish between possible infections occurring in utero or in early life, we examined the association between occupational social contact and childhood cancer during two developmental periods in relation to mothers' and fathers' occupations: (1) conception to birth and (2) after birth to diagnosis. Date of conception was determined by subtracting child's gestational age in days from their birth date (details in Supplemental file 1).

Within each period of susceptibility, parents were categorized as either having very high, high, medium or low occupational social contact based on a job exposure matrix replicating previous work by Kinlen, which was updated for the Danish population based upon the advice of experts in Danish occupational health [6]. In short, these categories were defined as follows:

(A) Very high social contact: occupations in the health care industry and those involving a high level of contact with children and young or ill people (physicians, dentists, midwives, physiotherapists, elementary school teachers and daycare workers).
(B) High social contact: occupations in the transportation industry or the providers of services to many different type of people (e.g. drivers, pilots, hotel workers, real estate agents, non-elementary school teachers, and hairdressers).
(C) Medium and low social contact: low social contact was assigned to subjects with occupations in agriculture. Due to sample size restrictions, we merged this group with medium social contact, which comprised of all other occupations and formed the reference category.

Children of parents who had an indeterminate job for longer than 6 months at any point during the relevant periods of exposure or who were unemployed for the entire period of interest were excluded from the study. Most parents held more than one job during the relevant periods of interest. For these individuals, we assigned them to an exposure level based on the job they held, for any amount of time, with the highest exposure.

Analyses were conducted using conditional logistic regression and adjusted for maternal age (≤25, 26–30, 31–35, 36+ years) and urbanicity (urban or small town/rural) of the place of birth. Selection of potential confounders for adjustment was based on previous literature as well as exploring associations present in our data [6]. Variables considered for inclusion in our adjusted model were number of previous pregnancies, number of previous live births, maternal smoking status and family socioeconomic status (SES), though most had large numbers of missing values due to registry non-collection (24%–78%). Due to limited sample size for many cancer types, we combined very high and high social contact.

To avoid competing exposures due to non-occupational high social contact experienced in urban settings, we performed analyses that restricted to individuals living in rural areas only. Given that children with older siblings have higher exposure to infections at an earlier age [2], we also conducted analyses restricted to first born children only. Whenever sample size allowed (N > 5), we performed sensitivity analyses that restricted to both rural households and first born children only. We performed additional sensitivity analyses in the form of a trend test that assessed the effects of very high and high occupational social contact on childhood cancers separately to determine whether any dose-response pattern was present. We also performed analyses that excluded all individuals diagnosed before 1980, as the Danish population evolved from rural and mostly small towns to mostly urban during that time [29]. Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA).

3. Results

Cases and controls shared similar demographic characteristics with regard to parental age, family SES and residency type, although slightly more hematopoietic cancer cases were male and fewer bone cancer cases had fathers 25 years of age or younger (Table 1). Table 2 shows the risk of leukemia, CNS tumors and bone cancers associated with "very high and high parental occupational social contact", herein referred to as high social contact. Children of mothers who had high social contact jobs had a reduced risk of ALL (OR: 0.86, 95% CI: 0.67–1.10), CNS (OR: 0.87, 95% CI: 0.69, 1.10) and bone cancer (OR: 0.54, 95% CI: 0.34-0.86). However, we estimated an increased risk of astrocytoma for children of mothers who had high social contact jobs between birth and diagnosis (OR: 1.22, 95% CI: 0.94–1.60). For fathers, high social contact jobs from conception to birth was also associated

Table 1
Demographic characteristics of cases and controls.

		Hematopoietic Cancers		Brain and Neural Cancers		
	All controls	All Leukemia	ALL	CNS	Astrocytoma	Bone
Age range	0-15	0-15	0-15	0-15	0-15	0-15
	N = 358,100(%)	N = 1438 (%)	N = 1160	N = 1330 (%)	N = 446 (%)	N = 205 (%)
Sex of child						
Male	194,300 (54.3)	776 (54.0)	649 (56.0)	701 (52.7)	211 (47.3)	108 (52.7)
Female	163,800 (45.7)	662 (46.0)	511 (44.1)	629 (47.3)	235 (52.7)	97 (47.3)
Missing	0	0	0	0	0	0
Maternal age						
< =25	104,656 (29.2)	371 (25.8)	292 (25.2)	414 (31.1)	145 (32.5)	55 (26.8)
26-30	137,725 (38.5)	552 (38.4)	447 (38.5)	521 (39.2)	181 (40.6)	87 (42.4)
31-35	85,649 (23.9)	357 (24.8)	285 (24.6)	294 (22.1)	87 (19.5)	43 (21.0)
36+	29,998 (8.4)	158 (11.0)	136 (11.7)	101 (7.6)	33 (7.4)	20 (9.8)
Missing	72 (0.0)	0	0	0	0	0
Paternal age						
< =25	54,273 (15.2)	187 (13.0)	142 (12.2)	211 (15.9)	70 (15.7)	20 (9.8)
26-30	121,446 (33.9)	482 (33.5)	387 (33.4)	478 (35.9)	169 (37.9)	80 (39.0)
31-35	108,202 (30.22)	433 (30.1)	357 (30.8)	388 (29.2)	119 (26.7)	64 (31.2)
36+	71,878 (20.1)	328 (22.8)	269 (23.2)	240 (18.1)	84 (18.8)	40 (19.5)
Missing	2301 (0.6)	8 (0.6)	5 (0.4)	13 (1.0)	4 (0.9)	1 (0.5)
Family SES						
High	34,776 (9.7)	129 (9.0)	105 (9.1)	130 (9.8)	44 (9.9)	17 (8.3)
Medium-high	44,316 (12.4)	181 (12.6)	148 (12.8)	166 (12.5)	51 (11.4)	27 (13.2)
Medium	50,192 (14.0)	185 (12.9)	155 (13.4)	197 (14.8)	76 (17.0)	39 (19.0)
Medium-low	89,173 (24.9)	363 (25.2)	299 (25.8)	327 (24.6)	111 (24.9)	48 (23.4)
Low	44,621 (12.5)	176 (12.2)	144 (12.4)	173 (13.0)	61 (13.7)	24 (11.7)
Missing	95,022 (26.5)	404 (28.1)	309 (26.6)	337 (25.3)	103 (23.1)	50 (24.4)
Residence type						
Urban	114,645 (32.0)	450 (31.3)	370 (31.9)	439 (33.0)	145 (32.5)	61 (29.8)
Rural	243,455 (68.0)	988 (68.7)	790 (68.1)	891 (67.0)	301 (67.5)	144 (70.2)
Missing	0	0	0	0	0	0

with lower point estimates for ALL (OR: 0.84, 95% CI: 0.64–1.10) but for bone cancer high social contact from birth to diagnosis related to increased risk (OR: 1.35, 95% CI: 0.91–2.00).

When we restricted to cases and controls living in rural areas, most odds ratios increased (Table 3). Specifically, for fathers having high social contact jobs from birth to diagnosis the estimated risk for bone cancer in children was increased (OR: 1.65, 95% CI: 1.03–2.63). We also estimated an increased risk of astrocytoma (OR: 1.37, 95% CI: 0.98–1.92) in children whose mothers had high social contact jobs from birth to diagnosis.

Among first born children (Table 4), associations between high maternal occupational social contact and astrocytoma strengthened; paternal occupational social contact from conception to birth was also associated with astrocytoma (OR: 1.82, 95% CI: 1.05–3.17). Among those living in rural areas and those who were first born, risk of astrocytoma was highest among children of fathers who had high social contact jobs from conception to birth (OR: 2.29, 95% CI: 1.12–4.69, table not shown).

In supplementary tables, lymphoma cases were more likely to live in urban areas, be male (NHL cases specifically) and have higher SES (Hodgkin cases specifically) than controls (Supplemental Table 1). We did not find parental occupational social contact to be associated with lymphomas (Supplemental Table 2). Among the other rare cancers we examined, we estimated increased risk for medulloblastoma (OR: 1.48, 95% CI: 0.89–2.47, Supplemental Table 3).

In analyses that separated very high and high social contact, we observed a trend for leukemia ($P < 0.05$) among fathers for very high and high social contact from conception to birth (Supplemental Table 4). For other rare cancers we examined in an exploratory subanalysis, tables not shown, very high (but not high) social contact was associated with an increased risk of Wilms tumor (OR: 2.04, 95% CI: 0.98–4.23). Analyses restricting to children born after 1980 were similar to those presented here (data not shown).

We also examined the association between childhood cancer and any high occupational social contact from conception to diagnosis among each parent individually and both parents combined (Supplemental table 5). Our findings indicate that high parental social contact during any time period was related to even lower risk for leukemia and ALL; however, our results for CNS and astrocytoma were null.

4. Discussion

Incidence of leukemia has increased at about 1% per year throughout the last two decades in the United States [30], suggesting that causal risk factors for the disease have become more prevalent. Some authors have proposed that the increased rates of leukemia in high income countries are due to altered patterns of infection [31], although other explanations include increasing parental age and changes in the racial/ethnic composition of the population [32,33]. In our study, high parental occupational social contact between conception and birth was related to an inverse association with childhood leukemia, signifying that perhaps the earliest exposures to infection in utero could stimulate the perinatal immune system. This is in line with findings from a meta-analysis compiling 15 studies on childcare attendance and risk of leukemia with a combined OR = 0.76 [12]. A possible underlying explanation is the “two-hit model” of carcinogenesis asserting that susceptibility to leukemia likely begins in utero with an additional postnatal event required for the disease to manifest [34]. Support that the first hit occurs in utero is found through analyses of identical twins with concordant ALL that revealed identical breakpoints in *TEL-AML1* genes from the leukemia cells of both twins [35]. Further, for identical twin infant leukemia, it is thought that the concordance rate approaches 100% [36]. However, for children 2–6 years of age, the concordance rate is around 5%, suggesting the need for some additional postnatal “hit” [36]. Infection is thought to be largely responsible for

Table 2
Risk of leukemia, CNS tumors and bone cancers relative to parental occupational social contact at various times from conception to diagnosis.

	All Controls (total N = 358,100)	All Leukemia (total N = 1438)			ALL (total N = 1160)			CNS (total N = 1330)			Astrocytoma (total N = 446)			Bone (total N = 205)		
		Average age at diagnosis: 5.4			Average age at diagnosis: 5.5			Average age at diagnosis: 7.2			Average age at diagnosis: 7.1			Average age at diagnosis: 10.4		
		N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)
Mother																
Conception to birth																
Very high & high	22087	91	0.93	0.93 (0.75, 1.15)	69	0.87	0.86 (0.67, 1.10)	77	0.87	0.87 (0.69, 1.10)	27	0.97	0.96 (0.65, 1.44)	10	0.75	0.75 (0.39, 1.43)
Medium & low	239280	1038	ref	ref	846	ref	ref	942	ref	ref	306	ref	ref	150	ref	ref
Birth to diagnosis																
Very high & high	44026	167	0.98	0.98 (0.83, 1.16)	130	0.93	0.93 (0.77, 1.12)	187	1.1	1.07 (0.91, 1.26)	68	1.23	1.22 (0.94, 1.60)	20	0.54	0.54 (0.34, 0.86)
Medium & low	258168	1092	ref	ref	887	ref	ref	979	ref	ref	327	ref	ref	168	ref	ref
Father																
Conception to birth																
Very high & high	20075	74	0.88	0.87 (0.69, 1.10)	59	0.87	0.84 (0.64, 1.10)	73	0.97	0.97 (0.77, 1.24)	22	0.93	0.95 (0.61, 1.47)	14	1.23	1.22 (0.70, 2.13)
Medium & low	271024	1125	ref	ref	912	ref	ref	1009	ref	ref	334	ref	ref	150	ref	ref
Birth to diagnosis																
Very high & high	35217	134	0.97	0.97 (0.81, 1.16)	107	0.95	0.94 (0.77, 1.15)	134	0.98	0.98 (0.82, 1.18)	45	1.01	1.01 (0.74, 1.39)	31	1.3	1.35 (0.91, 2.00)
Medium & low	264845	1111	ref	ref	900	ref	ref	1001	ref	ref	337	ref	ref	140	ref	ref

[a] Adjusted for maternal age and urban/rural residence status.

Table 3
Risk of leukemia, CNS tumors and bone cancers relative to parental occupational social contact at various times from conception to diagnosis among rural cases and controls only.

	All Controls (total N = 243,455)	All Leukemia (total N = 988)			ALL (total N = 790)			CNS (total N = 891)			Astrocytoma (total N = 301)			Bone (total N = 144)		
		Average age at diagnosis: 5.4			Average age at diagnosis: 5.4			Average age at diagnosis: 7.2			Average age at diagnosis: 7.0			Average age at diagnosis: 10.4		
		N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)
Mother																
Conception to birth																
Very high & high	12819	54	0.94	0.94 (0.71, 1.24)	43	0.94	0.94 (0.69, 1.28)	46	0.93	0.94 (0.70, 1.27)	15	0.93	0.93 (0.55, 1.58)	6	0.82	0.80 (0.35, 1.84)
Medium & low	165758	721	ref	ref	578	ref	ref	626	ref	ref	205	ref	ref	104	ref	ref
Birth to diagnosis																
Very high & high	26261	101	0.99	0.99 (0.80, 1.22)	80	0.97	0.97 (0.76, 1.22)	112	1.13	1.13 (0.92, 1.39)	42	1.36	1.37 (0.98, 1.92)	11	0.49	0.48 (0.26, 0.90)
Medium & low	179502	765	ref	ref	613	ref	ref	663	ref	ref	220	ref	ref	118	ref	ref
Father																
Conception to birth																
Very high & high	10390	40	0.92	0.90 (0.64, 1.24)	33	0.95	0.92 (0.65, 1.31)	44	1.18	1.21 (0.89, 1.65)	13	1.11	1.17 (0.66, 2.06)	8	1.34	1.32 (0.64, 2.74)
Medium & low	188655	782	ref	ref	623	ref	ref	678	ref	ref	226	ref	ref	106	ref	ref
Birth to diagnosis																
Very high & high	18556	76	1.05	1.04 (0.82, 1.32)	62	1.07	1.06 (0.81, 1.38)	78	1.11	1.13 (0.89, 1.43)	27	1.17	1.20 (0.80, 1.79)	22	1.66	1.65 (1.03, 2.63)
Medium & low	184305	774	ref	ref	617	ref	ref	681	ref	ref	228	ref	ref	101	ref	ref

[a] Adjusted for maternal age.

Table 4
Risk of leukemia, CNS tumors and bone cancers relative to parental occupational social contact at various times from conception to diagnosis among first born children only.

	All Controls (N = 120,209)	All Leukemia (total N = 443)			ALL (total N = 367)			CNS (total N = 497)			Astrocytoma (total N = 175)			Bone (total N = 80)		
		Average age at diagnosis: 6.1			Average age at diagnosis: 5.9			Average age at diagnosis: 7.4			Average age at diagnosis: 6.9			Average age at diagnosis: 11.0		
		N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)	N Exposed	Crude OR	Adjusted[a] OR (95% CI)
Mother																
Conception to birth																
Very high & high	7796	28	0.9	0.91 (0.61-1.35)	22	0.84	0.84 (0.54-1.31)	37	1.16	1.18 (0.83-1.66)	12	1.14	1.13 (0.62-2.06)	4	0.73	0.71 (0.25-1.97)
Medium & low	83564	327	ref	ref	276	ref	ref	348	ref	ref	125	ref	ref	63	ref	ref
Birth to diagnosis																
Very high & high	15325	55	1.02	1.02 (0.77-1.37)	43	0.97	0.97 (0.70-1.35)	76	1.21	1.24 (0.96-1.60)	30	1.52	1.54 (1.02-2.32)	10	0.67	0.66 (0.34-1.29)
Medium & low	88425	336	ref	ref	281	ref	ref	360	ref	ref	124	ref	ref	66	ref	ref
Father																
Conception to birth																
Very high & high	5891	21	0.93	0.93 (0.59-1.45)	17	0.89	0.87 (0.53-1.44)	30	1.23	1.26 (0.86-1.85)	15	1.81	1.82 (1.05-3.17)	6	1.42	1.34 (0.56-3.20)
Medium & low	91340	342	ref	ref	285	ref	ref	373	ref	ref	128	ref	ref	63	ref	ref
Birth to diagnosis																
Very high & high	11681	44	1.06	1.06 (0.77-1.47)	36	1.04	1.04 (0.73-1.49)	50	0.97	1.0 (0.74-1.35)	19	1.12	1.12 (0.68-1.84)	10	0.91	0.93 (0.46-1.84)
Medium & low	88662	335	ref	ref	278	ref	ref	380	ref	ref	132	ref	ref	60	ref	ref

[a] Adjusted for maternal age and urban/rural residence status.

promoting the second genetic hit through an underlying immune response, as infectious exposures are essential for the early organization of an adequate immune response to future infectious agents. Therefore, increasing exposure to infectious disease in utero or early life could stimulate modulation of the immune system, allowing it to adequately addresses and adapt to later challenges, in this case, one or more common infections responsible for indirectly promoting leukemia [3].

Kinlen's alternate theory is that leukemia is the result of some specific infectious agent rather than an unusual reaction to infection [9,13,37–39]. Kinlen's studies took place in the rural U.K. when small towns were more geographically and socially isolated, while in contrast, studies in more recent years, or in more mixed populations have not shown this effect [5,9,37]. Similarly, several other large European population-based studies did not find high social contact to increase the risk of leukemia or its subtypes when examining data from urban populations [7,8,28]. Recent evidence shows that using clusters to examine the association between childhood leukemia and population mixing generates artificial associations [40]. Instead, region-wide analytical strategies should be used. We did not observe increased risk of leukemia among children of parents with high social contact jobs in either urban or rural areas, or among first born children. Similarly, another study failed to find a positive association between high social contact and leukemia even after stratifying on urban and rural geographic area [4]. However, one study which examined both duration and contact level of paternal jobs reported a lower risk of ALL with increased duration of employment in a high social contact job in urban areas (OR: 0.79, 95% CI: 0.47–1.33) but an increased risk in rural areas (OR: 2.28, 95% CI: 0.76–6.85), yet confidence intervals were wide and included the null.

Our paper is among the first to report maternal exposure to high occupation social contact to be inversely associated with ALL. To our knowledge, only two other studies formally examined maternal occupational social contact and risk of leukemia and they report conflicting results, though neither had the power to stratify by urban/rural residency [5,14]. One additional study that utilized job titles to examine risk of childhood cancers found that assistant nurses were at an increased risk of having children diagnosed with leukemia [16]. Infections spread within families [41], thus either maternal and paternal social contact should result in similar risks for childhood cancer. In most instances, our results for maternal and paternal agreed, except for bone cancers, where we estimated effects in opposite directions. Early studies found that maternal and paternal occupations in teaching and healthcare were associated with a greater risk of childhood bone cancers, however neither study grouped jobs into social contact categories [17,18]. Another study reported excesses of bone cancer among offspring of women employed as postal or communication workers [16]. All published studies on childhood bone cancer and parental occupations, including our own, are based on small sample sizes suggesting a need for pooled or meta-analyses to draw conclusions about these rare cancers.

There is some evidence to suggest that maternal and early childhood exposure to common viral infections may result in an increased risk of childhood brain tumors, though few studies have had the power to examine tumor subtypes [42]. Cytomegalovirus infection was associated with increased risk of both medulloblastoma and gliomas, including astrocytoma [43]. Increased risk of astrocytoma was observed among mothers with high occupational social contact from child's birth to diagnosis, with stronger associations being observed in analyses that restricted to rural residence status and first born children. This timing is consistent with evidence examining space-time clustering of astrocytoma that suggests infection occurring postnatally, as opposed to prenatally, being related to brain tumors [42]. Similar to our findings for fathers, one other study found that the risk of astrocytoma was slightly increased for children of fathers with high social contact occupations (crude OR: 1.16, 95% CI: 1.00–1.35) [44]. Another study on parental occupation found that mothers employed as nurses, whom we categorized as having very high social contact, had an increased risk of having a child diagnosed with astrocytoma, based on a small number of case mothers working as nurses (N = 11, OR: 8.0) [15]. Though some researchers have examined a viral etiology for CNS tumors, this study is the first to report an association between CNS tumors and maternal social contact. Our associations disappeared when we examined any occupational social contact exposure from conception to diagnosis among mothers, fathers, or both; therefore, our results for astrocytoma should be interpreted with caution until future studies can corroborate these findings.

We did not have access to information on childcare attendance which is related to higher rates of infections in early childhood [45]. In Denmark, maternity and paternity leaves of 52 weeks are common since the passage of a 2002 law. In the years 1989–2004, 2% of children were enrolled in a childcare facility before 3 months of age, 21% at 6 months of age, 53% at one year of age and 75% from 3 to 5 years of age [46]. Thus, infections due to parental occupational exposures should be most relevant for younger infants and during pregnancy, when exposure through daycare attendance would not be relevant. Limitations of our study include the large number of missing values for potentially important covariates, including maternal smoking. However, sensitivity analyses adjusting for this and other variables, when available, resulted in no difference in point estimates. We created occupational social contact categories based on Kinlen's social contact matrix, but were unable to find validation studies to affirm the social contact levels for these jobs titles [7]; nonetheless, previous studies reported high rates of infectious diseases among the medical and teaching professions [47,48]. Some high social contact occupations, such as doctors, nurses and transportation workers, may be further exposed to radiation or other chemical exposures we could not account for.

In conclusion, our study reports a reduced risk of leukemia among children of parents with high occupational social contact between conception and birth and an increased risk of astrocytoma among children of parents with high occupational social contact. Further research is needed to uncover underlying biological relationships between occupational social contact and childhood cancers.

Authors' contributions

NO conducted all analyses and wrote the manuscript. JEH and BR were primary advisors on study design, statistical techniques, and interpretation of results. JH and JO provided valuable insight regarding the utilization of Danish registry data and were key resources during the writing phase of the manuscript. All authors reviewed the manuscript and made sufficient contributions for publication.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101575.

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