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Birth characteristics and Wilms tumors in children in the Nordic countries: a register-based case–control study

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Little is known about causes of Wilms tumor. Because of the young age at diagnosis, several studies have looked at various birth characteristics. We conducted a registry-based case–control study involving 690 cases of Wilms tumor aged 0–14 years, occurring in Denmark, Finland, Norway or Sweden during 1985–2006, individually matched to five controls drawn randomly from the Nordic childhood population. Information on birth characteristics was obtained from the population-based medical birth registries. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression analysis. We observed a distinct association between Wilms tumor and high birth weight (≥4 kg) for girls (OR 1.97, CI 1.50–2.59) but not for boys (1.04, 0.78–1.38); overall, the OR was 1.43 (1.17–1.74). Among girls, risk increased by 28% (15–42%) per 500 g increase in birth weight. Large-for-gestational age girls also had a higher risk (2.48, 1.51–4.05), whereas no effect was seen for boys (1.12, 0.60–2.07). An association was seen with Apgar score at 5 min < 7 for both sexes combined (5.13, 2.55–10.3). ORs close to unity were seen for parental age and birth order. In our large-scale, registry-based study, we confirmed earlier observations of an association between high birth weight and risk of Wilms tumor, but we found an effect only in girls. The higher risk of infants with low Apgar score might reflect hypoxia causing cell damage, adverse side effects of neonatal treatment or reverse causation as low Apgar score might indicate the presence of a tumor.

Epidemiology

Renal tumors in children are rare. Its major subtype, Wilms tumor or nephroblastoma, constituting >95% of all childhood renal tumors, is an embryonal malignancy arising from remnants of the immature kidney.[1–3] In Europe, the age-standardized incidence rate is about 8.5 cases per 1 million children aged 0–14 years per year, and time trend analysis suggested an increase in the incidence rate of 0.7% per year during the time period 1978–1997.[4]

Little is known about causes of Wilms tumor, but as 80% of cases are diagnosed before the age of 5 years, factors operating early in life or before birth are plausible candidates to provide some insight into its etiology. Several studies have looked at various birth characteristics and especially high birth weight has been associated with an increased risk of Wilms tumor with some degree of consistency.[5–23] Wilms tumor patients with either Beckwith-Wiedemann syndrome or hemihypertrophy were found to have high birth weights, but a positive association was also seen among children with no other congenital abnormalities.[5]

Two studies reported that the association between high birth weight and Wilms tumor was stronger in patients with perilobar nephrogenic rests (PLNR) than in patients with intralobar nephrogenic rests (ILNR),[6,7] whereas the presence of PLNR was associated with loss of imprinting of IGF2,[24–26] suggesting that patients with this loss of imprinting account for the birth weight association.[6,27,28] Two studies reported a somewhat more pronounced association among girls compared to boys, but numbers were small.[8,9]

For other perinatal factors, there is less consistency. The small number of cases of most previous studies and the possible impact of selection and reporting bias might have contributed to those diverse results. In a recent large United States case–control study, including 521 Wilms tumor cases, a positive association was seen between Wilms tumor and high birth weight, low gestational age and being large-for-gestational age. Furthermore, an inverse association was seen

Key words: Wilms tumor, nephroblastoma, birth weight, Apgar score, birth order, risk factors
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Table 1. Demographic distribution of cases (total and by country) and of controls (total)

	Cases by country								Total		
	Denmark		Finland		Norway		Sweden		Cases		Controls
	N	%[1]	*N*	%	*N*	%	*N*	%	*N*	%	*N*
Sex											
Girls	78	52	71	52	74	57	141	51	364	53	1,726
Boys	73	48	65	48	55	43	133	49	326	47	1,572
Sex ratio (G:B)	1.07:1		1.09:1		1.35:1		1.06:1		1.12:1		
Age at diagnosis (years)											
0	25	17	23	17	21	16	51	19	120	17	578
1–4	90	60	91	67	72	56	171	62	424	61	2,032
5–9	30	20	19	14	29	22	45	16	123	18	579
10–14	6	4	3	2	7	5	7	3	23	3	109
Mean age	3.1		2.7		3.4		2.7		2.9		
Total	151		136		129		274		690		3,298

[1]Percentages were rounded to whole numbers and therefore do not always add up exactly to 100%.

with being small for gestational age, and no associations were seen with maternal age, various obstetric events or maternal conditions before pregnancy.[7]

Here, we report results from a register-based case–control study involving all 690 cases occurring in Denmark, Finland, Norway or Sweden during 1985–2006, individually matched by date of birth, sex and country to 3,298 controls, using the medical birth certificates to assess information on birth weight, gestational age, paternal age, birth order, multiple births and Apgar score at 1 and 5 min after birth.

Material and Methods

This study was a register-based case–control study, following a study protocol previously used for childhood central nervous system (CNS) tumors.[29] Cases were all children with Wilms tumor (International Childhood Cancer Classification group VI(a): nephroblastoma and other nonepithelial renal tumors)[30] diagnosed before the age of 15 years. The time periods of diagnosis were January 1, 1985 to December 31, 2006 in Denmark, Norway and Sweden and during January 1, 1987 to December 31, 2006 in Finland. Case ascertainment was performed using the national population-based cancer registries of the Nordic countries, cross-checked with the childhood cancer registries (Sweden and Denmark) and the solid-tumor database of the Nordic Society of Paediatric Haematology and Oncology, to secure completeness.[31] Cases were individually matched to five controls by birth month and year, sex and country. Controls were drawn randomly from the Nordic childhood population, updated annually using the central population registries. Eligible controls had to be alive at the date of diagnosis of the corresponding case. Moreover, they had to have no previous diagnosis of a childhood solid tumor and had to be living in the respective country at the time of diagnosis of their corresponding case.

Information on birth characteristics of cases and controls was obtained from the population-based medical birth registries in Denmark (established 1973), Norway (established 1967), Finland (established 1987) and Sweden (established 1973). These registries contain mandatory, continuously updated reports on all births.[32] Registries were linked by the unique personal identification numbers assigned to all citizens of the Nordic countries, enabling perfect linkage between registries.

We investigated the effects of birth weight, gestational age, birth weight-by-gestational age, Apgar scores at 1 and 5 min after birth, parental age, birth order and multiple births. Gestational age was measured as completed weeks of gestation, which in the early period was determined by the date of the last menstrual period and in later years by ultrasound in early pregnancy. We estimated small- (SGA), appropriate- (AGA) and large-for-gestational age (LGA) as deviations from the expected birth weight by gestational age by using fetal growth charts based on ultrasonically estimated fetal weights of infants subsequently born at term,[33] derived from a combined Danish and Swedish cohort.[34] Infants were classified SGA when their birth weight was more than 2 standard deviations (SD) lower than the expected mean birth weight-for-gestational age, and LGA when their birth weight was greater than 2 SD above the mean birth weight. We calculated the SD of the mean from our own control sample. Birth order was dichotomized into first and later born children and based on siblings of the same mother.

Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) with the PHREG procedure in SAS (version 9.1).[35] In categorical analysis, we used contextual definitions of cutoff points [like low (<2.5 kg) and high (≥ 4 kg) birth weight, preterm births (<37 weeks of gestation) and low Apgar score (<7)], but sometimes used also finer categorizations because of our

Table 2. Odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between birth weight, gestational age and birth weight by gestational age, and Wilms tumors in children in the Nordic countries, 1985–2006[1]

							Boys only						Girls only					
	Cases		Controls				Cases		Controls				Cases		Controls			
	N	%	*N*	%	OR	95% CI	*N*	%	*N*	%	OR	95% CI	*N*	%	*N*	%	OR	95% CI
Birth weight (kg)																		
<2.5	25	4	113	4	1.10	0.71–1.71	14	4	53	3	1.27	0.70–2.33	11	3	60	4	0.91	0.47–1.76
2.5–4 (reference)	480	71	2,479	77	1.00		229	71	1,114	73	1.00		251	71	1,365	81	1.00	
≥4	172	25	627	19	1.43	1.17–1.74	78	24	366	24	1.04	0.78–1.38	94	26	261	15	1.97	1.50–2.59
Birth weight (kg)																		
<2	11	2	30	1	1.94	0.95–3.97	7	2	14	1	2.59	0.99–6.75	4	1	16	1	1.31	0.43–4.01
2–2.5	14	2	83	3	0.91	0.51–1.64	7	2	39	3	0.86	0.37–1.98	7	2	44	3	0.92	0.40–2.11
2.5–3	53	8	336	10	0.88	0.63–1.23	20	6	143	9	0.74	0.44–1.24	33	9	202	12	1.01	0.66–1.55
3–3.5 (reference)	185	27	1,037	32	1.00		87	27	436	28	1.00		98	28	601	36	1.00	
3.5–4	242	36	1,106	34	1.23	1.00–1.52	122	38	544	35	1.11	0.82–1.50	120	34	562	33	1.33	0.99–1.78
4–4.5	130	19	497	15	1.47	1.15–1.89	59	18	276	18	1.05	0.73–1.51	71	20	221	13	1.99	1.41–2.80
≥4.5	42	6	130	4	1.90	1.29–2.81	19	6	90	6	1.09	0.62–1.89	23	6	40	2	3.63	2.07–6.38
Per 500 g[1]					1.14	1.06–1.22					1.01	0.91–1.12					1.28	1.15–1.42
Gestational age[2] (weeks)																		
37+ (reference)	627	94	3,017	95	1.00		295	94	1,443	96	1.00		332	95	1,574	95	1.00	
32–36	33	5	136	4	1.13	0.76–1.68	16	5	61	4	1.32	0.74–2.34	17	5	75	5	1.00	0.58–1.72
<32	6	1	12	0	2.44	0.89–6.64	4	1	6	0	3.35	0.89–12.7	2	1	6	0	1.62	0.33–8.03
Birth weight-by-gestational age[2,3]																		
SGA	8	1	39	1	0.94	0.43–2.04	5	2	15	1	1.61	0.58–4.50	3	1	24	1	0.55	0.16–1.87
AGA (reference)	619	93	3,013	95	1.00		297	94	1,436	95	1.00		322	92	1,577	95	1.00	
LGA	39	6	113	4	1.76	1.21–2.57	13	4	59	4	1.12	0.60–2.07	26	7	54	3	2.48	1.51–4.05

[1]Multiple births omitted from the analyses: 13 cases and 79 controls. [2]Eleven cases and 54 controls have missing information on gestational age. [3]SGA (small-for-gestational age), AGA (appropriate-for-gestational age) and LGA (large-for-gestational age).

Table 3. Odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between Apgar score at 1 and 5 min of age and Wilms tumors in children in the Nordic countries, 1985–2006[1]

	Cases		Controls			
	N	%	*N*	%	OR	95% CI
Apgar score 1 min						
≥7 (reference)	475	94	2,292	96	1.00	
<7	31	6	94	4	1.63	1.07–2.48
Apgar score 5 min						
≥7 (reference)	489	97	2,369	99	1.00	
<7	17	3	17	1	5.13	2.55–10.3
Apgar scores 1 and 5 min						
Apgar 1/5 ≥ 7 (ref)	474	94	2,291	96	1.00	
Apgar 1 < 7, Apgar 5 ≥ 7	15	3	78	3	0.95	0.54–1.66
Apgar 5 < 7	17	3	17	1	5.12	2.55–10.3

[1]Information on Apgar scores available for 506 (73.3%) cases and 2,386 (72.3%) controls.

comparably large sample size. We examined the dose-response relationship between birth weight and Wilms tumors using birth weight as a continuous variable and applying a log-linear model.[36] The same approach was used for parental age and birth order. In all conditional analyses, we accounted for country, sex and age by keeping the individual matching. We investigated effect estimates separately by country (no major differences, therefore data not shown), by sex and by age group (0–4 years and 5+ years).

The study was approved by the national data protection boards of all four countries and by ethical committees in accordance with national laws and regulations. No direct contact with participants was required.

Results

From the 693 cases identified three were excluded because of missing information on birth weight ($n = 2$) or date of birth ($n = 1$). The majority of the 690 eligible cases were from Sweden (40%), followed by Denmark (22%), Finland (20%) and Norway (19%), reflecting the childhood population sizes of the four Nordic countries (average proportions of the total Nordic childhood population between 1985 and 2006: Sweden 37%, Denmark 22%, Norway 22% and Finland 20%). In all four countries, girls were more often affected with an overall sex ratio of 1.12:1 (Table 1). The sex ratio was similar for all ages, with ratios of 1.11, 1.11, 1.12 and 1.3 (only 23 cases) for age groups 0 years, 1–4 years, 5–9 years and 10+ years, respectively. Almost four of five cases were diagnosed before their fifth birthday; about one of five cases was diagnosed during the first year of life (Table 1). The median age at diagnosis was 2 years. There were no major differences between the four countries, only in Norway there was some stronger preponderance of girls and cases were slightly older at date of diagnosis (Table 1). Because of the individual matched design, the demographic distributions of controls correspond to the respective distributions among cases, with minimal differences introduced by the exclusion of children for whom the birth certificates were not available, *i.e.*, children born outside the respective country.

Table 2 shows the associations between Wilms tumors and birth weight, gestational age and birth weight-by-gestational age, with multiple births omitted from the effect estimation. Analyses of low (<2.5 kg) and high (≥ 4 kg) birth weight yielded no association for low birth weight and a 43% increased effect estimate for high birth weight for both sexes combined. However, although there was no association with high birth weight for boys, the effect was almost 2-fold for girls ($p = 0.001$ from homogeneity test). This sex-specific association became even more apparent with a finer categorization of birth weight, showing ORs of 1.09 in the highest exposure category for boys and 3.63 for girls. Overall, the finer categorization showed an elevated OR for very low birth weight babies (<2 kg), but based on only seven (2%) cases in this group. A log-linear trend showed again a clear association for girls but not for boys (given as an effect estimate per 500 g weight increase in Table 2). An elevated OR was also seen for gestational age < 32 weeks, which was somewhat more increased for preterm boys (Table 2). Applying the birth weight-by-gestational age algorithm showed no association for SGA babies, but an effect for LGA which was attributable to girls (Table 2). A combination of birth weight alone and birth weight-by-gestational age in girls revealed increased effect estimates for all combinations, with ORs of 1.86 (95% CI 1.38–2.51), 3.37 (95% CI 1.09–10.4) and 2.69 (95% CI 1.57–4.64) for AGA girls of high birth weight (≥4 kg), LGA girls of normal birth weight and LGA girls of high birth weight, respectively. Stratification by age showed similar effect estimates for young children (0–4 years) compared to older children (5+ years at diagnosis; data not shown). Adjustment for parental age did not alter the effect estimates. Keeping the 92 multiple births in the analyses did not alter the effect estimates for high birth weight, but the association in the very low birth weight category and for preterm babies became slightly weaker (data not shown). Birth order did have an effect insofar that, among girls, the association

Table 4. Odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between parental age, birth order and multiple birth, and Wilms tumors in children in the Nordic countries, 1985–2006

	Cases		Controls			
	N	%	*N*	%	OR	95% CI
Maternal age (years)						
<20	20	3	113	3	0.82	0.50–1.34
20–24	132	19	633	19	0.96	0.76–1.20
25–29 (reference)	272	39	1,239	38	1.00	
30–34	187	27	900	27	0.95	0.77–1.17
35–39	68	10	355	11	0.86	0.64–1.16
≥40	11	2	58	2	0.87	0.45–1.69
Per 5 years of age					0.98	0.92–1.03
Paternal age (years)						
<20	5	1	25	1	0.98	0.37–2.59
20–24	69	10	330	10	1.04	0.77–1.40
25–29 (reference)	208	30	1,034	31	1.00	
30–34	227	33	1,054	32	1.06	0.86–1.31
35–39	117	17	575	17	1.01	0.79–1.30
40–44	51	7	207	6	1.21	0.86–1.71
45–49	8	1	50	2	0.77	0.36–1.66
≥50	5	1	23	1	1.08	0.40–2.88
Per 5 years of age					1.01	0.97–1.06
Birth order						
First born	289	42	1,399	43	1.00	
Later born	401	58	1,892	57	0.98	0.83–1.16
Per order of 1					1.00	0.92–1.08
Multiple birth						
Singleton	677	98	3,219	98	1.00	
Multiple birth	13	2	79	2	0.77	0.43–1.40

with high birth weight was considerably weaker among first born girls (OR 1.14, 95% CI 0.60–2.16) compared to later born girls (OR 2.19, 95% CI 1.51–3.17) ($p = 0.08$ from homogeneity test), whereas ORs were virtually identical for first or later born boys.

Table 3 shows a modest association between Wilms tumors and Apgar score at 1 min and a strong association with Apgar score at 5 min, with an OR just above 5 for an Apgar score below 7. Further analyses showed that the increased OR for Apgar score at 1 min was attributable to children who continued to have a low Apgar score at 5 min. In contrast to birth weight, effect estimates were not significantly different for boys and girls ($p = 0.13$ from homogeneity test). Moreover, the effect estimates were similar for younger and older children (data not shown). A combination of Apgar score at 5 min with birth weight and gestational age showed that the observed association was not attributable to preterm or low birth weight babies having a low Apgar score. Conversely, the association seen with preterm and low birth weight shown in Table 2 disappeared when children with a low Apgar score were removed from this group (OR 1.01, 95% CI 0.65–1.58 for children who were either preterm (<37 weeks) or low birth weight (<2.5 kg) but had an Apgar score at 5 min of ≥7). As high birth weight could be the reason for a prolonged labor leading to a low Apgar score, we explored also the combination of Apgar score at 5 min with high birth weight or high gestational age, but both the associations with Apgar score and with large babies remained unchanged.

Table 4 shows the ORs for associations between Wilms tumors and maternal age, paternal age, birth order and multiple births. All ORs were close to unity.

Discussion

Although high birth weight has long been suspected to be associated with an increased risk of Wilms tumor, results of epidemiological studies were not entirely consistent, with some showing a positive association and some showing no association.[5–23] Much of the heterogeneity of results, however, might be due to the small size of the earlier studies involving between 50 and 150 cases and their vulnerability to selection and recall

bias, as more recent studies appear to converge. The only two cohort studies, one from the United States and one from Norway, reported relative risks of 1.5 (95% CI 1.0–2.4) and 1.2 (95% CI 0.7–2.0) for children weighing 4 kg or more at birth.[15,22] A German case–control study showed an elevated OR of 1.3 (95% CI 0.8–2.2) for high birth weight and of 1.5 (95% CI 0.9–2.6) for LGA babies.[21] A large United States case–control study using obstetric histories found elevated ORs of 1.2 (95% CI 0.8–1.7) and 1.7 (95% CI 0.9–3.3) for birth weights of 4–4.5 kg and $\geq$4.5 kg and of 1.3 (95% CI 0.9–1.9) for LGA babies, based on 521 cases.[7] Our study with 690 cases yielded an overall OR at $\geq$4 kg of 1.4 (95% CI 1.2–1.7), providing evidence that there is indeed an increased risk with high birth weight. Taken all studies together, the increase is between 30 and 50% at birth weights above 4 kg.

In our study, the association between birth weight and Wilms tumor was restricted to girls, with a rather strong effect of a 28% risk increase per 500 g increase in birth weight. The results are statistically robust and highly unlikely to be a play of chance or bias for the following reasons: (*i*) we had 94 female Wilms tumor patients weighing 4 kg or more at birth, a large number comparable to the total of cases of both sexes of most previous studies, (*ii*) the information on birth weight was collected in compulsory and complete medical birth registries before the date of diagnosis and (*iii*) the observed association was due to higher birth weights in female cases and not to a chance deviation of the birth weight distribution among the control sample; comparing our Wilms tumor controls with a sample of more than 15,000 controls drawn for a study on childhood CNS tumors showed similar proportions of low and high birth weights, namely 4.5, 80.4 and 15.2% for female Wilms tumor controls of birth weights $<$2.5, 2.5–4 and $\geq$4 kg, respectively, and accordingly 4.5, 81.6 and 13.9% for female CNS tumor controls (both distributions including multiple births).[29] In a large United States study, the association between Wilms tumor and birth weight at 4 kg was strongest among patients with PLNR, and PLNR was slightly more common among girls (17%) than boys (9%).[7] Nevertheless, sex-specific analyses have been reported from only two studies.[8,9] These two studies both showed a stronger effect for girls; Jepsen *et al.*[9] reported effect estimates of 1.55 and 2.86 for girls weighing 4–4.5 and $\geq$4.5 kg, respectively, but there were only nine and three girls in the respective categories, and Lindblad *et al.*[8] reported an effect estimate of 1.3 for girls compared to 1.1 for boys at a cutoff of 4 kg. The overlap of these two studies with our material is small. However, they were conducted in Denmark and Sweden, and therefore, the birth weight effect restricted to girls has only been reported from studies conducted in Nordic countries. Interestingly, the Wilms tumor cases attributable to high birth weight in girls broadly correspond to the higher incidence of Wilms tumors in girls. Using our own study base with complete case ascertainment, the average age-adjusted incidence rates of Wilms tumor between 1988 and 2006 were 6.75 in boys and 8.13 in girls per 1 million person-years, thus reflecting a 20% higher incidence rate in girls.

Olshan suggested that high birth weight could be associated with changes in expression in the IGF2 gene or other genes that regulate growth on the short end of chromosome 11 where the Wilms tumor 1 gene is also located.[27] Breslow *et al.* defined two "ideal" types of Wilms tumor, one characterized among other features by the presence of ILNR and with WT1 mutation as the critical molecular event and the other characterized by PLNR with molecular events involving dysregulated expression of genes in the region of IGF2.[6] They suggested that PLNR might be the result of excessive or prolonged exposure to IGF2 of nephrogenic blastema during the period of nephron formation. Although this type of Wilms tumor usually occurs later in life, we did not see an age-specific association with high birth weight or LGA.

The Apgar score is based on evaluating a newborn's appearance, *i.e.*, color, heart rate, reflex irritability, muscle tone and respiratory effort, and a score below 7 of 10 after 5 min indicates the need of medical care.[37,38] Puumala *et al.* did not observe lower Apgar scores at 1 or 5 min in Wilms tumor patients compared to controls,[22] but Heuch *et al.* did see an elevated OR of 2.15 at 1 min for a score $\leq$ 7.[15] We observed an OR above 5 based on 17 Wilms tumor cases with a low Apgar score at 5 min, which explained the association seen with a low Apgar score at 1 min and the increased risk for small babies, both in terms of low birth weight and short gestational age. There are three possible explanations. First, the low Apgar score might be a sign of hypoxia, leading to cell damage that subsequently leads to a Wilms tumor.[39,40] Second, the observed association might indicate that the neonatal treatment provided to newborns with a low Apgar score at 5 min could increase the risk of a subsequent Wilms tumor.[41–43] Third, it might also reflect reverse causation insofar that the yet undiagnosed Wilms tumor or predisposure to develop a Wilms tumor lead to symptoms related to a low Apgar score. The positive association with Apgar score, however, was not restricted only to young cases but seen in all age groups.

Most previous studies did not see an overall association between Wilms tumors and maternal age or birth order. However, some reported significant effect estimates although they were not consistently pointing in the same direction.[44] A large United States registry-based study involving 1,126 Wilms tumor cases found a somewhat increased effect estimate of 1.16 (95% CI 1.09–1.22) per 5-year increase in maternal age.[45] In this large population-based data set, we did not see any association, being in line with a recent large United States case–control study[7] and cohort studies from the United States, Norway and Sweden.[15,22,46]

An important strength of our study is the use of registers established for other purposes, which eliminates the impact of selection bias or recall bias that are otherwise common in interview-based case–control studies. The registry system in the Nordic countries provides both a complete case ascertainment through the high-quality population-based cancer registries and an optimal sampling frame for controls, and with the unique personal identification number perfect linkage with information obtained from the medical birth registries. In our study, we used factors that were reported to be recorded on birth certificates

with sufficient accuracy, so the impact of misclassification error is expected to be minor. Given the rarity of Wilms tumors in children, our study based on 690 cases is the largest to date and allows us more in-depth investigation of birth characteristics by examining risk in subgroups or finer categorizations of putative risk factors. A limitation of our study is that some of the investigated factors are extremely rare, thus our results for Apgar score and preterm birth are still based on small numbers. Another limitation is that we did not have information on congenital malformations or Wilms tumor histology and could not subdivide our cases into patients with PLNR or patients with ILNR.

In conclusion, the strong association between high birth weight and risk of Wilms tumor in girls but not in boys may explain the preponderance of this tumor in girls in the Nordic countries. Further studies are needed to clarify if this effect is restricted to specific Wilms tumor subtypes.

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