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Obstetric history and birth characteristics and Wilms Tumor: A report from the Children's Onocolgy Group

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Abstract

Previous epidemiologic studies have suggested that various pregnancy and birth characteristics may be associated with Wilms tumor, a childhood kidney tumor. We evaluated obstetric events and birth characteristics in relation to Wilms tumor using data from a large North American case-control study. Mothers of 521 children with Wilms tumor and 517 controls, frequency matched on child's age and geographic region, provided information about their labor and delivery history and their children's birth characteristics through detailed computer assisted telephone interviews. Most obstetric factors were not associated with Wilms tumor, but modest associations were observed for labor induction (OR:1.4, 95% Confidence Interval (CI): 1.1,1.8), prenatal vaginal infection (OR: 1.8, 95% CI: 1.2,2.8), and upper respiratory infection (OR: 1.5, 95% CI: 1.0,2.4). Low (<2500g) and high (>4500g) birth weight and preterm delivery (<37 weeks completed gestation) were associated with an elevated risk of Wilms tumor, as was neonatal respiratory problems. The association for high birth weight was present only among children with perilobar nephrogenic rests (OR: 2.1, 95% CI: 1.2,3.9), possibly distinguishing a specific association among a biologically distinct subgroup of Wilms tumor cases. The results of this large study did not support many of the earlier findings of smaller studies. However, additional investigations of the effects of certain obstetric and birth characteristics among more refined tumor subgroups may further our understanding of these factors in relation to Wilms tumor.

Keywords

childhood cancer; pregnancy; obstetrics; preterm; birth weight; infection; Wilms tumor

Introduction

Little is known about the etiology of Wilms tumor (nephroblastoma), which arises from remnants of immature kidney. This malignancy of the kidney is usually diagnosed before the child reaches 5 years of age[1,2], emphasizing the need to explore early life exposures,

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particularly those occurring around the time of conception through pregnancy. The effects of obstetric events and birth characteristics have been reported by previous studies, specifically the use of anesthesia during labor, older maternal age, high infant birthweight, and jaundice; but results of these studies have been equivocal and most have been limited by small sample size[3-9]. Recent reports suggest that high birth weight might be associated the subgroup of Wilms tumor characterized by the presence of perilobar nephrogenic rests[10,11]. Nephrogenic rests are embryonic remnants that persist in the fully developed kidney and precede Wilms tumor[2,10]. Perilobar rests are strongly associated with synchronous bilateral tumors and intralobar rests are associated with metachronous bilateral tumors. Distinguishing the presence and type of rests can provide some insight into the development and prognosis of Wilms tumor [2,10]. Investigation of specific risk factors for Wilms tumor subtypes characterized by child's age or tumor pathology requires larger studies with detailed data in order to produce stable results. We investigate whether obstetric events or birth characteristics were associated with Wilms tumor using data from a large, North American case-control study. Specifically, we evaluate maternal reproductive history, medical conditions during pregnancy, events of labor and delivery, and birth characteristics.

Methods

Cases were identified by the National Wilms Tumor Study Group (NWTSG), a consortium of two large national collaborative childhood cancer groups in North America: the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) (merged to form the Children's Oncology Group in 2000). Cases were children under 16 years of age who were newly diagnosed with Wilms tumor at one of 128 participating hospitals in the United States and Canada from 1999 to 2002. Cases were excluded if they had clear cell sarcoma or rhabdoid tumor of the kidney. The NWTSG sees approximately 94% of pathologically confirmed patients in the U.S.[12]. The treating institution obtained IRB approval for the study and the primary physician provided permission to contact the family. Cases were eligible if their biological mother was available for a telephone interview in either English or Spanish.

Controls were frequency matched by age at diagnosis (0-1, 2-3, and 4 or more years old) and geographic region of residence (4 U.S. Census regions and Canada). Controls were identified by telephone random-digit dialing (RDD)[12]. We employed a multi-stage list-assisted sampling process to accomplish frequency-based screening and selection methods[13], rather than the usual modified Waksberg approach (the addition of two random digits to the first eight digits of the case's home telephone number) as used in most previous childhood cancer studies [14]. The response proportion for the RDD screening phase was 51 percent.

Data were collected between February 2000 and January 2003 through computer assisted telephone interviews with the mother, after she returned a signed consent and received an interview guide. Mothers provided information about demographic factors, pregnancy history, pregnancy and birth complications, radiation exposure, occupational history, family medical history, and tobacco and alcohol use. On average, interviews were conducted 52 weeks after the diagnosis date (cases) or initial RDD screening date (controls).

This paper focuses on the relationship between maternal pregnancy history, child's birth characteristics and Wilms tumor. Women provided specific information about medical conditions and medication use during pregnancy, events associated with labor and delivery, and the child's size and basic health parameters at birth. Birth weight, as reported by the mother, was converted to grams and gestational age was recorded as completed weeks of pregnancy. Size for gestational age was calculated using Zhang and Bowes' method, which incorporates race-specific standards for birthweight at each gestational age, adjusting for birth order [15]. However, this method is only available for black and white births, thus size for gestational age

was not calculated for children of other races or Hispanic ethnicity. Inter-pregnancy interval was calculated based on the number of months from the end of last pregnancy to the estimated conception date of index pregnancy.

The frequency distributions of candidate factors were compared between cases and controls. Continuous variables were categorized based on *a priori* information or the distribution among controls. Categories with sparse data and similar effects were combined to reduce numbers of strata to increase sample size within each stratum. Accordingly, exposures occurring from the period one month prior to conception until delivery were combined as "prenatal" exposures. Unconditional logistic regression models with adjustment for matching variables, child's age at diagnosis and geographic regions, were used to estimate the odds ratio (OR) and 95% confidence intervals (CI) (model 1). Further adjustment for child's sex, maternal education, and household income at birth was applied to control potential confounding effects based on *a priori* information (model 2). Models evaluating prior pregnancy outcome also included gravidity, treated as a continuous variable. Analysis of inter-pregnancy interval was restricted to mothers for whom the index case was not the first born. Analyses stratified by child's age at diagnosis (<2, 2-3, 4+ years) and the presence and type of nephrogenic rests (rest negative, perilobar neprhogenic rest positive (PLNR), intralobar nephrogenic rest positive ILNR) were conducted to assess the potential for effect measure modification by markers of tumor subtype. The few cases that had both rest types were included in both PLNR positive and ILNR positive categories. All analyses were conducted using PC-SAS.

Results

Five hundred twenty-one (80%) of the 623 mothers of eligible cases and 517 (76%) of the 682 mothers of eligible controls were successfully interviewed. The sociodemographic characteristics of cases and controls were generally similar (Table 1). Children with Wilms tumor in this study, however, were more likely to be female (OR 1.5, 95%CI 1.2,1.9). There were no differences between cases and controls with respect to maternal age, education, or household income. Among the 442 cases with information on the presence of nephrogenic rests, 70 (16%) had only PLNR, 107 (24%) had only ILNR, 21 (5%) had both and 244 (55%) were rest negative. Rest status was not determined for 79.

Wilms tumor was not associated with most prenatal diagnostic procedures, mode of delivery, or other obstetric events, but modest associations were observed for induction of labor, use of anesthesia during labor, and proteinuria/ preeclampsia (Table 2). The effect associated with labor induction was primarily among the younger children (age < 2 years: OR 1.4, CI 0.8, 2.3 and age 2-3 years: OR 1.7 1.1-2.8), not children 4 years or older (OR 1.1, CI 0.7,1.7). Children whose mothers had Chorionic Villis Sampling (CVS) were less likely to have Wilms tumor, but results were very imprecise (Table 2).

Among the other maternal health conditions occurring during pregnancy that were considered in this analysis (Table 3), maternal vaginal infection in the month before or during pregnancy was associated with an 80% increase in likelihood of Wilms tumor in the child (OR 1.8, 95% CI: 1.2,2.8). In analysis stratified by child's age at diagnosis, the magnitude of this effect was stronger among children under 2 years of age at diagnosis (OR 3.3, 95%CI: 1.4,7.7) compared to children age 2-3 years (OR 1.3, 95%CI: 0.6,2.8) or 4 years or older (OR 1.2, 95%CI: 0.5,2.5). Maternal upper respiratory infection was also associated with an elevated risk of Wilms tumor (OR: 1.5, 95% CI: 1.0,2.4). This relationship was primarily among the older two age groups (age 2-3 years OR 1.7, 95% CI: 0.8,4.0, age 4 or more years OR 2.2, 95% CI: 1.0,4.8), but absent in the youngest group (OR 1.0, 95% CI: 0.5,2.2). Other types of infection and chronic health conditions reported during pregnancy were not associated with Wilms tumor.

Children with Wilms tumor were slightly more likely than controls to be born from a first pregnancy (33% vs. 28%; OR 1.2, 95%CI: 0.9, 1.6). Among multiparous mothers, Wilms tumor was unrelated to prior pregnancy loss, induced abortion, or the interval since the last pregnancy, after adjustment for maternal education, income, and child's sex and age (data not shown).

Case children were more likely to have been born preterm (<37 weeks completed gestation OR 1.5, 95% CI: 1.0,2.4). Both low and high birth weight were modestly associated with Wilms tumor, but the subtle U-shaped pattern was imprecise (Table 4). Among term children, there was no association between Wilms tumor and low birth weight (OR 1.0, 95% CI: 0.4,2.4) or high birth weight (OR 1.2, 95%CI: 0.88,1.8), data not shown in tables. Among the subgroup of black and white children for whom size for gestational age could be calculated, the odds ratio for Wilms tumor increased slightly with size for gestational age, but this comparison was imprecise. Cases with either no rests present or PLNR present tended to be of higher mean birth weight and older at diagnosis than those with ILNR (Table 5). The odds ratio for high birth weigh and Wilms tumor was primarily driven by the PLNR positive cases compared to controls (OR 2.1, 95% CI: 1.2,3.9), rather than ILNR positive cases or rest negative cases (Table 6). Conversely, the elevated risk associated with preterm birth was also most pronounced among the PLNR positive cases. Except where noted, none of the relationships examined in these data were modified by child's age.

Discussion

This study examined several complications of pregnancy and delivery using the largest case-control sample of Wilms tumor date. Few prenatal or obstetric factors were associated with Wilms tumor in our data. Labor induction and use of anesthetic or pain medication during labor were both modestly associated with Wilms tumor, but details on the method of or reason for induction or the type of anesthesia could not be determined. The extent to which the use of pain medication resulted from labor induction was unclear in these data. Lindblad, et al.[4] also reported an association with anesthesia in a data linkage study from Sweden. Prior investigations of other obstetric complications as risk factors for Wilms tumor have also used the case-control design and interviewed parents, but they have generally been smaller and their results have been inconsistent. Earlier studies reported Wilms tumor to be associated with maternal hypertension during pregnancy [3,4], threatened miscarriage, toxemia, other complications of pregnancy [5], and maternal age[7,16], which may be associated with other complications; but none of these were supported by this study. We found maternal infections during pregnancy, specifically vaginal or respiratory infections, to be modestly associated with Wilms tumor. We did not have information to distinguish whether the vaginal infection was yeast or bacterial, nor whether it was treated. Maternal vaginal infection was most important for very young cases, which may be etiologically distinct from older cases. Events during pregnancy might be most influential just after the child's birth; therefore, the association would be stronger among younger cases. Vaginal infections, or the heightened response to them, might be vertically transmitted to the child and result in altered the child's immune activity and subsequently affect Wilms tumor risk. Bunin et al also reported a relationship between vaginal infection and Wilms tumor, but these associations were not found in an earlier NWTS study [3,6]. The interaction between age and respiratory infection did not follow this pattern, as the relationship between infection and Wilms tumor was stronger among older children. The possibility that these interactions are spurious cannot be ruled out because the stratified data were sparse.

Others have reported a relationship between birth weight and Wilms Tumor[3,5,7-9]. Breslow et al. reported that tumors among low birth weight infants were often WAGR syndrome, which accounts for only 1% or less of cases and could not be evaluated here [10,11]. Our data revealed a subtle and imprecise U-shaped relationship between birth weight and Wilms tumor and an

inverse relationship between gestational age and Wilms tumor risk. However, when restricted to term births, there was no association between birth weight and Wilms tumor in our data, suggesting that the effects associated with low birth weight may be driven by gestational age. Gestational age may be more important than low birth weight when considering the etiology of Wilms tumor risk associated with small, early babies. Underdeveloped kidneys at the time of birth may retain some clusters of immature cells that progress toward tumorigenesis. It is possible that the natural migration and differentiation of embryonic cells may be interrupted by early delivery, leaving clusters of undifferentiated cells to develop into Wilms tumor. Alternately, other factors like maternal infection during pregnancy, may pose greater risk of Wilms tumor by contributing to or more greatly affecting smaller babies, or through other mechanisms that could not be explored here. The results from our evaluation of the relationship between maternal infection and Wilms tumor stratified by birth weight or nephrogenic rest status were too imprecise for interpretation in these data. However, the magnitude of the relationship between preterm birth and Wilms among PLNR positive cases warrants further investigation, especially in light of the juxtaposition with the finding that high birth weight was also important in this stratum and the overall finding that risk increased with size for gestational age.

The interpretation of the relationship with high birth weight is more complicated. Others have reported an increased risk of Wilms tumor among children with birth weight over 4000 grams [7]. Overall, the effects associated with high birth weight in our data were driven by PLNR positive cases and the stratum weighing more than 4500g, although both were imprecise. The association between high birthweight and PLNR is consistent with recent NWTS analyses in which the authors suggested that rests may serve to identify different etiologic pathways for Wilms tumor[10]. Our subgroups were small and results of subgroup analyses were imprecise. If either gestational age or birth weight are associated with Wilms tumor, it is unclear whether they serve as an early marker for an infant who is destined to develop a tumor, or whether birth weight or gestational age act by increasing the child's susceptibility to other factors that might contribute to Wilms tumor.

In general, refining case definitions by tumor subtypes and distinguishing whether traits such as birth weight, gestational age, and nephrogenic rests are subtype markers or independent risk factors is important for future large-scale etiological investigations. This case-control study is the largest to date and has considerable information on obstetric and neonatal characteristics and covariates, conferring the ability to begin exploring differences by tumor subtypes based on the presence of nephrogenic rests. The size of this study allowed us to investigate more homogenous subgroups of Wilms tumor by stratifying by the child's age at diagnosis; however many stratified analyses were still limited by sample size.

Several additional factors should be considered when interpreting these results. First, interviews were conducted about a year after diagnosis or reference date, which may have been long after the child's birth, thus some obstetric events may have been difficult to correctly remember and report. Details about pregnancy events, such as the *type* of anesthesia used during labor, were difficult for many women to report. For example, about twenty percent of case and control mothers could remember that they had anesthetic or pain medication they received during labor, but not report the type. Having "other" or "unknown" pain medication was more dramatically associated with Wilms tumor (OR 1.6, 95% CI: 1.0-2.4, data not shown) than specific reports of anesthesia or narcotics (OR 1.2, 95% CI: 0.9-1.7, OR 1.3, 95% CI: 0.9-1.9, respectively). However, other factors that seem susceptible to poorer recall (such as varying degrees of jaundice among newborns or presence of meconium prior to delivery), were not reported more often by case mothers, somewhat reducing concern about potential bias in reporting. The time required for recall varied among participants, as some children were older at the start of the study, but the time between reference date and birth date was similar among

cases and controls because of frequency matching by age. Finally, the case composition of this study is skewed slightly toward older females than would be expected some registries [17], but this has been noted by others [18]. Thus, it is unclear whether this is an artifact of these data or a meaningful biological difference that should be considered.

This large study indicates that Wilms tumor may be associated with preterm birth, labor induction, and some maternal infections; but it did not corroborate most findings of earlier studies. The complex relationship between birth weight and gestational age should be carefully considered when interpreting results of previous studies and when planning future research. Further refining biologic pathways in future large studies of Wilms tumor may help distinguish risk factors that are relevant to only some tumor subtypes.

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Abbreviations

CATI, computer-assisted telephone interviews; CCG, Children's Cancer Group; CI, 95% confidence interval; NWTS, National Wilms Tumor Study; NWTSG, National Wilms Tumor Study Group; OR, odds ratio; POG, Pediatric Oncology Group; RDD, random digit dialing.

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Table 1

Demographic factors among participants in the Wilms tumor case-control study.

Factors	Case No. (%)	Control No. (%)	OR[a]	95% CI[a]
Child's age at reference date (yrs)				
< 2	146 (28)	138 (27)	1.	--
2-3	164 (32)	145 (28)	1.1	0.8, 1.5
≥ 4	211(40)	234 (45)	0.9	0.6, 1.1
Geographic region of residence				
Midwest	159 (31)	154 (30)	1.	--
Northeast	69 (13)	60 (12)	1.1	0.7, 1.7
South	178 (34)	183 (35)	1.0	0.7, 1.3
West	58 (11)	64 (12)	0.9	0.6, 1.3
Canada	57 (11)	56 (11)	1.0	0.7, 1.6
Gender				
Male	223 (43)	273 (53)	1.	--
Female	298 (57)	244 (47)	1.5	1.2, 1.9
Maternal age at birth				
< 20	39 (8)	39 (8)	0.9	0.5, 1.5
20-24	113 (22)	103 (20)	1.	--
25-30	182 (35)	164 (32)	1.0	0.7, 1.4
31-45	187 (36)	211 (41)	0.8	0.6, 1.1
Maternal race				
White	389 (75)	404 (78)	1.	--
Black	72 (14)	58 (11)	1.3	0.9, 2.0
Hispanic	42 (8)	33 (6)	1.4	0.9, 2.3
Other	18 (4)	22 (4)	0.9	0.4, 1.6
Maternal education [b]				
< High school	43 (8)	41 (8)	1.1	0.7, 1.8
High school degree or equivalent	137 (26)	118 (23)	1.2	0.9, 1.6
More than high school	341 (66)	357 (69)	1.	--
Household income [b]				
< $10k	47 (10)	38 (8)	1.3	0.7, 2.2
$10-20k	81 (17)	96 (20)	0.9	0.5, 1.3
$21-30k	65 (13)	67 (14)	1.0	0.6, 1.6
$31-40k	66 (14)	66 (14)	1.	--
$41-50k	64 (13)	63 (13)	1.0	0.6, 1.6
≥ $51k	158 (33)	146 (31)	1.1	0.7, 1.6

[a] Odds ratios and 95% Confidence intervals adjusted for child's age at reference date and geographic region of residence (matching factors).

[b] 1 control had missing maternal education data; 40 cases and 41 controls had missing income data.

Table 2

The relationship between obstetric events and wilms tumor.

	Case No. (%)	Control No. (%)	Model 1 OR[a]	Model 1 95% CI[a]	Model 2 OR[a]	Model 2 95% CI[a]
Ultrasound [b]						
In 3 trimesters	127 (24)	129 (25)	1.	--	1.	--
In 2 trimesters	205 (39)	209 (41)	1.1	0.7, 1.4	1.0	0.7, 1.4
In 1 trimester	170 (33)	160 (31)	1.1	0.8, 1.6	1.1	0.8, 1.6
None	17 (3)	16 (3)	1.2	0.6, 2.4	0.8	0.4, 1.8
Amniocentesis [b]						
No	471 (91)	462 (90)	1.	--	1.	--
Yes	49 (9)	52 (10)	0.9	0.6, 1.4	0.9	0.6, 1.4
Chorionic Villis Sampling [b]						
No	513 (99)	504 (98)	1.	--	1.	--
Yes	6 (1)	10 (2)	0.6	0.2, 1.7	0.6	0.2, 1.8
Morning sickness [b]						
No	149 (29)	142 (27)	1.	--	1.	--
Yes without vomiting at all	126 (24)	148 (29)	0.8	0.6, 1.1	0.8	0.6, 1.1
Yes with vomiting	244 (47)	226 (44)	1.0	0.8, 1.4	1.0	0.8, 1.4
Hand swelling [b]						
No	263 (51)	262 (51)	1.	--	1.	--
Yes	255 (49)	254 (49)	1.0	0.8, 1.3	1.0	0.8, 1.3
Proteinuria/preeclampsia [b]						
No	430 (87)	437 (89)	1.	--	1.	--
Preeclampsia	18 (4)	16 (3)	1.2	0.6, 2.3	1.5	0.7, 3.2
Proteinuira	26 (5)	24 (5)	1.1	0.6, 1.9	1.2	0.6, 2.1
Both	19 (4)	14 (3)	1.4	0.7, 2.8	1.4	0.7, 2.9
Vaginal bleeding [b]						
No	431 (83)	424 (82)	1.	--	1.	--
Yes	89 (17)	91 (18)	1.0	0.7, 1.3	0.9	0.6, 1.2
Threatened miscarriage [b]						
No	483 (93)	471 (92)	1.	--	1.	--

	Case No. (%)	Control No. (%)	Model 1		Model 2	
			OR[a]	95% CI[a]	OR[a]	95% CI[a]
Yes	37 (7)	43 (8)	0.9	0.5, 1.3	0.8	0.5, 1.4
Vaccination during pregnancy [b]						
No	502 (97)	498 (97)	1.	--	1.	--
Yes	14 (3)	16 (3)	0.8	0.4, 1.7	0.9	0.4, 1.8
Labor induction [b]						
No	280 (54)	303 (59)	1.	--	1.	--
Yes	239 (46)	210 (41)	1.2	1.0, 1.6	1.4	1.1,1.8
Anesthetic or pain medication during labor [b]						
No	121 (23)	135 (26)	1.	--	1.	--
Yes	395 (77)	379 (74)	1.2	0.9, 1.6	1.3	1.0, 1.8
Delivery type [b]						
Vaginal delivery	393 (76)	399 (77)	1.	--	1.	--
C-section	127 (24)	116 (23)	1.1	0.8, 1.5	1.1	0.8, 1.5
Reason for C-section [b]						
Vaginal delivery	393 (76)	399 (78)	1.	--	1.	--
C-section because of previous c-section	35 (7)	42 (8)	0.9	0.5, 1.4	0.9	0.5, 1.4
C-section because of other reasons	92 (18)	74 (14)	1.3	0.9, 1.8	1.3	0.9, 1.8

[a]Odds Ratios and 95% Confidence Intervals adjusted for child's age at reference date and geographic region of residence (matching factors)in Model 1. Model 2 is additionally adjusted for child's sex, maternal education and household income at birth.

[b]Missing numbers: 2 cases and 3 controls for ultrasound/ sonogram examination; 1 cases and 3 controls for amniocentesis; 2 cases and 3 controls for CVS; 2 cases and 1 control for morning sickness; 3 cases and 1 control for hand swelling; 28 cases and 26 controls for proteinuria or preeclampsia; 1 cases and 2 controls for vaginal bleeding; 1 cases and 3 controls for threatened m iscarriage.5 cases and 3 control for vaccination during pregnancy; 2 cases and 4 controls for labor induction; 5 cases and 3 controls for anesthetic or pain medication during labor; 1 cases and 2 controls for delivery type.

Table 3

The relationship between maternal conditions before or during pregnancy and wilms tumor.

	Case No. (%)	Control No. (%)	Model 1		Model 2	
			OR[a]	95% CI[a]	OR[a]	95% CI[a]
Upper respiratory disease [b]						
No	463 (89)	476 (92)	1.	--	1.	--
Yes	56 (11)	40 (8)	1.4	0.9, 2.2	1.5	1.0, 2.4
Influenza or flu [b]						
No	455 (89)	460 (92)	1.	--	1.	--
Yes	55 (11)	42 (8)	1.3	0.8, 2.0	1.4	0.9, 2.1
Urinary tract /bladder /kidney infection or disease [b]						
No	436 (86)	426 (83)	1.	--	1.	--
Yes	72 (14)	85 (17)	0.8	0.6, 1.2	0.9	0.6, 1.3
Vaginal infection [b]						
No	454 (88)	473 (93)	1.	--	1.	--
Yes	62 (12)	38 (7)	1.7	1.1, 2.6	1.8	1.2, 2.8
Sexual transmitted disease [b]						
No	498 (96)	492 (96)	1.	--	1.	--
Yes	23 (4)	23 (5)	1.0	0.6, 1.8	1.1	0.6, 2.1
Hypertension [b]						
No	466 (90)	464 (90)	1.	--	1.	--
Yes	54 (10)	53 (10)	1.0	0.7, 1.5	1.1	0.7, 1.7
Heart disease [b]						
No	511 (98)	506 (98)	1.	--	1.	--
Yes	10 (2)	9 (2)	1.1	0.5, 2.8	1.4	0.5, 3.9
Anemia [b]						
No	435 (84)	429 (83)	1.	--	1.	--
Yes	83 (16)	87 (17)	1.0	0.7, 1.3	1.0	0.7, 1.4
Diabetes [b]						
No	499 (96)	486 (94)	1.	--	1.	--
Yes	22 (4)	30 (6)	0.7	0.4, 1.2	0.9	0.5, 1.6

	Case No. (%)	Control No. (%)	Model 1		Model 2	
			OR[a]	95% CI[a]	OR[a]	95% CI[a]
Thyroid disorder [b]						
No	506 (97)	499 (97)	1.	--	1.	--
Yes	14 (3)	15 (3)	0.9	0.4, 1.9	0.8	0.4, 1.7

[a]Odds ratios adjusted for child's age at reference date and study region (matching factors) in Model 1. Model 2 additionally adjusted for child's sex, maternal education and household income at birth.

[b]Missing numbers: 2 cases and 1 control for upper respiratory disease; 11 cases and 15 controls for influenza; 13 cases and 6 controls for urinary system disease; 5 cases and 6 controls for vaginal infection; 2 controls for sexual transmitted disease; only 1 case for hypertension; 2 controls for heart disease; 3 cases and 1 controls for anemia; 1 controls for diabetes; 1 cases and 3 controls for thyroid disorder.

Table 4

The relationship between child's characteristics at birth and wilms tumor.

	Case No. (%)	Control No. (%)	Model 1 OR[a]	Model 1 95% CI[a]	Model 6 OR[a]	Model 6 95% CI[a]
Gestational age (weeks)						
25-32	14 (3)	9 (8)	1.6	0.7, 3.7	1.6	0.9, 3.8
33-36	46 (9)	32 (6)	1.5	0.9, 2.4	1.5	0.9, 2.5
37-42	454 (87)	467 (90)	1.	--	1.	--
>42	7 (1)	9 (2)	0.8	0.3, 2.2	0.7	0.3, 2.0
Birth weight (g) [b]						
<1500	6 (1)	5 (1)	1.2	0.4, 4.0	1.4	0.4, 4.6
1500-<2500	34 (7)	27 (5)	1.4	0.8, 2.3	1.2	0.7, 2.1
2500-<4000	396 (76)	412 (80)	1.	--	1.	--
4000-<4500	60 (12)	55 (11)	1.2	0.8, 1.7	1.2	0.8, 1.9
>=4500	23 (4)	15 (3)	1.7	0.9, 3.3	1.6	0.8, 3.2
Birth weight for gestational age [c]						
Small for gestational age	31 (7)	50 (11)	0.6	0.4, 1.0	0.6	0.4, 1.0
Normal	354(78)	346 (77)	1.	--	1.	--
Large for gestational age	67 (15)	53 (12)	1.3	0.9, 1.9	1.2	0.8, 1.8
Jaundice [b]						
No	454 (88)	443 (86)	1.	--	1.	--
Yes	65 (13)	72 (14)	0.9	0.6, 1.3	0.8	0.6, 1.2
Respiratory problems [b]						
No	487 (94)	492 (96)	1.	--	1.	--
Yes	32 (6)	23 (4)	1.4	0.8, 2.4	1.6	0.9, 3.0
Meconium (antenatal) [b]						
No	514 (99)	507 (98)	1.	--	1.	--
Yes	5 (1)	8 (2)	0.6	0.2, 1.9	0.6	0.2, 2.0

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[a] Odds ratios adjusted for child's age at reference date and study region (matching factors) in Model 1. Model 2 additionally adjusted for child's sex, maternal education and household income at birth.

[b] 2 cases and 3 controls had missing birth weight data; 2 cases and 2 controls had missing medical problems data (jaundice, respiratory problems and meconium).

[c] SGA presented for only Black and White children, based on the Zhang and Bowes method[15]; which was not possible for 115 children who were Hispanic or another race/ethnicity or for 22 missing other needed information.

Table 5

The distribution of child's sex, age at diagnosis, and birth weight by case type, indicated by the presence of nephrogenic rests.

	Controls	Negative	PLNR[b]	ILNR[c]	PLNR & ILNR	Unknown
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Male						
<2 yrs	69 (25)	29 (27)	4 (20)	33 (60)	4 (44)	13 (41)
2-3 yrs	82 (30)	34 (32)	5 (25)	12 (22)	3 (33)	11(34)
4+ yrs	122 (45)	44 (42)	11 (55)	10 (18)	2 (22)	8 (25)
Female						
<2 yrs	69 (28)	16 (12)	5 (10)	21 (40)	3 (25)	18 (38)
2-3 yrs	63 (26)	45 (33)	17 (34)	18 (35)	7 (58)	12 (26)
4+ yrs	112 (46)	76 (56)	28 (56)	13 (25)	2 (17)	17 (36)
Total	517	244	70	107	21	79
	Mean (95%CI)[a]	Mean (95%CI)[a]	Mean (95%CI) [a]	Mean (95%CI)[a]	Mean (95%CI)[a]	
Age at Diagnosis	53 (49,57)	54 (47,62)	31 (25,36)	33 (20,46)	41.4 (34,48)	
Birth weight	3419 (3336,3502)	3578 (3421,3734)	3458 (3332,3583)	3575 (3293,3857)	3522 (3372,3673)	

[a] Means and 95% confidence intervals adjusted for child's sex.

[b] Perilobar Nephrogenic Rests

[c] Intralobar Nephrogenic Rests

Table 6

The relationship between birthweight and gestational age and wilms tumor, stratified by presence and type of nephrogenic rests.

Factor	All Cases		No Rests		PLNR[b]		ILNR[c]	
	OR[a]	95% CI[a]	OR[a]	95% CI[a]	OR[a]	95% CI[a]	OR[a]	95% CI[a]
Birth weight (g)								
<2500	1.3	0.8, 2.1	1.2	0.7, 2.3	1.0	0.4, 2.9	1.1	0.5, 2.5
2500-4000	1.	--	1.	--	1.	--	1.	--
>4000	1.3	0.9, 1.9	1.1	0.7, 1.8	2.1	1.2, 3.9	1.2	0.7, 2.3
Preterm birth								
Yes (≤37wks)	1.6	1.0, 2.4	1.4	0.8, 2.5	2.1	1.0, 4.5	1.2	0.6, 2.6
No	1.	--	1.	--	1.	--	1.	--

[a] Odds ratios and 95% confidence intervals study region and child's age at reference date (matching factors), in addition to child's gender, maternal education and household income at birth. Reference group for all analyses is controls.

[b] Perilobar Nephrogenic Rests

[c] Intralobar Nephrogenic Rests